—Original Article—

Development of a new risk score for invasive cancer in branch-duct intraductal papillary mucinous neoplasms according to morphological characterization by EUS

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ABSTRACT

Background and Objective: The management of branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) is determined by a number of guidelines. The current weight of risk factors by EUS predicting invasive cancer is unknown. The aim of this study is to develop a risk score for early prediction of invasive cancer according to morphological characterization by EUS in a surgical cohort. **Materials and Methods:** This is an observational, multicenter retrospective study. All consecutive patients with a histologically proven BD-IPMN who underwent previous EUS between 2005 and 2017 were included. Morphological features by EUS were evaluated. A score using a logistic regression model was performed to assess the risk of invasive cancer. **Results:** Of 335 patients who underwent pancreatic surgery, 131 (median age: 66 years, 50.4% – male) were included. By multivariable analysis, lymph nodes (odds ratio [OR]: 17.7 [confidence interval (CI) 95%: 2.8–112.6], $P = 0.002$, 4 points), main pancreatic duct ≥10 mm (OR: 8.6 [CI 95%: 1.9–39.5], $P = 0.006$, 2 points), abrupt change of pancreatic duct (OR: 5.5 [CI 95%: 1.4–22.2], $P = 0.016$, 1.5 points), and solid component (OR: 4.2 [CI 95%: 1.3–13.6], $P = 0.017$, 1 point) were independent factors associated with invasive cancer and included in the model. The following categories of the score (0–8.5 points) – A (0–1), B (1.5–3), C (3.5–5), and D (5.5–8.5 points) – presented a positive predictive value of 8.5%, 38.9%, 62.5%, and 100%, respectively. The area under the curve was 0.857 ($P < 0.001$), with an overall sensitivity and specificity of 84% and 70% in the internal validation of the score. **Conclusion:** This EUS predictive score for invasive cancer in BD-IPMN has a high accuracy and could be an additional tool to consider in patient management.

Key words: branch-duct intraductal papillary mucinous neoplasms, EUS, invasive cancer, score

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INTRODUCTION

Pancreatic cystic lesions (PCLs) are an increasingly common radiological finding, probably associated with the greater use of abdominal cross-sectional imaging in an aging population. An incidence of 1.2%–2.6% has been reported in patients undergoing abdominal computed tomography (CT)[1,2] and in up to 13.5% of patients undergoing a magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI-MRCP) for nonpancreatic indications.[3] Recently, a systematic review was published with 48,860 patients. The rate of incidentally detected PCLs was 8%. Mucinous lesions were the most common incidentally detected PCLs. This prevalence was higher in studies of higher quality, which the MRI-MRCP was employed.[4]

Branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) have been considered as one of the most frequently detected PCLs, which could progress slowly from adenoma to carcinoma. Many studies have analyzed the differential diagnosis of benign and malignant tumors, as well as the determination of surgical indications; however, the knowledge about their natural history and risk factors associated with the progression to malignancy are limited.[5-7] For this reason, their management is determined by a number of guidelines, which advocate a number of imaging techniques and criteria for deciding on the handling of mucinous tumors, classified such as "worrisome features (WFs)" and "high-risk stigmata" in the Fukuoka guidelines for the first time, and later in the European guidelines.[8-10] These guidelines have been mainly based on expert opinions, establishing different strategies in therapeutic and follow-up management. MRI-MRCP has been described as one of the main baseline diagnostic imaging techniques. EUS could be indicated in different scenarios as follows: the presence of selected WF, acute pancreatitis, or cyst size >3 cm confirmed by MRI-MRCP in the Fukuoka guidelines,[8] the visualization of at least two high-risk features in the American Gastroenterological Association guideline,[11] and in the presence of radiological concern features identified during the initial investigation or follow-up according to the European guidelines.[10] Therefore, according to the morphological findings observed by EUS, a different therapeutic management is established, and subsequently, the prognosis of the patient can be modified. Some patients may benefit from early surgery while others could avoid too close follow-up with invasive procedures. The aim of this study was to develop a risk score for early prediction of invasive cancer of BD-IPMN according to the morphological characterization by EUS, using the surgical specimens as a gold standard.

MATERIALS AND METHODS

Design of the study

This is an observational, multicenter retrospective study. All consecutive patients over 18 years old diagnosed with BD-IPMN by EUS who underwent pancreatic surgery with histological confirmation between January 2005 and December 2017 were included.

