Original article

Importance of main pancreatic duct dilatation in IPMN undergoing surveillance

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Background: The association between risk of pancreatic cancer and a dilated main pancreatic duct (MPD) in intraductal papillary mucinous neoplasm (IPMN) is debated. The aim of this study was to assess the role of MPD size in predicting pancreatic cancer in resected IPMNs and those kept under surveillance.

Methods: All patients with IPMN referred to the Pancreas Institute, University of Verona Hospital Trust, from 2006 to 2016 were included. The primary endpoint was the occurrence of malignancy detected at surgery or during follow-up.

Results: The final cohort consisted of 1688 patients with a median follow-up of 60 months. Main pancreatic duct dilatation was associated with other features of malignancy in both the resected and surveillance groups. In patients who underwent resection, only a MPD of at least 10 mm was an independent predictor of malignancy. In patients kept under surveillance, MPD dilatation was not associated with malignancy. Fifteen of 71 patients (21 per cent) with malignancy in the resection cohort had a dilated MPD alone, whereas only one of 30 (3 per cent) under surveillance with MPD dilatation alone developed malignancy. Patients with a dilated MPD and other worrisome features had an increased 5-year cumulative incidence of malignancy compared with those with a non-dilated duct (11 *versus* 1·2 per cent; $P < 0{\cdot}001$); however, the risk of malignancy was not significantly increased in patients with a dilated MPD alone (4 *versus* 1·2 per cent; $P = 0{\cdot}448$).

Conclusion: In patients under surveillance, a dilated MPD alone was not associated with an increased incidence of malignancy in IPMN.

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Introduction

Current clinical management of presumed intraductal papillary mucinous neoplasm (IPMN) of the pancreas mostly relies on the findings of retrospective surgical series, which have been condensed into several guidelines[1–3]. The aim of these guidelines is to characterize the risk of malignant progression of IPMNs, identifying patients who require preventive surgical treatment before developing pancreatic cancer. IPMNs of secondary ducts are associated with a low risk of malignant progression[4]; however, those with involvement of the main pancreatic duct (MPD) have a significantly higher risk[5–10]. The international guidelines[1] recommend surgery for patients with a MPD of 10 mm or larger, whereas for those with a MPD between 5 and 9 mm the indication is to proceed with endoscopic ultrasonography (EUS) to better define the risk of malignancy. Notably, the European guidelines[2] have a lower threshold, recommending resection if the MPD is larger than 6 mm. Regardless of the specific limit, a dilated MPD alone is currently considered a major indicator for surgical resection owing to the high risk of malignancy. Consistent with these recommendations, several surgical series[5–10] have reported relevant rates of cancer in IPMNs when the MPD is between 5 and 9 mm.

Main pancreatic duct dilatation could represent an indirect sign of the presence of neoplastic papillae growing into the duct, indicative of high-grade dysplasia or invasive components[11]. However, other conditions are associated with isolated MPD dilatation, including periampullary masses that cause obstruction, chronic pancreatitis[12],

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pancreas divisum[13] and mucous secretion from IPMNs arising in branch ducts[14]. Therefore, the association between dilatation of the MPD and the presence of malignancy or main-duct IPMN itself raises several concerns. There is a scarcity of data in this regard[5–10] and, in sharp contrast to the results from retrospective surgical series, a recent observational study[4] of non-operated IPMNs reported a 5-year disease-specific survival rate of over 95 per cent among patients with worrisome features, such as a MPD between 5 and 9 mm.

The aim of the present study was to assess the association between degree of MPD dilatation and the risk of developing pancreatic cancer in both resected IPMNs and those kept under surveillance. There was a particular focus on the surveillance cohort, as this group is a clinical challenge for decision-making.

Methods

The present study was consistent with STROBE recommendations[15] and was approved by the institutional review board.

Study cohort

All patients evaluated from 1985 to 2016 in the pancreatic cystic neoplasms outpatient clinic of the Department of Surgery and Oncology, General and Pancreatic Surgery, the Pancreas Institute, University of Verona Hospital Trust, were considered eligible for the present study. The data were extracted retrospectively from a prospectively collected institutional database and included: patient characteristics, clinical and radiological features, pathological diagnosis, and follow-up data obtained from clinics or telephone interviews. Only patients affected by presumed IPMNs according to the definitions provided by the International Association of Pancreatology (IAP)[16] were considered for further evaluation.

Patients with less than 6 months of follow-up were excluded. All patients underwent at least two rounds of abdominal MRI with contrast enhancement and cholangiopancreatography, apart from those sent immediately to surgery after the first scan.

Patients observed or treated before 2006 were excluded to obtain a more homogeneous sample in terms of the quality of MRI, pathological reports and management because the first IAP guidelines were published in that year[17].

