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Risk of advanced lesions in patients with branch-duct IPMN and relative indications for surgery according to European evidence-based guidelines

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ABSTRACT

Background: European evidence-based guidelines proposed surgery for branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) based on the presence of 1–2 relative indications, depending on the comorbidity burden.
Aims: To assess the accuracy of the guidelines in patients with relative indications in a surgical cohort of demonstrated BD-IPMNs.
Methods: This report describes a multi-centre, observational, retrospective study. All consecutive patients with relative indications and histologically confirmed BD-IPMN were included. The main outcome was risk of invasive carcinoma in patients with relative indications.
Results: Ninety-one patients with BD-IPMN underwent surgery because of absolute (n = 21), relative (n = 60), or no formal indications (n = 10). In total, there were 60 patients (mean age: 66 ± 9, 50% male) with one (n = 35, 58.3%) or ≥2 relative indications (n = 25, 41.7%). The global advanced lesion and invasive carcinoma rates were 40% and 13.3%, respectively. No risk factor was associated with high-grade dysplasia or invasive carcinoma. Patients with one indication had a lower risk of invasive carcinoma than did those with ≥2 relative indications (5.7% vs. 24%, respectively, p = 0.048); however, the advanced lesion rates were comparable (37.1% vs. 44%, p = 0.593).
Conclusions: Invasive carcinoma is considerably more frequent in patients with two or more relative indications. The surgical strategy in these selected cases should be decided on an individual basis.

1. Introduction

The decision-making strategy for treatment of branch-duct intraductal papillary mucinous neoplasms (BD-IPMN) can be challenging, as the features predicting an advanced lesion are not well-known. Furthermore, most patients presenting with BD-IPMN have relative indications or worrisome features, while absolute indications are less frequent.

A number of guidelines and expert consensuses have been published in recent years [1–3]. The indications for surgery appear clear in patients with absolute indications, such as jaundice, enhancing mural nodules, a solid mass or a main pancreatic duct (MPD) ≥10 mm. Similarly, follow-up appears to be the best approach in patients without risk factors. Nevertheless, there is no consensus regarding patients with "worrisome features" or relative indications, where the thresholds are uncertain. The new European evidence-based guidelines on pancreatic cystic neoplasms consider surgery for BD-IPMN based on the presence of relative risk factors depending on comorbidities [4]. Surgery is recommended in patients presenting with significant comorbidities and two or more relative indications, while intensive surveillance by magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) is recommended for those with only one relative indication (Table 1). Relative indications included a grow-rate ≥5 mm/year, serum Ca 19.9 ≥ 37 U/ml, MPD dilation between 5 and 9.9 mm, cyst size ≥40 mm, new onset of diabetes mellitus, acute pancreatitis and contrast-enhancing mural nodule <5 mm.

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Table 1
Indications for surgery in branch-duct intraductal papillary mucinous neoplasms according to the new European guidelines.

Absolute indications (≥1 indication)	
Positive cytology for malignant/high-grade dysplasia	Solid mass
Jaundice (tumor related)	Main pancreatic duct ≥10 mm
Enhancing mural nodule (≥5 mm)	
Relative indications[a]	
Grow-rate ≥5 mm/year	Ca 19.9 ≥ 37 U/ml
Main pancreatic duct from 5–9.9 mm	Cyst diameter ≥40 mm
New onset of diabetes mellitus	Acute pancreatitis
Enhancing mural nodules ≤5 mm	

[a] Surgery is indicated in patients with significant co-morbidities and two or more relative indications or those without significant co-morbidities and one or more relative indication.

This approach considering the number of features has already been suggested by some authors [5,6]; however, the inclusion of the comorbidities in the algorithm is novel. Although the risk of malignancy persists in long-term follow-up [7], the low progression of BD-IPMN [8,9] may justify a conservative approach in older patients or those with significant comorbidities.

Finally, the concept of "significant comorbidity" and "elderly" may be subjective, as may other individual factors, making surgical decisions more difficult. Determining the differential risk between patients with one to two criteria based on these guidelines could be valuable information and could assist further management.

