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Original Article

Margin clearance greater than 1 mm in nodal-positive pancreatic adenocarcinoma patients: multicentre retrospective analysis

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Abstract

Background: The introduction of the 1 mm cut-off for resection margin according to the Leeds Pathology Protocol has transformed the concept of surgical radicality. Its impact on nodal-positive resected pancreatic ductal adenocarcinoma patients is unclear. The aim of this study was to analyse the effect of margin clearance on survival among resected, nodal-positive pancreatic ductal adenocarcinoma patients whose specimens were analysed according to the Leeds Pathology Protocol.

Methods: Data were collected retrospectively from multicentre clinical databases. Resected patients with nodal involvement were included. Overall survival and disease-free survival were analysed according to minimum reported margin clearances of 0, 0.5, 1, and 2 mm. The results are reported separately for patients who had not undergone venous resection and for patients for whom data were available regarding the superior mesenteric vein-facing margin or the vein specimen. The eighth edition of TNM classification by the AJCC was used.

Results: The study comprised 290 stage IIB patients and 215 stage III patients without venous resection. The superior mesenteric vein margin analysis comprised 127 stage IIB patients and 198 stage III patients. The different resection margin distances were not associated with overall survival and disease-free survival among patients without venous resection ($P > 0.050$). Receiving adjuvant therapy was associated with longer overall survival among stage IIB patients ($P = 0.034$) and stage III patients ($P = 0.003$) and with longer disease-free survival among stage III patients ($P < 0.001$).

Conclusions: In this study, a margin clearance greater than 1 mm showed no clear effect on overall survival in pancreatic ductal adenocarcinoma patients with nodal involvement, whereas adjuvant therapy was confirmed to be essential to ensure longer overall survival.

Introduction

The prognosis among patients undergoing surgical resection of pancreatic ductal adenocarcinoma (PDAC) has recently improved with the introduction of chemotherapy combinations like folinic acid-fluorouracil-irinotecan-oxaliplatin (FOLFIRINOX), neoadjuvant therapy, and better surgical options for patients previously deemed unresectable, such as those with venous and arterial resections[1]. The radicality of the surgery is determined according to the margin clearance in the resection specimen. When this margin clearance is greater than 1 mm, the tumour is considered radically resected (R0 resection), whereas, when it is not, the resection is considered to be an R1 resection[2]. In 2006, a new axial slicing technique protocol called the Leeds Pathology Protocol (LEEPP) was introduced[3,4]. In this protocol, the anterior, posterior, and superior mesenteric vein (SMV-facing margin, previously groove margin) margins are coloured, followed by slicing the specimen perpendicularly to the duodenal axis. This new method led to the detection of significantly more R1 resections, in which the posterior resection margin was most often affected, followed by the SMV-facing margin[1]. How feasible categorizing R0 and R1 resections is and what their impact is on

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overall survival (OS) remain open questions. As most studies have only focused on the current R1 definition, data on other margin clearances is lacking. The results regarding the current R0/R1 definition and its impact on survival[5,6] are inconsistent, although they mostly point towards shorter OS in the case of an R1 resection[7]. The aim of this multicentre retrospective study was to investigate the role of different resection margin distances on the survival of patients with PDAC and nodal involvement. With increasing numbers of patients undergoing surgery for tumours involving the SMV/portal vein (PV), a subgroup analysis included those patients with detailed information on the SMV margin status.

Methods

This multicentre retrospective study was approved by the Ethics Committee of each participating centre. Only centres evaluating surgical specimens according to a standardized axial method (Leeds[3] or Royal Colleges of Pathologists[8] protocol) were eligible for inclusion in the study. The participating centres were: Birmingham University Hospital National Health Service Foundation Trust, UK; Klinikum rechts der Isar, Technical University of Munich, Germany; Karolinska Institute, Stockholm, Sweden; Tampere University Hospital, Tampere, Finland; IRCCS Ospedale San Raffaele, Milan, Italy; Amsterdam UMC, Amsterdam, The Netherlands; Vilnius University Hospital, Vilnius, Lithuania; and Acibadem Mehmet Ali Aydinlar University Hospital, Istanbul, Turkey.