Definitions

A presumed branch-duct IPMN was defined by the presence of a pancreatic cyst with a clear association with the MPD through a secondary duct, without MPD dilatation. A presumed mixed-type IPMN was defined by the presence of a pancreatic cyst connected to an enlarged MPD (larger than 5 mm). A presumed main-duct IPMN was defined by the presence of a MPD larger than 5 mm without other focal lesions and without reasons for MPD obstruction or enlargement.

According to the IAP Fukuoka guidelines[16], worrisome features were: a history of acute pancreatitis, cyst size greater than 30 mm, thickened/enhancing cyst walls and MPD size 5–9 mm. High-risk stigmata comprised: obstructive jaundice with a cystic lesion of the head of the pancreas, mural nodules and a MPD at least 10 mm in size.

Epithelial dysplasia was graded as low or high grade according to the Baltimore consensus meeting guidlines[18].

Imaging

Imaging was reviewed by an expert pancreatic radiologist. Only features described at MRI were considered. Pathological evaluation and reporting were undertaken by specialized pancreatic pathologists according to the international consensus guidelines for the diagnosis of pancreatic cystic neoplasms[19]. According to the IAP Fukuoka guidelines[16], an IPMN was considered to be malignant only if an invasive component was present. Patients with a final pathological diagnosis after surgical resection other than IPMN were excluded.

The IAP Sendai criteria[17] were applied from 2006, and subsequently replaced by the IAP Fukuoka guidelines[16] in 2012. Patients presenting with a suspected IPMN and obstructive jaundice, enhancing mural nodules or an associated solid component, as well as those with a MPD of at least 10 mm, were considered eligible for surgery. Some of these patients presenting with high-risk stigmata did not undergo surgery owing to personal choice, advanced age or severe co-morbidities. Patients with other potential predictors of malignancy, which could also have developed after the initial follow-up period, were further assessed by EUS. Those with mural nodules, solid components, or with MPD involvement or malignancy/high-grade dysplasia at cytology, were considered candidates for surgery. Notably, surgery was not attempted in patients with a single worrisome feature according to the IAP Fukuoka guidelines[16], and the patient always agreed after extensive counselling. Patients kept under surveillance were assessed by MRI and measurement of serum levels of CA19-9 and carcinoembryonic antigen 6 months after diagnosis and then yearly if there were no clinical or radiological signs of progression.

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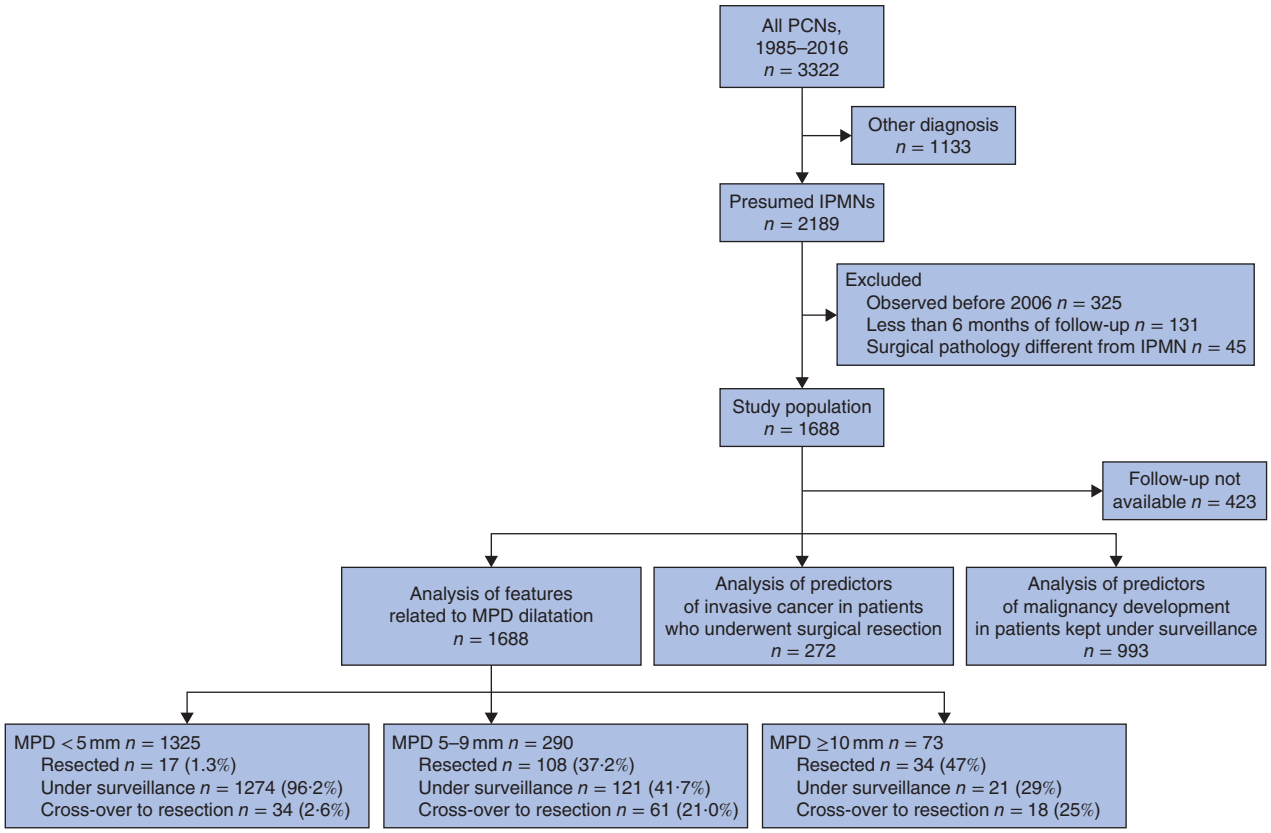

