

Cystic Pancreatic Neoplasms: A Review

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Introduction:

When most of us think of cystic lesions of the pancreas, pancreatic pseudocyst is likely the first entity to come to mind. However, as the use of abdominal imaging has increased so has the detection of incidental cystic pancreatic lesions which, in the asymptomatic patient, may represent a cystic pancreatic neoplasm. These cystic pancreatic neoplasms represent around 5-15% of pancreatic cystic lesions, and less than 10% of pancreatic neoplasms⁽¹⁾, however, they are becoming more and more clinically relevant as the frequency of their diagnosis increases. At Massachusetts General Hospital, for example, the proportion of pancreatic resections performed for cystic pancreatic neoplasms increased from 16 to 30% during the 1990s⁽¹⁾.

The cystic pancreatic neoplasms are composed of a somewhat diverse group of tumors which include: solid and pseudopapillary neoplasms, serous cystadenoma, mucinous cystic neoplasms, and intraductal papillary mucinous neoplasms. Other entities in the differential diagnosis of cystic pancreatic masses include: pseudocyst, cystic neuroendocrine tumor, cystic islet cell tumor, lymphatic cyst, cystic teratoma, ductal adenocarcinoma with cystic degeneration, acinar-cell cystadenocarcinoma, and pancreatic sarcoma^(1,9,17).

Solid and Pseudopapillary Neoplasm:

Solid and pseudopapillary neoplasms of the pancreas are the least commonly identified of the cystic pancreatic neoplasms, accounting for less than 10% of cystic pancreatic neoplasms⁽¹⁾ and around 1% of all exocrine pancreatic tumors⁽⁸⁾. They were initially named Frantz's tumor as they were first described in 1959 by V.K. Frantz^(5,8). They have also been referred to in the literature as papillary cystic tumor of the pancreas, papillary epithelial neoplasm, solid and cystic tumor, low-grade papillary tumor, and papillary cystic neoplasm^(8,21).

Solid and pseudopapillary neoplasms occur mostly in young women, with 90% occurring in women in their second to fourth decades of life⁽³⁾. Some studies suggest that they are more prevalent in Asian and Black women^(5,8). Patients often present with vague complaints of abdominal pain or fullness, and mass effect can cause symptoms such as early satiety and nausea⁽⁵⁾. Frequently, patients are asymptomatic and the neoplasms are discovered incidentally as a mass on physical examination of the abdomen, or an abdominal imaging study such as ultrasound, CT, or MRI^(5,8). They are discovered throughout the pancreas, and occasionally are found in an extrapancreatic location connected to the pancreas by a stalk⁽⁸⁾. They are notable for their low-grade malignant potential^(1,5,8,21), but can be locally aggressive, invading nearby structures^(8,21). In one series of 21 patients with solid and pseudopapillary neoplasm, 13 of the 21 patients were found to have locally aggressive tumors with invasion of the surrounding tissues⁽⁸⁾. Furthermore, 10-15% of these tumors may demonstrate metastatic spread, most commonly to the liver or peritoneum with very rare lymph node involvement⁽⁵⁾.

On CT imaging, the solid and pseudopapillary tumor has been described as a “round, encapsulated mass, characterized by the coexistence of both solid and fluid areas in different proportions. Possible calcifications”⁽¹⁵⁾. On imaging, the presence of intratumoral hemorrhage acts as an important clue to diagnosis as this is rarely found in other pancreatic neoplasms⁽⁵⁾. If aspiration of cystic fluid is performed, the aspirate is likely to demonstrate necrotic debris, with fluid containing papillary structures, and bland cells with round nuclei which may contain PAS positive globules. Myxoid stromal balls and macrophages may also be visible in cystic fluid⁽¹⁾.



Fig 4. 16 year-old girl who presented with mid epigastric pain and was found to have a solid and pseudopapillary tumor. CT scan shows a complex mass (arrow) in the head of the pancreas. (American Journal of Radiology 2001; 176: 921-929)

The cellular origin of solid and pseudopapillary pancreatic neoplasm remains controversial. There is still much debate on the pathogenesis, with some researchers attributing the tumors to endocrine cells and others believing that they arise from ductal or acinar cells^(3,8). One recent study that attempted to answer this question was the study by Geers et al. in 2006⁽⁸⁾. In this study, the researchers postulate a ductal origin of the solid and pseudopapillary pancreatic neoplasm based on the expression of the protein galectin-3 in both normal pancreatic ductal cells and the cells of solid and pseudopapillary pancreatic neoplasm, but not in normal pancreatic endocrine or acinar cells⁽⁸⁾.

Because of their propensity for young women of reproductive age, the role of sex hormones in the development of these tumors has been explored. Multiple studies have demonstrated the presence of progesterone receptors using immunohistochemical testing (77 of 95 cases tested for progesterone receptors were positive (81%))⁽⁸⁾. However, the role of estrogen receptors is less clear. Multiple studies of the alpha subtype of the estrogen receptor have been negative; however, one study by Geers et al, examined the presence of both the alpha and beta subtypes and demonstrated that in the five cases they examined, none were positive for the alpha subtype, but all were strongly positive for the beta subtype of the estrogen receptor⁽⁸⁾. The beta subtype of the estrogen receptor has been previously studied in both prostate and breast cancer, and its presence has been associated with favorable prognosis in these cancers. Studies in breast, ovarian, and colon cancer have also shown lower levels of the beta subtype in cancerous tissue when compared to benign tissue of the same type. This suggests that the beta subtype of the estrogen receptor may be “associated with nonproliferative states of the disease and thus could play a negative role on tumorigenesis”⁽⁸⁾. Therefore, the presence of the beta

subtype of the estrogen receptor may contribute to the relatively benign nature of solid and pseudopapillary neoplasms, though more research into this topic and into the roles of sex hormones on the development of solid and pseudopapillary neoplasms is needed.

