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Patients with a resected pancreatic mucinous cystic neoplasm have a better prognosis than patients with an intraductal papillary mucinous neoplasm: A large single institution series

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ABSTRACT

Background/Objectives: Mucinous cystic neoplasms (MCNs) are rare pancreas tumors distinguished from intraductal papillary mucinous neoplasms (IPMNs) by the presence of ovarian-type stroma. Historical outcomes for MCNs vary due to previously ambiguous diagnostic criteria resulting in confusion with IPMNs. This study seeks to characterize and clarify the clinical features and long-term outcomes of MCNs versus IPMNs in the largest single-institution series of pathology-confirmed MCNs to date.
Methods: We compared 142 MCNs and 746 IPMNs resected at a single institution. MCNs were reviewed for confirmation of ovarian-type stroma and reclassified according to current WHO guidelines.
Results: MCNs presented almost exclusively in middle-aged women (median 47.5 years, 96.5% female) as solitary (100%), macrocystic (94.2%) lesions in the distal pancreas (92.1%). IPMNs were distributed equally by sex in an older population (median 69.0 years, 49.6% female) and favored the proximal pancreas (67.6%). Compared with IPMNs, MCNs were larger (4.2 cm vs 2.5 cm) and more often low-grade (71.1% vs 13.8%). Associated invasive carcinoma was less common in MCNs than in IPMNs (9.9% vs 32.4%). Surgical resection was curative for 100% of noninvasive MCNs. Patients with an MCN-associated invasive carcinoma had a much better prognosis than did patients with an IPMN-associated invasive carcinoma with 10-year disease-specific survival of 79.6% versus 27.2%, respectively.
Conclusion: MCNs have a stereotypical clinical profile that is readily distinguishable from IPMNs based on demographic features, imaging, and pathology. Most MCNs are noninvasive and curable with surgical resection. Prognosis remains excellent even for invasive disease with 10-year survival approaching 80% following resection.

Introduction

Mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) are cystic precursors to invasive ductal adenocarcinoma (PDAC) characterized by a neoplastic mucin-producing epithelial lining. MCNs were originally described more than a century ago, but their significance wasn't fully appreciated until 1978 when Compagno and Oertel emphasized the malignant potential of mucin-producing cystic neoplasms over their serous counterparts [1]. The first description of IPMNs followed just a few years later in 1982 when Ohashi et al. reported four cases of a distinctive "mucus-secreting pancreatic cancer" originally thought to be a subtype of MCN disease rather than a separate neoplasm [2,3].

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MCNs are distinguished from IPMNs by the presence of a distinctive ovarian-type stroma comprised of densely packed spindle-cells that may express progesterone and estrogen receptors [4,5]. MCNs generally do not communicate with the ductal system and occur almost exclusively in the body and tail regions of the pancreas. They tend to be quite large with a median size of 4–5 cm, though some have been documented up to 35 cm. MCNs have a strong female preponderance (20:1) and are usually diagnosed in the fourth and fifth decades of life. IPMNs lack ovarian-type stroma and by definition involve the ductal system. They affect both sexes equally between the sixth and seventh decades of life and affect the head of the pancreas more often than the tail [6].

The World Health Organization (WHO) finally recognized IPMN disease as a distinct histopathological entity in 1996 [7], but ambiguous diagnostic criteria and terminology resulted in ongoing misclassification of branch-duct type IPMNs as MCNs. It was not until 2006 that the diagnostic criteria were revised to include ovarian-type stroma as a distinguishing feature of MCNs [8]. However, by this point, the growing body of MCN literature consisted mostly of flawed studies contaminated with IPMNs. The goal of the present study is to clarify the clinical features, malignant potential, and long-term outcomes of MCNs defined by the presence of ovarian stroma in the largest single-institution, pathology-confirmed series to date.

Methods

Patients

After obtaining approval from the Johns Hopkins Institutional Review Board, cases were identified from a prospectively managed pathology database. All potential MCNs were reviewed under the direct supervision of a single senior pathologist specializing in pancreatic pathology (RHH). Study inclusion was contingent upon the identification of ovarian stroma and confirmed cases were re-graded according to the 2010 WHO guidelines [9]. A comparison cohort of resected IPMNs was also identified consisting of cases resected after the 1996 WHO classification through 2015. Re-resections, cases with an unspecified grade of dysplasia, and IPMNs diagnosed secondary to an unrelated primary malignancy were all excluded. Clinical data for all study subjects were collected from the electronic medical record and original paper charts.