Fig. 1 Study flow chart. PCN, pancreatic cystic neoplasm; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct

Study outcome

The primary aim of the study was to assess the association between degree of MPD dilatation (5–9 mm, 10 mm or greater) and the occurrence of malignancy detected during surgery, or during follow-up for patients undergoing surveillance. In the latter group, the occurrence of malignancy was diagnosed by biopsy if performed, or otherwise on the basis of imaging, clinical features and laboratory results consistent with pancreatic cancer. Patients lost to follow-up were excluded from this analysis. However, the vital status of patients lost to follow-up was checked with the regional registry office to limit a potential source of bias, because these individuals could have been lost owing to disease-related death. The time from diagnosis to the development of malignancy was recorded for patients in the surveillance group. A subanalysis focused on evaluating whether the specific MPD diameter was associated with the primary endpoint. Main pancreatic duct size groups were based on the IAP Fukuoka guidelines[16] as less than 5 mm, 5–9 mm and at least 10 mm.

Table 1 Features of study population

	Resection (*n* = 272)	Surveillance (*n* = 1416)	*P**
Age > 65 years	163 (59·9)	791 (55·9)	0·213
Sex ratio (M : F)	158 : 114	519 : 897	< 0·001
Diabetes	57 of 227 (25·1)	85 of 569 (14·9)	< 0·001
Symptoms	108 of 251 (43·0)	203 of 1212 (16·7)	< 0·001
Acute pancreatitis	76 (27·9)	80 (5·6)	< 0·001
Presumed IPMN type			< 0·001†
Branch duct	66 (24·3)	1308 (92·4)	
Mixed type	134 (49·2)	71 (5·0)	
Main duct	72 (26·5)	37 (2·6)	
Cyst size > 30 mm	131 of 245 (53·5)	157 of 1286 (12·2)	< 0·001
Thickened walls (> 2 mm)	12 (4·4)	36 (2·5)	0·145
Jaundice	26 (9·6)	17 (1·2)	< 0·001
MPD size (mm)			
5–9	169 (62·1)	121 (8·5)	< 0·001
≥ 10	52 (19·1)	21 (1·5)	< 0·001
Mural nodules	61 (22·4)	46 (3·2)	< 0·001

Values in parentheses are percentages. IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct. *Fisher's exact test, except †χ^2 test.

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Table 2 Management stratified by features of malignancy according to Fukuoka guidelines

	Worrisome features				High-risk stigmata		
	Cyst size > 30 mm (*n* = 288)	Acute pancreatitis (*n* = 156)	Thickened walls (> 2 mm) (*n* = 48)	MPD 5–9 mm (*n* = 290)	MPD ≥ 10 mm (*n* = 73)	Mural nodules (*n* = 107)	Jaundice (*n* = 43)
Upfront resection (*n* = 159)	88 (30·6)	37 (23·7)	9 (19)	108 (37·2)	34 (47)	42 (39·3)	18 (42)
Cross-over to resection (*n* = 113)	43 (14·9)	39 (25·0)	3 (6)	61 (21·0)	18 (25)	19 (17·8)	8 (19)
Kept under surveillance (*n* = 1416)	157 (54·5)	80 (51·3)	36 (75)	121 (41·7)	21 (29)	46 (43)	17 (40)

Values in parentheses are percentages. MPD, main pancreatic duct.

