Pancreatology 19 (2019) 372–376

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Cystic pancreatic neuroendocrine tumors: A more favorable lesion?

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ARTICLE INFO

Article history:
Received 24 September 2018
Received in revised form
14 January 2019
Accepted 20 January 2019
Available online 22 January 2019

Keywords:
Pancreatic neuroendocrine tumors
Pancreatic cysts
Ki-67
Prognosis

ABSTRACT

Background: Pancreatic neuroendocrine tumors (PNETs) are predominantly solid lesions with malignant potential. Cystic PNETs are a small subset in which data are scarce. The aim of this study was to compare clinical and biologic differences between cystic and solid PNETs.
Methods: Patients with PNETs undergoing pancreatectomy between 1988 and 2016 at a high-volume center were reviewed retrospectively. Demographic, clinical, and histopathologic data were collected and analyzed.
Results: 347 patients with PNETs were identified; 27% (n = 91) were cystic. Patients with cystic PNETs were generally older (59 vs. 55 years, p = 0.05). Cystic PNETs were more commonly non-functional (95% vs. 82%, p = 0.004), asymptomatic (44% vs. 28%, p = 0.009), and located in the pancreatic body/tail (81% vs. 60%, p < 0.001) than solid PNETs. Although cystic and solid PNETs had similar sizes and pathologic stage at the time of resection, Ki-67 proliferation index (Ki-67 ≤ 9%: 98% vs. 85%; p = 0.007), and histologic grade (grade I: 84% vs. 59%; p = 0.009) had less aggressive features in cystic PNETs.
Conclusion: In addition to reporting a higher than previously published incidence of cystic PNET (27%), this study found significant differences in multiple clinicopathologic variables between cystic and solid PNETs. Cystic PNET may be a distinct and possibly less aggressive subtype of PNET yet have similar pathologic stage, recurrence, and survival to solid PNETs. Cystic PNETs require further attention to better understand the true natural history.
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Introduction

Pancreatic neuroendocrine tumor (PNET) is an uncommon neoplasm arising from islet cells and accounts for up to 5% of all primary pancreatic cancers [1–6]. PNETs are predominantly solid tumors with malignant potential. Cystic PNET is a rare subtype that is being recognized more frequently due to increased use of high-resolution cross-sectional imaging [7–10]. Cystic PNETs account for 7–17% of all resected PNETs [1,6,11–16], and a small minority (4–14%) of cystic pancreatic lesions [10,12,13]. Thus, maintaining a broad differential diagnosis is important as management of varies widely [2].

Cystic PNET may represent a discrete entity with more favorable prognosis than solid PNET [3,11,13,16]. A recent meta-analysis showed significant differences between cystic and solid PNETs with regards to tumor site, functionality, lymph node metastasis, World Health Organization classification, and Ki-67 index [3]. Cystic PNETs were more likely to be located in the body/tail of the pancreas (72% vs. 55%), be non-functional (86% vs. 76%), carry a benign/uncertain behavior based on WHO classification (90% vs. 66%), have a lower Ki-67 index (<2%: 82% vs. 54%), and less regional lymph node metastases (11% vs. 29%) [3]. Ki-67 index is a component of the WHO classification for PNET and has been shown to be a negative prognostic indicator of disease [17]. Additional reports have demonstrated a lower tumor grade and fewer distant metastases in cystic PNETs [6,11]. In order to address prognostic differences in cystic versus solid PNETs, studies have attempted to link specific cystic PNET characteristics with improved prognosis [17,18]. In the past, the most influential predictors of survival for PNET were resection of the primary tumor, lower tumor grade, smaller tumor size, lower Ki-67 index, and an absence of lymph node and distant metastases [17,18].

Cystic PNETs tend to have lower Ki-67 index, lower tumor grade,

Abbreviations: PNET, pancreatic neuroendocrine tumor; WHO, World Health Organization; EUS, endoscopic ultrasound; FNA, fine needle aspiration.

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https://doi.org/10.1016/j.pan.2019.01.017
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fewer distant metastases, and may have better long-term prognosis. However, existing data are limited and evidence for unique management is incomplete. The purpose of this study was to compare the clinicopathologic and prognostic features of cystic to solid PNETs and determine whether cystic variants represent a distinct, more favorable subtype of PNET.

Methods

In accordance with the guidelines defined by the Indiana University Institutional Review Board, 376 patients undergoing surgical resection of PNET between 1988 and 2016 at Indiana University Health University Hospital were retrospectively reviewed. Patients receiving palliative/diagnostic procedures without resection (n = 18), operations performed at outside hospitals (n = 3), or resections for recurrent PNET (n = 8) were excluded.