Therefore, the aim of the present study was to assess the accuracy of the new European guidelines in patients with relative indications for surgery in a surgical cohort of demonstrated BD-IPMNs with a focus on the number of criteria.

2. Methods

2.1. Patients

This report describes a multi-centre, observational, retrospective study. All consecutive patients who underwent pancreatic surgery because of a BD-IPMN detected by either EUS, MRI or computed tomography (CT), and confirmed by histopathological analysis between September 2006 and April 2017 were included. Only the largest cystic lesions per patient was considered. Medical records were reviewed and data, including age, gender and clinical presentation, were collected. Patients under 18 years old or presenting with absolute indications for surgery (positive cytology, solid mass, enhancing mural nodule ≥5 mm and MPD ≥ 10 mm) were excluded. In addition, cases with no formal indications according to the European guidelines were not considered in the analysis. The study protocol was approved by our local review board (2016/29DEC/567), and it conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Definitions and outcomes

A BD-IPMN was defined as a cystic lesion ≥5 mm communicating with the pancreatic duct with mucinous cystic epithelial lining proven by histopathological analysis. The location of the cyst, as well as the clinical and imaging features associated with advanced lesions according to the recent European guidelines, were considered [4]. Laboratory results were also reviewed for preoperative serum Ca 19.9.

The main outcome of the present study was risk of advanced lesions in patients with relative indications and no major risk factors. All cases were classified in two groups according to whether they presented one or ≥2 relative indications, and a subgroup analysis was carried out to assess the differential risk of advanced lesions. The "number needed to treat", defined as the average number of patients who need to undergo surgery to detect one invasive carcinoma, was assessed. An advanced lesion was defined as high-grade dysplasia or invasive cancer. When various degrees of dysplasia were present in the same specimen, lesions were categorized according to the most severe.

2.3. Procedures

All patients were evaluated by EUS and radiological examinations (MRI and/or CT) before surgery. To minimize data heterogeneity in this study, only variables by EUS were considered. The procedures were carried out using linear and radial ultrasound endoscopes (FGUX-36, EG3830UT, EG3870UTK, Pentax, Hamburg, Germany or GF-UCT180, GF-UE160, Olympus, Aartselaar, Belgium) on Hitachi 5500, 8500, or Aloka-SSD4000 processors (Hitachi, Hamburg, Germany). A contrast agent (SonoVue, Bracco Imaging, Milan, Italy) under real-time observation was used for BD-IPMNs with suspected mural nodules or septations. EUS fine-needle aspiration (EUS-FNA) was performed at the discretion of the endoscopist based on the cyst's characteristics. The procedures were performed under conscious sedation or general anaesthesia.

2.4. Statistical analysis

Categorical variables were compared using the χ^2 test or Fischer's exact test when necessary. Normally distributed continuous variables were analysed by Student'st test, and non-normally distributed variables were analysed using the Mann-Whitney U-test. All continuous data were presented as the mean ± SD, and non-parametric were expressed as median (range). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for invasive carcinoma and advanced lesions were calculated based on the number of relative indications. A p-value <.05 was considered to be statistically significant. All analyses were performed using SPSS version 24 (IBM, Bois-Colombes, France).

3. Results

3.1. Patients

Ninety-one patients with a BD-IPMN underwent pancreatic surgery because of absolute (n = 21), relative (n = 60), or no formal indications (n = 10) according to these guidelines, as presented in the flow-chart (Fig. 1). The 10 patients without absolute or relative indications underwent surgery because of worrisome features according to other guidelines (abrupt change of the main duct, cyst size ≥30 mm, lymphadenopathy or abdominal pain) and were excluded.

A total of 60 patients (mean age: 66 ± 9, 50% male) with one (n = 35, 58.3%) or ≥2 relative indications (n = 25, 41.7%) from two centres were finally included. There were no significant differences in age (66 ± 10 vs. 67 ± 8, p = 0.674) or male gender (57.1% vs. 40%, p = 0.190) between groups. There was no family history of pancreatic cancer. The surgical procedures were pancreaticoduodenectomy (n = 44, 73.3%), distal pancreatectomy (n = 15, 25%) and total pancreatectomy (n = 1, 1.7%).