Table 3 Features related to main pancreatic duct dilatation

	MPD size (mm)				
	< 5	5–9	≥ 10	*P*†	*P*‡
Resection (*n* = 272)	*n* = 51	*n* = 169	*n* = 52		
Age > 65 years	29 (57)	94 (55·6)	40 (77)	1·000	< 0·001
Sex ratio (M : F)	29 : 22	96 : 73	33 : 19	1·000	0·465
Diabetes	2 of 32 (6)	38 of 149 (25·5)	17 of 46 (37)	0·018	0·145
Symptoms	18 of 43 (42)	66 of 158 (41·8)	24 of 50 (48)	1·000	0·522
Any additional worrisome feature	32 (63)	116 (68·6)	37 (71)	0·656	1·000
Acute pancreatitis	15 (29)	45 (26·6)	16 (31)	0·754	0·500
Cyst size > 30 mm	19 of 48 (40)	84 of 147 (57·1)	28 of 50 (56)	0·042	1·000
Thickened walls (> 2 mm)	0 (0)	7 (4·1)	5 (10)	0·334	0·154
Any additional high-risk stigmata	9 (18)	48 (28·4)	21 (40)	0·109	0·031
Jaundice	5 (10)	14 (8·3)	7 (13)	0·723	0·233
Mural nodules	5 (10)	40 (23·7)	16 (31)	0·031	0·381
Invasive cancer	7 (14)	45 (26·6)	19 (37)	0·050	0·134
Surveillance (*n* = 1416)	*n* = 1274	*n* = 121	*n* = 21		
Age > 65 years	695 (54·6)	78 (64·5)	18 (86)	0·049	0·076
Sex ratio (M : F)	445 : 829	60 : 61	14 : 7	< 0·001	0·144
Diabetes	64 of 463 (13·8)	15 of 89 (17)	6 of 17 (35)	0·590	0·094
Symptoms	172 of 1106 (15·6)	28 of 91 (31)	3 of 15 (20)	< 0·001	0·556
Any additional worrisome feature	213 (16·7)	48 (39·7)	9 (43)	< 0·001	0·889
Acute pancreatitis	66 (5·2)	12 (9·9)	2 (10)	0·032	1·000
Cyst size > 30 mm	126 of 1185 (10·6)	25 of 89 (28)	6 of 12 (50)	0·013	0·178
Thickened walls (> 2 mm)	21 (1·6)	11 (9·1)	4 (19)	< 0·001	0·298
Any additional high-risk stigmata	29 (2·3)	25 (20·7)	7 (33)	< 0·001	0·278
Jaundice	5 (0·4)	10 (8·3)	2 (10)	< 0·001	0·623
Mural nodules	24 (1·9)	17 (14·0)	5 (24)	< 0·001	0·311
Development of malignancy*	8 of 930 (0·9)	3 of 52 (6)	0 of 11 (0)	0·011	1·000

Values in parentheses are percentages. *Assessed in only 993 patients with follow-up available. †Main pancreatic duct (MPD) less than 5 mm *versus* 5–9 mm; ‡MPD 5–9 mm *versus* 10 mm or greater (Fisher's exact test).

Statistical analysis

The χ^2 test was used for analysis of nominal data; Fisher's exact test was used in the case of small expected frequencies. Multivariable analysis was performed using a logistic regression model. The area under the receiver operating characteristic (ROC) curve (AUC) for the multivariable model was also calculated. Kaplan–Meier curves were used to assess the cumulative incidence of malignancy according to MPD dilatation. All tests were two-tailed. $P < 0{\cdot}050$ was considered statistically significant. Statistical analysis was carried out using SPSS® version 20 for Macintosh (IBM, Armonk, New York, USA).

Results

The study population consisted of 1688 patients with a median follow-up of 60 (range 7–281) months (*Fig. 1*). Most individuals (1416, 83·9 per cent) were enrolled in a clinical and radiological surveillance programme, whereas 272 (16·1 per cent) underwent surgery. Among patients who had surgical resection, 159 underwent resection after baseline evaluation, whereas 113 were initially considered for surveillance. In this latter subgroup, cross-over to surgery occurred after a median follow-up of 16 (7–136) months. According to imaging features, 1374 patients (81·4 per cent) were presumed to have branch-duct IPMNs,

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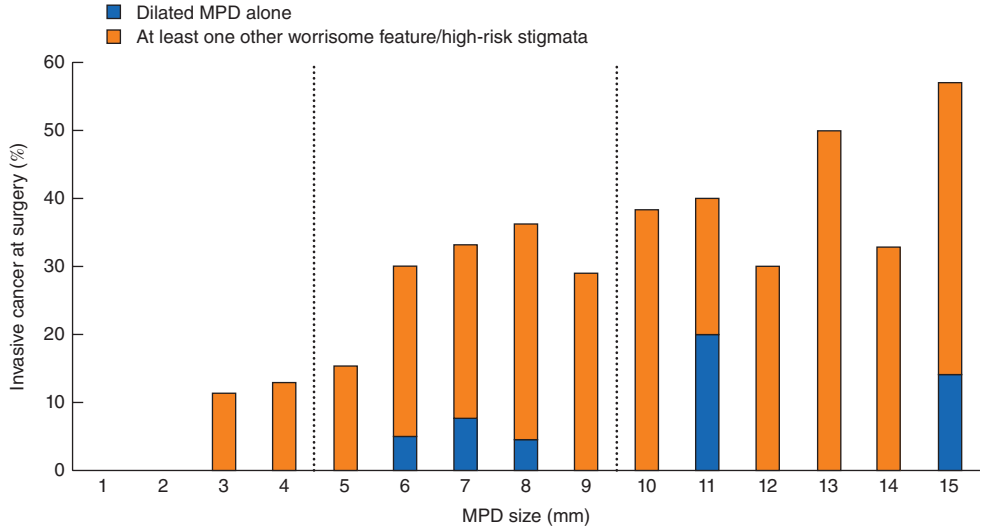

