

Management and outcomes of intraductal papillary mucinous neoplasms

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Background: This study evaluated the outcome and survival of patients with radiologically suspected intraductal papillary mucinous neoplasms (IPMNs).

Methods: IPMN management was reviewed according to Fukuoka risk factors and IPMN localization, differentiating main-duct (MD), mixed-type (MT) and branch-duct (BD) IPMNs. Perioperative results were compared with those of patients undergoing resection of pancreatic ductal adenocarcinoma (PDAC) over the same interval (2010–2014). Overall (OS) and disease-specific (DSS) survival rates were calculated and subgroups compared.

Results: Of 142 patients with IPMNs, 26 had MD-IPMN, eight had MT-IPMN and 108 had BD-IPMN. Some 74 per cent of patients with MD- and MT-IPMN were managed by primary resection, whereas this was used in only 27.8 per cent of those with BD-IPMN. The risk of secondary resection and malignant transformation for BD-IPMNs smaller than 20 mm was 8 and 2 per cent respectively during follow-up. Pancreatic head resection of IPMNs was associated with an increased risk of postoperative pancreatic fistula grade B/C compared with resection of PDAC (12 of 33 (36 per cent) *versus* 41 of 221 (18.6 per cent) respectively; $P = 0.010$), and greater morbidity and mortality (Clavien–Dindo grade III: 15 of 33 (45 per cent) *versus* 56 of 221 (25.3 per cent) respectively; grade IV: 1 (3 per cent) *versus* 7 (3.2 per cent); grade V: 2 (6 per cent) *versus* 2 (0.9 per cent); $P = 0.008$). Five-year OS and DSS rates in patients with MD-IPMN were worse than those for MT- and BD-IPMN (OS: 44, 86 and 97.4 per cent respectively, $P < 0.001$; DSS: 60, 100 and 98.6 per cent; $P < 0.001$). Patients with invasive IPMN had worse OS and DSS rates than those with non-invasive dysplasia (OS: IPMN–carcinoma (10 patients) 33 per cent, high-grade dysplasia 100 per cent, intermediate-grade dysplasia 63 per cent, low grade-dysplasia 100 per cent, $P < 0.001$; DSS: IPMN–carcinoma 43 per cent, all grades of dysplasia 100 per cent, $P < 0.001$). Patients with high-risk stigmata had poorer survival than those without risk factors (OS: high-risk stigmata (35 patients) 55 per cent, worrisome features (31) 95 per cent, no risk factors (76) 100 per cent, $P < 0.001$; DSS: 71, 100 and 100 per cent respectively, $P < 0.001$).

Conclusion: The risk of malignant transformation was very low for BD-IPMNs, but the development of high-risk stigmata was associated with disease-specific mortality. Patients with IPMN had greater morbidity after resection than those having resection of PDAC.

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Introduction

The management and risk of progression of intraductal papillary mucinous neoplasms (IPMNs) has been stratified by the Fukuoka guidelines^{1,2} into: IPMNs presenting with no risk factors, IPMNs with worrisome features and high-risk stigmata (Table 1). IPMNs are also

classified on the basis of location, distinguishing main pancreatic duct (MD-IPMN), branch duct-type (BD-IPMN) and mixed-type (MT-IPMN) neoplasms (Fig. 1).

Current guidelines recommend resection of lesions with high-risk stigmata, but in the context of BD-IPMN, in particular, this is still a matter of debate^{3–6}, balancing the

Table 1 High-risk stigmata and worrisome features according to the revised Fukuoka consensus guidelines²

High-risk stigmata	Worrisome features
Obstructive jaundice in a patient with cystic lesion of the head of the pancreas	Pancreatitis
Enhancing mural nodule ≥ 5 mm	Cyst ≥ 30 mm
Main pancreatic duct ≥ 10 mm	Thickened/enhancing cystic walls
	Enhancing mural nodule < 5 mm
	Main pancreatic duct 5–9 mm
	Abrupt change in calibre of pancreatic duct with distal pancreatic atrophy
	Lymphadenopathy
	Increased serum level of carbohydrate antigen 19-9
	Cyst growth rate ≥ 5 mm/2 years

risk of progression to cancer with morbidity and mortality following pancreatic resection^{7,8}, in addition to risks of long-term exocrine and endocrine insufficiency⁹.

The aim of this study was to evaluate the management, postoperative outcomes and survival of patients with radiologically suspected IPMNs.

Methods

Patients presenting with a cystic lesion or radiologically suspected IPMN at the Department of General and Visceral Surgery of the Medical Centre, University of Freiburg, between January 2010 and December 2014 were reviewed. Approximately 120 pancreatic resections are performed at this centre annually. The study was approved by the local ethics committee of the University of Freiburg (EK 142/17).

