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Long-term (10-year) outcomes and prognostic factors in resected intraductal papillary mucinous neoplasm tumors in Finland: A nationwide retrospective study



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ABSTRACT

Background: The degree of dysplasia is the most important prognostic factor for patients with resected intraductal papillary mucinous neoplasms. Intraductal papillary mucinous neoplasms are predominantly premalignant conditions; in most cases, surveillance is an adequate treatment. If worrisome features are present, surgery should be considered. However, there is limited data on the long-term prognosis of resected intraductal papillary mucinous neoplasms. We aimed to ascertain the nationwide survival of patients with resected intraductal papillary mucinous neoplasms and identify factors associated with survival.

Methods: This is a retrospective nationwide cohort study. All intraductal papillary mucinous neoplasms operated on in Finland between 2000 and 2008 were identified. Patient records were evaluated, and original radiologic data and histologic samples were re-evaluated. Survival data were collected after a 10-year follow-up period.

Results: Out of 2,024 pancreatic resections, 88 were performed for intraductal papillary mucinous neoplasm. The median age of the patients was 65 years. Histologic diagnoses were main duct intraductal papillary mucinous neoplasm 47/88 (53,4%), mixed-type intraductal papillary mucinous neoplasm 27/88 (30.7%), and branchduct intraductal papillary mucinous neoplasm 14/88 (15.9%). Of the tumors, 40/88 (45.5%) were low-grade dysplasia, 9/88 (10.2%) high-grade, and 39/88 (44.3%) were invasive cancer. The median survival was 121 (range 0–252) months. Ten-year survival was 72.5%, 66.7%, and 23.1% in the low-grade dysplasia, high-grade dysplasia, invasive cancer groups, respectively. Ten-year mortality for pancreatic cancer was 5%, 9.1%, and 71.8% in the low-grade dysplasia, high-grade dysplasia, invasive cancer groups, respectively.

Conclusion: Overall, 44.3% of the patients had a malignant tumor, and three-quarters (74.5%) of the main duct intraductal papillary mucinous neoplasms were malignant or high-grade dysplasia at the time of surgery. Ten-year survival was significantly better in patients operated on at the stage of a premalignant tumor (low-grade dysplasia + high-grade dysplasia) than in patients operated on at the stage of a malignant tumor.

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Introduction

The prognosis of patients with resected intraductal papillary mucinous neoplasms (IPMN) mostly depends on the degree of dysplasia.¹ Patients with low malignant potential tumors, such as low-grade (LG) branch duct (BD)—IPMN, have excellent prognoses compared to patients with invasive main duct (MD)— or mixed-

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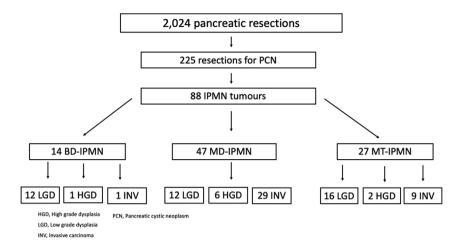


Figure 1. A flowchart of resected intraductal papillary mucinous neoplasm tumors in Finland between 2000 and 2008.

type (MT)–IPMN.² Beyond main pancreatic duct (MPD) involvement and the degree of dysplasia, other known factors influence long-term prognosis. Tumor size, positive lymph nodes, and positive resection margins worsen long-term outcomes.^{1,2} Also, histologic subtypes are factors for patients' long-term prognosis; gastric and intestinal-type IPMNs are usually associated with superior outcomes compared to pancreatobiliary type IPMNs, which represent the more aggressive type, usually associated with high-grade dysplasia (HGD) and invasive adenocarcinoma.^{3–5}

Since IPMN was included in the WHO classification system in 1996, it has been subjected to rigorous scrutiny. Several guidelines on managing IPMN tumors have been issued, such as the European Evidence-Based Guidelines on Pancreatic Cystic Neoplasms, 6 in 2017, the revised international consensus Fukuoka guidelines on the management of IPMN of the pancreas, 7 and the American Gastroenterological Association guidelines. 8 The most widely accepted risk factors for malignancy in these guidelines are main duct dilation, cyst diameter, and elevated levels of serum carbohydrate antigen 19-9. 9–16

The IPMNs are a fairly new entity; only limited long-term data is available, especially in a nationwide setting. ^{17–19} Because IPMN tumors are optimally operated on during the premalignant phase, it is probable that the median survival of these patients is excellent. Thus, data on long-term outcomes, even beyond 5 years, are needed to evaluate the actual benefit for the patients undergoing surgery instead of surveillance. This study aimed to identify nationwide patient characteristics and prognostic factors in a 10-year follow-up period.