Fig. 2 Rate of invasive cancer after surgical resection stratified by main pancreatic duct (MPD) size in patients with a dilated MPD alone and among those presenting with at least one other worrisome feature/high-risk stigmata

205 (12·1 per cent) mixed-type IPMNs and 109 (6·5 per cent) main-duct IPMNs. Patients who underwent surgery more frequently presented with both high-risk stigmata and worrisome features. These individuals were more likely to present with mural nodules, a dilated MPD, a cyst larger than 30 mm, acute pancreatitis or jaundice (*Table 1*). *Table 2* shows the proportion of patients presenting with either worrisome features or high-risk stigmata that underwent upfront surgery, surveillance or surgery after an initial follow-up.

Resection cohort

In the resection cohort, the median follow-up after surgery was 61 (range 7–265) months. The final pathological analysis revealed non-invasive IPMNs in 201 patients (73·9 per cent) and IPMNs with invasive cancer in 71 (26·1 per cent). Seventy-six patients with non-invasive IPMNs had high-grade dysplasia.

Considering the 113 patients who crossed over to resection, 79 (69·9 per cent) presented with a dilated MPD, but only 25 (22·1 per cent) had MPD dilatation as the sole predictor of malignancy. An additional worrisome feature or high-risk stigmata were present in 62·8 and 23·0 per cent of patients respectively who crossed over to resection. Invasive cancer was found in 23 of the 113 surgical specimens (20·4 per cent); only six patients with invasive carcinoma had isolated MPD dilatation as the unique predictor of malignancy.

Features associated with the presence of MPD dilatation in the overall surgical cohort are shown in *Table 3*. Main pancreatic duct diameter (less than 5 mm, 5–9 mm and at least 10 mm) was variably associated with age and other well known predictors of malignancy for IPMNs, such as diabetes, cyst size larger than 30 mm and the presence of mural nodules. Overall, MPD dilatation was significantly associated with invasive cancer detected at surgery (*Table 3* and *Fig. 2*). In most patients with invasive cancer (49, 69 per cent), a dilated MPD was associated with other features of malignancy according to the IAP Fukuoka guidelines[16]; however, in 15 patients (21 per cent), MPD dilatation was the sole predictor of malignancy ($P = 0{\cdot}021$). Cancer was detected in nine patients who had a MPD measuring 5–9 mm as the only predictor of malignancy, and in six with a duct of at least 10 mm as the sole predictor.

Table 4 shows the results of univariable and multivariable analyses for potential predictors of invasive cancer in surgically resected IPMNs. Only a MPD at least 10 mm in size was an independent predictor of invasive cancer. The AUC of the model was 0·84.

Surveillance cohort

The median follow-up after baseline observation was 58 (range 7–281) months. Data regarding the possible occurrence of malignancy were available for 993 patients (70·1 per cent), of whom 11 (1·1 per cent) developed cancer. Some 423 patients were not available for complete follow-up. Data after the first observation were completely lacking for 43 individuals. The regional registry offices confirmed that 11 patients of these patients had died. The cause of death was described as respiratory

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Table 4 Predictors of invasive cancer in surgically resected presumed IPMNs at first observation

	Univariable analysis			Multivariable analysis	
	No malignancy ($n = 201$)	Malignancy ($n = 71$)	P†	Odds ratio*	P‡
Age > 65 years	116 (57·7)	47 (66)	0·259		
Male sex	117 (58·2)	41 (58)	0·889		
Diabetes	40 of 169 (23·7)	17 of 58 (29)	0·495		
Symptoms	83 of 185 (42·7)	25 of 66 (38)	0·399		
Acute pancreatitis	63 (31·3)	13 (18)	0·042	0·47 (0·17, 1·28)	0·155
Cyst size > 30 mm	94 of 182 (51·6)	37 of 63 (59)	0·498		
Thickened walls (> 2 mm)	7 (3·5)	5 (7)	0·309		
Enhancing walls	3 (1·5)	3 (4)	0·183		
Mural nodules	42 (20·9)	19 (27)	0·323		
MPD 5–9 mm	126 (62·7)	43 (61)	0·777		
MPD ≥ 10 mm	32 (15·9)	20 (28)	0·032	6·34 (1·25, 32·28)	0·028

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct. †Fisher's exact test; ‡logistic regression.