Patients who were diagnosed with a different imaging test, patients not undergoing pancreatic surgery, or patients with a histological diagnosis different from BD-IPMN were excluded. Similarly, those cases with a personal history of pancreatic cancer or concomitant main-duct IPMN were not considered.

All investigations were conducted at the Departments of Gastroenterology and Hepatology of Complejo Hospitalario de Navarra, Cliniques Universitaires Saint-Luc, Hospital Universitario de Santiago de Compostela, and Hospital Universitario de Cruces.

Definitions

A BD-IPMN was defined as a cystic lesion of the pancreas ≥5 mm, associated with one or more dilated branch duct/s communicating with the main pancreatic duct (MPD) on MRI-MRCP and/or EUS and/or fine-needle aspiration (FNA) with cyst fluid carcinoembryonic antigen >30 ng/mL.[12] Histopathological analysis was performed in all cases, and BD-IPMN was defined as an intraductal proliferation of neoplastic duct epithelium, accompanied by mucin production. According to the degree of dysplasia, they were classified as low-grade dysplasia (LGD), high-grade dysplasia (HGD), or invasive cancer. When several degrees of dysplasia were present in the same sample, the lesion was categorized according to the most severe grade.

EUS technique

EUS was performed in the left lateral position under conscious sedation using midazolam and/or fentanyl or general anesthesia. All procedures were executed by experienced endosonographers (each having

performed more than 5000 procedures). They were carried out using linear and radial ultrasound endoscopes (FGUX-36, EG3830UT, Pentax, Hamburg, Germany, or GF-UCT180, Olympus, Aartselaar, Belgium) on a Hitachi 5500, 8500, or Aloka SSD-4000 processor (Hitachi, Hamburg, Germany). FNA was performed on an individual basis according at the discretion of the endoscopist according to the characteristics of the cyst. After aspiration, the cyst fluid was sent for cytological and biochemical analysis. Antibiotic prophylaxis was given to all patients following FNA in line with the local hospital policy. Patients were monitored for 4 h postprocedure before discharge if well. Contrast (Sonovue, Bracco Imaging, Milan, Italy) was used for the differentiation of enhanced and nonenhanced solid components within cyst in the most recent cases due to the availability of the technique. In older cases, the diagnosis of a mural nodule was retained when a clear evidence of a solid mass >5 mm in the interior of the lesion was observed. When several cysts were observed in the same patient, only the largest in size was considered in the analysis.

Data analysis and criteria

The following data were collected: cyst size, number of lesions, location, wall thickening (>2 mm), nonenhanced mural nodules, solid component, peripancreatic lymph nodes (≥1 cm), dilation of the MPD (≥5 mm), distal pancreatic atrophy with abrupt change in caliber of the MPD, and type of surgery. The location of the cyst was classified as follows: head (which included uncinate process) body, and tail. The type of surgery was categorized into pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy.

Statistical analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test when necessary. All continuous data were presented as mean ± standard deviation. Normally distributed continuous variables were analyzed by Student's *t*-test and nonnormally distributed variables by the Mann–Whitney U-test. The association between EUS risk factors and invasive carcinoma was calculated with univariable and multivariable models to adjust for multiple potential confounders. Parameters with $P < 0.05$ in the univariable analysis were candidates for the multivariable model. Subsequently, a risk score was made based on the odds ratios (ORs) in the multivariable model. One point was given to the smaller significant OR, and the remaining features were given score points accordingly. An internal validation was carried out, and accuracy values such as positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, and accuracy were calculated. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 24 (IBM, Bois-Colombes, France). The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

Patients

From 2005 to 2017, 335 patients underwent pancreatic surgery with a suspicion of BD-IPMN. Two hundred and four patients were excluded from the study because they had a histological diagnosis different from BD-IPMN (n = 152) or EUS was not performed before surgery (n = 52) [Figure 1].

Finally, a total number of 131 patients were included in the study. The median age was 66 years (range: 25–89, 50.4% – male). The presentation was incidental (n = 52, 39.7%), symptomatic (n = 76, 58%) with abdominal pain and/or weight loss, and unknown (n = 3, 2.3%).

