Pancreatic Cystic Neoplasms: Predictors of Malignant Behavior and Management

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ABSTRACT

Background/Aim: Pancreatic cystic neoplasms are being increasingly identified with the widespread use of advanced imaging techniques. In the absence of a good radiologic or pathologic test to preoperatively determine the diagnosis, clinical characteristics might be helpful. The objectives of this analysis were to define the incidence and predictors of malignancy in pancreatic cysts. Patients and Methods: Patients with true pancreatic cysts who were treated at our institution were included. Patients with documented pseudocysts were excluded. Demographic data, clinical manifestations, radiological, surgical, and pathological records of those patients were reviewed. Results: Eighty-one patients had true pancreatic cyst. The mean age was 47 ± 15.5 years. There were 28.4% serous cystadenoma, 21% mucinous cystadenoma, 6.2% intraductal papillary tumors, 8.6% solid pseudopapillary tumors, 1.2% neuroendocrine tumor, 3.7% ductal adenocarcinoma, and 30.9% mucinous cystadenocarcinoma. Malignancy was significantly associated with men (P = 0.04), older age (0.0001), cysts larger than 3 cm in diameter (P = 0.001), presence of solid component (P = 0.0001), and cyst wall thickening (P = 0.0001). The majority of patients with malignancy were symptomatic (26/28, 92.9%). The symptoms that correlated with malignancy included abdominal pain (P = 0.04) and weight loss (P = 0.0001). Surgical procedures were based on the location and extension of the lesion. Conclusion: The most common pancreatic cysts were serous and mucinous cysts. These tumors were more common in females. Old age, male gender, large tumor, presence of solid component, wall thickness, and presence of symptoms may predict malignancy in the cyst.

Key Words: Cystadenocarcinoma, cystadenoma, enucleation, pancreatic cyst, pseudocyst

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it is not routinely recommended to use these invasive and expensive diagnostic modalities. In the absence of a good radiologic or pathologic test to preoperatively determine the diagnosis, clinical characteristics such as age, gender, the presence of symptoms, cyst size, or location might be helpful.[6,8,10]

The ideal management of PCN remains controversial for a number of reasons including the difficulty in achieving an accurate preoperative diagnosis, the increasing detection of incidental lesions, the wide variability in malignant potential, and the poorly understood natural history of these lesions.[10‑12]

The aim of this study was to show the incidence and predictors of malignancy in true PC, and also to determine patients who can safely be observed and followed up and those who should undergo resection.

PATIENTS AND METHODS

A retrospective study was carried out including all patients who underwent surgery for PCN in the period between April 2001 and February 2012 at the Gastroenterology Surgical Center, Mansoura University, Egypt. The Institutional Review Board granted approval for the protocol. Patients with documented pseudocysts were excluded. Demographic data, clinical manifestations, radiological, surgical, and pathological records were reviewed for these patients. The hospital medical records were searched to determine the patient’s age, gender, presenting symptoms, and any history of pancreatitis, or diabetes mellitus. These data were collected manually from our hospital medical records by all authors.

Clinical presentation included abdominal pain, vomiting, jaundice, loss of weight, or abdominal mass; however, some cases were asymptomatic. Routine blood investigations were performed including hepatic and renal function tests. Cardiopulmonary assessments were done for all patients. Serum amylase and tumor markers (CEA and CA19-9) were done in some patients preoperatively. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) were done for patients presenting with obstructive jaundice to relieve the obstruction preoperatively. However, we did not do routine pancreatic duct cannulation and pancreatiogram for those patients for fear of inducing pancreatitis [Figure 1].

The morphology of the PC was recorded from the CT finding and the procedure report. CT was performed for all patients to show size of the cyst, site, loculations, calcification, central scar, wall thickness, and solid component. For oval-shaped cysts, the largest diameter was used [Figures 2-4]. Cyst fluid was collected by intraoperative needle aspiration or, when complete resection was planned, by needle aspiration immediately after surgical removal of the cyst. It was assessed for its viscosity and nature (serous, mucous, hemorrhagic, or hemorrhagic and necrotic).