Because of their locally invasive nature and their propensity for achieving a large size which may cause mass effects on nearby structures, most experts recommend removal of solid and pseudopapillary neoplasms if surgically possible^(5,8,21). Despite the fact that they are often large at the time of diagnosis⁽⁸⁾, they are associated with rates of surgical cure greater than 95% when confined to the pancreas at the time of diagnosis⁽⁵⁾. Local invasion, recurrence, and limited metastases should not be viewed as contraindications to resection, and complete removal of metastatic disease to the liver is often surgically possible⁽⁵⁾. Even when complete resection of metastatic disease is not possible, surgical debulking is recommended and the patients are often alive several years into follow up⁽⁵⁾.

Serous Cystadenoma:

Serous cystadenoma is, depending on the series, either the most common or second most common of the cystic pancreatic neoplasms^(21,25). They are most frequently diagnosed in middle-aged women around the 7th decade of life^(1, 21,25). In one series of 106 patients with the diagnosis of serous cystadenoma at Massachusetts General Hospital between 1976 and 2004, the mean age at presentation was 61 years, and 75% were female⁽²⁵⁾. Serous Cystadenomas are known for their characteristic honeycomb-like microcystic structure and their extremely low malignant potential^(1,25). In the Massachusetts General Hospital series noted above, the most common presenting symptoms were abdominal pain (25%), mass or fullness (10%), jaundice (7%), and fatigue/malaise (6%). However, 47% of the patients were asymptomatic with masses discovered during the workup of an unrelated problem⁽²⁵⁾.

Historically, serous cystadenomas have also been known in the literature as microcystic adenomas, and glycogen-rich cystadenomas⁽²⁾ and it was only in 1978 that Oertel and Compagno developed the classification system based on histologic and morphologic features that differentiated the serous cystadenoma from the mucinous cystic neoplasm⁽¹⁷⁾. This differentiation is extremely important in management, as serous cystadenomas are almost universally benign, with very few case reports of serous cystadenocarcinoma in the literature, while the mucinous cystic neoplasms are considered to be malignant or at the least to have malignant potential^(2,17,25).

Serous cystadenomas are typically surrounded by a thin, fibrous pseudocapsule which separates the tumor from the normal surrounding pancreatic tissue⁽²⁾. On gross examination the margin appears lobulated and the interior is composed of a honeycomb-like, or spongy network of multiple small cysts ranging in size from microscopic to generally less than 2cm in size⁽²⁾. There may be prominent fibrous bands which in some cases form the central scar described on radiographic imaging⁽²⁾. On Histologic examination, the cysts are lined by a simple cuboidal epithelium which is rich in glycogen^(1,2,6). The cellular cytoplasm is clear to eosinophilic, and the nuclei are usually small, centrally located, hyperchromatic, and with a notable absence of mitotic forms^(10, 25). Analysis of cystic fluid reveals a thin, clear, non-mucinous fluid. Cuboidal epithelial

cells as described above may be found in the fluid, and stain PAS positive^(1,2). Tumor markers such as carcinoembryonic antigen (CEA) and amylase levels are generally low⁽¹⁾. Interestingly, there has been some association made between serous cystadenoma and von Hippel-Lindeau disease based on findings of chromosomal alterations of the von Hippel-Lindeau gene on chromosome 3p25⁽¹⁾ in some serous cystadenomas. This was supported by a study of 158 patients with von Hippel-Lindeau, which found that 9% of these patients were diagnosed with a serous cystadenoma⁽²¹⁾. Frequently in patients with von Hippel-Lindeau, the entire pancreas is involved⁽¹⁷⁾.

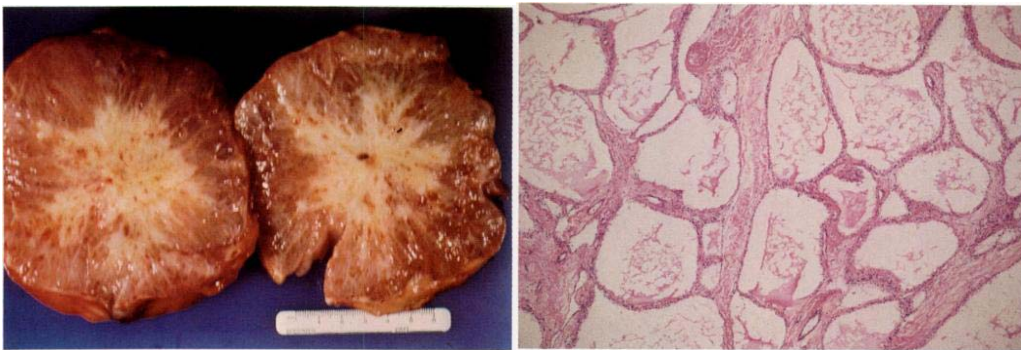


Fig 1a. gross specimen of microcystic adenoma showing a central stellate fibrotic scar and numerous very small, barely visible cysts. b. Histologic sample of a microcystic adenoma showing cysts lined by flat epithelium and filled with proteinaceous fluid. (Radiology 1983; 149: 45-50)

On CT or MRI imaging, the serous cystadenoma is typically seen as a multilobular mass with a microcystic structure often described as honeycomb-like^(1,17). This structure typically consists of at least six tiny cysts that are 2 cm or smaller⁽¹³⁾. Serous cystadenomas are generally well demarcated from the surrounding normal pancreatic tissue⁽²⁾. In about 20% of cases, a central scar, which may be calcified, is present and is highly diagnostic⁽¹⁾. Solid and macrocystic/oligocystic variants have also been described, which are frequently misdiagnosed on imaging studies as mucinous cystic neoplasms^(1,13), and which have led some to divide the serous cystadenomas into microcystic and macrocystic variants in their classification schemes^(17,29). In the series from Massachusetts General, 6 of 86 patients (7%) who underwent surgical resection were found to have macrocystic or oligocystic variants⁽²⁵⁾. Serous cystadenomas are distributed throughout the pancreas with no clear predilection for one specific location. In fact, some series show a slight predominance of lesions in the head and neck while others show a propensity for the body or tail of the pancreas^(2, 21, 25).

