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ORIGINAL ARTICLE – PANCREATIC TUMORS

Preoperative Characteristics of Patients with Presumed Pancreatic Cancer but Ultimately Benign Disease: A Multicenter Series of 344 Pancreatoduodenectomies

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ABSTRACT

Background. Preoperative differentiation between malignant and benign pancreatic tumors can be difficult. Consequently, a proportion of patients undergoing pancreatoduodenectomy for suspected malignancy will ultimately have benign disease. The aim of this study was to compare preoperative clinical and diagnostic characteristics of patients with unexpected benign disease after pancreatoduodenectomy with those of patients with confirmed (pre)malignant disease.

Methods. We performed a multicenter retrospective cohort study in 1,629 consecutive patients undergoing pancreatoduodenectomy for suspected malignancy between 2003 and 2010 in 11 Dutch centers. Preoperative characteristics were compared in a benign:malignant ratio of 1:3. Malignant cases were selected from the entire cohort by using a random number list. A multivariable logistic regression prediction model was constructed to predict benign disease.

Results. Of 107 patients (6.6 %) with unexpected benign disease after pancreatoduodenectomy, 86 fulfilled the inclusion criteria and were compared with 258 patients with (pre)malignant disease. Patients with benign disease

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presented more often with pain (56 vs. 38 %; $P = 0.004$), but less frequently with jaundice (60 vs. 80 %; $P < 0.01$), a pancreatic mass (13 vs. 54 %, $P < 0.001$), or a double duct sign on computed tomography (21 vs. 47 %; $P < 0.001$). In a prediction model using these parameters, only 19 % of patients with benign disease were correctly predicted, and 1.4 % of patients with malignant disease were missed.

Conclusions. Nearly 7 % of patients undergoing pancreatoduodenectomy for suspected malignancy were ultimately diagnosed with benign disease. Although some preoperative clinical and imaging characteristics might indicate absence of malignancy, their discriminatory value is insufficient for clinical use.

Pancreatoduodenectomy is the treatment of choice for resectable (pre)malignant tumors in the pancreatic head or periampullary region.[1] Preoperative differentiation between malignant and benign disease in patients with a pancreatic tumor can, however, be difficult. The presence of jaundice, weight loss. and a pancreatic mass on computed tomography (CT) and/or endoscopic ultrasonography (EUS) frequently provides sufficient arguments to proceed to surgery, as recommended by the recent International Study Group of Pancreatic Surgery consensus statement on pancreatoduodenectomy in the absence of histology.[2] However, benign diseases can clinically mimic pancreatic malignancy by causing jaundice and weight loss.[3–6] Also, on imaging, benign diseases such as groove or autoimmune pancreatitis can be mistaken for pancreatic or periampullary carcinoma.[4–9] Consequently, a proportion of patients undergoing pancreatoduodenectomy for suspected malignancy will ultimately have benign disease. Previous studies reported an incidence of benign disease between 4.5 and 13.6 %.[10–25]

Although operative techniques and perioperative care have improved over the past decades, mortality rates after pancreatoduodenectomy still range from 2.6 % in high-volume centers up to 16.3 % in low-volume centers.[26–28] It is therefore clear that attempts should be made to prevent unnecessary pancreatoduodenectomies, since treatment of (symptomatic) benign disease rarely requires a pancreatoduodenectomy. Pain in most patients with chronic pancreatitis can be managed by analgesics, endoscopic intervention, or a less invasive surgical procedure, and autoimmune pancreatitis is highly responsive to steroids.[29,30]

The aim of this study was to identify patients who underwent pancreatoduodenectomy for suspected malignancy but were ultimately diagnosed with benign disease. Additionally, we aimed to compare preoperative clinical and diagnostic characteristics of patients with confirmed (pre)malignant disease and patients with unexpected benign disease after pancreatoduodenectomy to evaluate their predictive value for the presence of benign disease.

METHODS

Patients

We performed a multicenter retrospective cohort study in patients undergoing pancreatoduodenectomy between January 2003 and July 2010 in 11 medium- to high-volume centers in The Netherlands. All adult patients who underwent either a pyloric-preserving pancreatoduodenectomy or a classic Whipple for suspected malignancy were included. This suspicion could be based on a mass identified on CT, a mass on EUS, duct dilatation with symptoms, and/or at least highly suspicious histopathology or cytopathology. Surgery for recurrence of pancreatic cancer is not performed in the participating centers. Patients with a history of chronic pancreatitis or preoperative suspected duodenal carcinoma or of whom no preoperative digital CT scan was available were excluded from this study.