Patients who had undergone a pancreatic resection for PDAC with nodal involvement (stage IIB according to the seventh edition of TNM classification by the AJCC) between 2012 and 2017 were included. Patients with no data available on resection margins, with R2 resections, with an unknown number of positive lymph nodes, with an arterial resection, who received neoadjuvant therapy, or with a distant metastasis (M1) were excluded from the study.

Preoperative, histopathological, and oncological follow-up data were retrieved from patient files. All data available on margin clearance at specific sites (SMV-facing margin, superior mesenteric artery-facing margin, and anterior, posterior, and pancreatic transection margins) were gathered, as well as data on the pathology of the portal vein (PV) or SMV specimen if these were resected. Follow-up data regarding adjuvant therapy, disease-free survival (DFS), and OS were recorded retrospectively.

The tumours were recategorized according to the eighth edition of TNM classification by the AJCC to stage IIB (less than or equal to three positive regional lymph nodes) and stage III (greater than three positive regional lymph nodes) PDAC[9]. Data were subsequently analysed separately for stage IIB and stage III PDAC.

The margin clearance of the patients who had not undergone a venous resection was analysed according to the minimum reported margin (MRM), at four different cut-offs: 0, greater than 0.5, greater than 1, and greater than 2 mm. In addition, whether a wider SMV-facing margin achieved by a PV/SMV resection leads to longer survival was analysed in a separate analysis. This analysis included both patients without a venous resection, but with data on SMV-facing margin distances, and patients with a venous resection and data available on venous specimens. This analysis is referred to as SMV margin analysis and the results are reported according to the following categories: cancer involvement in the venous specimen; no cancer involvement in the venous specimen; SMV-facing margin clearance less than or equal to 0.5 mm; and SMV-facing margin clearance greater than 0.5 mm.

Primary outcomes were OS and DFS in relation to the resection margin clearance. Patients who died within 90 days after surgery were excluded from the survival analysis.

Statistical analysis was performed using SPSS® (IBM, Armonk, NY, USA; Statistics for Windows, Version 26.0, 2019). The results are reported as *n* (%) and median (interquartile range (i.q.r.)). Univariable analysis was performed using Pearson's chi-squared test and Cox regression analysis. HRs for margins and the use of adjuvant therapy are presented centre adjusted. Multivariable analysis was performed using Cox regression analysis. A variable was included in the multivariable analysis when the *P* value was <0.100 in the univariable analysis. Kaplan–Meier survival curves are presented and differences are presented with log rank *P* values.

Results

Patient characteristics

A total of 653 patients with nodal involvement were identified. Of these, 290 stage IIB patients and 215 stage III patients underwent a pancreatic resection without a venous resection. Out of these patients, 86 stage IIB patients and 91 stage III patients had detailed information on the SMV-facing margin available. A total of 41 stage IIB patients and 107 stage III patients underwent a venous resection. This resulted in a total of 127 stage IIB patients and 198 stage III patients for the SMV margin analysis. The most common resection was a pancreatoduodenectomy.

Without venous resection

The median preoperative carbohydrate antigen 19-9 (CA19-9) concentration was 140 and 143 kU/l for stage IIB patients and stage III patients respectively. The proportion of patients receiving adjuvant therapy was 67% (193 of 290) for stage IIB patients and 59.1% (127 of 215) for stage III patients. See *Table 1*.

SMV margin analysis

The median preoperative CA19-9 concentration was 112 and 153 kU/l for stage IIB patients and stage III patients respectively. The proportion of patients receiving adjuvant therapy was 73.2% (93 of 127) for stage IIB patients and 64.6% (128 of 198) for stage III patients. See *Table 1*.