The circumstances of diagnosis were as follows: acute pancreatitis (n = 26, 43.3%), incidental (n = 16, 26.7%), abdominal pain (n = 9, 15%) and diabetes (n = 9, 15%). The location of the cyst was in the head (n = 39, 65%), body (n = 11, 18.3%) or tail (n = 10, 16.7%). Multifocality was observed in 13.3% of cases.

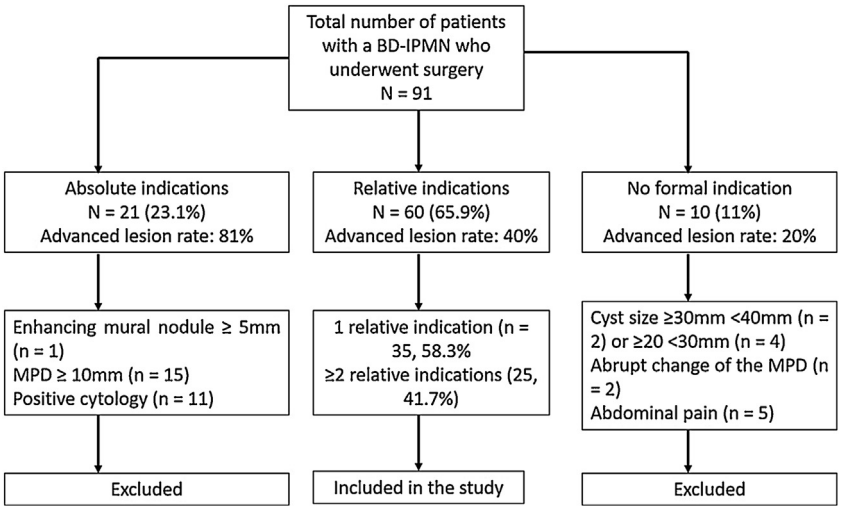

Fig. 1. Included and excluded patients with a branch-duct intraductal papillary mucinous neoplasms according to the presence of relative indications in the European evidence-based guidelines. BD-IPMN, branch-duct intraductal papillary mucinous neoplasms; MPD, main pancreatic duct. Advanced lesion: high-grade dysplasia or invasive carcinoma.

Table 2
Relative indications for surgery and association with advanced lesions (univariable analysis) according to the European evidence-based guidelines on branch-duct intraductal papillary mucinous neoplasms.

Relative indication	N (%)	Advanced lesions[a]	OR (CI95%)	P-value	Inv. Ca.	P-value
Radiological features (by endoscopic ultrasound)						
Grow-rate ≥5 mm/year	15 (25%)	7 (29.2%)	0.69 (0.21–2.26)	0.543	3 (20%)	0.380
MPD from 5 to 9.9 mm	28 (46.7%)	12 (42.9%)	0.8 (0.28–2.25)	0.673	4 (14.3%)	1
Cyst diameter ≥40 mm	7 (11.7%)	2 (28.6%)	0.564 (0.1–3.17)	0.691	1 (12.5%)	0.937
Enhancing mural nodule <5 mm	8 (13.3%)	3 (37.5%)	0.89 (0.19–4.11)	1	2 (25%)	0.297
Clinical features						
New-onset of diabetes mellitus	8 (13.3%)	4 (16.7%)	1.6 (0.36–7.13)	0.702	2 (25%)	0.297
Acute pancreatitis	29 (48.3%)	11 (37.9%)	1.2 (0.42–3.332)	0.752	6 (20.7%)	0.140
Biological features						
Ca 19.9 ≥ 37 U/ml	2 (8.3%)	2 (100%)	2.63 (1.9–3.66)	0.156	1 (50%)	0.251

OR, odds ratio; CI, confidence interval; MPD, main pancreatic duct; Inv. Ca., invasive cancer.
[a] Advanced lesion was defined as high-grade dysplasia or invasive cancer.