Patients were divided into two groups based on the final diagnosis of the postoperative pathology report. All patients diagnosed with carcinoma, duodenal/ampullary adenoma, mucinous cystadenoma, intraductal papillary mucinous neoplasm or neuroendocrine tumor of uncertain malignant potential were assigned to the (pre)malignant group. All other diagnoses were assigned to the benign group.

For pragmatic reasons, given the expected ratio of benign:malignant diagnoses of 1:10, patients with malignant disease were selected in a 1:3 ratio (i.e., for each patient with benign disease, 3 cases of malignant disease were randomly selected). Patients with benign disease were screened for eligibility in a consecutive backward fashion until approximately 100 patients could be included. The required number of patients with malignant disease was randomly selected from the entire cohort by using a random number list, likewise in a consecutive backward fashion.

Data Collection

Data were retrospectively collected from (digital) patient charts. Baseline characteristics collected included patient demographics (age and sex), symptoms (weight loss, pain, and jaundice), and smoking. Original reports of the most recent preoperative imaging [CT, EUS, endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography, or magnetic resonance imaging] were collected. Data on the presence of a mass, vascular involvement, and dilatation of the common bile duct (CBD) and/or pancreatic duct (PD) were extracted from these reports. When available, serum carcinoembryonic antigen, CA 19-9, IgG4, and blood type

were collected. Details on preoperative histopathology or (brush) cytology and postoperative pathology reports were also recorded.

Radiologic Reassessment

The most recent preoperative CT scan of all included patients was reassessed by two expert radiologists (TLB, CYN) with special interest in pancreatic disease. Both reviewers were blinded to any clinical data, results from previous investigations, and the final diagnosis. Each scan was evaluated for the presence of a mass and dilatation of the CBD and/or PD. A lesion was considered a mass when it concerned a measurable space occupying soft tissue density, except for an enlarged papilla or focal steatosis. The PD was defined to be dilated when the diameter was at least 4 mm. The CBD was considered dilated when the diameter measured at least 8 mm (plus 1 mm for each 10 years above 70 years of age). Disagreement between radiologists was addressed by discussion and consensus review.

Statistical Analysis

Data were analyzed by using SPSS for Windows version 20 (SPSS Inc., Chicago, IL). Categorical variables were compared by the chi-square or Fisher's exact test as appropriate. Continuous variables were compared by using the unpaired *t*- or Mann–Whitney *U*-test. A two-tailed *P* value <0.05 was considered statistically significant. Continuous variables are expressed either as the mean (±SD) or the median (interquartile range) as appropriate. Associations between the individual predictors and the presence of benign disease were assessed by univariable logistic regression. Predictors potentially associated with benign disease ($P < 0.20$) were entered in multiple multivariable logistic regression models to identify the most optimal model for the prediction of benign disease. Results are shown as odds ratios and 95 % confidence intervals. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for this model. Taking into account the 1:3 sampling fraction and original 107:1522 (1:14.22) benign:malignant ratio, the malignant cases were multiplied by factor 4.74 (i.e., 14.22 divided by 3) for the calculation of the PPV, NPV, and accuracy, under the assumption that the proportions of patients not fulfilling the inclusion criteria were similar in the benign and malignant group. Sensitivity analysis was performed after exclusion of patients with cystic lesions. In addition, we analyzed the distribution of the presence of a mass and PD and/or CBD dilatation between patients with benign and malignant disease, again after multiplying the malignant cases by a factor of 4.74.

TABLE 1 Histopathologic diagnoses of 344 patients who underwent pancreatoduodenectomy for suspected malignancy

Unexpected benign	$n = 86$
Chronic fibrosing pancreatitis	52 (60 %)
Chronic fibrosing cholangitis	17 (20 %)
Autoimmune pancreatitis	9 (11 %)
Serous cystadenoma	2 (2 %)
No abnormalities	2 (2 %)
Other[a]	4 (5 %)
Malignant	$n = 258$
Pancreatic adenocarcinoma	135 (52 %)
Ampullary adenocarcinoma	60 (23 %)
Cholangiocarcinoma	30 (12 %)
Adenoma	11 (4 %)
NET	6 (2 %)
Carcinoma derived from IPMN	5 (2 %)
Duodenal adenocarcinoma	4 (2 %)
IPMN	3 (1 %)
Mucinous cystadenoma	3 (1 %)
Other[b]	1 (0.4 %)

NET neuroendocrine tumor, *IPMN* intraductal papillary mucinous neoplasm

[a] Ectopic gastric tissue, Brunners gland adenoma, and purulent inflammation

[b] Metastasis of colorectal carcinoma

RESULTS

Patients

During the study period, 1,629 consecutive patients underwent pancreatoduodenectomy for suspected malignancy. One hundred seven patients (6.6 %) were ultimately diagnosed with benign disease.

