Microscopic resection margin status in pancreatic ductal adenocarcinoma: a nationwide analysis

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Microscopic resection margin status in pancreatic ductal adenocarcinoma – A nationwide analysis

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ABSTRACT

Introduction: First, this study aimed to assess the prognostic value of different definitions for resection margin status on disease-free survival (DFS) and overall survival (OS) in pancreatic ductal adenocarcinoma (PDAC). Second, preoperative predictors of direct margin involvement were identified.
Materials and methods: This nationwide observational cohort study included all patients who underwent upfront PDAC resection (2014–2016), as registered in the prospective Dutch Pancreatic Cancer Audit. Patients were subdivided into three groups: R0 (≥1 mm margin clearance), R1 (<1 mm margin clearance) or R1 (direct margin involvement). Survival was compared using multivariable Cox regression analysis. Logistic regression with baseline variables was performed to identify preoperative predictors of R1 (direct).
Results: 595 patients with a median OS of 18 months (IQR 10-32 months) months were analysed. R0 (≥1 mm) was achieved in 277 patients (47%), R1 (<1 mm) in 146 patients (24%) and R1 (direct) in 172 patients (29%). R1 (direct) was associated with a worse OS, as compared with both R0 (≥1 mm) (hazard

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ratio (HR) 1.35 [95% and confidence interval (CI) 1.08–1.70); P < 0.01) and R1 (<1 mm) (HR 1.29 [95%CI 1.01–1.67]; P < 0.05). No OS difference was found between R0 (≥1 mm) and R1 (<1 mm) (HR 1.05 [95% CI 0.82–1.34]; P = 0.71). Preoperative predictors associated with an increased risk of R1 (direct) included age, male sex, performance score 2–4, and venous or arterial tumour involvement.

Conclusion: Resection margin clearance of <1 mm, but without direct margin involvement, does not affect survival, as compared with a margin clearance of ≥1 mm. Given that any vascular tumour involvement on preoperative imaging was associated with an increased risk of R1 (direct) resection with upfront surgery, neoadjuvant therapy might be considered in these patients.

Introduction

Resection margin status is an important prognostic factor for survival after resection of pancreatic ductal adenocarcinoma (PDAC) [1,2]. However, the microscopic margin clearance defining a complete resection remains a matter of debate. Both the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) previously considered tumour resection to be complete (R0) in case of a margin clearance of >0 mm and incomplete (R1) when tumour cells directly infiltrate the surgical margin [3,4]. However, there is evidence to support a "1 mm rule" for defining completeness of PDAC resections. This rule indicates significantly improved survival for resections with a margin clearance of ≥1 mm as compared with a margin clearance of <1 mm [5–7]. Accordingly, the AJCC has changed their definitions to R0 (≥1 mm) and R1 (<1 mm) in its latest edition, whilst the UICC kept the R0 (>0 mm) and R1 (direct) definitions [8,9]. Further research showed that survival was significantly worse in patients with R1 (direct) resections as compared with R1 (<1 mm), supporting an additional subdivision of the R1 definition [10].

Unfortunately, the different definitions for resection margin status impede a proper comparison of the literature and contribute to widespread reported R0 rates between 15% and 83% [11]. Therefore, uniform and generalizable definitions are of great importance and merit further investigation. In the Netherlands, a pathology protocol for synoptic reporting of pancreatic cancer was released in 2015 by the nationwide Pathological-Anatomical National Automated Archive (PALGA). All pathology laboratories are affiliated to this network, subsequently improving standardization.

Neoadjuvant treatment strategies with chemo (radio)therapy are increasingly considered to downsize the tumour, increase margin-negative resection rates, and for early treatment of micrometastases [12,13]. Preoperative stratification of patients with a high risk of a positive surgical margin, in whom neoadjuvant therapy might be an option, could therefore be useful. First, we aimed to assess the prognostic significance of different definitions for R0 and R1 resections, in a nationwide cohort of unselected PDAC patients who underwent pancreatoduodenectomy without neoadjuvant treatment. Second, preoperative predictors of a positive surgical margin were identified.

Methods

Study design

A multicentre observational cohort study was performed, in which all 16 Dutch centres for pancreatic cancer surgery participated. All patients who underwent macroscopically complete resection of histologically proven (borderline) resectable PDAC between 2014 and 2016, as registered in the nationwide, mandatory, prospective database of the Dutch Pancreatic Cancer Audit, were included. Exclusion criteria were missing information on resection margin status, 90-day mortality not related to early disease recurrence, and neoadjuvant chemo(radio)therapy. Patients with a primary diagnosis of locally advanced PDAC were also excluded, as these patients are normally initially treated with systemic therapy.

