Neuroendocrine tumors of the pancreas: Degree of cystic component predicts prognosis

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Background. *Although most pancreatic neuroendocrine tumors are solid, approximately 10% are cystic. Some studies have suggested that cystic pancreatic neuroendocrine tumors are associated with a more favorable prognosis.*

Methods. *A retrospective review of all patients with pancreatic neuroendocrine tumors who underwent operative resection between 1999 and 2014 at a single academic medical center was performed. Based on cross-sectional imaging performed before operation, pancreatic neuroendocrine tumors were classified according to the size of the cystic component relative to the total tumor size: purely cystic (100%), mostly cystic (≥50%), mostly solid (<50%), and purely solid (0%). Clinicopathologic characteristics and recurrence-free survival were assessed between groups.*

Results. *In the study, 214 patients met inclusion criteria: 8 with purely cystic tumors, 7 with mostly cystic tumors, 15 with mostly solid tumors, and 184 with purely solid tumors. The groups differed in terms of tumor size (1.5 ± 0.5, 3.0 ± 1.7, 3.7 ± 2.6, and 4.0 ± 3.5 cm), lymph node positivity (0%, 0%, 26.7%, and 34.2%), intermediate or high grade (0%, 16.7%, 20.0%, and 31.0%), synchronous liver metastases (0%, 14.3%, 20.0%, and 26.6%) and need for pancreaticoduodenectomy (0%, 0%, 6.7%, and 25.0%), respectively. No cases of purely cystic pancreatic neuroendocrine tumors were associated with synchronous liver or lymph node metastasis, intermediate/high grade, recurrence, or death due to disease. Among patients presenting without metastatic disease, 10-year recurrence-free survival was 100% in patients with purely and mostly cystic tumors versus 53.0% in patients with purely and mostly solid tumors; however, this difference did not reach statistical significance.*

Conclusion. *Pancreatic neuroendocrine tumors demonstrate a spectrum of biologic behavior with an increasing cystic component being associated with more favorable clinicopathologic features and prognosis. Purely cystic pancreatic neuroendocrine tumors may represent 1 subset that can be safely observed without immediate resection. (Surgery 2016;160:708-13.)*

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Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of neoplasms that originate from progenitor islet cells. They can exhibit a wide range of biologic behavior from entirely benign and indolent to frankly malignant and capable of locally invasive growth and metastasis. Identifying factors that help distinguish the biologic aggressiveness of these tumors, especially in the preoperative setting, is critical.

Although most PNETs are solid, approximately 10% are cystic in nature.[1-3] Several studies have compared cystic PNETs with either solid PNETs[2-4] or nonendocrine cystic tumors of the pancreas.[5] Some have suggested that cystic PNETs may be less biologically aggressive than their solid counterparts.[6] Our experience is that cystic PNETs exist across a morphological spectrum that includes purely cystic lesions, cystic tumors with a solid component, and mostly solid PNETs with a smaller cystic component. Previous studies have not investigated the biologic or clinical importance of this observation. Therefore, the purpose of this study

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is to present our institutional experience with all forms of cystic PNETs and to compare their clinicopathologic characteristics and outcomes with those of solid PNETs. In addition, we set out to determine the existence of a subset of PNETs that, due to their benign nature, could be safely observed without resection.

METHODS

A retrospective review of all patients with PNETs who underwent operative resection between 1999 and 2014 at Stanford University Medical Center was performed. The study was approved by the institutional review board. PNETs were classified as either cystic or solid based on preoperative cross sectional imaging (computed tomography or magnetic resonance imaging). The maximal diameter of the cystic component relative to the maximal diameter of the overall tumor was measured to further characterize them as purely cystic (no solid component), mostly cystic (cystic component ≥50% of tumor diameter), mostly solid (cystic component <50% of tumor diameter), or purely solid (no cystic component). Images were reviewed independently by 2 separate reviewers, and cases of discordance were settled by a third reviewer.

Individual patient data were then abstracted from the electronic medical record. Clinicopathologic data included age, sex, symptomatology, presence of multiple endocrine neoplasia (MEN) or other genetic syndrome, functional status, location of tumor, presence of distant metastases, operation performed, whether a minimally invasive approach was utilized, additional organs resected, synchronous hepatectomy or liver directed therapy performed, need for vascular resection, pathologic size, total number of lymph nodes (LNs) harvested, presence of positive LN, margin status, World Health Organization grade, presence of lymphovascular invasion, perineural invasion, and tumor necrosis. Time to locoregional recurrence, distant metastasis, and death was recorded.

Clinicopathologic characteristics were first compared among patients with purely cystic, mostly cystic, mostly solid, and purely solid PNETs. Because preliminary analyses demonstrated that purely and mostly cystic as well as mostly and purely solid PNETs behaved similarly, statistical comparisons were made between these 2 groups. Overall survival was compared between patients with purely/mostly cystic and purely/mostly solid PNETs. Among patients who presented without metastatic disease, recurrence-free survival was compared. Statistical significance was assessed using the Student *t* test, Fisher exact test, or Mantel-Cox log-rank test, when appropriate. Statistics were performed via SPSS version 20.0 (IBM Corporation, Armonk, NY) and GraphPad Prism 6.0 (GraphPad Software, Inc, La Jolla, CA).

RESULTS

Of the 214 resected PNETs that met all inclusion criteria during the study period (1999–2014), 30 (14.0%) were at least partially cystic. Specifically, 8 (3.7%) were purely cystic, 7 (3.3%) mostly cystic, 15 (7.0%) mostly solid, and 184 (86.0%) purely solid. Indications for operation in the patients with purely cystic lesions included preoperative fine needle aspirate (FNA) consistent with a neuroendocrine neoplasm (2), preoperative FNA with atypical cells (1), symptoms (1), interval growth (1), patient or surgeon preference (2), and unknown (1). Purely cystic PNETs exhibited the most favorable features, as none were associated with synchronous liver metastases, LN involvement, intermediate- or high-grade biology, need for pancreaticoduodenectomy or vascular resection, or recurrence during the follow-up period.

Complete demographic, clinical, operative, and histopathologic data for patients are listed in Table I. Compared with PNETs that were purely/mostly solid, PNETs that were purely/mostly cystic tended to be smaller (2.3 cm vs 3.9 cm, $P = .05$), more likely to be associated with MEN (26.7% vs 6.5%, $P = .01$), less likely to be functional (0% vs 23.6%, $P = .04$), less likely to be associated with lymph node involvement (0% vs 33.7%, $P < .01$) with a trend toward less frequent synchronous liver metastases (6.7% vs 26.1%, $P = .09$), less likely to undergo pancreatoduodenectomy (0% vs 23.6%, $P = .04$), more likely to have a minimally invasive approach (53.3% vs 17.1%, $P < .01$), and more likely to be associated with low-grade histology (73.3% vs 47.7%, $P = .05$).

Overall survival at both 5 and 10 years was 100% in patients with purely/mostly cystic tumors compared with 88.7% and 78.2%, respectively, in patients with purely/mostly solid PNETs ($P = .37$; Fig 1). Among patients with nonmetastatic disease at the time of presentation, recurrence-free survival at 10 years was 53.0% in the purely/mostly solid group versus 100% in the purely/mostly cystic group, although this difference did not reach statistical significance ($P = .24$; Fig 2). On Cox proportional hazards regression analysis, increasing size (hazard ratio 1.32; 95% confidence interval, 1.19–1.47) and higher tumor grade (hazard ratio 3.05; 95% confidence interval, 1.14–8.19) were associated with recurrence-free survival, although purely/mostly solid morphology (hazard