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ORIGINAL RESEARCH—CLINICAL

Pancreatic Cancer is More Frequently Early Stage at Diagnosis in Surgically Resected Intraductal Papillary Mucinous Neoplasms With Preoperative Surveillance

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BACKGROUND AND AIMS: Management of intraductal papillary mucinous neoplasms (IPMNs) relies on clinical and imaging features to select patients for either pancreatectomy or periodic image-based surveillance. We aimed to compare outcomes in patients with IPMNs who underwent surgery at diagnosis with those who underwent surgery after a period of surveillance and identify preoperative clinical and imaging features associated with advanced neoplasia. **METHODS:** Patients with surgically resected IPMN (n = 450) were divided into 2 groups: "immediate surgery": resection within 6 months of IPMN detection, and "surveillance surgery": resection after surveillance >6 months. Survival was analyzed with Kaplan-Meier estimates and Cox proportional hazard models. **RESULTS:** Pancreatic cancers in the surveillance surgery group (n = 135) was more frequently stage I compared with the immediate surgery group (9/13, 69.2% vs 41/110, 37.3%; $P = .027$). Among Fukuoka "worrisome features," only main pancreatic duct dilation 5–9 mm (odds ratio [OR] = 3.12, 95% confidence interval [CI]: 1.72–5.68; $P < .001$) and serum CA 19-9≥ 35 U/mL (OR = 2.82, 95% CI: 1.31–6.06; $P = .008$) were significantly associated with advanced neoplasia. In addition, smoking history was associated with increased risk of advanced neoplasia (OR = 2.05, 95% CI: 1.23–3.43). Occurrence of future cancer was 16-fold higher in IPMN with high-grade dysplasia when compared with low-grade dysplasia (hazard ratio: 16.5; 95% CI: 4.19–64.7). **CONCLUSION:** Surveillance-detected pancreatic cancers in patients with IPMNs are more frequently stage I, and IPMN-HGD on surgical pathology is associated with significant risk of future pancreatic cancer. In addition to known "high-risk" features, main pancreatic duct dilation 5–9 mm, CA 19-9 elevation, and smoking history are significantly associated with advanced neoplasia.

Keywords: Intraductal Papillary Mucinous Neoplasm (IPMN); Dysplasia; Pancreatic Cancer; Surveillance

Introduction

Pancreatic cystic lesions (PCLs) are a frequent incidental finding on abdominal cross-sectional imaging.[1] Within PCLs, intraductal papillary mucinous neoplasms (IPMNs) are the most common subtype.[2,3] IPMNs are dysplastic PCLs with malignant potential, although the majority of them will never progress to cancer.[3,4] Currently, there are several guidelines for the management of PCLs,[4,5] specifically IPMNs,[3] but optimal management remains controversial and is often guided by expert opinion.

Presently, surgical resection is the only definitive treatment for IPMNs. Despite the morbidity and mortality associated with pancreatic resection, the presence of advanced neoplasia (high-grade dysplasia [HGD] or invasive carcinoma) justifies surgery, as it offers the only possibility to cure or prevent future development of pancreatic cancer. However, accurate diagnosis of advanced neoplasia preoperatively remains a clinical challenge, as there is no reliable imaging marker of HGD, and definitive histologic diagnosis can be challenging.[3–5] This has led experts to rely on a combination of imaging and clinical findings to predict the risk of advanced neoplasia at the time of IPMN diagnosis to

Abbreviations used in this paper: **AP, acute pancreatitis; CA, carbohydrate antigen; CI, confidence interval; F-HR, Fukuoka high risk; F-LR, Fukuoka low risk; F-W, Fukuoka worrisome; HGD, high-grade dysplasia; HR, hazard ratio; IPMNs, intraductal papillary mucinous neoplasms; IS, immediate surgery; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma; PCLs, pancreatic cystic lesions; SS, surveillance surgery.**

Most current article

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determine the need for surgical resection vs surveillance.[3–5] Although there are some "high-risk" characteristics, which have consistently been associated with advanced neoplasia, other "worrisome" features remain inconsistent predictors with limited data on the strength of association between advanced neoplasia and individual risk factors.[4–8] Based on risk stratification at IPMN diagnosis, patients either undergo surgical resection or surveillance. During surveillance, patients are monitored for clinical and imaging changes concerning for the development of advanced neoplasia. This approach is supported by previous studies that have established excellent disease-free survival during surveillance of IPMNs at low risk for advanced neoplasia.[9,10] Currently, surveillance of IPMNs, that do not meet criteria for surgical resection, is clinically indicated, but it remains unclear if IPMN surveillance leads to early-stage detection in the subset that progress to cancer.

In this study, it is our hypothesis that surveillance-detected pancreatic cancers in IPMNs will be diagnosed at an earlier stage compared with patients with sporadically detected resectable cancer. We test this hypothesis in a retrospective cohort of patients who have undergone pancreatectomy and hence have histopathologic confirmation of the dysplasia grade. In addition, we aim to assess the strength of association between individual "worrisome" and "high-risk" features and advanced neoplasia using surgical pathology as gold standard, and develop a risk prediction nomogram that can be used to predict the probability of advanced neoplasia in IPMN patients undergoing surgical resection.