Cystic lesions were examined by MRI, or by CT if MRI was contraindicated. In selected patients, endoscopic ultrasonography and analysis of cyst fluid was performed. Follow-up was performed according to Fukuoka consensus guidelines, usually every 3–6 months, with extended intervals for lesions that were stable during observation.

Cystic pancreatic tumours were categorized as IPMNs, serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs) and pancreatic pseudocysts.

Radiologically suspected IPMNs were classified as MD-, MT- and BD-IPMNs. Surgical resection was considered according to the Sendai or Fukuoka guidelines^{1,2}, and patients considered appropriate for surveillance were rescheduled for regular MRI or CT. The indication for surgical resection was reassessed throughout surveillance. Resection was also performed upon patient request for cystic tumours greater than 10 mm.

Morbidity and mortality following IPMN-related resections were compared with rates in patients having

resection of pancreatic ductal adenocarcinoma (PDAC) in the same time period. Complications were classified according to International Study Group of Pancreatic Surgery (ISGPS) definitions of postoperative pancreatic fistula (POPF)¹⁰, delayed gastric emptying (DGE)¹¹ and postpancreatectomy haemorrhage (PPH)¹², and the Clavien–Dindo general classification of postoperative complications¹³.

Statistical analysis

Variables are expressed as median (range) values or as numbers with percentages. Categorical variables were compared using Pearson's χ^2 test. The Mann–Whitney *U* test was used for descriptive analysis of non-parametric variables.

Survival data were obtained from the Comprehensive Cancer Center registry of the University of Freiburg Medical Centre. Disease-specific mortality was defined as death related to pancreatic malignancy. Actuarial survival was calculated by univariable analysis using the Kaplan–Meier method, with log rank testing for comparison of subgroups.

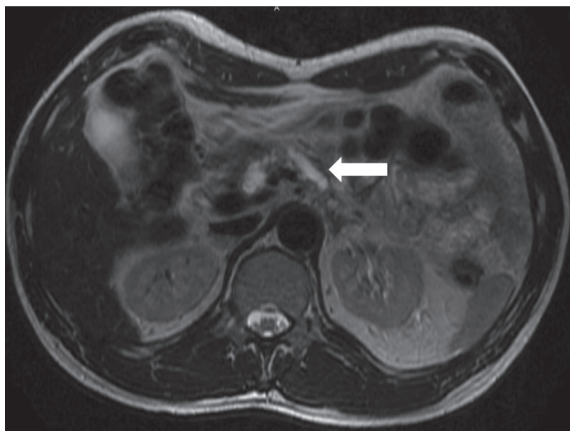
Statistical analysis was performed using SPSS® version 24.0.0.1 (IBM, Armonk, New York, USA). $P < 0.050$ was considered statistically significant.

Results

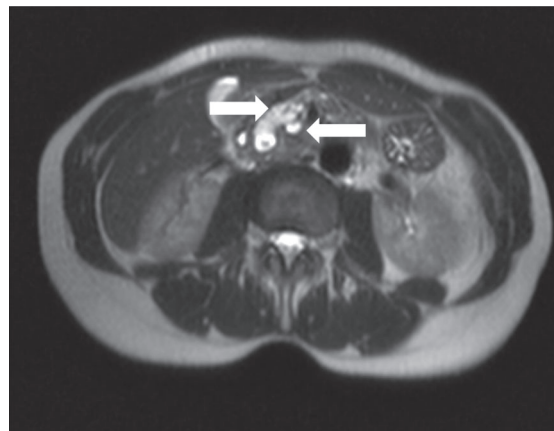
Data from 269 patients with cystic pancreatic lesions were reviewed. Radiological findings were consistent with a possible IPMN in 142 patients (52.8 per cent); a MD-IPMN was suspected in 26 patients, MT-IPMN in eight and BD-IPMN in 108. Seventy-six of these 142 patients (53.5 per cent) were men, and the median age was 69 (range 36–88) years. Postoperative morbidity and mortality of IPMN-related pancreatic resections in 53 patients

Fig. 1 MRI scans illustrating the morphological aspects of intraductal papillary mucinous neoplasm subtypes. **a** Main-duct intraductal papillary mucinous neoplasm (MD-IPMN) showing dilated main pancreatic duct (arrow). **b** Mixed-type (MT) IPMN with dilated main duct (left arrow) and branch duct (right arrow). **c** Branch-duct (BD) IPMN with undilated main pancreatic duct (right arrow) and dilated branch duct (left arrow), with no involvement of main pancreatic duct