The rate of unexpected benign disease was 7.4 % in the first half of the study period (2003–2006) and 5.9 % in the second half (2007–2010; $P = 0.24$). After excluding 11 patients because of a history of chronic pancreatitis and 10 patients because no digital CT scan was available, 86 patients with benign disease were eligible for further analysis. These were compared with 258 patients with malignant disease (1:3 ratio). Specifications of histopathologic diagnoses are shown in Table 1. Patients with benign disease were significantly younger as compared with patients with malignant disease (Table 2).

Clinical Characteristics

Patients with benign disease presented less frequently with jaundice, but more often with pain, as compared with

TABLE 2 Preoperative general, clinical, imaging, biochemical, and histopathologic characteristics of 344 patients undergoing pancreatoduodenectomy for suspected malignancy

	Unexpected benign ($n = 86$)	Malignant ($n = 258$)	P value
General			
Male	53/86 (62 %)	156/258 (60 %)	0.85
Age, years (mean ± SD)	60 ± 11	64 ± 10	0.001
Clinical			
Symptoms			
Weight loss	52/73 (71 %)	144/188 (77 %)	0.36
Median, kg (IQR)	9 (6–12)	8 (5–10)	0.16
Jaundice	47/79 (60 %)	194/242 (80 %)	<0.001
Pain	44/78 (56 %)	86/228 (38 %)	0.004
Smoking	22/38 (58 %)	38/101 (38 %)	0.03
CT			
Mass	11/86 (13 %)	139/258 (54 %)	<0.001
PD dilatation	22/86 (26 %)	148/258 (56 %)	<0.001
CBD dilatation	55/86 (69 %)	200/258 (82 %)	0.01
Double duct sign	17/86 (21 %)	113/258 (47 %)	<0.001
EUS performed	46/86 (53 %)	116/258 (45 %)	0.17
Mass	30/40 (75 %)	85/101 (84 %)	0.20
PD dilatation	11/26 (42 %)	52/68 (77 %)	0.002
CBD dilatation	11/22 (50 %)	35/44 (80 %)	0.01
Double duct sign	5/23 (22 %)	23/45 (51 %)	0.02
ERCP performed	52/86 (61 %)	193/258 (75 %)	0.01
Double duct sign	5/16 (31 %)	28/53 (53 %)	0.13
Biochemical			
CA 19-9 >37 U/ml	15/37 (41 %)	46/81 (57 %)	0.10
Median CA 19-9 (U/ml)	27 (8–161)	69 (20–267)	0.14
CEA >5 μg/L (>10 in smokers)	3/20 (15 %)	6/48 (13 %)	>0.99
Median CEA (μg/L)	2.9 (2.2–5.7)	3.2 (2.0–4.2)	0.99
IgG4 >1.4 g/L	0/6 (0 %)	3/22 (14 %)	>0.99
Median IgG4 (g/L)	0.76 (0.16–0.81)	0.62 (0.14–1.08)	0.77
Non-O blood type	36/76 (47 %)	138/232 (60 %)	0.06
Histopathologic			
Suspicious histopathology or cytopathology	19/54 (35 %)	109/163 (67 %)	<0.001
Brush	13/32 (41 %)	44/77 (57 %)	0.11
FNA	5/13 (39 %)	24/38 (63 %)	0.12
Biopsy[a]	1/28 (4 %)	51/91 (56 %)	<0.001

IQR interquartile range, *PD* pancreatic duct, *CBD* common bile duct

[a] From papilla ($n = 62$), duodenum ($n = 18$), CBD ($n = 17$), liver ($n = 9$), LNN ($n = 7$), or other location ($n = 3$)

patients with malignant disease. Smoking was more frequently present in patients with benign disease (Table 2).

Imaging

On CT, patients with benign disease presented less frequently with a mass, PD dilatation, CBD dilatation, and double duct sign as compared with patients with malignant disease. A mass was reported in the original report in 66 % of patients, as compared with 44 % of patients on reassessment by the two expert radiologists ($P < 0.001$).