Methods

We conducted a single-center retrospective study between January 1, 2000, and December 31, 2015, inclusive, of consecutive adult patients (aged >18 years) who underwent surgical resection for IPMNs. The study was approved by the Mayo Clinic Institutional Review Board. IPMNs that were incidentally identified on surgical pathology of unrelated pancreatic resections were excluded. Other exclusion details are described in Figure A1. Patients who underwent surgical resection within 6 months of index IPMN diagnosis at our institution were assigned to "immediate surgery" (IS) group. Those who were followed with surveillance imaging >6 months at our institution and subsequently underwent pancreatic surgery were assigned to the "surveillance surgery" (SS) group. The decision to select 6 months as the cutoff of the 2 groups was decided a priori. This was based on current consensus-based guidelines that describe 3–6 months as the shortest surveillance interval for IPMNs.[3–5]

Patient demographics, relevant clinical history, imaging, and histopathologic/surgical features were collected. Pancreatic ductal adenocarcinoma (PDAC) staging was ascertained using the American Joint Committee on Cancer 8th edition.[11] Preoperative history of acute pancreatitis (AP) was confirmed using revised Atlanta criteria[12] before or at the time of index IPMN diagnosis. Date of death or last follow-up, postoperative recurrence of pancreatic malignancy for all study subjects, and any postoperative recurrence of AP in those subjects with a history of AP before IPMN resection were recorded.

Abdominal cross-sectional imaging before surgical resection, including abdominal magnetic resonance imaging/magnetic resonance cholangiopancreatography and/or abdominal computed tomography, were collected. For the IS group, the most recent computed tomography/magnetic resonance imaging/magnetic resonance cholangiopancreatography before surgery was selected for evaluation. For the SS group, both the index scan at our institution and most recent scan before surgery were reviewed. If endoscopic ultrasound was performed before surgery, endosonographic features were also separately recorded. Mural nodule(s) when present on cross-sectional imaging were reviewed by an expert pancreas radiologist to confirm presence, size, and enhancement. Mural nodule(s) were defined as small solid lesions on the wall of the cyst, whereas a mass (≥2 cm) implied a larger soft tissue component, usually involving the surrounding pancreatic parenchyma. Based on the 2017 international Fukuoka consensus guidelines,[3] IPMNs were classified as high-risk stigmata present (Fukuoka high risk [F-HR]), worrisome features present (Fukuoka worrisome [F-W]), or low-risk (Fukuoka low risk [F-LR]) if no high-risk or worrisome features were noted. All data for our study were stored and managed with Research Electronic Data Capture tool.[13]

Statistical Analysis

Continuous variables are summarized as mean (standard deviation) and/or median (25^{th}, 75^{th} percentile) and compared with the Wilcoxon rank sum test. Discrete data are presented as frequency (percent) and tested with Pearson's chi-squared test. Cox proportional hazards models were used to estimate the age- and sex-adjusted association between histopathology results and treatment approach with postsurgical survival. Age was modeled linearly because nonlinear terms had little effect on the model fit. An interaction between age and sex was included. Adjusted survival curves were created by setting the age and sex distribution of one group to the other and averaging over the predicted survival curves. For adjusted survival, histopathology and treatment were included as strata so as not to force a proportional hazards relationship between the adjusted curves. Incidence of malignancy was modeled with death and benign tumor as competing risk events. Fine-Gray methods were used to estimate the adjusted incidence curves.

A multivariable logistic regression model for advanced neoplasia was constructed using known "high-risk" and "worrisome" features.[3] High-risk and worrisome features that were unavailable or had very low prevalence (<2%), mural nodule <5 mm, and wall/septa thickening/enhancement were excluded. For subjects in the IS group without multiple images, the growth rate was categorized as "cannot assess." For CA 19-9 ≥ 35 U/mL, missing data were treated as "normal" in the final model, as initial models indicated that normal and missing groups had very similar outcomes. Other features with low levels of missingness (n < 5) had "missing" set to "No." The c-statistic was used to assess discriminatory ability, and a risk prediction nomogram was constructed for visual presentation. Internal validation of the risk prediction model was performed through bootstrapping. Other potential risk factors that are not consistently considered in current IPMN guidelines (age, sex, family history of PDAC, smoking, cyst calcification, diabetes mellitus, and weight loss) were explored for hypothesis-generating results by including each risk factor separately in a logistic regression model with the Fukuoka model predictor

