Ann Surg Oncol (2018) 25:1746–1751
https://doi.org/10.1245/s10434-018-6425-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

What is the Incidence of Malignancy in Resected Intraductal Papillary Mucinous Neoplasms? An Analysis of Over 100 US Institutions in a Single Year

Rym El Khoury, MD[1,2], Christopher Kabir, MS[3], Vijay K. Maker, MD[1,2], Mihaela Banulescu, MSRC[2], Margaret Wasserman, BSN, RN[2], and Ajay V. Maker, MD[1,2]

[1]Division of Surgical Oncology, Department of Surgery, University of Illinois at Chicago, Chicago, IL; [2]Department of Surgery, Creticos Cancer Center at Advocate Illinois Masonic Medical Center, Chicago, IL; [3]Advocate Research Institute, Creticos Cancer Center at Advocate Illinois Masonic Medical Center, Chicago, IL

ABSTRACT

Background. A subset of intraductal papillary mucinous neoplasms (IPMNs) will progress to invasive adenocarcinoma, however identifying invasive from non-invasive disease preoperatively remains challenging. The rate of malignancy in resected IPMNs in the US remains unclear.

Objective. We aimed to determine the rate of malignancy and factors associated with high-risk pathology in resected IPMNs.

Methods. The most recent annual cohort of patients undergoing pancreatectomy included in the American College of Surgeons National Surgical Quality Improvement Program were assessed, and contributions of demographics, preoperative laboratory values, and outcome data to level of IPMN dysplasia were analyzed. The main outcomes were incidence of invasive carcinoma or high-grade dysplasia.

Results. Of 5025 pancreatectomies in 1 year, 478 patients underwent pancreatectomy for IPMN. Invasive carcinoma/high-grade dysplasia was identified in 23% of resected lesions, and there was no difference in patient characteristics or type of resection performed in patients with invasive versus non-invasive pathology. Patients with invasive IPMNs presented significantly more often with high liver function tests, >10% weight loss, clinical jaundice and stent placement, and were more likely to undergo an open operation ($p = 0.03$). There were no differences in perioperative outcomes. Adjusted logistic regression identified an association between invasive disease and non-soft pancreatic gland texture (odds ratio 0.19, 95% confidence interval 0.05–0.68, $p < 0.01$).

Conclusions. Approximately 10% of all pancreatectomies in the US are for IPMNs. In these patients, treated after the revised international consensus guidelines, only 23% of IPMNs contained invasive or high-grade histology. Resections carried similar morbidity regardless of pathology. Improved biomarkers are needed to aid in surgical selection.

Widespread use and technological improvements in high-resolution cross-sectional imaging[1,2] have led to an increase in the incidence of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. Invasive adenocarcinoma is identified in ≤ 18% of branch-duct cysts and up to 64% of main-duct disease,[3] thus surgical intervention is often recommended for these cysts that have known malignant potential. The decision of whether to perform surveillance or to proceed with pancreatic resection[4] is clinically challenging and is the topic of ongoing refinements to consensus statements and international guidelines. As we have previously shown, fine-needle aspiration cytology and biopsy are often not helpful in surgical decision making for this disease,[5] therefore the development of scoring systems[6–8] evaluating the risk of IPMNs for invasive pathology are emerging. Nonetheless, up to 27% of patients without high-risk preoperative

This work was presented at the Society of Surgical Oncology Annual Cancer Symposium 2017, Boston, MA, USA, and The Pancreas Club 2017, Chicago, IL, USA.

First Received: 18 December 2017;
Published Online: 20 March 2018

A. V. Maker, MD
e-mail: amaker@uic.edu

clinicopathologic predictors of malignancy will harbor invasive disease at the time of resection.[9–11] Accurate clinical, biological, and morphological risk factors for invasive IPMNs warranting surgical management rather than surveillance remain to be optimized.

IPMNs have a cumulative incidence of 2.04 per 100,000 person-years,[12] therefore data on the incidence of invasive malignancy in large groups have been limited. Furthermore, the indications for resection of IPMNs have evolved tremendously over the last few decades, from resection of all lesions[13] to resection of only those meeting specific radiographic criteria.[14,15] As a result, the incidence of malignancy in surgically treated patients has also fluctuated based on the time period of reporting. Thus, our purpose was to conduct a large, nationwide study including multiple institutions to determine the rate of malignancy in resected IPMNs in the current era post-establishment of the recent international (Fukuoka) consensus guidelines.