Table 5 Predictors of malignancy development for presumed IPMNs kept under surveillance in 993 patients

	Univariable analysis			Multivariable analysis	
	No malignancy ($n = 982$)	Malignancy ($n = 11$)	P†	Odds ratio*	P‡
Age > 65 years	538 (54·8)	10 (91)	0·028	6·44 (0·74, 55·49)	0·091
Male sex	347 (35·3)	5 (45)	0·533		
Diabetes	26 (2·6)	1 (9)	0·262		
Symptoms	121 (12·3)	4 (36)	0·038	7·63 (1·51, 38·30)	0·012
Acute pancreatitis	55 (5·6)	2 (18)	0·128		
Cyst size > 30 mm	92 (9·4)	3 (27)	0·049	1·72 (0·24, 12·09)	0·599
Thickened walls (> 2 mm)	14 (1·4)	2 (18)	0·012	9·01 (1·82, 21·78)	0·014
Jaundice	4 (0·4)	2 (18)	< 0·001	120·12 (7·70, 872·80)	< 0·001
Mural nodules	25 (2·5)	1 (9)	0·254		
MPD 5–9 mm	43 (4·4)	3 (27)	0·012	1·73 (0·09, 30·60)	0·798
MPD ≥ 10 mm	12 (1·2)	0 (0)	1·000		

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct. †Fisher's exact test; ‡logistic regression.

or cerebrovascular disease by closest relatives of seven patients, and was unknown for the other four. Features associated with progressive MPD dilatation in the surveillance group are shown in *Table 3*. Main pancreatic duct dilatation was progressively associated with other features of malignancy, such as symptoms, cyst size, thickened walls, mural nodules and jaundice. A dilated MPD was also associated with advanced age and male sex. None of the patients with a MPD of 10 mm or greater developed cancer, whereas patients with a MPD measuring 5–9 mm had a significantly increased incidence of pancreatic cancer during follow-up (6 per cent). However, only one of 30 patients under surveillance (3 per cent) with a MPD measuring 5–9 mm as the sole predictor developed malignancy. Considering other risk features, malignancy was found in the presence of jaundice (2 of 6 patients), mural nodules (1 of 26), acute pancreatitis (2 of 57), cyst size larger than 30 mm (3 of 95) and thickened walls (2 of 16).

The results of univariable and multivariable analyses of potential predictors of malignancy for IPMNs kept under surveillance are shown in *Table 5*. Multivariable analysis revealed that the presence of symptoms, thickened walls and jaundice were independent predictors of malignancy. The AUC of the model was 0·87.

Fig. 3 shows Kaplan–Meier curves for the cumulative risk of malignancy in patients under surveillance. Patients with a dilated MPD associated with other features of malignancy had a significantly higher 5-year cumulative risk of malignancy than those without a dilated MPD (11 *versus* 1·2 per cent; $P < 0·001$). However, there was no significant difference in the 5-year cumulative risk of malignancy between patients with a dilated MPD alone and those with a non-dilated MPD (4 *versus* 1·2 per cent; $P = 0·448$). The 5-year cumulative risk of malignancy in patients with jaundice, mural nodules, thickened walls, acute pancreatitis and cysts larger than 30 mm were 100, 14, 11, 5 and 5 per cent respectively.

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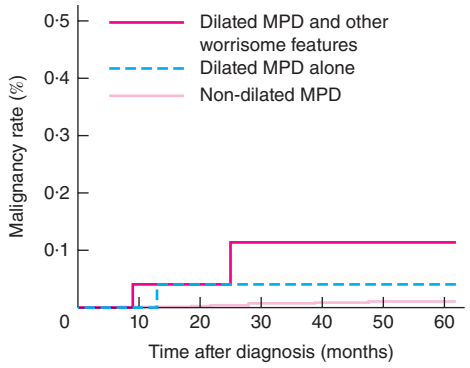

No. at risk							
Dilated MPD and other worrisome features	26	22	16	10	6	5	5
Dilated MPD alone	29	25	22	18	17	16	13
Non-dilated MPD	935	880	714	582	471	274	289

Fig. 3 Kaplan–Meier curves showing cumulative risk of malignancy in patients kept under surveillance with a dilated main pancreatic duct (MPD) and other worrisome features, a dilated MPD alone, or a non-dilated MPD. $P = 0{\cdot}448$ (non-dilated MPD *versus* dilated MPD alone), $P < 0{\cdot}001$ (non-dilated MPD *versus* dilated MPD associated with other worrisome features) (log rank test)

Discussion

In this study, MPD dilatation of at least 10 mm in IPMN of the pancreas was an independent predictor of malignancy in patients selected for surgical resection. However, in patients with IPMN who remained under surveillance, a MPD measuring either 5–9 mm or at least 10 mm was not. Main pancreatic duct dilatation is often associated with other known predictors of malignancy. Considering patients kept under surveillance, the development of malignancy in the presence of MPD dilatation alone was very rare. Therefore, a dilated MPD in the absence of other clinical and radiological predictors of malignancy, namely worrisome features or high-risk stigmata, should not be a direct indication for surgery in patients with presumed IPMNs. Rather, it should demand further assessment and short-interval surveillance to allow better risk stratification.

