Cystic Tumors of the Pancreas: High Malignant Potential

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ABSTRACT: **Background:** Cystic tumors of the pancreas are rare, accounting for 10% of pancreatic cysts and 1% of all pancreatic tumors; surgery is dictated by their malignant potential.

Objectives: To evaluate the malignancy rate of pancreatic cystic tumors and patient outcome, and to determine predictors for malignant potential.

Methods: We retrospectively reviewed the medical records of patients who underwent pancreatic resection for cystic tumors between January 1996 and December 2007.

Results: The charts showed that 116 patients were operated on for a pancreatic cystic tumor; most were women (63%). The chief complaint was abdominal pain (57%). Incidental detection occurred in 27%. Preoperative workup included ultrasound, tomography, endoscopic ultrasound and fine-needle aspiration biopsy. Indications for surgery were mucinous tumor, symptomatic or enlarging cyst under surveillance, high carcinoembryonic antigen levels within the cyst, and typical manifestations of intraductal papillary mucinous tumor (IPMT). All tumors but one were resectable. Whipple operation was performed in 40%, distal pancreatectomy in 55% and total pancreatectomy in 5%. Mucinous tumors were found in 40%, of which 37% were cystadenocarcinoma and/or borderline tumor. IPMT was found in 39%; 38% of them with cancer. Other pathologies included symptomatic serous cystadenomas, neuroendocrine cystic tumors and pseudopapillary tumors. The perioperative mortality rate was 2.6%. Five-year survival rates for patients with benign vs. invasive/borderline mucinous neoplasms was 90% vs. 59%, and for non-invasive vs. invasive IPMT 89% vs. 45% respectively.

Conclusions: Cystic tumors of the pancreas should be carefully evaluated. Surgery should be considered when a mucinous component is suspected due to the high rate of malignancy. Complete resection carries a high cure rate even in the presence of cancer.

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KEY WORDS: pancreatic cyst, cystic tumors, pancreatectomy, malignant potential, predictors

Primary cystic neoplasms of the pancreas are rare, accounting for only 10–15% of pancreatic cysts and 1% of all pancreatic tumors. In 1978 Compagno and Oertel [1,2] characterized the histopathological features of serous and mucinous cystic neoplasms. Since then, many groups have further refined the classification, diagnostic features, and management of these unusual neoplasms. Ohashi et al. [3] reported a new type of cystic neoplasm of the pancreas that is now known as intraductal papillary mucinous tumor. Subsequently, the World Health Organization and the Armed Forces Institute of Pathology clearly differentiated IPMT from mucinous cystic tumors [4,5]. IPMT is a newly recognized pathological definition rather than a "new" entity secondary to a new mutation or environmental exposure [6]. MCT, serous cystadenomas, and IPMT comprise more than 90% of primary cystic neoplasms of the pancreas. Cystic islet cell tumor, solid pseudopapillary tumor, and other pathologies with cystic appearance are less common. The last decade has witnessed a remarkable increase in the number of cystic tumors diagnosed; this is attributed, in part, to clinical awareness but mainly to advanced imaging technology.

The management of pancreatic cystic tumors is controversial. These tumors may be asymptomatic with an innocent appearance in imaging studies that might mislead the inexperienced clinician [7]. Many such lesions are diagnosed and followed by gastroenterologists and some by surgeons who often treat these patients with conservative watchfulness. Many clinicians still hesitate to refer patients with pancreatic cancer to surgery [8], contributing to the low rate of surgically treated pancreatic cysts.

Accurate diagnosis of these cystic lesions is important because of their malignant potential. Whereas MCT, IPMT and several rarer tumors are overtly or premalignant, serous cysts have a very low potential for malignancy and therefore may be observed [9]. MCT and IPMT share common characteristics and bear a better prognosis than pancreatic ductal carcinoma [10,11]. Both tumors have a high cure rate after surgical treatment; however, erroneous diagnosis can result in prolonged observation, missing the chance for cure in those cases that become unresectable or metastatic. The aims of this study are to further emphasize the role of timely surgery in the management of pancreatic cystic tumors, to identify preoperative predictive

IPMT = intraductal papillary mucinous tumor

MCT = mucinous cystic tumors

factors of malignancy, and to assess the long-term outcomes in a large patient cohort of a single institution serving as a referral center for pancreatic surgery in Israel.