In 46 of 86 (53 %) patients with benign disease and 116 of 258 (45 %) patients with malignant disease, an EUS was performed ($P = 0.17$). On EUS there was no difference in the presence of a mass, but PD dilatation, CBD dilatation, and double duct sign were less common in the benign group (Table 2).

The rate of double duct sign on ERCP was not different between patients with benign and malignant disease. An additional magnetic resonance imaging was performed in 5 of 86 (6 %) patients with benign and 11 of 258 (4 %) patients with malignant disease ($P = 0.55$), but there were no significant differences in the presence of mass, PD, or CBD dilatation or double duct sign. Also on magnetic resonance cholangiopancreatography, performed in 15 and 5 % of patients, respectively, no differences in the presence of a double duct sign were seen.

TABLE 3 Univariable and multivariable analysis of predictors of benign disease

	Univariable analysis			Multivariable analysis		
Predictor	OR	95 % CI	*P*	OR	95 % CI	*P*
Clinical						
Age <65 years	1.85	1.12–3.06	0.01			
No jaundice	2.75	1.59–4.77	<0.001	2.79	1.39–5.60	0.004
Pain	2.14	1.27–3.60	0.004	1.89	0.99–3.57	0.05
CT						
No mass	7.96	4.04–15.70	<0.001	7.31	3.41–15.681	<0.001
No PD dilatation	3.91	2.27–6.74	<0.001			
No CBD dilatation	2.11	1.19–3.76	0.01			
No double duct sign	3.22	1.78–5.82	<0.001	2.62	1.29–5.31	0.007
EUS						
No PD dilatation	3.90	1.53–9.93	0.004			
No CBD dilatation	3.39	1.14–10.02	0.02			
No double duct sign	3.00	1.01–8.92	0.04			

PD pancreatic duct, *CBD* common bile duct

Biochemical and Histopathologic Characteristics

Table 2 shows the biochemical and histopathologic characteristics. No significant differences were found in the CA 19-9, carcinoembryonic antigen, or IgG4 levels between both groups. There was a trend toward a lower incidence of a non-O blood type in patients with benign disease. In 19 of 54 (35 %) patients with benign disease, in whom an ERCP with a brush was performed or who underwent an EUS with fine-needle aspiration (FNA) and/or biopsy (FNB), malignant cells ($n = 1$) or cells with high suspicion of malignancy ($n = 18$) were found.

Prediction of Benign Disease

In Table 3, the results of univariable and multivariable logistic regression analyses are shown. In the most accurate prediction model, including the presence of pain, the absence of jaundice, and the absence of a mass and double duct sign on CT, only 13 of 70 patients with benign disease that could be included in this model were correctly predicted, resulting in a sensitivity of 19 %. Moreover, 3 of 208 (1.4 %) patients with malignant disease in this model were falsely identified as benign (specificity 99 %). However, to be able to identify benign patients at all in this model, the cut value was set at 0.6, and consequently this small proportion of false benign patients had to be accepted. The PPV of this model was 48 %, NPV was 95 %, and overall accuracy was 93 % (Appendix 1). Sensitivity analysis showed that exclusion of patients with cystic lesions ($n = 13$) had no effect on the diagnostic value of the model.

TABLE 4 Relevance of mass and pancreatic duct or common bile duct dilatation in patients undergoing pancreatoduodenectomy for suspected malignancy

Mass[a]	PD and/or CBD dilatation[b]	PA confirmed diagnosis		
		Benign $n = 86$	Malignant[c] $n = 1,222$	Total $n = 1,308$
No	No	10 (34 %)	19 (66 %)	29 (100 %)
	Yes	39 (10 %)	360 (90 %)	399 (100 %)
Yes	No	10 (18 %)	47 (82 %)	57 (100 %)
	Yes	27 (3 %)	796 (97 %)	823 (100 %)

PD pancreatic duct, *CBD* common bile duct

[a] Mass either on CT or EUS

[b] PD and/or CBD dilatation detected on CT, EUS, or ERCP. No difference made between double-duct and single-duct dilatation

[c] Multiplied by factor 4.74 to restore original 107:1,522 ratio benign:malignant

Common Clinical Vignettes

Table 4 shows the distribution of the presence of a mass on CT or EUS and the presence of PD and/or CBD dilatation on CT, EUS, or ERCP between patients with benign and malignant disease.

Patients who presented with both a mass and dilatation of either PD or CBD had benign disease in 3 % of all cases. When focusing on CT only, 1 % of patients with a mass and PD and/or CBD dilatation ultimately had benign disease.