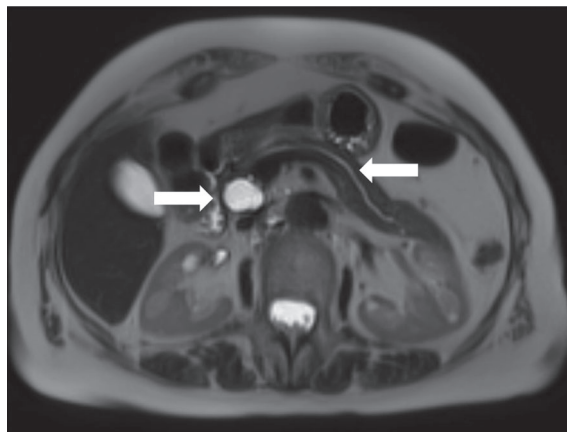
a MD-IPMN with dilated main duct



b MT-IPMN with dilated main and branch ducts



c BD-IPMN with undilated main duct and dilated branch duct



were compared to 260 pancreatic resections undertaken for PDAC in the same period (January 2010 to December 2014).

Main-duct intraductal papillary mucinous neoplasms

Surgery was recommended for 23 (88 per cent) of 26 patients with MD-IPMN; three patients were deemed ineligible owing to age and co-morbidity (Table 2).

Surgical procedures consisted of pylorus-preserving partial duodenopancreatectomy (PPPD) (13 patients),

classic Whipple procedure (1), distal pancreatectomy (2) and total pancreatectomy (3). Histopathological examination showed five IPMNs with low-grade dysplasia (25 per cent), four with intermediate-grade dysplasia (20 per cent) and eight with IPMN-associated carcinoma (40 per cent), and one each of PDAC, chronic pancreatitis and carcinosarcoma.

Four of these patients did not consent to surgery at first and decided to undergo surveillance. After an initial observation of 27 months, one of them underwent a PPPD and the histological findings were consistent with IPMN and low-grade dysplasia. Of the six patients

Table 2 Summary of the clinical course of different intraductal papillary mucinous neoplasm subtypes and postoperative histopathological examination

		MD-IPMN (n = 26)	MT-IPMN (n = 8)	BD-IPMN		
				< 20 mm (n = 69)	20–29 mm (n = 19)	≥ 30 mm (n = 20)
Age*		65 (52–83)	68 (53–76)	69 (36–82)	70 (51–88)	71 (47–77)
Men		16 (62)	6 (75)	34 (49)	9 (47)	11 (55)
Family history of PDAC		1 (4)	0 (0)	3 (4)	0 (0)	2 (10)
Extrapancreatic tumour		2 (8)	2 (25)	8 (12)	5 (26)	2 (10)
Cyst size (mm)*		22 (6–115)	17 (8–70)	11 (3–19)	23 (20–29)	34 (30–60)
Cyst localization	Head	16 (62)	5 (63)	18 (26)	12 (63)	13 (65)
	Body	2 (8)	1 (13)	13 (19)	2 (11)	0 (0)
	Tail	2 (8)	2 (25)	14 (20)	0 (0)	4 (20)
	Multiple locations	6 (23)	0 (0)	24 (35)	5 (26)	3 (15)
Diagnostic procedure	MRI	17 (65)	7 (88)	63 (91)	16 (84)	16 (80)
	CT	14 (54)	2 (25)	23 (33)	7 (37)	9 (45)
	EUS	2 (8)	0 (0)	2 (3)	0 (0)	3 (15)
Fukuoka classification	No risk factors	0 (0)	0 (0)	57 (83)	16 (84)	0 (0)
	Worrisome features	2 (8)	1 (13)	8 (12)	3 (16)	19 (95)
	High-risk stigmata	24 (92)	7 (88)	4 (6)	0 (0)	1 (5)
High-risk stigmata	Jaundice	2 (8)	1 (13)	1 (1)	0 (0)	0 (0)
	Enhanced mural nodule ≥ 5 mm	1 (4)	0 (0)	3 (4)	0 (0)	1 (5)
	Main duct dilatation ≥ 10 mm	23 (88)	6 (75)	0 (0)	0 (0)	0 (0)
Worrisome features	Pancreatitis	9 (35)	3 (38)	6 (9)	2 (11)	3 (15)
	Cyst ≥ 30 mm	9 (35)	0 (0)	0 (0)	0 (0)	20 (100)
	Enhanced mural nodule < 5 mm	1 (4)	0 (0)	2 (3)	1 (5)	2 (10)
	Thickened/enhanced cyst wall	1 (4)	0 (0)	1 (1)	0 (0)	1 (5)
	Main duct dilatation 5–9 mm	3 (12)	2 (25)	0 (0)	0 (0)	0 (0)
	Calibre change of main pancreatic duct	3 (12)	2 (25)	0 (0)	0 (0)	0 (0)
	Lymphadenopathy	5 (19)	3 (38)	1 (1)	0 (0)	0 (0)
Raised serum CA19-9	4 of 16 (25)	3 (38)	2 of 57 (4)	0 of 16 (0)	3 of 13 (23)	
Growth ≥ 5 mm/2 years			1 of 2 (50)	5 of 51 (10)	1 of 12 (8)	2 of 7 (29)
Suspicious cytology		0 of 2 (0)		1 of 2 (50)		2 of 3 (67)
Symptoms	No symptoms	4 (15)	3 (38)	38 (55)	11 (58)	11 (55)
	Epigastric pain	14 (54)	4 (50)	25 (36)	6 (32)	9 (45)
	Jaundice	2 (8)	1 (13)	0 (0)	0 (0)	0 (0)
	Weight loss	2 (8)	0 (0)	6 (9)	2 (11)	0 (0)
	Other	4 (15)	0 (0)	0 (0)	0 (0)	0 (0)
Pre-existing conditions	Insulin-dependent diabetes mellitus	4 (15)	2 (25)	3 (4)	5 (26)	4 (20)
	Cardiovascular	10 (38)	3 (38)	24 (35)	11 (58)	9 (45)
	Pulmonary	3 (12)	0 (0)	1 (1)	0 (0)	2 (10)
	Renal	2 (8)	1 (13)	7 (10)	3 (16)	2 (10)
	Gastrointestinal	15 (58)	3 (38)	38 (55)	8 (42)	12 (60)
	Neurological	3 (12)	0 (0)	8 (12)	3 (16)	2 (10)
	Endocrine	6 (23)	0 (0)	7 (10)	0 (0)	0 (0)
	Other	6 (23)	0 (0)	21 (30)	4 (21)	4 (20)
Primary resection		19 (73)	6 (75)	10 (14)	7 (37)	13 (65)
Not eligible for surgery		3				2