The location of the cyst was as follows: head/uncinate (n = 89, 67.9%), body (n = 24, 18.3%), and tail (n = 18, 13.7%). The type of surgery was pancreaticoduodenectomy (n = 86, 65.6%), distal pancreatectomy (n = 37, 28.2%), and total pancreatectomy (n = 8, 6.1%). Histological analysis

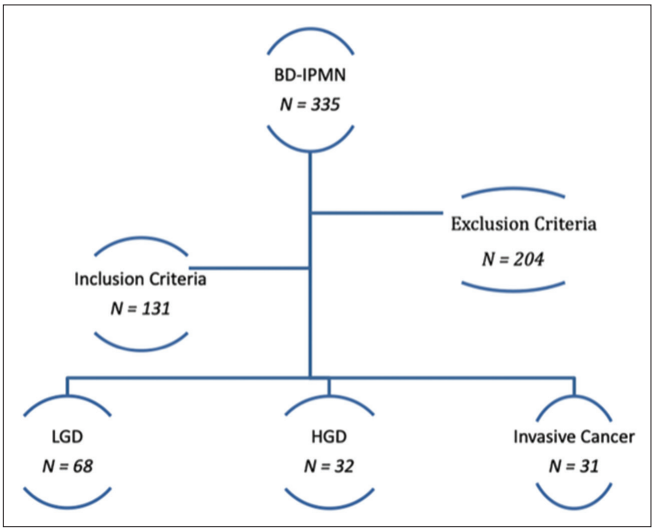

Figure 1. Flowchart on included patients presenting with a branch-duct intraductal papillary mucinous neoplasm who underwent pancreatic surgery. LGD: Low-grade dysplasia, HGD: High-grade dysplasia

revealed LGD (*n* = 68, 51.9%), HGD (*n* = 32, 24.4%), and invasive cancer (*n* = 31, 23.7%).

Risk features detected by EUS

Risk features according to histopathological analysis are shown in Table 1. The median cyst size was 25 mm (range: 5–130), and there were 24 cases (18.3%) with a cyst size ≥40 mm. Most of the cysts ≥30 mm were located in the head compared to body/tail (61.5% *vs.* 38.5%, *P* = 0.151), but this difference was not statistically significant. The contrast enhancement was performed in 45 patients (34.4%). Among 31 patients with invasive cancer, the most common risk features diagnosed by EUS were solid component (*n* = 19, 61.3%), cyst size (*n* = 18, 58.1%), MPD ≥10 mm (*n* = 14, 45.2%), and lymph nodes (*n* = 14, 45.2%). Furthermore, an abrupt change in the MPD caliber (*n* = 10, 32.3%), dilated MPD from 5 to 9 mm (*n* = 9, 29%), and wall thickening (*n* = 6, 19.4%) were observed. Nonenhanced mural nodules were rare (*n* = 3, 9.7%).

Score model

By multivariable analysis, lymph nodes, MPD ≥10 mm, abrupt change in the MPD, and solid component were independent factors associated with invasive cancer and included in the score [Table 2]. They were given 4, 2, 1.5, and 1 score points, respectively. The Nagelkerke index of the model was 0.539. Cyst size ≥30 mm was associated with invasive cancer in univariable but not in the multivariable model. The score was classified into the following categories (0–8.5points): A (0–1), B (1.5–3), C (3.5–5), and D (5.5–8.5 points). The PPVs for invasive cancer were 8.5%, 38.9%, 62.5%, and 100%, respectively. Accuracy values for the different categories are described in Table 3. The area under the curve was 0.857 (*P* < 0.001), with an overall sensitivity and specificity of 84% and 70% in the internal validation of the model [Figure 2]. Notably, most of the patients with invasive carcinoma were in D category (*n* = 11, 35.5%). The median score value of BD-IPMN with cancer was three points (range: 0–8.5) compared to zero points (range: 0–4) in patients with noninvasive forms (*P* < 0.001). There were five patients with a negative score (zero points) and cancer (3.8% false negatives). Similarly, 30 patients presented with a positive score (≥1 point) LGD or HGD (22.9% false positives), but no patient with >4 score points had a noninvasive histology.

