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Resected Serous Cystic Neoplasms of the Pancreas: Locally Aggressive Behavior as a Predictor of Malignant Disease? A Review of 158 Patients with Recommendations for Treatment.

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ABSTRACT

Background: Serous cystic neoplasms of the pancreas are regarded as a benign entity with rare malignant potential. Surgical resection is generally considered curative.

Objective: To perform the largest single institution review of patients who underwent surgical resection for serous cystic neoplasms of the pancreas in the hopes of guiding future management.

Methods: Between June 1988 and January 2005, 158 patients with serous cystic neoplasms of the pancreas underwent surgical resection. A retrospective analysis was performed. Univariate and multivariate models were used to determine factors influencing perioperative morbidity and mortality. Major complications were defined as pancreatic fistula or anastomotic leak, postoperative bleed, retained operative material, or death. Minor complications were defined as wound infection, postoperative obstruction/ileus requiring TPN, delayed gastric emptying, arrhythmia, or other infection.

Results: The mean age of the patients was 62.1 years, with 75% being female. The majority of patients were symptomatic at presentation (63%), with abdominal pain as the most common symptom. Of the 158 patients, 75 underwent distal pancreatectomy, 65 underwent pancreaticoduodenectomy, 9 underwent central pancreatectomy, 5 underwent local resection or enucleation, and 4 underwent total pancreatectomy. Mean tumor diameter was 5.1 cm. Mean operative time was 277.5 minutes. Mean postoperative length of hospital stay was 11 days. One patient was diagnosed at presentation with serous cystadenocarcinoma. The remaining 157 patients were initially diagnosed with benign serous cystadenoma. One of three patients with locally aggressive benign disease

later presented with metastatic disease. Resection margins for all 158 patients were negative for tumor, and only 1 (0.6%) showed lymph node involvement. There was one intraoperative death. The incidence of major perioperative complications was 18%, while the incidence of minor complications was 33%. Men were significantly more likely to experience minor perioperative complications (OR = 3.74, P = .008), while patients greater than 65 years showed a trend toward fewer major complications (OR = 0.36, P = .09).

Conclusions: Serous cystic neoplasms of the pancreas which are surgically resected are typically seen in asymptomatic women, as 5 cm neoplasms which are predominantly benign. Most are resected via either a left or right sided pancreatectomy with low mortality risk, but with notable major or minor morbidity. Cystadenocarcinoma is a rare finding on initial resection of serous cystic neoplasms. However, initial pathology specimens exhibiting benign but locally aggressive neoplasia may indicate an increased likelihood of recurrence or metachronous metastasis.

INTRODUCTION

Serous cystic neoplasms (SCNs) of the pancreas are almost always benign. They are one of the most common primary pancreatic cystic neoplasms, and are distinguished from mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) (1). SCNs constitute 10-15% of all cystic masses of the pancreas and 1-2% of all pancreatic neoplasms (2,3). However, SCNs are being increasingly diagnosed with more widespread use and improving technology of imaging techniques (4,5). These neoplasms show a predilection for middle-aged and older women and are often discovered incidentally (6). Symptoms are frequently non-specific, with abdominal pain being the most common, occurring in 50-60% of all cases (7). Computed tomography is thought to be the diagnostic test of choice to properly identify this tumor type (8). SCNs are typically unifocal and present as large, well-demarcated, often honeycombed cystic masses which can grow as large as 25 cm. Diffuse or multifocal disease is uncommon. The cysts are loculated, consist of mucin-free serous fluid, and are surrounded by cuboidal or flattened epithelium. (9)

Unlike MCNs and IPMNs, SCNs are generally regarded as almost always benign, though their potential for malignant conversion remains a topic of debate (10). Due in large part to the uncertainty over malignant potential and the natural history of the disease, currently there is no accepted standard of treatment or follow-up for SCNs. For many, observation and routine surveillance are preferred (11). Some investigators recommend complete resection of all SCNs because of the perceived malignant potential of the disease, the relative frequency of symptoms and complications, and the challenge

of an accurate preoperative diagnosis (2,12,13). Those that utilize a selective approach

advocate for resection in the setting of tumors that are symptomatic, poorly defined, and

larger sized (7,14). Indeed, symptomatology appears to be the predominant and only

universally accepted indication for operative intervention. In all cases, resection is

considered curative, with no postoperative surveillance recommended.

