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Association of Preoperative Risk Factors With Malignancy in Pancreatic Mucinous Cystic Neoplasms:

A Multicenter Study

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Abstract

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IMPORTANCE—Pancreatic mucinous cystic neoplasms (MCNs) harbor malignant potential, and current guidelines recommend resection. However, data are limited on preoperative risk factors for malignancy (adenocarcinoma or high-grade dysplasia) occurring in the setting of an MCN.

OBJECTIVES—To examine the preoperative risk factors for malignancy in resected MCNs and to assess outcomes of MCN-associated adenocarcinoma.

DESIGN, SETTING, AND PARTICIPANTS—Patients who underwent pancreatic resection of MCNs at the 8 academic centers of the Central Pancreas Consortium from January 1, 2000, through December 31, 2014, were retrospectively identified. Preoperative factors of patients with and without malignant tumors were compared. Survival analyses were conducted for patients with adenocarcinoma.

MAIN OUTCOMES AND MEASURES—Binary logistic regression models were used to determine the association of preoperative factors with the presence of MCN-associated malignancy.

RESULTS—A total of 1667 patients underwent resection of pancreatic cystic lesions, and 349 (20.9%) had an MCN (310 women [88.8%]; mean (SD) age, 53.3 [14.7] years). Male sex (odds ratio [OR], 3.72; 95% CI, 1.21–11.44; $P = .02$), pancreatic head and neck location (OR, 3.93; 95% CI, 1.43–10.81; $P = .01$), increased radiographic size of the MCN (OR, 1.17; 95% CI, 1.08–1.27; $P < .001$), presence of a solid component or mural nodule (OR, 4.54; 95% CI, 1.95–10.57; $P < .001$), and duct dilation (OR, 4.17; 95% CI, 1.63–10.64; $P = .003$) were independently associated with malignancy. Malignancy was not associated with presence of radiographic septations or preoperative cyst fluid analysis (carcinoembryonic antigen, amylase, or mucin presence). The median serum CA19-9 level for patients with malignant neoplasms was 210 vs 15 U/mL for those without ($P = .001$). In the 44 patients with adenocarcinoma, 41 (93.2%) had lymph nodes harvested, with nodal metastases in only 14 (34.1%). Median follow-up for patients with adenocarcinoma was 27 months. Adenocarcinoma recurred in 11 patients (25%), with a 64% recurrence-free survival and 59% overall survival at 3 years.

CONCLUSIONS AND RELEVANCE—Adenocarcinoma or high-grade dysplasia is present in 14.9% of resected pancreatic MCNs for which risks include male sex, pancreatic head and neck location, larger MCN, solid component or mural nodule, and duct dilation. Mucinous cystic neoplasm-associated adenocarcinoma appears to have decreased nodal involvement at the time of resection and increased survival compared with typical pancreatic ductal adenocarcinoma. Indications for resection of MCNs should be revisited.

Mucinous cystic neoplasms (MCNs) of the pancreas are rare cysts with malignant potential that typically occur in the pancreatic body or tail of perimenopausal women.[1] Mucinous cysts were first distinguished from the typically benign serous cysts by Compagno and Oertel[2,3] in the 1970s. Later, in 2000, the World Health Organization (WHO) proposed criteria that further defined MCNs by their ovarian stroma on histologic analysis; these diagnostic criteria better distinguish MCNs from premalignant mucinous pancreatic ductal cysts of intraductal papillary mucinous neoplasms (IPMNs).[4,5] The risk of high-grade dysplasia (HGD) or invasive adenocarcinoma within an MCN has varied in the literature from 10% to 39%.[6–11]

Given the possibility of malignant transformation, resection is a consideration for management of IPMNs and MCNs. Recent international consensus guidelines have proposed that branch-duct IPMNs with concerning features (symptoms, ductal dilatation, presence of mural nodule, and size >3 cm) should be managed operatively in appropriate patients; however, for IPMNs that lack any of these features, radiographic surveillance may be appropriate.[12,13] These resection guidelines for IPMNs have been found to be sensitive but not specific for malignancy.[14] For the management of MCNs, however, these same consensus guidelines recommend resection of all MCNs in patients who are operative candidates.[12,13]