		MD-IPMN (n = 26)	MT-IPMN (n = 8)	BD-IPMN		
				< 20 mm (n = 69)	20–29 mm (n = 19)	≥ 30 mm (n = 20)
Denied consent for primary resection		4		1	1	1
Surveillance		7 (27)	2 (25)	59 (86)	12 (63)	7 (35)
Secondary resection during follow-up		1	1	4	1	2
Denied consent for secondary resection		3	1	1	1	2
Operation		20 of 26 (77)	7 of 8 (88)	14 of 69 (20)	8 of 19 (42)	15 of 20 (75)
PPPD		14 of 20 (70)	5 of 7 (71)	5 of 14 (36)	6 of 8 (75)	11 of 15 (73)
Whipple procedure		1 of 20 (5)				
Distal pancreatectomy		2 of 20 (10)	2 of 7 (29)	6 of 14 (43)	2 of 8 (25)	4 of 15 (27)
Pancreatectomy		3 of 20 (15)				
Central pancreatectomy				2 of 14 (14)		
Enucleation				1 of 14 (7)		
Histological examination						
IPMN with low-grade dysplasia		5 of 20 (25)	3 of 7 (43)	5 of 14 (36)	6 of 8 (75)	4 of 15 (27)
IPMN with intermediate-grade dysplasia		4 of 20 (20)	2 of 7 (29)	2 of 14 (14)		4 of 15 (27)
IPMN with high-grade dysplasia			1 of 7 (14)	2 of 14 (14)		1 of 15 (7)
IPMN-carcinoma		8 of 20 (40)	1 of 7 (14)			1 of 15 (7)
PDAC		1 of 20 (5)				1 (7%)
SCN/MCN				2 of 14 (14)	1 of 8 (13)	3 of 15 (20)
MCN-associated adenocarcinoma				1 of 14 (7)		
NET				1 of 14 (7)		
Chronic pancreatitis		1 of 20 (5)			1 of 8 (13)	
Pancreatic pseudocyst						1 of 15 (7)
Other		1 of 20 (5)		1 of 14 (7)		
Malignant transformation during observation		1 of 7 (14)		1 of 59 (2)	0 of 12 (0)	2 of 7 (29)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). MD, main duct; IPMN, intraductal papillary mucinous neoplasm; MT, mixed type; BD, branch duct; PDAC, pancreatic ductal adenocarcinoma; EUS, endoscopic ultrasonography; CA, carbohydrate antigen; PPPD, pylorus-preserving partial duodenopancreatectomy; SCN, serous cystic neoplasm; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumour.

with suspected MD-IPMN who did not have surgery, one died from metastatic pancreatic cancer after 2 years, one died from liver cirrhosis and four have been lost to follow-up.