Current guidelines provide valuable information in terms of the prevention of pancreatic cancer owing to their high sensitivity. A low specificity, however, has led to high rates of unnecessary surgical resection worldwide[20–28]. The risk of malignancy associated with MPD dilatation is a controversial issue. The IAP guidelines[1,16,17] consider only the presence of a MPD at least 10 mm in size as a direct indication for surgery, whereas the European guidelines[2] recommend surgical resection for a MPD of 6 mm or larger.

The present study investigated whether a dilated MPD should be considered as a major indication for surgery by evaluating both surgically resected and monitored presumed IPMNs. A MPD of at least 10 mm was associated with an increased rate of malignancy only in patients who underwent surgical resection. However, regarding MPD dilatation alone, one in every five such patients showed malignancy in the resected cohort, but only one patient of 30 under surveillance. Of note, in the surveillance group, a dilated MPD was associated with a significantly increased incidence of cancer only when associated with other features of malignancy and not when presenting alone.

Several studies[5–10] have already evaluated the association between MPD dilatation and presence of invasive carcinoma or high-grade dysplasia, reporting a rate of malignancy ranging from 30 to 91 per cent in patients with a MPD larger than 5 mm. In particular, the Heidelberg group[6] recently reported a rate of invasive carcinoma or high-grade dysplasia in resected and pathologically confirmed IPMNs of 59·2 per cent in patients with a MPD between 5 and 9 mm, and 73·8 per cent among those with a duct of 10 mm or larger. Notably, MPD dilatation might be the foremost predictor of malignancy. Comparing patients with a MPD between 5 and 9 mm *versus* those with a duct of at least 10 mm, a significant increase was reported only in the rate of high-grade dysplasia or invasive cancer in the latter group, without a concomitant increase in other direct clinical and radiological signs of malignancy[6]. This finding was not consistent with the present results, where duct dilatation was progressively associated with the appearance of other worrisome features and high-risk stigmata in both resection and surveillance groups, and this association correlated with malignancy. However, in the present surveillance cohort, a dilated MPD alone was not associated with an increased risk of malignancy. Other studies[5,7–10] have focused on identifying a more accurate MPD cut-off for detecting malignancy. The most recent study set a 7·2-mm threshold as optimal for detection of malignancy, which slightly moved the tip of the scale[29]. Notably, the results of these studies[5,7–10] should be interpreted with caution because they considered only patients who had surgical resection, with a clear case selection bias. Therefore, these studies might have failed to express the actual risk of malignancy for all-comers with a dilated duct.

Conditions other than IPMNs can cause MPD dilatation; other frequent aetiologies, such as periampullary masses, chronic pancreatitis, pancreas divisum and other anatomical conditions[12–14], should be considered when there are no other concomitant signs of malignancy. Not all patients

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with a dilated MPD require surgical intervention as a dilated duct does not necessarily hide a malignant tumour. The diagnostic error rate ranges from 22 to 39 per cent of cases[30,31], even at high-volume institutions, and is consistent with the present results and those of previously published studies. However, because of the frequent association with other high-risk stigmata and worrisome features, the authors acknowledge that MPD dilatation should not be neglected. Of note, a MPD between 5 and 9 mm was associated with other worrisome features in 39·7 per cent of patients in the present surveillance cohort. On the other hand, when the MPD was 10 mm or more in size, another high-risk stigma was detected in one in every three patients. Therefore, a dilated MPD demands careful evaluation of the entire gland and surrounding abdominal structures.

As reported in other surgical series[5–10], analysis of predictors of malignancy confirmed that a dilated MPD was an independent predictor of pancreatic cancer for patients in the resection group. In particular, above a threshold of 6 mm in patients who have surgical resection, the rate of malignancy is constantly above 30 per cent[5,7–10]. This was not confirmed in the present surveillance group because jaundice and symptoms were the most important predictors as they are direct signs of a solid mass. However, the presence of MPD dilatation along with other features of malignancy was associated with an increased 5-year risk of cancer development in patients under surveillance. These findings reinforce the concept that, once a dilated MPD has been detected, further assessment by EUS should be performed, and surgical resection considered if there are specific features that point to tumour involvement of the MPD. However, this approach should be adopted with caution for the following reasons. First, diagnosis of IPMN involving the MPD should be well supported, and potential differential diagnoses ruled out. Second, patients with a presumed IPMN and a dilated MPD may have a lower likelihood of harbouring an invasive carcinoma than reported in surgical series[5–10] if the MPD dilatation is not associated with other features predictive of malignancy. Consistent with the current guidelines and rather than proceeding with immediate surgical resection, close follow-up with MRI and magnetic resonance cholangiopancreatography may be a reasonable choice considering that the progression to malignancy occurs within the first 24 months in most patients who develop cancer. However, the cost-effectiveness of any of these approaches needs to be further assessed and validated.