Despite these aggressive recommendations, the risk factors for developing malignant MCNs are not well characterized.[13,15] The literature that addresses factors associated with malignant MCNs is limited by single-institution series and small sample sizes and has primarily focused on pathologic factors that are determined postoperatively rather than on preoperative factors that could potentially optimize management strategy.[6–9,11,15–21] We sought to determine preoperative factors associated with increased risk of malignancy in patients with resected MCNs in a modern US cohort of patients undergoing resection of MCNs at 8 institutions after the 2000 WHO diagnostic guidelines were in place.[4]

Methods

Patient Population

The Central Pancreas Consortium represents a collaboration of 8 academic medical centers in the United States: Winship Cancer Institute of Emory University, Atlanta, Georgia; Vanderbilt University Medical Center, Nashville, Tennessee; Washington University School of Medicine, St Louis, Missouri; University of Wisconsin School of Medicine and Public Health, Madison; University of Louisville, Louisville, Kentucky; Northwestern University Feinberg School of Medicine, Chicago, Illinois; University of North Carolina at Chapel Hill; and University of Cincinnati Cancer Institute, Cincinnati, Ohio. All patients who underwent resection of pancreatic cystic lesions from January 1, 2000, to December 31, 2014, were identified. Patients with a pathologic diagnosis of pancreatic MCNs were included. Clinicopathologic, treatment, recurrence, and outcome data were collected through retrospective medical record review. Survival data were primarily gathered from documented clinical follow-up and were confirmed using the Social Security Death Index database. This study was approved by the institutional review boards of all participating centers, and ethical standards of the committees on human experimentation of these institutions were maintained and consent waived.

Statistical Analysis

Comparisons of categorical variables were conducted with χ^2 or Fisher exact tests. Two-tailed t tests were used to compare parametric data, whereas Mann-Whitney tests were used for assessment of nonparametric data. Associations between preoperative factors and adenocarcinoma or HGD were determined with univariate binary logistic regression analysis. Variables with a statistically significant association on univariate analyses were included in a multivariable binary logistic regression model. Survival was estimated by

Kaplan-Meier log-rank analyses; 90-day postoperative mortalities were excluded from recurrence and survival analyses. Statistical analyses were conducted using SPSS statistical software, version 23.0 (IBM). $P < .05$ was considered statistically significant.

Results

Patient Population and Risk of Adenocarcinoma or HGD

A total of 1667 patients underwent resection of pancreatic cystic lesions, and 349 (20.9%) had an MCN (310 women [88.8%]; mean (SD) age, 53.3 [14.7] years). All MCNs were solitary lesions, with most occurring in the distal pancreas (294 [84.2%]). Most patients were symptomatic at presentation (223 [63.9%]), with symptoms of abdominal pain or discomfort, abdominal fullness, pancreatitis, and jaundice. The mean (SD) radiographic size of the resected MCNs was 5 (4.1) cm, with a solid component or mural nodule in 71 of 289 MCNs (24.6%) and pancreatic duct dilation present in 50 of 293 patients (17.1%). Further data on presentation, clinicopathologic factors, and treatment of all patients undergoing MCN resection are described in Table 1.

Fifty-two MCNs (14.9%) had associated adenocarcinoma (44 [12.6%]) or HGD (8 [2.3%]). Male sex (15 [28.8%] vs 24 [8.1%]; $P < .001$), pancreatic head and neck location (19 [38.8%] vs 36[12.5%]; $P < .001$), increased radiographic size of the MCN (7.2 vs 4.6 cm; $P = .004$), radiographic presence of a solid component or mural nodule (22 [53.7%] vs 49 [19.8%]; $P < .001$), and duct dilation (19 [43.2%] vs 31 [12.4%]; $P < .001$) were associated with adenocarcinoma or HGD compared with benign MCNs. Adenocarcinoma or HGD was not associated with the presence of radiographic septations or preoperative cyst fluid analysis (carcinoembryonic antigen, amylase, or mucin presence). The median serum CA19-9 level for patients with adenocarcinoma or HGD was 210 U/mL (range, 2–546 470 U/mL) (n = 102) compared with 15 U/mL (range, 1–10 529 U/mL) (n = 29) for those without ($P = .001$). These differences between patients with and without adenocarcinoma or HGD are further outlined in Table 1.