Mixed-type intraductal papillary mucinous neoplasms

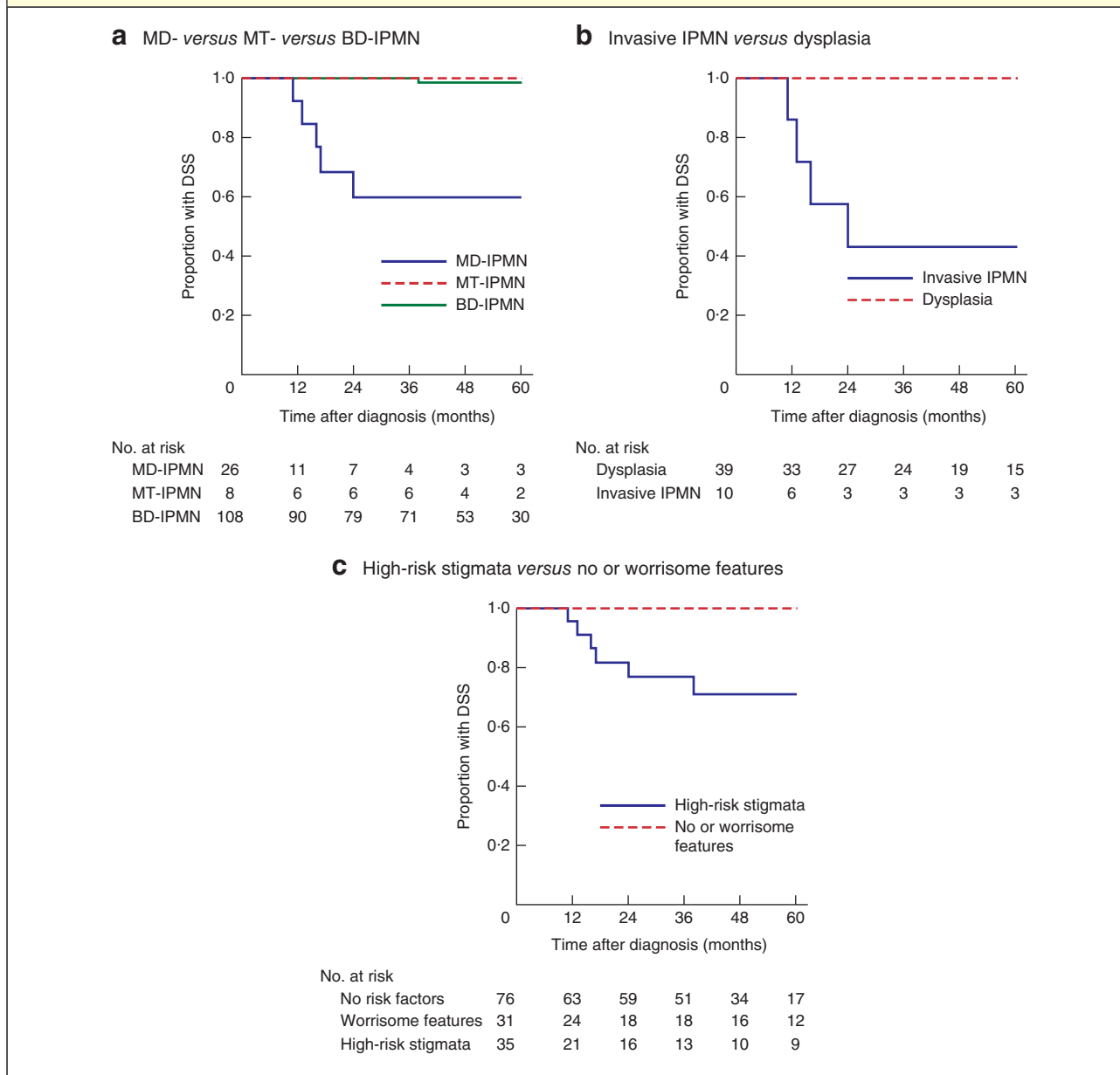
Of eight patients presenting with a radiological diagnosis of MT-IPMN, seven underwent resection. Histological examination showed three IPMNs with low-grade dysplasia (43 per cent), two with intermediate-grade dysplasia (29 per cent), one high-grade dysplasia (14 per cent) and one IPMN-associated carcinoma (14 per cent) (Table 2).

Two patients opted not to have a resection initially. One of these patients had a resection after 24 months for low-grade dysplasia, and the other remains under observation after 36 months with no signs of malignant transformation.

Branch-duct intraductal papillary mucinous neoplasms

The 108 BD-IPMNs were classified as lesions with no risk factors, those with worrisome features or those with high-risk stigmata. The presence of risk factors together with age and co-morbidity were all taken into account to determine further management.

Fig. 2 Kaplan–Meier analysis of disease-specific survival of patients with intraductal papillary mucinous neoplasms. Comparison of disease-specific survival (DSS) in: **a** patients with main-duct (MD) intraductal papillary mucinous neoplasms (IPMNs) and those with mixed-type (MT) and branch-duct (BD) IPMNs; **b** patients with invasive IPMN-carcinoma versus those with low-, intermediate- and high-grade dysplasia; and **c** patients with high-risk stigmata versus those with worrisome features or no risk factors. **a–c** $P < 0.001$ (log rank test)



Sixty-nine (63.9 per cent) of the cystic lesions were less than 20 mm in size, 19 (17.6 per cent) were 20–29 mm, and 20 (18.5 per cent) were equal to or greater than 30 mm.