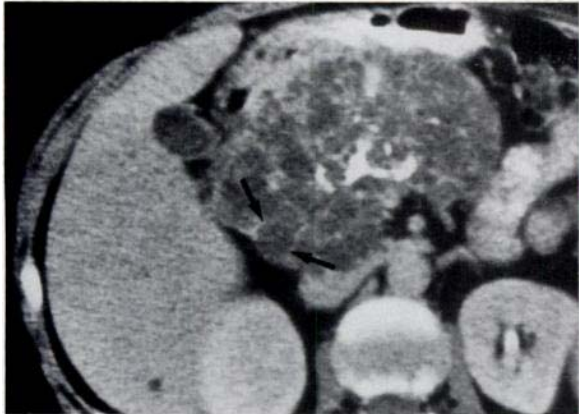


Figure 2. 66-year-old asymptomatic woman with abdominal mass was found during routine physical examination. CT scan demonstrates a large, well-defined mass in the pancreatic head with honeycombed pattern (arrows) due to fibrous septa, and a calcified central scar. This appearance is classic for a serous cystadenoma. (RadioGraphics 1990; 10: 313-322)

Current recommendations for treatment of serous cystadenomas are based on the size of the lesion and the presence of symptoms. Because of their extremely low potential for malignant degeneration, small, asymptomatic, slow-growing lesions may be observed⁽²¹⁾. However, if the mass is symptomatic or rapidly enlarging it should be resected if possible⁽²¹⁾. In the series from Massachusetts General, 24 patients underwent serial radiography allowing for the analysis of tumor growth rates. The median growth rate was 0.6 cm per year; however, the researchers found that a difference in growth rate existed based on the size of the mass at first presentation⁽²⁵⁾. If the tumor was less than 4 cm at presentation, the growth rate was 0.12 cm per year, whereas if the tumor was greater than or equal to 4cm at the time of presentation, the growth rate was 1.98 cm per year⁽²⁵⁾. This led to a doubling time of 2.84 years for tumors less than 4 cm and 0.64 years for tumors greater than or equal to 4cm in diameter⁽²⁵⁾.

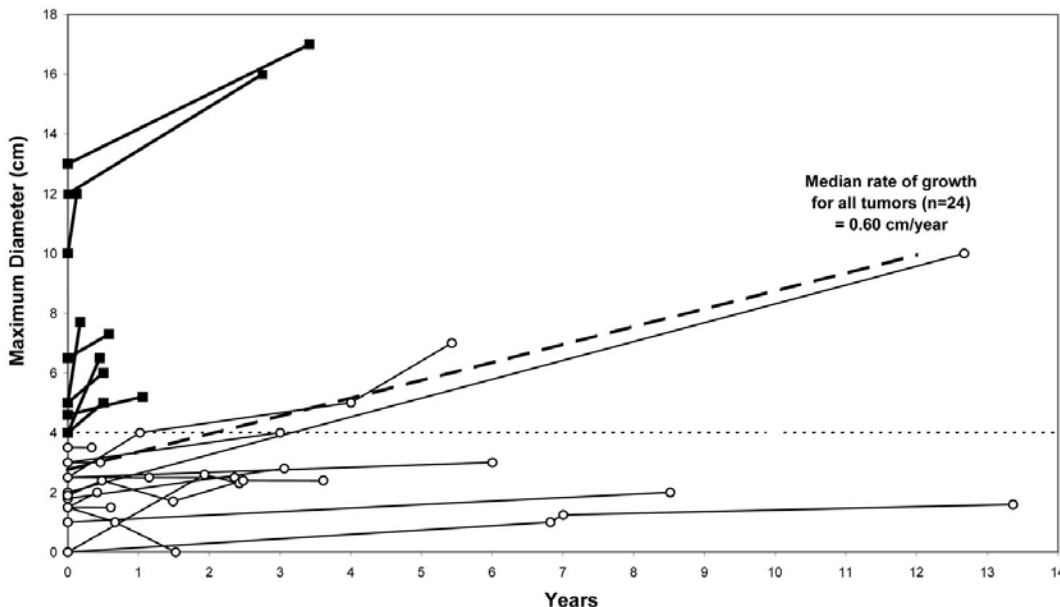


Fig 3. Serous cystadenoma growth rates over time. Open circles represent tumors less than 4 cm at presentation, solid squares tumors greater than or equal to 4 cm. (Annals of Surgery 2005; 242: 413-420)

Mucinous Cystic Neoplasm:

As discussed above with the serous cystadenomas, it was not until 1978 that mucinous pancreatic neoplasms were differentiated from serous cystadenomas. More recently, the mucinous pancreatic tumors have been divided into two groups: the mucinous cystic neoplasm and the intraductal papillary mucinous neoplasm⁽⁹⁾. The mucinous cystic neoplasm is differentiated from the intraductal papillary mucinous neoplasm by its lack of communication with the pancreatic ductal system and its characteristic stroma of ovarian-like tissue^(9,29). Mucinous cystic neoplasms are generally considered the most common of the cystic pancreatic neoplasms, and are found most commonly in middle-aged women⁽²¹⁾. In one series of 56 patients with mucinous cystic neoplasm all were women⁽²⁹⁾, while in a second series 70 of 84 patients (80%) were women⁽¹⁸⁾. They also show a predilection for the body and tail of the pancreas, with one series of 56 mucinous cystic neoplasms demonstrating 93% of tumors in the body or tail⁽²⁹⁾.