Data collection

Baseline characteristics were extracted from the prospective clinical audit database. According to the Dutch Pancreatic Cancer Group criteria, patients were deemed to have locally advanced PDAC in case of arterial involvement >90° or venous involvement >270° or occlusion [14]. Borderline resectable PDAC was defined as arterial involvement ≤90°, or 90°–270° venous contact without occlusion [14]. Data on follow-up, detection of PDAC recurrence and survival were collected retrospectively from the patients' records within each participating hospital, and pathology reports were acquired. Tumours were staged according to the 8th AJCC TNM classification [8]. Techniques for dissection of the pancreatic specimen included axial slicing and bi-valving along the common bile duct [15,16]. Margin status was determined for the transection margins (pancreatic neck, proximal and distal enteric margins, and common bile duct), as well as for the circumferential resection margins (posterior, superior mesenteric artery (SMA) and superior mesenteric vein/portal vein (SMV/PV) margins, or combined vascular groove margin if not separately reported). Based on the closest margin, patients were subdivided into three groups: R0 (≥1 mm), meaning a margin clearance of 1 mm or more; R1 (<1 mm), defined as a margin clearance of less than 1 mm but no direct margin involvement; and R1 (direct), comprising infiltration of tumour cells directly into one of the margins. Isolated involvement of the anterior margin was not deemed R1, as this is considered a free anatomical surface rather than a true resection margin [15,17]. In case of uncertainty, resection margin status was discussed with a specialized pathologist. For R1 (<1 mm) or R1 (direct), the number and location of involved margin(s) were obtained. To determine the extent of tissue sampling, the number of tumour blocks were counted.

Outcomes

Our primary focus was the prognostic value of the different definitions for resection margin status on disease-free survival (DFS) and overall survival (OS). PDAC recurrence was either pathologically proven, or suspected through cross-sectional imaging. DFS was measured from the date of resection until the date of recurrence diagnosis. OS was defined as the time from the date of resection to the date of death from any cause or last follow-up. If survival data were missing, patients were censored at the time of their last follow-up. DFS and OS were compared between patients with R0 (≥1 mm), R1 (<1 mm) and R1 (direct) resections. Also, recurrence and survival rates were compared after regrouping of

patients according to the 8th AJCC guidelines, i.e. R0 (≥1 mm) and R1 (<1 mm), and 8th UICC guideline definitions, i.e. R0 (>0 mm) and R1 (direct), and the impact of the number of R1 margins was evaluated.

Our secondary focus was to identify preoperative predictors of an R1 (direct) resection in patients with (borderline) resectable PDAC who undergo upfront pancreatoduodenectomy.

Statistical analysis

Descriptive statistics were used to compare baseline characteristics between patients with R0 (≥1 mm), R1 (<1 mm) and R1 (direct) status. Parametric continuous variables were reported as mean ± standard deviation (SD) and compared using one-way ANOVA. Non-parametric continuous variables were reported as median (interquartile range [IQR]) and compared using the Kruskal-Wallis rank sum test. Categorical parameters were presented as frequencies and compared using the Chi-square test or Fishers' exact test. To account for missing data, multiple imputation was performed according to a Markov chain Monte Carlo method (5 imputations, 10 iterations) [18,19]. Kaplan-Meier curves were used to estimate unadjusted median DFS and OS and their 95% confidence intervals (CI), and compared using the log-rank test. Hazard ratios (HRs) with 95% CIs for DFS and OS were obtained through univariate Cox-proportional hazard analysis. Multivariable Cox-proportional hazard analysis was performed to assess the association between resection margin status and both DFS and OS, adjusted for potential confounders including age, sex, Eastern Cooperation Oncology Group (ECOG) performance score, preoperative serum CA 19–9, vascular resection, T- and N-stage, tumour differentiation, lymphovascular and perineural invasion, major postoperative complications and adjuvant chemotherapy. A two-tailed *P*-value of <0.05 indicated statistically significance.

Multivariable logistic regression with baseline variables was performed to assess which preoperative factors were independently associated with an R1 (direct) resection. Potential preoperative predictors included age, sex (male vs. female), BMI, ECOG performance score (2–4 vs. 0–1), log serum carbohydrate antigen (CA) 19–9, and radiologically assessed tumour size, venous tumour involvement (<90°, 90–180° and 180–270° vs. no involvement), arterial tumour involvement (<90° vs. no involvement), and presence of lymph nodes ≥10 mm on CT imaging (yes vs. no). Odds ratios (OR) obtained from both univariate and multivariable were presented with 95% CIs. Statistical analyses were performed using R version 3.5.1 (Bell Laboratories, NH, USA), including the "survival", "ggplot", and "mice" packages.

Results

A total of 595 patients were included, with a median follow-up of 38 months (IQR 31–48 months), and a median OS of 18 months (IQR 10–32 months) (Table 1). Pylorus preserving pancreatoduodenectomy was performed in 357 patients (60%) and a Whipple procedure in 238 patients (40%). Of 515 patients with a known recurrence status, 422 patients (82%) developed PDAC recurrence after a median DFS of 11 months (IQR 6–25 months).

Of all patients, R0 (≥1 mm) resection was achieved in 277 patients (47%), whereas respectively 146 patients (24%) and 172 patients (29%) had R1 (<1 mm) and R1 (direct) resections (Table 1). Between these groups, there were significant differences in age, radiologically assessed venous and arterial involvement, presence of lymphadenopathy on preoperative imaging, vascular resection, tumour differentiation, lymphovascular and perineural invasion, number of tissue blocks pathologically examined, number of positive lymph nodes, pathologically assessed tumour size, and corresponding T, N and TNM stages (Table 1). R1 (<1 mm) resections most frequently involved the SMV/PV margin (31%), combined vascular bed (22%), or posterior margin (21%). R1 (direct) mostly comprised the SMV/PV margin (25%), multiple margins (22%), or pancreatic neck (18%).