Methods

This nationwide retrospective study of resected IPMNs with a 10-year follow-up includes all pancreatic lesions operated on in Finland from 2000 to 2008. The patients were identified by combining data from the national operations register and hospital patient archives. Patients with resected IPMNs formed the final study population (Figure 1).

Patient demographics, comorbidities, symptoms, radiological findings, operation details, and histologic findings were obtained from the patient records. Postoperative complications were registered and graded according to the Clavien-Dindo (CD) classification of surgical complications.²⁰

The preoperative imaging studies were reanalyzed for the study by an experienced pancreatic radiologist. Histologic evaluation with immunohistochemistry was repeated from the original histologic glasses by an experienced pancreatic pathologist. The findings were classified according to the World Health Organization classification of pancreatic tumors using hematoxylin and eosin—stained sections.²¹ The presence of dysplasia was recorded, and grading was based on a 2-step grading system (low and high-grade dysplasia). The variables with incomplete data were displayed with data available; some radiological studies and pathological slides were not available for this study.

The minimum follow-up time for all patients was 10 years (range 10–21 years). Survival data, including time of death, total mortality, and mortality for pancreatic cancer, was gathered from the Finnish Registry Office on November 26, 2020.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 for Windows (IBM SPSS, Inc, Armonk, NY). Descriptive statistics are reported using count, percentage, median, and range unless otherwise specified. The χ^2 analysis was used in univariate analyses. Kaplan-Meier analysis was used to analyze long-term survival.

Ethical aspects

Permission to review patient files and histologic slides was obtained from the National Supervisory Authority for Welfare and Health (Valvira) (permission 10263/06.01.03.01/2012) and from the National Institute for Health and Welfare (permission 1854/5.05.00/2012).

Results

Epidemiology

Between 2000 and 2008, 2,024 pancreatic resections were performed in Finland. Of those 2,024 resections, 225 operations were performed for pancreatic cystic neoplasms. Finally, reevaluated histology was IPMN in 88/225 (34.5%) cases (Figure 1), and these patients were included in the study database. Resections for IPMN were performed at 12 centers; 49/88 (55.6%) of the resections were performed in the 2 largest centers, Tampere and Helsinki University Hospitals. The population of Finland was roughly 5.25 million during the study period from 2000 to 2008, and thus a resection for an IPMN was performed yearly on 0.19/100,000 patients. For reference, between 2013 and 2018, the rate of

Table 1Preoperative findings, radiologic imagining, and operating centers of patients with resected IPMNs (2000–2008) in Finland

Finding	Total, n	% of the patients
Sex F	51/88	58%
Sex M	37/88	42%
Type 1 diabetes	2/74	2.7%
Type 2 diabetes	17/74	22.9%
Smoking	4/44	9.7%
Previous cancer	9/65	13.8%
Symptomatic	64/88	72.7%
Duration of symptoms before operation (mo)	Mean 6.88	1-37
CT	84/88	95.5%
MRI	25/88	28.4%
CT + MRI	21/88	23.8%
EUS	5/88	5.7%
Median age at surgery	65.4	(40-87)
Number of centers	12	
Number of cases on 2 high-volume centers	49	
Number of cases in other 10 centers	39	

IPMN, intraductal papillary mucinous neoplasm; *MPD*, main pancreatic duct.*BD*, branch duct; *HGD*, high-grade dysplasia; *INV*, invasive carcinoma; *IPMN*, intraductal papillary mucinous neoplasm; *LGD*, low-grade dysplasia; *MD*, main duct; *MPD*, main pancreatic duct; *MT*, mixed-type.*CT*, computed tomography; *EUS*, endoscopic ultrasound; *IPMNs*, intraductal papillary mucinous neoplasms; *MRI*, magnetic resonance imaging.

resections for IPMN in the Pirkanmaa Hospital District was 0.76/y/ 100,000 patients (Table I).