The goals of our large (158 patients) single institution review were to evaluate

clinical parameters, pathologic features, and overall patient outcome following resection

of SCNs of the pancreas, in the hopes of guiding future management.

METHODS

Between June 1988 and January 2005, 158 patients with serous cystic neoplasms of the pancreas underwent surgical resection. A retrospective analysis of a database was performed. The study was approved by the Institutional Review Board for Human Research and complied with Health Insurance Portability and Accountability Act (HIPAA) regulations.

Major complications were defined as pancreatic fistula or anastomotic leak, postoperative bleed, retained operative material, or death. Minor complications were defined as wound infection, postoperative obstruction/ileus requiring TPN, bowel obstruction responsive to conservative non-operative treatment, delayed gastric emptying, arrhythmia, or other infection. Follow-up data were collected from postoperative admissions and/or clinic visits. Univariate and multivariate models were used to determine factors influencing perioperative morbidity and mortality. The chi square test was used for comparison between categorical outcome variables versus categorical independent variables, while t test was used to compare between continuous outcome variables versus categorical independent variables. Multiple logistic regression was used in final analysis. Statistical significance was defined as $p<0.05$. Statistical analysis was performed using Stata 9. Data are given as mean +/- standard deviation, where appropriate.

RESULTS

Demographics

Table 1 outlines the patient population in our series. The mean age of patients was 62.1. $\pm$ 13.3 years with most patients being non-Hispanic whites (81%). The majority of patients (75%) were female. There was no significant difference in age of presentation between males and females.

Presentation

Most patients presented with symptoms (64%). The most common symptoms were abdominal pain (74%), weight loss (22%), nausea/vomiting (10%), jaundice (6%), and GI bleed (3%). Men tended to be symptomatic more than women (45% of men versus 34% of women, not significant). Symptoms did not correlate with location or size of tumor. Of 158 patients, 66 (42%) underwent a computed tomography (CT) scan at our institution while the remaining were referred and treated with outside studies. Figure 1 shows two representative CT scans of patients with SCNs.

Operative and Postoperative Course

All patients in this series were treated operatively. Of the 158 patients, 75 (47%) underwent distal pancreatectomy for neoplasm of the body or tail of the pancreas, 65 (41%) underwent pancreaticoduodenectomy for right-sided tumors, 9 (6%) underwent central pancreatectomy for neoplasms of the neck or proximal body, 5 (3%) underwent local resection or enucleation, and 4 (3%) underwent total pancreatectomy for neoplasms extensively involving the gland. The average operative time was 277.5 minutes. The average transfusion requirement was 0.8 ± 3.9 units of packed red blood cells. There was

one operative death due to intraoperative hemorrhage from visceral vessels. Overall, the incidence of major complications was 18% while the incidence of minor complications was 33%. The most common major complication was pancreatic leak or fistula with an incidence of 13%. Men were significantly more likely to have minor complications than women (OR = 3.75, p = .008). Patients >65 years of age also showed a trend toward fewer major complications (OR = 0.36, p = .088). Table 2 and Table 3 describe complications by age and gender respectively. Mean postoperative length of hospital stay was 11.3 (SD = 8.9 days).