PDAC recurrence and overall survival

Median DFS was 10 months (95% CI 8–11 months) for patients with R1 (direct) resections, as compared with 12 months (95% CI 11–16 months) for patients with R1 (<1 mm) resections (HR 1.29 [95% CI 1.01–1.64]; $P = 0.04$) and 14 months (12–17 months) for patients with R0 (≥1 mm) resections (HR 1.57 [95% CI 1.27–1.94]; $P < 0.001$) (Fig. 1A; Table 2). The difference between R1 (<1 mm) and R0 (≥1 mm) resections resulted in a HR of 1.22 (95% CI 0.97–1.52) ($P = 0.08$).

Median OS was 14 months (95% CI 13–17 months) for patients with R1 (direct) resections, as compared with 19 months (95% CI 17–24 months) for patients with R1 (<1 mm) resections (HR 1.37 [95% CI 1.07–1.76]; $P = 0.01$) and 21 months (95% CI 18–28 months) for patients with R0 (≥1 mm) resections (HR 1.58 [95% CI 1.27–1.97]; $P < 0.001$) (Fig. 1B; Table 2). The difference between R1 (<1 mm) and R0 (≥1 mm) resections resulted in a HR of 1.15 (95% CI 0.91–1.46; $P = 0.24$).

Multivariable analysis showed that R1 (direct) resection was independently associated with a worse DFS, as compared with R0 (≥1 mm) (HR 1.31 [95% CI 1.06–1.64]; $P < 0.05$), whilst R1 (<1 mm) was not (HR 1.12 [95% CI 0.89–1.41]; $P = 0.34$) (Table 3). DFS did not significantly differ when comparing R1 (direct) with R1 (<1 mm) (HR 1.17 [95% CI 0.92–1.50]; $P = 0.20$). Moreover, R1 (direct) was independently associated with a worse OS, as compared with both R0 (≥1 mm) (HR 1.35 [95% CI 1.08–1.70); $P < 0.01$) and R1 (<1 mm) (HR 1.29 [95% CI 1.01–1.67]; $P < 0.05$). The hazard ratio for OS reflected no difference between R0 (≥1 mm) and R1 (<1 mm) (HR 1.05 [95% CI 0.82–1.34]; $P = 0.71$).

AJCC and UICC definitions

When applying the R0 and R1 definitions of the 8th AJCC guidelines, 277/595 patients (47%) had an R0 (≥1 mm) resection, whilst the resection was considered R1 (<1 mm) in 318/595 patients (53%) (Table 2). According to the 8th UICC definitions, 423/595 patients (71%) had an R0 (>0 mm) resection and 172/595 (29%) had an R1 (direct) resection.

Using the R0 (≥1 mm) and R1 (<1 mm) definitions of the 8th AJCC edition, both DFS and OS were worse for patients with R1 resections, as compared with R0 resections. This resulted in a HR of 1.39 (95% CI 1.16–1.67) ($P < 0.001$) for DFS and 1.36 (95% CI 1.13–1.64) ($P < 0.01$) for OS (Table 2; Fig. 2AB). Using the 8th UICC definitions for R0 (>0 mm) and R1 (direct) resections, R1 resection was also associated with poor DFS and OS, as compared with R0 resection, reflected by a HR of 1.46 (95% CI 1.21–1.78) ($P < 0.001$) and 1.50 (95% CI 1.23–1.84) ($P < 0.001$) for respectively DFS and OS (Table 2; Fig. 2CD). For both definitions, the number of R1 margins was found to be negatively associated with DFS and OS, with an increase in number of R1 margins resulting in an increased hazard of disease recurrence and death (Table 2).

Preoperative predictors of R1 (direct) resection

Baseline variables that were independently associated with an R1 (direct) resection included increased age, male sex, ECOG performance score 2–4, and any venous or arterial tumour involvement (Supplementary Table 1).

Table 1
Baseline characteristics of 595 PDAC patients after pancreatoduodenectomy stratified by resection margin status.