Patient characteristics and preoperative findings

In 88 patients, the final histology was IPMN. The median age was 65.4~(40-87) years, and 51/88~(58%) were females. Most patients, 64/88~(72.7%), were symptomatic at the time of surgery. Patients with symptoms had symptoms for a median of 6.9~(1-37) months before surgery (Table I).

The most used (95.5%) preoperative radiologic modality was computed tomography. All preoperative used examinations (and re-examined later in this study) are presented in Table I. The median diameter of the largest cyst was 37.7 mm (7–100); in 68/88 patients (77.3%), there was a single cyst. The median main pancreatic duct (MPD) diameter was 5.1 mm (1–17). Distributions for MPD calibers were MPD <4.9 mm 40/68 (58.8%), MPD 5 to 9.9 mm 18/68 (26.5%), and MPD >10 mm 10/68 (14.7%). Cysts were detected to communicate with MPD in 35/68 (51.5%) cases. The location of the largest cyst was in the pancreatic head in 42/80

(52.4%), in the body in 19/80 (23.8%), and in the tail in 19/80 (23.8%). Parenchymal atrophy in any location of the pancreas was detected in 33/56 (58.9%) of the cases. Thickening of the cyst wall >2 mm was present in 27/54 (50%), septa of the cyst were seen in 39/68 (57.4%), mural nodules of the cyst in 17/64 (26.6%), and calcification of the cyst in 7/73 (6.8%) of the cases. An experienced radiologist suspected malignancy in re-evaluating 12/55 (21.8%) cases (Tables II and III).

Surgery and complications

Pancreaticoduodenectomy was performed on 43/88 (48.9%), distal pancreatic resection (tail resection or body and tail resection) on 33/88 (37.6%), total pancreatectomy on 11/88 (12.5%), and enucleation on 1/88 (1.15%) of the patients. Overall morbidity (CD 1-5) was 43/88 (49.9%), 22/88 (25%) of the patients had serious postoperative complications (CD 3-5), and 30-day mortality was 2/88 (2.3%) (Table IV).

Histopathologic analysis

Histologic diagnoses were MD-IPMN 47/88 (53.4%), MT-IPMN 27/88 (30.7%), and BD-IPMN 14/88 (15.9%). Overall, 40/88 (45.5%) of the tumors were LGD, 9 (10.2%) HGD, and 39/88 (44.3%) INV. Distributions of dysplasia were for MD-IPMN; LGD 12/47 (25.5%), HGD 6/47 (12.8%), INV 29/47 (61.7%), MT-IPMN; LGD 16/27 (59.3%), HGD 2/27 (7.4%), INV 9/27 (33.3%), and BD-IPMN; LGD 12/14 (85.7%), HGD 1/14 (7.1%), and INV 1/14 (7.1%). The histological subtypes were analyzed for 23 patients, of whom 11/23 (47.8%) had intestinal (INT), 8/23 (34.8%) oncocytic, and 4/23 (17.4%) pancreatobiliary (PB) subtype of IPMN tumor. For INT, oncocytic, and PB, the respective distributions of dysplasia were LGD 4/11 (36.4%), HGD 4/11 (36.4%), INV 3/11 (27.3%), LGD 5/8 (62.5%), HGD 0/8 (0.0%), INV 3/8 (37.5%), LGD 0/4 (0.0%), HGD 0/4 (0.0%), and INV 4/4 (100%) (Table V). Histologic subtype expressions are presented in Supplementary Table S1.