Surgical treatment depends on the location and extension of the cyst. Distal pancreatectomy was performed for cyst located in the body. Small lesions of the body and neck of the pancreas were treated by median pancreatectomy or enucleation, with closing of proximal pancreatic segment and drainage of the distal segment with a Roux en Y pancreaticojejunostomy [Figure 5]. Tumors of the head and/or uncinate process were treated by pancreatoduodenectomy (PD), with or without pylorus preservation, with pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ) based on surgeon’s preference. Advanced tumors underwent bypass if obstructing the
common bile duct and/or stomach. In the enucleation group, intraoperative US imaging was used routinely to assess the relationship between the pancreatic duct and the cystic lesion. In addition, the pancreatic defect after enucleation was closed. Frozen section of the surgical margins had an important role in the intraoperative management of cysts in some patients to determine free safety margin. Closure was usually performed with 3-0 absorbable sutures, taking care not to injure the pancreatic duct. Sandostatin was given for all patients postoperatively. Operative time, morbidity, and hospital stay were collected from medical records. Follow-up data including recurrence, morbidity, and survival information were collected.

All pathologic specimens were reviewed and tumors were classified as benign (including SCA, SPT, MCN, intraductal papillary mucinous neoplasm (IPMN), and cystic neuroendocrine tumors) and malignant as cystadenocarcinoma, and ductal adenocarcinoma with degeneration.[2,3,6] Statistical analysis of the data in this study was performed using SPSS software, version 17 (Chicago, IL). For continuous variables, descriptive statistics were calculated and were reported as mean ± standard deviation (SD) or as median with range. Categorical variables were described using frequency distributions. Independent sample t-test was used to detect differences in the means of continuous variables and Chi-square test was used in cases with low expected frequencies. One-way ANOVA test was used to detect differences between three groups. P values < 0.05 were considered significant.

RESULTS

Eighty-one patients (34 men) with median age 45 years (range, 15-72 years), had undergone surgery for cystic pancreatic neoplasms at the Gastroenterology Surgical Center, Mansoura University, Egypt, in the period between April 2001 and February 2012. Of the 81 patients, 53 patients had benign cysts and 28 patients had malignant cysts (25 mucinous cystadenocarcinoma and three ductal adenocarcinomas) based on pathological results [Table 1].
Clinical manifestations varied according to the size and location of the cyst. Sixty patients had one or more symptoms including abdominal pain, jaundice, weight loss, nausea, vomiting, and mass. However, 21 (25.9%) patients were asymptomatic as seen in Table 1. Abdominal pain on presentation was recorded more often in malignant group (16/28; 57.12%) than in benign group (18/53; 34%); \( P = 0.04 \). Weight loss occurred more often in the malignant group (18/28, 64.3%) than in benign group (13/53, 24.5%); \( P = 0.0001 \). Nausea, vomiting, jaundice, and palpable abdominal mass were not helpful in predicting malignancy. Asymptomatic patients were more in benign group than in malignant group (35.8% vs 7.1%, respectively); \( P = 0.005 \) [Table 2].

ERCP was performed for 17 patients presenting with obstructive jaundice revealing stricture in lower third common bile duct with stent insertion to relieve jaundice preoperatively.

Older age was significantly associated with malignancy in patients with benign cyst, (40 years vs 64 years; \( P = 0.0001 \)) [Table 2]. Regardless of the type of tumor, there was a greater prevalence of PC in female (47, 58%). The overall incidence of malignancy was higher in men (\( P = 0.004 \)) [Table 2]. The majority of patients with mucinous cystadenoma were female (13/17, 76.4%), 65.2% (15/23) in SCA, 100% (7/7) in SPT , and 42.9% (12/28) in malignant cyst [Table 3].

The mean transverse diameter of the PC was 4.7 ± 2.3 cm. The maximum cyst diameter was significantly greater in the malignant cysts (6.5 ± 2.5) as compared with benign cysts (3.7 ± 1.4) (\( P = 0.008 \)). Five of 34 (14.7%) patients with cystic pancreatic lesions < 3 cm had malignant tumors [Table 2].