	Missing, n (%)	Total, n = 595	R0 (≥1 mm)*, n = 277 (47%)	R1 (<1 mm)*, n = 146 (24%)	R1 (direct)*, n = 172 (29%)	*P* Value
Age in years, mean ± SD	0 (0)	67 ± 9	67 ± 9	67 ± 9	69 ± 9	0.04
Male sex, n (%)	0 (0)	329 (55)	149 (54)	74 (51)	106 (62)	0.12
BMI in kg/m^2, mean ± SD	3 (1)	25 ± 4	25 ± 4	25 ± 4	24 ± 4	0.40
Charlson Age-Comorbidity Index, n (%)	0 (0)					0.51
<4		319 (54)	147 (53)	84 (58)	88 (51)	
≥4		276 (46)	130 (47)	62 (43)	84 (49)	
ECOG performance score at primary diagnosis, n (%)	230 (39)					0.12
0–1		325 (89)	155 (91)	89 (92)	81 (84)	
2–4		40 (11)	16 (9)	8 (8)	16 (17)	
Preoperative serum CA 19–9, median (IQR)	199 (33)	170 (42–524)	145 (38–470)	160 (40–480)	199 (46–685)	0.40
Tumour size on CT imaging in cm, mean ± SD	182 (31)	2.9 ± 1.1	2.8 ± 1.1	2.8 ± 1.0	2.9 ± 1.0	0.79
Resectability primary tumour**	41 (7)					<0.001
Resectable		422 (76)	223 (86)	85 (66)	114 (68)	
Borderline resectable		132 (24)	35 (14)	44 (34)	53 (32)	
Vascular involvement on CT imaging, n (%)						
Venous involvement	50 (8)					<0.001
No		352 (65)	200 (78)	65 (51)	87 (53)	
<90°		74 (14)	24 (9)	21 (17)	29 (18)	
90–180°		102 (19)	26 (10)	37 (29)	39 (24)	
180–270°		17 (3)	5 (2)	4 (3)	8 (5)	
Arterial involvement	43 (7)					0.03
No		528 (96)	252 (98)	122 (95)	154 (93)	
<90°		24 (4)	5 (2)	7 (5)	12 (7)	
Lymph nodes ≥ 10 mm on CT imaging, n (%)	43 (7)	83 (15)	29 (11)	26 (20)	28 (17)	0.07
Type of surgery, n (%)	2 (0)					0.44
Open		549 (93)	252 (91)	137 (94)	160 (94)	
Laparoscopic		42 (7)	24 (9)	8 (5)	10 (6)	
Robot-assisted		2 (0)	0 (0)	1 (1)	1 (1)	
Type of resection, n (%)	0 (0)					0.90
Whipple		238 (40)	111 (40)	56 (38)	71 (41)	
PPPD		357 (60)	166 (60)	90 (62)	101 (59)	
Vascular resection, n (%)	2 (0)	156 (26)	47 (17)	45 (31)	64 (37)	<0.001
Pathologic tumour size in cm, mean ± SD	6 (1)	3.2 ± 1.2	3.0 ± 1.0	3.2 ± 1.1	3.4 ± 1.1	<0.001
Tumour differentiation, n (%)	62 (10)					<0.01
Well		72 (14)	45 (18)	15 (11)	12 (8)	
Moderate		287 (54)	111 (45)	82 (61)	94 (61)	
Poor		174 (33)	90 (37)	37 (28)	47 (31)	
Microscopic lymphovascular invasion, n (%)	152 (26)	303 (68)	131 (64)	73 (66)	99 (77)	0.05
Microscopic perineural invasion, n (%)	72 (12)	473 (90)	197 (85)	130 (94)	146 (85)	<0.01
Number of tissue blocks pathologically examined, median (IQR)	2 (0)	13 (10–18)	13 (10–17)	13 (10–17)	14 (11–19)	<0.01
Location of R1 resection, n (%)	NA					NA
Pancreatic neck		NA	NA	3 (2)	31 (18)	
SMA		NA	NA	15 (10)	10 (6)	
SMV/PV		NA	NA	45 (31)	43 (25)	
Vascular groove		NA	NA	32 (22)	24 (14)	
Posterior		NA	NA	31 (21)	21 (12)	
Distal bile duct		NA	NA	0 (0)	2 (1)	
Multiple		NA	NA	20 (14)	38 (22)	
Proximal enteric		NA	NA	0 (0)	3 (2)	
T stage 8th AJCC edition, n (%)	6 (1)					0.02
T1		84 (14)	49 (18)	18 (12)	17 (10)	
T2		420 (71)	196 (72)	104 (72)	120 (70)	
T3		85 (14)	28 (10)	23 (16)	34 (20)	
N stage 8th AJCC edition, n (%)	2 (0)					<0.01
N0		145 (25)	83 (30)	33 (23)	29 (17)	
N1		235 (40)	110 (40)	59 (40)	66 (39)	
N2		213 (36)	83 (30)	54 (37)	67 (44)	
Positive lymph nodes, median (IQR)	2 (0)	2 (1–5)	2 (0–4)	2 (1–5)	3 (1–6)	<0.001
Total lymph nodes, median (IQR)	11 (2)	15 (11–21)	15 (11–20)	16 (11–21)	14 (11–21)	0.84
TNM stage 8th AJCC edition, n (%)	8 (1)					0.04
IA		29 (5)	19 (7)	7 (5)	3 (2)	
IB		101 (17)	56 (21)	23 (16)	22 (13)	
IIA		12 (2)	6 (2)	3 (2)	3 (2)	
IIB		233 (40)	109 (40)	58 (40)	66 (39)	
III		212 (36)	82 (30)	54 (37)	76 (45)	
Major postoperative complications, n (%)	0 (0)	136 (23)	68 (25)	30 (21)	38 (22)	0.62
Hospital stay in days, median (IQR)	0 (0)	11 (8–17)	12 (8–16)	11 (8–18)	11 (9–17)	0.99
Adjuvant chemotherapy, n (%)	23 (4)	384 (67)	184 (69)	99 (69)	101 (63)	0.37
PDAC recurrence, n (%)	80 (13)	422 (82)	179 (76)	108 (85)	135 (89)	<0.01
Disease-free survival in months, median (IQR)		11 (6–25)	13 (6–29)	12 (6–24)	9 (5–16)	<0.01

(*continued on next page*)

Table 1 (*continued*)

