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American Gastroenterological Association Technical Review on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

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See related Commentaries (pages 685-692); Guideline and Clinical Decision Tool (pages 819-823); and related Commentary by RP Harris in the April issue of *Annals of Internal Medicine*.

Pancreatic cysts are being identified with increasing frequency as a result of the escalating use of cross-sectional imaging, typically for unrelated reasons.[1,2] The incidence of pancreatic cysts in the US population is estimated to be between 3% and 15%, with increasing prevalence with age.[3] Identification of a cystic lesion in the pancreas creates anxiety for both patients and clinicians related to the potential specter of a deadly malignancy. Historically, non-neoplastic inflammatory pancreatic pseudocysts were believed to be the most common pancreatic cysts; however, as imaging has become more sensitive, smaller, neoplastic cysts are more frequently detected. The finding of a pancreatic abnormality with potential association with malignancy is an increasing source of referral to specialists and an important driver of resource utilization, particularly in the United States. Imaging studies vary widely in their quality and interpretation, fueling the need for additional investigation. This technical review discusses the challenges in evaluating pancreatic cysts and critically examines the existing data set for evidence-based medical decision making.

Although the concern for current or future malignancy is justified, a rational, evidence-based, cost-effective approach to care of the patient with a pancreatic cyst remains poorly defined. Despite the high prevalence of these lesions, investigators have recently questioned just how frequently a clinically relevant adverse outcome occurs, that is, the development of a life-threatening malignancy. This is a critical consideration given the cost of repeat imaging, performance of invasive procedures such as endoscopic ultrasonography (EUS) with or without fine-needle aspiration (FNA), and consideration of a major pancreatic resection with the substantial attendant morbidity and mortality, particularly in the aging population with a high rate of prevalent cysts. In a recent analysis, investigators using the Surveillance, Epidemiology, and End Results (SEER) database estimated an annual prevalence of 1137 mucin-producing pancreatic adenocarcinomas with a concurrent prevalence of nearly 3.5 million cysts in the same population, concluding that malignant transformation is a very rare event.[4] In this clinical context, the American Gastroenterological Association has commissioned an evidence-based review of the diagnosis and management of pancreatic cysts.

Differential Diagnosis

Cystic lesions of the pancreas have a broad differential diagnosis. In general, they can be categorized into non-neoplastic (eg, pseudocysts) and neoplastic cystic lesions. The latter group, often referred to as cystic neoplasms of the pancreas, can be broadly subcategorized into those that produce a mucin-rich fluid (ie, mucin-producing cystic neoplasms) and those that do not. This distinction is important, because an increased risk of pancreatic adenocarcinoma has been attributed to all of the mucin-producing variants, which include branch duct intraductal papillary mucinous neoplasm (IPMN), main duct IPMN, and mixed IPMN (which has features of branch duct and main duct IPMN). The classic example of a cystic neoplasm that is not mucin producing, to which an increased risk of cancer is not attributed, is a serous cystadenoma. Papillary cystic neoplasms (eg, solid pseudopapillary tumors of the pancreas) and cystic pancreatic neuroendocrine tumors are additional examples of cystic neoplasms of the pancreas. There are many challenges associated with achieving an accurate diagnosis and, arguably more importantly, identifying reliable and reproducible methods to stratify risk of cancer for these patients, making clinical decision making difficult. Several groups, including an international consensus panel, have proposed management recommendations (including algorithms) for patients with suspected cystic neoplasms of the pancreas.[5,6] These are commonly used in clinical practice; however, these are consensus guidelines and not

Abbreviations used in this paper: **CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; ERCP, endoscopic retrograde pancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LR, likelihood ratio; MCN, mucinous cystic neoplasm; MeSH, Medical Subject Heading; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; OR, odds ratio; PICO, population, intervention, comparison, and outcome; SEER, Surveillance, Epidemiology, and End Results.**

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necessarily evidence based. Following a basic description of the different types of cystic neoplasms, we provide results from our evidence-based systematic literature review, which was designed to assess the strength of the evidence for specific focused clinical questions commonly encountered in the management of patients with pancreatic cysts. The purpose of this report is to assess the existing evidence to address specific clinical questions related to the evaluation and management of pancreatic cysts with a focus on indeterminate cysts.

Pseudocysts

Inflammatory pseudocysts historically were believed to represent up to 90% of all pancreatic cysts, but recent data obtained with high-resolution imaging showed a high prevalence of incidentally noted cysts among patients without a history or evidence of pancreatitis, suggesting that neoplastic cysts are likely far more common. The critical patient management issue is differentiating these non-neoplastic lesions from neoplastic lesions. When a cyst without an associated solid mass arises in a patient with known chronic pancreatitis, the clinical concern of a neoplasm is minimal. When patients present with unexplained pancreatitis for the first time with a cyst, or have only subtle changes of chronic pancreatitis on EUS alone, the clinician should consider whether the cyst may be a neoplasm and the lesion is the cause of the pancreatitis instead of assuming it is the consequence of pancreatitis. Review of imaging studies performed before the episode of pancreatitis, if available, may address this critical question.

Serous Cystadenomas

Serous cystadenomas were originally termed "microcystic adenomas," referring to the small (<2 cm) cystic compartments that make up the tumors. The term "microcystic adenoma" is still used synonymously with serous cystadenomas but has recently been criticized because of reports of macrocystic variants.[7]

Serous cystadenomas occur more commonly in women, who typically present in their 60s. Lesions with serous morphology in a young woman or a man may therefore lead to diagnostic confusion. Although nearly always benign, malignant serous cystadenocarcinomas have rarely been described.[8] They can become symptomatic by increasing in size with "invasive features," leading to the recommendation by some surgical experts to remove them in younger patients. The low risk of malignancy should forestall the need for frequent surveillance. However, if the diagnosis is not confirmed, or if there is concern for local invasiveness, surveillance and management for these cysts remains controversial.

Serous cystadenomas are generally slow-growing tumors that are symptomatic in less than one-half of patients. The pathology of these tumors shows well-circumscribed masses enclosed in a fibrous capsule containing numerous small fluid-filled cysts arranged in a classic "honeycomb" pattern.[9] Fibrous bands within the lesions often converge centrally, forming a stellate scar that may calcify, giving a pathognomonic "sunburst" appearance on computed tomography (CT).[10]

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCNs) represent nearly one-half of the tumors removed in contemporary surgical series. MCNs occur almost exclusively in women (>98%) and are generally diagnosed in patients in their 40s and 50s.[11,12] The patient may present with pain, an abdominal mass, or weight loss, but up to one-third of series report discovery by cross-sectional imaging for unrelated reasons. Ninety percent of cases occur in the pancreatic body or tail.[13]

MCNs are characterized by a thick fibrous capsule that encircles the cystic spaces. A characteristic spindle cell stroma containing epithelioid cells similar to ovarian stroma surrounds the tumor. The cyst lining is composed of mucin-producing duct-like cells frequently exhibiting a papillary architecture. However, the epithelial lining may be denuded, leading to misdiagnosis of a "pseudocyst" on limited tissue samples such as operative frozen sections.

The prognosis of MCNs is defined by the presence or absence of invasive adenocarcinoma. Cancer has been described in approximately one-third of operated tumors; these patients have a variable prognosis, with 5-year survival up to 60% after surgery for cancer to poor outcomes similar to those for ductal adenocarcinoma.[14] One explanation for the disparate findings may reflect sampling, because the invasive component may be only a small part of the lesion.

IPMNs

IPMNs are also mucin-producing lesions, which characteristically communicate with the main pancreatic duct as their main point of distinction from MCNs. These increasingly recognized lesions are characterized by intraductal dysplastic epithelium resembling colorectal villous adenomas, with papillae covered by columnar epithelium and the occasional goblet cell with extensive mucin production. This category includes several previously used terms and was most commonly referred to as mucinous ductal ectasia in the past. These tumors always exhibit at least low-grade dysplasia and should be considered premalignant in all clinical situations.[14] However, the natural history with regard to progression to cancer is not well characterized. Gastric, intestinal, pancreatobiliary, and oncocytic subtypes of the papillary epithelium have been described with clinicopathological significance.[15]

IPMNs principally occur in men, with a mean age of diagnosis in the mid-60s. The lesions are frequently (50%) confined to the head; if symptomatic, a typical presenting complex is recurrent unexplained pancreatitis with ductal dilation or symptoms similar to those of chronic pancreatitis, typically without risk factors.[14] IPMNs may involve the main duct and/or side branches, and mixed variants can occur. Pure main duct IPMNs have a dilated main pancreatic duct without an associated "cystic" component, whereas branch duct IPMNs are composed of cysts that communicate with the main pancreatic duct. Identification of the

communication to the main pancreatic duct can be difficult to determine with imaging techniques, which can make it difficult to differentiate a branch duct IPMN from other cystic lesions such as MCNs or serous cysts. It has been proposed that the side branch type has a better prognosis than the variant that involves the main duct. Surgical resection must consider the extent of intraductal growth to achieve a negative margin to prevent recurrence. In the absence of carcinoma, prognosis is excellent with definitive surgical resection.[16] A patulous papilla at endoscopy extruding mucus is pathognomonic for the main duct variant.

Less Common Neoplastic Cystic Lesions

Cystic pancreatic neuroendocrine tumors are quite rare and may or may not be associated with symptoms of excess hormone production. If clinical or imaging data suggest this as a relevant diagnostic consideration, attempts to confirm the diagnosis by resecting localized disease should be undertaken due to its malignant potential.[17]

Papillary cystic tumors of the pancreas have a characteristic appearance on imaging and should not be confused with the far more common lesions that are the focus of this review. The vast majority of papillary cystic neoplasms are found in female patients (~90%), most often in the third decade of life.[18] Although most of these tumors are benign, approximately 15% may be malignant, leading to the recommendation for surgical resection when they are identified.[19]

Clinical Approach

A detailed history to determine if the patient is experiencing symptoms related to the lesion itself or a related condition such as pancreatitis is important. If previous cross-sectional imaging is available, it should be reviewed to determine if the lesion was present and evaluate for change in size or appearance. Most asymptomatic patients have small lesions that do not cause symptoms because of their small size. Although large cysts may cause vague symptoms of pain, obstructive jaundice is uncommon, even for lesions located in the head. Typical symptoms of malignancy, such as weight loss, epigastric/back pain, nausea, vomiting, and severe malaise, are usually absent. Clinical decision making is driven by an understanding of the differential diagnosis of a cyst and, in the case of the asymptomatic patient, its likelihood of causing harm with testing and/or treatment. The fundamental issue to be addressed is whether the cyst is neoplastic or not. If the cyst is neoplastic, what is the risk of malignant progression? More simply stated, is the upfront risk of surgery justified by the long-term risk of malignancy? If so, does it provide a survival benefit to the patient?

Imaging Studies

High-resolution CT using thin sections with both enhanced and unenhanced technique provides detailed information about the structure of the cyst and may provide a presumptive diagnosis if characteristic features are present. Magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) has the potential added advantage of determining communication between the cyst and pancreatic duct as well as lack of ionizing radiation. The presence of a central scar is a highly diagnostic feature of serous lesions but is seen in only 20% of serous cysts.

Despite the high quality of contemporary CT and MRI, their ability to distinguish neoplastic from non-neoplastic cystic pancreatic lesions remains imperfect. Because of this, EUS has emerged as a useful tool in evaluating these lesions because its resolution is superior to that of CT and MRI. Although some enthusiastic reports were able to differentiate benign from malignant neoplastic tumors and from non-neoplastic cysts with an accuracy of >90% based on the endosonographic appearance of the lesion, other reports emphasize that the technique is not sufficiently accurate to differentiate between benign and malignant lesions unless there is evidence of a solid mass or invasive tumor.[20,21] Further, although EUS is quite sensitive in detection and evaluation of cyst morphology, it is highly operator dependent, as is the performance of all imaging studies.

Overview

This technical review (and the accompanying guideline) was based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[22] In developing this technical review, the authors first formulated a series of specific questions that were to be answered by the guideline (Appendix 1). The authors then identified the outcomes that were significant to answering each question and rated them as critical or important. Next, the group systematically reviewed and summarized the evidence for each outcome across studies, assessed the quality of evidence for each outcome, and finally integrated the evidence across all the outcomes to answer each specific question. The quality of the evidence was classified into 4 categories: high, moderate, low, and very low. Assessment of the quality for each outcome took into account the study design, risk of bias, inconsistency (or heterogeneity), indirectness, imprecision, and potential publication bias. The GRADE methodology requires clinical questions to be framed in terms of a designated population (P) undergoing a specific intervention or diagnostic test (I) with an explicit comparator (C) and a defined outcome (O) (the so-called PICO format). If the question does not explicitly state a comparator, then the comparison with no intervention is implied. Initially, we outlined a total of 7 PICO questions (Table 1). The patient populations with pancreatic cysts were further analyzed for risk of malignancy based on imaging studies, analysis of cyst fluid, and pathological findings. In addition, an analysis of the prevalence of pancreatic cysts in the population was performed, followed by an estimation of the risk of malignant progression of all pancreatic cysts. We used a consensus decision-making process (http://seedsforchange.org.uk/consensus.pdf) to reach unanimous agreement among the 3 authors on all statements.

Table 1. PICO Questions

Question	PICO question				Method
	Population(s)	Intervention(s)	Comparator	Outcome(s)	
Initial imaging evaluation of pancreatic cysts					
1	Adults with findings of a pancreatic cyst on cross-sectional imaging	Additional MRI imaging	No further investigation	Benefits: Detection of early pancreatic cancer or precancerous cyst Harms: Unnecessary surgery/invasive procedures	RCT, observational studies
2	Adults with concerning findings of a pancreatic cyst on MRI	Additional EUS-FNA	No further investigation	Benefits: Detection of early pancreatic cancer or precancerous cyst Harms: Unnecessary surgery/invasive procedures	RCT, observational studies
Surveillance for pancreatic cysts					
3	Adults with low-risk pancreatic cysts on imaging	Annual MRI surveillance	No surveillance	Benefits: Detection of early pancreatic cancer Harms: Unnecessary surgery/invasive procedures	RCT, observational studies
Surgery for pancreatic cysts					
4	Adults with pancreatic cyst with concerning features on MRI and EUS-FNA	Surgical pancreatic resection	Continued annual MRI/CT/EUS surveillance	Benefits: Treatment of early pancreatic cancer and prevention of malignancy developing Harms: Unnecessary surgery, morbidity of pancreatic surgery, mortality associated with pancreatic surgery	RCT, observational studies
Surveillance after surgery					
5	Patients with successful resection of an early pancreatic malignancy	Annual MRI/CT/EUS surveillance	No surveillance	Benefits: Detection of early pancreatic cancer Harms: Unnecessary surgery/invasive procedures	RCT, observational studies
6	Patients with successful resection of a pancreatic cyst with no dysplasia	Annual MRI/CT/EUS surveillance	No surveillance	Benefits: Detection of early pancreatic cancer Harms: Unnecessary surgery/invasive procedures	RCT, observational studies
When to discontinue surveillance					
7	Pancreatic cysts with no change after 5 y of surveillance	Continued annual EUS/MRI/CT surveillance	No surveillance	Benefits: Detection of early pancreatic cancer Harms: Unnecessary surgery/invasive procedures	RCT, observational studies

RCT, randomized controlled trial.