METHODS

Study Population

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) is a national quality improvement program that prospectively gathers patient and outcome data to assess the quality of surgical care and hospital performance.[16] After review by our Institutional Review Board, the most recent year of complete pathologic data, spanning 1 January to 31 December 2014, at the time of analysis was queried. Pancreatic resections were identified by the following Current Procedural Terminology (CPT) codes: 48140, 48145, and 48146 for distal pancreatectomy; 48150 and 48152-4 for Whipple-type procedure; and 48155, 48160, 48999, and 49329 for other pancreatic resections. IPMN diagnoses were extracted. Demographic data, preoperative laboratory values, and perioperative outcome data, including fistulae occurrence, length of stay, readmission, and reintervention, were analyzed, and staging and histologic features were reviewed. The database classified pathology as 'invasive' or 'non-invasive', and invasive disease was further classified by T-stage and included Tis (high-grade dysplasia). Lesions classified as 'invasive' without available T-stage data defaulted to the invasive carcinoma group. High-risk lesions in this study were classified as those IPMNs that contained high-grade dysplasia or invasive pathology.

Statistical Analysis

Results are displayed as mean ± standard deviation or number and percentage. Baseline characteristics and intra- and perioperative data were compared using the Chi-square test and independent Student's *t*-test for categorical and continuous variables, respectively. Odds ratios (ORs) with 95% confidence intervals (CIs) from univariate and multivariate analyses are reported. Patient characteristics were selected into univariate analysis based on clinicopathologic relevance. NSQIP data stratified main pancreatic duct size into < 6 and > 6 mm. A p-value < 0.05 was used for significance in univariate analysis and entry criteria for the adjusted model. Analyses were performed using SPSS version 23.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA: IBM Corporation) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Incidence of Invasive Intraductal Papillary Mucinous Neoplasms (IPMNs)

Of 5025 pancreatic resections from 106 participating institutions, 478 (9.5%) patients had pathologically proven IPMNs. In 108 patients (23% of IPMN patients, 2% of all pancreatectomy patients), IPMN was of a 'high-risk' pathology, consisting of 11 tumors with Tis (high-grade dysplasia; 10%) and 97 tumors (90%) with invasive adenocarcinoma. The remaining 370 patients (77%) had pathologic 'low-risk', i.e., low- or moderate-grade dysplasia, non-invasive IPMNs. Eleven percent of high-risk IPMNs were staged T1, and 22% of invasive IPMNs were node positive. Full pathologic characteristics are displayed in Table 1.

IPMN Patient Characteristics and Perioperative Data

Patient Demographics and Preoperative Characteristics Demographic characteristics are presented in Table 2. Of 478 IPMN patients, 232 were male and 246 female, with a mean age of 66 years. There was no significant difference in comorbid conditions, including obesity, diabetes, or ascites, between high- and low-risk pathology. Patients with high-risk IPMNs were more likely to present with weight loss (15% vs. 6%, $p < 0.01$) and to have undergone preoperative biliary stent placement (18% vs. 5%, $p < 0.01$) for obstructive jaundice (18% vs. 3%, $p < 0.01$). This corresponded with preoperative laboratory values, demonstrating significantly higher total bilirubin, alkaline phosphatase, and aspartate aminotransferase levels.

Intraoperative Data and Perioperative Outcomes Open approach to pancreatic resection was more commonly performed in patients with high-risk lesions (76% vs. 65%,

TABLE 1 Pathologic characteristics of invasive and non-invasive IPMNs

Variable	Invasive IPMNs [$n = 108$] (23%)	Non-invasive IPMNs [$n = 370$] (77%)
High-grade dysplasia	11 (10)	
Invasive carcinoma	97 (90)	
Local invasion		
T stage[a]		
T1	11 (11)	
T2	21 (22)	
T3	33 (34)	
Tumor size[a] (cm)		
< 2		94 (25)
2–5		190 (51)
> 5		38 (10)
Nodal involvement		
N0	76 (78)	
N1	21 (22)	
Metastatic disease		
M1	1 (1)	
Associated benign features, i.e., chronic pancreatitis	2 (2)	