Of these 108 patients, 73 (67.6 per cent) had no risk factors for malignant transformation, 30 (27.8 per cent) had worrisome features and five (4.6 per cent) had high-risk

stigmata. Primary resection was performed in 30 patients (27.8 per cent) with BD-IPMN (no risk factors, 6; worrisome features, 21; high-risk stigmata, 3), and high-grade dysplasia was detected in three patients (10 per cent). No IPMN-carcinoma or PDAC was detected in the primary histological examination of BD-IPMN lesions (Table 2).

Some 78 patients with BD-IPMN underwent observation, mostly by MRI, with a median follow-up of 47 (range 3–144) months. Of these patients, 67 (86 per cent) had no risk factors, nine (12 per cent) had worrisome features and two (3 per cent) had high-risk stigmata.

During the study, 11 (14 per cent) of the 78 patients with BD-IPMN who were initially considered for surveillance were referred for surgery, six owing to increasing size of the cysts, one for a newly developed neuroendocrine tumour of the pancreatic tail and four due to persisting worrisome features or high-risk stigmata, already observed during their initial assessments. Of these patients, four had lesions smaller than 20 mm and one was found to have a pT1 pN0 cM0 MCN-associated carcinoma (disease-free at 36 months); the other resected patients had IPMN with low-grade dysplasia or SCN on postoperative histopathological assessment. The malignant MCN was diagnosed owing to a rapid increase in cyst size, from 15 mm initially to 21 mm at 6 months.

In the subgroup of seven patients with BD-IPMN of 30 mm or above (2 considered ineligible for surgery for medical reasons) who did not undergo primary resection despite worrisome features (6 patients) or high-risk stigmata (1), surgery was recommended in four patients. Two of these patients did not consent to surgery and were lost to follow-up, and two underwent resection. An IPMN-associated carcinoma was found in one patient and PDAC diagnosed in the surgical specimen of the other.

The risk of malignant transformation during observation increased from 2 per cent in BD-IPMNs smaller than 20 mm to 29 per cent in those of 30 mm or more ($P = 0.005$) (Table 2).

Perioperative morbidity and mortality following resection

The outcomes of 53 histologically documented IPMNs were compared with those of 260 pancreatic resections for PDAC performed over the same interval.

The rate of POPF grade B and C after pancreatic head resection for IPMN was higher than that seen after pancreatic head resection for PDAC: 12 of 33 (36 per cent) versus 41 of 221 (18.6 per cent) respectively ($P = 0.010$). Patients with resected IPMN had significantly more DGE grade B/C than those with resected PDAC (7 (21 per cent) versus 39 (17.6 per cent) respectively; $P = 0.027$) and more severe complications (Clavien–Dindo grade III: 15 (45 per cent) versus 56 (25.3 per cent); grade IV: 1 (3 per cent) versus 7 (3.2 per cent); grade V: 2 (6 per cent) versus 2 (0.9 per cent); $P = 0.008$) (Table 3).

	IPMN (n = 33)	PDAC (n = 221)	P†
Age (years)*	68 (48–82)	70 (31–86)	0.375‡
Men	18 (55)	111 (50.2)	0.643
BMI (kg/m ²)*	25.5 (16.9–37.4)	24.6 (17.6–38.8)	0.498‡
ASA fitness grade			0.200
I	3 (9)	12 of 218 (5.5)	
II	24 (73)	126 of 218 (57.8)	
III	6 (18)	78 of 218 (35.8)	
IV	0 (0)	2 of 218 (0.9)	
Co-morbidity			
Coronary heart disease	1 (3)	36 (16.3)	0.043
Hypertension	14 (42)	125 (56.6)	0.121
Pulmonary disease	4 (12)	26 (11.8)	0.960
Kidney disease	3 (9)	28 (12.7)	0.590
Liver disease	2 (6)	21 (9.5)	0.124
Pre-existing diabetes mellitus	12 (36)	55 (24.9)	0.019
Operation			0.072
Whipple procedure	0 (0)	20 (9.0)	
PPPD	33 (100)	201 (91.0)	
Surgical approach			0.087
Open surgery	17 (52)	159 (71.0)	
Laparoscopically assisted	9 (27)	31 (14.0)	
Laparoscopic	1 (3)	2 (0.9)	
Conversion rate	6 of 16 (38)	29 of 62 (46.8)	
Intraoperative blood loss (ml)*	500 (100–2200)	600 (0–5500)	0.049‡
Duration of surgery (min)*	420 (170–631)	425 (230–714)	0.404‡
Reconstruction			0.124
Pancreatogastrostomy	23 (70)	113 (51.1)	
Pancreatojejunostomy	10 (30)	105 (47.5)	
No reconstruction	0 (0)	3 (1.4)	
POPF grade			0.010
B	8 (24)	35 (15.8)	
C	4 (12)	6 (2.7)	
PPH grade B/C	5 (15)	19 (8.6)	0.336
DGE grade B/C	7 (21)	39 (17.6)	0.027
Clavien–Dindo complication grade			0.008
III	15 (45)	56 (25.3)	
IV	1 (3)	7 (3.2)	
V	2 (6)	2 (0.9)	
Reoperation	10 (30)	29 (13.1)	0.011
Intervention	14 (42)	52 (23.5)	0.021

