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Citation

Roessel, S. van, Soer, E. C., Daamen, L. A., Dalen, D. van, Sarasqueta, A. F., Stommel, M. W. J., ... Besselink, M. G. (2021). Preoperative misdiagnosis of pancreatic and periampullary cancer in patients undergoing pancreatoduodenectomy: a multicentre retrospective cohort study. *Ejso - European Journal Of Surgical Oncology*, 47(10), 2525-2532. doi:10.1016/j.ejso.2021.03.228

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).



Preoperative misdiagnosis of pancreatic and periampullary cancer in patients undergoing pancreatoduodenectomy: A multicentre retrospective cohort study



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ARTICLE INFO

Article history:

Received 24 November 2020

Received in revised form

16 February 2021

Accepted 3 March 2021

Available online 15 March 2021

Keywords:

Pancreatoduodenectomy

Neoadjuvant therapy

Pancreatic cancer

Distal cholangiocarcinoma

Epidemiology

Diagnosis

ABSTRACT

Introduction: Whereas neoadjuvant chemo(radio)therapy is increasingly used in pancreatic cancer, it is currently not recommended for other periampullary (non-pancreatic) cancers. This has important implications for the relevance of the preoperative diagnosis for pancreatoduodenectomy. This retrospective multicentre cohort study aimed to determine the frequency of clinically relevant misdiagnoses in patients undergoing pancreatoduodenectomy for pancreatic or other periampullary cancer.

Methods: Data from all consecutive patients who underwent a pancreatoduodenectomy between 2014 and 2018 were obtained from the prospective Dutch Pancreatic Cancer Audit. The preoperative diagnosis as concluded by the multidisciplinary team (MDT) meeting was compared with the final postoperative diagnosis at pathology to determine the rate of clinically relevant misdiagnosis (defined as missed pancreatic cancer or incorrect diagnosis of pancreatic cancer).

Results: In total, 1244 patients underwent pancreatoduodenectomy of whom 203 (16%) had a clinically relevant misdiagnosis preoperatively. Of all patients with a final diagnosis of pancreatic cancer, 13% (87/679) were preoperatively misdiagnosed as distal cholangiocarcinoma (n = 41, 6.0%), ampullary cancer (n = 27, 4.0%) duodenal cancer (n = 16, 2.4%), or other (n = 3, 0.4%). Of all patients with a final diagnosis of periampullary (non-pancreatic) cancer, 21% (116/565) were preoperatively incorrectly diagnosed as pancreatic cancer. Accuracy of preoperative diagnosis was 84% for pancreatic cancer, 71% for distal cholangiocarcinoma, 73% for ampullary cancer and 73% for duodenal cancer. A prediction model for the preoperative likelihood of pancreatic cancer (versus other periampullary cancer) prior to pancreatoduodenectomy demonstrated an AUC of 0.88.

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Discussion: This retrospective multicentre cohort study showed that 16% of patients have a clinically relevant misdiagnosis that could result in either missing the opportunity of neoadjuvant chemotherapy in patients with pancreatic cancer or inappropriate administration of neoadjuvant chemotherapy in patients with non-pancreatic periampullary cancer. A preoperative prediction model is available on www.pancreascalculator.com.

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Introduction

Pancreatoduodenectomy is performed for both pancreatic cancer and periampullary non-pancreatic cancer (i.e. distal cholangiocarcinoma, ampullary cancer, duodenal cancer). Each of these cancers differ in terms of prognosis and (neo)adjuvant treatment [1,2]. Based on recent randomized trials [3,4], preoperative chemo(radio)therapy is increasingly used in the treatment of pancreatic cancer, but not recommended for periampullary cancers according to the current guidelines [5,6]. Therefore, certainty about the diagnosis prior to pancreatoduodenectomy is important, as it determines the pretreatment strategy and, as such, has direct clinical consequences.

The most likely diagnosis is typically agreed on at multidisciplinary team (MDT) meeting by incorporating clinical presentation, laboratory tests, radiological characteristics and, if available, preoperative cytology/histology. Some studies have previously reported on the accuracy of preoperative diagnostics in pancreatic and periampullary tumours [7,8]. However, most studies only report on the significance of the various diagnostic modalities, such as cross-sectional imaging (CT/MRI) and endoscopic ultrasound (EUS), or investigate staging accuracy rather than distinguishing pancreatic from other periampullary cancers preoperatively [9–11]. No studies have evaluated the accuracy of the diagnosis prior to pancreatoduodenectomy based on all available information presented at the MDT meeting.

This multicentre cohort study aims to evaluate the accuracy and rate of clinically relevant misdiagnosis during the preoperative MDT in a large cohort of patients who underwent pancreatoduodenectomy for pancreatic or periampullary cancer.