	Missing, n (%)	Total, n = 595	R0 (≥1 mm)*, n = 277 (47%)	R1 (<1 mm)*, n = 146 (24%)	R1 (direct)*, n = 172 (29%)	*P* Value
Location of initial recurrence, n (%)	16 (3)					0.13
Local only		89 (22)	34 (20)	28 (26)	27 (21)	
Liver only		55 (14)	33 (19)	10 (9)	12 (9)	
Lung only		23 (6)	9 (5)	9 (8)	5 (4)	
Multiple sites***		228 (56)	90 (53)	58 (54)	80 (63)	
Other isolated distant***		11 (3)	5 (3)	3 (3)	3 (2)	
Vital status, n (%)	5 (1)					<0.001
Dead		441 (74)	187 (68)	110 (75)	144 (84)	
Alive		154 (26)	90 (33)	36 (25)	28 (16)	
Overall survival in months, median (IQR)*		18 (10–32)	19 (11–34)	19 (11–32)	14 (9–28)	0.01

PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; CA, carbohydrate antigen; IQR, interquartile range; CT, computed tomography; cm, centimetre; NA, not applicable; SMA, superior mesenteric artery; SMV/PV, superior mesenteric vein/portal vein; AJCC, American Joint Committee on Cancer.
*R0 (≥1 mm) indicates a margin clearance of ≥1 mm; R1 (<1 mm) indicates a margin clearance of <1 mm but no direct margin involvement; R1 (direct) comprises infiltration of tumour cells directly into one of the resection margins.
** According to the Dutch Pancreatic Cancer Group criteria, resectable PDAC was defined as no arterial contact and ≤90° venous contact; borderline resectable PDAC was defined as arterial involvement ≤90°, or venous involvement 90°–270° without occlusion.
*** Multiple site recurrence included peritoneal carcinomatosis; other isolated distant sites included pleuritis carcinomatosis (n = 6), bone metastases (n = 2), cutaneous metastases (n = 2), and cervical metastases (n = 1).
Disease-free survival is measured from the date of primary resection until the date of recurrence diagnosis.
Overall survival is measured from the date of primary resection until the date of death or last follow-up.
Percentages within each variable are calculated based on the number of complete cases for that particular variable.

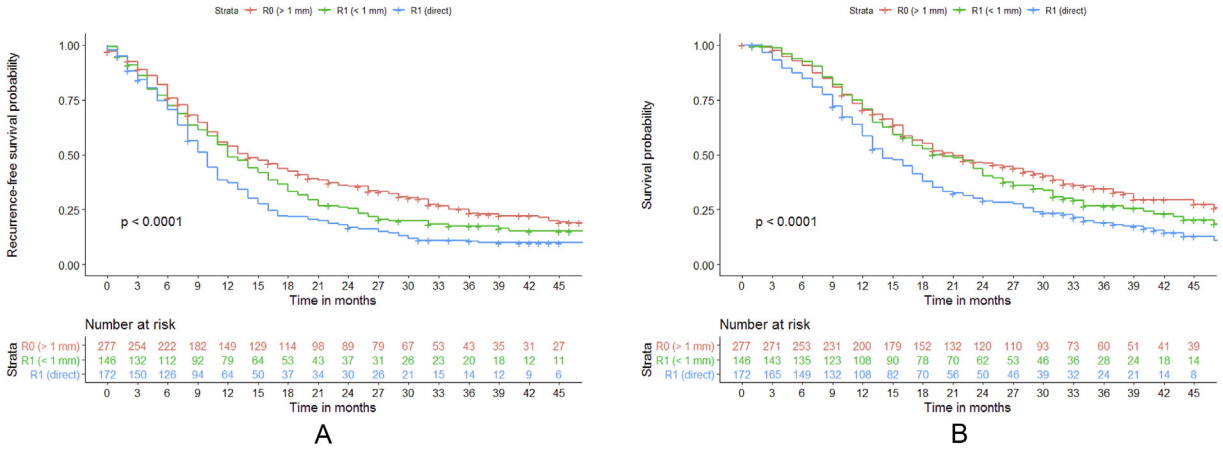

Fig. 1. Kaplan-Meier analysis comparing (A) recurrence-free survival and (B) overall survival between patients with R0 (≥1 mm), R1 (<1 mm) and R1 (direct) resections.

Discussion

This study shows that a margin clearance of <1 mm, but without direct margin involvement, does not affect survival after pancreatoduodenectomy for PDAC, as compared with a margin clearance of ≥1 mm. Direct margin involvement was highly correlated to a decreased DFS and OS, as compared with both R0 (≥1 mm) and R1 (<1 mm). This supports the definition of a margin clearance of >0 mm to indicate a complete PDAC resection. Given that any vascular tumour involvement on preoperative imaging was associated with an increased risk of R1 (direct) resection with upfront surgery, neoadjuvant therapy might be considered in these patients.

The results of our study favour the preserved UICC criteria rather than the newest AJCC definitions for R0 and R1 resections [8,9]. The significant difference in prognosis shown between the 8th AJCC R0 and R1 resections mainly seem to result from the poor prognosis of R1 (direct) resections, which are included in the 8th AJCC R1 (<1 mm) definition. Unlike some other studies, our findings do not necessarily support the "1 mm rule" for defining a complete PDAC resection, indicating a survival difference between R0 (≥1 mm) and R1 (<1 mm) [1,5–7,20,21]. However, at the end of the follow-up period, the three groups did show distinct survival curves according to the Kaplan-Meier analysis, although the sample sizes of each group were small. In addition, both DFS and OS were found to be significantly worse for R1 (direct), as compared with R1 (<1 mm), to which a further subdivision of the R1 definition might be justified.