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Immediate surgery (N = 315)	Surveillance surgery (N = 135)	Total (N = 450)	*P* value
Age (at time of imaging)				**.015**
Mean (SD)	67.9 (9.5)	65.5 (9.5)	67.2 (9.6)	
Median (Q1, Q3)	69.0 (62.0, 75.0)	66.0 (59.5, 72.0)	68.0 (61.0, 74.0)	
Women	135 (42.9%)	64 (47.4%)	199 (44.2%)	.37
Race				.96
White	292 (92.7%)	127 (94.1%)	419 (93.1%)	
Black	3 (1.0%)	1 (0.7%)	4 (0.9%)	
Asian	6 (1.9%)	2 (1.5%)	8 (1.8%)	
Other/unknown	14 (4.4%)	5 (3.7%)	19 (4.2%)	
Smoking status				**.037**
Never	138 (43.8%)	74 (54.8%)	212 (47.1%)	
Former	141 (44.8%)	50 (37.0%)	191 (42.4%)	
Current	36 (11.4%)	11 (8.1%)	47 (10.4%)	
Family history of PDAC	33 (10.5%)	14 (10.4%)	47 (10.4%)	.97
Diabetes mellitus status				.72
Nondiabetic	234 (74.3%)	106 (78.5%)	340 (75.6%)	
New onset diabetes[a]	32 (10.2%)	6 (4.4%)	38 (8.4%)	
Long-standing diabetes	49 (15.6%)	23 (17.0%)	72 (16.0%)	
History of chronic pancreatitis	22 (7.0%)	19 (14.1%)	41 (9.1%)	**.017**
Type of IPMN				**.004**
Branch duct	133 (42%)	80 (59%)	213 (47%)	
Main duct	53 (17%)	16 (12%)	69 (15%)	
Mixed duct	129 (41%)	39 (29%)	168 (37%)	
Asymptomatic	109 (34.6%)	65 (48.1%)	174 (38.7%)	**.007**
Symptoms leading to cyst discovery				
Abdominal pain	147 (46.7%)	56 (41.5%)	203 (45.1%)	.31
Acute pancreatitis	50 (15.9%)	43 (31.9%)	93 (20.7%)	**<.001**
Weight loss				**.002**
Nonsignificant	33 (10.5%)	9 (6.5%)	42 (9.3%)	
Significant[b]	53 (16.8%)	10 (7.4%)	63 (14.0%)	
Unknown	2 (0.6%)	0 (0.0%)	2 (0.4%)	
Back pain	37 (11.7%)	9 (6.7%)	46 (10.2%)	.10
Jaundice	45 (14.3%)	1 (0.7%)	46 (10.2%)	**<.001**
Fatigue	28 (8.9%)	5 (3.7%)	33 (7.3%)	.053

The bold entries signify statistical significance.
IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.
[a]New-onset diabetes is diagnosed within 3 years of first abdominal imaging.
[b]≥10% of body weight loss.

included as an offset to estimate the additional effect of the risk factor beyond the Fukuoka criteria.

All analyses were conducted with R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), including the *rms, survival,* and *arsenal* packages. All *P* values are 2 sided with a .05 significance level.

Results

Baseline Patient and IPMN Characteristics

A total of 450 patients with pathology confirmed IPMN underwent surgical resection during the study period and met study inclusion and exclusion criteria. Study cohort diagram is depicted in Figure A1. Subjects were mostly male (55.8%), white (93.1%), ever smokers (52.9%), and had a mean age of 67.2 ± 9.6 years. A history of diabetes mellitus was present in 24.4%, whereas chronic pancreatitis (9.1%) or a family history of PDAC (10.4%) was relatively uncommon. Most subjects had branch or mixed duct IPMNs. Demographic and clinical characteristics of the study population are summarized in detail in Table 1.

IPMN histopathology was categorized as low-grade dysplasia (LGD; n = 283, 62.9%), HGD (n = 44, 9.8%), and invasive cancer (n = 123, 27.3%). Surgical resection was most commonly pancreaticoduodenectomy (54.7%), followed by distal pancreatectomy (35.3%) and total pancreatectomy (9.3%). Margin status had no dysplasia (≥1 mm) in 78.2% of resections. Most positive margins (n = 98) were LGD (n = 72), with HGD (N = 6) and cancer (n = 20) positive margins being less frequent. For the IPMNs with invasive cancer on pathology, the vast majority (87.8%) were found to be involving the IPMN. Stage at resection of those with cancer was stages I (40.7%), II (41.5%), III (17.1%), and IV (0.8%). In 1 patient with stage IV disease, metastasis was detected at the time of surgery. Characteristics of IPMN histopathology and pancreatic surgery are summarized in Table 2.