On imaging studies, mucinous cystic neoplasms are usually unilocular, or multilocular. Cysts are typically greater than 2cm in diameter and less than 6 in number, in contrast to the serous cystadenomas, which are typically composed of at least 6 smaller cysts^(1,9). Mucinous cystic neoplasms can also be characterized by the presence of an eggshell-like calcification around the periphery that is highly predictive of malignancy⁽¹⁾.

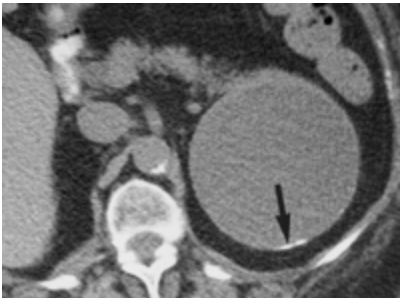


Figure 5- Incidental mass found on lumbar spine MRI of an 80-year-old woman with low back pain. A large, unilocular mass in the pancreatic tail can be seen on this CT scan. Note calcification in the wall at the site of the arrow. (American Journal of Radiology 2001; 176: 921-929)

Other features of the mucinous cystic neoplasm that may help distinguish it from a serous cystadenoma include the presence of mucin and high levels of tumor markers CEA, CA 72-4 and CA15-3 in the cystic fluid, which are usually low in serous cystadenomas⁽¹⁾. The use of tumor markers is somewhat controversial, however, with little agreement in the literature as to the sensitivity and specificity of the various tumor markers and which of these tumor markers should be used either alone or in combination. One study sites CA 72-4 as having a sensitivity of 80% and a specificity of 95% when a value of greater than 4 units/mL is used as a cutoff for the detection of malignancy⁽⁹⁾. However, another review article summarizes a second study of 341 patients that demonstrates that a level of CEA of 192 ng/ml was most accurate for differentiating mucinous versus non-mucinous lesions with a sensitivity of 73% and specificity 84%, and that no other test or combination of tests provided greater accuracy⁽²¹⁾.

Mucinous cystic neoplasms are divided into three pathological classifications based on a classification scheme developed by the World Health Organization. This includes adenomas (benign), borderline tumors (low-grade malignant), and non-invasive and invasive carcinoma^(1,29). The adenomatous tumors demonstrate columnar epithelium with only mild dysplasia, mildly enlarged, basally located nuclei, and no evidence of mitosis (Figure 6). Borderline tumors demonstrated crowded, pseudostratified epithelium with moderate dysplasia, which may be only focal, but which shows increasingly irregular nuclei with occasional mitosis (Figure 7). Carcinomatous changes included multilayered epithelium forming papillary projections with high grade dysplasia, severe nuclear atypia and frequently observed mitosis (Figure 8). These carcinomas are further characterized into invasive versus non-invasive, or carcinoma-in-situ, by the presence or absence of malignant tissue beyond the cyst lining⁽²⁹⁾. There are also often differences between the three classifications on gross examination. In the above mentioned series of 56 mucinous cystic neoplasms, most of the adenomatous tumors examined were unilocular, while nearly all of the carcinomas examined were multilocular with frequent papillary projections and mural nodules⁽²⁹⁾. In fact, in this series, the presence of papillary projections and mural nodules strongly correlated with the diagnosis of carcinoma as 75% of the carcinomatous tumors had papillary projections and mural nodules whereas none of the adenomatous or borderline tumors examined exhibited these features⁽²⁹⁾.

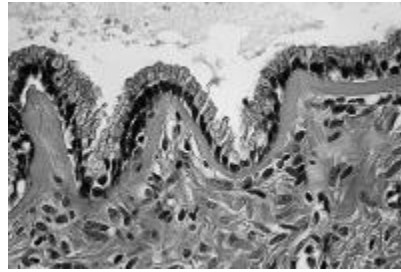


Figure 6. (Annals of Surgery 2000; 231: 205-212)

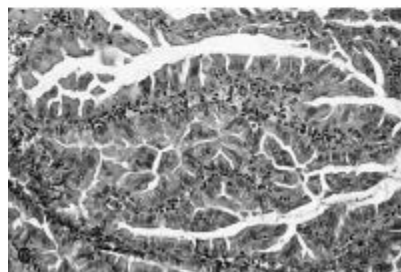
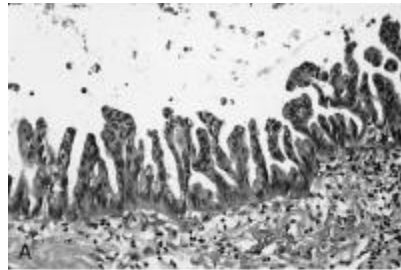


Figure 7 (Annals of Surgery 2000; 231: 205-212)

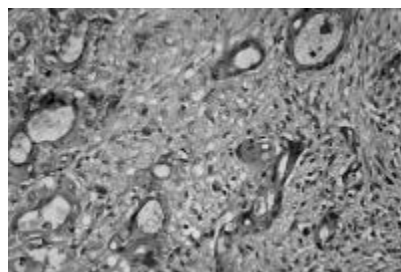


Figure 8 (Annals of Surgery 2000; 231: 205-212)