Methods

Study design and data collection

All consecutive patients who underwent pancreatoduodenectomy in the Netherlands between January 2014 and December 2018 for cancer on final pathology were eligible for this study. Data were retrieved from the mandatory prospectively maintained nationwide Dutch Pancreatic Cancer Audit (DPCA). This audit covers all pancreatic resections and demonstrates a high degree of accuracy and case ascertainment [12]. Centres of the Dutch Pancreatic Cancer Group (DPCG) were asked to participate in the current study [13]. Additional variables, not available in the DPCA, were collected locally by each participating centre. Collected additional data were subsequently matched with the DPCA data based on an encrypted key ID, resulting in an anonymized dataset. Study proposals and data requests utilizing the DPCA are reviewed by the scientific board of the DPCG and need unanimous approval for research purposes [13]. Institutional Review Boards (IRB) of the participating institutions either gave ethical approval or waived the need for ethical approval due to the retrospective and anonymized nature of this study.

Preoperative work-up

The diagnostic workup for pancreatic and periampullary tumours is protocolized within the participating centres, yet minor inter-hospital differences might exist due to the multicentre nature of this study. A multiphase computed tomography (CT) scan of the abdomen, including arterial, venous, and portal contrast phase axial scans performed, using 3-mm slice thickness (i.e. pancreas protocol). As advised in the Dutch treatment guideline online in cases where the CT scan does not reveal a pancreatic or periampullary mass a EUS was performed. EUS is performed by or under the direct supervision of senior gastroenterologists. Contrast-enhanced EUS and elastography was rarely used. MRI is only performed in case of suspect lesions in the liver which cannot be characterized by CT. A weekly multidisciplinary tumour board is held each week and attended by at least one pancreatic surgeon, gastroenterologist, (interventional) radiologist, radiotherapist and pathologist. Each surgical case is discussed. No significant changes were made in the preoperative workup during the study period.

Definitions

Throughout this manuscript, pancreatic ductal adenocarcinoma is referred to as pancreatic cancer and all other non-pancreatic periampullary cancers (distal cholangiocarcinoma, ampullary, and duodenal cancer) are referred to as periampullary cancer. The preoperative diagnosis was collected from the report of the preoperative MDT meeting. When multiple diagnoses were mentioned (for example a differential diagnosis), only the most probable diagnosis was noted if explicitly mentioned or otherwise the first one mentioned. Final pathology was considered as reference standard in the current study. A clinically relevant misdiagnosis was defined as either pancreatic cancer preoperatively misdiagnosed as periampullary cancer, or periampullary cancer preoperatively misdiagnosed as pancreatic cancer. Also, the performed grossing technique during pathology assessment of the pancreatoduodenectomy specimen was collected, defined as either axial slicing as described by Verbeke et al., bivalving as described by Adsay et al., or as other or unknown [14,15]. Vascular involvement on imaging was defined as 90° or more on cross-sectional imaging. Survival was calculated as the time in months between date of diagnosis (if available, otherwise date of surgery) and date of death, or censored at the date of last time of follow-up. Neoadjuvant therapy for pancreatic cancer was not standard treatment during the study period and mostly administered in the setting of the DPCG PREOPANC trial and consisted of 3 courses of Gemcitabine with concurrent radiotherapy (15 × 2.4 Gy) [4]. Inclusion criteria for the PREOPANC trial (i.e. neoadjuvant therapy) were a WHO performance status of 0 or 1, and adequate hematologic, renal, and hepatic function. Exclusion criteria were cT1 tumour (<2 cm, without vascular involvement), history of malignancy within 5 years, and previous radiotherapy or chemotherapy that precluded

treatment.

Statistical analysis

Baseline characteristics were presented with median and interquartile range (IQR) for continuous variables and frequencies with proportions for categorical variables. Chi-square or Fisher's exact test were used for comparing categorical variables as appropriate and Wilcoxon rank-sum test for comparing continuous variables between groups. Preoperative and postoperative diagnoses were cross tabulated to assess accuracy and misdiagnosis rates. Accuracy was defined as the proportion of patients with a preoperative diagnosis that was concordant with final pathology (i.e. the predictive value of the preoperative diagnosis). Misdiagnosis rates were calculated as missed pancreatic cancer preoperatively (1-sensitivity) and incorrectly diagnosed pancreatic cancer preoperatively (1-specificity). A subgroup analysis was performed in all patients in whom preoperatively cytology or histology was performed. Post-hoc survival analyses (per-protocol) were performed using the Kaplan-Meier method and statistical differences between groups were tested using the log-rank test. To evaluate the potentially missed benefit from neoadjuvant therapy, survival of all pancreatic cancer patients was also evaluated in three groups; 1) pancreatic cancer patients who did not receive neoadjuvant therapy, 2) pancreatic cancer patients who did receive neoadjuvant therapy, and 3) pancreatic cancer patients who were preoperatively misdiagnosed as periampullary cancer and did not receive neoadjuvant therapy in accordance with national guidelines.