PATIENTS AND METHODS

From January 1996 to December 2007, 116 pancreatic resections for cystic lesions were performed in our center. The medical records were evaluated following institutional review board approval. The clinical, imaging and pathological data of all patients were retrospectively reviewed. Tumors were categorized according to the WHO and AFIP classification [4,5]. IPMTs and MCTs were categorized according to their most severe degree of dysplasia as adenoma, borderline tumor (moderate or high-grade dysplasia) or invasive carcinoma. Preoperative clinicopathological features were evaluated, including gender, age, symptoms and signs, imaging findings, carcinoembryonic antigen and cancer antigen 19-9 levels in the serum and in the cystic fluid. Prior to surgery patients underwent imaging evaluation by ultrasound, computed tomography and endoscopic ultrasound; patients who had an endoscopic ultrasound also had a fine-needle aspiration or biopsy with cyst fluid aspiration. A biopsy usually gives more information. Operative findings that were evaluated included tumor location, tumor size, type of pancreatic resection and operating time.

The overall incidence and type of postoperative complications were recorded. Perioperative mortality was defined as in-hospital death after surgery and was also evaluated. Macroscopic appearance and histological findings were obtained from the pathology reports. We evaluated the tumor type, resection margins and tumoral malignancy. Resected lymph nodes were also evaluated for metastatic disease.

Follow-up clinical information was obtained by direct patient contact and outpatient clinic charts after obtaining informed consent. Follow-up time was also recorded by tumor type.

Survival analysis was performed by Kaplan and Meier methods [12]. Comparison between patient groups with regard to demographics and clinical factors was performed using the Mann-Whitney and chi-square tests as applicable. All values are expressed as mean ± SD for parametric and median for non-parametric variables. Statistical analysis was performed to identify preoperative predictors for malignancy. Categorical variables examined were weight loss, presence of jaundice, mucin within the cyst, and atypia. The continuous variables examined were tumor size, CEA and CA 19-9 levels within the cyst. The statistical significance level was set at 0.05 and the SPSS for windows software version 12.0 was used for the analysis.

WHO = World Health Organization
AFIP = Armed Forces Institute of Pathology
CEA = carcinoembryonic antigen
CA = cancer antigen

RESULTS

CLINICAL FEATURES

From January 1996 to December 2007 a total of 116 patients underwent surgery for primary cystic tumor of the pancreas: 74 women (63%) and 42 men (27%). There was a female predominance in all three main pathologies: MCT, SCT and IPMT, most prominent in the MCT group. Patients diagnosed with SCT were younger with a mean age of 52.8 ± 15.4 years, compared to 60.5 ± 14.9 years for MCT and 70.1± 11.1 years for IPMT patients ($P < 0.05$).

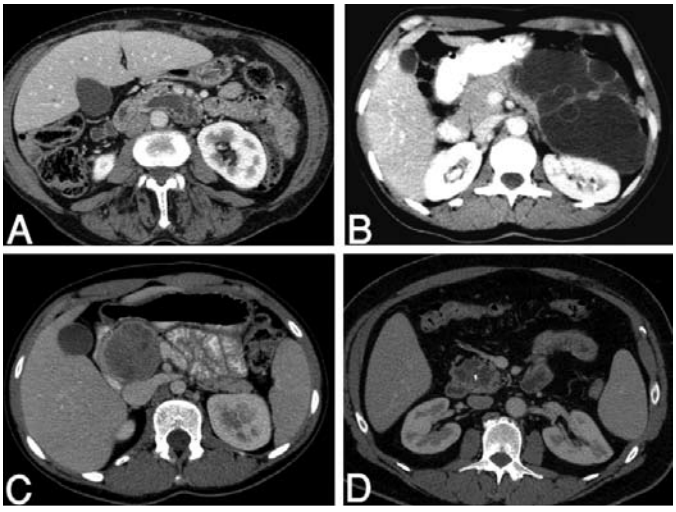
Thirty-one patients (27%) were asymptomatic: SCT (45.4%, n=6), MCT (23%, n=11) and IPMT (24.4%, n=11). Eighty-five patients (73%) were symptomatic. The most common complaint was abdominal pain or discomfort which was mainly epigastric (57%, n=48). A palpable mass and pancreatitis were less common. Early satiety, nausea, weight loss and jaundice were rare.