Table 2. Intraductal Papillary Mucinous Neoplasm Histopathology and Pancreatic Surgery Characteristics in the Immediate Surgery and Surveillance Surgery Groups

Characteristic	Immediate surgery (N = 315)	Surveillance surgery (N = 135)	Total (N = 450)	*P* value
Age (at time of surgery)				.81
Mean (SD)	68.0 (9.5)	67.8 (9.4)	68.0 (9.5)	
Median (Q1, Q3)	70.0 (62.0, 75.0)	69.0 (62.0, 75.0)	69.0 (62.0, 75.0)	
Days from imaging to surgery				**<.001**
Mean (SD)	36 (36)	833 (905)	275 (616)	
Median (Q1, Q3)	25 (10, 48)	429 (281, 1033)	42 (16, 239)	
Type of surgery				.35
Pancreaticoduodenectomy	179 (56.8%)	67 (49.6%)	246 (54.7%)	
Distal pancreatectomy	103 (32.7%)	56 (41.5%)	159 (35.3%)	
Total pancreatectomy	31 (9.8%)	11 (8.1%)	42 (9.3%)	
Other[a]	2 (0.6%)	1 (0.7%)	3 (0.7%)	
Field histology				.25
Chronic pancreatitis	106 (33.7%)	53 (39.3%)	159 (35.3%)	
Normal	209 (66.3%)	82 (60.7%)	291 (64.7%)	
IPMN pathology				**<.001**
LGD	170 (54.0%)	113 (83.7%)	283 (62.9%)	
HGD	35 (11.1%)	9 (6.7%)	44 (9.8%)	
Invasive carcinoma	110 (34.9%)	13 (9.6%)	123 (27.3%)	
Margin status				.24
Normal/negative	245 (77.8%)	107 (79.3%)	352 (78.2%)	
LGD	48 (15.2%)	24 (17.8%)	72 (16.0%)	
HGD	5 (1.6%)	1 (0.7%)	6 (1.3%)	
Invasive carcinoma	17 (5.4%)	3 (2.2%)	20 (4.4%)	
PanIN present	21 (6.7%)	16 (11.9%)	37 (8.2%)	.067
PanIN grade				.058
1	13 (61.9%)	14 (77.8%)	27 (73.0%)	
2	5 (23.8%)	2 (12.5%)	7 (18.9%)	
3	3 (14.3%)	0 (0.0%)	3 (8.1%)	
Invasive carcinoma location				.71
Involves cyst	97 (88.2%)	11 (84.6%)	108 (87.8%)	
Outside of cyst	13 (11.8%)	2 (15.4%)	15 (12.2%)	
TMN stage at surgery				**.027**
I	41 (37.3%)	9 (69.2%)	50 (40.7%)	
II/III/IV	69 (62.7%)	4 (30.8%)	73 (59.3%)	

The bold entries signify statistical significance.
PanIN, pancreatic intraepithelial neoplasia; SD, standard deviation; TNM, tumor, nodes, and metastases.
[a]Central pancreatectomy and localized pancreatic resection.

Comparing IS and SS groups

Of the 450 patients included in the study, 315 (70.0%) underwent surgical resection within or at 6 months of initial IPMN detection and were assigned to the IS group. The remaining 135 (30.0%) who were initially followed with surveillance imaging >6 months and subsequently underwent surgery were assigned to the SS group. Baseline characteristics of SS and IS groups were comparable with no differences in sex, race, diabetes mellitus, and family history of PDAC. Patients in the SS group were younger at the time of imaging (65.5 ± 9.5 vs 67.9 ± 9.5; $P = .015$), with a lower frequency of smoking history (45.2% vs 56.2%; $P = .037$) and had a significantly higher prevalence of chronic pancreatitis on past medical history (14.1% vs 7.0%; $P = .017$). Main and mixed duct IPMNs were more prevalent in the IS group compared with the SS group. SS group patients were frequently asymptomatic at the time of IPMN discovery compared with the IS group (48.1% vs 34.6%; $P = .007$), There was a significant difference between SS and IS groups in terms of some presenting symptoms: AP (31.9% vs 15.9%; $P < .001$), weight loss (14.1% vs 27.9%; $P = .002$), and jaundice (0.7% vs 14.3%; $P < .001$). Comparisons of baseline characteristics and symptoms at the time of IPMN discovery are summarized in Table 1.

The prevalence of advanced neoplasia was lower in the SS group (16.3% vs 46.0%; $P < .001$). Cancers in the SS group were more frequently stage I at diagnosis compared with the IS group (9/13, 69.2% vs 41/110, 37.3%; $P = .027$). Other histopathologic/surgical findings summarized in Table 2 did not significantly differ between SS and IS groups.

Survival and Pancreatic Cancer Recurrence

Age- and sex-adjusted survival of the total IPMN cohort from the time of pancreatic surgery is depicted in Figure 1. Survival was significantly worse for IPMN-cancer