Postoperative histopathological findings

Without venous resection

The median tumour size was 30 for both stage IIB patients and stage III patients. According to the eighth edition of TNM classification by the AJCC, 68.6% (199 of 290) of stage IIB patients and 67.9% (146 of 215) of stage III patients had a T1–2 tumour. Perineural invasion was present among 79.0% (229 of 290) and 87.4% (188 of 215) of stage IIB patients and stage III patients respectively. The differentiation stage was low for 59.2% (171 of 290) of stage IIB patients and 59.5% (128 of 215) of stage III patients. Among stage IIB patients and stage III patients, 67% (193 of 290) and 64.2% (138 of 215) respectively had an MRM of less than or equal to 1 mm. See *Table 1*.

SMV margin analysis

The median tumour size was 30 and 33 mm for stage IIB patients and stage III patients respectively. A T1–2 tumour was found in 79.5% (101 of 127) of stage IIB patients and in 63.9% (129 of 198) of stage III patients. Perineural invasion was detected in 89.8% (114 of 127) and 91.1% (180 of 198) of stage IIB patients and stage

Table 1 Characteristics of patients with stage IIB and III pancreatic ductal adenocarcinoma and histopathological findings for pancreatic specimens

	Without venous resection		SMV margin analysis	
	Stage IIB	**Stage III**	**Stage IIB**	**Stage III**
Total	290	215	127	198
Sex				
Male	160 (55.2)	122 (56.7)	65 (51.2)	94 (47.5)
Female	1230 (44.8)	93 (43.3)	62 (48.8)	104 (52.5)
Age (years), median (i.q.r.)	68 (61–74)	68 (62–74)	67 (63–74)	69 (62–74)
Preoperative BMI (kg/m^2), median (i.q.r.)	24 (22–27)	24 (22–28)	24 (22–28)	24 (22–28)
Unknown	65 (22.4)	51 (17)	16 (12.6)	25 (12.3)
ASA grade				
I–II	219 (75.5)	157 (73.0)	97 (76.4)	148 (74.7)
III–IV	70 (24.1)	56 (26.0)	29 (22.8)	48 (24.2)
Unknown	1 (0.3)	2 (0.9)	1 (0.8)	2 (1.0)
Preoperative CA19-9 (kU/l), median (i.q.r.)	140 (32–530)	143 (38–624)	112 (27–498)	153 (34–660)
Unknown	82 (28.3)	59 (20)	14 (11)	28 (13.9)
Type of surgery				
Pancreatoduodenectomy	235 (81.0)	202 (94)	120 (94.5)	178 (89.9)
Distal pancreatectomy	38 (13.1)	6 (2.8)	3 (2.4)	7 (3.5)
Total pancreatectomy	17 (5.9)	7 (3.3)	4 (3.1)	13 (6.6)
Venous resection	NA	NA	40 (31.5)	107 (54.0)
Adjuvant therapy	193 (66.6)	127 (59.1)	93 (73.2)	128 (64.6)
Unknown	26 (9.0)	25 (11.6)	16 (12.5)	17 (8.4)
Tumour size (mm), median (i.q.r.)	30 (25–40)	30 (25–40)	30 (21–35)	33 (25–40)
Unknown	10 (3.4)	5 (1.7)	1 (0.78)	3 (1.5)
T stage				
T1–2	199 (68.6)	146 (67.9)	101 (79.5)	129 (63.9)
T3	91 (31.4)	69 (32.1)	22 (17.3)	67 (33.8)
Unknown	13 (4.5)	5 (2.3)	4 (3.1)	5 (2.5)
Differentiation stage				
1–2	171 (59.2)	128 (59.5)	74 (58.1)	120 (60.6)
3–4	109 (37.7)	76 (35.3)	46 (36.5)	73 (36.9)
Unknown	9 (3.1)	11 (5.1)	6 (4.8)	5 (2.5)
Number of harvested lymph nodes, median (i.q.r.)	22 (16–32)	22 (15–31)	24 (16–32)	25 (19–37)
Perineural invasion	229 (79.0)	188 (87.4)	114 (89.8)	180 (90.8)
Unknown	12 (4.2)	7 (3.2)	3 (2.4)	4 (2.0)
Angioinvasion	144 (49.7)	162 (75.3)	73 (57.5)	134 (67.7)
Unknown	29 (10.0)	22 (10.2)	14 (11.0)	17 (8.6)
Minimum reported margin				
Margin 0 mm	55 (19.0)	77 (35.8)	NA	NA
Unknown	23 (7.9)	16 (7.4)	–	–
Margin >0.5 mm	186 (64.1)	97 (45.1)	NA	NA
Unknown	20 (6.9)	16 (7.4)	–	–
Margin >1 mm	97 (33.4)	77 (35.8)	NA	NA
Unknown	–	–	–	–
Margin >2 mm	38 (13.1)	18 (8.4)	NA	NA
Unknown	40 (13.8)	51 (23.7)	–	–
SMV margin analysis				
SMV margin >0.5 mm	NA	NA	46 (36.2)	41 (20.7)
SMV margin ≤0.5 mm	NA	NA	40 (31.5)	50 (25.3)
No cancer in the vein specimen	NA	NA	16 (12.6)	37 (18.7)
Cancer in the vein specimen	NA	NA	25 (19.7)	70 (35.4)