DISCUSSION

In this multicenter observational study, we report on a score predicting invasive cancer of BD-IPMN according

Table 1. Morphological features detected by EUS according to histopathological analysis in 131 patients with branch-duct intraductal papillary mucinous neoplasms who underwent surgery

Feature	Overall (%)	LGD (%)	HGD (%)	Invasive cancer (%)
Size ≥30 mm	52 (39.7)	20 (15.3)	14 (10.7)	18 (13.7)
Abrupt change MPD	20 (15.3)	8 (6.1)	1 (0.8)	11 (8.4)
Wall thickening	21 (16)	8 (6.1)	7 (5.3)	6 (4.6)
Nonenhanced mural nodule	19 (14.5)	12 (9.2)	4 (3.1)	3 (2.3)
Solid component	36 (27.5)	13 (9.9)	4 (3.1)	19 (14.5)
MPD 5-9 mm	45 (34.4)	25 (19.1)	11 (8.4)	9 (6.9)
MPD ≥10 mm	18 (13.7)	1 (0.8)	3 (2.3)	14 (10.7)
Lymphadenopathy	16 (12.2)	1 (0.8)	1 (0.8)	14 (10.7)

LGD: Low-grade dysplasia; HGD: High-grade dysplasia; MPD: Main pancreatic duct.

Table 2. Univariable and multivariable analysis of EUS risk factors associated with invasive carcinoma in 131 patients with a histologically confirmed branch-duct intraductal papillary neoplasm

Risk factor	Univariable analysis		Multivariable analysis		Score points
	OR (95% CI)	*P*	OR (95% CI)	*P*	
Size ≥30 mm	2.69 (1.2-6.1)	0.017*			
Abrupt change MPD	5.56 (2-15.2)	<0.001*	5.5 (1.4-22.2)	0.016*	1.5
Wall thickening	1.36 (0.5-3.9)	0.564			
Nonenhanced mural nodule	0.56 (0.15-2.1)	0.382			
Solid component	7.73 (3.2-18.9)	<0.001*	4.2 (1.3-13.6)	0.017*	1
MPD 5-9 mm	0.7 (0.3-1.7)	0.475			
MPD ≥10 mm	19.8 (5.8-67.3)	<0.001*	8.6 (1.9-39.5)	0.006*	2
Lymphadenopathy	40.4 (8.4-193.7)	<0.001*	17.7 (2.8-112.6)	0.002*	4

*Statistically significant. OR: Odds ratio; CI: Confidence interval; MPD: Main pancreatic duct.

Table 3. Accuracy values of a new EUS score predicting the risk of invasive cancer in 131 branch-duct intraductal papillary neoplasms according to four categories (internal validation).

Score category	Points	*n* (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
A	0-1	94 (71.8)	8.5	91.5	100	100
B	1.5-3	18 (13.7)	38.9	91.5	46.7	88.7
C	3.5-5	8 (6.1)	62.5	86.6	25	97
D	5.5-8.5	11 (8.4)	100	83.3	35.5	100

PPV: Positive predictive value; NPV: Negative predictive value.

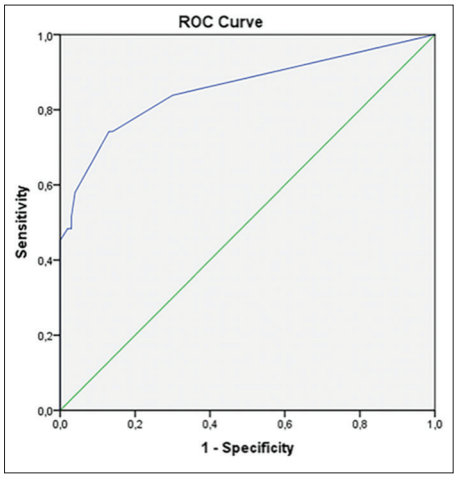

Figure 2. Receiver operating characteristic curve analysis. Sensitivity and specificity of the predictive model assessing the risk of invasive carcinoma of branch-duct intraductal papillary mucinous neoplasm

to the morphological characterization by EUS. The score has shown a high accuracy in our local series of 131 patients who underwent pancreatic surgery with histological confirmation.