Values in parentheses are percentages unless indicated otherwise; *values are median (range). IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; PPPD, pylorus-preserving partial duodenopancreatectomy; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy haemorrhage; DGE, delayed gastric emptying. † χ^2 test, except ‡Mann–Whitney U test.

Table 4 Perioperative morbidity and mortality after distal pancreatectomy

	IPMN (n = 20)	PDAC (n = 39)	P†
Age (years)*	69 (53–83)	66 (40–88)	0.405‡
Men	11 (55)	21 (54)	0.933
BMI (kg/m ²)*	24.4 (15.9–37.1)	23.8 (17.9–32.9)	0.798‡
ASA fitness grade			0.997
I	2 (10)	4 (10)	
II	12 (60)	23 (59)	
III	6 (30)	12 (31)	
IV	0 (0)	0 (0)	
Co-morbidity			
Coronary heart disease	2 (10)	8 (21)	0.308
Hypertension	14 (70)	21 (54)	0.232
Pulmonary disease	2 (10)	4 (10)	0.975
Kidney disease	4 (20)	5 (13)	0.468
Liver disease	0 (0)	1 (3)	0.470
Pre-existing diabetes mellitus	5 (25)	11 (28)	0.880
Surgical approach			0.005
Open surgery	6 (30)	28 (72)	
Laparoscopically assisted	9 (45)	4 (10)	
Laparoscopic	2 (10)	1 (3)	
Conversion rate	3 of 14 (21)	6 of 11 (55)	
Intraoperative blood loss (ml)	350 (100–1000)	550 (100–5500)	0.181‡
Duration of surgery (min)	261 (151–391)	314 (140–623)	0.074‡
Distal pancreatectomy with splenectomy	9 (45)	36 (92)	<0.001
POPF grade			0.221
B	7 (35)	8 (21)	
C	0 (0)	2 (5)	
PPH grade B/C	1 (5)	3 (8)	0.697
DGE grade B/C	1 (5)	3 (8)	0.277
Clavien–Dindo complication grade			0.737
III	6 (30)	10 (26)	
IV	0 (0)	0 (0)	
V	0 (0)	1 (3)	
Reoperation	1 (5)	8 (21)	0.117
Intervention	5 (25)	7 (18)	0.524

Values in parentheses are percentages unless indicated otherwise; *values are median (range). IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy haemorrhage; DGE, delayed gastric emptying. † χ^2 test, except ‡Mann–Whitney *U* test.

Following distal pancreatectomy for IPMN or PDAC, there were no significant differences in rates of clinically relevant POPF grade B/C (7 of 20 (35 per cent) *versus* 10 of 39 (26 per cent) respectively; $P = 0.221$), PPH grade B/C (1 (5 per cent) *versus* 3 (8 per cent); $P = 0.697$), DGE grade B/C (1 (5 per cent) *versus* 3 (8 per cent); $P = 0.277$), or morbidity and mortality (Clavien–Dindo grade III: 6 (30 per cent) *versus* 10 (26 per cent); grade IV: 0 (0 per cent) for both; grade V: 0 (0 per cent) *versus* 1 (3 per cent); $P = 0.737$) (Table 4).

Table 5 Perioperative morbidity and mortality after laparoscopic or laparoscopically assisted pancreatic head resection including conversion to open surgery

	IPMN (n = 16)	PDAC (n = 62)	P*
POPF grade			0.002
B	4 (25)	12 (19)	
C	2 (13)	0 (0)	
PPH grade B/C	3 (19)	5 (8)	0.400
DGE grade B/C	4 (25)	8 (13)	0.244
Clavien–Dindo complication grade			0.006
III	7 (44)	13 (21)	
IV	0 (0)	1 (2)	
V	2 (13)	0 (0)	
Reoperation	4 (25)	3 (5)	0.012
Intervention	8 (50)	13 (21)	0.020

Values in parentheses are percentages. IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy haemorrhage; DGE, delayed gastric emptying. * χ^2 test.