When the behavior of mucinous cystic neoplasms of the pancreas is compared to the behavior of other mucinous neoplasms including those in the ovary, liver, and retroperitoneum, there is a tremendous amount of similarity suggesting a similar cellular origin and pathway for tumor development⁽²⁹⁾. The similarities begin with the fact that mucinous cystic tumors are almost exclusively limited to women as we have discussed, which is similar to the mucinous tumors found in the liver and retroperitoneum. They also demonstrate the same type of cellular differentiation found in ovarian and retroperitoneal mucinous tumors, with their epithelium composed of gastroenteropancreatic cells, and their intraepithelial endocrine cells staining for similar hormones in similar proportions. The ovarian-like stroma of the pancreatic mucinous cystic tumors also demonstrates similar protein staining patterns to the stromal cells found in pancreatic, hepatobiliary and retroperitoneal mucinous tumors⁽²⁹⁾. Part of this staining pattern includes high proportions of staining for estrogen and progesterone receptors as was also noted in the solid and pseudopapillary neoplasms discussed above⁽²⁹⁾. Zambini et al hypothesize that the relationship of the pancreatic, hepatobiliary, retroperitoneal, and ovarian mucinous cystic tumors may stem from their embryonic origins. They note that during the 4th to 5th weeks of development, the left primordial gonad and the dorsal pancreatic anlage, which becomes the pancreatic body and tail are found directly next to each other. Therefore, they believe it is theoretically possible that because of their close proximity, primordial ovarian cells could become incorporated into the pancreas, which would explain why these tumors show a predilection for the pancreatic body and tail. They then theorize that these islands of ectopic ovarian stroma may release hormones and growth factors which cause the development of the mucinous cystic pancreatic neoplasm⁽²⁹⁾.

Because of their high potential for malignancy, experts currently recommend resection for all mucinous cystic neoplasms^(1,18,21). Research indicates that there is an adenoma to carcinoma progression as suggested by the fact that multiple series have documented that patients found to have carcinoma are an average of 10 years older than those found to have adenomatous disease^(18,29). One such series is that of Sarr et al, which demonstrated the mean age of patients diagnosed with a mucinous adenoma to be 48 years and the mean age of those with invasive carcinoma 64 years⁽¹⁸⁾. If complete resection is possible and there is no evidence of invasion, the prognosis is excellent with five year survival near 100%⁽¹⁾. In the series of 56 cases analyzed by Zamboni et al, there were no deaths attributable to the disease in those diagnosed with adenomatous or borderline pathology. Of the 6 patients diagnosed with non-invasive carcinoma, all were alive with no signs of recurrence at a median follow up time of 76 months. However, 8 of the 16 patients with invasive carcinoma died between 2 and 45 (median 11) months post definitive diagnosis⁽²⁹⁾. Similarly, other series have demonstrated a 5 year survival rate of less than 20% for those with invasive carcinoma^(9,18).

Intraductal Papillary Mucinous Neoplasm:

Like the mucinous cystic neoplasm, the Intraductal Papillary Mucinous Neoplasm (IPMN) is known for its mucin-producing epithelial cells. IPMN differs from mucinous cystic neoplasm in that it communicates with the pancreatic ductal system^(1,20). This differentiation was only recognized around 1982 when a series of 4 cases of IPMN were described by Ohashi et al. and termed mucinous ductal ectasia^(11,20,26). They are also referred to in the literature as mucinous pancreatic tumors, mucin producing carcinoma, mucin hypersecreting carcinoma, intraductal papillary hyperplasia, villous adenoma of the pancreatic duct, and intraductal mucin producing tumors^(11,20,26).

Unlike the other cystic pancreatic neoplasms, IPMN is more commonly seen in men in their 60s and 70s⁽²⁰⁾. Like the other cystic neoplasms, many are detected incidentally. However, when symptoms are present they may include back pain, jaundice, weight loss, anorexia, steatorrhea, diabetes, and often symptoms of recurrent episodes of pancreatitis secondary to mucin from the tumor intermittently obstructing the pancreatic ducts⁽²⁰⁾. Some series suggest that as many as half of cases may be associated with a history of recurrent pancreatitis and diabetes⁽¹¹⁾.

IPMN is considered a precancerous lesion with a progression from adenoma to carcinoma. Most evidence seems to indicate, however, that this progression occurs at a slow rate over 15 to 20 years⁽²⁰⁾. IPMNs have been divided into two classifications based on their location within the pancreatic ductal system: main duct and branch duct type. Main duct type generally begin in the pancreatic head and extend distally, and may or may not involve side branches. They are generally considered to be more aggressive than the branch duct type^(20,26). Branch duct type are confined to a branch duct without evidence of involvement of the main pancreatic duct. They are often found in the uncinate process and head, but can also be found in the body or tail of the pancreas⁽¹²⁾. Branch duct type are generally less aggressive with a lower malignant potential^(1,20). Some of the literature divides this classification into three types with the third type being a combined type with involvement of both the main pancreatic duct and a side branch^(12,23).

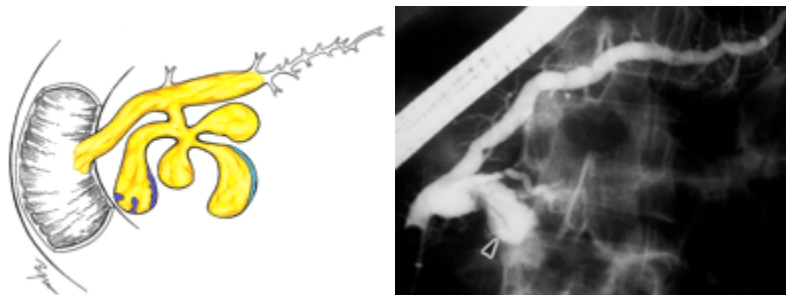


Fig 9 a. Schematic drawing of a side branch IPMN showing a distended side branch system in the uncinate process. Note mucus can spill over and enlarge the adjacent main pancreatic duct, and the papillary orifice gapes with extruding mucus. b. ERCP showing side branch IPMN in a 38 year-old man presenting with recurrent bouts of epigastric abdominal pain. The abnormally dilated side branch can be readily seen at the arrow. (American Journal of Radiology 2001; 176: 921-929)