Predictive preoperative factors associated with correct diagnosis of pancreatic cancer (versus periampullary cancer) were assessed on univariable and multivariable logistic regression, with only statistically significant variables (i.e. P value below 0.05) on univariable analysis selected for the final model. Cut-off values for continuous variables were determined using the receiver operating characteristics (ROC-) curve with highest combination of sensitivity and specificity. Predictive accuracy of the final model was assessed with the area under the curve (AUC) of the ROC-curve. Two-sided P values of lower than 0.05 were considered statistically significant. All analyses were performed using R version 3.6.2 (cran.r-project.org).

Results

Baseline characteristics

In total, 1244 patients who underwent a pancreatoduodenectomy were included from seven DPCG centres. Of those, 679 (55%) underwent pancreatoduodenectomy for what ultimately appeared to be pancreatic cancer, 230 (19%) for distal cholangiocarcinoma, 215 (17%) for ampullary cancer, and 105 (8.4%) for duodenal cancer. Other cancers (15 patients, 1.2%) were mainly pancreatic metastases from renal cell cancer or colorectal cancer. Baseline characteristics are presented in [Table 1](#). Neoadjuvant therapy was administered in 97 patients (12% of all pancreatic cancer patients, 1.8% of all patients with periampullary cancer). Preoperative cytology/histology was performed in 932 out of 1244 patients (75%). Positive pathology (i.e. adenocarcinoma) was obtained in 473 out of 601 cytology assessments (79%) and 246 out of 331 histology assessments (74%). The prevailing grossing technique was axial slicing (799 patients, 64%), whereas bivalving was performed in 269 patients (22%), other techniques were used in 50 patients (4%) and technique was not reported in 126 patients (10%). The incidence of pancreatic and periampullary cancers did not differ between the axial slicing and bivalving technique ([supplementary table S1](#), $p = 0.37$).

Preoperative misdiagnosis

The preoperative and postoperative diagnosis are cross tabulated in [Table 2](#). Concordance with final pathology was 84% (592/708) for patients with the preoperative diagnosis of pancreatic cancer, 71% (145/203) for distal cholangiocarcinoma, 73% (146/201) for ampullary cancer, and 73% (85/116) for duodenal cancer. In total, 203 (16%) patients had a clinically relevant preoperative misdiagnosis. Of all patients with pancreatic cancer, 13% (87/679) were preoperatively misdiagnosed as periampullary cancer. Of all patients with periampullary cancer, 21% (116/565) were preoperatively misdiagnosed as pancreatic cancer. Concordance percentages with final pathology did not increase when preoperatively cytology or histology was obtained ([supplementary table S2](#)). Pancreatic cancer rates varied from 51% to 65% of all pancreatoduodenectomies per institution ($p = 0.14$). Preoperatively missed pancreatic cancer rates varied from 4% to 17% per institution ($p < 0.001$) and preoperatively misdiagnosed pancreatic cancer rates varied from 4% to 14% ($p < 0.001$), see [Table 3](#).

Preoperative factors associated with pancreatic cancer

On multivariable analysis, factors predictive of pancreatic cancer as compared to periampullary cancer were weight loss $> 10\%$ (odds ratio [OR] 1.47, 95% CI 1.06–2.04), CA 19.9 level > 160 u/mL (OR 1.50, 95% CI 1.09–2.05), any vascular involvement on imaging (OR > 3 for venous involvement, arterial involvement or both), tumour size > 20 mm (OR 1.49, 95% CI 1.10–2.02), and positive pathology obtained using EUS fine needle aspiration (OR 1.57, 95% CI 1.06–2.34) (see [Table 4](#)). Negative predictive factors for pancreatic cancer were location on imaging (ampullary region OR 0.09, 95% CI 0.06–0.14; duodenum OR 0.05, 95% CI 0.02–0.10) and positive pathology obtained using biopsy performed during gastro-duodenoscopy (OR 0.20, 95% CI 0.11–0.35) or using ERCP with brush (OR 0.51, 95% CI 0.35–0.70). The final model including all aforementioned predictors demonstrated an AUC of 0.88. The prediction model was turned into an online calculator (www.pancreascalculator.com, [Figure S3](#)).