Direct infiltration of tumour cells into the resection margin could be considered to prove residual disease, indicating the need for additional treatment. Moreover, half of patients (n = 318) within this cohort were found to have an R1 (direct + <1 mm) resection, which substantially increases the risk of developing disease recurrence. The merit of systemic therapy in the treatment of resectable pancreatic tumours is highly recognized to improve disease-free and overall survival rates. Considering the impressive survival benefits shown with adjuvant FOLFIRINOX chemotherapy, optimal delivery of systemic therapy is increasingly emphasized [22]. In our study, 67% of all patients (n = 384) received adjuvant chemotherapy. Given that an important part of patients does not receive optimal systemic therapy in the adjuvant setting, a rising interest in initial systemic treatment of patients with resectable

Table 2
Univariate Cox-regression analysis comparing overall and disease-free survival in 595 PDAC patients after pancreatoduodenectomy according to the various definitions for R0 and R1 resections.

	Disease-free survival in months				Overall survival in months			
	Median (95% CI)	HR	95% CI	*P* Value	Median (95% CI)	HR	95% CI	*P* Value
Resection margin status								
R0 (≥1 mm)* (n = 277)	14 (12–17)	*ref*			21 (18–28)	*ref*		
R1 (<1 mm)* (n = 146)	12 (11–16)	1.22	0.97–1.52	0.08	19 (17–24)	1.15	0.91–1.46	0.24
R1 (direct)* (n = 172)	10 (8–11)	1.57	1.27–1.94	<0.001	14 (13–17)	1.58	1.27–1.97	<0.001
R1 (direct) vs. R1 (<1 mm)		1.29	1.01–1.64	0.04		1.37	1.07–1.76	0.01
8th AJCC definitions								
Resection margin status								
R0 (≥1 mm)** (n = 277)	14 (12–17)	*ref*			21 (18–28)	*ref*		
R1 (<1 mm)** (n = 318)	11 (10–12)	1.39	1.16–1.67	<0.001	17 (14–19)	1.36	1.13–1.64	<0.01
Number of R1 (<1 mm)** margins								
0 (n = 277)	14 (12–17)	*ref*			21 (18–28)	*ref*		
1 (n = 192)	12 (11–15)	1.20	0.97–1.48	0.09	19 (17–23)	1.19	0.96–1.48	0.12
≥2 (n = 126)	9 (7–11)	1.78	1.41–2.25	<0.001	13 (12–17)	1.70	1.34–2.16	<0.001
≥2 vs. 1		1.48	1.16–1.90	<0.01		1.43	1.11–1.84	<0.01
8th UICC definitions								
Resection margin status								
R0 (>0 mm)*** (n = 423)	13 (12–16)	*ref*			21 (18–24)	*ref*		
R1 (direct)*** (n = 172)	10 (8–11)	1.46	1.21–1.78	<0.001	14 (13–17)	1.50	1.23–1.84	<0.001
Number of R1 (direct)*** margins								
0 (n = 423)	13 (12–16)	*ref*			21 (18–24)	*ref*		
1 (n = 130)	10 (8–11)	1.40	1.13–1.74	<0.01	17 (13–19)	1.38	1.10–1.72	<0.01
≥2 (n = 42)	10 (8–11)	1.68	1.21–2.34	<0.01	13 (11–16)	1.94	1.38–2.71	<0.001
≥2 vs. 1		1.20	0.83–1.73	0.34		1.40	0.97–2.03	0.07

PDAC, pancreatic ductal adenocarcinoma; CI, confidence interval; HR, hazard ratio; ref, reference category; AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer.
*R0 (≥1 mm) indicates a margin clearance of ≥1 mm; R1 (<1 mm) indicates a margin clearance of <1 mm but no direct margin involvement; R1 (direct) comprises infiltration of tumour cells directly into one of the resection margins.
** 8th AJCC definitions: R0 (≥1 mm) indicates a margin clearance of ≥1 mm; R1 (<1 mm) indicates a margin clearance of < 1 mm.
*** 8th UICC definitions: R0 (>0 mm) indicates a margin clearance of >0 mm; R1 (direct) comprises infiltration of tumour cells directly into one of the resection margins.

Table 3
Pooled multivariable Cox-proportional hazard analysis after multiple imputation in 595 PDAC patients after pancreatoduodenectomy.