IPMNs intraductal papillary mucinous neoplasms, *NSQIP* National Surgical Quality Improvement Program

[a]NSQIP reports TNM staging for invasive IPMNs, and tumor size (cm) for benign disease

$p = 0.03$), with similar rates of distal pancreatic resections and Whipple-type procedures. The pancreatic fistula rate, need for repeat intervention, and length of hospital stay did not significantly differ between high- and low-risk pathology. Perioperative outcomes are displayed in Table 3. Intraoperative identification of a main pancreatic duct > 6 mm trended towards an increased association with high-risk pathology (OR 1.82, 95% CI 0.98–3.35, $p = 0.056$). Adjusted logistic regression modeling (Table 4) identified an association between high-risk disease and increased alkaline phosphatase level (OR 1.01, 95% CI 1.00–1.02, $p < 0.01$). A soft pancreatic gland was associated with low-risk histology ($p < 0.05$). Using the two features independently associated with pathology risk from this analysis (preoperative alkaline phosphatase and gland texture), low- versus high-risk disease could be stratified with an area under the curve (AUC) of 0.70. As gland texture is not known preoperatively, an additional model was created based on associated features from the univariate analysis utilizing alkaline phosphatase level (β coefficient 0.28), weight loss (β coefficient 1.08), jaundice (β coefficient 1.44), and preoperative biliary stent placement (β coefficient 0.51) [AUC 0.62].

DISCUSSION

In this large, national database including over 100 US institutions, 478 patients underwent resection for IPMNs in a single year. Of these, 23% showed evidence of high-risk disease consisting of high-grade dysplasia or invasive carcinoma. This offers a snapshot of the current incidence of high-risk IPMNs in surgically resected tumors in the US. Factors associated with malignant histology included > 10% weight loss in the 6 months preceding pancreatic resection, and biological and clinical evidence of obstructive jaundice. It was determined that elevated alkaline phosphatase levels may be an independent risk factor for invasive IPMNs, while a soft gland was independently associated with low-risk IPMNs.

The incidence of malignant IPMNs is in line with prior reports on smaller populations collected over longer periods of time during which surgical criteria for resection continued to evolve.[6,17] Hyperbilirubinemia was also found to be a risk factor for malignancy on univariate analysis, consistent with findings by Hackert and colleagues.[18] It follows that obstructive jaundice at presentation was associated with invasive pathology, further reinforcing the 'high-risk stigmata' as defined by the Fukuoka guidelines;[15] however, it was not found to be an independent risk factor on multivariate analysis.[19] Pancreatitis[9] and pancreatic fibrosis have also been considered as high-risk factors for malignant histology in IPMNs, and, herein, gland texture, as a potential correlate for pancreatic gland inflammation, was also associated with invasive IPMNs.

Interestingly, a main pancreatic duct diameter > 6 mm was not found to be associated ($p = 0.056$) with invasive disease in this analysis. This finding is a partial limitation of the categories of data collected in the database, with duct dimensions stratified by < 3, 3–6, or > 6 mm. Thus, patients with clinically 'worrisome' duct dilation of 5–9 mm were included with 'high-risk' lesions of > 10 mm[15,17] and > 12 mm[20] in the abstracting of data within NSQIP.

Limitations of this retrospective study include the absence of data on preoperative imaging findings and the risk of underreporting and coding errors associated with large data sets. Furthermore, as invasive adenocarcinoma may be reported without acknowledging underlying IPMNs, there is a potential for underreporting of the IPMN component in non-synoptic pathology reports. It is also unclear whether international consensus guidelines were followed in patient selection for resection, even though this study took place after the most recent 2012 update to the Sendai criteria, but before the final publication of the AGA guidelines. Clearly, many surgeons may deviate from the guidelines and personalize treatment based on patient and tumor characteristics and the number of worrisome or high-