There was a higher rate of laparoscopic procedures for pancreatic head resections of IPMN than for PDAC. The outcomes of minimally invasive pancreatic head resections in these subgroups were compared; rates of POPF, postoperative interventions, reoperation, overall morbidity and mortality were significantly higher for IPMN (Table 5).

Survival analysis of patients with intraductal papillary mucinous neoplasms

With a median follow-up of 47 months, median survival was reached only for patients with MD-IPMN (17 months).

The 5-year OS rate was 44 per cent for the 26 patients with MD-IPMN, 86 per cent for the eight with MT-IPMN, and 97.4 per cent for the 108 with BD-IPMN ($P < 0.001$). DSS was 60 per cent for MD-IPMN, 100 per cent for MT-IPMN and 98.6 per cent for BD-IPMN ($P < 0.001$) (Fig. 2a).

The 5-year OS rate was also reduced in patients with invasive IPMN-carcinoma compared with that in patients with non-invasive dysplasia, despite oncological pancreatic resection: IPMN-carcinoma, 33 per cent (10 patients); high-grade dysplasia, 100 per cent (4 patients); intermediate-grade dysplasia, 63 per cent (12 patients); low-grade dysplasia, 100 per cent (23 patients); ($P < 0.001$). Five-year DSS rates were also reduced (43 per cent for the 10 patients with IPMN-carcinoma *versus* 100 per cent for the 39 with non-invasive dysplasia; $P < 0.001$) (Fig. 2b).

The 35 patients with high-risk stigmata had poorer 5-year survival than the 31 with worrisome features and the 76 with no risk factors (OS: 55, 95 and 100 per cent respectively; $P < 0.001$). Similar results were obtained for DSS (71, 100 and 100 per cent; $P < 0.001$) (Fig. 2c).

Discussion

Results from this study are in line with the Sendai and Fukuoka recommendations^{1,2} in terms of malignant transformation of IPMNs to pancreatic cancer. MD- and MT-IPMN had high rates of high-grade dysplasia, IPMN-associated carcinoma and PDAC in the histopathological examination of surgical specimens. MD-IPMN, in particular, showed malignant transformation in approximately 45 per cent of resected specimens: IPMN-carcinoma in 40 per cent (8 of 20) and PDAC in 5 per cent (1 of 20), in accordance with previous findings^{14,15}.

The rate of high-grade dysplasia and malignancy in BD-IPMN was only 19 per cent (7 of 37), lower than in other series^{16,17}, although it was 29 per cent (4 of 14) in small BD-IPMNs. Of note, in BD-IPMNs undergoing surveillance, signs of malignant transformation rarely developed after initiating the observation. Patients with BD-IPMNs smaller than 20 mm had an 8 per cent risk of developing factors necessitating a secondary resection, although the median follow-up was only 47 months.

A recent study¹⁸ reported that an initial cyst size of 30 mm or above in BD-IPMN was not associated with development of invasive IPMN or PDAC. In contrast, patients in the present study with primarily large cysts (at least 30 mm) who underwent initial surveillance had an increased risk (29 per cent) of malignant transformation during observation, compared with those with cysts smaller than 20 mm. It has also been reported^{19–24} that patients with initially small cysts of less than 20 mm rarely develop signs of progression to malignancy, whereas those with larger cysts frequently develop additional risk factors.

As the indication for resecting IPMNs depends both on the risk of progression to cancer and on operative risk assessment, the consequences of surgery for IPMNs are important. An increased risk of perioperative morbidity in patients with IPMN has been suggested²⁵, largely reflecting the risk of POPF as a result of the soft pancreatic texture that is often found in IPMN²⁶. The present results appear to confirm this.

Survival analysis indicated that MD-IPMN was associated with disease-specific mortality. Patients with high-risk stigmata also had decreased DSS, whereas worrisome features and the diagnosis of IPMN without risk factors were not associated with mortality independent of the degree

of dysplasia, unless invasive IPMN occurred. This supports previous reports^{27–29} of the low risk of progression of IPMN with worrisome features, but higher mortality, in patients with high-risk stigmata under surveillance.

The present study also confirms the recently reported accurate prediction rate of progression to PDAC by the Fukuoka risk stratification³⁰.

The main limitation of this study is the median follow-up period of 47 (range 3–144) months. The risk of progression of IPMN is not limited to 5 years, and malignant transformation can occur in the long-term follow-up of patients²⁴. Therefore, the need for a longer follow-up and large high-quality registries must be acknowledged.

From this series, application of the Fukuoka criteria² for managing IPMNs would seem to be safe. This includes surveillance for specific categories and resection of IPMNs with high-risk stigmata. The histopathological degree of dysplasia did not correlate with the outcome unless IPMN-associated carcinoma was present.

Pancreatic resection of IPMN is associated with increased perioperative risk. The decision to proceed to resection merits careful consideration in elderly patients and those with major co-morbidities.

Disclosure

The authors declare no conflict of interest.

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