Values are *n* (%) unless otherwise indicated. i.q.r., interquartile range; NA, not available; CA19-9, carbohydrate antigen 19-9; SMV, superior mesenteric vein.

III patients respectively. The differentiation stage was low for 58.1% (74 of 127) of stage IIB patients and 60.69% (120 of 198) of stage III patients. Venous resection was performed on 31.5% (40 of 127) of stage IIB patients and on 54.0% (107 of 198) of stage III patients. Of these patients, 40% (16 of 40) of stage IIB patients and 35% (37 of 107) of stage III patients had no malignancy in the final vein specimen. See *Table 1*.

Survival analysis

Postoperative mortality

Thirty-day mortality was 0.9% among stage IIB patients and 2.1% among stage III patients. Ninety-day mortality was 3.0% among stage IIB patients and 5.2% among stage III patients.

Without venous resection

The median OS was 19.2 months among stage IIB patients. In the multivariable analysis, T stage T3 (HR 2.27, 95% c.i. 1.48 to 3.48; $P < 0.001$) and differentiation stage 3–4 (HR 1.47, 95% c.i. 1.06 to 2.02; $P = 0.020$) were associated with shorter OS. Among stage IIB patients, the multivariable analysis showed that receiving adjuvant therapy (HR 0.69, 95% c.i. 0.48 to 0.97; $P = 0.034$) and greater than 0 mm margin clearance (HR 0.59, 95% c.i. 0.38 to 0.91; $P = 0.018$) were associated with longer OS. A greater than 0 mm margin clearance did not show a significant survival benefit in Kaplan–Meier analysis (log rank $P = 0.692$). See *Fig. 1* and *Table 2*.

Among stage III patients, the multivariable analysis showed that a higher preoperative CA19-9 concentration (HR 1.01,