Survival

[Fig. 1](#) shows survival after pancreatoduodenectomy stratified by preoperative diagnosis and postoperative pathology. Median overall survival was 18.7 months (95% CI 17.6–20.5) for patients with pathology-proven pancreatic cancer, 23.2 months (95% CI 19.4–28.5) for distal cholangiocarcinoma, 47.3 months (95% 27.6 – not reached) for ampullary cancer and 48.7 months (95% 40.2 – not reached) for duodenal cancer ($p < 0.001$). The difference in survival after resection of pancreatic cancer and distal cholangiocarcinoma was not statistically significant ($p = 0.17$), neither was the survival after ampullary and duodenal cancer ($p = 0.42$). [Fig. 2](#) shows survival of all patients who underwent pancreatoduodenectomy for pancreatic cancer stratified by three groups (per-protocol, not intention-to-treat). Patients with missed preoperative diagnosis of pancreatic cancer had a median overall survival of 21.5 months (95% CI 19.4–32.0) as compared to a median overall survival of 19.4 months (95% CI 17.8–21.4) of patients correctly diagnosed with pancreatic cancer who did not receive neoadjuvant therapy ($p = 0.08$). Patients with pancreatic cancer who received neoadjuvant therapy had median overall survival of 25.9 months (95% CI 21.4–42.3) which was significantly longer than patients with correctly diagnosed pancreatic cancer without neoadjuvant therapy ($p = 0.021$) but not compared to those with missed pancreatic cancer ($p = 0.69$).

Table 1
Baseline characteristics of 1244 patients who underwent pancreatoduodenectomy.

	Final pathology					P value
	Total cohort n = 1244 (100%)	Pancreatic cancer n = 679 (55%)	Distal cholangiocarcinoma n = 230 (19%)	Ampullary cancer n = 215 (17%)	Duodenal cancer n = 105 (8.4%)	
Age in years, median (IQR)	69 (61–75)	68 (61–74)	68 (60–75)	70 (63–76)	68 (60–75)	0.15
Male sex, n (%)	705 (57%)	379 (56%)	132 (57%)	121 (56%)	62 (59%)	0.92
Weight loss >10%, n (%)	331 (32%)	205 (37%)	50 (27%)	49 (26%)	25 (29%)	0.02
Preoperative lab						
Anaemia, n (%)	126/502 (25%)	64/269 (24%)	23/99 (23%)	15/82 (18%)	22/46 (48%)	0.002
Hypoalbuminemia, n (%)	89/275 (32%)	38/153 (25%)	27/58 (47%)	11/36 (31%)	13/27 (48%)	0.006
CA 19.9 level, median (IQR)	91 (26–294)	120 (35–410)	120 (42–324)	41 (15–142)	39 (11–120)	<0.001
CA 19.9 > 37 u/mL, n (%)	593/857 (69%)	357/481 (74%)	119/153 (78%)	83/152 (55%)	33/65 (51%)	<0.001
CEA level, median (IQR)	3 (2–5)	3 (2–5)	3 (2–5)	3 (2–5)	3 (2–5)	0.10
CEA > 7 u/mL, n (%)	97/646 (15%)	54/357 (15%)	16/107 (15%)	16/121 (13%)	10/56 (18%)	0.88
Location of tumour on imaging, n (%)						
Pancreatic head	535 (71%)	426 (91%)	62 (60%)	35 (30%)	7 (13%)	<0.001
Pancreatic body	16 (2.1%)	15 (3.2%)	0 (0%)	1 (0.9%)	0 (0%)	
Ampullary region	140 (19%)	23 (4.9%)	41 (40%)	65 (57%)	10 (19%)	
Duodenum	59 (7.9%)	6 (1.3%)	0 (0%)	14 (12%)	36 (68%)	
Vascular involvement on imaging, n (%)						
No vascular involvement	879 (71%)	365 (54%)	196 (85%)	206 (96%)	99 (94%)	<0.001
Yes, venous involvement (>90°)	265 (21%)	226 (33%)	27 (12%)	7 (3.3%)	3 (2.9%)	
Yes, arterial involvement (>90°)	25 (2.0%)	20 (2.9%)	2 (0.9%)	0 (0%)	3 (2.9%)	
Yes, both venous and arterial (>90°)	75 (6.0%)	68 (10%)	5 (2.2%)	2 (0.9%)	0 (0%)	
Tumour size (mm) on imaging, median (IQR)	24 (18–33)	25 (20–33)	20 (15–25)	22 (15–30)	40 (20–45)	<0.001
Preoperative biliary drainage, n (%)						
Yes, by ERCP	612 (49%)	329 (49%)	156 (68%)	113 (53%)	12 (8.4%)	<0.001
Yes, by PTC	52 (4.2%)	29 (4.3%)	10 (4.3%)	7 (3.3%)	5 (4.8%)	
No biliary drainage	580 (47%)	321 (47%)	64 (28%)	95 (44%)	88 (84%)	
Preoperative pathology obtained, n (%)						
Yes, cytology	601 (48%)	358 (53%)	154 (67%)	69 (32%)	14 (13%)	<0.001
Yes, histology	331 (27%)	102 (15%)	34 (15%)	116 (54%)	16 (71%)	
No pathology obtained	312 (25%)	129 (32%)	42 (18%)	30 (14%)	75 (15%)	
Positive pathology obtained through, n (%)						
No pathology obtained/no positive pathology	525 (42%)	327 (48%)	88 (38%)	72 (34%)	31 (30%)	<0.001
Duodenoscopy with biopsy	139 (11%)	19 (2.8%)	6 (2.6%)	67 (31%)	47 (45%)	
ERCP with brush	240 (19%)	104 (15%)	98 (43%)	34 (16%)	3 (2.9%)	
EUS with FNA	284 (23%)	214 (32%)	34 (15%)	28 (13%)	6 (5.7%)	
Other/unknown	56 (4.5%)	15 (2.2%)	4 (1.7%)	14 (6.5%)	18 (17%)	
Diagnosis on preoperative MDT meeting, n (%)						
Pancreatic cancer	708 (57%)	592 (87%)	70 (30%)	43 (20%)	3 (2.9%)	<0.001
Distal cholangiocarcinoma	203 (16%)	41 (6.0%)	145 (63%)	14 (6.5%)	1 (1.0%)	
Ampullary cancer	201 (16%)	27 (4.0%)	12 (5.2%)	146 (68%)	16 (15%)	
Duodenal cancer	116 (9.3%)	16 (2.4%)	3 (1.3%)	12 (5.6%)	85 (81%)	
Other cancer	16 (1.3%)	3 (0.4%)	0 (0%)	0 (0%)	0 (0%)	
Neoadjuvant treatment, n (%)	97 (7.8%)	83 (12.2%)	1 (0.4%)	6 (2.8%)	3 (2.9%)	<0.001