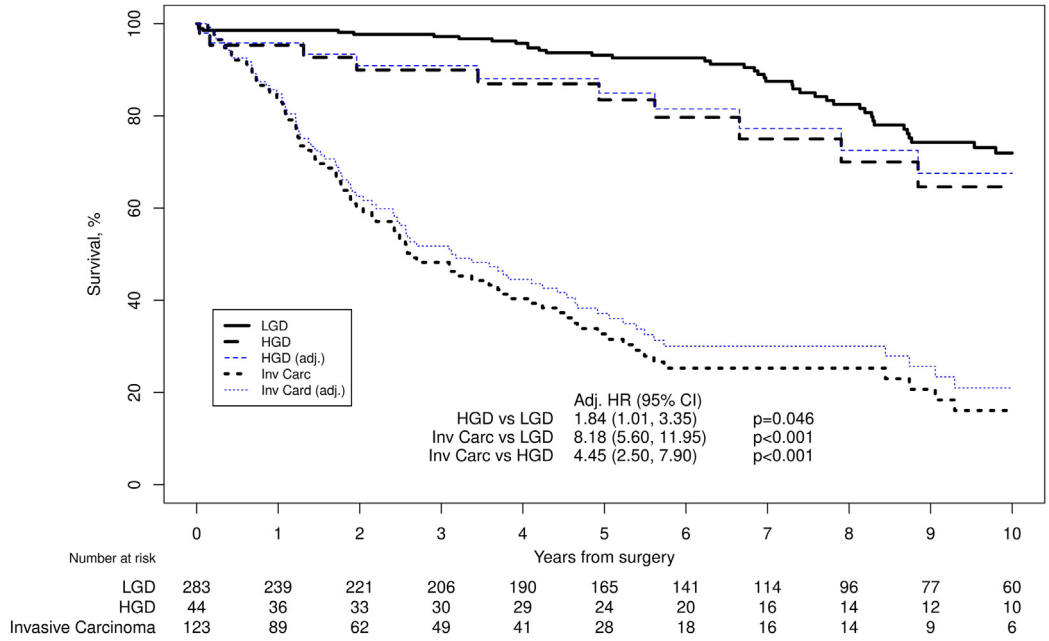

Figure 1. Age- and sex-adjusted survival of surgically resected intraductal papillary mucinous neoplasms. LGD, low-grade dysplasia; HGD, high-grade dysplasia, Inv Carc, invasive carcinoma.

when compared with IPMN-LGD (hazard ratio [HR], 8.18; 95% confidence interval [CI]: 5.60–12.0) and IPMN-HGD (HR, 4.45; 95% CI: 2.50–7.90). In subjects with advanced neoplasia, postoperative survival adjusted for age and sex in the IS group was not significantly different compared with the SS group (HR, 1.36; 95% CI: 0.70–2.67). There was no difference in overall survival for IPMN-cancer comparing the 2 groups (HR, 1.28; 95% CI: 0.58–2.84) when controlling for age and sex.

At 10 years of follow-up, subsequent PDAC was rare in IPMN-LGD (n = 3, 1.6% at 10 years) with malignant occurrence more common in IPMN-HGD (n = 7, 25% at 10 years). As depicted in Figure 2, subsequent occurrence of pancreatic cancer was 16-fold higher in IPMN-HGD when compared with IPMN-LGD (HR, 16.5; 95% CI: 4.19–64.7), even when adjusting for age and sex. Of those with IPMN-HGD, there were 12 patients with isolated branch-duct IPMN, and none had subsequent PDAC. Within the cohort, 29 subjects (6.4%) were lost to follow-up, defined as less than 3 months of post-operative follow-up. The median follow-up for was 6.4 years, 6.6 years, and 7.9 years for LGD, HGD, and cancer, respectively.

Predictors of Advanced Neoplasia

The results of the multivariable logistic regression model for the association of F-HR and F-W features with advanced neoplasia on pathology are summarized in Table 3 and are represented as a risk prediction nomogram in Figure 3. The model had very good discriminatory ability (c = 0.845) for predicting advanced neoplasia in our study cohort with a bias-corrected c-statistic after internal validation of 0.825. Of the F-HR features, main pancreatic duct (MPD) ≥10 mm (odds ratio [OR] = 4.33, 95% CI: 2.14–8.77), presence of solid mass (OR = 28.1, 95% CI: 9.38–84.3), and jaundice (OR = 9.59, 95% CI: 2.89–31.8) were all significantly associated with advanced neoplasia. Among the F-W features, only MPD 5–9 mm (OR = 3.12, 95% CI: 1.72–5.68) and serum CA 19-9 ≥ 35 U/mL (OR = 2.82, 95% CI: 1.31–6.06) were significantly associated with advanced neoplasia. AP, a clinical "worrisome" feature often used as an indication for surgical resection in clinical practice primarily for symptom relief, was not significantly associated (OR = 0.81, 95% CI: 0.43–1.53) with advanced neoplasia.

Among other examined risk factors of pancreatic cancer that are currently not included in the international consensus guidelines, after adjusting for the Fukuoka risk factors, a history of smoking (OR = 2.05, 95% CI: 1.23–3.43) was the only factor that was found to be significantly associated with advanced neoplasia. Additional risk factors such as age, sex, weight loss, past medical history of diabetes mellitus, and a family history of pancreatic cancer were not significant predictors, summarized in Table A1.