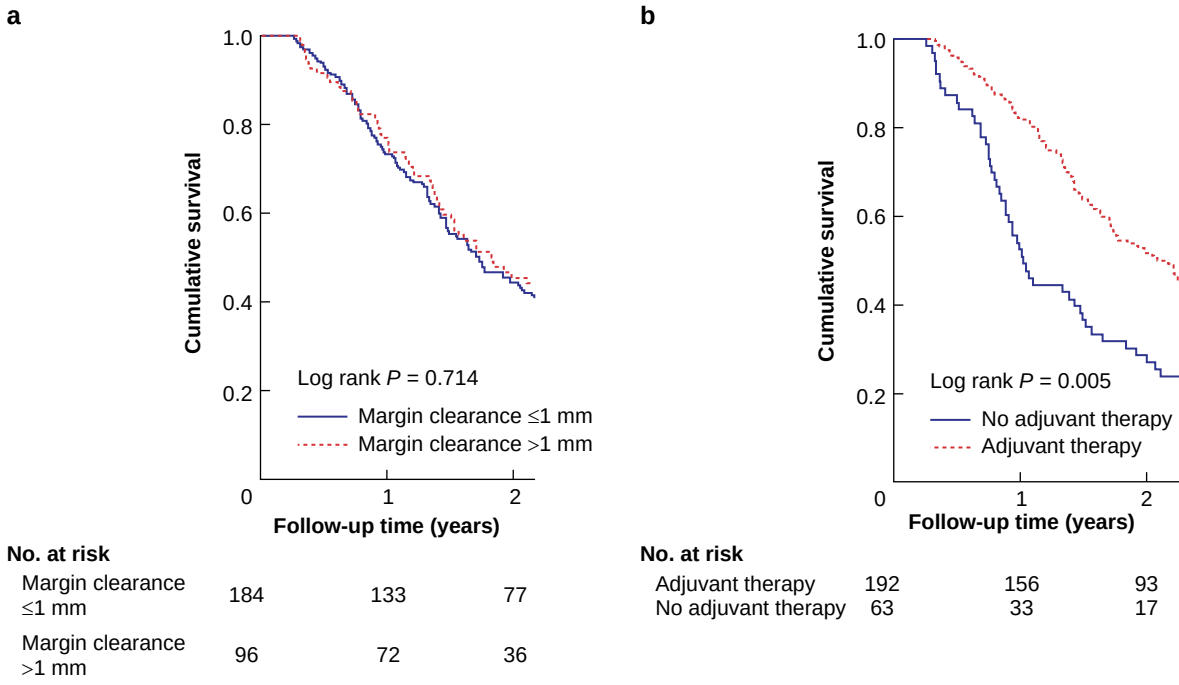

Fig. 1 Kaplan–Meier survival curves of stage IIB patients
a In relation to 1 mm cut-off. **b** In relation to adjuvant therapy.

95% c.i. 1.00 to 1.02; $P = 0.005$), differentiation stage 3–4 (HR 2.14, 95% c.i. 1.36 to 3.36; $P = 0.001$), and ASA grade III–IV (HR 1.49, 95% c.i. 1.02 to 2.18; $P = 0.040$) were associated with shorter OS, whereas receiving adjuvant therapy (HR 0.56, 95% c.i. 0.38 to 0.82; $P = 0.003$) and female sex (HR 0.66, 95% c.i. 0.47 to 0.92; $P = 0.015$) were associated with longer OS. The median survival was 14.4 months among stage III patients. See *Fig. 2* and *Table 2*.

SMV margin analysis

Among stage IIB patients, the multivariable analysis showed that T stage T3 (HR 2.29, 95% c.i. 1.05 to 5.02; $P = 0.038$) and differentiation stage 3–4 (HR 2.29, 95% c.i. 1.33 to 3.95; $P = 0.003$) were associated with shorter OS, whereas receiving adjuvant therapy (HR 0.31, 95% c.i. 0.15 to 0.62; $P < 0.001$) and histopathological cancer involvement in the vein specimen (HR 0.47, 95% c.i. 0.24 to 0.93; $P = 0.030$) were associated with longer OS. See *Table 3*.

Among stage III patients, the multivariable analysis showed that receiving adjuvant therapy (HR 0.47, 95% c.i. 0.30 to 0.72; $P < 0.001$) was associated with longer OS, whereas a higher preoperative CA19-9 concentration (HR 1.01, 95% c.i. 1.00 to 1.02; $P = 0.013$) was associated with shorter OS. See *Table 3*.

Disease-free survival

Without venous resection

Among stage IIB patients, the multivariable analysis showed that increased tumour size (HR 1.33, 95% c.i. 1.15 to 1.55; $P < 0.001$) and a higher preoperative CA19-9 concentration (HR 1.13, 95% c.i. 1.00 to 1.03; $P = 0.035$) were associated with shorter DFS. Among stage III patients, the multivariable analysis showed that receiving adjuvant therapy (HR 0.35, 95% c.i. 0.23 to 0.55; $P < 0.001$) and a BMI greater than 25 kg/m^2 (HR 0.61, 95% c.i. 0.42 to 0.90; $P = 0.012$) were associated with longer DFS, whereas a higher preoperative CA19-9 concentration (HR 1.02, 95% c.i. 1.01 to 1.03; $P < 0.001$) was associated with shorter DFS. See *Table 4*.