Outcomes of Interest

When using the GRADE process, it is important that the outcomes assessed are patient focused. The most important outcome that would benefit a patient with a pancreatic cyst would be to prevent mortality from cystadenocarcinoma. There are no randomized trials or observational studies comparing screening with no screening in patients with a pancreatic cyst that quantify mortality from adenocarcinoma as an outcome. Numerous studies have described the histological findings of pancreatic cysts in patients who have undergone surgery for resection of a concerning lesion. These studies evaluated a highly selected population in whom surgery has been deemed an appropriate intervention and do not reflect the average patient with a pancreatic cyst. Nevertheless, they give an indication of the histopathology identified in those with "concerning" cystic lesions. These reports often suggest that removal of lesions that contain dysplasia is a successful outcome. Dysplasia is a risk factor for progression to malignancy in other tissues, although the majority of patients do not develop invasive cancer.[23] Surgical intervention would be appropriate if there was little risk to the patient, but this is not the case with pancreatic surgery, which carries a risk of morbidity (approximately 20%–40%) and mortality (<1% in high-volume centers).[24,25] An analogous situation would be Barrett's esophagus, for which current guidelines do not support surgery when dysplasia is found because the risks of surgery outweigh the benefits.[26]

Reports on findings in patients undergoing surgery are further complicated by the inclusion of those with carcinoma in situ as "malignancy." Although these lesions are of undoubted major concern, there is a large body of evidence that this histological lesion does not always progress to invasive adenocarcinoma.[27,28] Indeed, these lesions result in an excess of surgery in other screening programs such as breast cancer, where it is estimated that 70,000 US women each year undergo surgery for a lesion that would not lead to mortality if left alone.[29] This does not mean that surgery is inappropriate for these women because breast surgery still has more benefits than risks, but this may not apply to pancreatic cyst surgery because the morbidity and mortality rates are higher. Other outcomes of interest that may be prevented by surgery are episodes of acute pancreatitis due to mucus plugs and obstructive jaundice by cysts in the head, neck, and uncinate process.

All of these uncertainties mean that there are a limited number of PICO questions with relevant patient outcomes (survival) that can be answered with any directly relevant data. Normally a guideline that uses the GRADE approach would provide a summary of findings table, but this was not possible due to the paucity of data available. This technical review therefore simply outlines the evidence from these surgical series in a narrative manner to provide the risk of invasive malignancy in this select group according to type of cyst. This will indirectly inform the type of pancreatic cyst that is likely to harbor dysplasia or malignancy. We then evaluated the data according to which imaging modality best diagnosed the type of cyst and malignant risk and then conducted systematic reviews of the literature to address risk of malignant progression in pancreatic cysts that would not undergo initial surgery.

Literature Search

The literature search is described in detail in Appendix 1. MEDLINE was searched from 1946 to July 2013, and reports evaluating pancreatic cystic neoplasms were identified by combining the exploded Medical Subject Heading (MeSH) term "pancreatic cyst" with text words that contained "pancrea" (eg, pancreas or pancreatic) and "cyst" that were separated by ≤2 adjectives (eg, such a search would detect "cyst of the pancreas" and "pancreatic cysts"). This was combined with the set operator "OR" and the exploded MeSH term "pancreatic neoplasm," with a similar text word approach as described in the preceding text to identify other pancreatic neoplasms. Case reports, letters, and non–English language reports were excluded.

A second search was performed to identify diagnostic studies. This identified pancreatic cysts as described in the preceding section combined with MeSH terms and text words that described ultrasonography (including EUS), CT, MRI, and endoscopic retrograde pancreatography (ERCP). Furthermore, reports that identified tumor markers and cyst fluid analysis were also identified with exploded MeSH terms and text words (see Appendix 1 for details).

The first search identified more than 2000 reports and the second search more than 1500 reports, with duplicates excluded. These references were imported into EndNote version 7.0.1 (Thomson Reuters, Philadelphia, PA) and manually assessed for relevance by 2 reviewers (P.M. and Cathy Yuan). The same 2 reviewers also extracted data relevant for the guideline.

Results

The literature search showed that reports are largely retrospective case series; there are no randomized controlled trials. A key limitation of the current literature is that management recommendations are based on knowledge of the specific cyst histology, which rarely can be determined using current imaging and cyst sampling techniques. This highlights the challenges of providing evidence-based recommendations regarding the management of patients with pancreatic cysts.

Imaging Features of Pancreatic Cysts Predictive of Risk of Malignancy

To address which patients to offer surgery versus surveillance once a lesion is identified, the literature was reviewed to identify such predictive features. The evidence for risk factors for malignancy in pancreatic cysts, including size of the pancreatic cyst, dilation of the pancreatic duct, and a solid component associated with the cyst, was reviewed. We focused on studies of imaging features in which surgical resection was performed so that an accurate diagnosis of the presence or absence of malignancy could be established. Studies that retrospectively

selected one type of cyst (eg, MCN or IPMN) and evaluated risk factors in that type of cyst were excluded because it is not possible to establish the diagnosis with certainty before surgery. Therefore, only studies that evaluated all pancreatic cysts that were operated on were included in the analysis, which differs from other reviews in this area that have looked at risk factors in IPMNs specifically.[30] Studies with <20 patients were also excluded. We intended to focus on malignant cysts only; however, there were insufficient data in some areas, so we included studies that reported the diagnostic accuracy of imaging studies on both malignant cysts and cysts with high-grade dysplasia (HGD). The review found no evidence that multiple cysts are predictive of risk of malignancy.

Size of cyst >3 cm. We identified 6 studies evaluating 644 patients undergoing surgery that provided information regarding cyst size.[31–36] Overall, 381 of 644 patients (59%) had a cyst >3 cm, and malignancy was found in 163 of the 381 patients (43%) with a cyst >3 cm compared with 57 of the 263 patients (22%) with a cyst <3 cm. The risk of malignancy was significantly increased in patients with a cyst >3 cm (odds ratio [OR], 2.97; 95% confidence interval [CI], 1.82–4.85), with no significant heterogeneity between studies (I^2 = 30%; Cochran Q test = 7.15 [df = 5]; P = .21). The pooled sensitivity and specificity and positive and negative likelihood ratios (LRs) are given in Table 2.

Solid component associated with the cyst. We identified 7 studies evaluating 816 patients undergoing surgery that provided information regarding the presence or absence of a solid component associated with the pancreatic cyst.[31–33,36–39] Overall, 186 of 816 patients (23%) had a solid component, and malignancy was found in 136 of the 186 patients (73%) with a solid component compared with 147 of the 630 patients (23%) without a solid component. The risk of malignancy was significantly increased in those with a solid component (OR, 7.73; 95% CI, 3.38–17.67), with significant heterogeneity between studies (I^2 = 70%; Cochran Q test = 20.1 [df = 6]; P = .003). The pooled sensitivity and specificity and positive and negative LRs are given in Table 2.

Dilated pancreatic duct. We identified 4 studies evaluating 609 patients undergoing surgery that provided information regarding the presence or absence of a dilated pancreatic duct.[33,36–38] Overall, 148 of 609 patients (24%) had a dilated pancreatic duct, and malignancy was found in 69 of the 148 patients (47%) with a dilated pancreatic duct compared with 150 of the 461 patients (33%) without a dilated duct. The risk of malignancy was not significantly increased in those with a dilated duct (OR, 2.38; 95% CI, 0.71–8.00), with significant heterogeneity between studies (I^2 = 84%; Cochran Q test = 18.8 [df = 3]; P = .0003). The pooled sensitivity and specificity and positive and negative LRs are given in Table 2.

Interval Growth in Pancreatic Cysts and Risk of Adenocarcinoma

Analogous to other gastrointestinal premalignant lesions, it would be anticipated that an increase in size of a pancreatic cyst would herald malignant transformation. To address this issue, we evaluated studies that reported on changes in the size of a pancreatic cyst. There were no studies that addressed this issue according to the criteria we set out in the preceding text; therefore, we relaxed the inclusion criteria and allowed any number of patients, but the case series had to include at least one invasive cancer as well as at least one patient with a cyst that had an increase in interval growth and one patient that did not. Using these very broad eligibility criteria, we found 5 eligible studies.[40–44] These studies are summarized in Table 3. Two reports[41,42] are from the same institution but different time periods, so both were included. Another report[45] from the same institution was excluded because it was also from the same institution and the time period overlapped with the other 2 studies. There were a total of 572 patients with pancreatic cysts, and 125 (22%) had an interval growth in cyst size according to the individual definition used in each report. There was some heterogeneity between studies (I^2 = 35%; Cochran Q test = 6.18 [df = 4]; P = .19), but none of the studies individually showed a statistically significant effect of growth rate on risk of cancer and the pooled result was also not statistically significant (OR, 1.65; 95% CI, 0.52–5.23). It must be emphasized that most reports included any increase in cyst size and malignancy may have been better predicted if a strict definition of increase in size (eg, >50% increase in size) had been used. It is also important to exclude other reasons why a malignant cyst may have been identified. For example, one report[43] noted that all of the malignant cysts that were identified by an increase in size also had a solid component.

There were also 7 studies[25,46–51] that reported an increase in cyst size but did not report any malignancy occurring in these cysts or did not associate malignancy with cyst growth (Table 4).

Four additional studies[52–55] reported specifically on serous cystic neoplasms in a total of 500 patients. Follow up was for 10 to 12 years, and a total of 132 patients

Table 2. Summary of Pooled Data Evaluating Pancreatic Cyst Features Predictive of Malignancy

Feature	No. of studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)	LR positive (95% CI)	LR negative (95% CI)
>3 cm	6	644	74% (68%–80%)	49% (44%–54%)	1.47 (1.24–1.75)	0.53 (0.39–0.72)
Dilated pancreatic duct	4	609	32% (25%–38%)	80% (75%–84%)	1.93 (0.78–4.79)	0.85 (0.66–1.10)
Solid component to cyst	7	816	48% (42%–54%)	91% (88%–93%)	4.42 (2.42–8.07)	0.60 (0.39–0.94)

Table 3. Summary of Eligible Studies Included in the Review Reporting on Interval Growth

Reference	Definition of interval growth	Type of cysts reported	Definition of malignancy
Maguchi et al,[40] 2011	Any increase in size of cyst	Branch duct IPMN	Invasive cancer + HGD
Woo et al,[41] 2009	>20% increase in size of cyst	Branch duct IPMN	Invasive cancer + HGD
Ahn et al,[42] 2012	Any increase in size of cyst	Cystic lesions of the pancreas	Invasive cancer + HGD
Nougaret et al,[43] 2014	Any increase in size of cyst	Cystic lesions of the pancreas	Invasive cancer
Wu et al,[44] 2014	Any increase in size of cyst	Cystic lesions of the pancreas	Invasive cancer + HGD

underwent a pancreatic resection during follow-up. An increase in size of the pancreatic cyst was the reason for surgery in 7 patients, but cyst growth was more commonly reported; it was noted in one report that cyst growth was more likely in tumors >4 cm.[54] None of the 132 patients had cystadenocarcinoma.[52–55] Interestingly, one of these studies recommended resection of cysts that doubled in size in <12 years despite not finding any cases of cancer and having one postoperative death.[55]

Rate of adenocarcinoma in surgically resected cysts. A key limitation of the literature is that malignancy is not commonly found among surgical series of resection of pancreatic cysts.[12,56] Although this reflects the goal to prevent cancer, it precludes an assessment of the impact of the intervention given the lack of a comparison group observed over time (ie, surgical resection vs surveillance). This is relevant because removing precancerous lesions in elderly patients may not provide any survival benefit. The benefit of surgery is most evident for pancreatic cysts that are found to harbor invasive malignancy, and we have evaluated this in a review of the literature. Surgical case series that reported on unselected pancreatic cysts where surgery was deemed appropriate and reported both the final diagnosis for type of pancreatic cyst and the presence or absence of invasive malignancy were included. Studies that evaluated only one type of cyst (eg, IPMN) diagnosed after surgery were excluded in this analysis but are discussed later. Studies that combined invasive malignancy with HGD and did not report the results for invasive malignancy only were not included. We did include studies from the same center/group that could have reported on the same patients more than once, provided that this impact was small.

A total of 27 studies were identified that fulfilled our criteria and reported on 2796 patients with surgically resected cysts evaluated for the presence of malignancy.[32–39,57–75] Overall, 418 cysts harbored invasive adenocarcinoma, with proportions in each individual study varying between 0 and 32%. The pooled proportion of cysts with invasive adenocarcinoma was 15% (95% CI, 12%–18%), with marked heterogeneity between studies ($I^2 = 76.5\%$; Cochran Q test = 111 [$df = 26$]; $P < .0001$). There was also funnel plot asymmetry (Begg–Mazumdar test: Kendall τ-b = 0.38, $P = .0045$), suggesting publication bias or other small study effects. However, if only the studies that included more than 100 patients were selected,[32,33,35–38,59–61,63,64,66,68] the pooled proportion with

Table 4. Summary of Papers Reporting on Interval Growth That Were Excluded From the Review Because There Were No Cases of Cancer or There Was No Report That Associated Growth of Lesion With Development of Cancer

Reference	Description of cyst growth	No. of patients	Duration of follow-up
Walsh et al,[46] 2005	19% had an increase in cyst size	98 patients with pancreatic cysts	Mean of 24 mo, no cancers
Irie et al,[47] 2004	24% had an increase in cyst size (defined as >20% in cyst diameter)	35 patients with branch duct IPMN	Mean of 34 mo, one cancer
Allen et al,[25] 2006	10 patients with proven cystadenoma had a median growth rate of 0.5 cm per year; none had malignancy	369 patients with pancreatic cysts	Median of 24 mo (range, 1–172 mo)
Das et al,[48] 2008	11% of cysts showed significant growth; more likely in cysts >3 cm (44% of cysts) compared with those <3 cm (5.6% of cysts had growth)	150 patients with pancreatic cysts	Median of 32 mo, 26 had surgical resection, none had cancer
Lahav et al,[49] 2007	4% had cyst growth	57 with pancreatic cysts	Median not stated, one cancer
Chalian et al,[50] 2011	Serous (n = 8) and mucinous (n = 12) cysts had similar growth rates; median doubling times 1.8 y	20 patients with pancreatic cysts	Repeat CT after 1–2 y
Megibow et al,[51] 2001	10% had cyst growth	21 patients with pancreatic cysts	Mean of 30 mo, one with growth operated on, hard mass found but no histological analysis performed

invasive malignancy was still 15% (95% CI, 11%–18%; $I^2 = 80\%$; Cochran Q test = 61 [$df = 12$]; $P < .0001$), suggesting that small study effects were not a major driver of the overall estimate of the proportion of patients with invasive malignancy.

Risk of malignancy in patients undergoing surgery: data specific for IPMNs. We have shown that the overall risk of malignancy when a patient undergoes surgery for a pancreatic cyst is approximately 15%. However, this does not identify the risk of malignancy for each type of cyst. We have evaluated this in surgical series that reported on the risk of malignancy in retrospective case series by analyzing their data on IPMNs. Studies with ≤20 patients and those that evaluated only main duct IPMN were excluded. Only studies that reported the presence or absence of invasive malignancy were evaluated. The diagnosis of carcinoma in situ or HGD was not considered to be an invasive malignancy in this analysis; however, these studies were evaluated separately.