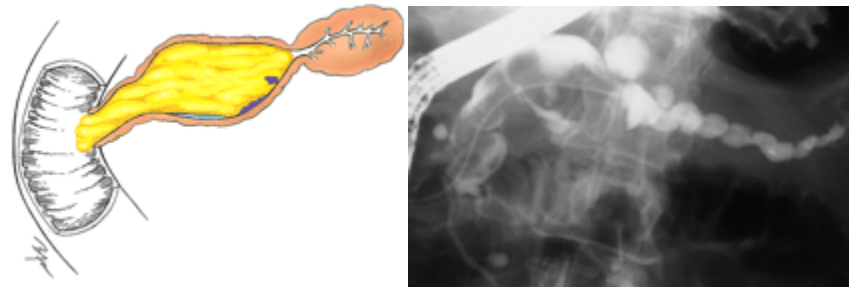


Fig 10a- Schematic of main ductal type IPMN which illustrates a marked dilation of the main pancreatic duct and atrophy of the pancreatic parenchyma. b. ERCP demonstrating the main pancreatic duct of a 66-year-old renal transplant patient with abdominal pain and diabetes. This image shows a massively dilated main pancreatic duct with diffuse filling defects (American Journal of Radiology 2001; 176: 921-929).

Histologically, IPMNs have a mucin-producing columnar epithelium with the same classification scheme as the mucinous cystic neoplasms: adenoma, borderline, and carcinoma with or without invasion⁽²⁰⁾. Additional classification is also based on the structure the epithelial lining takes. IPMNs may form either ductal mucin hypersecreting variant where the ductal lining is flat but the duct is dilated with mucin, or papillary villous variant where the epithelial cells form papillary structures which project into the duct and can be seen as filling defects on MRCP, ERCP, or endoscopic ultrasound⁽²⁰⁾. Analysis of cystic fluid yields results similar to that of mucinous cystic neoplasm with mucin rich fluid and columnar epithelial cells⁽¹⁾. The fluid is also likely to contain elevated levels of CEA and CA 72-4 as is seen in the mucinous cystic neoplasms⁽¹⁾.

On CT and MRI imaging, side branch IPMNs are usually visualized as mass of 1-2 cm cysts, while main duct IPMNs usually appear as a “diffusely and markedly dilated main pancreatic duct with only a thin remnant of pancreatic parenchyma⁽⁹⁾.”



Fig 11a. -Side branch IPMN in 46-year-old man with abdominal pain and pancreatitis. CT through pancreatic head shows numerous small cysts (arrow) b. CT scan 10 mm caudad to a shows cyst is actually composed of dilated main pancreatic duct (d) and enlarged uncinete side branch (b), which forms curvilinear tube. (American Journal of Radiology 2001; 176: 921-929)

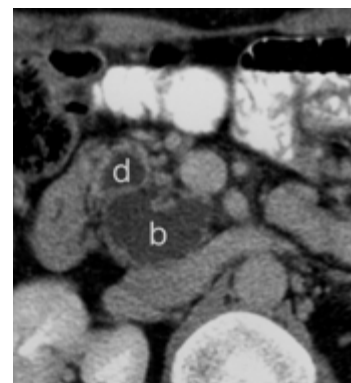




Fig 12. Main duct IPMN in 66-year-old male renal transplant patient with abdominal pain and recent onset of diabetes. Unenhanced CT scan through pancreatic body shows diffusely dilated main pancreatic duct (*arrows*) with severe parenchymal atrophy. (note this is the same patient in figure 10b above) (American Journal of Radiology 2001; 176: 921-929)

MRCP and ERCP are often used when an IPMN is suspected, as they can more adequately evaluate the possibility of communication with the ductal system and the extent of involvement of the ductal system^(1,12,20). Furthermore, on ERCP, the appearance of mucin being extruded from a widely patent or “fish-mouthed” ampulla is pathognomonic for IPMN^(1,21,26). One study by Fukukura et al found that communication between a cystic lesion and the pancreatic ductal system was visualized in 80.8% of cases of IPMN with ERCP, 55.7% with MRCP, 53.8% with CT, and 42.3% with MR imaging⁽¹²⁾. Often on MRCP/ERCP a definable mass projecting into the ductal system cannot be visualized, and in fact, some studies indicate that when this finding is present there is a markedly increased chance that the lesion contains areas of malignancy⁽⁹⁾. Some studies have also indicated that the presence of a mural nodule and dilation of the pancreatic duct to greater than 10-15mm in diameter strongly correlate with the development of carcinoma in IPMN^(1,9,12,23).

Like the other cystic pancreatic neoplasms, treatment of IPMN is surgical. However, surgical treatment for IPMN can be more complicated than that of the other cystic pancreatic neoplasms because of the extensive involvement of the pancreatic duct typically seen in IPMN. Some literature indicates that almost 20% of patients with IPMN who undergo surgical resection require a total pancreatectomy because of widespread involvement of the ductal system⁽¹⁾. Because of their likelihood of recurrence without clean surgical margins and considering their malignant potential, most of the surgical literature indicates that it is imperative to examine frozen sections during surgery to obtain clean margins^(1,20,26).

Prognosis varies greatly based on the stage and type of the IPMN at the time of resection. In patients with invasive cancer and positive surgical margins, the 3 year survival is about 20%, whereas it is upwards of 80% in patients with early stage branch duct type carcinoma⁽²⁰⁾. In a series of 80 resections for IPMN at Massachusetts General Hospital from 1990 to 2002, 17 patients had died by 2003, 16 of those had invasive carcinoma and 1 had carcinoma in situ at the time of their resection. The patients who had adenomatous or borderline disease were all alive at the time of follow up⁽²⁶⁾. Also of interest, 65% of the 80 patients in that series had at least carcinoma in situ at the time of resection, with more than half of those 65% having invasive carcinoma⁽²⁶⁾. Other studies have shown rates of carcinoma in situ ranging from 7-34% and invasive carcinoma ranging from 25-44% in surgical specimens⁽¹²⁾.