Pathology

For 158 resected tumors, the mean tumor size was 5.1 cm $\pm$ 3.7 cm. Tumors were located in the head (42%), body or tail (48%), proximal neck or body (7%), and with diffuse involvement of the entire gland (3%). Tumor size did not significantly vary by tumor location. Of all 158 patients, one patient at primary resection was noted to have biopsy proven serous cystic neoplasm of the liver and was therefore diagnosed with serous cystadenocarcinoma. The remaining 157 patients were diagnosed at primary resection with serous cystadenoma of the pancreas. Of these 157 patients, 3 were noted in final pathology report to have "locally aggressive disease" on histologic examination. One of these 3 patients recurred 13 years later with disease in the liver and retroperitoneal tissue and was therefore diagnosed with serous cystadenocarcinoma.

DISCUSSION

Classified as a benign neoplasm, serous cystic neoplasm (SCN) of the pancreas is the most common primary cystic neoplasm of the pancreas and accounts for 1-2% of all primary pancreatic neoplasms (1). SCNs had long been classified with mucinous cystic neoplasms, until Compagno and Oertel as well as Hodgkinson and others defined and separated serous from mucinous cystic neoplasms (15, 16). They recognized that the mucinous variants such as mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) have a significantly greater malignant potential than SCNs.

George et al. first introduced a malignant variant known as serous cystadenocarcinoma (10). There have since been multiple case reports of malignant SCN histologically indistinguishable from benign SCN of the pancreas but marked by malignant behavior, most commonly invasive or metastatic disease (12,17-23). One study suggested that up to 3% of reported SCNs were in fact malignant or had malignant potential (8). This malignant variant is defined by the presence of metastases to extrapancreatic organs or tissues (24). Vascular and perineural invasion, and local invasion into the duodenum or stomach, are not criteria for the diagnosis of malignancy.

There currently exists no consensus for management of SCNs. Many advocate simple surveillance given the almost universally benign nature of the disease and the relative morbidity and mortality associated with resection (11). However, a schedule of surveillance which adequately defines when expectant management should yield to

intervention has yet to be agreed upon. Furthermore, because other cystic neoplasms of the pancreas have significant malignant potential, it is imperative that the diagnosis of SCN be certain before committing to expectant management and surveillance. Others support a selective approach to resection based on symptoms, tumor size, or indeterminate preoperative diagnosis, among other factors (13,14). There continue to be those who support resection of all SCNs. They cite the real, albeit rare, malignant potential, the risk of an incorrect preoperative diagnosis, and the potential for symptoms and complications. Resection is generally considered curative and no postoperative monitoring is advocated.

Here we report the largest single institution experience with SCNs to date. The mean age of the 158 patients was 62.1 years with 75% being female (Table 1). This is consistent with previous studies which have also shown a predilection for the disease in middle aged to elderly females. Most patients were symptomatic at presentation (64%). Among symptomatic patients, the most common symptoms were abdominal pain (74%), weight loss (22%), nausea/vomiting (10%), jaundice (6%), and GI bleed (3%). The proportion of symptomatic patients is similar to or higher than that found in most other reviews. (8,14,15) The higher rate of symptomatic patients may partly be explained by the extensive referral nature of the practice at Johns Hopkins. In our series, 41% of the SCNs arose in the head of the pancreas, 48% in the body or tail, 6% in the neck or proximal body, and only 3% of lesions exhibited diffuse involvement of the entire gland. Mean tumor diameter was 5.1 cm, similar to the size found in Tseng et al.'s

contemporary series (14). All resection margins were negative, with only one SCN exhibiting lymph node involvement. There was one intraoperative death, due to excessive hemorrhage. In our experience, surgery for these lesions carried minimum mortality risk (0.6%) but notable major (18%) and minor (33%) morbidity risk. This risk of complications approximates the risk of pancreatic surgery for other conditions (such as adenocarcinoma of the pancreas) but the mortality rate for resection of SCN is less (25). It is worth noting that males had a significantly greater risk of experiencing minor complications than women. The reasons for this difference are not immediately apparent and warrant further investigation. No patient died of his or her disease. This fact, in conjunction with the aforementioned risks of surgery, would support a cautious approach to the resection of these neoplasms.