The majority of PC located in the tail (49.4%), 35.8% in the head, and 14.8% in the body of the pancreas [Table 1]. Location of cystic lesion did not predict malignant pathology [Table 2]. The majority of serous and mucinous tumors located in the tail (14/23; 60.8% and 12/17; 70.6%, respectively). All of intraductal papillary mucinous tumors were found in the head and 85.7% of the SPT located in the head [Table 5].

Solid component inside the cyst was recorded in 20 patients (24.7%). Of the 20 patients, 4 cysts were benign and 16 cysts were malignant; \( P = 0.0001 \). Calcification was found in 20 patients (24.7%), of which, 15 were in benign cysts; \( P = 0.96 \). Wall thickening was recorded in 29 cases (35.8%), of which, 18 were malignant; \( P = 0.0001 \) [Tables 1 and 2].

Serum CA19-9, CEA, and serum amylase were measured in

### Table 1: Demographic data of the 81 patients

| Variables                        | All cases |
|----------------------------------|-----------|
| The median age (years)           | 45 (15-72)|
| Sex                              |           |
| Male                             | 34 (42%)  |
| Female                           | 47 (58%)  |
| Site                             |           |
| Head                             | 29 (35.8%)|
| Body                             | 12 (14.8%)|
| Tail                             | 40 (49.4%)|
| Size (cm)                        | 4.7±2.3 (2-10)|
| Clinical picture                 |           |
| Asymptomatic                     | 21 (25.9%)|
| Pain                             | 34 (42%)  |
| Mass                             | 13 (16%)  |
| Jaundice                         | 22 (27.2%)|
| Weight loss                      | 31 (38%)  |
| Vomiting                         | 14 (17.3%)|
| CT finding                       |           |
| Wall thickness                   |           |
| Thick wall                       | 29 (35.8%)|
| Thin wall                        | 52 (64.2%)|
| Solid part                       | 20 (24.7%)|
| Calcification                    | 20 (24.7%)|
| Pathological diagnosis           |           |
| Serous cystadenoma               | 23 (28.4%)|
| Mucinous cystadenoma             | 17 (21%)  |
| Intra ductal papillary tumor     | 5 (6.2%)  |
| Solid pseudopapillary tumor      | 7 (8.6%)  |
| Mucinous cystadenocarcinoma      | 25 (30.9%)|
| Ductal adenocarcinoma with cystic degeneration | 3 (3.7%) |
| Neuroendocrine tumor             | 1 (1.2%)  |
| Surgery                          |           |
| Pancreatoduodenectomy            | 25 (30.9%)|
| Distal pancreatectomy            | 36 (44.4%)|
| Median pancreatectomy            | 7 (8.6%)  |
| Exploration                      | 7 (8.6%)  |
| Bypass                           | 3 (3.7%)  |
| Enucleation                      | 3 (3.7%)  |

66/81 cysts. They were not helpful in differentiating benign from malignant pathology.

All surgeries were performed with a curative intent, 25 patients (30.9%) underwent PD operation with PG (in 19 patients) or PJ (in 6 patients), and 7 patients underwent pylorus preserving PD and 18 patients underwent classic PD, 36 patients (44.4%) underwent distal pancreatectomy, 7 patients (8.6%) underwent median pancreatectomy, 3 patients (3.7%) underwent enucleation, and 10 patients (12.4%) had advanced tumor (underwent bypass in 3 patients and nothing was done in 7 patients). The mean postoperative stay was 7.5 ± 2.5 days (4-21 days) for the
benign cyst and 8.3 ± 8.2 days (2-36 days) for the malignant group.

Univariate analysis showed 10 variables to be significantly predictive of malignancy in cyst: male gender, abdominal pain, loss of weight, tumor size, presence of solid part, pancreatic duct dilatation, wall thickness, content of the cyst, location of the cyst, and cyst amylase. These 10 predictive factors of malignancy in PC identified in univariate analysis were further analyzed in multivariate analysis. The \( P \) values for only 3 factors (tumor size, presence of solid part, and wall thickness) in the multivariate analysis were < 0.05 [Table 4].