Missing values are omitted in calculation of the percentages. Cumulative percentages may not exactly equal 100% due to rounding. Missing values: age in 27 patients, weight loss for 214 patients, anaemia in 742 patients, hypoalbuminemia in 969 patients, CA 19.9 in 387 patients, CEA in 598 patients, tumour size on imaging in 513 patients, location on imaging in 494 patients.

Abbreviations: IQR, interquartile range; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; FNA, fine needle aspiration; MDT, multidisciplinary team.

Discussion

This multicentre cohort study of 1244 patients who underwent pancreatoduodenectomy demonstrated that 16% of the patients had a preoperative clinically relevant misdiagnosis. In view of the growing role of neoadjuvant treatment for (potentially) resectable pancreatic cancer this may lead to either missed treatment options or incorrect neoadjuvant treatment. 16% of patients with presumed pancreatic cancer, but did not have pancreatic cancer on final pathology, would receive unintended neoadjuvant treatment (116 out of 708 patients). Conversely, 16% of patients with presumed periampullary cancer, who in fact had pancreatic cancer would miss the opportunity of neoadjuvant therapy (87 out of 536 patients). Lastly, a prediction model including clinical, radiological and preoperative pathological parameters demonstrated an AUC of 0.88, which might be of help to systematically determine eligibility for clinical

trials on neoadjuvant therapy in pancreatic cancer.

Assessing eligibility for clinical trials on neoadjuvant therapy in pancreatic cancer is typically performed at the preoperative MDT meeting but remains challenging in some cases [16]. The recently published DPCG PREOPANC trial on neoadjuvant therapy in (borderline) resectable pancreatic cancer also included 9 patients (4%) with distal cholangiocarcinoma on final pathology [4]. Another neoadjuvant trial from South Korea did not report on misdiagnosed patients [3]. The misdiagnosis rate of 4% in the PREOPANC trial is lower than found in this study (ranging from 5 to 14% per institution). Presumably, patients with an ambivalent preoperative tumour origin were not included to avoid contamination with non-pancreatic cancer patients in this trial. As mentioned before, during the study period neoadjuvant therapy was only administered in trial setting. This explains the low rate of neoadjuvant therapy for patients with pancreatic cancer (12%). Based on the of the Dutch

Table 2
Cross tabulation preoperative and postoperative diagnoses of 1244 patients who underwent pancreatoduodenectomy.