One study out of Japan noted the importance of the type (branch vs. main ductal) in prognosis. In this study of 120 cases of IPMN, 64% of the main duct type tumors resected were malignant as compared to only 19.5% of the branch duct type⁽¹⁹⁾. Furthermore, in those patients who did not undergo surgical resection all patients with main duct type showed progression and eventually died as a result of their disease⁽¹⁹⁾.

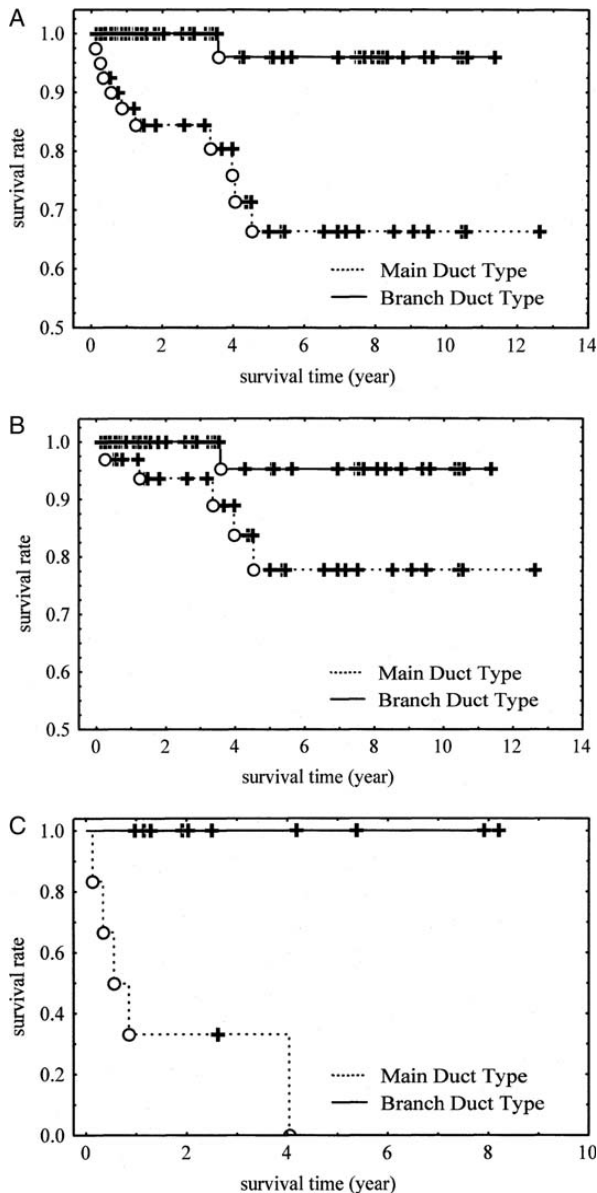


FIGURE 13. Cumulative survival rate in IPMN based on morphologic diagnosis.

A. Kaplan-Meier curves examining the cumulative survival rate in all patients with IPMN. The prognosis in patients with main duct type was significantly worse than in patients with branch duct type ($P = 0.0012$).

B. Analysis of surgical patients. All but one of the branch duct type surgical patients survived, for a survival rate of 96% while the main duct patients had a survival rate of 78% ($P = 0.0871$).

C. Analysis of nonsurgical patients. All nonsurgical branch duct type patients survived without evidence of disease progression, while all the nonsurgical main duct type patients died due to progression of pancreatic disease ($P = 0.00077$).

The symbols in the figure designate either complete (O) or incomplete cases (+). (Journal Clinical Gastroenterology; 40: 856-862)

Because of the significant morbidity that can be associated with pancreatic surgery, especially when total pancreatectomy is required as is the case in 20% of IPMNs⁽¹⁾, much research has focused on attempts to determine which of these tumors are benign and which are malignant. As discussed above, main branch type appear much more likely to be malignant and consensus is that they should be resected if possible. However, there are some who advocate non-invasive follow up for branch duct type that appear benign^(12,19). With this concept in mind, many studies have attempted to determine criteria for malignancy that can be seen using either radiologic or endoscopic imaging. Serikawa et al demonstrated in their study with 56 cases of branch duct type IPMN that the presence of a mural nodule and main duct dilation were significantly more common in malignant than benign lesions⁽¹⁹⁾. With this information they propose that a main duct diameter greater than or equal to 6 mm or a mural nodule diameter greater than or equal to 3 mm are reasonable criteria for the diagnosis of malignancy⁽¹⁹⁾. Unfortunately, review of these criteria in the literature reveals that different studies have all come up with different cutoffs for malignancy including a main duct size greater than 6,7,8,10, and 15mm in 5 different studies⁽¹²⁾. The study by Kawamoto et al looked at the sensitivity and specificity of 3 separate cutoffs for main pancreatic duct dilation finding that for a threshold of 6mm the sensitivity was 73% and specificity 81%, for 10mm 33% and 86% respectively, and for 15mm 20% and 95% respectively⁽¹²⁾. There have also been inconsistent reports in the literature looking at the presence and size of mural nodules, overall tumor size, the presence of calcification, the presence of diabetes, and the presence of common bile duct dilation and jaundice as predictive factors for malignancy⁽¹²⁾. Though again, no consensus on these issues has been reached and the question remains weather there is any reliable way to predict the presence or absence of malignancy preoperatively.