TABLE 2 Demographic characteristics and perioperative data

Variable	Invasive IPMNs [$n = 108$] (23%)	Non-invasive IPMNs [$n = 370$] (77%)
Demographic characteristics		
Male	53 (49)	179 (48)
Age, years ± SD	66 ± 12	66 ± 11
Caucasian	84 (78)	312 (84)
BMI, kg/m^2 ± SD	26.9 ± 5.5	27.7 ± 6.0
Diabetes	32 (30)	83 (22)
Ascites	1 (0.9)	1 (0.3)
> 10% weight loss in the last 6 months†	16 (15)	21 (6)
Preoperative obstructive jaundice†	19 (18)	11 (3)
Preoperative biliary stent placement†	18 (18)	16 (5)
Preoperative laboratory values (± SD)		
Albumin (g/dL)	3.9 ± 0.8	4.1 ± 0.5
Total bilirubin† (mg/dL)	1.5 ± 2.6	0.7 ± 1.0
AST†	44 ± 68	29 ± 25
Alkaline phosphatase†	150 ± 171	94 ± 61
INR	1.1 ± 0.4	1.1 ± 0.6
Perioperative data		
Operative approach*		
Open	82 (76)	239 (65)
Laparoscopic or minimally invasive	26 (24)	131 (35)
Operative time, min ± SD	326 ± 132	302 ± 126
Pancreatic resection		
Distal pancreatectomy	32 (30)	136 (37)
Whipple-type procedure	64 (60)	202 (55)
Other	12 (11)	32 (9)
Main pancreatic duct size		
Duct < 6 mm	33 (31)	169 (46)
Duct > 6 mm	22 (20)	62 (17)
Pancreatic gland texture†		
Soft pancreatic gland	23 (42)	155 (67)
Intermediate gland	6 (11)	12 (5)
Hard pancreatic gland	26 (47)	63 (27)

Data are expressed as *n* (%) unless otherwise specified

IPMNs intraductal papillary mucinous neoplasms, *BMI* body mass index, *SD* standard deviation, *AST* aspartate aminotransferase, *INR* international normalized ratio

$^\dagger p < 0.01$

$^* p < 0.05$

TABLE 3 Outcomes and complications

Variable	Invasive IPMNs [$n = 108$] (23%)	Non-invasive IPMNs [$n = 370$] (77%)
Pancreatic fistula	14 (13)	74 (20)
Delayed gastric emptying	11 (11)	38 (11)
Percutaneous drain placement	9 (9)	41 (12)
Reoperation	5 (5)	16 (4)
Length of stay, days ± SD	11.3 ± 9.6	10.0 ± 9.8
Readmission	14 (13)	56 (15)

Data are expressed as *n* (%) unless otherwise specified

IPMNs intraductal papillary mucinous neoplasms, *SD* standard deviation

TABLE 4 Unadjusted and adjusted logistic regression models relating population characteristics to invasive IPMNs

Variable	Unadjusted [OR (95% CI)]	Adjusted [OR (95% CI)]
Male	1.03 (0.67–1.58)	
Age	1.0 (0.98–1.02)	
Diabetes	1.46 (0.90–2.35)	
Ascites	3.45 (0.21–55.60)	
> 10% weight loss in the last 6 months	2.89 (1.45–5.76)†	1.25 (0.33–4.82)
Preoperative obstructive jaundice	7.12 (3.27–15.53)†	3.9 (0.84–18.42)
Preoperative biliary stent placement	4.13 (2.02–8.46)†	1.16 (0.27–4.99)
Preoperative laboratory values		
Total bilirubin	1.29 (1.11–1.50)†	0.83 (0.58–1.19)
AST	1.01 (1.002–1.014)†	0.99 (0.98–1.00)
Alkaline phosphatase	1.005 (1.002–1.007)†	1.01 (1.00–1.02)†
INR	1.11 (0.74–1.67)	
Pancreatic duct size	1.82 (0.98–3.35)	
Pancreatic gland texture		
Hard vs. intermediate	0.83 (0.28–2.43)	0.53 (0.15–1.87)
Soft vs. intermediate	0.30 (0.10–0.87)*	0.19 (0.05–0.68)*

IPMNs intraductal papillary mucinous neoplasms, *OR* odds ratio, *CI* confidence interval, *AST* aspartate aminotransferase, *INR* international normalized ratio

$^\dagger p < 0.01$

$^* p < 0.05$

risk features; however, the result of this inherent limitation reflects realistic and accurate data of the incidence of malignancy specifically in resected IPMNs currently in the US, which was the goal of this study. In this largest study of resected IPMNs in a single year, patients were treated after publication of the revised international consensus criteria;[15] therefore, patient selection, the information available to the surgeon in the literature upon which decision making was based, and time bias for the decision to operate was minimized.