Preop. diagnosis	Postop. diagnosis					
	Pancreatic cancer	Distal cholangiocarcinoma	Final pathology Ampullary cancer	Duodenal cancer	Other cancer	Total
Pancreatic cancer	592 84% (row) 87% (column)	70 9.9% 30%	43 6.1% 20%	3 0.4% 2.9%	0 0% 0%	708 57% (column)
Distal cholangiocarcinoma	41 20% (row) 6.0% (column)	145 71% 63%	14 6.9% 6.5%	1 0.5% 1.0%	2 1.0% 13%	203 16%
Ampullary cancer	27 13% (row) 4.0% (column)	12 6.0% 5.2%	146 73% 68%	16 8.0% 15%	0 0% 0%	201 16%
Duodenal cancer	16 14% (row) 2.4% (column)	3 2.6% 1.3%	12 10% 5.6%	85 73% 81%	0 0% 0%	116 9.3%
Other cancer	3 19% (row) 0.4% (column)	0 0% 0%	0 0% 0%	0 0% 0%	13 81% 87%	16 1.3%
Total	679 55% (row)	230 19%	215 17%	105 8.4%	15 1.2%	1244

The first percentage is a row percentage and the second percentage a column percentage. Cumulative percentages may not exactly equal 100% due to rounding.

Table 3
Clinically relevant preoperative misdiagnosis rates for pancreatic cancer.

Centre	Total n	Pathology confirmed Pancreatic cancer, n (%)	Missed pancreatic cancer preoperatively, n (%)	Misdiagnosed as pancreatic cancer preoperatively, n (%)
Institution 1	291	153 (53%)	16 (5%)	17 (6%)
Institution 2	160	91 (57%)	6 (4%)	23 (14%)
Institution 3	186	95 (51%)	11 (6%)	26 (14%)
Institution 4	200	107 (54%)	11 (6%)	9 (5%)
Institution 5	151	98 (65%)	25 (17%)	12 (8%)
Institution 6	161	81 (50%)	12 (7%)	23 (14%)
Institution 7	95	54 (57%)	6 (6%)	6 (6%)
P value ^a		0.14	<0.001	<0.001
Total	1244	679 (55%)	87 (7%)	116 (9%)

Shown percentages are of the total of patients per institution.

^a Chi-square tests to test statistical differences among institutions.

randomized PREOPANC trial, neoadjuvant chemo-radiotherapy has now (February 2021) become the standard approach to borderline resectable pancreatic cancer in the Netherlands [4]. For all other periampullary cancers, the current Dutch guideline does not advise neoadjuvant treatment as is probably the case in most countries worldwide. Identifying patients who qualify for neoadjuvant therapy should be patient-tailored and based on patient- and tumour characteristics (including patient preference). The current workup for neoadjuvant therapy requires extra invasive tests, yet when these are overcome, neoadjuvant therapy might offer oncological benefits as suggested by several studies [3,4]. The trade-off between risk and benefits is up to the particular treating physician to discuss with the patient.

Pancreatic cancer and distal cholangiocarcinoma are from an oncological perspective very comparable entities in terms of tumour biology and prognosis [17]. These cancers are also not histologically distinguishable, neither morphologically nor immunohistochemically. Final diagnosis is based on macroscopic

assessment by the pathologist of the most likely origin (e.g., pancreas or bile duct) of the cancer in the resected specimen. Since (randomized) studies on neoadjuvant therapy for (borderline) resectable distal cholangiocarcinoma are still lacking, one cannot exclude the possibility that these patients might also benefit from comparable preoperative chemotherapy as in pancreatic cancer. Some non-randomized series indeed suggest a survival benefit for neoadjuvant therapy in distal cholangiocarcinoma [18]. If this were to be proven correct, than the definition of clinically relevant misdiagnosis would change and shift towards a distinction between pancreatobiliary cancer (i.e. preoperative chemotherapy recommended) and ampullary-duodenal cancer (i.e. not requiring preoperative chemotherapy). In theory, the clinically relevant misdiagnosis rate according to such a definition would decrease to 9.9% (124 out of 1244 patients) in this study. Although the rationale of neoadjuvant therapy also being effective for distal cholangiocarcinoma is still speculative, distinction based on histologic subtype (pancreatobiliary versus intestinal) might be more sound

Table 4
Univariable and multivariable analysis of predictors to distinguish pancreatic cancer from non-pancreatic periampullary cancer preoperatively.