On univariate binary logistic regression, neither cyst fluid analysis nor serum CA19-9 was predictive of malignancy (Table 2). However, male sex, increased radiographic size of the MCN, pancreatic head and neck location, presence of a solid component or mural nodule, and duct dilation were associated with adenocarcinoma or HDG on final pathologic analysis (Table 2). When accounting for these factors in multivariable analysis, all persisted as independent preoperative risk factors for adenocarcinoma or HGD (Table 2). Ten patients with adenocarcinoma or HGD had MCNs smaller than 3 cm. For these patients with small malignant lesions, 6 (60%) had at least 2 other high-risk features: male sex, pancreatic head and neck location, solid component, or dilated duct.

MCN-Associated Adenocarcinoma, Recurrence, and Survival

In the 44 patients with adenocarcinoma, 41 (93.2%) had lymph nodes harvested, with nodal metastases in only 14 patients (34.1%). One patient with adenocarcinoma died within 90 days of surgery. These patients are further described in Table 3. The median follow-up for patients with adenocarcinoma was 27 months (range, 0.21–143.1 months). The 3-year

recurrence-free survival was 64% (Figure 1), and overall survival for patients with MCN-associated adenocarcinoma was 59% at 3 years (Figure 2). For patients who did not have invasive MCNs, there were no events of recurrence.

Discussion

To our knowledge, this study represents the largest series in the literature describing preoperative factors associated with malignancy in patients undergoing resection of MCNs. In 349 patients, 52 (14.9%) had MCN-associated adenocarcinoma or HGD. Male sex, pancreatic head and neck location, increased radiographic size of the MCN, presence of a solid component or mural nodule, and pancreatic duct dilation on preoperative imaging were independently associated with adenocarcinoma or HGD. For the 44 patients with invasive adenocarcinoma, the 3-year recurrence-free and overall survival rates were 64% and 59%, respectively, whereas there were no recurrences in patients with noninvasive MCN.

With increased use and advancements in cross-sectional imaging, the diagnosis of MCNs has been increasing over time.[22] In a 15-year series of resections of pancreatic cystic lesions, MCNs constituted 21% of all pathologic findings. Similarly, in other series that span decades, 10% to 45% of resected pancreatic cystic lesions were MCNs.[23,24] Unlike the more common cystic lesion IPMNs, for which consensus guidelines offer clear criteria for surveillance or resection, resection is recommended in all patients with MCNs who are deemed surgical candidates.[12,13] However, there are limited data to support these aggressive recommendations for MCNs, and understanding the preoperative risk of MCN-associated malignancy becomes integral in determining appropriate treatment strategies. In addition, as diagnoses of MCN become more frequent, defining criteria for resection to better balance operative morbidity with potential benefit in a larger population becomes even more essential.

Despite its increasing importance, the natural history of MCNs is not well understood. Although some have argued that all MCNs represent premalignant entities,[13,15] others have contended that some MCNs may be indolent and do not pose that risk.[25] Until now, studies[6–9,11,15–21] that have attempted to elucidate the risks of malignancy in resected MCNs have been limited by small sample sizes, which may not be representative of MCNs as a whole and did not allow for creation of multivariable models, exhibited single institutional bias, or focused on postoperative pathologic predictors rather than factors that can be assessed before surgical intervention. To circumvent these issues, the current study included a large population from 8 centers across the United States with a goal of determining preoperative rather than pathologic factors associated with malignancy that could be applied to treatment algorithms before resection.