3.2. Relative indications for surgery

The advanced lesion rate was 40%, including invasive cancer (n = 8, 13.3%) and high-grade dysplasia (n = 16, 26.7%). As shown in Table 2, the main pancreatic duct from 5 to 9.9 mm and enhancing mural nodules <5 mm achieved the highest advanced lesion rates (42.9% and 37.5%); nevertheless, there was no statistically significant association between these features and advanced lesions. Notably, main pancreatic ducts of 5–9.9 mm were notably more frequent in patients with ≥2 criteria (n = 19/25, 76%), while the isolated presence of this feature was less frequent (n = 9/35, 25.7%) (p < 0.001). Furthermore, the growth-rate ≥ 5 mm/year was not associated with larger cyst size (p = 0.246).

Considering only risk factors detected by EUS and excluding the clinical and biological criteria, the risk of advanced lesions and invasive carcinoma in patients with at least one relative indication by EUS were 39.5% and 14%, respectively. EUS-FNA was performed in 38 lesions (63.3%) and was negative for advanced lesions in all cases.

The histopathological analysis according to the number of indications is shown in Table 3. The risk of advanced lesions in patients with 1 relative indication was 37.1% compared to 44% in the ≥2 relative indications subgroup (p = 0.593, not significant). Therefore, the estimated risk difference was 6.9%. Nevertheless, the risks of invasive carcinoma were lower in patients with only one relative indication (5.7% vs. 24%, p = 0.048) with a statistically significant risk difference of 18.3%. Considering patients with two (n = 17, 28.3%), three (n = 6, 10%) and four criteria (n = 2, 3.3%), the stratified risks of advanced lesions were 41.2%, 33.3% and 100%, respectively.

Overall, patients with invasive carcinoma had more indications (median: 3, range: 1–4) than did those with low- or high-grade dysplasia (median: 1, range: 1–3) (p = 0.007). The number needed to treat for invasive carcinoma in patients with 1 relative indication was 17.5 compared to 4.17 in the group of ≥2 relative indications.

Table 3
Histopathological analysis of patients presenting with a branch-duct intraductal papillary mucinous neoplasm according to the number of relative indications.

Subgroup	N (%)	Low-grade dysplasia	High-grade dysplasia	Invasive carcinoma	Advanced lesions[a]
1 relative indication	35 (58.3%)	22 (62.9%)	11 (31.4%)	2 (5.7%)	13 (37.1%)
≥2 relative indications	25 (41.7%)	14 (56%)	5 (20%)	6 (24%)	11 (44%)
p-value		0.593	0.324	0.048[b]	0.593

[a] Advanced lesions: high-grade dysplasia or invasive carcinoma.
[b] There were statistically significant differences using the Fisher test.

Table 4
Characteristics of patients presenting with a branch-duct intraductal papillary mucinous neoplasm, a proven invasive carcinoma, and relative indications for surgery according to the European evidence-based guidelines.

Nb	Age, sex	Size	Location	MPD Size	Grow-rate ≥5 mm/year	Enhancing MN <5 mm	Diabetes mellitus	Acute pancreatitis	Ca 19.9 (U/ml)
1	79 F	30	Tail	3	Yes	No	No	No	11.3
2	66 M	35	Tail	3	No	No	No	No	38
3	71 F	27	Head	3	No	No	No	Yes	7.8
4	73 M	12	Head	5	No	No	No	Yes	13.4
5	64 F	15	Head	8	Yes	No	No	Yes	17.4
6	66 F	30	Head	6	Yes	No	Yes	Yes	15.6
7	77 F	50	Head	3	No	Yes	Yes	Yes	6.2
8	72 M	38	Head	5	no	Yes	Yes	Yes	5

M, male; F, female; MPD, main pancreatic duct; MN, mural nodule.