Based on a summary of 20 different studies including 3.568 IPMN, the risk of invasive carcinoma arising in association with BD-IPMN was approximately 17%.[8] In another study, this risk was <10%[13] and in our study was almost 25%. Thus, the risk for malignancy varies widely across different reports. This could be related to the different recommendations for surgery according to different guidelines. In addition, the risk factors for malignancy in BD-IPMN are not very well known and have shown a low accuracy to detect invasive pathology with a lack of specificity.[14] In this sense, we have previously reported that invasive carcinoma is considerably more frequent in patients with two or more relative indications according to the last European guidelines.[15] Indeed, the association between the number of risk factors and the risk of malignancy has already been described.[16]

However, most of the patients who undergo surgery present with "relative indications" or "WFs," and most of the studies and guidelines analyzing the number of these common risk features are not weighted and considered all of them at the same level of risk in the decision-making strategy. In addition, most of the authors considered radiological and endoscopic examinations altogether. In the present study, we sought to determine whether EUS could predict invasive carcinoma using a score based on the number of features with a proportional balanced weight. In addition, we have not considered CT or MRI to increase the homogeneity of the population, making the score easier to apply in daily practice. Notably, our score has shown a very low PPV for those patients in A category (8.5%) and a very high PPV in these cases included in the D category (100%). However, in clinical practice, most of the patients will probably have intermediate values. In this sense, this score does not pretend to be the only tool in the decision-making strategy but to give additional support to the management.

The risk features associated with invasive carcinoma included in our score are quite similar to those previously described. However, most of the previous studies are focused on radiological examinations, or EUS exclusive data are not described, making the comparison difficult. Overall, the presence of abrupt change in the MPD caliber with distal pancreatic atrophy, solid component, MPD ≥10 mm, and lymphadenopathy were independent factors associated with an increased risk of malignancy in our series.

A multicenter retrospective study in Japan reported that the incidence of malignant transformation was low in patients with a mural nodule if the size was <10 mm.[17] Although we have not assessed the nodule size, there was no association between the presence of nonenhanced mural nodules and invasive carcinoma. Cyst size has also been associated with an increased probability of harboring HGD or invasive cancer, but the cutoff to quantify the risk remains uncertain.[9,18] In addition, the predictive value for invasive carcinoma and HGD is poor.[19-24] Similarly, we observed that a cyst size >3 cm was not associated with invasive cancer in multivariable analysis.

Furthermore, some studies have reported that a marked dilatation of the MPD could be a major risk factor for malignancy.[25-29] In our series, we also observed that a MPD dilation ≥10 mm was a significant predictor for invasive carcinoma both in the univariable and multivariable analysis.

The significance of lymphadenopathy remains unclear.[18,30,31] One study found that lymphadenopathy was a significant predictor for malignant MD-IPMN, with high specificity (92.6% for CT and 96.3% for MRI) and relatively low sensitivity (34.1% for CT and 29.6% for MRI).[30] In another study involving 350 BD-IPMNs, lymphadenopathy was significant only in univariable analysis, with a sensitivity of 7.2% and a specificity of 99.6%, but not in multivariable analysis.[18] Accordingly, lymphadenopathy was associated with invasive carcinoma in our series.

Finally, another study published that the best predictors of malignancy in IPMN were the solid component (OR 3.98), abrupt change in the MPD caliber (OR: 5.1), and common bile duct dilation (OR: 31.26).[32] In our case, both the presence of a solid component (OR: 4.2) and abrupt change in the MPD caliber with distal pancreatic atrophy dilation (OR: 5.5) were significantly associated with invasive carcinoma.

Our study has several strengths and limitations. This is a multicenter study with a significant number of patients providing information on EUS features independently of radiological examinations. Moreover, we included patients who underwent pancreatic surgery with histological confirmation, being most of these studies performed with diagnostic suspicion. In addition, our score is accurate and may be an additional tool in the management of these patients.

However, this is a retrospective study across four centers with differing criteria for EUS evaluation in BD-IPMN under surveillance, such as the performance of contrast enhancement. We also accept that the diagnostic accuracy of EUS is strongly related to the physician's experience and available local expertise, which may bias test selection.

CONCLUSION

In this multicenter study of 131 patients with BD-IPMNs, we have determined four categories of EUS score for predicting invasive carcinoma. The score includes weighted risk factors such as a solid component, abrupt change, MPD ≥10 mm, and lymphadenopathy, achieving high accuracy. These results suggest a high precision of the model in the evaluation of the risk for early prediction of invasive cancer associated with BD-IPMN. This can be an additional tool for improving the management of selected patients with BD-IPMN, reducing morbidity and mortality. External validation may provide a reliable noninvasive prognostic tool for clinicians.

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Conflicts of interest

There are no conflicts of interest.

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