We identified 111 studies involving 10,812 patients with IPMNs identified at surgery that reported on the presence or absence of invasive malignancy.[35,37–39,60,63,70,76–179] There was significant heterogeneity between studies reporting on the rate of invasive malignancies in IPMNs (Cochran Q test = 626 [$df = 110$]; $P < .0001$; $I^2 = 82\%$; 95% CI, 79%–85%), with an overall invasive malignancy rate of 25% (95% CI, 23%–27%) using a random effects model. There was statistically significant funnel plot asymmetry (Begg–Mazumdar test: Kendall τ-b = 0.26; $P < .0001$), suggesting publication bias or other small study effects. However, any effect of this is likely to be small because graphically the data look reasonably symmetrical.

There were 99 studies assessing 9249 patients that evaluated both the invasive malignancy rate as well as HGD and/or carcinoma in situ rates in IPMNs.[32,35,37–39,58,60–64,70,97–114,116–151,153–185] Again, there was significant heterogeneity between studies reporting on the rate of HGD/carcinoma in situ in IPMNs (Cochran Q test = 846 [$df = 98$]; $P < .0001$, $I^2 = 88\%$; 95% CI, 87%–90%), with an overall high-risk lesion rate of 42% (95% CI, 39%–45%) using a random effects model. Conversely, this means that in these 99 studies of 9249 patients, 58% (95% CI, 55%–61%) had low-risk (eg, low-grade dysplasia) or benign lesions. There was statistically significant funnel plot asymmetry (Begg–Mazumdar test: Kendall τ-b = −0.18; $P = .01$), suggesting publication bias or other small study effects. However, any effect of this is likely to be small because graphically the data look reasonably symmetrical. This latter figure needs to be treated with caution because many studies only reported the high-risk group and we inferred that all others were low risk, but this may not be the case.

Risk of malignancy in patients undergoing surgery in cases in which the investigators reported data specifically for MCNs and serous cystic neoplasms. We evaluated the risk of malignancy in MCNs and serous cystic neoplasms in retrospective surgical series that reported on the presence or absence of invasive malignancy in these lesions. Studies with <20 patients and studies that did not use the term "invasive malignancy" were excluded from the analysis. Cases of carcinoma in situ or HGD were not considered to be invasive malignancies and were evaluated separately.

We identified 12 studies involving 603 patients with MCNs identified at surgery.[33,37,58,60,61,64,130,186–190] There was significant heterogeneity between studies for proportions of invasive malignancy with MCNs (Cochran Q test = 57 [$df = 11$]; $P < .0001$; $I^2 = 81\%$; 95% CI, 66%–88%), with an overall invasive malignancy rate of 15% (95% CI, 9%–22%) using a random effects model. Test for funnel plot asymmetry was statistically significant (Begg–Mazumdar test, $P = .02$).

There were 5 studies assessing 295 patients that evaluated the proportion of invasive malignancy in serous cystic neoplasms.[191–194] There was heterogeneity between studies (Cochran Q test = 8 [$df = 4$]; $P = .08$; $I^2 = 52\%$; 95% CI, 0%–81%), with an overall high-risk lesion rate of 2.2% (95% CI, 0.3%–5.7%) using a random effects model.

Imaging Evaluation

The rationale for invasive testing and serial imaging of patients with pancreatic cysts is that they will develop pancreatic malignancy at a greater rate than the general population. We found no observational data that address this question, so this fundamental assumption remains uncertain. We therefore approached the problem from another perspective and modeled the likely risk of a pancreatic cyst progressing to invasive malignancy and causing death. These data are fundamentally necessary to understand the predictive value of diagnostic testing. For example, for conditions with a low risk of invasive malignancy, Bayesian analysis would indicate that very high levels of diagnostic test accuracy are needed to increase posttest disease probability to a clinically meaningful degree. Therefore, a systematic review to estimate the prevalence of pancreatic cysts in the population and estimate the risk of progression from national cancer statistics on mucinous pancreatic adenocarcinomas was conducted, expanding the approach of Gardner et al.[4] These investigators used the "two most rigorous cross-sectional imaging studies." A more objective approach would be to conduct a systematic review and synthesize all prevalence studies. We have therefore conducted a systematic review to estimate the prevalence of pancreatic cysts in the population.

Overall prevalence of pancreatic cysts in the general population. We identified 7 reports[1,2,195–199] that were eligible for inclusion in the review. The characteristics of the studies are summarized in Table 5. Six studies that evaluated pancreatic cysts using MRI identified 1021 cysts in 8890 subjects.

The reported prevalence of pancreatic cysts varied between 2% and 38%, with an overall prevalence of 15% (95% CI, 7%–24%). Two studies[1,199] evaluated pancreatic cysts using CT and found 465 cysts in 20,275 subjects, for an overall prevalence of 3% (95% CI, 2%–3%).

Two studies showed an increase in prevalence with each age band, with a prevalence of 0.5% in those younger than 40 years of age, 25% in those 70 to 79 years of age, and

Table 5. Summary of Studies Included in the Review to Estimate the Prevalence of Pancreatic Cysts

Reference	Country	Design	Imaging	Population
de Jong et al,[2] 2010	Germany	Retrospective	MRI	Subjects paying for MRI as part of a preventative medical examination
Girometti et al,[195] 2011	Italy	Retrospective	MRI/MRCP	Patients undergoing MRCP to investigate hepatobiliary disease, pancreatic disease not suspected (for this analysis, liver transplant patients were excluded)
Ip et al,[199] 2011	United States	Retrospective	CT/MRI	All patients undergoing CT or MRI for any reason (in 78% of cases, the lesion was not suspected)
Laffan et al,[1] 2008	United States	Retrospective	CT on 16-slice multidetector CT	Patients referred for abdominal CT who had known or suspected pancreatic disease excluded
Lee et al,[198] 2010	United States	Retrospective	MRI on 1.5-T units	Patients referred for abdominal MRI who had known or suspected pancreatic disease excluded
Matsubara et al,[197] 2012	Japan	Retrospective	MRI-RARE and MRCP	Patients referred for abdominal MRI/MRCP who had known or suspected pancreatic disease excluded
Zhang et al,[196] 2002	United States	Retrospective	MRI	All patients undergoing MRI of the abdomen (suspected pancreatic disease NOT excluded)

RARE, rapid acquisition with refocused echoes.

37% in those 80 years or age or older (Table 5).[2,198] These data are consistent with a Japanese autopsy study that found cysts in 19% of those 70 to 79 years of age and in 30% of those 80 to 89 years of age.[200]

Five studies reported cyst size of >2 cm in 25,195 subjects.[2,196–199] Overall, there were 194 subjects with cysts >2 cm, for an overall prevalence of 0.8% (95% CI, 0.5%–1.1%).

Estimating the risk of malignancy of pancreatic cysts. We applied the approach used by Gardner et al[4] with US population data and SEER cancer statistics. Using the prevalence of cysts from our systematic review and the risk of cystadenocarcinoma or any descriptor of a mucinous pancreatic adenocarcinoma mortality from the SEER cancer database, the overall risk that a pancreatic cyst is malignant at the time of diagnosis is a maximum of 0.01%. If we assume that only those cysts >2 cm have malignant potential, then the risk that a cyst >2 cm is malignant is a maximum of 0.21%. This is reasonably consistent over all age bands, because although the risk of cancer progression increases with age, so does the prevalence of pancreatic cysts. The overall risk of malignancy for pancreatic infiltrating ductal carcinoma using the SEER cancer database is 0.017%, and even if we assume that all pancreatic cancer arises from a cyst of any size, the probability that a cyst harbors malignancy at the time of imaging is 0.25%. This extremely low risk of cancer is based on several assumptions that could overestimate or underestimate risk. Risk could be overestimated because we assumed that only cysts visible on imaging would progress to cancer. Although size of the cyst is a risk factor, the effect is only modest, and it is possible for small cysts not detected by imaging to become malignant. Risk could also be overestimated because the prevalence could be higher than estimated from the systematic review. The screening studies recruited subjects who volunteered for screening. Such subjects are usually more affluent and have more healthy lifestyles, and this "healthy volunteer effect" reduces their risk of many serious pathologies, including cancer.[201]

Patients with a pancreatic cyst identified on cross-sectional imaging should undergo further imaging with MRI. Our literature review indicates that accurate initial characterization of the pancreatic cyst as benign or malignant is critical, because the rate of progression of premalignant mucinous lesions is very slow in the absence of features that increase the risk of malignancy. The initial imaging test should be evaluated for its quality and reviewed by a radiologist experienced in the accurate assessment of pancreatic cystic lesions. Additional imaging may be necessary if the initial test, such as CT or MRI, was performed to evaluate an unrelated symptom. Either dedicated pancreatic CT or MRI may be performed based on availability and local expertise, but high-quality MRI with MRCP should be performed if available; it offers improved delineation of IPMNs from other lesions without radiation exposure because it may be able to determine whether there is communication between the cyst and the pancreatic duct.[202] Although there are no prospective studies to confirm this, ERCP is not recommended for evaluation of pancreatic cysts to define ductal communication because this can be determined with MRCP without subjecting the patient to the risk of pancreatitis.

Patients with a pancreatic cyst with concerning features on MRI should undergo further evaluation with EUS and FNA. Although CT and MRI are sensitive for detecting cysts, there is a high rate of misdiagnosis of the etiology of the cyst on cross-sectional imaging even when the operator certainty is high.[203] The need for additional studies, including EUS, on a routine basis is not supported for most cysts based on the results of this systematic review because studies suggest that the risk of invasive malignancy is very low. However, if there are concerning features, the probability of malignancy may increase to an extent that makes further imaging worthwhile. Our analysis suggested that cyst size >3 cm (OR, 2.97; 95% CI, 1.82–4.85) and presence of a solid component (OR, 7.73; 95% CI, 3.38–17.67) increase the probability of a malignant cyst. In addition, a dilated pancreatic duct showed a trend

toward increasing risk (OR, 2.38; 95% CI, 0.71–8.00) that was not statistically significant. The number of studies evaluating this risk factor in undifferentiated cysts was small, and another review that specifically evaluated IPMNs[30] found this to be a risk factor, so we included dilated pancreatic duct as a risk factor for malignancy. If any of these features are identified on cross-sectional imaging, then further investigation with EUS and/or FNA may provide additional information. However, the performance of EUS and/or FNA has not been systematically reviewed in this setting.

Characterization of the cyst fluid. Although EUS morphology alone has limitations regarding definitive diagnosis of pancreatic cysts, aspiration and characterization of the contents of the cyst fluid has shown somewhat greater value in selected patients.[21] EUS-guided aspiration of a cyst is well tolerated and safe in the hands of an experienced operator, with a complication rate of 1% to 2% for bleeding, perforation, or infection.[204] Most experts use periprocedural antibiotics to reduce the risk of infection, limit the number of needle passes, and remove as much fluid as possible to reduce the risk of bacterial inoculation of the fluid.[205] Considerations include the size of the lesion because the volume of aspirate may be very limited for small lesions. The volume of the cyst fluid can be estimated from the size of the cyst by using the formula $(4/3)\pi r^3$, with r representing the radius of the cyst.

EUS can target any solid lesion associated with the cyst as well as apparent mural nodules. Differentiation of such nodules from adherent mucus can be challenging, and the performance of FNA in excluding malignancy in this setting has not been systematically analyzed.[206] Aspirated fluid has been evaluated by cytology and chemical measurements of amylase and tumor markers. Measurement of the carcinoembryonic antigen (CEA) level in cyst fluid is useful in differentiating mucinous from nonmucinous cysts. As previously discussed, mucinous cysts include IPMNs and MCNs, both of which have malignant potential; nonmucinous cysts, such as serous cysts and pseudocysts, have very low or no malignant potential. Unfortunately, the absolute CEA level is not predictive of current or future risk of malignancy. A systematic review of 12 studies with data from 450 patients found cysts with an amylase concentration of <250 U/L were serous or mucinous (not pseudocyst) with a sensitivity of 44% and specificity of 98%. A CEA level <5 ng/mL suggested a pseudocyst or serous lesion with 50% sensitivity and 95% specificity, whereas a CEA level >800 ng/mL suggested a mucinous lesion (sensitivity of 48% and specificity of 98%). A low cancer antigen 19-9 level in the fluid suggested a pseudocyst or serous lesion (sensitivity of 19% and specificity of 98%),[207] but this test is rarely used because it appears to be no better than measurement of CEA level. The largest prospective study concluded that measurement of CEA level was most useful. Using receiver operator curve analysis, the optimal cutoff for CEA level in cyst fluid was determined to be 192 ng/mL. This resulted in a sensitivity of 75% and a specificity of 84% for diagnosing a mucinous cyst. EUS morphology and cytology were also evaluated individually and in combination. Although the combination of EUS morphology, cytology, and CEA level had a higher sensitivity than CEA level alone (91% vs 75%, respectively), the combination had a lower specificity than CEA level alone and had a smaller area under the receiver operator characteristic curve ($P < .0001$). Therefore, the combination of EUS morphology, cytology, and CEA level did not improve the ability to differentiate between a mucinous and nonmucinous cyst.[208]

Cytology. Cytology revealed malignancy in only 48% of mucinous cancers in the systematic review noted in the preceding text. A recent systematic review highlighted the limitation of EUS-FNA–based cytology for differentiating pancreatic cystic lesions, noting major limitations in studies characterized by significant heterogeneity.[209] Combining 11 studies with confirmed histopathology, the pooled sensitivity and specificity for differentiating mucinous from nonmucinous lesions was 0.63 (95% CI, 0.56–0.70) and 0.88 (95% CI, 0.83–0.93), respectively. The positive and negative LRs were 4.46 and 0.46.[209] These performance characteristics mandate the selective use of EUS with FNA to obtain a specimen if the purpose of FNA is to confirm if the cyst is mucinous, with the understanding that negative cytology has a poor negative predictive value. Although performance of cytology in confirming malignancy is reportedly higher, the studies are limited by selection bias in that only resected lesions are reported. However, it remains reasonable to perform FNA on solid lesions associated with a cyst to determine if a malignancy is present.

Molecular testing. Testing for molecular alterations in the fluid from a pancreatic cyst is currently available and reimbursed by Medicare under certain circumstances. Case series have confirmed that malignant cysts have a greater number and quality of molecular alterations, but no study has been properly designed to identify how the test performs in predicting outcome with regard to need for surgery, surveillance, or predicting interventions leading to improved survival.[40,210,211] This adjunct to FNA may provide value in distinct clinical circumstances, such as confirmation of a serous lesion due to a lack of *KRAS* or *GNAS* mutation in a macrocystic serous cystadenoma, but its routine use is not supported at the present time.

EUS-FNA provides additional information for characterizing cystic lesions; however, in the absence of positive cytology (rare) or CEA levels at the extremes of the scale, it rarely provides absolute diagnostic certainty for lesion type or its risk of malignancy. This leads to an approach to monitor lesions for change in size or morphology, assuming the lack of worrisome features at initial imaging.

Postoperative mortality and morbidity for patients undergoing surgery for pancreatic cysts. Although patients with pancreatic cysts may harbor malignancy, the only approach to ensure the cyst is not malignant is to resect that portion of the pancreas. However, surgery to resect a pancreatic cyst has associated risks of morbidity and mortality, and it is important to balance potential benefits with potential harms. There has been no systematic review of the harms of pancreatic surgery related to resection of cysts. Given the limited data, we were unable to conduct a systematic review of this topic;

however, a comprehensive search of the literature and data extraction for this technical review was performed.