The present study has several limitations. A definitive diagnosis is established pathologically in patients who undergo resection, whereas the clinical and radiological picture in patients kept under surveillance could lead to a certain rate of misdiagnosis, both of presumed IPMN and presumed IPMN with associated malignancy[30,31]. The authors are aware of these biases, which may have affected the results for the surveillance cohort. However, MRI at a high-volume centre is probably the most cost-effective and non-operator-dependent way of achieving high diagnostic accuracy for presumed IPMNs. This is probably the only way to obtain a true population-based picture because most patients with IPMN do not undergo surgical resection.

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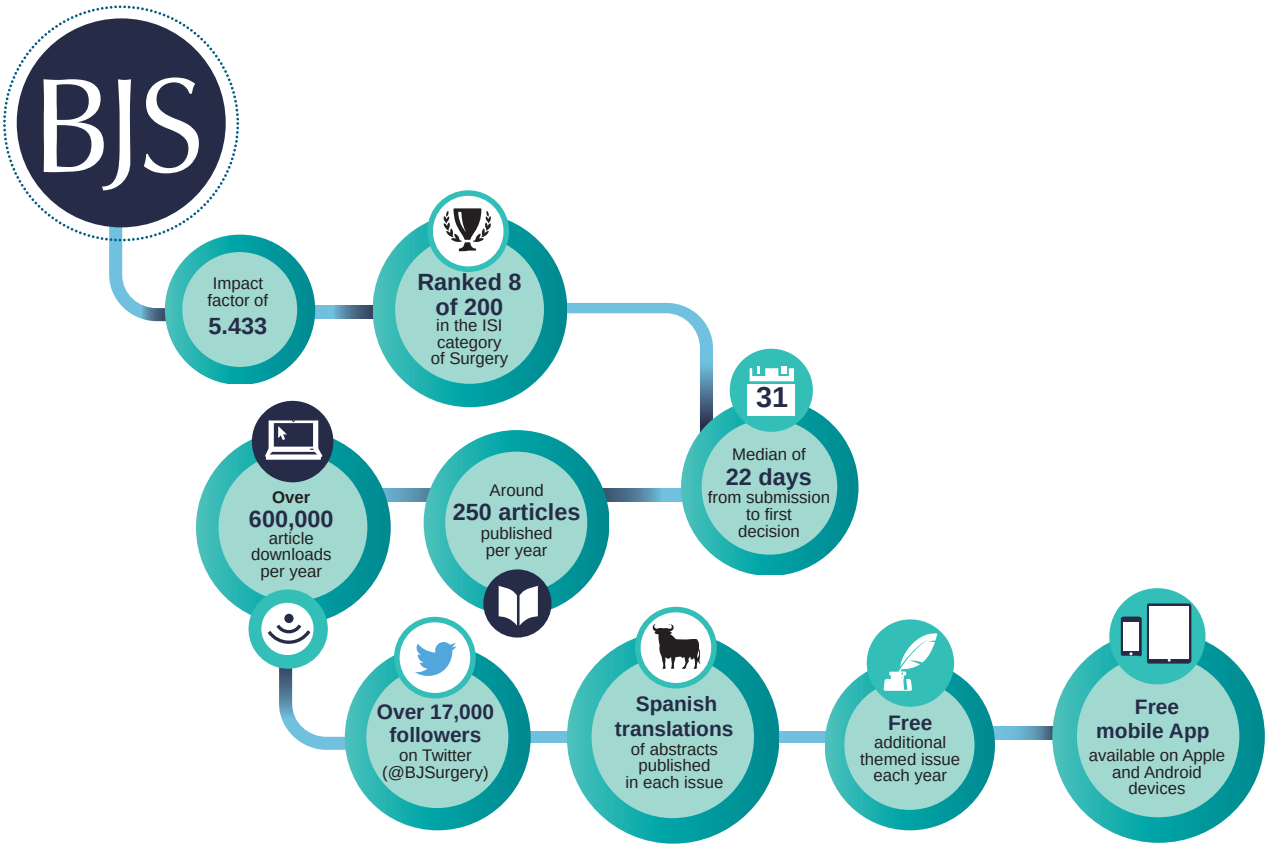

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