TABLE 5 Incidence of unexpected benign disease after pancreatoduodenectomy for suspected malignancy

Author	Country	Study period	Number of participating centers	Total pancreatoduodenectomies for suspected malignancy	Benign disease	%
Cohen[13]	USA	1940–1980	1	106	10	9.4 %
Thompson[20]	USA	1978–1993	2	59	8	13.6 %
Smith[19]	USA	1956–1990	1	603	27	4.5 %
Van Gulik[21]	The Netherlands	1983–1993	1	220	14	6.4 %
Böttger[11]	Germany	1985–1997	1	186	10	5.4 %
Weber[23]	USA	1985–2001	1	1287	159	12.4 %
Abraham[10]	USA	1999–2001	1	435	40	9.2 %
Camp[12]	USA	1990–2002	1	120	7	5.8 %
Kennedy[17]	USA	1993–2004	1	162	21	13.0 %
Sasson[18]	USA	1998–2005	1	132	17	12.9 %
Kavanagh[16]	Ireland	1987–2002	1	112	8	7.1 %
De la Fuente[15]	USA	1992–2007	1	494	37	7.5 %
De Castro[14]	The Netherlands	1992–2005	1	631	55[a]	8.7 %
Hurtuk[25]	USA	1993–2007	1	451	35	7.8 %
Manzia[24]	UK	1997–2008	1	459	49	10.6 %
Van Heerde[22]	The Netherlands	2000–2009	1	274	23	8.4 %
Current study	The Netherlands	2003–2010	11	1629	107	6.6 %

[a] Only patients with pancreatitis were included in this study; other benign diseases were not identified

DISCUSSION

In this multicenter retrospective cohort study we observed that 6.6 % of patients undergoing pancreatoduodenectomy for suspected malignancy were ultimately diagnosed with benign disease. The presence of pain, the absence of jaundice, and the absence of a mass or double duct sign on CT were strongly associated with the presence of benign disease, but when combined into a prediction model, the PPV reached only 48, and 1.4 % of the patients with malignant disease were falsely identified as benign.

Several previous studies have reported the incidence of unexpected benign disease in patients undergoing pancreatoduodenectomy for presumed malignancy.[10–25] Details of these studies are shown in Table 5. The incidence of 6.6 % unexpected benign disease after pancreatoduodenectomy in our study ranks among the lower ranges of the overall reported incidences between 4.5 and 13.6 %. Most previous studies included patients who underwent pancreatoduodenectomy before 2000, whereas our study comprises the period between 2003 and 2010. As previously reported, we observed a slight but nonsignificant decrease in the incidence of benign disease from 7.4 % in the first half of this study to 5.9 % in the second half.[22] Although one might expect that this putative decline is explained by the improved diagnostic work-up and modalities, this is not reflected in the literature over time (Table 5). Also, a retrospective cohort study on the effect of improvement in radiographic imaging in 132 patients undergoing pancreatoduodenectomy found no change over time (8.9 % benign disease in 1998–2001 vs. 14.9 % in 2002–2005; $P = 0.39$).[18]

This is the largest study to date comparing the preoperative characteristics of patients with unexpected benign pathology after pancreatoduodenectomy with those of patients with confirmed (pre)malignant disease. Most studies on benign disease in patients undergoing pancreatoduodenectomy specifically focused on one single disease. The study with the largest cohort of patients with unexpected benign disease ($n = 159$) from one center only focused on the small subset of patients with autoimmune pancreatitis ($n = 31$).[23] Also, the most recent studies on this subject lack comparison with characteristics of patients with confirmed malignant disease or only include patients with pancreatitis or pancreatic adenocarcinoma specifically.[14,15,22,24,25]

In this study we aimed to identify predictors of benign disease to prevent a subset of unnecessary pancreatoduodenectomies. Two previous retrospective cohort studies, including 150 and 102 patients, respectively, aimed to identify predictors of malignancy.[31,32] Both studies found weight loss, jaundice/hyperbilirubinemia, and increased CA 19-9 levels to be strong predictive factors for malignancy (individually and in combination). However, in the study by Sivarman et al., malignancy was based on preoperative tissue diagnosis in 65 % of cases, which is known to be associated with limited sensitivity.[32,33] Tessler et al. also considered the presence of a mass and bile duct abnormalities as predictors, but found low specificity of both variables as single predictor.[31] Moreover, both

variables showed no additional value over the presence of weight loss, hyperbilirubinemia, and increased CA 19-9 levels. In the present study, weight loss was not significantly associated with malignancy, and data on CA 19-9 levels were too scarce for inclusion in our prediction model, because it is still not part of the regular work-up for patients with suspected malignancy in the Netherlands.