Patient demographic information, clinical data, and histopathologic data were collected from clinic, operative, radiographic imaging, and pathology reports. Diagnoses were confirmed by the Department of Pathology at the Indiana University School of Medicine and graded according to WHO and American Joint Committee on Cancer classifications for neuroendocrine tumors [19,20]. Histologic grade was assigned if both elements, Ki-67 and mitotic index, of the WHO grading system were available within histopathologic reports. Follow-up data from patients diagnosed between 2010 and 2016 were gathered and centralized by the Indiana Cancer Registry in a prospective database. Additional follow-up data were obtained from electronic medical record and online obituaries. Patients with cystic PNETs were compared to patients with solid PNETs. Lesions were defined as cystic if at least partially cystic on preoperative imaging or surgical pathology.

Differences in patient demographics, lesion functionality, symptomatology, tumor site, lesion size, multifocality, operation performed, histologic grade, Ki-67, mitotic index, TNM stage, presence of concurrent pancreatic adenocarcinoma, and survival data were compared between the groups. Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) 24. Continuous data were analyzed with 2-sample *t*-test or ANOVA. Categorical data were analyzed with chi-square. P-values $\leq$0.05 were considered statistically significant. Multivariate logistical regression analysis was performed to assess for confounding and effect modification. Estimates of overall survival were made using Kaplan-Meier curves with log rank testing used for survival comparison.

Results

Of the 376 patients with surgical PNETs, 347 met inclusion criteria, and 330 had data available for cystic versus solid classification. Ninety-one (27%) pancreatic lesions were cystic PNET. Demographic information of patients with cystic versus solid PNET is provided in Table 1. The ratio of cystic:solid PNET increased over time from 0.3 prior to the year 2000, to 0.5 post-2010 (p = 0.009) (Fig. 1). Patients with cystic PNETs were generally older (59 ± 1.4 years vs. 55 ± 1.0 years; p = 0.048) and more commonly male (64% vs. 51%; p = 0.036) than those with solid PNETs. Among patients undergoing preoperative endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) (n = 237; 73 cystic), 81.7% were correctly diagnosed as PNET. The accuracies of preoperative EUS-guided FNA biopsy were similar for cystic and solid PNET (81% vs. 82%; p = 0.81). Clinical features of cystic versus solid PNET are included in Table 1. Cystic PNETs were less likely to be functional (5% vs. 18%; p = 0.004). Among the functional tumors, no differences were observed in the incidence of gastrinomas, insulinomas, VIPomas, or glucagonomas between cystic and solid PNETs. Cystic PNETs were more likely located in the body/tail of the pancreas (81% vs. 60%; p < 0.001) and less commonly symptomatic (56% vs. 72%; p = 0.009). Symptoms experienced were most commonly abdominal pain, pancreatitis, jaundice, nausea, vomiting, loss of appetite, and symptoms according to type of functional tumor (i.e. hypoglycemia with insulinoma). Tumor site was the only independently significant variable on multivariate regression analysis. Lesions in the body/tail of the pancreas were 2.6 times more likely to be cystic PNET (95% CI: 1.0–7.1; p = 0.05).

Histopathologic features of cystic versus solid PNETs are summarized in Table 2. Although there was no difference in mitotic index (<2/10 hpf: 84% vs. 76%, 2–20/hpf: 16% vs. 21%, and >20/hpf: 3% vs. 0%; p = 0.34), tumor histologic grade (Grade 1: 84% vs. 59%, Grade 2: 16% vs. 33%, and Grade 3: 8% vs. 0%; p = 0.009) and Ki-67 index (<3%: 83% vs. 63%, 3–20%: 17% vs. 28%, and >20%: 0% vs. 9%; n = 149; p = 0.02) were lower in cystic PNETs. According to a study

Table 1
Demographic/clinical data of patients with cystic and solid PNET.