Local recurrence was not associated with margin widths among stage IIB patients or stage III patients (stage IIB: $P = 0.800$ for margin clearance greater than 0 mm, $P = 0.731$ for margin clearance greater than 0.5 mm, $P = 0.398$ for margin clearance greater than 1 mm, and $P = 0.200$ for margin clearance greater than 2 mm; stage III: $P = 0.467$ for margin clearance greater than 0 mm, $P = 0.536$ for margin clearance greater than 0.5 mm, $P = 0.913$ for margin clerance greater than 1 mm, and $P = 0.426$ for margin clearance greater than 2 mm).

SMV margin analysis

Among stage IIB patients, the multivariable analysis showed that T stage T3 (HR 8.01, 95% c.i. 3.352 to 19.2; $P < 0.001$) was associated with shorter DFS, whereas an SMV margin greater than 0.5 mm (HR 0.35, 95% c.i. 0.17 to 0.69; $P = 0.002$) and female sex (HR 0.59, 95% c.i. 0.36 to 0.96; $P = 0.032$) were associated with longer DFS. Among stage III patients, the multivariable analysis showed that receiving adjuvant therapy (HR 0.60, 95% c.i. 0.36 to 0.98; $P = 0.041$) was associated with longer DFS, whereas angioinvasion (HR 0.46, 95% c.i. 0.25 to 0.85; $P = 0.013$), a higher preoperative CA19-9 concentration (HR 1.01, 95% c.i. 1.00 to 1.02; $P = 0.008$), and differentiation stage 3–4 (HR 1.83, 95% c.i. 1.09 to 3.08; $P = 0.023$) were associated with shorter DFS. See *Table 5*.

Discussion

In this study, a margin clearance greater than 1 mm showed no clear effect on OS in PDAC patients with nodal involvement, whereas adjuvant therapy was confirmed to be essential to ensure longer OS.

Previous articles have reported survival advantages for a margin clearance greater than 1 mm[10–12], but most of them also