Multicenter, retrospective analyses have reported varying incidences of high-risk IPMNs and node positivity;[9,20] however, these and many other more recent analyses included patients dating back to 2000 and 1992, respectively, during which time the guidelines, consensus statements, and general surgical culture for IPMNs has radically evolved, highlighting the importance of the current study design. Furthermore, the NSQIP dataset does not capture main/mixed/branch-duct classification, histotype, the presence of mural nodes,[15] tumor markers,[21] or cyst fluid analysis/cytology;[22] therefore, this study's objectives and conclusions are necessarily focused on the proportion of pancreatectomies being performed for all IPMNs currently in the US and the incidence of high-risk pathology in these tumors without further IPMN subtype analysis.

Knowledge of the proportion of pancreatectomies being performed today for IPMNs, and the incidence of high-risk pathology, is lacking and is critical to know in order to determine the adequacy of current surgical practice in the US to highlight areas where education can be focused, and to identify areas of research that may help in fine-tuning patient selection and advancing our understanding of the disease. Clearly, based on this study, the vast majority of IPMNs resected in this country are ultimately determined to be low-risk lesions, e.g., low- or moderate-grade dysplasia. This may be appropriate since resection of a low-risk lesion provides the opportunity to prevent progression to invasive disease of a cancer for which current treatments are limited at best. Arguably, based on our current, although limited, understanding of the natural history of IPMNs, some of these lesions may have been suitable for a surveillance strategy.[23]

CONCLUSIONS

This study captures a snapshot of the current incidence of high-grade dysplasia and invasive cancer in resected IPMNs as is currently being practiced by surgeons across the US. The majority of lesions resected are clearly low-risk, which is a reflection of the limitations of our current decision-making algorithms and guidelines. Additional biomarkers of high-risk lesions are likely necessary to decrease the number of pancreatic resections being performed for low-risk disease.[24–27]

CONFLICTS OF INTEREST Dr. Ajay Maker is supported by an NIH/NCI Grant (K08CA190855). Rym El Khoury, Christopher Kabir, Vijay K. Maker, Mihaela Banulescu, and Margaret Wasserman report no conflicts of interest.

DISCLOSURES The ACS NSQIP and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

REFERENCES

1. Fernández-del Castillo C, Targarona J, Thayer SP, et al. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. *Arch Surg*. 2003;138(4):427–34; discussion 433–4.
2. Moris M, Bridges MD, Pooley RA, et al. Association between advances in high-resolution cross-section imaging technologies and increase in prevalence of pancreatic cysts from 2005 to 2014. *Clin Gastroenterol Hepatol*. 2016;14(4):585–93.
3. Schnelldorfer T, Sarr MG, Nagorney DM, et al. Experience with 208 resections for intraductal papillary mucinous neoplasm of the pancreas. *Arch Surg*. 2008;143(7):639–46; discussion 646.
4. Farnell MB. Surgical management of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. *J Gastrointest Surg*. 2008;12(3):414–6.
5. Maker AV, Lee LS, Raut CP, et al. Cytology from pancreatic cysts has marginal utility in surgical decision-making. *Ann Surg Oncol*. 2008;15(11):3187–92.
6. Suzuki Y, Nakazato T, Yokoyama M, et al. Development and potential utility of a new scoring formula for prediction of malignant intraductal papillary mucinous neoplasm of the pancreas. *Pancreas*. 2016;45(9):1227–32.
7. Shin SH, Han DJ, Park KT, et al. Validating a simple scoring system to predict malignancy and invasiveness of intraductal papillary mucinous neoplasms of the pancreas. *World J Surg*. 2010;34(4):776–83.
8. Fujino Y, Matsumoto I, Ueda T, et al. Proposed new score predicting malignancy of intraductal papillary mucinous neoplasms of the pancreas. *Am J Surg*. 2007;194(3):304–7.
9. Wilson GC, Maithel SK, Bentrem D, et al. Are the current guidelines for the surgical management of intraductal papillary mucinous neoplasms of the pancreas adequate? A multi-institutional study. *J Am Coll Surg*. 2017;224(4):461–9.
10. Sahora K, Mino-Kenudson M, Brugge W, et al. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. *Ann Surg*. 2013;258(3):466–75.
11. Fritz S, Klauss M, Bergmann F, et al. Pancreatic main-duct involvement in branch-duct IPMNs: an underestimated risk. *Ann Surg*. 2014;260(5):848–55; discussion 855–6.
12. Reid-Lombardo KM, St Sauver J, Li Z, et al. Incidence, prevalence, and management of intraductal papillary mucinous neoplasm in Olmsted County, Minnesota, 1984–2005: a population study. *Pancreas*. 2008;37(2):139–44.
13. Fernández-del Castillo C, Warshaw AL. Cystic tumors of the pancreas. *Surg Clin N Am*. 1995;75(5):1001–16.
14. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology*. 2006;6(1–2):17–32.
15. Tanaka M, Fernández-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology*. 2012;12(3):183–97.
16. Fink AS, Campbell DA Jr, Mentzer RM Jr, et al. The National Surgical Quality Improvement Program in non-veterans administration hospitals: initial demonstration of feasibility. *Ann Surg*. 2002;236(3):344–53; discussion 353-4.
17. Shimizu Y, Yamaue H, Maguchi H, et al. Predictors of malignancy in intraductal papillary mucinous neoplasm of the pancreas: analysis of 310 pancreatic resection patients at multiple high-volume centers. *Pancreas*. 2013;42(5):883–8.