	Cystic	Solid	p-value
Total Patients	91	239	
Age			**0.048**
	59 yrs ± 1.4	55 yrs ± 1.0	
Gender			**0.036**
Male	58 (64%)	121 (51%)	
Female	33 (36%)	118 (49%)	
PNET type			**0.004**
Non-functional	86 (95%)	197 (82%)	
Functional	5 (5%)	42 (18%)	
Gastrinoma	1 (1%)	10 (4%)	
Insulinoma	4 (4%)	27 (11%)	
VIPoma	0 (0%)	4 (1.7%)	
Glucagonoma	0 (0%)	1 (0.4%)	
Symptomatic			**0.009**
No	40 (44%)	66 (28%)	
Yes	51 (56%)	166 (72%)	
Site[a]			**<0.001**
Head/Uncinate/Neck	17 (19%)	93 (40%)	
Body/Tail	73 (81%)	138 (60%)	
Multifocal			0.23
No	85 (93%)	212 (89%)	
Yes	6 (7%)	27 (11%)	
Operation			**<0.001**
PD	13 (15%)	64 (29%)	
DP	65 (76%)	109 (50%)	
Enucleation	8 (9%)	47 (21%)	

PD = Pancreaticoduodenectomy.
DP = Distal pancreatectomy.
[a] Site = independently significant on multivariate analysis.

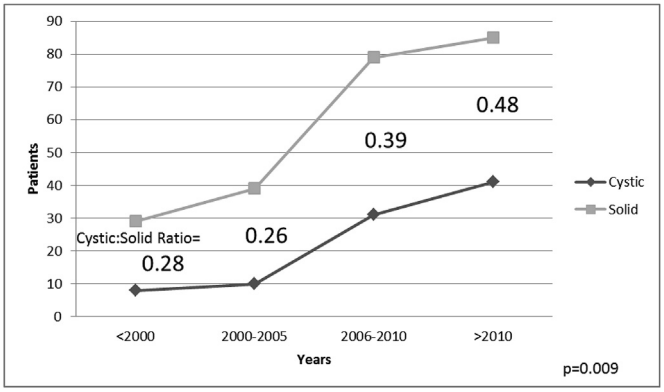

Fig. 1. Ratio of Cystic to Solid PNET Over Time: The change in number of cystic and solid PNET resected over time is plotted here. The ratio of cystic to solid PNET increased with time.

Table 2
Histopathologic data of patients with cystic and solid PNET.

	Cystic	Solid	p-value
Mitotic Count	(n = 50)	(n = 104)	0.336
<2/10 hpf	42 (84%)	79 (76%)	
2–20/10 hpf	8 (16%)	22 (21%)	
>20/10 hpf	0 (0%)	3 (3%)	
Ki-67	(n = 47)	(n = 102)	**0.021**
<3%	39 (83%)	64 (63%)	
3–20%	8 (17%)	29 (28%)	
>20%	0 (0%)	9 (9%)	
Grade	(n = 41)	(n = 90)	**0.009**
1	37 (84%)	53 (59%)	
2	4 (16%)	30 (33%)	
3	0 (0%)	7 (8%)	
Size	(n = 91)	(n = 239)	0.66
	3.3 ± 0.2 cm	3.5 ± 0.2 cm	
T Stage	(n = 91)	(n = 239)	0.24
1	33 (36%)	87 (36%)	
2	42 (46%)	88 (37%)	
3	16 (18%)	62 (26%)	
4	0 (0%)	2 (1%)	
N Stage	(n = 91)	(n = 239)	0.076
0	72 (79%)	165 (69%)	
1	19 (21%)	74 (31%)	
M Stage	(n = 91)	(n = 239)	0.058
0	83 (91%)	197 (82%)	
1	8 (9%)	42 (18%)	
TNM Stage	(n = 91)	(n = 239)	0.31
IA	29 (32%)	79 (33%)	
IB	28 (31%)	58 (24%)	
IIA	8 (9%)	19 (8%)	
IIB	18 (20%)	41 (17%)	
III	0 (0.0%)	0 (0%)	
IV	8 (9%)	42 (18%)	
PDAC	(n = 91)	(n = 239)	0.73
Not present	89 (98%)	230 (96%)	
Present	2 (2%)	9 (4%)	

*PDAC: pancreatic ductal adenocarcinoma.

by Hamilton et al., cystic PNET with a Ki-67 index of ≥9% were more aggressive, defined as more disease recurrences and shorter overall survival [17]. In this series, cystic PNETs had a lower rate of Ki-67 index ≥9% (2% vs. 15%). Histologic grading based on 2010 WHO guidelines was performed on 131 PNET with both mitotic index and Ki-67 available. This testing became available at our institution in 2001 and became routinely documented starting in 2009. Ninety-one percent of patients had documentation of either mitotic index or Ki-67 after 2009. Tumor (T), nodal (N), and metastases (M) staging were compared independently. No statistical difference was found in T, N, or M stage. No significant differences were observed between cystic and solid PNETs with regards to pathologic stage. On final pathology, no difference was found in rate of concurrent pancreatic ductal adenocarcinoma with PNET in cystic and solid lesions.