DIAGNOSTIC TESTS

Cystic lesions were evaluated by ultrasound in 40/116 patients (34%), CT in 104/116 (90%) and EUS in 75/116 (65%); in 45 of the latter (59%) FNA/B was performed. CEA and CA 19-9 levels within the cyst were recorded in more than half of them. Typical CT imaging diagnostic features of SCT, MCT, IPMT, and solid and cystic pseudo-papillary tumor are presented in Figure 1.

SCT = serous cystadenomas
EUS = endoscopic ultrasound
FNA/B = fine-needle aspiration biopsy

Figure 1. Axial CT scan images of: **[A]** IPMT, showing marked dilatation of the main pancreatic duct. **[B]** MCT, demonstrating a hypodense septated cystic mass in the pancreatic tail containing a few small cysts. **[C]** Solid and papillary cystic neoplasm in the upper abdomen, showing a round well-defined slightly heterogeneous mass with a well-defined hyperdense border. **[D]** Serous cystadenoma, showing a hypodense mass in the pancreatic head with fibrous septa and a small calcification.



SURGICAL DATA

All patients underwent pancreatic resection: 46 (40%) pancreaticoduodenectomy, 64 (55%) distal pancreatectomy, and 6 (5%) total pancreatectomy. Most of the MCTs (88%) and SCTs (70%) were located in the body or tail of the pancreas. In contrast, most IPMTs (67%) were located in the pancreatic head. Mean operative time was 257 ± 37 minutes. The complication rate was 35%, most were minor. Septic complications occurred in 17 patients (14.6%), of whom 5 (4.3%) had an intraabdominal abscess. Pancreatic fistula occurred in 7 patients (6%). Two patients were reoperated due to bleeding. Perioperative mortality rate was 2.6% (3/116) due to sepsis and multi-organ failure (one patient), bleeding (one patient) and pulmonary embolism (one patient). Mean hospital stay was 15.9 ± 7.2 days (range 5–120).

HISTOPATHOLOGICAL FEATURES

There were 46 MCTs (40%), 45 IPMTs (39%), 11 SCTs (9%), 4 cystic islet cell tumors (3.5%) and 10 papillary solid and cystic tumors (8.5%) [Table 1]. Most tumors – 104/116 (90%) – were resected with clear histological margins. All serous cysts were benign. Of the mucinous cysts, 28/46 (62%) were benign whereas 9 (20%) had invasive cancers and 8 (17%) were categorized as borderline tumors. Most IPMTs were invasive – 17/45 (38%), 14 (36%) were borderline tumors, and 14/46 (36%) were benign. Of the four neuroendocrine tumors two were malignant. Metastatic lymph nodes were found in 5/45 IPMT patients (11.2%) and in 3/46 MCT patients (6.5%). Lymph node involvement occurred in 1/10 patients with papillary solid and cystic tumor (10%). Two patients with IPMT were reoperated on due to positive margins.