We identified 77 studies evaluating 5790 patients that reported data on morbidity and/or mortality related to surgery performed for resection of pancreatic cysts.[9,16,32,55,61,63,65,70,78,80,82,83,85,92,93,96,98,106,112,114,116,120,131–134,139,141–143,146,147,153,160,167,170,171,174,175,187,191,192,194,212–245] The characteristics of the studies are shown in Supplementary Table 1.

There were 74 studies that reported data on mortality involving 5484 patients.[9,32,55,61,63,65,70,80,82,83,85,92,93,96,98,106,112,114,116,120,131–134,139,141–143,146,147,153,160,167,170,171,174,175,187,191,192,194,212–225,227–245] There was significant heterogeneity between studies in regard to mortality rates (Cochran Q test = 155 [$df = 73$]; $P < .0001$; $I^2 = 53\%$; 95% CI, 37%–64%) with an overall mortality rate of 2.1% (95% CI, 1.5%–2.7%) using a random effects model. There was statistically significant funnel plot asymmetry (Begg–Mazumdar test: Kendall τ-b = 0.49; $P < .0001$), suggesting publication bias or other small study effects. This suggests that the overall mortality is probably underestimated because the overall result is driven by small studies with no mortality. Furthermore, the majority of studies are reported from centers of excellence with high volumes of pancreatic surgery, where outcomes are likely to be better. The national mortality rate in the United States is therefore likely to be >2.3%. Indeed, it is important to note that the SEER database, which contributed 729 US patients to this review, reported an overall mortality of 6.6%, which was no different from that for pancreatic surgery for standard adenocarcinoma of the pancreas.[216]

A total of 49 studies involving 3392 patients reported data on morbidity after surgery for pancreatic cysts.[32,55,61,70,80,91,92,93,120,132,133,139,142,143,153,167,170,171,174,187,191,192,194,213,215,217,218,219,220,222,223,225,226,232,233,235,236,238,240,242,243] Where possible, we restricted data to that related to major events, such as formation of a pancreatic fistula. If the investigators only reported events, we assumed that these did not happen in the same patient when the events were rare (<25%) but did not make this assumption when they were common. There was significant heterogeneity between studies in regard to morbidity rates (Cochran Q test = 403 [$df = 48$]; $P < .0001$; $I^2 = 88\%$; 95% CI, 85%–90%), with an overall morbidity rate of 30% (95% CI, 25%–35%) using a random effects model. However, there was no statistically significant funnel plot asymmetry (Begg–Mazumdar test: Kendall τ-b = 0.08; $P = .41$), suggesting there was no publication bias or other small study effects. There is substantial variation between study results, and the reasons for this are not clear. Some will relate to different thresholds for the investigators describing an event as a complication or a major complication.

Patients with pancreatic cysts who are surgical candidates but do not have features that would warrant resection should undergo surveillance with MRI every 1 to 2 years. No cohort studies have analyzed the impact of surveillance and subsequent surgical intervention on the risk of pancreatic cancer among patients with cystic lesions. Given the very low rate of overall malignancy development, it is clear that surveillance imaging in patients should be limited to those who can benefit from major pancreatic resections should the lesion develop cancer. Given the mortality and morbidity of pancreatic resections, this careful determination should be assessed for each patient. Patients who are not surgical candidates because of age or severe comorbidities should not undergo surveillance. However, if the patient is reasonably fit, our review suggests that surveillance once per year or once every 2 years may be prudent, although the evidence base for this is limited.

The imaging modality and frequency of surveillance imaging has also not been subjected to informative studies in the literature. Current guidelines suggest annual (or more frequent) surveillance, particularly for lesions near a size cutoff associated with malignancy (3 cm).[6] These recommendations are not evidence based and should be individualized for each patient. Although the literature contains reports of small lesions harboring malignancy, the vast number of these lesions mandates a rational approach to patient care. Because cancer is rarely found in patients with resected lesions, these size recommendations are likely to be modified upward, particularly as patients age and the mortality benefit of surgery remains undefined.

Although more costly than CT and EUS, MRI in expert hands offers lack of radiation and is an ideal surveillance modality. EUS can be used in those with claustrophobia who require anesthesia for MRI because they are generally equivalent (and can be complementary) and similarly invasive under these circumstances.

Incidence of invasive malignancy in follow-up of pancreatic cysts. International consensus guidelines on the management of pancreatic cysts have suggested follow-up of cysts that do not have concerning features.[6,127,246] The frequency of follow-up depends on the size of the cyst. Guidelines generally do not address whether surveillance can be discontinued at any stage. This has important implications because it could reduce the cost of surveillance of pancreatic cysts if this is not a lifelong commitment. However, it is important to evaluate the risk of malignant progression for pancreatic cysts in determining the interval and duration of surveillance. We have suggested that the risk of developing malignancy is low based on population data, with a lifetime risk of <1% provided the cyst has no concerning features at presentation. The overall risk of malignancy in cysts identified on imaging but not resected remains unclear. We conducted a systematic review of the literature to answer this question.

The search strategy identified 102 potentially relevant reports, of which 62 were eligible for this systematic review.[24,40–42,44,45,47–49,51,53,57,68,73,195,247–293] Overall, there were 154 invasive malignancies in 10,496 patients with a median of 34,460 patient-years of follow-up. Studies were from Japan, Italy, the United States, Korea, France, the United Kingdom, and Israel, and all were retrospective case series. The characteristics of the patients are summarized in Supplementary Table 2.

Follow-up of general pancreatic cystic lesions seen on imaging. There were 22 case series

predominantly from the United States and Japan.[24,42,44,48,49,51,57,68,73,195,247–258] that evaluated pancreatic cystic lesions that were of mixed origin but mainly or exclusively mucinous on imaging studies. Overall, 42 invasive cancers were observed in 6240 patients during 18,079 patient-years of follow-up. There was only marginally significant heterogeneity ($I^2 = 29.5\%$; Cochran $Q = 30$ [$df = 21$]; $P = .1$). There was no funnel plot asymmetry (Egger bias = 0.23; 95% CI, −0.29 to 0.74; $P = .38$), suggesting there is no evidence that there is publication bias or other small study effects. The proportion of cases developing invasive malignancy is estimated at 0.24% per year (95% CI, 0.12%–0.36%).

Follow-up of suspected IPMNs on imaging. There were 37 case series predominantly from Japan and Italy that evaluated suspected IPMNs on imaging studies.[259–291] Overall, 112 invasive cancers were observed in 3980 patients during 14,830 patient-years of follow-up. The proportion of patients developing invasive neoplasia was 2.8% (95% CI, 1.8%–4.0%), with statistically significant heterogeneity ($I^2 = 74\%$; Cochran Q test = 136 [$df = 36$]; $P < .0001$). There was also funnel plot asymmetry (Egger bias = 1.33; 95% CI, 0.70–1.96; $P = .0001$), with smaller studies showing a greater proportion with invasive cancer, suggesting publication bias or other small study effects. The proportion of cases developing invasive malignancy is estimated at 0.72% per year (95% CI, 0.48–1.08). This is higher than predicted from the population-based data, but our analysis included all pancreatic cysts, not just suspected IPMNs, and this may explain the higher risk seen in this review of the literature.

Follow-up of suspected serous cystic neoplasms seen on imaging. There were 3 case series from Italy and Canada that evaluated pancreatic cystic lesions that were believed to be serous cystic lesions on imaging.[237–239] Overall, no invasive cancers were observed in 276 patients during 1551 patient-years of follow-up.

This systematic review suggests that the overall rate of conversion to invasive cancer is low and for pancreatic cysts in general is approximately 0.24% per year. The rate of conversion is highest for IPMN but this may be an overestimate as the outliers with the highest conversion rates[61,120,132,216] were somewhat unclear on whether initial cancer cases had been excluded from the cohort or were retrospective and designed to show risk factors of neoplastic progression where we suspect that the case series were enriched with cancer cases to ensure their analyses had sufficient power.

The limitations of this systematic review are related to the quality of the underlying studies. All were retrospective case series, and some presented information whereby it was unclear which patients had invasive malignancy. Whenever this was unclear, worst case scenario assumptions were made. The follow-up of patients was often poorly described, and often the median follow-up time was given; for calculation purposes, we assumed that this was similar to the mean.

Patients with pancreatic cysts undergoing surveillance with no or minimal change in the characteristics of the cyst over a 5-year period should have surveillance discontinued. When to discontinue surveillance is not defined by the current literature, which indicates a very slow progression to malignancy in a population with mortality defined by age and other comorbidities. It seems reasonable to perform imaging in selected patients for up to 4 years and discontinue surveillance if there is no change in size, but this area of uncertainty would benefit from additional study.

Our data suggest that the rate of progression to invasive cancer is very low, and this is consistent with our earlier analysis evaluating the risk of cysts progressing to invasive cancer from the systematic review of the prevalence of pancreatic cysts and US population statistics on cystic adenocarcinoma. Furthermore, the vast majority of surgical resections in these case series were performed within the first 2 years of surveillance. Therefore, it may be reasonable to propose extending the surveillance period to 4 years. If there has been no significant change in the characteristics of the cyst over that period, then the probability the patient will have invasive cancer is very low and it is therefore reasonable to discontinue surveillance. We realize that this approach may be controversial; however, based on the analysis of this review showing the low rate of progression of pancreatic cysts to malignancy, we believe that this view is evidence based, although the evidence is weak. Of course, such decisions also need to be made on an individual basis; there are circumstances in which further surveillance beyond 4 years may be warranted, particularly for presumed mucinous lesions in fit patients younger than 70 years of age and in patients who may have an equivocal change in cyst appearance and/or size.

Patients with pancreatic cysts that have concerning features should be offered surgical resection. The selection of patients with pancreatic cysts for surgical resection continues to be a source of controversy in the absence of confirmed malignancy. This technical review has identified major gaps in the literature to define evidence-based decision making in the management of pancreatic cysts. Given the lack of data to support a survival benefit for cyst resection, the approach to proceed with a major pancreatic resection whenever a mucinous lesion is found requires reevaluation. The ability of imaging to accurately define malignancy is poor, and indicating surgery based on size alone or a presumed nodule on imaging will subject many low-risk patients to surgery, along with a significant risk of immediate postoperative morbidity and mortality and uncertain long-term benefits.

The surgical dogma that all MCNs should be resected is not supported by our literature review. Unfortunately, we cannot make definitive recommendations on when surgery should be offered to patients with pancreatic cysts. It would be reasonable to offer surgical resection if there are

concerning features that prompted the decision to evaluate the patient with EUS-FNA and the results showed malignant cells on cytology and worrisome imaging features. It is also reasonable to offer surgery if there are more than one of 3 features (size >3 cm, dilated pancreatic duct, or solid component to the cyst) that suggest concern regarding malignancy. Thus, a cyst >3 cm alone should usually not warrant surgical resection; however, a large cyst combined with a dilated pancreatic duct may indicate that there is enough increased risk to justify surgery. We should emphasize that there is little evidence that combined risk factors are additive or synergistic, but we support this simply based on expert opinion.[5,6]

Another issue that should be considered with regard to offering resection is the age and health of the patient. Age is a particular issue that argues both for and against offering resection. Young patients are usually healthier and are likely to live for many years, so any risk of cancer over time is likely to increase. On the other hand, on a population level, their pretest probability of having malignancy is much lower, so this makes the positive predictive value of any of the previously described tests even lower. Although the anxiety and cost of long-term monitoring may sway patients and providers to a surgical intervention, careful consideration of the risks and benefits outlined in this review should be undertaken.

Surgery for symptomatic patients is another category where the evidence remains unclear. Offering surgery to symptomatic patients may seem reasonable, but again the evidence base for this is weak. Many case series have shown that symptoms improve after resection, but undergoing surgery is likely to have a strong placebo response and follow-up of these cohorts over long periods is limited. Given that resection carries a significant risk of morbidity and mortality, the literature review does not support surgical resection on the basis of symptoms alone; instead, symptoms should be taken into consideration with other concerning features of the cyst that may tip the balance of benefits versus harm in favor of offering resection. Such decision making should be performed by a multidisciplinary team of physicians.

Survival after resection of an invasive/malignant pancreatic cyst. We have reviewed the potential harms of resection of pancreatic cysts as well as their malignant potential. It is also important to establish the benefits of removing a pancreatic cyst. There is the potential benefit of preventing a cyst from becoming malignant. The risk of this is likely to be very low in benign lesions, but there is likely to be some benefit for lesions with HGD. Unfortunately, quantifying this benefit is difficult because there are no data on the natural history of cysts with HGD. This is therefore very difficult to determine.

Another benefit is that early removal of an invasive malignant cyst before spread of the lesion may lead to long-term survival of the patient. The literature was reviewed to address this question. Studies with <20 patients and that combined invasive cancer and HGD were excluded. Reports that did not provide 5-year survival data for patients with invasive cancer (either overall or disease-free) were also excluded. We identified 37 studies evaluating 3842 patients.[16,80,82,84,91,93,103,105,106,108,110,113,120,122,132,133,135,137,144,159,166,168,174,215,218,220,230,294–303] All of these studies found that survival in those

Table 6. Summary of Studies Evaluating 5-Year Survival of Malignant Pancreatic Cysts

Reference	Type of cyst	No. of patients with invasive malignancy	5-year survival (%)
Kang et al,[103] 2013	IPMN	59	62.7
Wong et al,[159] 2013	Branch duct IPMN	39	25.0
Caponi et al,[294] 2013	IPMN	64	30.0
Ohtsuka et al,[105] 2012	IPMN	36	31.0
Worni et al,[295] 2012	IPMN	972	24.1
De Moor et al,[106] 2012	IPMN	21	25.8
Kim et al,[91] 2011	IPMN	52	20
Waters et al,[296] 2011	IPMN	113	31.0
Mino-Kenudson et al,[297] 2011	IPMN	61	47.0
Jang et al,[108] 2011	IPMN	41	61.9
Yamaguchi et al,[110] 2011	IPMN	122	37.0
Yopp et al,[215] 2011	IPMN	59	68.0
Shin et al,[113] 2010	IPMN	41	58.3
Lubezky et al,[80] 2010	IPMN	23	41.0
Turrini et al,[93] 2010	IPMN	98	30.0
Sadakari et al,[298] 2010	IPMN	30	32.4
Partelli et al,[218] 2010	IPMN	104	54.5
Poultsides et al,[299] 2010	IPMN	132	42.0
Swartz et al,[300] 2010	IPMN	70	45.3
Crippa et al,[166] 2010	IPMN	62	64
Schnelldorfer et al,[120] 2008	IPMN	63	31.0
Nara et al,[168] 2008	IPMN	25	38
Nagai et al,[220] 2008	IPMN	30	57.6
Nakagohri et al,[122] 2007	IPMN	31	24.0
Riall et al,[301] 2007	IPMN	992	3.0
Winter et al,[302] 2006	IPMN	90	48.0
Wada et al,[84] 2005	IPMN	25	46.0
Jang et al,[303] 2005	IPMN	51	36.9
Sohn et al,[132] 2004	IPMN	52	43.0
Salvia et al,[174] 2004	IPMN	58	60.0
D'Angelica et al,[133] 2004	IPMN	30	58.0
Kitagawa et al,[135] 2003	IPMN	28	44.0
Chari et al,[137] 2002	IPMN	40	36.0
Maire et al,[230] 2002	IPMN	51	36.0
Yamao et al,[144] 2000	IPMN	32	44.0
Tobi et al,[82] 2001	IPMN	25	62.5
Wilentz et al,[16] 1999	MCN	20	33.0

without malignancy was 80% to 100% at 5 years. It was not possible to pool the data accurately because very few studies provided the detailed information required to perform a pooled analysis. Five-year survival ranged from 3% to 68% (Table 6), and most studies reported on invasive IPMNs.[80,82,84,91,93,103,105,106,108,110,113,120,122,132,133,135,137,144,165,166,168,173,174,215,218,220,230,294–297,299–301,303] Using a simple average, the overall 5-year survival is 28%. This figure is similar to the most recent SEER data on survival after surgery for a malignant cyst.[295] This is better than survival for standard pancreatic adenocarcinomas but is still disappointing. There was, however, one clear outlying low value reported from early SEER data that evaluated IPMNs treated with surgery from 1983 to 1991.[301] If this study were excluded on the basis that imaging techniques were not as sophisticated for that period, then the 5-year survival rate increases to 36.5%. This is still disappointing but at least more optimistic for the patient. However, there is a major concern that any apparent benefit of survival may simply reflect lead and/or length time bias. Indeed, the few studies that did report survival longer than 5 years would strongly suggest that lead time bias was a factor because mortality for IPMNs approached that of standard pancreatic adenocarcinomas with longer follow-up. There is only one study that reported on 20 invasive MCNs.[16] The overall survival in this small group was 33%, which does not appear better than results for IPMNs.