Survival data were available for 77 (85%) patients with cystic PNETs and 208 (73%) with solid PNETs. Median follow-up was 44.4 months. No difference in median overall survival was found between cystic and solid PNETs (151.5 vs. 131.5months; p = 0.6) (Fig. 2). Disease recurrence data was available for a minority of patients. Recurrence data was collected on 186 patients although many of these had only short term follow up. Many of these might have had recurrence after leaving our health system.

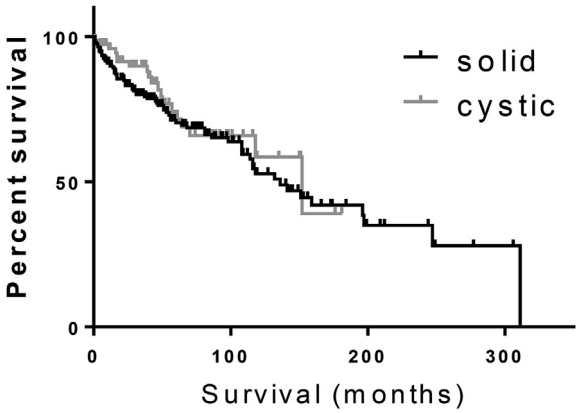

Fig. 2. Overall Survival of Patients with Cystic vs. Solid PNET: Kaplan Meier plots are shown here for overall survival of patients with PNET. Percent of patients surviving is plotted on the y-axis and median survival in months is plotted on the x-axis. Median survival was the same between patients with cystic (black line) vs. solid (grey line) PNET (151.5, range: 93.5–131.7 vs. 131.5, range: 101.7–161.3 months; p = 0.6).

Discussion

This study represents the largest single-institution population of patients with cystic PNETs (n = 91), accounting for 27% of patients with resected PNET. Cystic PNETs have defining features that distinguish them from solid PNETs. Cystic PNETs are diagnosed in older patients who are more likely male (64% vs 51%). Cystic PNETs were more commonly non-functional (95% vs 82%), asymptomatic (44% vs 28%), and located in the pancreatic body/tail (81% vs 60%) than solid PNETs. Although cystic and solid PNETs had similar sizes and pathologic stage, Ki-67 index and WHO histologic grade were significantly lower in cystic PNETs suggesting the possibility of a less aggressive subtype.

The incidence of cystic PNET (27%) within this series was considerably higher than the incidence reported previously, which peaked at 17% [1,6,11–16]. This may be a function of the increased use of high-resolution cross-sectional imaging resulting in the detection of incidental lesions. Historically, diagnosis of pancreatic lesions mainly followed symptomatic presentation. In the setting of pervasive cross-sectional imaging, the more indolent, asymptomatic, cystic PNET may be increasingly detected relative to solid PNET. The incidence of cystic PNET at a high-volume, tertiary referral center specializing in pancreatic disease may also reflect selection bias. Due to the referral pattern of patients with pancreatic cysts to the Indiana University Pancreatic Cyst and Cancer Early Detection Center, the incidence may be higher at a specialized center and not generalizable to the general population.

The differences in clinicopathologic features of cystic PNET suggest this disease is a distinct, less aggressive tumor with its own unique biology. Traditionally, cystic PNET was believed to represent a solid PNET that had undergone necrosis and degenerative changes [3,6,12,13,15,16]. The two most commonly described mechanisms included: 1, a slow-growing PNET that develops a thick, fibrous capsule eventually restricting blood supply resulting in infarction, liquefactive necrosis, and cystic change; 2, an internal hemorrhage within the highly vascular PNET resulting in cyst development [3,6,15]. If cystic PNET were merely the result of cystic degeneration of a solid PNET, the presumption is that there would exist an identical biologic origin. Under this premise, cystic and solid PNETs would be expected to have nearly identical preoperative and molecular characteristics. Multiple studies support this, showing no difference in overall survival between resected cystic and solid PNETs [1,6,11–13,15,16]. However, this theory remains contentious. While Koh et al. also found similar long-term outcomes in review of PNET, the authors concluded a less aggressive biology of cystic PNET based on lower rates of malignancy, node positivity, and decreased Ki-67 index [3]. Several studies have identified very few cystic PNETs with signs of necrosis on surgical

pathology, in contrast to what would be expected if cystic PNETs developed from solid lesions [6,16]. Furthermore, cystic PNETs tend to present more commonly in the body and tail of the pancreas [3,6,11,12], have lower Ki-67 index [3,6,16], and have fewer distant metastases compared with their solid counterparts [6,21], all of which corroborate the results reported in this series. As evidenced by the multiple cited independent institutional studies, cystic PNETs carry disparate features from solid PNETs that likely represent a distinct entity.