### DISCUSSION

Due to widespread use of radiological studies, cystic pancreatic tumor cases are increasing. The diagnosis of malignancy in cystic pancreatic tumor cases requires pancreatic resection. Little information is presently available on the incidence and behavior of PC. Clinical and laboratory features of cystic pancreatic lesions may predict underlying malignancy.\(^6,13\)

Many studies reported that SCAs occurred in patients with a median age around 50 years.\(^9,10,12‑16\) Solid and cystic papillary tumors as well as simple cysts have generally been reported in younger patients.\(^6,8,13,17,18\) Benign mucinous cystic neoplasm have a median age around 50 to 55 years, whereas mucinous cystadenocarcinoma generally have a median age of 60 to 65 years.\(^8,13,15,19\)

In our study, patients with malignant cysts were older than patients with benign cysts with statistical significance (the median age was 40 years in patients with benign cysts, compared with 64 years in patients with malignant cyst, \( P = 0.0001 \)); thus, older patients are more likely to have premalignant or malignant cystic pancreatic neoplasms.

The majority of cystic neoplasms in our study occurred in women. The overall incidence of malignancy was higher in men (18/53; 34% in benign group vs 16/28; 57.1% in malignant group; \( P = 0.004 \)). The majority of patients with mucinous cystadenoma were females, 65.2% in SCA, 100% in SPT, and 42.9% in malignant cyst. Prevalence of cystic neoplasms in female patients has been observed in other studies as well.\(^6,8,13,17,18\) Lee et al.\(^22\) reported that the overall incidence of malignancy was significantly higher in men, 14 of 67 (28%), compared to women, 12 of 99 (12%) \( (P < 0.02) \). Thus, male gender may suggest malignant behavior of PC.

In this study, 60 patients had one or more symptoms including abdominal pain, jaundice, weight loss, nausea, vomiting, and mass. However, 21 patients were...
Table 3: Histopathological type of cystic pancreatic tumors