Malignancy in MCNs is neither uncommon nor pervasive. Series of resected MCNs during the past few decades have reported adenocarcinoma or HGD in 10% to 39% of surgical specimens; similarly, the rate of adenocarcinoma or HGD in this modern Western series was 15%.[6,7,9–11,18–21,23] When studies[6,8,9,11,18–21] have distinguished between invasive disease and carcinoma in situ, invasive adenocarcinoma rates ranged from 1% to 16%, which is comparable to the 13% reported in this series. In addition, although other series have

reported HGD in 4% to 12% of MCNs, the rate was lower in the current series (2%).[6,9,11,18–21]

Although MCNs are more common in females because the presence of ovarian stroma represents one of the diagnostic criteria per the WHO 2000 definition,[4] this pathologic entity also occurs in men.[6,15,18–21] In the present study, 11% of patients with MCNs were male, and male sex was associated with increased risk of malignancy. When studies[6,9,16,18,20,21,23,26] have included only patients with MCNs defined by their ovarian stroma, the occurrence of MCNs in men has been reported at frequencies between 0% and 20%. In previous studies,[6,15,18–21] adenocarcinoma or HGD has been common in males with MCNs; however, the present study is the first, to our knowledge, to identify an independent association between male sex and increased risk of malignancy in MCNs.

In addition to patient demographics, preoperative laboratory values could help to predict malignancy risk. Few other series have evaluated the preoperative CA19-9 value and risk of malignancy within an MCN.[6,11] Like these previous studies,[6,11] the present study found that an elevated CA19-9 level was associated with increased risk of malignancy; however, this association did not persist in multivariable analysis. Analyses of MCN cyst fluid for carcinoembryonic antigen, amylase, and presence of mucin have also been investigated. When evaluating pancreatic cysts, carcinoembryonic antigen cystic fluid levels can help predict whether a cyst is mucinous (MCN or IPMN); however, beyond that distinction, these markers do not reliably distinguish between IPMNs and MCNs or malignancy.[13,27] Similarly, in the present study, no association was found between these MCN cyst-fluid values and the presence of malignancy.

Cross-sectional imaging findings perhaps can provide the greatest insight into the risk of malignancy through elucidation of MCN location and size and determination of the presence of mural nodules or pancreatic ductal dilation. Most MCNs have been reported in the pancreatic body and tail (89%–99%), with 84.2% in the present series.[6,7,9,16,18–21] Although less common, MCN location in the pancreatic head has been associated with malignancy in other studies[15,23] and in the present series. As in IPMNs, increased radiographic size also appears to be associated with malignancy in MCN. The mean size of all MCNs resected in this series was 5 cm, with increased size being associated with increased risk of malignancy, comparable to previous findings in the literature.[6,15,18,20,21] In this study, no specific size was predictive of malignancy because adenocarcinoma or HGD was present even in small MCNs (<3 cm). In most of those cases, however, other risk factors, such as mural nodule or location in the pancreatic head and neck, were present. Such patterns have previously been described where tumors smaller than 3 to 5 cm without other concerning features (mural nodule or elevated CA19-9 level) were found to be benign.[6,8,9,11,18–20] Across most studies,[6,7,11,19–21] including the present one, mural nodules or solid components within an MCN have carried the highest risk of malignancy. In fact, in the small series of Le Baleur et al,[18] a mural nodule on a computed tomogram was 100% sensitive and 98% specific for adenocarcinoma or HGD in MCNs. As such, presence of a mural nodule should be an indication for resection in appropriate surgical candidates. In IPMNs, duct dilation has been described as 1 risk factor for malignancy.[13] Similarly, we found that, for MCNs, pancreatic ductal dilation represents an imaging finding that creates concern for malignancy.[13]

The aforementioned risk factors (sex, location, radiographic size of the MCN, mural nodularity, and ductal dilation) could be considered in management strategies for patients with MCNs. As in IPMNs, perhaps not all patients with MCNs need to undergo resection but could be kept under radiographic surveillance. Furthermore, patients preoperatively identified to have low-risk MCNs may be candidates for parenchyma-sparing procedures rather than formal oncologic resections.[28] This recommendation seems appropriate because, in the present series and the published literature,[7,8,15,19,20] resection of an MCN that does not have an invasive component generally represents a curative procedure because events of recurrence after resection are extraordinarily rare. There are isolated reports of diffuse peritoneal recurrence after operative rupture of noninvasive MCNs and one instance of adenocarcinoma recurrence in a patient whose original pathologic findings were noninvasive, perhaps attributable to incomplete initial pathologic review.[9,21] This finding thereby suggests resection of nonmalignant disease to be curative.