The sensitivity, specificity, PPV and NPV for invasive carcinoma in patients with at least two criteria were 75%, 63.5%, 24% and 94.3%, respectively. The accuracy was 65%. Characteristics of the 8 patients with a BD-IPMN harbouring invasive carcinomas are described in Table 4. A total of 80% of the patients presented with at least one relative indication by EUS, while there were two patients presenting only with acute pancreatitis or a high Ca 19.9 and no other predictive criteria.

4. Discussion

We reported a series of 60 patients with BD-IPMN and relative indications for surgery according to the most recent European evidence-based guidelines [4]. The global advanced lesion rate was 40%, and no risk factors were associated with high-grade dysplasia or invasive carcinoma. Following the consideration of the guidelines, a subgroup analysis based on the number of indications was performed. This analysis showed that patients with only one indication had a lower risk of invasive carcinoma than did those with ≥2 relative indications (5.7% vs. 24%); nevertheless, the advanced lesion rates in both groups were comparable.

The risk factors for advanced lesions in BD-IPMN are not well-known and have shown low accuracy and a lack of specificity for the detection of invasive pathology [10]. This finding may be one of the reasons why a proportion of patients undergo pancreatic surgery without following the guidelines. Indeed, patients with BD-IPMN and no surgical indications according to Sendai/Fukuoka guidelines could have a risk of malignancy of 11–25% [10–12]. Most published series on surgical cohorts validating the various consensuses on BD-IPMNs considered patients with absolute indications or high-risk stigmata and those with worrisome features together [13]. Thus, the association between individual worrisome features and advanced lesions may be overestimated or biased in these studies because patients may also have high-risk stigmata or several worrisome features simultaneously [14].

In our study, we only included patients with relative indications according to the European evidence-based guidelines; this resulted in an advanced lesion rate of 40%. Furthermore, we only considered EUS features, while most of the published data report radiological examinations alone or in combination with EUS. No relative indication was associated with advanced lesions or invasive cancer on univariable analysis, probably because we analysed a "low-risk population". As previously described [15], cyst growth was not associated with advanced lesions. The overall advanced lesion rate was comparable to those in previously published studies.

Notably, the current guidelines proposed a new algorithm based on the number of relative indications and the comorbidity burden. Although the long-term risk of malignant evolution persists in BD-IPMN [7,16], conservative management has been proposed in old patients who have worrisome features, as 80% of patients with indications for surgery are alive 5 years after initial diagnosis [17] and the IPMN-related mortality may be low [18]. An individualized approach for those aged 76–85 years should be considered, including an informed discussion regarding surgery [8,19].

Thus, the number of criteria can be a useful predictive tool, increasing the probability of advanced lesions, as most of predictive features are not accurate as the sole indicators for surgery. However, there are few studies analysing the combination of relative indications. These studies often assessed the association of the most accurate criteria predicting advanced lesions as the combination of mural nodules and jaundice [20]. In our series, the risk of advanced lesions in patients with 1 or ≥2 relative indications and no absolute indications was not significantly different (37.1% vs. 44%, p = 0.593); however a risk difference of 18.3% for invasive carcinoma was observed between both groups (5.7% vs. 24%, p = 0.048). All patients with invasive pathology had relative indications for surgery as previously described [21,22].

The present study has a number of limitations. The retrospective design, various operators and ultrasound endoscopes may have influenced the results. Moreover, patients with positive cytology were excluded; however, FNA was not performed in all cases. The strong point of our work is that we specifically analysed the most frequent BD-IPMN population who undergo surgery in daily practice, patients with relative indications.

In conclusion, our analysis shows that invasive carcinoma is considerably more frequent in patients with two or more relative indications and no absolute indications for surgery according to European evidence-based guidelines on BD-IPMN. No association was found between individual relative indications and advanced lesions or invasive cancer. These results support the new guidelines in this subgroup, suggesting that the surgical strategy in patients with one or two relative indications should be decided on an individual basis, considering that there is a significant differential risk of invasive carcinoma between groups. In this sense, the comorbidity characteristics, individual surgical and anaesthetic risk and the type of surgery should also be considered in the decision-making process.

Conflict of interest
None declared.

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