Diagnostic Challenges

Much of the recent research on the topic of cystic pancreatic neoplasms focuses on the preoperative differentiation of the various cystic neoplasms from each other and other cystic pancreatic lesions, and in differentiating benign from malignant lesions in those that have malignant potential. One of the most telling studies regarding the accuracy of CT in differentiating cystic pancreatic neoplasms was done by Procacci et al. This study retrospectively examined 100 cystic masses of the pancreas and found that CT findings could correctly identify the type of mass in only 60% of the cases⁽¹⁶⁾. It should be noted that this study was from 1999, so during the time that has elapsed since then better scanning devices and increased recognition of cystic pancreatic neoplasms may have increased diagnostic accuracy; however, this study continues to serve as an example of the difficulties in obtaining an accurate pre-operative diagnosis.

Studies have also been conducted with ERCP to attempt to differentiate benign from malignant lesions. One retrospective study by Gazelle et al found that obstruction of the pancreatic duct was virtually diagnostic of malignancy. However, the authors could not identify any specific finding or combination of findings that could reliably predict benign disease⁽⁷⁾.

Because of the inability of imaging studies alone to identify possibly malignant lesions, researchers have looked for additional testing, which, when combined with radiographic or endoscopic findings, may increase the accuracy of diagnosis. Serum tumor markers including CA 19-9 and CEA have been examined for their ability to distinguish benign from malignant lesions. One study by Kimura et al reported that CEA and CA 19-9 both had a good specificity (91 and 82% respectively) but a poor sensitivity of 27 and 48% respectively⁽¹⁴⁾. In a small observational study by Yamada et al, 4 patients with branch type IPMN were followed. They all initially had normal levels of CA 19-9, but 3 of 4 eventually demonstrated an increase in their levels to greater than normal, which corresponded with the development of a solid mass on CT which was histologically shown to be adenocarcinoma infiltrating into the pancreatic parenchyma⁽²⁹⁾. This observation led the authors to a conclusion that elevation of a previously normal CA 19-9 is likely an indicator of progression to invasive carcinoma⁽²⁸⁾.

Cystic fluid analysis can also be used to aid in diagnosis, though this area also remains fraught with controversy. Cystic fluid is often obtained by biopsy during endoscopic ultrasound, but is also sometimes obtained percutaneously⁽²⁷⁾. Some researchers suggest that CA 72-4 may provide a reasonable screen for malignancy. This marker tends to be elevated in the mucinous cystic neoplasms and IPMNs and in a study by Sperti et al. showed a sensitivity of 80% and a specificity of 95% for underlying malignancy at a level greater than 4u/mL^(1,9). However, a second study that examined CA 72-4 in addition to CEA, CA 19-9, CA 15-3, and CA 125 demonstrated that CEA at a cutoff of 192ng/ml provided the most accuracy for differentiating mucinous from non-mucinous lesions with a sensitivity of 73% and a specificity of 84%, and that no marker or combination of markers provided greater diagnostic accuracy than CEA alone⁽²¹⁾. Furthermore, because the sensitivity and specificity found in this study were so low, it calls into question the usefulness of fluid tumor marker examination as it applies to individual patients⁽²¹⁾. A third study, the aforementioned by Kimura et al found a sensitivity of 57 and 69% for CEA and CA 19-9 respectively, with a specificity of 100% in the cystic fluid for both⁽¹⁴⁾. With the variation in results from just these three studies, it is easy to see why controversy over tumor marker screening remains.

In addition to looking at cystic fluid tumor markers, cytologic analysis of cystic fluid has also been proposed as a mechanism to differentiate between benign and malignant lesions. In this case the specificity has also proven to be high and when positive a diagnosis of malignancy is likely. However, the sensitivity has been shown to be around 50% making it impossible to use cystic fluid cytologic analysis to exclude malignancy^(9,19,21,27). In the Japanese study by Serikawa et.al, the sensitivity was even less at only 23.5% for branch duct type and 33.3% for main duct, while the specificity was 100% and 96.4% respectively⁽¹⁹⁾. The low sensitivity of cytologic analysis is often attributed to the fact that in mucinous cystic tumors, the tumor lining is often discontinuous with areas where it has been denuded⁽²⁹⁾. In IPMN this has been attributed to the fact that one lesion may have different areas with dramatically different degrees of atypia, so that even if an area of adenoma is sampled, a nearby area may contain carcinoma⁽¹²⁾.

Cystic fluid can also be analyzed for the presence or absence of other substances such as amylase. A high amylase level is highly suggestive of pseudocyst, and along with a history of pancreatitis can be helpful in differentiating pseudocyst from a cystic neoplasm ^(1,27). Cystic fluid can also be analyzed for the presence or absence of mucin, which may help to differentiate the potentially malignant mucinous cystic neoplasm and IPMN from the benign serous cystadenoma if mucin is present, but like many of the other tests described should not be used to rule out malignant potential if testing for mucin is negative ^(1,27). Small studies have also been conducted testing for telomerase activity and various gene mutation such as K-ras and p53 in cystic fluid, however, small study size and the lack of reproducibility of these results prevents their routine use ^(19,20).

Areas of Future Research:

From the discussion above regarding the diagnostic challenges in differentiating the cystic pancreatic neoplasms and determining their malignant potential, it is clear that the accurate preoperative diagnosis of cystic pancreatic lesions is an area that requires additional research. More research into the imaging techniques described above and additional modalities like PET scanning should be undertaken to help determine whether potentially malignant lesions like mucinous cystic tumor and IPMN contain any foci of malignancy. There must also be more research into alternate treatment modalities for patients who do not wish to undergo surgical resection, or for whom complete surgical resection is not possible. Treatments such as chemotherapy, either as a primary or adjuvant tool, estrogen and progesterone receptor modulators, and ethanol or radiofrequency ablation should undergo further research. Even the possibility of using agents like cyclooxygenase inhibitors to arrest the progression from adenoma to carcinoma in the mucinous cystic neoplasms and IPMNs warrant future research ⁽¹⁾.

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