Patients should undergo annual surveillance with MRI after surgical resection if the resected cyst shows evidence of dysplasia or malignancy. No studies have tested the value of surveillance after pancreatic resection for a precancerous lesion. Case series have supported the concept of a field defect in such patients with IPMNs who may develop tumors due to continued exposure to risk factors (such as alcohol or smoking) as well as a genetic background promoting tumor development. No studies define the outcome of such an approach or define the optimal imaging modality and its frequency. It seems reasonable to follow the principles of surveillance noted in the preceding text. However, given that such patients likely have a much higher long-term risk of malignancy, discontinuation of surveillance cannot be recommended and should commence when the patient is no longer a candidate for surgical resection. If nonsurgical treatment of such lesions becomes a viable alternative providing curative potential, these considerations will change.

Patients should not be offered surveillance after surgical resection if the resected cyst shows no evidence of dysplasia. Again, there is no evidence for this group of patients. However, if the resection shows a simple mucinous or serous cyst with no evidence of dysplasia, then there is unlikely to be a field change and the overall risk of malignancy in this group of patients is likely to be very low. Given that the risk of cystic lesions progressing is low and the patient is currently free of any concerning lesion, it is not appropriate to offer continued surveillance. This would only add cost to the health care system and anxiety for the patient with little likelihood of any long-term benefit.

Table 7. Variations in the Positive and Negative Predictive Values of a Test as the Prevalence of a Disease Becomes Rarer for a Test That Is 90% Sensitive and Specific

Prevalence (%)	Positive predictive value (%)	Negative predictive value (%)
50	90	90
30	79.4	95.5
20	69.2	97.3
10	50	98.8
5	32.1	99.4
1	8.3	99.9
0.5	4.3	99.9
0.1	0.9	99.99

Bringing Together the Findings From the Technical Review

This review of the literature suggests that pancreatic cysts are common in the general population and the proportion of cysts found to have invasive malignancy at surgery is relatively modest. Malignant transformation is rare in pancreatic cysts that are followed up. The pooled estimates from this review of the literature are subject to some uncertainty, so it is important to evaluate whether the figures outlined in this review are consistent with what would be predicted from the accuracy of diagnostic tests applied to a disorder that is common in the population (pancreatic cysts) with an serious outcome that is rare (pancreatic adenocarcinoma).

A well-known characteristic of the performance of a test is that the positive predictive value decreases and the negative predictive value increases as the disease becomes rarer, despite the sensitivity and specificity of the test being constant[304] (Table 7). This review suggests that pancreatic malignancy is rare in a cyst, so it is predicted that the negative predictive value of any strategy that is applied will

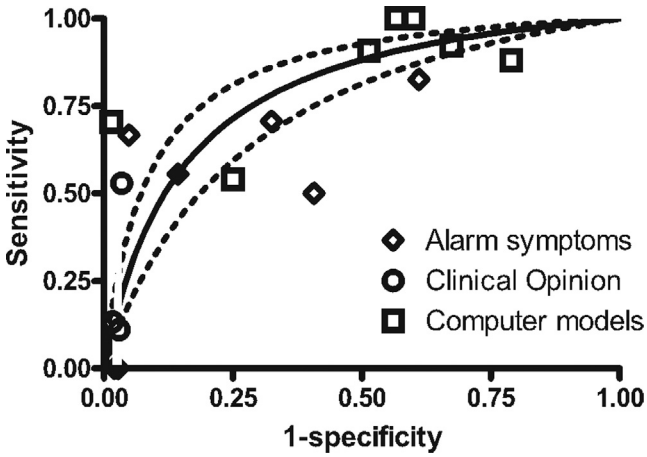

Figure 1. Receiver operator curve for the diagnosis of upper gastrointestinal malignancy using alarm symptoms, clinical opinion, or computer models applied to symptom questionnaires.[305]

be high but the positive predictive value (ie, the probability that the cyst is malignant) will be low. Another area of uncertainty is the actual performance of an overall strategy of following up a pancreatic cyst and the multifactorial decision-making process to decide to operate. Faced with a disorder that is common, a serious outcome that is rare, and a test that is not particularly accurate, clinicians opt for a strategy that is highly specific and not very sensitive to maximize their chances of ruling a disease in. For example, a systematic review of clinicians trying to diagnose upper gastrointestinal malignancy based on clinical features have a specificity of 97% but a sensitivity of only 29%.[305] In contrast, computer models that attempt to predict malignancy have a high sensitivity, so that few cancers are missed, but a low specificity (Figure 1).[305]

Clinicians have a specificity of 97% and sensitivity of 29% when deciding to refer a patient for an endoscopy to rule out upper gastrointestinal malignancy. When deciding to perform a pancreatic resection, we would expect even more caution and an even higher specificity at the expense of sensitivity. We have modeled this based on a prevalence of invasive malignancy of 0.25%, which was the highest estimate from the systematic review of the population with cysts and extrapolation from the SEER database. We applied 99.75% specificity and 17.5% sensitivity to a prevalence of 0.25%, resulting in a 15% probability that a cyst will harbor invasive malignancy. Our technical review identified 27 studies evaluating 2796 patients undergoing surgical resection of pancreatic cysts and found that 15% had invasive malignancy. Conversely, if a decision is made to simply follow up the cyst with the same test characteristics described in the preceding text, then we can predict that 0.21% of malignant cysts will be missed. This is similar to our technical review, which identified 22 case series that evaluated 6240 patients for a median follow-up of 18,079 years and estimated that 0.24% developed malignancy.

This modeling adds face validity to our estimates. It is possible that the risk of malignancy in a cyst varies modestly from our predictions but is unlikely to be dramatically different, because it would then not be possible to model the test accuracy to the findings of the literature review.

Discussion

In this technical review, we attempted to evaluate the evidence for diagnosing and managing pancreatic cysts. Unfortunately, there is insufficient evidence to make definitive recommendations based on defined measures of risk and patient outcomes (survival benefit).

The approach to the patient with a pancreatic cystic lesion begins with a detailed history and consideration of the differential diagnosis to assess the risk of malignancy. A history that suggests prior pancreatitis or trauma is important because this would increase the likelihood that the lesion is a pseudocyst without malignant potential. In the absence of a history of pancreatitis or trauma, a pseudocyst is unlikely and the concern of a cystic neoplasm is paramount. In general, patients with symptomatic lesions should be evaluated by a multidisciplinary team of physicians to determine if surgical resection is indicated based on symptoms and other findings, weighing the likelihood of malignancy against the risk of surgery. If preoperative characterization of the lesion will change management, EUS and/or FNA for cytological analysis and fluid analysis may provide information of diagnostic and prognostic value. Risk stratification should occur during the initial evaluation, because our analysis suggests that progression is rare.

For patients who have benign-appearing lesions with low-risk features on imaging, a decision regarding the patient's willingness to undergo observation of the lesion should be developed in collaboration with a pancreatic surgeon. In many circumstances, surveillance with noninvasive imaging, typically MRI, and selected use of EUS with or without FNA with cytological analysis and measurement of fluid will allow watchful waiting of a presumed mucinous lesion, including both MCNs and branch duct IPMNs. This approach clearly represents a trade-off of delayed surgery and a low risk of progression to malignancy with the risk of morbidity and mortality associated with surgery; however, given the high prevalence of patients with pancreatic cysts and the low rate of malignant transformation over time, this appears to be the most prudent approach to provide patients with the best overall survival. Given the lack of clear, convincing data, management of patients with pancreatic cysts should be individualized, incorporating the data and recommendations presented in this review along with the clinical judgment of an experienced multidisciplinary team.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.01.014.

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Conflicts of interest
All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report. The authors disclose no conflicts.

Appendix 1. AGA Guideline: Pancreatic Cysts

Note there are an initial set of evidence reviews and questions that are not PICO based to establish high-risk pancreatic cyst definitions and also evidence for benefit of detecting pancreatic cancer early.

Search to identify risk of malignancy

No.	Searches	Results
1	exp Pancreatic Cyst/ use mesz	5937
2	exp pancreas cyst/ use emez	8179
3	(pancrea* adj2 cyst*).ti,ab.	6912
4	or/1-3	17,699
5	exp Pancreatic Neoplasms/ use mesz	56,348
6	exp pancreas tumor/ use emez	83,597
7	(pancrea* adj2 (neoplas* or malignan* or cancer* or tumo?r*)).ti,ab.	74,964
8	or/5-7	152,666
9	4 and 8	5809
10	limit 9 to english language	4317
11	limit 10 to (case reports or comment or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,Embase; records were retained]	721
12	Case Report/ use emez	1,929,266
13	10 not (11 or 12)	2976
14	remove duplicates from 13	2112

Search to identify diagnostic accuracy

Searches	Results	Search type
1	exp Pancreatic Cyst/ use mesz	5937
2	exp pancreas cyst/ use emez	0
3	(pancrea* adj2 cyst*).ti,ab.	2801
4	or/1-3	7444
5	exp Ultrasonography/	243,348
6	(ultrasound* or ultrasonic or ultrasonogra* or sonogra* or echotomogra* or endosonogra* or (echo adj2 endoscop*) or echo-endoscop*).ti,ab.	248,057
7	exp Tomography, X-Ray Computed/	294,155
8	((ct or cat or computed or computer assisted or electron beam) adj (tomograph* or scan* or xray or x-ray)).ti,ab.	186,365
9	((nmr adj tomograph*) or mr imaging or MRI or magnetic resonance imaging).ti,ab.	221,516
10	exp Biopsy, Fine-Needle/	8657
11	(fine needle biops* or fna).ti,ab.	7300
12	exp Cholangiopancreatography, Endoscopic Retrograde/	12,643
13	(endoscopic adj retrograde adj cholangiopancreatograph*).ti,ab.	5094
14	ercp.ti,ab.	6356
15	Antigens, Neoplasm/	39,532
16	exp Tumor Markers, Biological/	179,660
17	(CEA or CA 19-9 or ca-19-9 or CA 72-4 or ca-72-4 or CA-125 or ca 125 or (antigen* adj carcinoembryonic)).mp. or cd66e.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	23,205
18	exp Cyst Fluid/	374
19	((imaging or surveillance) adj5 (pancrea* adj2 cyst*)).ti,ab.	78
20	exp Pancreatic Cyst/su [Surgery]	2172
21	((surgery or surgical or surgeries or operat*) adj5 (pancrea* adj2 cyst*)).ti,ab.	163
22	exp ras Proteins/ or exp Mutation/	644,693
23	(k-ras or kras).ti,ab.	9051
24	or/5-23	1,718,526
25	4 and 24	4828
26	limit 25 to english language	3305
27	limit 26 to (case reports or comment or editorial or letter)	1511
28	26 not 27	

Supplementary Table 1. Characteristics of the Included Studies for Evaluating Morbidity and Mortality Related to Surgical Resection of Pancreatic Cysts

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
El-Hayek et al,[55] 2013	United States	Serous cystadenoma	Cyst enucleation, 2 DP with or without splenectomy, 16 PD, 6 Central pancreatectomy, 1	2 major complications Pancreatic fistula, 1 Aspiration pneumonia, 1 1 minor complication Wound infection	25
He et al,[212] 2013	United States	IPMN	PD, 91 DP with splenectomy, 39	NA	130
Winner et al,[78] 2013	United States	IPMN	PD, 68 DP, 54 14 were completed laparoscopically, 5 were converted to open operations Central pancreatectomy, 25 Enucleation for benign disease, 2	NA	183
Hwang et al,[191] 2012	Korea	Serous cystadenoma	Open pancreatectomy, 27 Laparoscopic DP, 11	Total of 8 patients: Pancreatic fistula, 5 Delayed gastric emptying, 1 Pneumonia with acute myocardial infarction, 1 Wound failure, 1	38
De Moor et al,[106] 2012	Belgium	IPMN	PD, 12 PPPD, 30 DP, 7 Central pancreatectomy, 5 TP, 1	Total of 24 patients: Bleeding, 3 Pancreatic fistula, 5 Biliary fistula, 3 Collections, 6 Pulmonary complications, 3 Wound infection, 1 Morphine intoxication, 1 Sepsis, 1 Gastrojejunal anastomotic ulceration, 1	55
Okabayashi et al,[160] 2013	Japan	IPMN	TP, 6 PD, 58 DP, 34 Minimally invasive surgery, 10	NA	100

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
de Castro et al,[32] 2011	The Netherlands	SCN, 32 MCN, 30 IPMN, 26	DP, 39 PPPD, 41 Resection of uncinate process, 1 PD, 7 TP, 6 Central pancreatectomy, 6	Total of 39 patients: Surgical, 27 Pancreaticojejunostomy leakage, 4 Hepaticojejunostomy leakage, 2 Bleeding, 4 Abscess, 6 Wound infection, 2 Delayed gastric emptying, 6 Other, 9 Systemic, 15 Pulmonary, 9 Renal, 6	88
Lahat et al,[61] 2011	Israel	Mucinous tumor, 46 IPMN, 45 Serous cystic tumor, 11 Cystic islet cell tumor, 4 Pseudopapillary tumor, 10	PD, 46 DP, 64 TP, 6	Total of 26 patients: Septic complications, 17 (of whom 5 had an intra-abdominal abscess) Pancreatic fistula, 7 Reoperated due to bleeding, 2	116
Fujii et al,[213] 2011	Japan	IPMN, 84 Serous cyst neoplasm, 8 (out of 132 surgical patients)	Pancreatic head resection with segmental duodenectomy, 77 PPPD, 55	55 for all patients Pancreatic fistula, 45 Delayed gastric emptying, 29	132
Ferrone et al,[214] 2011	United States	MCN, 35 IPMN, 22 Serous cystadenoma, 23 Simple cyst, 5	DP with preservation of the spleen	NA	85
Turrini et al,[92] 2011	United States and France	IPMN	Enucleation, 7 PD, 100 (with 17 of these radiographically amenable to enucleation)	Total of 39 patients: Pancreatic fistula, 28 Bleeding, 2 Cardiovascular/pulmonary, 8 Gastric emptying, 6 Biliary leak, 3 Wound infection, 4 Fascial dehiscence, 2 Other, 6	107
Yopp et al,[215] 2011	United States	IPMN with an associated invasive carcinoma	PD 32 PPPD 10 DP with or without splenectomy, 11 Total or subtotal pancreatectomy, 6	Major complications, 5 (no detailed information provided)	59