In our series, only 0.6% (1/158) of the patients with an SCN presented with metastatic disease. This patient presented initially with multifocal disease in the pancreas and liver, and was therefore diagnosed with a serous cystadenocarcinoma. Indeed, after resection of her pancreatic tumor, she returned to clinic one year later with extensive growth of a biopsy proven SCN in the liver which was nonoperable. Remarkably, both her primary and the liver metastases had a histologically bland appearance, lacking both architectural and cytologic atypia. An additional 3 patients in this study were noted to have "locally aggressive" neoplasms at the time of initial resection. These neoplasms were histologically identical to the more benign behaving tumors, but showed locally aggressive behavior by growing into neighboring structures (Figure 2). Margins were negative for these tumors. One of these patients returned in follow-up 13 years after

resection with biopsy proven recurrence in the liver and retroperitoneal soft tissue. Again, both the primary and the liver metastases had a histologically bland appearance, lacking both architectural and cytologic atypia. As this represented an extrapancreatic recurrence, the diagnosis for this patient was adjusted to reflect a serous cystadenocarcinoma. Thus, a total of two of the 158 patients (1.3%) in this series either presented with or ultimately developed metastatic disease.

Currently, resection for SCN is considered curative with no follow-up beyond postoperative care recommended. Here we report one case of recurrence following resection of the primary tumor. This tumor exhibited locally aggressive behavior at time of initial resection. Only two of the remaining 157 resected specimens exhibited a similar pattern. Locally aggressive growth therefore may offer an important clue as to which neoplasms have the potential to recur as cystadenocarcinoma. It will be interesting to follow the 2 additional patients whose tumors exhibited locally aggressive growth. Their lack of metastatic disease or recurrence may be explained by the fact that their primary resections were relatively recent (1999 and 2000) as compared to the primary resection for the patient whose disease later recurred (1992). Further follow-up of this tumor characteristic is warranted, and may offer a tool in determining a subpopulation of patients who do not have metastases at presentation, but for whom additional follow-up surveillance is warranted.

The proper management of patients with a SCN remains elusive. The first step is to distinguish this lesion from the more aggressive and premalignant lesions: IPMNs and MCNs. Beyond that, there are divergent paths. Based on our findings, we propose the

following algorithm (Figure 3). If SCN cannot confidently be distinguished from MCN

or IPMN, the patient should undergo resection. When the diagnosis of SCN is

confidently determined based on clinical and radiographic evidence, perhaps only

symptomatic tumors should be resected. If the decision is made to avoid resection

initially, we do recommend serial imaging at a 6 to 12 months interval, with resection for

growth (more than 1 cm change in diameter) or the development of symptoms. Post

resection, gross and microscopic review of the neoplasm should document not only the

presence or absence of metastases, but also any locally aggressive growth. For

neoplasms exhibiting this rare characteristic, patients should be counseled that although

in most cases SCNs are cured with primary resection, a small sub-population of cases

may recur, and may require additional imaging follow-up and treatment, as indicated.

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	n (%)	Mean ± SD
Total patients	158	
Sex		
Male	70 (25)	
Female	118 (75)	
Age (years)		62.1 ± 13.2
Symptomatic	101 (64)	
Abdominal pain	75 (47)	
Weight loss	22 (14)	
Nausea/vomiting	10 (6)	
Jaundice	6 (4)	
Gastrointestinal bleed	3 (2)	
Operation		
Distal pancreatectomy, splenectomy	75 (47)	
Whipple	65 (41)	
Central pancreatectomy	9 (6)	
Local resection or enucleation	5 (3)	
Total pancreatectomy	4 (3)	
Tumor size (cm)		5.1 ± 3.7
Operative time (minutes)		277.5 ± 117.4
Hospital stay (days)		11.3 ± 8.9
Death	1 (0.6)	
Major complication	29 (18)†	
Hemorrhage	2 (1.2)	
Pancreatic leak	21 (13)	
Bile leak	5 (3)	
Retained operative material	1 (0.6)	
Minor complication	52 (33)*	
Wound infection	8 (5)	
Delayed gastric emptying	5 (3)	
Postoperative ileus	4 (2)	
Arrhythmia	8 (5)	
Other infection	21 (12)	
Final pathologic diagnosis		
Serous cystadenoma	156 (98)	
Serous cystadenocarcinoma	2 (2)**	