Pancreatitis in IPMN

Of 450 patients with surgically resected IPMNs, 96 had a prior history of AP that met revised Atlanta criteria.[12] Two of those subjects were diagnosed with gallstone pancreatitis. Within the remaining 94, no specific etiology for the pancreatitis was clinically evident, and IPMN was

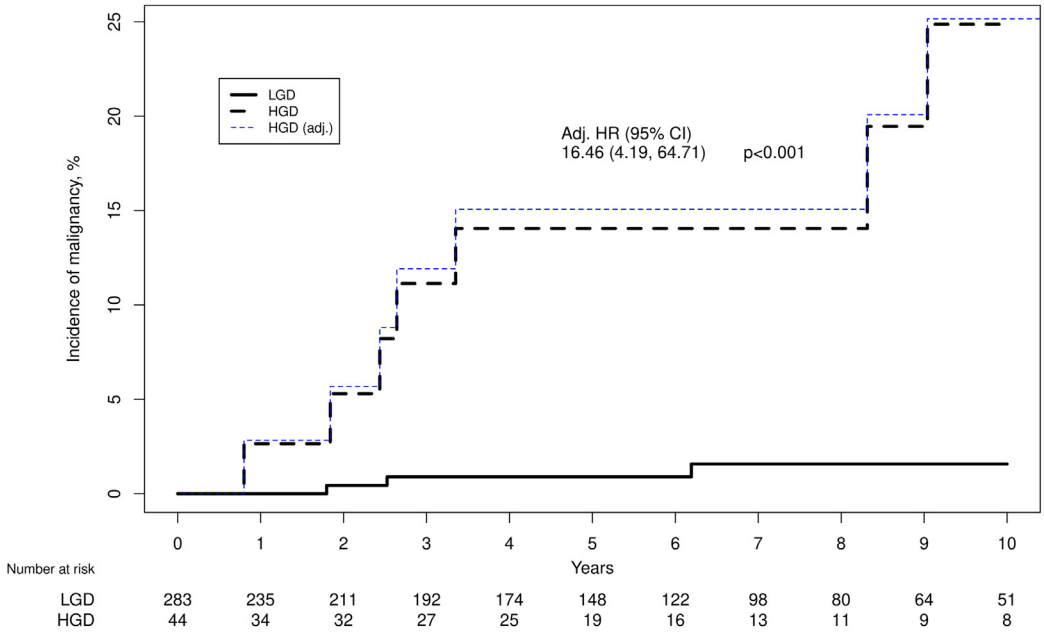

Figure 2. Age- and sex-adjusted malignancy occurrence in intraductal papillary mucinous neoplasms with low-grade (LGD) and high-grade dysplasia (HGD).

considered the potential etiology. Most patients (83.0%) had recurrent AP before surgical IPMN resection. Specific number of AP episodes per patient is demonstrated in Table A2. Surgical pathology demonstrated HGD in 10 of 94 (10.6%) and cancer in 13 of 94 (13.8%) patients. Thirteen patients were lost to follow-up after surgery. In the remaining 81 patients, the median (Q1, Q3) follow-up was 6.37 (4.41, 9.80) years. Ten patients (12.3%) developed recurrent postoperative AP within a median of 2.8 (1.17, 2.51) years.

Discussion

Comparing patients with IPMNs who underwent IS to those who underwent surgery after a period of surveillance, we found that surveillance-detected IPMN cancers were

Table 3. Multivariable Model Using "High-Risk" and "Worrisome" Fukuoka Features (C-Statistic 0.845)

	Univariable analysis		Multivariable analysis	
High-risk feature	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Jaundice	23.10 (9.10, 78.1)	**<.001**	9.59 (2.89, 31.8)	**<.001**
MPD ≥10 mm	2.56 (1.57, 4.18)	**<.001**	4.33 (2.14, 8.77)	**<.001**
Mural nodule ≥5 mm	0.42 (0.14, 1.07)	.093	1.14 (0.38, 3.43)	.82
Solid mass	47.2 (18.9, 158.1)	**<.001**	28.1 (9.38, 84.3)	**<.001**
Worrisome feature	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Acute pancreatitis	0.45 (0.26, 0.75)	**.003**	0.81 (0.43, 1.53)	.51
Cyst size ≥3 cm	0.81 (0.54, 1.22)	.31	1.21 (0.69, 2.13)	.50
Mural nodule <5 mm	0.83 (0.04, 8.78)	.88	0.38 (0.00, 34.9)	.67
Wall/septa enhancement	0.83 (0.12, 4.32)	.83	0.75 (0.09, 6.28)	.79
MPD 5–9 mm	2.58 (1.73, 3.88)	**<.001**	3.12 (1.72, 5.68)	**<.001**
Abrupt change in MPD with distal atrophy	3.28 (1.89, 5.81)	**<.001**	1.57 (0.76, 3.24)	.22
Lymphadenopathy	2.96 (1.29, 7.20)	**.012**	1.38 (0.44, 4.33)	.58
CA 19-9 ≥35 U/mL	5.43 (2.66, 11.5)	**<.001**	2.82 (1.31, 6.06)	**.008**
Cyst growth ≥5 mm/2 y	0.69 (0.22, 1.95)	.50	0.99 (0.31, 3.15)	.99
Growth rate cannot be assessed	3.61 (1.92, 7.29)	**<.001**	1.63 (0.74, 3.59)	.23

The bold entries signify statistical significance.
CA, carbohydrate antigen; CI, confidence interval; MPD, main pancreatic duct.