18. Hackert T, Fritz S, Klauss M, et al. Main-duct intraductal papillary mucinous neoplasm: high cancer risk in duct diameter of 5 to 9 mm. *Ann Surg*. 2015;262(5):875–80; discussion 880–1.
19. Fan F, Lai EC, Xie F, Yang JM, et al. Intraductal papillary mucinous neoplasms of the pancreas–predictors of malignancy. *Hepatogastroenterology*. 2010;57(99–100):635–9.
20. Jang JY, Kim SW, Ahn YJ, et al. Multicenter analysis of clinicopathologic features of intraductal papillary mucinous tumor of the pancreas: is it possible to predict the malignancy before surgery? *Ann Surg Oncol*. 2005;12(2):124–32.
21. Kim JR, Jang JY, Kang MJ, et al. Clinical implication of serum carcinoembryonic antigen and carbohydrate antigen 19-9 for the prediction of malignancy in intraductal papillary mucinous neoplasm of pancreas. *J Hepatobiliary Pancreat Sci*. 2015;22(9):699–707.
22. Maire F, Voitot H, Aubert A, et al. Intraductal papillary mucinous neoplasms of the pancreas: performance of pancreatic fluid analysis for positive diagnosis and the prediction of malignancy. *Am J Gastroenterol*. 2008;103(11):2871–7.
23. Honselmann KC, Patino M, Mino-Kenudson M, et al. Ductal carcinoma arising in a largely unchanged presumed branch-duct IPMN after 10 years of surveillance. *Ann Surg*. 2017;266(6):e38–40.
24. Maker AV, Katabi N, Gonen M, et al. Pancreatic cyst fluid and serum mucin levels predict dysplasia in intraductal papillary mucinous neoplasms of the pancreas. *Ann Surg Oncol*. 2011;18(1):199–206.
25. Maker AV, Katabi N, Qin LX, et al. Cyst fluid interleukin-1beta (IL1beta) levels predict the risk of carcinoma in intraductal papillary mucinous neoplasms of the pancreas. *Clin Cancer Res*. 2011;17(6):1502–8.
26. Maker AV, Carrara S, Jamieson NB, et al. Cyst fluid biomarkers for intraductal papillary mucinous neoplasms of the pancreas: a critical review from the international expert meeting of pancreatic branch-duct-intraductal papillary mucinous neoplasms. *J Am Coll Surg*. 2015;220(2):243–53.
27. Tulla KA, Maker AV. Can we better predict the biologic behavior of incidental IPMN? A comprehensive analysis of molecular diagnostics and biomarkers in intraductal papillary mucinous neoplasms of the pancreas. *Langenbecks Arch Surg*. 2017. https://doi.org/10.1007/s00423-017-1644-z.