Long-term outcomes

The minimum follow-up time was 10 years (range 10–21). The median survival was 121 (range 0–252) months. One-year, 5-year, and 10-year survival was 88.6%, 63.6%, and 50.0%, respectively. In the subgroups formed according to the degree of dysplasia, 1-, 5,-and 10-year survival was 97.5%, 87.5%, 72.5% for LGD, 100%, 77.8%, and 72.5% for HGD, and 76.9%, 35.9%, and 23.1% for INV. There was a

Table IIRadiologic findings, type of tumor, and degree of dysplasia of resected IPMN tumors

Radiological findings	Total n (%)	BD-IPMN n (%)	MD-IPMN n (%)	MT-IPMN n (%)	LGD n (%)	HGD n (%)	INV n (%)
Diameter of largest cyst, mm, median (range)	37.7 (7-100)	32.4 (12-50)	38.9 (9-86)	38.5 (7-100)	37.9 (7-100)	42.4 (20-64)	36.0 (9–86)
Single cyst	68/88 (77.3)	6/14 (42.9)	41/47 (87.2)	21/27 (77.8)	28/40 (70.0)	8/9 (88.9)	32/39 (82.1)
MPD <4.9 mm	40/68 (58.8)	13/13 (100)	13/32 (40.6.)	14/23 (60.9)	25/34 (73.5)	2/6 (33.3)	13/28 (46.4)
MPD 5-9.9 mm	18/68 (26.5)	0/14 (0.0)	12/32 (37.5)	6/23 (26.1)	7/34 (20.6)	1/6 (16.7)	10/28 (35.7)
MPD >10 mm	10/68 (14.7)	0/14 (0.0)	7/32 (21.9)	3/23 (13.0)	2/34 (5.9)	2/6 (50)	5728 (17.9)
MPD diameter mm, median (range)	5.1 (1-17)	2.58 (2-6)	6.32 (2-15)	4.84 (1-17)	4.1 (1-17)	7.3 (2-11)	5.9 (2-14)
Cyst communicating with MPD	35/68 (51.5)	8/13 (61.5)	17/32 (53.1)	10/23 (43.5)	19/33 (57.6)	4/7 (57.1)	12/28 (42.9)
Location caput - Head	42/80 (52.4)	6/14 (42.9)	22/41 (53.7)	14/25 (56.0)	17/37 (45,9)	5/8 (62.5)	20/35 (57)
Location korpus - Boby	19/80 (23.8)	5/14 (35.7)	8/41 (19.5)	6/25 (24.0)	9/37 (24.3)	2/8 (25)	8/35 (22.9)
Location cauda - Tail	19/80 (23.8)	3/14 (21.4)	11/41 (26.8)	5/25 (20.0)	11/37 (29.7)	1/8 (12.5)	7/35 (20.0)
Parenchymal atrophy	33/56 (58.9)	5/10 (50)	18/29 (62.1)	10/17 (58.8)	15/24 (62.5)	4/7 (57.1)	11/25 (44.0)
Cyst wall >2 mm	27/54 (50)	3/10 (30.0)	16/27 (59.3)	8/17 (47.1)	5/22 (22.7)	6/7 (85.7)	16/25 (64.0)
Septation of cyst	39/68 (57.4)	7/13 (53.8)	20/31 (64.5)	12/24 (50.0)	20/34 (58.8)	4/7 (57.1)	15/27 (55.6)
Mural nodules of the cyst	17/64 (26.6)	1/13 (7.7)	11/32 (34.4)	5/19 (26.3)	3/31 (9.7)	4/7 (57.1)	10/26 (38.5)
Calcification of the cyst	7/73 (6.8)	0/13 80.0)	3/36 (8.8)	2/24 (8.3)	1/35 (2.9)	2/8 (25)	2/30 (6.7)
Suspected malignancy	12/55 (21.8)	1/10 (10.0)	7/28 (25)	4/17 (23.5)	0/23 (0.0)	3/7 (42.9)	9/25 (36)

BD, branch duct; HGD, high-grade dysplasia; INV, invasive carcinoma; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MD, main duct; MPD, main pancreatic duct; MT, mixed-type.