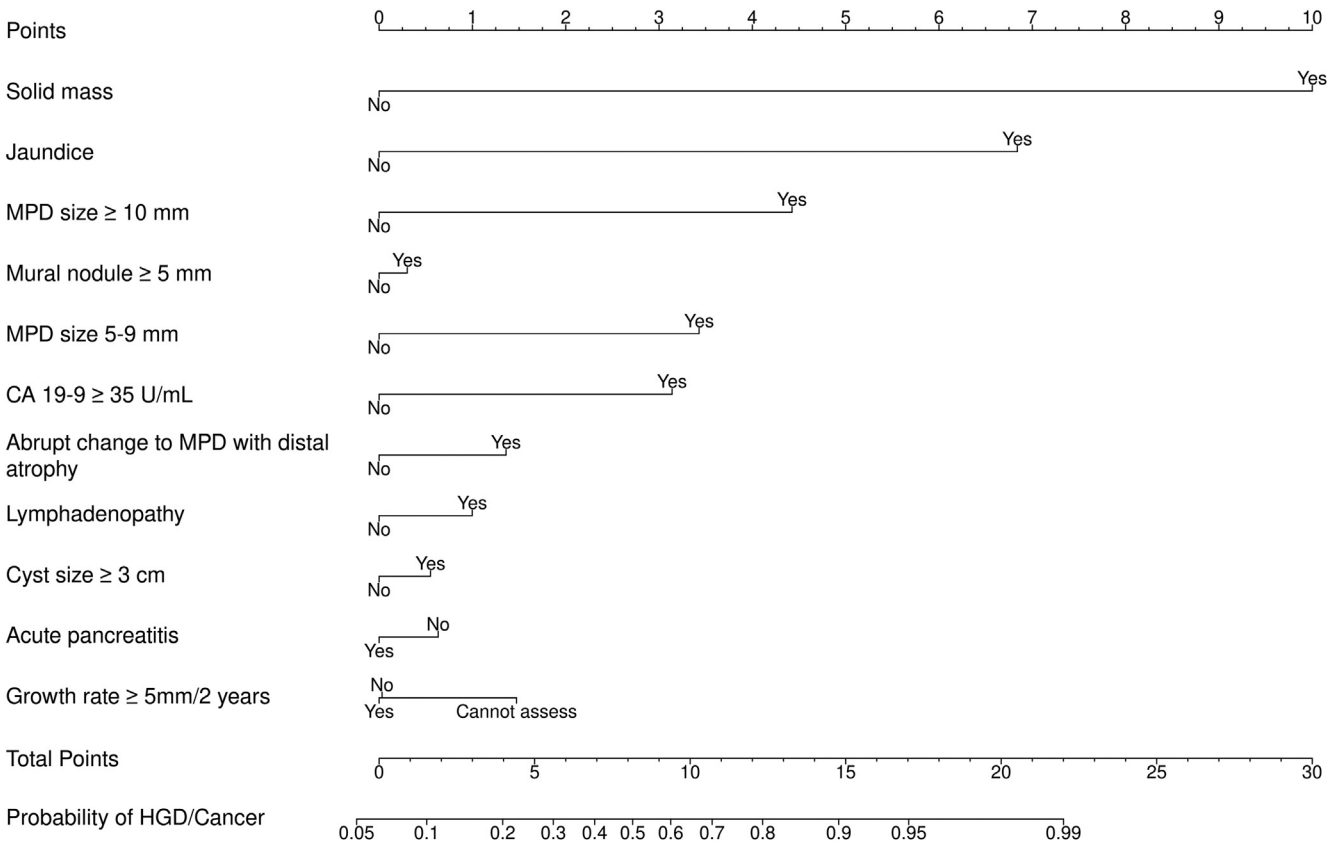

Figure 3. Nomogram predicting the presence of advanced neoplasia in intraductal papillary mucinous neoplasms determined to undego surgical treatment. MPD, main pancreatic duct, CA, carbohydrate antigen.

more frequently stage I. When examining association of Fukuoka worrisome features with IPMN dysplasia grade, only MPD $\geq$5 mm, and serum CA 19-9 $\geq$ 35 U/mL were significantly associated with advanced neoplasia. We also demonstrate that IPMN-HGD, when compared with IPMN-LGD, had significantly higher risk of subsequent cancer in the remnant pancreas, justifying postoperative surveillance in patients with resected IPMN-HGD.