Analysis

Statistical analyses were performed using the Stata 13 statistical software package (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP) and GraphPad Prism version 7.00 for Mac (GraphPad Software, La Jolla California USA, www.graphpad.com). All datasets were non-normally distributed based on the Shapiro-Wilk *W* test and nonparametric tests of significance were used for analyses. All analyses were performed as two-tailed tests with a significance threshold of $\alpha = 0.05$.

Categorical data were expressed as relative frequencies (%) with total observations (*n*) and evaluated using Fisher's exact test or the chi-square test. Continuous data were summarized as medians with interquartile ranges (IQR) and compared using the Wilcoxon or Kruskal-Wallis rank tests depending on the number of comparison groups. For matched datasets, analogous evaluations were performed using either the Wilcoxon signed-rank test, McNemar test, or Stuart-Maxwell marginal homogeneity test. The last is a generalization of the McNemar test that allows for comparison of multilevel categorical variables in matched pairs.

Survival analysis

Overall (OS) and disease-specific survival (DSS) were assessed by the Kaplan-Meier method with log-rank comparisons between cohorts and subgroups of interest. Survival was defined as the total time in years between resection and death or date of censoring. DSS includes only those deaths attributed to pancreatic cancer or its complications. Follow-up time and survival were calculated using the most recent confirmed medical encounter based on our records. Patients without confirmed deaths were not assumed to be alive at the time of publication and were censored at their most recent follow-up. Deaths were determined by chart review and through the Social Security Death Index (SSDI) with causes obtained from the medical record and death certificates.

Results

Demographics and clinicopathological features

From 1984 through 2015, 142 pathology-confirmed MCNs were resected at the Johns Hopkins Hospital, accounting for <2% of all pancreatic resections during that timeframe. Of 142 MCNs, 101 (71.1%) had low-grade dysplasia (LGD), 15 (10.6%) intermediate-grade dysplasia (IGD), 12 (8.5%) high-grade dysplasia (HGD), and 14 (9.9%) had an associated invasive cancer (ICA). The IPMN cohort consisted of 746 cases resected between 1996 and 2015. Pathology results included 103 (13.8%) cases with LGD, 247 (33.1%) with IGD, 154 (20.6%) with HGD, and 242 (32.4%) with an associated ICA. Detailed patient demographics and clinicopathological data are presented in Table 1.

Males with an MCN were extremely uncommon in our series (n = 5, 3.5%) and tended to be much older than their female counterparts [59.0 (56.0–61.0) years vs 47.0 (37.0–57.0) years, $p = 0.03$]. Among female patients, 66 (48.2%) were premenopausal and 71 (51.8%) were peri- (n = 6) or postmenopausal (n = 65). Ten (14.9%) premenopausal women presented during or shortly after pregnancy and 16 (22.5%) peri/postmenopausal patients reported a history of estrogen-based HRT. No baseline demographics evaluated in this study were associated with the pathological finding of invasive disease. However, MCNs with an associated ICA were significantly larger on pathology compared to those without an associated ICA ($p = 0.0002$). As demonstrated by Fig. 1, increasing tumor size was also associated with increasing grade of dysplasia ($p = 0.0001$).

Clinical features in IPMNs associated with the presence of ICA included advanced age ($p = 0.003$), decreased body mass index (BMI) ($p = 0.001$), history of heavy alcohol use ($p = 0.04$), preoperative diabetes mellitus ($p = 0.003$), and American Society of Anesthesia (ASA) class ($p < 0.001$). For the purpose of this study, "heavy alcohol use" was defined as a documented history of alcoholic pancreatitis, alcohol dependence, or reported consumption at or approaching daily use. Surgical resections for IPMNs with an associated ICA consisted of more TPs and fewer DPs compared to IPMNs without an associated ICA ($p < 0.001$). Invasive disease was also associated with greater lymph node yield ($p < 0.0001$) and larger tumor size ($p < 0.001$) on pathology.

MCN presenting symptoms

Patients were considered symptomatic if complaints were consistent with a pancreatic source defined as left upper quadrant (LUQ) or epigastric pain in the absence of another obvious and identifiable causes (e.g., cholelithiasis, diverticulitis, nephrolithiasis). Abdominal pain was the most common presenting complaint (n = 93, 65.5%), but only 72 (50.7%) had pancreas-type

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