Table IIIRisk factors for malignancy in resected IPMN tumors

Risk factors for malignancy	Benign	Malignant	P value
Age	65 (40-87)	65 (43-79)	.798
Age >60 years	16/22 (73%)	6/22 (27%)	.063
Age <60 years	33/66 (50)	33/66 (50)	
Symptomatic	31/63 (49)	32/63 (51)	.052
Incidental	18/25 (72)	7/25 (28)	
MPD diameter	3 (1-17)	6 (2-14)	.129
Single cyst	36/68 (53)	32/68 (47)	.340
Multifocal	13/20 (65)	7/20 (35)	
MPD <4.9 mm	27/40 (68)	13/40 (32)	.212
MPD 5-9.9 mm	8/18 (44)	10/18 (56)	
MPD >10 mm	5/10 (50)	5/10 (50)	
Diameter of largest cyst	40 (7-100)	31 (9-86)	.409
Cyst not communicating with MPD	17/33 (52)	16/33 (48)	.234
Cyst communicating with MPD	23/35 (66)	12/35 (34)	
Location head	22/42 (52)	20/42 (48)	.724
Location body	11/19 (58)	8/19 (42)	
Location tail	12/19 (63)	7/19 (37)	
No parenchymal atrophy	12/23 (52)	11 (23 (48)	.689
Parenchymal atrophy	19/33 (58)	14/33 (42)	
Cyst wall >2 mm	11/27 (41)	16/27 (59)	.056
Cyst wall <2 mm	18/27 (67)	9/27 (33)	
No septa	17/29 (59)	12/29 (41)	.808
Septation of cyst	24/39 (62)	15/39 (38)	
No mural nodules of the cyst	31/47 (66)	16/47) 34	.75
Mural nodules of the cyst	7/17 (41)	10/17 (59)	
No calcification of the cyst	40/68 (59)	28/68 (41)	.959
Calcification of the cyst	3/5 (60	2/5 (40)	
No suspected malignancy	27/43 (63)	16/43 (37)	
Suspected malignancy	3/12 (25)	9/12 (75)	.02

IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct.

statistically significant difference (P < .01) in survival between invasive cancers and noninvasive tumors (LGD + HGD). Survival percentages for other subgroups are presented in Table VI. Disease-

specific 5-year survival was 97.1% in the LGD group compared to 40.0 in the INV group. In the LGD group, 2/40 (5%) patients died of pancreatic cancer during the 10-year follow-up. Ten-year mortality from pancreatic cancer was 1/9 (11.1%) in the HGD group and 28/39 (71.8%) in the INV group (Table VI, Figure 2).

Discussion

The degree of dysplasia is considered the most important factor in determining the patient's survival after pancreatic resection for IPMN, but only limited long-term follow-up data are available. We aimed to investigate the nationwide 10-year survival of all resected IPMN patients and to identify factors associated with survival. We found that survival was significantly better when the resection was performed before the malignant transformation. However, 5% to 11% of the patients operated on at the stage of LGD and HGD died of pancreatic cancer during the 10-year follow-up.

The IPMN treatment guidelines aim to define tumors with elevated malignant potential and time the resection before the malignant transformation.^{1,22} It is well-established that only a few IPMN tumors will present features necessitating surgical resection. Some studies even suggested that small BD-IPMN tumors should not be followed up at all.²³ Once worrisome features are present, resection is recommended, although the predictive value of these known features is not optimal. The prognosis of resected IPMNs depends mainly on the degree of dysplasia.¹ A BD-IPMN with only LGD has an excellent prognosis, although the remnant pancreas needs lifelong surveillance. Also, in tumors with HGD, the prognosis is better than in invasive IPMN carcinoma.¹ In the early 2000s in Finland, the treatment of pancreatic tumors was not centralized, and operations were carried out in many low-volume centers. The quality of diagnostics was not always at the level expected today.