| Variables                                  | Serous cystadenoma (23) | Mucinous cystadenoma (17) | Solid pseudopapillary (7) | Intra ductal papillary tumor (5) | Mucinous cystadenocarcinoma (25) | Adenocarcinomawithcystic degeneration (3) | P value |
|--------------------------------------------|-------------------------|---------------------------|--------------------------|-------------------------------|----------------------------------|-------------------------------------------|---------|
| The median age (years)                     | 39 (19-58)              | 42 (24-65)                | 28 (16-64)               | 65 (57-70)                    | 64 (15-75)                       | 61 (59-65)                                | 0.0001  |
| Sex                                        |                         |                           |                          |                               |                                  |                                           | 0.004   |
| Male                                       | 8                       | 4                         | 0                        | 5                             | 14                               | 2                                         |         |
| Female                                     | 15                      | 13                        | 7                        | 0                             | 11                               | 1                                         |         |
| Cyst size (cm)                             | 3.4±1 (2-6)             | 4.5±1.8 (2-8)             | 3.5±0.8 (2.8-5)          | 2.5±0.4 (2-3)                 | 6.4±2.5 (2.8-10)                 | 7.3±3.7 (3-10)                            | 0.0001  |
| CT finding                                 |                         |                           |                          |                               |                                  |                                           |         |
| Solid part                                 | 1                       | 2                         | 0                        | 0                             | 12                               | 3                                         | 0.0001  |
| Calcification                              | 9                       | 1                         | 2                        | 1                             | 6                                | 1                                         | 0.38    |
| Cyst location                              |                         |                           |                          |                               |                                  |                                           |         |
| Head                                       | 4                       | 3                         | 6                        | 5                             | 9                                | 1                                         |         |
| Body                                       | 5                       | 2                         | 1                        | 0                             | 4                                | 0                                         | 0.009   |
| Tail                                       | 14                      | 12                        | 0                        | 0                             | 12                               | 2                                         |         |
| Appearance                                 |                         |                           |                          |                               |                                  |                                           |         |
| Unilocular                                 | 20                      | 14                        | 5                        | 4                             | 12                               | 1                                         | 0.04    |
| Multilocular                               | 3                       | 3                         | 2                        | 1                             | 13                               | 2                                         |         |
| Wall thickness                             |                         |                           |                          |                               |                                  |                                           |         |
| Thick wall                                 | 1                       | 5                         | 3                        | 1                             | 16                               | 2                                         |         |
| Thin wall                                  | 22                      | 12                        | 4                        | 4                             | 9                                | 1                                         | 0.001   |
| Cyst fluid                                 |                         |                           |                          |                               |                                  |                                           |         |
| Viscosity                                  |                         |                           |                          |                               |                                  |                                           |         |
| Low                                        | 20                      | 5                         | 5                        | 2                             | 15                               | 3                                         | 0.007   |
| High                                       | 3                       | 12                        | 2                        | 3                             | 10                               | 0                                         |         |
| Nature                                     |                         |                           |                          |                               |                                  |                                           |         |
| Serous                                     | 19                      | 1                         | 1                        | 2                             | 2                                | 1                                         |         |
| Mucous                                     | 2                       | 14                        | 0                        | 3                             | 17                               | 0                                         | 0.0001  |
| Haemorrhage                                | 2                       | 2                         | 0                        | 0                             | 4                                | 1                                         |         |
| Haemorrhage and necrosis                   | 0                       | 0                         | 6                        | 0                             | 2                                | 1                                         |         |
| Serum                                      |                         |                           |                          |                               |                                  |                                           |         |
| CA19-9                                     | 47.3±59                 | 29.3±18.2                 | 22.8±22.8                | 40.7±46.2                     | 26.3±27.2                        | 17.5±9.8                                 | 0.55    |
| CEA                                        | 8.3±5.1                 | 2.9±3.9                   | 9.8±16.7                 | 33.7±61                       | 4.3±10.5                         | 2.11±0.4                                 | 0.06    |
| Amylase                                    | 145.7±148.9             | 216.6±148.9               | 209.1±168.2              | 137±66.4                      | 178.6±138.8                      | 142.7±27.6                               | 0.75    |
| Surgery                                    |                         |                           |                          |                               |                                  |                                           |         |
| Pancreatoduodenectomy                      | 4                       | 3                         | 6                        | 5                             | 6                                | 0                                         |         |
| Distal pancreatectomy                      | 14                      | 12                        | 0                        | 0                             | 10                               | 0                                         |         |
| Median pancreatectomy                      | 2                       | 2                         | 1                        | 0                             | 2                                | 0                                         | 0.0001  |
| Enucleation                                | 3                       | 0                         | 0                        | 0                             | 0                                | 0                                         |         |
| Bypass                                     | 0                       | 0                         | 0                        | 0                             | 2                                | 1                                         |         |
| Exploration                                | 0                       | 0                         | 0                        | 0                             | 5                                | 2                                         |         |
Asymptomatic. Asymptomatic patients were more in the benign group than in the malignant group (35.8% vs 71.2%, respectively; P = 0.005). Symptoms of abdominal pain and weight loss had a significant association with malignant tumors. Fernandez-del Castillo et al. reported that 134 of their 212 patients (63%) with PC were symptomatic. Malignant lesions were found in 40% of their symptomatic patients compared with only 17% of their asymptomatic patients (P = 0.001). Lee et al. reported that the presence of one or more symptoms was a significant predictor of malignant pathology. Symptoms of jaundice, weight loss, and anorexia had associations with malignant tumors. Moesinger et al. found that less than half of their patients with SCAs and benign mucinous cystic tumors had symptoms, whereas 80% to 85% of their patients with mucinous cystadenocarcinoma were symptomatic. Spinelli et al. reported that the presence of symptoms predicted premalignant or malignant pathology. Javle et al. found that palpable abdominal mass on presentation was significantly more in the malignant group (7/17 patients) than in the benign group (0/18 patients). Weight loss occurred more in the malignant group (7/17 patients) than in the benign group (2/18 patients) with statistical significance.