Image-based pancreatic cancer screening in high-risk individuals (based on genetic factors and/or family history) has been shown to detect PDAC at an earlier stage.[14] Our study demonstrates a similar stage shift in surveillance-detected IPMN cancers, as 70% of cancers in the SS group were stage I at diagnosis, significantly higher than those in the IS group. In current management guidelines,[3–5] postoperative surveillance of noncancer IPMNs remains unclear. Previous literature has described the presence of IPMN-HGD as an important predictor of subsequent PDAC recurrence, and this finding is further confirmed in our cohort.[15] The high incidence of pancreatic cancer in 25% after 10 years of follow-up in IPMN-HGD is likely secondary to a "field effect" in the pancreas previously described in IPMNs, and this subset of patients with resected IPMN-HGD should be considered for postsurgical imaging surveillance as long as they remain surgical candidates. The value of routine postoperative surveillance of IPMN-LGD is much less apparent with differing opinions among experts.[3–5] Our study would suggest that for patients with resected IPMN-LGD, development of PDAC in the remnant gland within 10 years is a rare event. Considering IPMNs commonly affect the elderly,[1] postoperative surveillance in IPMN-LGD is unlikely to be beneficial in most patients.

Currently, identification of IPMNs with advanced neoplasia relies on certain clinical and imaging characteristics. Our study demonstrated, as others have described,[3,4,10,16] that F-HR stigmata are highly associated with advanced neoplasia. However, in clinical practice, F-HR features remain infrequent, and most patients under surveillance are either F-W or F-LR.[17] Despite evidence to suggest that F-W IPMNs have a low rate (<5%)[10] of progressing to PDAC, management guidelines indicate invasive diagnostic testing with endoscopic ultrasound in this relatively large subset of F-W IPMNs.[3] Using our multivariable model, we observe that MPD dilation 5–9 mm and elevated CA 19-9 were the only worrisome features significantly associated with advanced neoplasia. Recently, in other studies, these 2 factors have been consistently shown to be strong predictors of advanced neoplasia.[18–20] Other F-W factors in our cohort were not significantly associated with advanced neoplasia.

Although not currently included in management algorithms, we identified smoking status as a risk factor

associated with advanced neoplasia. Capurso et al were able to depict heavy smoking a factor of progression of branch-duct IPMN that were F-LR to either F-W or F-HR.[21] Our finding would be congruent with the well-known risk association between smoking and PDAC.[22] AP caused by the IPMN has shown variable results in terms of its association with advanced neoplasia.[6–8] Prior studies that demonstrated this association[6,7] used definitions that did not consistently meet the criteria for AP diagnosis.[12] In our cohort applying the revised Atlanta criteria for AP diagnosis, we found no significant association between AP with advanced neoplasia, and only a small subset of patients experienced recurrent AP after surgery. Therefore, in IPMN patients with AP, the indication for resection should primarily be relief of symptoms and not neoplastic risk reduction.

We would like to highlight some of the limitations of our study. First, it is a single-center retrospective surgical cohort in a tertiary care center. As surgical resection is a key determinant of survival in PDAC, the true impact of surveillance on IPMN-cancer-associated mortality requires study in a cohort that includes both patients managed with and without surgery. The limited number of cancers in the SS group and the fact that patients with advanced-stage IPMN cancers managed without surgery were not included in our study offsets the comparative benefit of early-stage detection in this cohort, and is the likely reason why a significant difference in survival between IS and SS groups was not appreciated. Second, the risk estimates for predictors for advanced neoplasia identified in this study are not transferrable to a clinical surveillance cohort. However, the findings in our study can be used to predict the likelihood of advanced neoplasia and may be valuable in decision-making for patients with IPMN where surgical resection is indicated but considered high risk because of comorbidities or age. Finally, although we had long-term follow-up on many patients, loss to follow-up may have impacted our estimates of true PDAC risk after partial pancreatectomy. Despite these limitations, we anticipate that our findings will be informative to future risk stratification guidelines and provide rationale for prospective outcome studies in the clinical surveillance setting.

In conclusion, we demonstrate that surveillance-detected pancreatic cancers in patients with IPMNs are more frequently early stage. Subsequent PDAC in non-cancerous IPMN is mainly limited to IPMN-HGD. Among the multiple Fukuoka "worrisome features," MPD dilation $\geq$5 mm and serum CA 19-9 elevation were the only characteristics significantly associated with advanced neoplasia and may warrant closer attention during surveillance, whereas some of the other F-W features may be considered not as worrisome. In addition, history of smoking, a risk factor currently not in PCL guidelines, was demonstrated to be associated with advanced neoplasia, which may warrant its inclusion as a "worrisome" feature in future iterations of cyst management guidelines. The overall trend in IPMN management over the past few years has favored a more conservative approach to minimize the risks associated with surgical resection while maximizing the benefit of improved survival in those at highest risk of advanced neoplasia. The results of our study advance the understanding of the role of surveillance in IPMN management and provide informative risk estimates for the association between commonly used clinical and imaging risk factors and histologic dysplasia grade in surgically resected IPMNs.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.07.004.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Availability of data and study material from a secure Mayo Clinic server is subject to approval from the authors and the Mayo Clinic Internal Review Board. Analytic methods are included in the main article.