Table IVComplications classified by Clavien-Dindo score and 30-day mortality of resected IPMNs

Clavien-Dindo score	N	0 n, (%)	1 n, (%)	2 n, (%)	3 n, (%)	4 n, (%)	5 n, (%)	30-day n, (5)
Pancreaticoduodenectomy	43	14 (32.6)	4 (9.3)	11 (25.6)	10 (23.3)	4 (9.3)	0 (0.0)	1
Distal pancreatectomy	33	24 (72.7)	1(3.0)	4 (12.1)	3 (9.1)	0 (0.0)	1 (3.0)	1
Total pancreatectomy	11	6 (53.5)	0 (0.0)	1 (9.1)	3 (27.3)	1 (9.1)	0 (0.0)	0
Enucleation	1	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
Total	88	45 (51.1)	5 (5.7)	16 (18.2)	16 (18.2)	5 (5.7)	1 (1.1)	2 (2.3)

IPMNs, intraductal papillary mucinous neoplasms.

Table VDegree of dysplasia and rate of malignancy in IPMN subtypes and histological subtypes

		BD-IPMN	MD-IPMN	MT-IPMN
All		14 (15.9)	47 (53.4)	27 (30.6)
LGD		12/14 (85.8)	12/47 (25.5)	16/27 (59.3)
HGD		1/14 (7.1)	6/47 (12.8)	2/27 (7.4)
INV		1/14 (7.1)	29/47 (61.7)	9/27 (33.3)
	Non-INV	13/14 (93)	18/47 (38)	18/27 (67)
	P value			0.001
Oncocytic subtype*		3/8 (37.5)	3/8 (37.5)	2/8 (25)
	Invasive	0/3 (0.0)	1/3 (33)	2/2 (100)
	Non-INV	3/3 (100)	2/3 (66)	0/2 (0.0)
Intestinal subtype*		1/11 (9.1)	5/11 (45.5)	5/11 (45.5)
	Invasive	0/1 (0.0)	1/5 (20)	2/5 (40)
	Non-INV	1/1 (100)	4/5 (80)	3/5 (60)
Pancreatobiliary subtype [†]		0/4 (0.09	1/4 (25)	3/4 (75)
	Invasive	0/0 (0.0)	1/1 (100)	3/3 (100)
	Non-INV	0/0 (0.0)	0/1 (0.0)	0/3 (0.0)

BD, branch duct; HGD, high-grade dysplasia; INV, invasive carcinoma; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MD, main duct; MT, mixed-type.

 $^{^*}$ No statistically significant difference (P > .05) in share of patients with malignant disease.

[†] All patients with pancreatobiliary cysts had malignant disease.

Table VI One-year, 5-year, and 10-year survival for IPMN patients

	Median (range)	IQR	1-year survival%	5-year survival%	10-year survival%	5-year disease-specific survival %	Pancreatic cancer mortality n (%)
BD	155 (3-252)	74.75-232.25	92.9	85.7	64.3	100	1/14 (7.1)
MD	87 (1-240)	21-141	85.1	59.6	44.7	65.1	20/47(42.6)
MT	124 (6-240)	17-171	92.6	59.3	51.9	66.7	10/27 (37.0)
LGD	142 (3-252)	101-185.75	97.5	87.5	72.5	97.1	2/40 (5)
HGD	118 (15-229)	58.5-168.5	100	77.8	66.7	87.3	1/9 (11.1)
INV	25 (1-226)	12-109	76.9	35.9	23.1	40.0	28/39 (71.8)
ONC	60.5 (3-242)	5.25-133.5	50	50	50	57.1	3/8 (37.5)
INT	124 (12-240)	15-178	100	72.7	72.7	80.0	2/11 (18.2)
PB	19 (12-34)	13.25-30.75	100	0.0	0.0	0.0	4/4 (100)
All	121 (0-252)	24.25-161.5	88.6	63.6	50.0	70.9	31/88 (35.2)

BD, branch duct; HGD, high-grade dysplasia; INT, intestinal; INV, invasive carcinoma; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MD, main duct; MPD, main pancreatic duct; MT, mixed-type; ONC, oncocytic; PB, pancreatobiliary.