	Pancreatic cancer, %	Periampullary cancer, %	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age > 65 years	61%	63%	0.94 (0.74–1.18)	0.61		
Male sex	56%	58%	1.08 (0.86–1.35)	0.51		
Weight loss > 10%	36%	27%	1.54 (1.21–1.97)	<0.001	1.47 (1.06–2.04)	0.02
Anaemia	24%	26%	0.88 (0.68–1.14)	0.32		
CA 19.9 > 160 u/mL	44%	29%	1.88 (1.48–2.38)	<0.001	1.50 (1.09–2.05)	0.01
CEA > 5 ng/mL	27%	25%	1.08 (0.84–1.40)	0.54		
Location on imaging						
Pancreatic head	90%	39.5%	2.75 (2.36–3.21)	<0.001	Ref	–
Pancreatic body	3.2%	4.6%	3.05 (0.99–14.67)	0.09	2.80 (0.83–14.69)	0.14
Ampullary region	5.1%	40.3%	0.06 (0.04–0.08)	<0.001	0.09 (0.06–0.14)	<0.001
Duodenum	1.3%	19.8%	0.03 (0.01–0.05)	<0.001	0.05 (0.02–0.10)	<0.001
Vascular involvement						
No vascular involvement	54%	91%	0.71 (0.62–0.81)	<0.001	Ref	–
Venous involvement	33%	6.9%	8.16 (5.73–11.91)	<0.001	3.73 (2.48–5.73)	<0.001
Arterial involvement	2.9%	0.9%	5.63 (2.26–17.05)	<0.001	4.75 (1.41–20.81)	0.02
Both venous and arterial	10%	1.2%	13.68 (6.66–33.06)	<0.001	4.48 (2.55–13.71)	<0.001
Tumour size > 20 mm	66%	56%	1.51 (1.20–1.90)	<0.001	1.49 (1.10–2.02)	0.01
Preoperative pathology						
No positive pathology	48%	35%	1.65 (1.39–1.97)	<0.001	Ref	–
Duodenoscopy biopsy	2.8%	21%	0.10 (0.06–0.16)	<0.001	0.20 (0.11–0.35)	<0.001
ERCP with brush	15%	24%	0.46 (0.34–0.63)	<0.001	0.51 (0.35–0.75)	<0.001
EUS with FNA	32%	12%	1.85 (1.35–2.57)	<0.001	1.57 (1.06–2.34)	0.03
Other/unknown	2.2%	7.3%	0.22 (0.12–0.40)	<0.001	0.33 (0.14–0.77)	0.01

Abbreviations: OR, odds ratio; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration.

Cumulative percentages may not exactly equal 100% due to rounding.

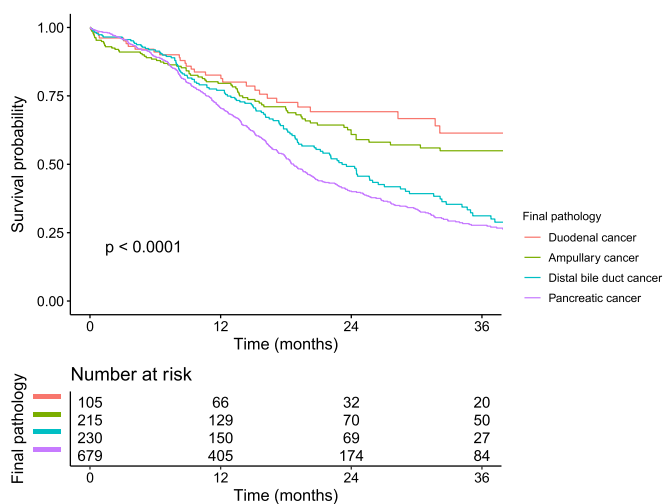


Fig. 1. Survival after pancreatoduodenectomy stratified by final diagnosis based on pathology.

than distinction based on anatomical site of tumour origin [19]. Further studies on the efficacy of neoadjuvant regimens for periampullary cancers are to be awaited, as is conclusive evidence on the effect of neoadjuvant therapy for (resectable) pancreatic cancer.

Our study also demonstrates that survival after resection of pancreatic cancer and distal cholangiocarcinoma is comparable. Prognoses after resection of ampullary cancer and duodenal cancer are also comparable but considerably more favourable than pancreatic cancer and distal cholangiocarcinoma. When looking further at the survival curves of patients who underwent pancreatoduodenectomy for pancreatic cancer, neoadjuvant therapy was associated with improved survival (26 months with neoadjuvant therapy versus 19 months without neoadjuvant therapy, $p = 0.021$). Interestingly, patients whose pancreatic cancer