	Disease-free survival			Overall survival		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age (continuous)	1.00	0.99–1.01	0.86	1.01	0.99–1.02	0.18
Sex (male vs. female)	0.91	0.76–1.10	0.33	0.90	0.74–1.09	0.29
ECOG performance score (2–4 vs. 0–1)	0.86	0.65–1.13	0.27	0.77	0.58–1.04	0.09
Preoperative serum CA 19–9 (continuous)	1.00	0.99–1.01	0.66	1.00	0.99–1.01	0.94
Vascular resection (yes vs. no)	1.37	1.12–1.69	<0.01	1.41	1.14–1.74	<0.01
8th AJCC T stage						
T1	*ref*			*ref*		
T2	1.34	0.99–1.79	0.06	1.22	0.90–1.67	0.20
T3	1.84	1.28–2.66	<0.01	1.72	1.18–2.53	<0.01
8th AJCC N stage						
N0	*ref*			*ref*		
N1	1.38	1.08–1.78	<0.05	1.46	1.12–1.91	<0.001
N2	2.21	1.69–2.90	<0.001	2.16	1.63–2.86	<0.001
Tumour differentiation (poor vs. well/moderate)	1.44	1.19–1.76	<0.001	1.44	1.17–1.78	<0.001
Lymphovascular invasion (yes vs. no)	0.98	0.79–1.21	0.86	1.03	0.82–1.28	0.82
Perineural invasion (yes vs. no)	1.24	0.90–1.71	0.19	1.42	0.99–2.03	0.06
Resection margin status						
R0 (≥1 mm)*	*ref*			*ref*		
R1 (<1 mm)*	1.12	0.89–1.41	0.34	1.05	0.82–1.34	0.71
R1 (direct)*	1.31	1.06–1.64	<0.05	1.35	1.08–1.70	<0.01
R1 (direct) vs. R1 (<1 mm)*	1.17	0.92–1.50	0.20	1.29	1.01–1.67	<0.05
Major postoperative complications (yes vs. no)	1.18	0.95–1.47	0.14	1.20	0.96–1.50	0.12
Adjuvant chemotherapy (yes vs. no)	0.54	0.44–0.67	<0.001	0.50	0.40–0.61	<0.001

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CA, carbohydrate antigen; AJCC, American Joint Committee on Cancer.
Disease-free survival is measured from the date of primary resection until the date of recurrence diagnosis.
Overall survival is measured from the date of primary resection until the date of death or last follow-up.
*R0 (≥1 mm) indicates a margin clearance of ≥1 mm; R1 (<1 mm) indicates a margin clearance of <1 mm but no direct margin involvement; R1 (direct) comprises infiltration of tumour cells directly into one of the resection margins.

PDAC exists. Initial treatment with either chemotherapy or chemoradiation has the potential to downsize the tumour and increase the number of R0 resections [23–25]. As a result, neoadjuvant therapy has become the preferred treatment strategy for borderline resectable PDAC, and promising results for resectable PDAC have been shown as well [13,26,27].

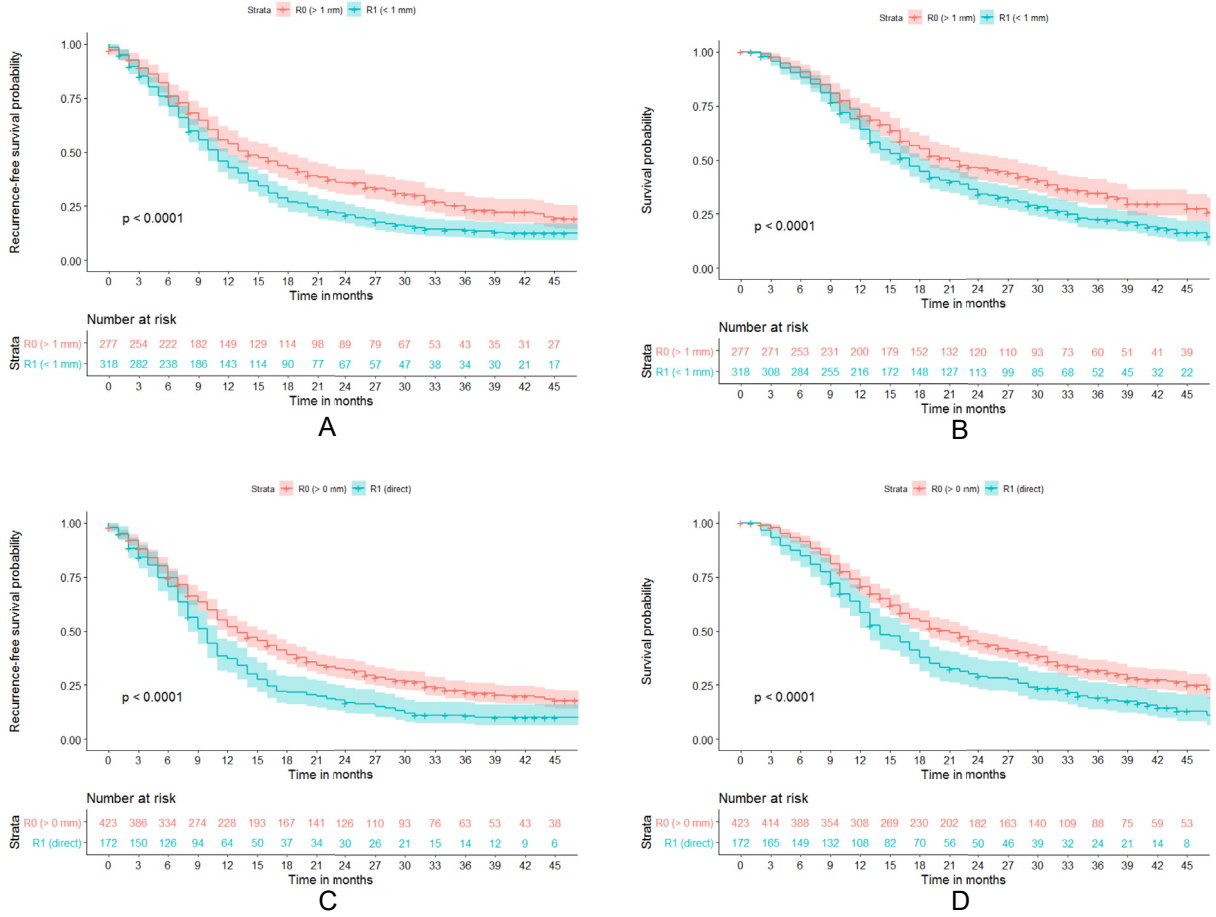

Fig. 2. Kaplan Meier analyses comparing respectively recurrence-free and overall survival between patients with R0 and R1 resections according to the (A,B) 8th AJCC definitions and (C,D) 8th UICC definitions.