LONG-TERM OUTCOME

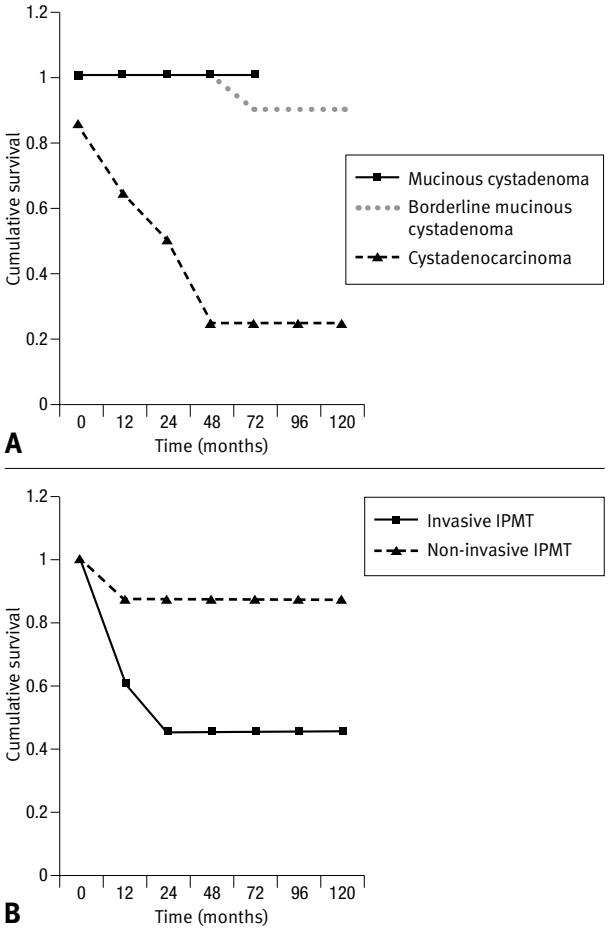
- *Mucinous cystic tumors.* The median follow-up time for all patients was 47 months (range 3–129). One patient with mucinous cystadenoma died 41 months after surgery due to myocardial infarction. Actuarial 5-year survival for that group was 90%. All surviving patients are disease-free. Only eight patients with borderline cystadenomas had a relatively short median follow-up time of 36 months. No death or recurrence occurred in that group. Of the 10 patients with mucinous cystadenocarcinoma 6 (60%) died with a median follow-up time of 25 months. Five-year survival for benign and/or borderline MCTs (87%) was better than for malignant MCTs (23%, $P < 0.001$); Kaplan Meier curves are shown in Figure 2A.
- *IPMT.* The mean follow-up time for IPMT patients was 31.5 months (range 3–122). The overall actuarial survival curves are shown in Figure 2B. The 5-year survival rate was 87% and 45% for patients with non-invasive and invasive IPMT respectively ($P < 0.05$). Recurrence of IPMT in the remaining pancreas occurred in two patients (8%) with non-invasive IPMT, both following distal pancreatectomy with negative surgical margins. One patient developed additional cystic tumors, which were observed on follow-up EUS; the patient was reoperated and underwent near-total pancreatectomy after 15 months. She remained without evidence of disease 6 months after the second operation. The second patient

Table 1. Postoperative pathological diagnosis

Pathology	N	% of total
MCT	46	40
SCT	11	9
IPMT	45	39
Cystic islet cell tumor	4	3.5
Papillary cystic tumor	10	8.5
Total	116	100

MCT = mucinous cystic tumor, SCT = serous cystic tumor, IPMT = intrapapillary mucinous cystic tumor

Figure 2. Cumulative survival curve for **[A]** patients with mucinous cystic tumors, **[B]** patients with IPMT



had recurrence with diffuse peritoneal spread of pancreatic carcinoma 24 months after the second intervention and died within 2 months. This was the only patient with non-invasive IPMT in this series who died of pancreatic cancer. Six patients operated on for non-invasive IPMT had involved margins with IPMT adenoma; all were without evidence of disease after a mean follow-up time of 19 months (range 11–28). Of the 17 patients treated for invasive IPMT, 4 had margins involved with invasive cancer, one with borderline tumor and one with adenoma. One of these patients died during the perioperative course. Two died of recurrent disease 10 and 17 months postoperatively. One patient had local recurrence 6 months postoperatively and is still alive with disease 12 months postoperatively. Two are alive without evidence of disease 13 and 8 months postoperatively.

PREDICTIVE FACTORS FOR MALIGNANCY

Statistical analysis was performed to identify preoperative predictors for malignancy [Table 2]. The categorical variables examined were weight loss, presence of jaundice, mucin within the cyst, and atypia. Continuous variables examined were tumor size, CEA and CA 19-9 levels within the cyst.