Table 2 Overall survival analysis: without venous resection

	Stage IIB				Stage III			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% c.i.)	P	HR (95% c.i.)	P	HR (95% c.i.)	P	HR (95% c.i.)	P
Age (>65 *versus* ≤65 years)	1.08 (0.82,1.43)	0.594	–	–	1.08 (0.84,1.49)	0.636	–	–
Sex (female *versus* male)	0.95 (0.73,1.23)	0.687	–	–	0.71 (0.52,0.96)	0.028	0.66 (0.47,0.92)	0.015
BMI >25 kg/m^2 (yes *versus* no)	0.86 (0.65,1.16)	0.324	–	–	0.89 (0.65,1.22)	0.462	–	–
ASA grade (III–IV *versus* I–II)	0.98 (0.72,1.33)	0.885	–	–	1.48 (1.05,2.08)	0.024	1.49 (1.02,2.18)	0.040
ASA grade (unknown *versus* I–II)	1.14 (0.16,8.14)	0.898	–	–	1.00 (0.14,7.19)	0.999	1.00 (0.13,7.81)	0.996
CA19-9 (per 100 kU/l increase)	1.01 (1.00,1.11)	0.153	–	–	1.01 (1.00,1.02)	0.043	1.01 (1.00,1.02)	0.005
Tumour size (per cm increase)	1.17 (1.06,1.29)	0.001	1.03 (0.88,1.21)	0.731	1.06 (0.95,1.19)	0.309	–	–
T stage (T3 *versus* T1–2)	2.24 (1.64,2.98)	<0.001	2.27 (1.48,3.48)	<0.001	0.93 (0.67,1.27)	0.660	0.86 (0.58,1.26)	0.431
T stage (unknown *versus* T1–2)	1.69 (0.83,3.45)	0.152	–	–	0.19 (0.03,1.35)	0.096	0.15 (0.02,1.11)	0.063
Perineural invasion (yes *versus* no)	0.90 (0.64,1.27)	0.546	–	–	1.11 (0.62,2.01)	0.723	–	–
Perineural invasion (unknown *versus* no)	0.69 (0.33,1.42)	0.314	–	–	1.17 (0.41,3.32)	0.775	–	–
Angioinvasion (yes *versus* no)	0.89 (0.68,1.17)	0.410	–	–	1.25 (0.79,1.96)	0.344	1.62 (0.94,2.79)	0.085
Angioinvasion (unknown *versus* no)	1.17 (0.75,1.85)	0.492	–	–	2.08 (1.12,3.86)	0.020	3.36 (1.51,7.47)	0.003
Differentiation stage (3–4 *versus* 1–2)	1.52 (1.16,2.00)	0.003	1.47 (1.06,2.02)	0.020	1.39 (1.00,1.93)	0.050	2.14 (1.36,3.36)	0.001
Differentiation stage (unknown *versus* 1–2)	2.08 (1.05,4.10)	0.035	1.62 (0.72,3.65)	0.244	1.24 (0.57,2.66)	0.589	0.82 (0.31,2.21)	0.697
Adjuvant therapy* (yes *versus* no)	0.66 (0.47,0.92)	0.016	0.69 (0.48,0.97)	0.034	0.61 (0.42,0.87)	0.006	0.56 (0.38,0.82)	0.003
Adjuvant therapy* (unknown *versus* no)	0.92 (0.47,1.78)	0.796	0.83 (0.40,1.71)	0.607	0.70 (0.39,1.27)	0.238	0.43 (0.21,0.88)	0.022
MRM >0 mm* (yes *versus* no)	0.60 (0.40,0.91)	0.016	0.59 (0.38,0.91)	0.018	1.04 (0.68,1.58)	0.857	–	–
MRM >0 mm* (unknown *versus* no)	0.68 (0.37,1.27)	0.227	0.64 (0.33,1.21)	0.167	1.54 (0.83,2.86)	0.172	–	–
MRM >0.5 mm* (yes *versus* no)	0.76 (0.53,1.10)	0.147	–	–	1.13 (0.76,1.69)	0.538	–	–
MRM >0.5 mm* (unknown *versus* no)	0.70 (0.37,1.32)	0.272	–	–	1.61 (0.89,2.93)	0.117	–	–
MRM >1 mm* (yes *versus* no)	0.94 (0.69,1.28)	0.947	–	–	1.16 (0.79,1.69)	0.433	–	–
MRM >2 mm* (yes *versus* no)	1.05 (0.70,1.58)	0.812	–	–	1.57 (0.84,2.92)	0.158	–	–
MRM >2 mm* (unknown *versus* no)	0.80 (0.48,1.32)	0.381	–	–	1.06 (0.69,1.64)	0.782	–	–

*Centre adjusted. CA19-9, carbohydrate antigen 19-9; MRM, minimum reported margin.

included patients with no nodal involvement (stages I and IIA). Also, various meta-analyses have reported survival benefits of a greater than 1 mm margin clearance, but they were often biased by different slicing techniques, the definition of margins, and the incomplete data on oncological treatment[7,13,14].

It has been reported that, after meticulous pathological analysis of a specimen, a greater than 1 mm margin clearance is detected among a minority of patients[15]. The results of the present study demonstrate the same effect. Moreover, the location and the size of a tumour affect the potential margin widths. Increasing margin clearance towards the anterior surface is impossible, but in the transection line of the pancreas the margin width can be expanded until a total pancreatectomy is performed. In this study, the T stage T3 was a prognostic factor for shorter OS, demonstrating the importance of tumour size.