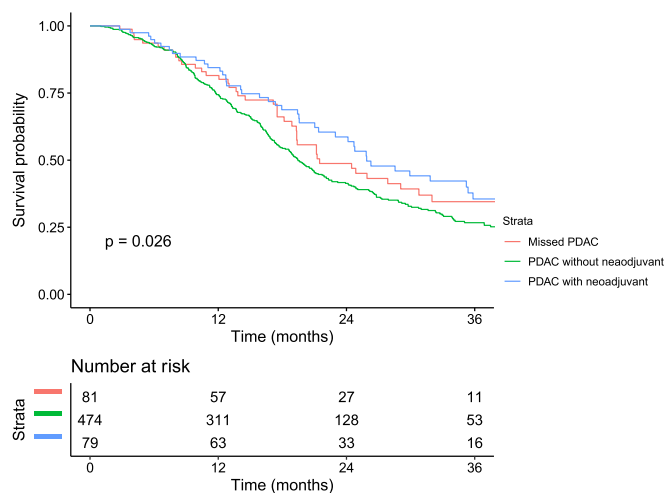


Fig. 2. Survival after pancreatoduodenectomy of patients with pancreatic cancer, stratified by preoperative diagnosis and preoperative treatment. Legend: PDAC = pancreatic ductal adenocarcinoma.

diagnosis was missed preoperatively had a median overall survival of 22 months, which did not significantly differ from those with a correct pancreatic cancer diagnosis whether or not treated with neoadjuvant therapy. It is unclear whether this is due to a type II-error (underpowered) or that patients with a missed pancreatic cancer diagnosis actually had more favourable disease (more similarities with periampullary cancers).

While final pathology was considered the reference standard in this study, it should be kept in mind that even during pathology assessment distinction between pancreatic and periampullary can be very challenging [20]. The frequent reclassification of tumour origin following slide review, and the wide variation in published incidence of pancreatic (33–89%), ampullary (5–42%) and distal

bile duct (5–38%) cancers indicate that the histopathological distinction between these cancer groups is less accurate than generally believed [21]. The different types of cancers emerge from a continuum of duodenum-ampulla-distal bile duct-pancreatic duct junction, basically hampering to distinguish truly different entities as they are biologically, histologically and embryologically ambiguous [17,22]. Tumour markers and other molecular techniques might further help to distinguish these different types of cancer, preferably prior to surgical/oncological treatment [23–25]. At the same time, more potent chemotherapeutic regimens become available, such as FOLFIRINOX, which shows to be an effective treatment against a broad spectrum of tumours [26]. It will be interesting to watch the outcome of future randomized trials assessing the impact of neoadjuvant FOLFIRINOX in the other periampullary (non-pancreatic) cancers.

Currently, the exact diagnosis on final pathology remains of paramount importance, since it determines the indication for adjuvant treatment. Adjuvant therapy after resection of distal cholangiocarcinoma remains controversial [5,6,27]. In some countries, adjuvant therapy is standard of care, whereas in the Netherlands it is only administered in trial setting [28]. Distinguishing pancreatic cancer and distal cholangiocarcinoma also depends on many pathological parameters, including grossing technique, level of expertise, tumour size, et cetera. In the present study, the incidence of pancreatic and periampullary cancers did not differ considerably between performed grossing technique (Table S1). The exact cause of the wide variability in reported pathology outcomes by different centres (Table 3) remains unknown. It might be partly explained by the unclear classification of (peri) ampullary tumours and the lack of consensus on what is the basis of the classification (macroscopy vs. microscopy vs. immunohistochemistry). This study did not include data on patients with ultimately benign disease since we studied this topic several years ago. In 1629 consecutive pancreatoduodenectomies in the Netherlands (2003–2010) we found a 6.6% rate of unexpected design disease [7].

This study has some limitations. First, when multiple preoperative diagnoses were considered (i.e. a differential diagnosis) this was not taken into account in the analyses. For each patient one preoperative diagnosis was extracted from the MDT report, either the first one listed in the differential diagnosis or the most probable one if explicitly mentioned. Therefore, clinical (un)certainly of the preoperative diagnosis is not reflected. Second, the diagnosis on final pathology is not always entirely independent, as the pathologist might also incorporate preoperative diagnostic findings in his/her judgment. Misdiagnosis rates might even be higher in case of completely independent assessments. Third, the retrospective nature of additional data collection might have led to information bias. Additional data collection might have been influenced by information already known, either from the prospective database or from other clinical information in the medical chart. Also, the neoadjuvantly treated patients are mostly trial participants and are therefore carefully screened for eligibility criteria. Besides, the survival curves are not based on an intention-to-treat principle and should therefore not be interpreted as such. Hence, these figures are solely for illustrative purposes and one should not draw hard conclusions from these survival estimates.

In conclusion, this is the first study to evaluate the accuracy of the preoperative diagnosis as established during MDT meeting before pancreatoduodenectomy. One in every six patients planned for oncological resection is misdiagnosed either as pancreatic cancer or periampullary cancer. With the increasing use of neoadjuvant therapy for pancreatic cancer (and no indication for neoadjuvant therapy for periampullary cancers), this finding warrants further research to reduce the rate of clinically relevant misdiagnoses.

Financial disclosures

None to declare.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2021.03.228>.

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