Eleven of the 17 patients (64.3%) who lost weight (mean 3.4 kg) had malignancy compared to 6 (35.7%) with benign cysts ($P < 0.05$). Seven of 9 patients (77.8%) with jaundice had malignancy compared to 2 (22.2%) who had benign tumors ($P = 0.028$). There were six patients with cellular atypia in the FNA sample; all (100%) had malignancy as compared to 2/16 (12.5%) without atypia ($P < 0.0001$). The presence of mucin was recorded in 20 patients, 9 of whom (45%) had malignancy as compared to 6/11 patients (54.5%) without mucin ($P = 0.61$). The median benign and malignant cyst size was 4 cm (range 0.5–16 cm) and 3.5 cm (range 0.6–13) respectively ($P = 0.43$).

Malignant cysts had higher median levels of CEA within the cyst, 780 vs. 140 ng/ml, although this difference was not significant ($P = 0.33$). Conversely, median CA 19-9 levels within the cyst were higher in benign tumors, 5250 vs. 298.5 ng/ml ($P = 0.056$).

Table 2. Categorical predictors for malignancy

Parameter	Benign cyst N (%)	Malignant cyst N (%)	P value
Weight loss	6 (35.7)	11 (64.3)	0.05 *
Jaundice	2 (22.2)	7 (77.8)	0.028 *
Mucin component	11 (55)	9 (45)	0.61
Cellular atypia	14 (87.5)	6 (100)	< 0.0001*
Tumor size (cm) median (range)	4 (0.5–16)	3.5 (0.6–13)	0.43
CEA* (ng/ml) median (range)	140 (16–5200)	780 (59–39,640)	0.33

*Carcinoembryogenic antigen level within the cyst fluid

DISCUSSION

Cystic lesions of the pancreas are not uncommon; however, pancreatic cystic tumors are far less frequent. Most cystic lesions are pseudocysts that must be differentiated from pancreatic cystic tumors, mainly SCT, MCT and IPMT. These cystic tumors are distinct entities differing in their biological behavior as well as their clinical and radiological appearance [13,14]. Despite the increasing awareness of pancreatic cystic tumors and the currently advanced imaging techniques, misdiagnosing a cystic tumor of the pancreas as a pseudocyst still reaches 10% [15]. One of our patients was followed for an unresolved large cystic lesion and a history of recurrent episodes of pancreatitis. During a period of 10 years the enlarging "pseudocyst" was re-drained and operated twice: Roux-en-y cystojejunostomy was followed by cystogastrostomy with no resolution of the cyst. Eventually, distal pancreatectomy was performed disclosing a cystadenoma with invasive carcinoma.

Preoperative differentiation of a cystic tumor from a pseudocyst is usually based on a history of acute pancreatitis and increased amylase or lipase activity within the cyst. Positive history and high enzyme levels strongly suggest the diagnosis of a pseudocyst [16], but it is the reverse that is more conclusive; absence of increased amylase almost excludes a pancreatic pseudocyst.

However, all cystic tumors may cause pancreatitis due to a mass effect, although our data show that such presentation is relatively uncommon (11.6%). Moreover, MCTs infrequently contain increased amylase lipase activity [17]. Increased levels of these enzymes within an IPMT reflect the communication between the cyst and the main or branch pancreatic ducts.

Excluding a pseudocyst, the clinician should then differentiate serous cyst from mucin-secreting tumors, namely IPMTs and MCTs. The latter are either premalignant or frankly malignant, thus mandating resection. The same applies to islet cell tumors and ductal adenocarcinoma that may appear as a cystic lesion. In contrast to the largest series reported by Allen et al. [18], our study group comprised a markedly low number of patients operated for a serous cyst. Of the 11 patients who underwent surgery for a symptomatic serous cyst, none had cancer, correlating the expectations and current literature. Our results correlate with both our expectations and the current literature. Consequently, diagnosing a serous cyst should exclude surgery in nearly all cases. We found mechanical compression causing symptoms to be the only justification for operating on such patients.

The differentiation of serous from mucinous tumors is based on imaging appearance and analysis of intracystic fluid. Imaging appearance is important but sometimes misleading. The pathognomonic image of a serous cyst on a CT scan is that of a spongy mass with a central sunburst calcification.