Survival Functions

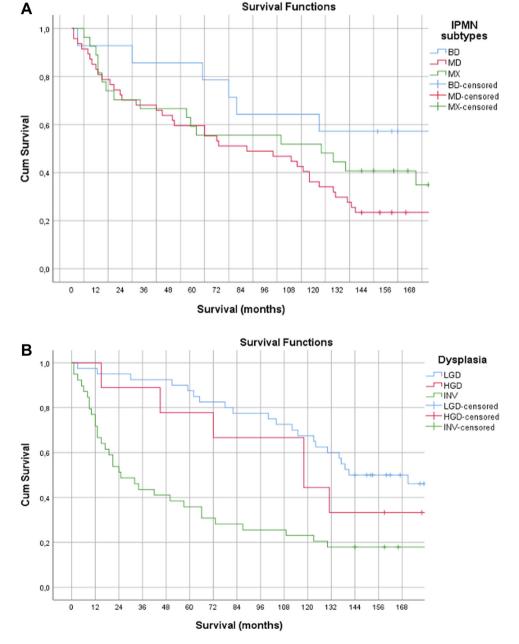


Figure 2. (A) Kaplan-Meier survival curves by intraductal papillary mucinous neoplasm subtypes. (B) Kaplan-Meier survival curves by the degree of dysplasia. (C) Kaplan-Meier survival curves by immunohistochemical intraductal papillary mucinous neoplasm subtypes.

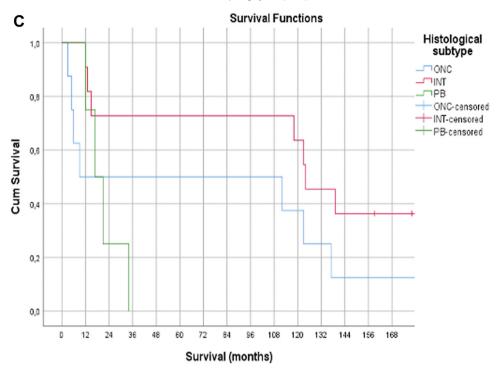


Figure 2. (continued).

For example, magnetic resonance imaging was performed on only 25/88 (28.4%) patients, which obviously affects the ability to evaluate features such as a cyst communicating with the MPD. Suboptimal diagnostics may have led to numerous misdiagnoses both preoperatively and postoperatively. Also, some tumors may have been diagnosed as PDAC rather than IPMN, which may partially explain the low number of resections performed in the earlier years of the study period.

The first IPMN guidelines were issued in 2006; the effect of these guidelines on managing patients in this cohort was negligible. Decisions to operate likely were based on the clinical judgment of the individual surgeon, with cyst size being the most important factor in this decision-making. Currently, surgeons in Finland rely primarily on the European guidelines. Since applying new guidelines for treating IPMN, the number of patients undergoing surgery and under surveillance has increased significantly. Although the indications for surgery have been tightened, the overall increase in the number of patients on surveillance programs has led to more resections. Population aging and increased volumes of cross-section imaging have likewise increased the likelihood of asymptomatic pancreatic cysts being detected.²⁴

In our nationwide cohort, the patients were predominantly female, and the median age was slightly above 60. The number of incidentally found, asymptomatic cysts was low (27.3%) and can be explained by the less frequent use of cross-section imaging for other reasons in the early 2000s.

The rate of complications was high but similar to those found in other studies; after pancreaticoduodenectomy, 29/43 (67.4%) patients had any complication, and for 14/43 (32.5%) of the patients, the complications were considered severe (CD 3–5). In comparison, in a nationwide register study from Finland from 2012 to 2014, the rate of severe complications after pancreaticoduodenectomy was 23.3%.

Most tumors (53.4%) were classified as MD-IPMN (MT-IPMN 30.6% and BD-IPMN 16.3%). The proportion of resected BD-IPMN is low compared to the resection rates in more recent publications. Although the indications for surgery in BD-IPMN patients have been tightened, the increased volume of BD-IPMN patients under surveillance has also increased the proportion of resected BD-IPMNs compared to other subtypes.