Several studies correlating size and malignancy risk have revealed that smaller cystic neoplasms are less likely to be malignant. In our study, the maximum cyst diameter was significantly greater (P = 0.008) in the malignant cysts (6.5 ± 2.5 cm) as compared with the benign group (3.7 ± 1.4 cm). Five of 34 (14.7%) patients with cystic pancreatic lesions < 3 cm had malignant tumor. Spinelli et al. reported that cyst size did not correlate with final pathology. Sarr et al. found no difference in the mean size of benign mucinous cystadenoma and mucinous cystadenocarcinoma. On the other hand, Chari et al. found that their 73 noninvasive IPMN was 5.2 cm in diameter, whereas their 40 invasive IPMN was 6.6 cm. Lee et al. reported that 31 of 166 (19%) patients with cystic pancreatic tumors < 3 cm had malignancy, which is in accordance with the results of other series that report malignancy rates ranging between 13 and 20% in small lesions. Thus, cysts of small size do not exclude its malignant potential but malignancy is more with larger cyst size.

In our study, cyst location did not predict malignant behavior of the cyst. In some studies, the mucinous types of PC arise from the duct epithelium, are often large (sometimes >10 cm), and usually located in pancreatic body or tail; SCAs are smaller (<2 cm), and often seen on head of the pancreas and conversely, mucinous cystadenocarcinoma have a tendency to occur more often in the head of the pancreas.

Many studies have reported the presence of solid component inside the cyst to be a significant predictor of malignancy. In our study, the most significant radiological findings associated with malignancy were the presence of a solid component (P = 0.0001), loculation (P = 0.001), and wall thickening (0.0001). Both the presence of solid component and wall thickening were found to be independent predictors when considered in a multivariate analysis.

Endoscopic US with fine needle aspiration has been suggested as a diagnostic tool to differentiate between benign and malignant cysts. However, aspiration by the needle has the potential to spill malignant cells with possibility of reducing survival. For this risk, as well as the accuracy of fluid analysis, several studies and as also in our study, did routinely use endoscopic US which is expensive, invasive, and needs experience. Recently, positron emission tomography has been found to be accurate in detecting small pancreatic cancers, but it is very expensive.

The management of pancreatic cystic lesions remains controversial. Although an aggressive resectional approach is advocated by some, an increasing number of clinicians are now questioning the practicality of this strategy with the marked increase in the incidence of PC detected incidentally on radiologic imaging.

In the absence of randomized controlled data to guide treatment recommendation, the International Association of Pancreatology identified several factors as indication for resection of PC IPMNs. These include diameter > 3 cm, any solid component, and the presence of symptoms attributable to the cyst. However, any lesion thought to be MCN should be resected. SCA should be resected only if symptomatic, or if the diagnosis remains doubtful. Malignant SPT can be cured when completely excised,
and prolonged survival can be seen even in the presence of metastatic disease. Management of PCN is based upon a balance of malignant potential and risk of surgical resection.[12]

In our study, major pancreatic resection was recommended for symptomatic cysts, large lesions and for cysts that have potential malignancy or are malignant. Spinelli et al.[6] reported that majority of benign lesions are SCAs as well as solid and cystic papillary tumors. These benign tumors frequently can become large and symptomatic; eventually may lead to major pancreatectomy, whereas early management might allow limited resection. Similarly, early surgery in patients with mucinous cystadenoma, cystic neuroendocrine tumor, and benign IPMN will prevent malignant transformation and is likely to be more cost-effective than observation. James M. Kiely et al.[31] reported that for small cystic tumors in the uncinate, head, neck, and body of the pancreas, enucleation has advantages over pancreatic resection as regards to operative time, blood loss, and preservation of pancreatic parenchyma. Because the pancreas is otherwise normal in these patients, the risk of pancreatic leakage is high.

Allen et al.[26] have recommended follow up by high-quality CT or MRCP every year for asymptomatic cysts smaller than 2.5 cm. Also, Fernandez-del Castillo and Warshaw[25] have recommended periodic imaging for small, asymptomatic PC. They recommend resection for larger cysts in young and middle-aged patients and cyst fluid aspiration for analysis for older patients.

CONCLUSION

In conclusion, this study demonstrated that preoperative clinical characteristic such as patients’ age, male gender, tumor size, and presence of symptoms can predict malignancy in the cyst. CT scan is not sufficiently accurate to differentiate among the benign and malignant pancreatic cystic lesions. Surgical treatment depends on the location and extension of the lesion. Pancreatic resection is recommended for symptomatic cysts, large lesions and for cysts that have potential malignancy or are malignant. Further prospective studies are required to confirm these results.

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