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Cone et al,[112] 2011	United States	IPMN	PD, 37 DP, 14 TP, 8 Bypass, 1	NA	60
Hwang et al,[98] 2011	Korea	IPMN	PD 32 PPPD 76 TP, 5 DP, 65 Spleen-preserving DP, 20 Subtotal pancreatectomy, 5 Hepatopancreatoduodenectomy, 1 Median pancreatectomy, 12 Duodenum-preserving resection of the head of the pancreas, 4 Pancreatic head resection with segmental duodenectomy, 3 Excision, 14	NA	237
Turrini et al,[93] 2010	United States	Invasive IPMN	PD, 62 DP, 19 TP, 17	Total of 43 patients (no detailed information provided)	98
Lubezky et al,[80] 2010	Israel	IPMN	PD, 32 Subtotal DP, 16 TP, 13 Palliative bypass, 1	Total of 31 patients: Major bleeding requiring reoperation, 1 Pancreatic fistula, 6 Delayed gastric emptying, 6 Intra-abdominal collection, 6 Pseudomembranous colitis, 4 Pulmonary embolus, 5 Wound dehiscence or infection, 4 Pneumonia, 3	62
Fan et al,[114] 2010	China	IPMN	PD, 23 DP, 14 TP, 3	Total of 13 patients (no detailed information provided)	40
Wasif et al,[216] 2010	United States	Invasive IPMN	PD, 541 DP, 109 TP, 79	NA	729
Cheon et al,[116] 2010	Korea	IPMN	TP, 1 Extended PD, 4 PD, 19 Medial pancreatectomy, 2 DP, 14	NA	40

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Coelho et al,[217] 2010	Brazil	Serous cystic tumor, 10 Mucinous cystic tumor, 10 IPMN, 4 Solid pseudopapillary tumor or Frantz tumor, 3	Only laparotomy with tumor biopsy, 2 Cholecystectomy with Roux-en-Y hepaticojejunostomy for treatment of jaundice, 1 PD, 6 Partial pancreatectomy, 18	Total of 7 patients: Pancreatic fistula, 5 Wound infection, 3 Incisional hernia, 3 Pneumonia, 1 Gastroenteroanastomosis stricture, 1 Diabetes mellitus, 1 Necrotizing acute pancreatitis, 1	27
Partelli et al,[218] 2010	Italy	Invasive intraductal papillary carcinoma	PD, 69 DP, 14 TP, 19 Middle pancreatectomy, 2	Total of 46 patients (no detailed information provided)	104
Correa-Gallego et al,[63] 2010	United States	Cystic neoplasms in 136 early surgical patients: IPMN, 61 MCN, 25 Serous cystadenoma, 22 Solid pseudopapillary neoplasm, 9 Cystic pancreatic endocrine neoplasm, 8 Unclear, 6 Other, 5	For early surgery: DP, 60 PD, 56 Middle pancreatectomy or other atypical resection, 20 For delayed surgery: PD, 11 DP, 11 Middle pancreatectomy, 1	NA	159
Sachs et al,[65] 2009	United States	Some were cystic lesions: IPMN, 19 Solid pseudopapillary tumor, 2 Mucinous cystadenoma, 5 Serous cystadenoma, 15 Simple cyst, 2 Benign multiloculated cyst, 2 Pseudocyst, 2	Distal/subtotal pancreatectomy, 42 PD, 32 Central pancreatectomy, 7 Cyst enucleation, 5 TP, 3 Diagnostic laparotomy/laparoscopy, 7 Ampullectomy, 4 Partial gastrectomy, 3 Retroperitoneal cyst excision, 3 Excision mass, 2 Diversion, 2	NA	110

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Gumbs et al,[167] 2008	France	Noninvasive IPMN	Laparoscopically, 9 Open techniques, 13 Laparoscopic duodenopancreatectomy, 3 Open group, 5 TP laparoscopically, 2	Total of 14 patients: In laparoscopic group: Pancreatic fistula, 3 Postoperative hemorrhage, 1 Upper gastrointestinal bleeding, 1 In open group: Pancreatic fistula, 3 Postoperative hemorrhage, 1 Intra-abdominal abscess, 3 Necrotizing pancreatitis, 1 Urinary tract infection, 1 Gastric volvulus, 1 Biliary fistula, 1 Wound infection, 1	22
Schnelldorfer et al,[120] 2008	United States	IPMN	Partial pancreatectomy, 168 TP, 40	In-hospital morbidity, 77 patients (no detailed information provided)	208
Crippa et al,[187] 2008	Italy	MCN	Distal pancreatic resection, 153 (standard DP with splenectomy, 119; spleen-preserving DP, 28; extended DP, 6) PD, 4 Atypical resection, 5 (enucleation, 3; middle pancreatectomy, 2) TP for a large MCN, 1 Laparoscopic DP, 14	Total of 81 patients: Abdominal complication, 54 Overall pancreatic fistula, 39 Grade B–C pancreatic fistula, 15 Intra-abdominal collection/abscess, 19 Extra-abdominal complication, 39	163
Niedergethmann et al,[219] 2008	Germany	IPMN	PD/PPPD, 78 DP, 14 TP, 5	Total of 55 patients: Leakage pancreaticojejunostomy, 4 Leakage hepaticojejunostomy, 2 Bleeding, 8 Intra-abdominal abscess, 4 Postoperative pancreatitis, 7 Delayed gastric emptying, 11	97

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Nagai et al,[220] 2008	Japan	IPMN	PPPD, 29 PD, 8 DP, 20 (including 1 spleen-preserving DP) TP, 10 Partial resection of the pancreas, 4 Middle segmental pancreatectomy, 1	Total of 18 patients: Gastrointestinal anastomotic leakage, 1 Pancreatic fistula, 4 Intra-abdominal abscess, 1 Pancreatitis, 1 Pancreatic pseudocyst, 2 Anastomotic stenosis, 2 Cholangitis, 2 Delayed gastric emptying, 3 Ascites, 1 Diarrhea, 2 Pneumonia, 2	72
Rodriguez et al,[170] 2007	Italy	IPMN	PD, 97 (with pylorus preservation in 28 cases) DP, 29 (14 with splenic preservation) Middle pancreatectomy, 15 TP, 2 Enucleation, 1 Combined PD and DP, 1	Total of 74 patients: Abdominal complication, 39 (pancreatic fistula, 25; biliary fistula, 4; delayed gastric emptying, 9; intra-abdominal collection/abscess, 13) Nonsurgical complication, 45	145
Galanis et al,[192] 2007	United States	SCN of the pancreas	DP, 75 PD, 65 Central pancreatectomy, 9 Local resection or enucleation, 5 TP, 4	29 major complications (defined as defined as pancreatic fistula or anastomotic leak, postoperative bleed, retained operative material, or death) 52 minor complications	158
Nakao et al,[171] 2007	Spain	IPMN	Pancreatic head resection with segmental duodenectomy (Nakao technique), 35 PPPD, 32	Total of 31 patients: In pancreatic head resection with segmental duodenectomy: Pancreatic fistula, 4 Delayed gastric emptying, 5 Pleural effusion, 1 Pneumonia, 1 Postoperative diabetes mellitus, 2 In PPPD: Pancreatic fistula, 7 Delayed gastric emptying, 10 Postoperative diabetes mellitus, 2	67

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
White et al,[221] 2007	United States	Noninvasive IPMN	PD, 38 PPPD 12 Distal TP or sub-TP, 23 (splenic preserving, 15; with splenectomy, 8) TP, 2 Enucleation, 3 All patients underwent complete gross resection	NA	78
Hardacre et al,[70] 2007	United States	SCN, 16 MCN, 7 IPMN, 37	PPPD, 15 PD, 8 DP and splenectomy, 23 DP, 4 TP, 5 Enucleation, 2 Central pancreatectomy, 1 Laparoscopic DP, 2	Total of 33 patients: Overall pancreatic fistula by operation, 8 Delayed gastric emptying by operation, 2 Readmission, 8 Wound infection, 6 Abscess, 6 Urinary tract infection, 5 *Clostridium difficile* colitis, 4 Atrial fibrillation, 3 Pneumonia, 2 Pneumothorax, 2 Chylous ascites, 1 Reintubation, 1 Enterocutaneous fistula, 1	60
Allendorf et al,[222] 2007	United States	Serous cystadenoma, 10 Mucinous cystadenoma, 9 Hemorrhagic cyst, 2 Solid cystic pseudopapillary tumor of the pancreas (Frantz's tumor), 1 IPMN, 1 Neuroendocrine neoplasm, 2 Lymphangioma, 1	Central pancreatectomy with pancreaticogastrostomy reconstruction	Total of 8 patients: Developed fluid collections in the resection bed consistent with a pancreatic leak, 2 Developed pancreatitis in the remnant distal gland with a peripancreatic phlegmon, 2 Minor complications, 4 (urinary tract infection, 2; pneumonia, 1; *C difficile* colitis, 1)	26
Goh et al,[223] 2006	Singapore	SCN, 33 MCN, 21 IPMN, 21 Solid pseudopapillary neoplasm, 14 Cystic pancreatic endocrine neoplasm, 5 Ductal adenocarcinoma, 5 Lymphangioma, 2 Non-neoplastic cyst, 8	TP, 5 PD, 22 Minor subtotal, 13 Minor distal, 64 Minor enucleation, 5	Total of 34 patients: Most common complications: Pancreatic fistula, 11 Intra-abdominal abscess or infected collection, 11 Delayed gastric emptying, 4	109

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Kang et al,[224] 2006	Korea	Solid pseudopapillary tumor	PPPD, 5 PD, 5 DP with splenectomy, 17 Enucleation, 5	NA	33
Carboni et al,[225] 2006	Italy	Serous cystadenoma, 13 MCN, 12 (9 mucinous cystadenomas, 3 mucinous cystadenocarcinomas) IPMN, 4 Solid pseudopapillary neoplasm, 1	Curative resection, 29 PD, 10 (2 performed laparoscopically) PPPD, 3 DP, 3 DP with spleen preservation, 1 Median pancreatectomy, 5 Median pancreatectomy with a concurrent transverse colectomy, 1 TP, 1 Enucleation, 9 (1 performed laparoscopically) Duodenum-preserving pancreatic head resection, 1 Explorative laparotomy with biopsy, 1	Total of 12 patients: Pancreatic fistula, 7 Delayed hemorrhage, 2 Biliary fistula, 2 Abscess, 1 Delayed gastric emptying, 1 Enteric fistula, 1	30
Raut et al,[96] 2006	United States	IPMN	PD, 23 DP, 4 TP, 8 (15 patients had one or more adjuvant therapy)	NA	35
Lee et al,[131] 2005	Korea	IPMN	PD, 17 PPPD, 15 TP, 11 Partial or DP, 13	NA	56
Sohn et al,[132] 2004	United States	IPMN	PD, 96 TP, 21 DP, 16 Central pancreatic resection, 3	Total of 47 patients: Delayed gastric emptying, 18 Pancreatic fistula, 15 Intra-abdominal abscess, 8 Bile leak, 6 Wound infection, 4 Pancreatitis, 2 Pneumonia, 3 Cholangitis, 1	136
Salvia et al,[174] 2004	United States	IPMN	PD, 88 DP, 24 TP, 26 Middle pancreatectomy, 2	Pancreatic fistula, 22 Biliary fistula, 1 Delayed gastric emptying, 11 Abdominal collection, 9	140

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
D'Angelica et al,[133] 2004	United States	IPMN	TP, 6 Partial pancreatectomy, 56 Unresectable, 1	Total of 31 patients; the majority of complications were gastrointestinal or anastomotic (40%) and infectious (18%); urinary, cardiovascular, and hemorrhagic complications accounted for 13%, 10%, and 10% of all complications, respectively	63
Tollefson et al,[134] 2003	United States	IPMN	TP, 8 PD, 7 DP, 1 5 patients had unresectable disease; 4 of these patients had biliary and/or gastric diversion for symptomatic relief, and 1 underwent biopsy alone	NA	21
Kiely et al,[226] 2003	United States	MCN, 16 Serous cystadenoma, 10 cystic islet cell tumor, 4	Enucleation, 11 PD, 8 DP, 11	Total of 15 patients: Enucleation group: Fistula, 3 Partial small bowel obstruction, 1 Resection group: Pancreatic fistula, 5 Abdominal abscess, gastric outlet obstruction, pneumonia, and a urinary tract infection, 4 2 late complications (small bowel obstruction, pseudocyst)	30
Sheehan et al,[227] 2003	United States	SCN, 26 MCN, 20 (15 cystadenoma, 5 cystadenocarcinoma) Solid pseudopapillary neoplasm, 9 IPMN, 18	PD, 20 DP, 43 (2 without splenectomy) Central pancreatectomy, 5 TP, 2 Biliary bypass for a serous cystadenoma (too large for resection), 1	Total of 20 patients: Pancreatic fistula, 7 Intra-abdominal abscess, 2 Wound infection, 1 Hemorrhage from the cut end, 1 Miscellaneous complications, 7 (stroke, deep venous thrombosis, urinary tract infection, delayed gastric emptying, and aspiration pneumonia)	73
Harper et al,[228] 2002	United States	Serous cystadenoma, 14 Mucinous cystadenoma, 11 Mucinous cystadenocarcinoma, 5	PD/PPPD, 14 DP with or without splenectomy, 15 TP, 1	Total of 8 patients: Postoperative pancreatitis, 1 New-onset diabetes mellitus, 1 Wound infection, 1 Erosive gastritis, 1 Pancreatic fistula, 3 Prolonged ileus, 1	30

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Walsh et al,[229] 2002	United States	Mucinous neoplasm, 18 Serous neoplasm, 8 Ductal or neuroendocrine carcinoma, 4 Pseudocyst, 3 Other, 2	DP, 20 PPPD, 9 Internal cyst drainage, 2 Cyst excision without pancreatectomy, 3 Transduodenal biopsy, 1	NA	35
Maire et al,[230] 2002	France	IPMN	PD, 46 DP, 14 TP, 11 Segmentary pancreatectomy, 2	Total of 18 patients: Infection, 9 Pancreatic fistula, 4 Hemorrhage, 3 Abdominal occlusion, 2	73
Kalil et al,[231] 2002	Brazil	Serous cystadenoma, 15 Mucinous cystadenoma, 4 Cystadenocarcinoma, 2	Cephalic gastroduodenopancreatectomy, 4 Body and tail pancreatectomy, 11 Only tail pancreatectomy, 2 Enucleation, 2 Internal drainage through cystogastrostomy or cystojejunostomy, 3	Total of 3 patients: Respiratory tract infection, 1 Surgical wound infection, 1 Large abdominal abscess, 1	21
Sugiura et al,[139] 2002	Japan	IPMN	Duodenum-preserving pancreatic head resection, 12 DP, 8 Segmental pancreatectomy, 6 Conventional PD, 4	Total of 8 patients: Pancreatic fistula, 7 Necrosis of the preserved bile duct, 1	30
Adsay et al,[141] 2002	United States	IPMN	PD, 23 DP, 3 TP, 2	NA	28
Tobi et al,[82] 2001	United States	IPMN	PD, 33 DP, 10 TP, 6 Segmental, 1	NA	50
Kanazumi et al,[142] 2001	Japan	IPMN	PD, 10 PPPD, 10 Pancreatic head resections with segmental duodenectomy, 13 DP, 17 Segmental resection of the pancreas, 9 Duodenum-preserving pancreatic head resection, 2 TP, 1	Total of 2 major complications: Necrosis of the common bile duct, 1 Stenosis of that duct due to ischemia after duodenum-preserving pancreatic head resection, 1	62