For patients with MCN-associated adenocarcinoma, the tumor behavior and biological features appear distinct from typical pancreatic ductal adenocarcinoma. The lymph node positivity rate in this series was only 34% and has been as low as 0% to 17% in the literature.[8,19–21] The 3-year survival was 59% in the present series and has been reported at 44% to 83% previously.[6,21] Historically, typical pancreatic ductal adenocarcinoma is an aggressive disease process, being the fourth leading cause of cancer-related mortality in men and women in the United States.[29] In typical pancreatic adenocarcinoma, the median survival is far less than 3 years, reported to be 17 to 24 months, whereas in the present series of MCN-associated carcinoma, the median survival extended beyond 3 years. This finding suggests that perhaps these are distinct malignant tumors with differing outcomes or that MCN-associated adenocarcinoma is typically resected earlier in the disease.[30]

To our knowledge, this study represents the first multi-institutional Western study of this latitude conducted in a population undergoing MCN resection *after* the publication of the WHO 2000 criteria that define MCNs by ovarian stroma.[4,5] Thus, it is likely that during this timeframe in these academic institutions, MCNs were diagnosed using these pathologic criteria; however, given the scope and scale of the project across 8 different centers, pathologic re-review was not feasible to confirm the presence of ovarian stroma in all cases. Apart from the application of the WHO *pathologic* criteria, the ability to distinguish between IPMNs and MCNs with diagnostic certainty by imaging, preoperative laboratories, and cytologic testing is limited.[13,27] As such, without strictly applying WHO pathologic criteria to define MCNs, some IPMNs can be misclassified as MCNs and thereby contaminate series of MCNs that have not strictly used WHO criteria.[10,31] Therefore, the possibility exists that this series as well includes some patients with IPMNs; however, this contamination represents a clinical reality at the time point when physicians are determining treatment strategies for these patients. These WHO *pathologic* diagnostic criteria are only determined postoperatively on examination of surgical specimens. As such, these *pathologic* criteria are not available and thereby not applicable to the management decisions of these patients *preoperatively*. Thus, inclusion of patients who were diagnosed with MCNs not strictly defined by ovarian stroma is not only appropriate but also represents a clinical reality. In addition, in a study by Gil et al[19] that examined MCNs diagnosed by WHO criteria

compared with MCNs less stringently diagnosed, no differences were found in the demographics, invasive cancer rates, or outcomes of these groups.

This study was limited by its retrospective design. All included patients underwent resection of MCNs, and thus the natural history of the disease in patients who did not undergo resection could not be studied. In addition, because this series only includes patients who underwent resection, there could be a potential selection bias for patients with more aggressive MCNs. Radiographic re-review was not conducted; thus, data were gathered solely from the radiologic reports from cross-sectional imaging and/or endoscopic ultrasonography, and missing data were treated as unknown data points. Patients were treated at 8 centers across the United States where diagnostic and treatment algorithms were not standardized. However, this diversity through potential differences among practice patterns across institutions also represents a strength because results can likely be generalized to the US population treated at academic institutions nationally.

Conclusions

Adenocarcinoma or HGD is present in 14.9% of resected pancreatic MCNs for which risks include male sex, pancreatic head and neck location, larger radiographic size of the MCN, solid component or mural nodule, and duct dilation. Mucinous cystic neoplasm-associated adenocarcinoma appears to have decreased nodal involvement and thus increased survival compared with typical pancreatic ductal adenocarcinoma. Indications for resection of MCNs should be revisited.

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Key Points

Question What are the preoperative risk factors for malignancy in pancreatic mucinous cystic neoplasms?

Findings In this multicenter retrospective analysis of 349 patients, independent preoperative risk factors for malignancy were male sex, pancreatic head and neck location, larger mucinous cystic neoplasm, solid component or mural nodule, and duct dilation.