Unfortunately, it occurs in only a minority of patients (10%). We found endoscopic ultrasound to be an essential diagnostic tool. EUS provides detailed images without interference by bowel or air. In addition, it can direct fine-needle aspiration or biopsy of the lesion, providing cyst fluid for macroscopic, cytologic and histological examination, as well as tumor markers [19]. Two-thirds of our patients underwent EUS prior to their operation. FNA/B was performed in most cases.

The presence of mucin within the cyst excludes the diagnosis of serous cyst. Furthermore, in this series, as shown by others, serous cyst fluid analysis characteristically revealed low viscosity, low levels of CEA, and negative cytology [20]. Brugge and co-workers [21] found that cyst fluid CEA > 192 ng/ml was the most accurate test for the diagnosis of a mucinous lesion. The accuracy of this test is 79%; therefore, absence of mucin or low CEA levels should not exclude a mucinous cystic tumor.

When the diagnosis of a serous cyst is doubtful, given the safety of pancreatic resection in specialized centers, we support resection as the treatment of choice. Selected patients can be observed with repeated endoscopic ultrasound and FNA/B, considering the limitations of both.

The differential diagnosis between IPMT and MCT can be difficult. We believe that potential malignant transformation in both tumors justifies surgery; however, there are accumulating data showing that branch-type IPMT without main duct involvement has a low risk of prevalent cancer. Since these tumors rarely progress to invasive cancer, careful non-operative management seems to be safe in asymptomatic patients [21].

Endoscopic ultrasound and CT successfully demonstrate many characteristics of these tumors. Solid elements may imply the existence of malignancy. Cyst fluid analysis, which is generally recommended, reveals high viscosity and elevated tumor markers (CEA), and may show malignant cytology. Although the diagnosis of both entities is almost a clear indication for surgery, preoperative distinction between IPMT and MCT may be important. The more diffuse involvement of IPMT and its tendency to grow along ducts, in contrast to MCT which is usually localized, may necessitate routine intraoperative examination of resection margins by pancreatoscopy, intraoperative ultrasound or frozen section in IPMT cases [21]. The role of total pancreatectomy for IPMT is currently being reappraised. This procedure would be indicated as a treatment for benign or malignant IPMT with extensive involvement subject to the patient's condition [22]. These issues are yet to be studied.

Our experience shows that surgery for pancreatic cystic tumors is increasing, reaching 20% in our series of all pancreatectomies. Pancreatic surgery in high-volume centers is safe and the rates of morbidity and mortality are acceptable. Therefore, in general, we support surgery for every symptomatic, enlarging or suspicious pancreatic cystic tumor in a fit patient. Surveillance would be appropriate in the presence of sensitive predictors for existing malignancy. In our series we found that weight loss, jaundice and cell atypia were highly significant predictors for malignancy. Higher levels of intracystic CEA were found in malignant cysts, although this difference was not significant. These factors can be used in the decision-making process of individual cases.

Our results demonstrate that early intervention in cystic pancreatic tumors allows better long-term outcome even in the presence of malignancy. Complete resection of a mucinous cyst lacking any invasive component is curative in more than 90% of cases**.** In the past, several reports claimed survival rates above 50% for mucinous cystadenocarcinoma [23]. Reappraising the pathologies, 5-year survival rates appear to be somewhat better than those for pancreatic ductal cancer and range from 15% to 33% [24]. In our series the 5-year survival rate for mucinous cystadenocarcinoma was 25%. As for IPMTs, our 5-year survival rate for invasive tumors was 45% and almost 90% for non-invasive IPMTs. These numbers correlate with the rates reported by others [25]. Our series of operated cystic tumors of the pancreas is relatively large, enabling possible conclusions and lessons. However, this should be cautiously interpreted given the retrospective analysis of the data and the fact that they include only patients who were selected for surgery, precluding a large group of patients under surveillance.

CONCLUSIONS

Pancreatic cystic tumors carry a well-established potential for malignant transformation. The premalignant lesions have a clear favorable prognosis and therefore should be resected early. Only surgery and complete pathological examination exclude malignancy. Long-term outcomes for mucinous cystadenocarcinoma or malignant IPMT are better than for pancreatic ductal adenocarcinoma. Better clinical and mainly cytological and molecular predictors for malignancy would enable selection of patients for surveillance.

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