The poor overall survival of 14 months for patients with R1 (direct) resections highlights the need for adequate patient selection for PDAC resection and necessitates separate classification of this subgroup. In particular for patients with a high risk of R1 (direct) resection, initial systemic therapy might be considered over upfront surgery. As shown in this study, the vascular bed was found to be most frequently involved in R1 (either <1 mm or direct) resections. This could signify the need for initial systemic therapy in patients with any vascular involvement on preoperative imaging, despite having a primary resectable pancreatic tumour at diagnosis. However, some patients who were deemed resectable at first might become unresectable during neoadjuvant therapy. Therefore, for patients with primary resectable tumours, the benefit of neoadjuvant therapy has yet to be proven in ongoing clinical trials. For R1 (direct) resections, the pancreatic neck margin was affected in 18% of cases. To this purpose, standardized intraoperative frozen section assessment of the pancreatic neck margin might be considered. Nevertheless, the true value of additional resection after frozen section assessment remains controversial, as does the reliability of margin clearance assessment of the pancreatic neck margin included for frozen section [28–30].

Other preoperative predictors that were found to be associated with R1 (direct) resection, were age, male sex and ECOG performance score 2–4. Hypothetically, it could be that less extensive resections are performed in elderly patients and patients with a worse performance status, which might have resulted in an increased number of R1 (direct) resections [31]. Data to test this hypothesis was, however, lacking. As the difference in mean age was only two years (i.e. 69 years for patients with R1 (direct) resections and 67 for patients with R0 (≥1 mm) and R1 (<1 mm) resections), the clinical relevance of this association could be questioned. In the Netherlands, pancreatic cancer surgery is centralized to 16 expert centres, in which all patients are screened by an anaesthesiologist and receive a multidisciplinary work-up to optimize their performance status prior to surgery. Therefore, the small number of patients (n = 40; 70%) with an ECOG performance score of 2–4 have nonetheless been determined eligible for surgery by a specialized team of pancreatic cancer clinicians. Additional analysis showed that the percentage of T3 tumours was higher in men than in women, which potentially explains the association between male sex and R1 (direct) resection. The relation between tumour stage and gender, however, is not clearly understood.

Furthermore, this study showed that for R1 (direct) tumours, a significantly higher number of tissue blocks were pathologically examined. This is in line with previous studies, in which the rate of R1 resections was increased with a larger extent of tissue sampling [32–34]. However, the relevance of examining just one additional tissue block could be questioned, and it is unclear whether the higher R1 resection rate resulted from or caused a more extensive tissue examination. A higher number of R1 (either <1 mm or direct) resection margins was found to be associated with a worse prognosis. Consequently, thorough examination of all margins in a standardized fashion as well as standardized delivery of surgical information to the pathologist seems to be mandatory to accurately

inform patients on their prognosis [34]. A standardized pathology protocol has been released by the International study Group of Pancreatic Surgery (ISGPS) in 2014, in which axial slicing with multicolour inking and a minimum assessment of 7 margins is recommended [35]. However, bi-valving with orange peeling remains the recommended technique for margin assessment after PDAC resection in the United States [16].

Several limitations of the present study have to be acknowledged. The number of R1 resections might be underreported due to retrospective evaluation of histopathological reports and a lack of standardized protocols for examination and documentation during the first year of inclusion (2014). Consequently, in some cases it remained ambiguous if all, and to which extent, resection margins were assessed. This also hampered proper validation of specific extents of margin clearance and locations of margin involvement and their correlation with DFS and OS. Furthermore, patients who received neoadjuvant chemo(radio)therapy were excluded, considering that consensus on optimal pathology reporting after neoadjuvant treatment is lacking, which could affect resection margin assessment [36]. Patients who were planned for upfront surgery, in whom tumour resection was not performed due to occult metastases noticed during surgery, were not included in the analysis, nor were patients with macroscopically incomplete (R2) resections. This should be taken into account when interpreting the results of this study.

In conclusion, presence of tumour cells <1 mm of the resection margin, but without direct involvement, does not affect survival after pancreatoduodenectomy for PDAC, as compared with a margin clearance of ≥1 mm. This supports the UICC criteria for R0 and R1 status rather than the adjusted AJCC definitions and emphasizes the need for optimal delivery of systemic therapy in particular for R1 (direct) patients. Given that the risk of an R1 (direct) resection is increased for tumours with any vascular involvement on preoperative imaging, neoadjuvant therapy might be considered in these patients.

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Declaration of competing interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Appendix B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2020.11.145.

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