Although the clinicopathologic features appeared disparate, the data found that surgical pathology, recurrence, and survival were identical between cystic and solid PNETs. TNM staging and the presence of metastatic disease, an important prognostic indicator for malignant disease was no different between cystic and solid PNET, despite less aggressive Ki67 and WHO histologic grading. Survival, the ultimate prognostic outcome, was similarly not different. These data suggest that Ki67 and histologic grading may be less important than other clinicopathologic features in PNET disease prognostication.

The unique clinicopathologic features may call for distinct management specific to cystic PNET. Surgical resection has been the standard treatment in the diagnosis of PNET, regardless of size, cystic/solid nature, or nodal status. However, several studies comparing outcomes of operative and nonoperative management have identified certain PNET patients that were deemed suitable for surveillance [12,18,22–25]. Small (<2 cm), asymptomatic, nonfunctioning PNETs demonstrated minimal to no growth over time and rarely developed malignancy or metastatic disease in limited follow-up [12,18,22–25]. Cystic PNETs often fall under these specifications and as such, patients with cystic PNET may be candidates for non-operative management as well. Although the annual number of pancreatic resections performed for cystic pancreatic neoplasms has quadrupled over the last decade [7], surgical resection does not come without inherent risks [8,22,25]. Preoperative surgical risk stratification is therefore of the upmost importance. While select PNETs may be observed, the risk for malignancy in functional, large (>4 cm), symptomatic tumors outweighs the risk of morbidity following pancreatic resection and should therefore undergo resection [18,22–24]. We suggest careful selection of patients for surveillance versus surgical management with continued reassessment. Although further studies are necessary to define criteria for non-operative management of cystic PNETs, surgeons and patients should currently only discuss alternatives to resection in select circumstances as resection is still the primary recommendation based on the data that is available.

While this study was able to demonstrate clinicopathologic features of cystic PNET largely in agreement with current literature, there are important recognized limitations. First, the retrospective design carried intrinsic limitations and biases, particularly when analyzing medical records prior to the advent of electronic medical records. Incomplete documentation within patient records was a prevailing theme across all variables. Furthermore, cystic lesions of the pancreas were managed differently in 1988 as compared to the present time. Historically, the various cystic lesions were all approached the same way, almost exclusively being treated with surgical resection since accurate diagnosis was difficult until after resection and malignant potential/tumor aggressiveness of each lesion was unclear [10]. Patients undergoing resection at the beginning of our study period were potentially quite different from those undergoing resections towards the end of the study period. The ratio of cystic to solid PNET increased over time in the current series. Changing thresholds for operating on cystic lesions could account for the increase in resected lesions. This would also explain our higher rate of total cystic PNET compared to existing literature. Second, this study was limited to only surgical patients. Indication for surgical resection strengthened when concerning features exist. Therefore, a surgical PNET population likely represented more aggressive tumors than the entire PNET population, which would include many who never had surgery and potentially treated with nonoperative therapies. Finally, the major limitation to this study was the lack of complete, available patient follow-up after surgical resection. Patients in our center often travel long distances to have an operation. Postoperatively, the patient in some cases elected to follow-up with local surgeons, gastroenterologists, or medical oncologists as adjuvant chemotherapy serves limited value in this patient population. The Indiana Cancer Registry currently tracks all patients in Indiana with tumors and serves as a major source of follow-up data. However, PNET patients were not followed before 2010. Available data were further biased by patients more likely returning to the Indiana University Indiana Health System if experiencing disease recurrence.

Conclusions

Our data suggest cystic PNET is a distinct and possibly less aggressive subtype of PNET based on differences in patient demographics, symptoms, tumor functionality, tumor location, Ki-67 index, and histologic grade. These differences indicate that the pathogenesis of cystic PNETs follow a separate course from solid PNETs. However, in spite of the differences seen in clinicopathologic features, no difference was seen between pathologic stage, recurrence, or long-term survival. Additional study of cystic PNET focused on both surgical and surveillance patients are necessary to more accurately define cystic PNET as possibly a unique, more favorable lesion that would alter contemporary management.

Acknowledgements

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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