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Falconi et al,[143] 2001	Italy	IPMN	PD, 17 (Whipple resection, 15; extended Whipple resection, 2) PPPD, 15 DP with splenectomy, 10 TP, 5 Middle pancreatectomy, 3	Total of 19 patients (including 14 pancreatic fistulas)	51
Formentini et al,[194] 2000	Germany	SCN (serous cystadenoma, 22; serous cystadenocarcinoma, 3)	PPPD, subtotal left pancreatectomy with splenectomy, or segmental pancreatic resection Concomitant resection of the left adrenal gland in 1 patient	Total of 3 patients (lymph node metastasis, invasion, infiltration of the adjacent adrenal gland, 2 associated with ductal adenocarcinoma)	25
Cuillerier et al,[83] 2000	Belgium and France	IPMN	Partial pancreatectomy, 35 TP, 10	NA	45
Paye et al,[153] 2000	France	IPMN	All patients but one underwent a partial pancreatic resection	Total of 18 patients: Pancreatic fistula, 6 Pancreatitis of remnant pancreas, 2 Hemorrhage on pancreatic anastomosis, 1 Transient gastric emptying impairment, 2 Small bowel obstruction, 1 Biliary fistula (from the cystic duct), 1 Acute cholangitis, 2 Regressive portal vein thrombosis, 1 Pulmonary embolism, 1 Transient ischemic cerebral stroke, 1	41
Colovic et al,[232] 1999	Serbia	Serous cystadenoma, 6 Mucinous cystadenoma, 16	DP, 1 DP with splenectomy, 12 Excision with splenectomy, 2 Excision, 7	Total of 4 patients: Left subphrenic abscess and left pleural effusion, 1 Transient pancreatic fistula, 1 Malignant alteration, 2 Melena, 1	22
Horvath et al,[233] 1999	United States	Serous cystadenoma, 12 Mucinous cystadenoma, 4 Mucinous cystadenocarcinoma, 3 Intraductal papillary cystic neoplasm, 5 Serous cystadenocarcinoma, 1	Curative resection, 23 Palliative resection, 2 Partial pancreatectomy, 1 DP, 4 DP with splenectomy, 9 PD, 11	Total of 5 major complications: (abscess, bleeding, erosive gastritis); no pancreatic fistulas, delayed gastric emptying in 1, severe erosive gastritis in 1 Total of 5 minor complications: mild pancreatitis, pneumonia, vocal cord injury, diarrhea/dehydration, delayed gastric emptying	25
Wilentz et al,[16] 1999	United States	MCN	DP, 32 PD, 26 Complete pancreatectomy, 2	NA	60

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Paal et al,[234] 1999	United States	IPMN	Complete pancreatectomy, 7 PD, 13 Biopsy only, 2	NA	22
Siech et al,[235] 1998	Germany	Serous cystadenoma, 30 Mucinous cystadenoma, 21	Segmental resection (including duodenum-preserving pancreatic head resection), 7 Oncological resection, 44	Pancreatic fistula, 3 Sepsis 3 Pulmonary complications, 4	51
Sugiyama et al,[236] 1998	Japan	IPMN	All 41 patients underwent exploratory laparotomy Tumor resection, 39 TP, 5 Pylorus-preserving TP, 4 PD, 5 PPPD, 13 DP, 4 Duodenum-preserving pancreatic head resection, 3 Spleen-preserving DP, 2 Segmental resection of the pancreatic body, 1 Tumor enucleation, 2 Bypass operation, 2 Combined resection: Portal vein, 3 Stomach, 1 Transverse colon, 1 Right kidney, 1	Two major postoperative complications: Leakage of the pancreatogastrostomy after a duodenum-preserving pancreatic head resection, 1 Pancreatic fistula after tumor enucleation, 1	41
Talamini et al,[237] 1998	United States	Mucinous cystadenoma	PD or DP, 26 Enucleation, 10 (4 underwent another concomitant abdominal procedure)	NA	26
Yasuda et al,[238] 1998	Japan	Mucin-producing pancreatic tumors, 24 Intraductal papillary carcinoma, 13 Mucinous cystadenocarcinoma, 5 Intraductal papillary adenoma, 3 Mucinous cystadenoma, 3	TP, 4 PD, 1 PD with a transverse colectomy, 1 PPPD, 13 Duodenum-preserving pancreatic head resection, 1 Resection of the posterior segment of the pancreas (posterior segmentectomy), 1 Medial segment of the pancreas, 1	Total of 2 patients Development of transient duodenal stenosis after duodenum-preserving pancreatic head resection, 1 Mucus leaked from the pancreatic duct in the operating field during pancreatectomy (intraductal papillary carcinoma after PPPD), 1	23

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Martin et al,[239] 1998	United Kingdom	Serous cystadenoma, 6 Mucinous cystic adenoma, 3 Mucinous cystadenocarcinoma, 10 Ductal adenocarcinoma with cystic degeneration, 1 Cystic islet cell tumor, 1	PD, 4 DP and splenectomy, 14 Palliative procedure, 3	NA	21
Cellier et al,[175] 1998	France	IPMN	Partial pancreatectomy, 37 TP, 10	NA	47
Fukushima et al,[146] 1997	Japan	Intraductal papillary tumor, 28 Mucinous cystic tumor, 10	No detailed information for "surgical intervention"	NA	38
Azar et al,[85] 1996	Belgium	IPMN	PD, 17 Caudal and segmental pancreatectomy, 6 Palliative surgery, 1 TP was not performed	NA	24
Brenin et al,[240] 1995	United States	Cystadenocarcinoma, 7 Serous cystadenoma, 10 Mucinous cystadenoma, 5	DP, 10 Bypass, 4 Open biopsy only, 3 PD, 3 Cystenterostomy, 1 Enucleation, 1	Total of 4 patients: Pancreaticocutaneous fistula, 1 Biliary fistula that required reoperation, 1 Postoperative lower-extremity deep venous thrombosis, 4 Postoperative pneumonia, 3	22
Sessa et al,[147] 1994	Italy	IPMN	PD for tumors involving the pancreas head or head-body and DP for tumors in the body tail (no other details)	NA	26
Grieshop et al,[241] 1994	United States	MCN benign, 6 MCN malignant, 6 Serous cystadenoma, 5 Ductal adenocarcinoma with cystic degeneration, 2 Papillary cystic neoplasm, 1 Intraductal mucin hypersecreting neoplasm, 1	DP, 14 PD, 5 TP, 1	Total of 11 patients: Enteric fistula, 3 Abdominal abscess, 3 Delayed gastric emptying, 2 Biliary fistula, 1 Pseudocyst, 1 Hemorrhage, 1 Wound infection, 1 Ischemic bowel, 1 Pancreatic fistula, 1 Wound dehiscence, 1 Fluid collection, 1	21

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Delcore et al,[242] 1992	United States	Serous cystadenoma, 6 Mucinous cystadenoma, 2 Mucinous cystadenocarcinoma, 13	All patients underwent exploratory laparotomy Benign: Excision, 2 DP, 5 PD, 1 Malignant: PD, 4 DP, 4 TP, 2 Palliative procedure, 3	No postoperative complications	21
Talamini et al,[243] 1992	United States	Serous (microcystic) cystadenoma, 9 Mucinous cystadenoma, 14 Mucinous cystadenocarcinoma, 12 Mucin-producing adenocarcinoma, 9 Adenocarcinoma with an associated pseudocyst or simple cyst, 6	PD, 18 DP, 16 Palliative bypass, 7 Biopsy only, 6 TP, 2 Enucleation, 1 47 patients underwent laparotomy	Total of 17 patients: Delayed gastric emptying, 8 Pancreatic fistula, 5 Antibiotic-associated diarrhea, 2 Wound infection, 2 Pancreatitis, 1 Enterocutaneous fistula, 1	50
Pyke et al,[9] 1992	United States	Serous cystadenoma	Radical PD, 11 DP, 17 Enucleation, 8 Bypass, 2 Biopsy, 2	Total of 15 patients: Pancreatic fistula developed, 6 Postoperative bile leak required revision hepaticojejunostomy, 1 Other surgical problems requiring reoperation included a revision gastrojejunostomy for gastric stasis, cystoenteric drainage of a postoperative pancreatic pseudocyst, revision of a hepaticojejunostomy for stenosis, and conversion of an enucleated lesion in the head of the pancreas to a PD for postoperative pancreatitis	40
Warshaw et al,[244] 1990	United States	Serous cystic adenoma, 18 Benign MCN, 15 Mucinous cystadenocarcinoma, 27 Papillary cystic tumor, 3 Cystic islet cell tumor, 2 Mucinous ductal ectasia, 2	DP, 25 Proximal resection, 29 TP, 1 Explorations with biopsy of cancer unresectable because of local extension of distant metastases, 10	NA	67

Supplementary Table 1. Continued

Reference	Country	Type of cyst	Type of surgery performed, n	Type of complication	Total no. of patients
Katoh et al,[245] 1989	Japan	Cystadenoma, 26 Serous cystadenoma, 17 Mucinous adenoma, 9 Cystadenocarcinoma, 19	Cystadenoma: PD, 4 DP, 13 TP, 3 Near TP, 2 Biopsy with or without bypass, 3 Autopsy, 1 Cystadenocarcinoma: PD, 6 DP, 5 Near TP, 1 Biopsy with or without bypass, 7	NA	45

DP, distal pancreatectomy; PD, pancreatoduodenectomy; NA, not applicable; PPPD, pylorus-preserving pancreatoduodenectomy; TP, total pancreatectomy; SCN, serous cystic neoplasm.

Supplementary Table 2. Summary of Eligible Studies Used to Evaluate Incidence of Malignancy in Cysts That Are Followed up by Imaging

Reference	Country	Patients	Diagnostic method
Kamata et al,[259] 2014	Japan	Data from clinical records and imaging studies that were collected prospectively; during 2001–2009, 167 consecutive patients with IPMNs underwent EUS, ultrasonography, CT, and MRI; the 102 patients whose BD-IPMNs lacked mural nodules/symptoms and thus did not qualify for resection were followed up by semiannual EUS and annual ultrasonography, CT, and MRI	With all of the imaging modalities, IPMN was defined as a dilation of the MPD or its branches; to exclude simple cysts, a lesion was suspected to be an IPMN if it was >5 mm in diameter; IPMN was classified from imaging studies as either main duct or BD-IPMN according to the new Fukuoka criteria
Castelli et al,[260] 2013	Italy	155 patients with multifocal IPMN of the side branches were examined with MRI and MRCP; those with a follow-up period <12 mo (n = 33) and those with a diagnosis of multifocal IPMN of the side branches without any follow-up (n = 14) were excluded from the study	MRI/MRCP with ≥2 dilated side branches involving any site of the parenchyma; presence of communication with the MPD and previous investigations by MRI/MRCP within at least 6 mo
Ogura et al,[261] 2013	Japan	Consecutive follow-up of 20 patients with "high-risk stigmata" MPD IPMN, in whom the diameter of the MPD was >10 mm and BD was <5 mm and who underwent clinical follow-up for ≥2 y; no history of pancreatitis	Diameter of MPD was >10 mm on MRCP, ERCP, or EUS, and BD was <5 mm; another lesion of MPD obstruction such as pancreatic cancer or pancreatic stone was excluded; and mucus was identified by ERCP or duodenoscopy, or imaging consistent with mucus by EUS
Piciucchi et al,[262] 2013	Italy	Meeting criteria (Sendai positive) and not operated; 35 patients enrolled, 40% with main duct IPMN and 60% with BD-IPMN (19 ruled out for surgery due to comorbidities, 7 because age older than 80 y, 9 refused surgery)	Histological diagnosis obtained by EUS-FNA or biopsy; cytological diagnosis obtained by EUS-FNA based on the accepted criteria: presence of one or several MPD and/or BD dilations and/or pancreatic cystic lesions communicating with pancreatic ducts at CT, MRCP with secretin stimulation, ERCP, or EUS
Baiocchi et al,[263] 2013	Italy	234 patients with IPMN with a median follow-up of 39.5 mo (range, 12–72 mo)	Based on computer files, from the radiological folder, and from the MRCP report
Ohno et al,[264] 2012	Japan	142 patients who underwent contrast-enhanced EUS for initial diagnosis from January 2001 with more than 12 mo of follow-up	Asymptomatic BD-IPMNs on EUS without any dilation of the MPD and obvious mural nodules
Khannoussi et al,[265] 2012	France	53 BD-IPMNs had no criteria suggestive of malignancy 60 mo after diagnosis and were followed up beyond that time in a prospective surveillance program	Based on the presence of one or several BD dilation(s) or pancreatic cystic lesions clearly communicating with pancreatic ducts seen on CT, MRCP, ERCP, or EUS; confirmed by EUS-FNA or EUS-FNA and biopsy
Arlix et al,[266] 2012	France	49 patients with nonoperated BD-IPMN who displayed a low probability for malignancy	Based on radiological criteria whereby unilocular or multilocular lesions with a grape-like appearance communicate with the MPD; without signs of malignancy; using a minimum of 2 of the conducted morphological examinations (CT, MRCP, EUS, or ERCP), in addition to the extrusion of mucus via the major or minor papilla, or from cytological data
Bae et al,[267] 2012	United States	194 patients with BD-IPMNs	CT, MRI, EUS, or ERCP showed unilocular or multilocular lesions with a grape-like appearance communicating with pancreatic ducts, but without any dilation of the MPD >6 mm
Inui et al,[268] 2011	Japan	195 patients with IPMNs	Ultrasonography, EUS, intraductal ultrasound, ERCP, contrast-enhanced computed tomography, and MRCP
Kawakubo et al,[269] 2011	Japan	642 patients with IPMNs prospectively followed up for 4.8 y	Imaging modalities included abdominal ultrasonography, EUS, contrast-enhanced CT, or MRCP; ERCP and EUS-FNA if necessary; main duct IPMNs and BD-IPMNs were radiologically defined