Meaning Indications for resection of mucinous cystic neoplasms should be revisited.

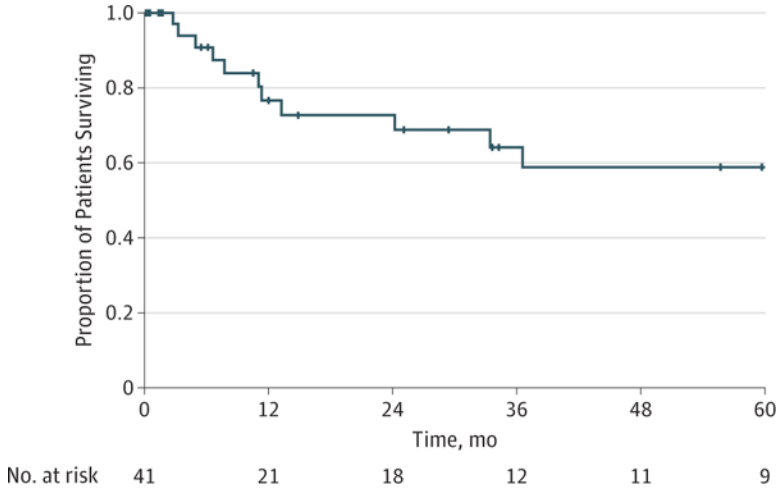

Figure 1. Recurrence-Free Survival of Patients With Mucinous Cystic Neoplasm-Associated Adenocarcinoma

The 3-year recurrence-free survival was 64%. Sixty months of follow-up was considered a reasonable length of time to illustrate; however, some patients continued follow-up beyond that point.

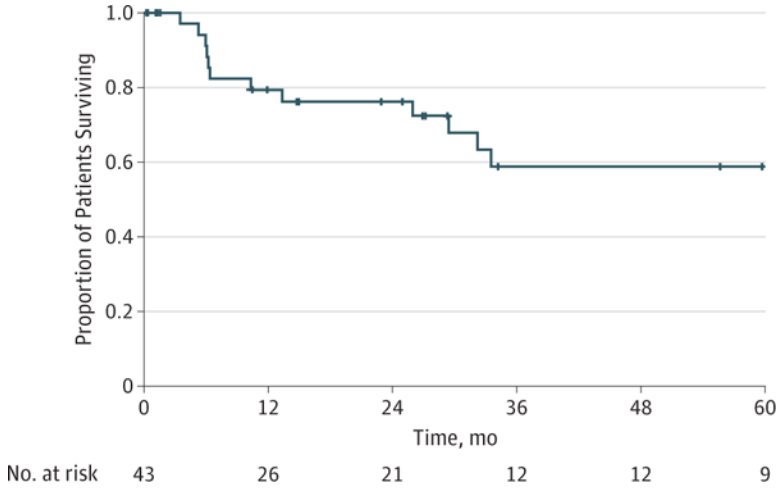

Figure 2. Overall Survival of Patients With Mucinous Cystic Neoplasm-Associated Adenocarcinoma

The 3-year overall survival was 59%. Sixty months of follow-up was considered a reasonable length of time to illustrate; however, some patients continued follow-up beyond that point.

Table 1

Clinicopathologic and Treatment Factors in All Patients Stratified by the Presence of Adenocarcinoma or HGD[a]