TABLE 1: Patient characteristics. †Patients greater than 65 years showed a trend toward fewer major complications (OR = 0.36, P = .09). *Men had significantly more minor complications than women (OR = 3.74, p = .008). ** One patient who was diagnosed with serous cystadenoma on initial resection later recurred and was therefore re-diagnosed with cystadenocarcinoma.

	≤ 65 years	> 65 years	p value
Number of patients	89	69	
Major Complications (total)	19	9	.088
Hemorrhage	1	1	
Pancreatic leak	14	7	
Bile leak	3	2	
Retained operative material	1	0	
Minor Complications (total)	31	19	N.S.
Wound infection	4	4	
Delayed gastric emptying	3	2	
Postoperative ileus	3	1	
Small bowel obstruction*	3	0	
Arrhythmia	5	3	
Deep Vein Thrombosis	1	0	
Other infection	12	9	

TABLE 2: Complications compared with age of patients. Note that patients greater than 65 years showed a trend toward fewer major complications (OR = 0.36, P = .09).

	Male	Female	p value
Number of patients	40	118	
Major Complications (total)	6	23	N.S.
Hemorrhage	0	2	
Pancreatic leak	6	15	
Bile leak	0	5	
Retained operative material	0	1	
Minor Complications (total)	17	33	.008
Wound infection	3	5	
Delayed gastric emptying	1	4	
Postoperative ileus	1	3	
Small bowel obstruction*	1	2	
Arrhythmia	3	5	
Deep Vein Thrombosis	1	0	
Other infection	7	14	

TABLE 3: Complications compared with patient gender. Note that males had significantly more minor complications than women (OR = 3.74, p = .008).

FIGURE LEGENDS

FIGURE 1: Computed tomography (CT) scans of two patients, each with serous cystadenoma of the pancreas. The image on the right is from a 64 year old female who presented with abdominal pain. Her 10 cm neoplasm in the head of the pancreas was resected with a Whipple procedure without complication. The image on the left is from a 59 yo female who presented with pain and "fullness." Her 27 cm mass originating from the tail of the pancreas was resected with a distal pancreatectomy and splenectomy without complication.

FIGURE 2: Locally aggressive SCN. Although classically benign, SCNs may rarely exhibit locally aggressive behavior. In one patient, tumor compresses the pancreatic duct (a). On microscopic examination, this neoplasm exhibits bland histological appearance, lacking both architectural and cytologic atypia (b). However, this SCN shows uncommon locally aggressive behavior by growing up against and into a neighboring lymph node (arrows).