Supplementary Table 2. Continued

Reference	Country	Patients	Diagnostic method
Uehara et al,[270] 2011	Japan	100 patients who had BD-IPMNs without mural nodules or who had BD-IPMNs with mural nodules of <9 mm	Ultrasonography, EUS, or CT and confirmed by a dilated BD with a minimum size of 10 mm and mucus in it on ERCP
Maguchi et al,[40] 2011	Japan	349 patients with BD-IPMN being followed up who had no mucinous neoplasms on EUS at initial diagnosis	ERCP, EUS, MRCP, CT, or histology if surgery was performed; BD-IPMN was defined as a grape-like multilocular cystic lesion communicating with the MPD <10 mm
Takuma et al,[271] 2011	Japan	Long-term outcome in 20 conservatively followed up patients with main duct IPMN	CT or MRCP
Kang et al,[45] 2011	Korea	201 patients with BD-IPMN who were followed up for more than 3 mo with repeated CT at least twice, an initial cyst size of <30 mm without dilation of the MPD, or mural nodules at presentation were enrolled in this study	CT, MRCP, or ERCP
Lee et al,[272] 2010	United States	Patients with IPMN; the aim of this preliminary study was to determine if differences in anxiety and quality of life exist between patients who undergo surgery or undergo surveillance	MRI, CT, EUS, or fluid analysis
Tanno et al,[273] 2010	Japan	68 patients with BD-IPMN	ERCP
Ikeuchi et al,[274] 2010	Japan	145 patients with BD-IPMN	Not mentioned except for review of records
Sawai et al,[275] 2010	Japan	103 patients with SB-IPMN and conservatively followed up for at least 2 y	EUS database
Shin et al,[276] 2010	United States	23 consecutive patients with BD-IPMN who were followed up by MRI with MRCP over a period of more than 9 mo after initial MRI examination	MRI with MRCP
Kanno et al,[277] 2010	Japan	159 patients with BD-IPMN	IPMN: when a pancreatic cyst >1 cm was found to communicate with the MPD by EUS and one or more additional imaging studies, including CT, MRI, and ERCP; CT and EUS or surgery (histological) or biopsy were used to confirm invasive cancer
Woo et al,[41] 2009	Korea	190 patients with radiological imaging or histological findings consistent with BD-IPMN, identified retrospectively from the database (8/190 had acute pancreatitis, history of malignancy [n = 60])	Diagnosed by CT and pancreatography in 105 patients; 2 or more imaging studies (CT, MRI, EUS, ERCP) showed one or more pancreatic cysts communicating with the MPD but without any dilation of the main duct
Salvia et al,[278] 2009	Italy	131 patients had a clinicoradiologic or a histopathological diagnosis of multifocal BD-IPMN	Clinicoradiologic or histopathological diagnosis: the diagnosis of multifocal BD-IPMN was based on the presence of 2 cystic lesions in any part of the pancreatic gland that clearly communicated with the MPD; MRCP from 2000, others used EUS and/or ERCP
Manfredi et al,[279] 2008	Italy	52 patients with IPMN, evaluated serial changes at MRCP	Imaging criteria: largest diameter of the mass <35 mm; absence of papillary proliferations; caliber of the MPD <5 mm Clinical criteria: no abdominal symptoms, no evidence of diabetes, no laboratory evidence of biliary obstruction, and normal tumor markers
Guarise et al,[280] 2008	Italy	26 patients with multifocal IPMN of the side branches	≥2 ectatic side branches, presence of communication with the MPD, and 2 MRI/MRCP examinations after 6–12 mo

Supplementary Table 2. Continued

Reference	Country	Patients	Diagnostic method
Rautou et al,[281] 2008	France	Highly suspected IPMNs confined to the BD without criteria suggesting development of a malignancy (mural nodule, cyst wall thickness >2 mm, BD diameter >30 mm, or MPD involvement) were followed up prospectively	Diagnosis was highly suspected when patients with a normal MPD had 1 or several BD dilation(s) or pancreatic cystic lesions communicating with pancreatic ducts, observed with atleast 2 of the following imaging techniques: CT, MRCP, ERCP, or EUS
Pelaez-Luna et al,[282] 2007	United States	147 patients with BD-IPMN, of whom 66 underwent surgical resection at diagnosis; 81 were followed up conservatively, of whom 11 underwent resection during follow-up	BD-IPMN was diagnosed when one or more imaging studies (CT, MRI, EUS, ERCP) showed one or more pancreatic cysts ≥1 cm in size communicating with a main duct <6 mm in diameter
Hanada et al,[283] 2006	Japan	60 of 92 cases of BD-IPMN were followed up for more than 1 y	Diagnosed as BD-IPMN by ultrasonography, CT, EUS, and MRCP/ERCP
Carbognin et al,[284] 2006	Italy	65 BD-IPMNs; 29 patients underwent surgery, and the other 36 patients were followed up with cross-sectional imaging	CT, MRI, and MRCP for observed patients
Lévy et al,[285] 2006	France	106 patients with a diagnosis of highly probable (n = 30) or histologically proven (n = 76) IPMN; was confined to the BD in 53 cases	Histological diagnosis obtained by EUS-FNA or biopsy (EUS-FNAB) or surgical specimen; cytological diagnosis obtained by EUS-FNA; extrusion of mucus via the major or minor papilla; a high suspicion of IPMN was based on the presence of one or several MPD and/or BD dilation(s) and/or pancreatic cystic lesions communicating with pancreatic ducts seen on CT, MRCP, ERCP, or EUS
Yamaguchi et al,[286] 2005	Japan	81 patients with IPMN were periodically subjected to ultrasonography (>3 y); 27 were reviewed retrospectively (12 with benign neoplasms [adenoma, borderline] and 15 with malignant tumors [carcinoma in situ, invasive cancer]) and 54 prospectively	Histopathology of resected specimens periodically by ultrasonography
Kobayashi et al,[287] 2005	Japan	51 patients with IPMN (BD type, 47; main duct type, 4) who had undergone a follow-up study by EUS; those who had been determined to be inoperable due to advanced disease and had been followed up were excluded	EUS, ERCP, CT
Irie et al,[47] 2004	Japan	35 patients who had BD-IPMN underwent initial and follow-up MRCP over a period of more than 12 mo	CT, ERCP, MRCP
Sai et al,[288] 2003	Japan	26 of 33 patients with BD-IPMN diagnosed by ERCP were prospectively examined with MRCP followed by dynamic gadolinium-enhanced MRI examinations, and patients with no findings suggestive of malignancy, including a solid mass, mural nodules, an MPD >5 mm in diameter, and stenosis of the MPD, were prospectively followed up with sequential MRI examinations once or twice a year	ERCP
Wakabayashi et al,[289] 2001	Japan	23 patients were followed up for ≥1 y after clinical diagnosis (follow-up group), including 6 who underwent surgery or autopsy after the follow-up period (also included in the confirmed group)	52 patients; transabdominal US (n = 52), CT (n = 52), ERCP (n = 50), or EUS (n = 39); 6 patients had follow-up by surgery OR died and had follow-up by autopsy
Lafemina et al,[290] 2013	United States	356 patients with IPMN were evaluated for pancreatic cysts; initial resection was selected for 186 patients; 170 patients underwent initial nonoperative management	Radiological and pathological confirmation of IPMN and/or cyst fluid CEA level 200 ng/mL
Cauley et al,[291] 2012	United States	292 patients were diagnosed with IPMN, with more than 3 mo of surveillance	Radiology and cytopathology, serology, clinical

Supplementary Table 2. Continued

Reference	Country	Patients	Diagnostic method
Wu et al,[44] 2014	United States	Patients older than 18 years of age with confirmed PCN from January 2005 to December 2010 in a community-based integrated care setting in Southern California (excluded acute or chronic pancreatitis)	Diagnosis based on ICD-9 codes
Manfredi et al,[247] 2013	Italy	Incidentally discovered benign, noncommunicating cystic neoplasms of the pancreas	Incidentally discovered cystic pancreatic neoplasm with nonmeasurable wall and lack of mural nodules, absence of communication with the pancreatic ductal system, and availability of one or more MR/MRCP examinations
Morris-Stiff et al,[57] 2013	United States	338 asymptomatic patients with pancreatic cystic neoplasms underwent evaluation; 63 patients underwent resection	Cross-sectional imaging studies and EUS-FNA
Cocieru et al,[248] 2011	United States	62 patients with incidental pancreatic cystic lesions who were evaluated by EUS with cystic fluid analysis	EUS
Chung et al,[249] 2013	Korea	1386 patients with pancreatic cysts	All patients underwent radiographic imaging, including CT, MRI, or EUS; radiological findings, histopathologic results after surgical resection, or other diagnostic modalities were recorded
Girometti et al,[195] 2011	Italy	24 of 152 patients with incidental pancreatic cysts were followed up	3-dimensional turbo spin echo MRCP
Oh et al,[250] 2011	Korea	Unilocular or oligolocular cysts, indeterminate cystic lesions that required EUS-FNA, and cystic lesions that grew during the observation period; 47 patients who were followed up for more than 12 months were analyzed (pseudocysts or overt carcinomas with pancreatic invasion were excluded)	EUS-FNA
Gaujoux et al,[251] 2011	United States	539 patients managed from 1995 to 2005 were compared with 885 patients managed from 2005 to 2010	ICD-9 codes of maintained registry
Bose et al,[252] 2010	United States	942 patients were identified with pancreatic cysts; 350 patients remained with incidental pancreatic cysts; those with symptoms or pseudocysts were excluded; the majority of pancreatic cystic lesions in this study were identified during interpretation of CT performed for staging of a nonpancreatic malignancy	Database was reviewed for patients with ICD-9 codes for pancreatic cysts; CT and EUS, with or without FNA, was performed
Pausawasdi et al,[253] 2010	Japan	Asymptomatic patients with incidental pancreatic cysts who underwent EUS evaluation and/or FNA, 97 of 317 patients underwent EUS for evaluation of pancreatic cysts from 1995 to 2005; 71 of them with lesions <3 cm were followed up	EUS database
Ferrone et al,[68] 2009	United States	401 patients with cystic lesions; 117 were symptomatic, 284 were incidental cysts	Clinical data collected included CT findings, EUS characteristics, cyst fluid cytology results, and tumor markers obtained by FNA; histological diagnosis was obtained from the pathology report in all patients who underwent surgical resection of their cysts
Das et al,[48] 2008	United States	A retrospective analysis of longitudinal medical records of patients with pancreatic cystic neoplasms, 150 patients, excluded small (<10 mm) cysts (n = 144) and inadequate clinical follow-up of <6 mo (n = 79) and those with a clinical diagnosis of pancreatic pseudocysts, serous cystadenoma, main duct IPMN (n = 29), and neuroendocrine tumor (n = 3)	Pancreatic cystic lesions were identified retrospectively by searching patient billing records via ICD-9 codes of benign neoplasm pancreas (211.6) and pancreatic cyst/pseudocyst (577.2) from 1997 to 2005, independent review by 2 authors of the reports, and digitized images of MRI, CT, and EUS studies; information was also recorded from FNA and/or surgical pathology reports of these cystic pancreatic lesions whenever available

Supplementary Table 2. Continued

Reference	Country	Patients	Diagnostic method
Walsh et al,[254] 2008	United States	500 patients from the prospective pancreatic cystic neoplasm database	From the prospective database, imaging study, FNA with EUS, resection, and secretin-stimulated MRI were selectively used during the initial evaluation of asymptomatic cysts suspected to have side branch IPMN
Gomez et al,[24] 2008	United Kingdom	79 patients with cystic lesions of the pancreas, excluding chronic or acute pancreatitis	Pathology database and radiology computer coding system, patients with a cystic lesion of the pancreas stated in radiology reports, which included abdominal ultrasonography, CT, MRI, ERCP, and EUS
Lahav et al,[49] 2007	Israel	Patients referred for EUS between 1994 and 2003 because of pancreatic cystic lesions, only asymptomatic patients with an incidental finding of a cystic lesion identified by abdominal imaging; excluded those who were symptomatic or had pancreatic pseudocysts; 14 underwent surgery, 90 patients were defined as having indeterminate or mucinous cysts managed conservatively after excluding 8 patients with serous cystadenoma and pseudocysts from the analysis	EUS, medical records, CT studies, and images were reviewed
Tada et al,[255] 2006	Japan	197 patients with pancreatic cystic lesions, 80 with IPMN and 117 with non-IPMN cysts, were followed up for 3.8 years on average; excluded typical pseudocyst or cystic tumor of the pancreas by imaging techniques and clinical signs or resection without follow-up	Lesions were detected by imaging modalities such as ultrasonography, CT, EUS, and MRCP and then evaluated by CT with injection of contrast material, EUS, and MRCP for differential diagnosis of cystic lesions and for possible existence of pancreatic malignancy; ERCP was performed if needed
Sahani et al,[256] 2006	United States	Patients with cysts that were $\leq$3 cm on ultrasonography-guided cyst fluid aspiration and biopsy	Identified on CT and/or MRI (of the 86 patients, 52 underwent CT only, 20 MRI only, and 14 both CT and MRI); imaging findings were compared with surgical and pathology records and with endoscopic ultrasonography features
Handrich et al,[257] 2005	United States	79 patients had small simple pancreatic cysts; 49 patients had adequate radiological, clinical, or questionnaire follow-up: 22 patients had radiological follow-up (mean follow-up, 9 years) and 27 patients had clinical or questionnaire follow-up (mean follow-up, 10 years); 18 patients died within 8 years without adequate radiological follow-up, and 12 were lost to follow-up	Diagnosed with one or more small ($\leq$2 cm) simple pancreatic cysts on ultrasonography or CT, MRI, endoscopy, pathology, and/or cytology
Spinelli et al,[73] 2004	United States	All radiological, surgical, and pathology records were reviewed for the presence of pancreatic cysts; included 79 patients with 103 cysts who had more than one scan with an average interval of 16 months; excluded pancreatitis or pseudocyst (still 7 with pancreatitis in the surgical group); only patients with 2 scans more than 1 month apart were included	Radiological records included CT and MRI; some patients underwent ERCP, EUS with FNA, and surgical resection
Megibow et al,[51] 2001	United States	30 patients with cystic pancreatic masses, the majority of whom underwent imaging surveillance; excluded patients with a history of pancreatitis with or without pseudocyst; excluded 35 patients who presented with unilocular masses $>$4 cm in diameter and underwent immediate surgery	CT report database; underwent 90 CT, 17 MRI, and 9 ERCP examinations

Supplementary Table 2. Continued

Reference	Country	Patients	Diagnostic method
Ikeda et al,[258] 1993	Japan	31 of 82 patients with small and asymptomatic cysts diagnosed as being non-neoplastic by EUS and followed up for ≥3 y (excluded pseudocysts, surgical or autopsy cysts, or followed up for <3 y)	Ultrasonography and/or CT
Ahn et al,[42] 2012	Korea	112 patients with cystic lesions of the pancreas with additional follow-up, received follow-up with repeated imaging studies for more than 3 mo	Ultrasonography and/or CT
Malleo et al,[53] 2012	Italy	145 patients with serous cystic neoplasms; followed up for 7 y	(1) Certain radiological diagnosis: MRI with MRCP was used as the standard, high-resolution imaging modality; (2) availability of serial MRI
Menard et al,[292] 2011	Canada	31 serous cystadenomas of the pancreas who had at least 18 mo of follow-up	Diagnostic imaging report database, identified from 1141 patients
Bassi et al,[293] 2003	Italy	100 consecutive cases of pancreatic serous cystadenomas	Ultrasonography, CT, MRI, EUS, exploratory needle aspiration of the cyst, and/or resection

BD, branch duct; MPD, main pancreatic duct.