Notably, in the current study in one patient with ultimately benign disease, malignant cells had been identified in the preoperative FNA of a lesion in the pancreatic head. Additionally, 18 patients with ultimately benign disease had "highly suspicious cells" in preoperative histopathology or cytopathology samples. In both scenarios proceeding to surgery is inevitable. This is in line with the known specificity of FNA of 98 % for malignant cytology and the somewhat lower 94 % for atypical and suspicious cytology.[33] Consequently, it seems yet inevitable to prevent unnecessary pancreatic resections completely. Even when we would proceed to surgery only in patients with preoperative histologic proof of pancreatic or periampullary cancer, the false-positive biopsies would still lead to unnecessary resections. Moreover, the false-negative biopsies would lead to missing the diagnosis of cancer and the window of opportunity for a potentially curative resection. Therefore, it is commonly accepted, and also incorporated in a recent International Study Group of Pancreatic Surgery consensus statement, that biopsy proof is not required before proceeding to surgery in the presence of a solid pancreatic mass that is suspicious for malignancy, provided that autoimmune pancreatitis is not suspected.[2]

One main limitation of this study is its retrospective design introducing a risk of information bias concerning the preoperative parameters. Therefore, all original preoperative CT scans were reassessed by two independent expert radiologists to ensure the quality of data on the presence of a mass and duct dilatation to ensure the quality of the data.

Another limitation of this study is the potential risk of bias because only a small proportion of patients with malignant disease were included in the final analysis because data collection of the entire cohort from many different centers was practically not feasible. To reduce the risk of bias, the included subset of patients was randomly selected from the entire consecutive cohort by using a random number list.

Additionally, the number of patients per center per year seems limited. This is, however, the consequence of the relative rareness of patients undergoing pancreatoduodenectomy in general and those with unexpected benign disease in particular. Nonetheless, this study represents a nationwide series and incidence of unexpected benign disease as compared with previous mainly monocenter studies.

Because we did not assess follow-up data in our study, information on mortality, survival, and recurrence of the included patients is not available. The final diagnosis therefore entirely depends on the pathology report, which, albeit rare, includes the risk of malignancy being missed in the examined slides (measurement bias). Previous studies comparing patients with unexpected benign pathology after pancreatoduodenectomy to patients with confirmed (pre)malignant disease, showed no significant difference in between mortality rates after pancreatoduodenectomy between these two patient categories.[11–14,17,20–22]

Over the past few years, the knowledge on benign diseases such as autoimmune and groove pancreatitis has rapidly increased.[4] These diseases are likely to be underreported in the early years of our study because of unfamiliarity at the time. Revision of the slides of 39 patients with benign disease in three high-volume centers (AMC Amsterdam/EMC Rotterdam/UMC Utrecht) by two expert pathologists yielded 10 (26 %) additional cases of autoimmune ($n = 6$) and groove pancreatitis ($n = 4$), which were originally classified as chronic fibrosing pancreatitis or purulent inflammation. Surgery could potentially have been prevented in three of these cases, because they were now also recognized by the expert radiologists.

Future research should focus on reliable tumor markers and effective diagnostic strategies for suspected benign disease, so that the diagnosis of malignancy can be refuted with a high degree of certainty, as is currently the case with autoimmune cholangitis and autoimmune pancreatitis.[4]

In conclusion, this study shows that although some preoperative clinical and imaging characteristics might indicate the absence of malignancy, their discriminatory value is not sufficient for clinical use. Despite improvements in diagnostic imaging, a low percentage of unexpected benign disease after pancreatoduodenectomy seems yet inevitable. This uncertainty is important to keep in mind during multidisciplinary tumor board meetings and especially when counseling patients for pancreatoduodenectomy for presumed malignancy.

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APPENDIX

See Appendix Table 6.

TABLE 6 Diagnostic value of the presence of pain and absence of jaundice, mass, and double duct sign on CT for the prediction of benign disease

Predicted diagnosis	PA-confirmed diagnosis	
	Benign	Malignant
Benign	13	3
Malignant	57	205

Sensitivity 19 %, specificity 99 %, positive predictive value 48 %[a], negative predictive value 95 %[a], and overall accuracy 93 %[a]

* Taking into account the original benign:malignant ratio of 107:1,522

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