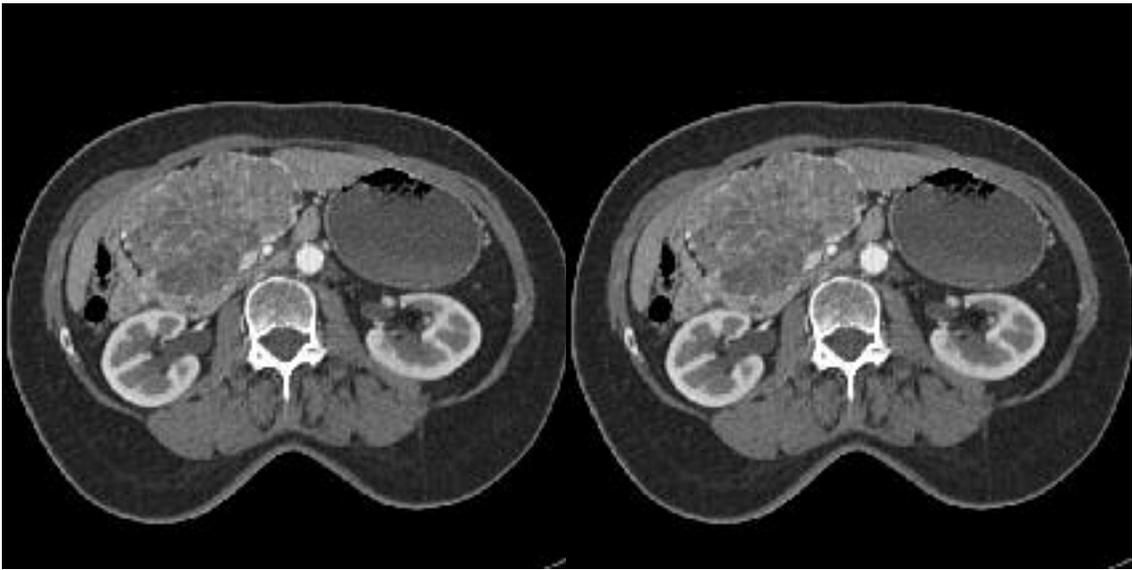**FIGURE 3:** Proposed approach to the patient with a cystic neoplasm of the pancreas.