Variable	No. of Patients With Data Available	All Patients	Patients Without Adenocarcinoma or HGD	Patients With Adenocarcinoma or HGD	*P* Value
Male	349	39 (11.2)	24 (8.1)	15 (28.8)	<.001
BMI, mean (SD)	326	28.4 (6.9)	28.7 (7)	26.9 (6.3)	.10
Alcohol abuse	344	23 (6.7)	18 (6.1)	5 (9.8)	.51
Smoking	344	84 (24.4)	69 (23.5)	15 (29.4)	.47
Symptomatic	346	223 (64.5)	185 (62.9)	38 (73.1)	.21
Pancreatic head and neck	338	55 (16.3)	36 (12.5)	19 (38.8)	<.001
Radiographic size, mean (SD), cm	316	5.0 (4.1)	4.6 (3.7)	7.2 (5.6)	.004
Solid component or mural nodule	289	71 (24.6)	49 (19.8)	22 (53.7)	<.001
Duct dilation	293	50 (17.1)	31 (12.4)	19 (43.2)	<.001
Septations	296	114 (38.5)	100 (39.4)	14 (33.3)	.57
Cyst					
Mucin present	151	88 (58.3)	81 (60)	7 (43.8)	.33
CEA, median (range), ng/L	151	832 (0–7 484 620)	144 (0–7 484 620)	2438 (2–10 000)	.72[b]
Amylase, median (range), U/mL	117	4946 (1–657 500)	4946 (1–657 500)	6030 (30–23 529)	.57[b]
Preoperative serum CA19-9, median (range), U/mL	131	21 (1–546470)	15 (1–10 529)	210 (2–546470)	.001[b]
Pancreatectomy	349				
Distal		288 (82.5)	258 (86.9)	30 (57.7)	<.001
Whipple		51 (14.6)	30 (10.1)	21 (40.4)	
Central		6 (1.7)	6 (2)	0	
Total		4 (1.1)	3 (1)	1 (1.9)	
Lymph nodes harvested					
No. (%)	339	264 (77.9)	215 (74.9)	49 (94.2)	.001
Mean (SD)	339	8 (9)	7 (8)	12 (8)	<.001

Abbreviations: BMI, body mass index (calculated as the in kilograms divided by the square of height in meters); CEA, carcinoembryonic antigen; HGD, high-grade dysplasia; MCN, mucinous cystic neoplasm.

[a]Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Mann-Whitney test.

Table 2

Binary Logistic Regression of Preoperative Risk Factors for Adenocarcinoma or High-Grade Dysplasia

	OR (95% CI)			
Variable	**Univariate Analysis**	***P* Value**	**Multivariable Analysis**	***P* Value**
Male	4.61 (2.22–9.58)	<.001	3.72 (1.21–11.44)	.02
BMI	0.96 (0.91–1.01)	.10	NA	NA
Alcohol abuse	1.66 (0.59–4.69)	.34	NA	NA
Smoking	1.35 (0.70–2.62)	.37	NA	NA
Symptomatic	1.60 (0.83–3.09)	.16	NA	NA
Radiographic size	1.12 (1.06–1.20)	<.001	1.17 (1.08–1.27)	<.001
Pancreatic head and neck lesion	4.45 (2.27–8.72)	<.001	3.93 (1.43–10.81)	.01
Solid component or mural nodule	4.70 (2.36–9.36)	<.001	4.54 (1.95–10.57)	<.001
Duct dilation	5.35 (2.64–10.82)	<.001	4.17 (1.63–10.64)	.003
Septations	0.77 (0.39–1.53)	.46	NA	NA
Cyst fluid analysis				
Mucin presence	0.52 (0.18–1.48)	.22	NA	NA
CEA level	1.00 (1.00–1.00)	.63	NA	NA
Amylase level	1.00 (1.00–1.00)	.51	NA	NA
Preoperative serum level				
CEA	1.00 (1.00–1.00)	.73	NA	NA
CA19-9	1.00 (1.00–1.00)	.18	NA	NA

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; NA, not applicable; OR, odds ratio.

Table 3

Mucinous Cystic Neoplasm-Associated Adenocarcinoma, Recurrence, and Survival in the 44 Patients With Adenocarcinoma[a]

Variable	Finding
Lymph node positive	14 (34.1)
No. of positive lymph nodes, mean (SD)	0.8 (1.6)
Neoadjuvant	
Chemotherapy	5 (12.2)
Radiotherapy	1 (2.4)
Adjuvant	
Chemotherapy	25 (61)
Radiotherapy	15 (36.6)
Recurrence	11 (25.6)
Recurrence-free survival, % at 3 y	64
Death	12 (27.9)
Overall survival, % at 3 y	59

[a]Data are presented as number (percentage) of patients unless otherwise indicated.