Overall, 44.3% of the patients had a malignant operated tumor, and three-quarters (74.5%) of the MD-IPMNs were malignant or HGD. In comparison, 12/14 (85.8%) patients had an LGD tumor in the BD-IPMN group. The instance of HGD was present more equally in all groups (BD-IPMN 7.1%, MT-IPMN 7.1%, and MD-IPMN 12.8%). The rate of malignancy was high compared to other surgical series. The tumors were large (median 40.4, range 3.4–120.0 mm), symptomatic (72.7%), and detected late (length of symptoms before operation 6.88 months). Also analyzed retrospectively, several features (ie, MPD diameter, thickened cyst wall, and size of the cyst) were present that relate to malignancy. In the current guidelines, MPD dilation, among others, is a well-established radiologic feature predicting malignancy. There was a tendency for an elevated risk of malignancy in factors such as patients with symptoms, an MPD diameter of \geq 5 mm, and a cyst wall >2 mm. However, the numbers did not reach statistical significance. The only preoperative factor of statistical significance in detecting malignancy was if a radiologist suspected malignancy. Based on this finding, the "gut feeling" of the experienced radiologist should be considered when IPMN cases are discussed in a multidisciplinary setting. Poor quality of preoperative imaging studies also may have negatively affected the ability to detect any signs of malignant transformation. The number of patients in the histologic subtype analyses was low; thus, there was no significant difference among IPMN subtypes (BD, MD, MT) or malignancy, although 75% of the PB group was MT, and all were malignant.

Survival percentages beyond 5 years in nationwide settings were not published in large quantities before this study. In our

material, the median survival overall was 121 (0-252) months, and 5- and 10-year survival was 63.6% and 50.0%. The most important prognostic factor for patients with resected IPMN is the degree of dysplasia. It is evident that when IPMN is deemed invasive carcinoma, the prognosis is dismal; for INV compared to LGD, 5- and 10-year survival was 35.9 vs 87.5 and 72.5 vs 23.1. The distinction between LGD and HGD is not so clearcut from the perspective of survival. Some, although not all, authors have reported differences in survival in these 2 groups. 1,18 In this cohort, there were no statistically significant differences in survival for LGD and HGD in 5 and 10-year surveillance. In the general population (in this age group) at the time of this study, 10-year survival was roughly 80% compared to 72.5% in the LGD group. One factor explaining this difference is the risk of a malignant tumor in the remnant pancreas if total pancreatectomy has not been performed, even if the histology of the specimen was benign.

In this study, mortality from pancreatic cancer was 2/40 (5%) in the LGD group. Mortalities from pancreatic cancer in the LGD group included deaths 59 months after the primary operation (MT-IPMN) and deaths 79 months after primary operation (BD-IPMN). The risk of a malignant tumor in the remnant advocates the surveillance of the remnant pancreas after resection as long as the patient is fit enough for surgery. ⁶ There are probably more factors than described above that could explain the decrease in survival in benign cases compared to the general population. As expected, mortality from pancreatic cancer was higher in HGD, especially in the INV group. Among MD, MT, and BD, survival was higher in the BD group (which can be explained by the smaller number of malignant tumors in the BD group). Still, there was no statistical significance among the groups. Also, there were no significant differences in survival between histologic subtypes (oncocytic, PB, INT), although the small number of patients may have affected this analysis.

Strengths and limitations of the study

The strength of this study is the nationwide setting. All resected patients were included; thus, there was no selection bias. Another strength of this study is the long follow-up time for all patients. This is longer than in any other published series of nationwide data. However, even though nationwide, the sample size can be considered small, and we could not complete radiologic and histologic data sets for all patients. This hurt our ability to conduct meaningful qualitative analyses and can be considered a limitation of the study. Also, the poor quality of preoperative radiologic studies (the small number of magnetic resonance imaging studies) may have impaired the detection of significant risk factors for malignancy in our analysis.

In conclusion, based on this nationwide cohort with a 10-year survival analysis, we conclude that patients with an IPMN tumor resected before malignant transformation have a good prognosis. In comparison, in the case of invasive carcinoma, 10-year survival is <25%. Also, the IPMN subtype is an important prognostic factor; in this cohort, mortality due to pancreatic cancer was 7.1% in the BD-IPMN group compared to around 40% in the MD-IPMN and MT-IPMN groups. The timing of the surgery before malignant transformation and, at the same time, avoiding unnecessary operations remains a challenge for all surgeons working with IPMN tumors.

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Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

Supplementary materials

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