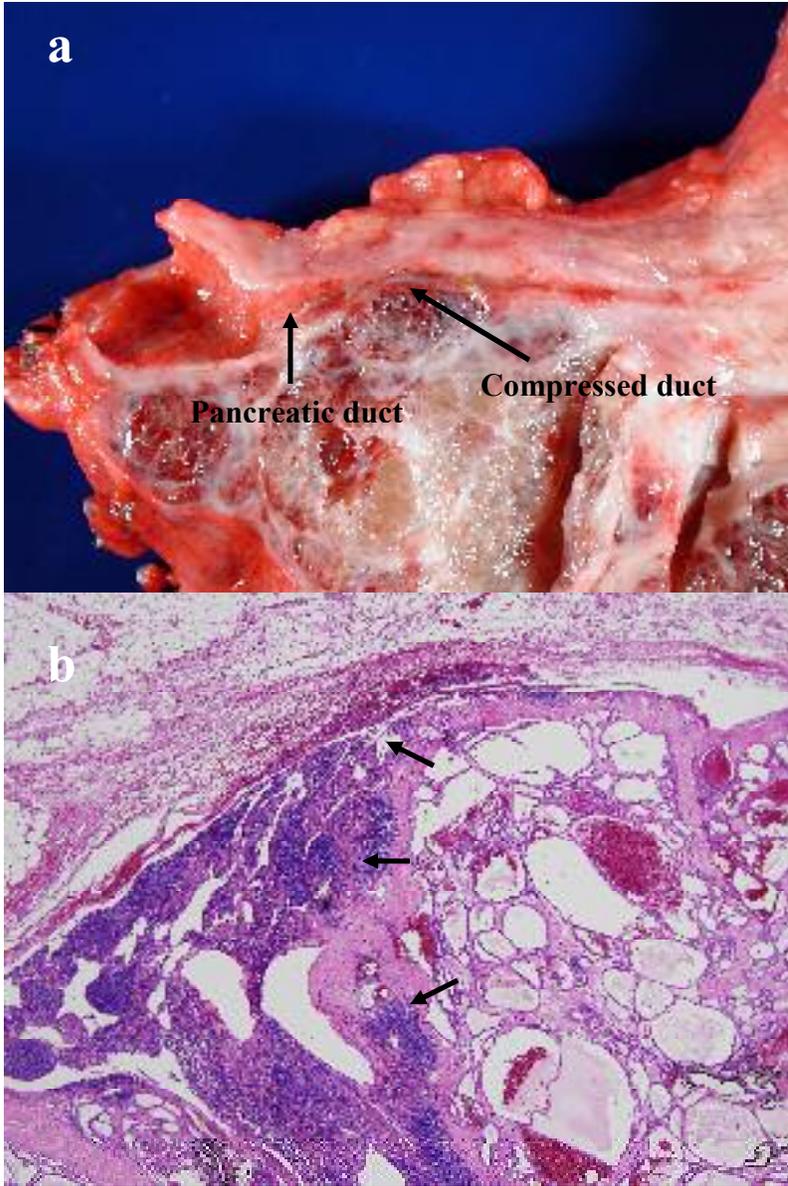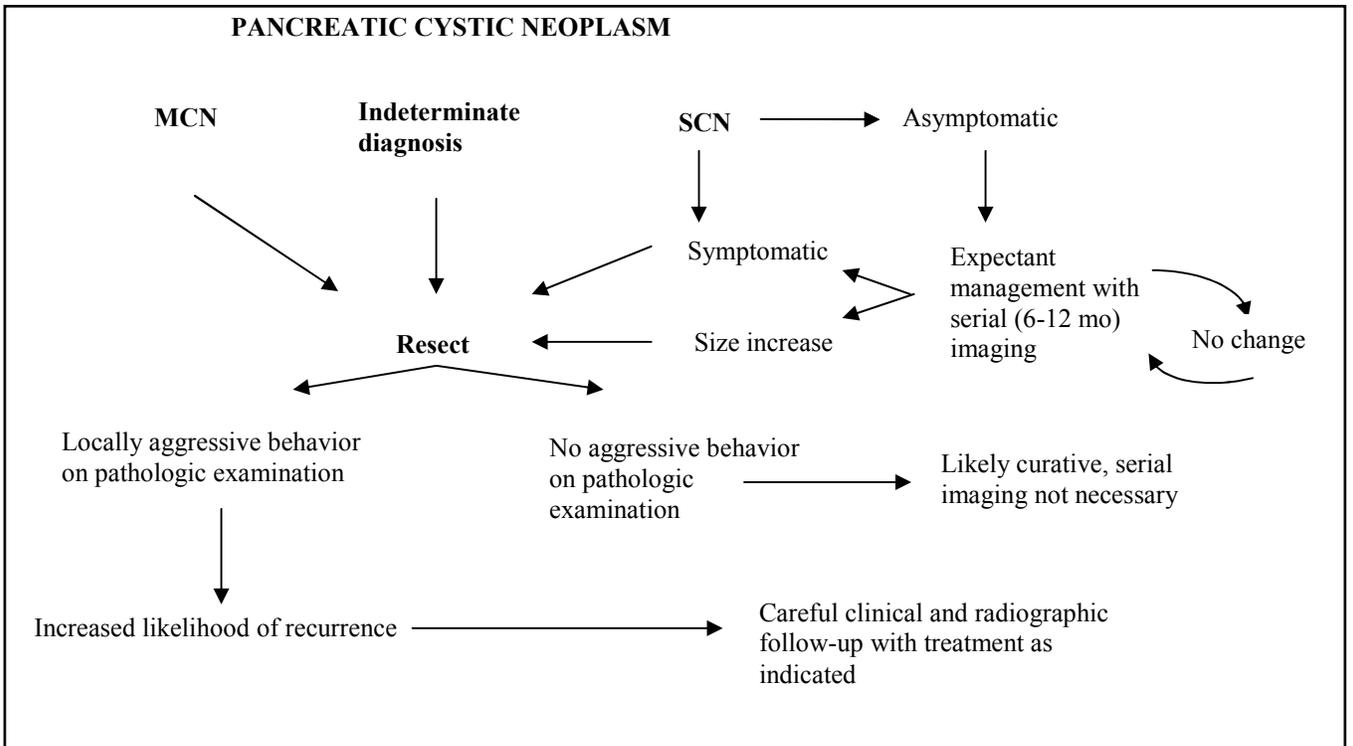
FIGURE 1

a

Pancreatic duct

Compressed duct

b

FIGURE 2

FIGURE 3