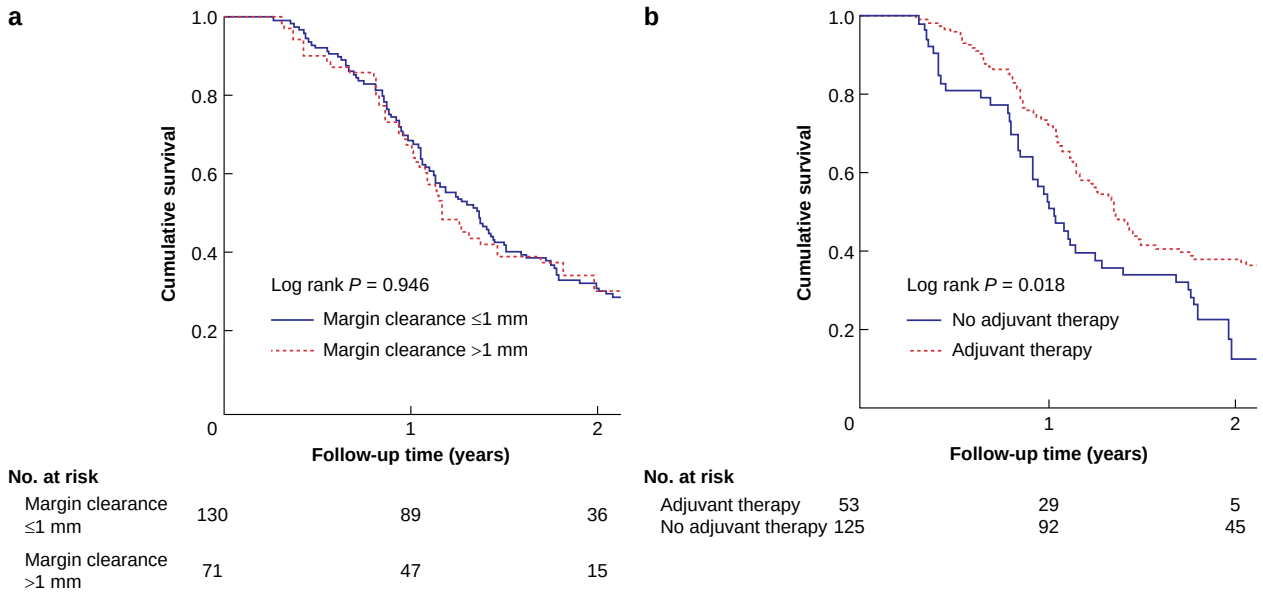

Fig. 2 Kaplan–Meier survival curves of stage III patients

a In relation to 1 mm cut-off. **b** In relation to adjuvant therapy.

Table 3 Overall survival analysis: SMV margin analysis

	Stage IIB				Stage III			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% c.i.)	P	HR (95% c.i.)	P	HR (95% c.i.)	P	HR (95% c.i.)	P
Age (>65 *versus* ≤65 years)	0.93 (0.60,1.43)	0.728	–	–	1.05 (0.76,1.46)	0.766	–	–
Sex (female *versus* male)	0.90 (0.61,1.34)	0.605	–	–	1.13 (0.84,1.53)	0.425	–	–
BMI >25 kg/m^2 (yes *versus* no)	1.34 (0.87,2.07)	0.188	–	–	0.88 (0.64,1.22)	0.450	–	–
ASA grade (III–IV *versus* I–II)	1.27 (0.80,2.00)	0.311	–	–	1.16 (0.818,1.63)	0.412	–	–
ASA grade (unknown *versus* I–II)	1.34 (0.19,9.70)	0.774	–	–	0.99 (0.14,7.09)	0.990	–	–
CA19-9 (per 100 kU/l increase)	1.01 (1.00,1.02)	0.049	1.01 (0.99,1.03)	0.374	1.01 (1.00,1.02)	0.018	1.01 (1.00,1.02)	0.013
Tumour size (per cm increase)	1.21 (1.04,1.40)	0.015	1.01 (0.85,1.43)	0.48	1.04 (0.95,1.15)	0.393	–	–
T stage (T3 *versus* T1–2)	1.74 (1.07,2.83)	0.025	2.29 (1.05,5.02)	0.038	1.05 (0.764,1.45)	0.761	1.14 (0.75,1.73)	0.547
T stage (unknown *versus* T1–2)	1.06 (0.14,7.78)	0.955	0.11 (0.01,1.74)	0.118	0.16 (0.02,1.14)	0.138	0.22 (0.03,1.63)	0.138
Perineural invasion (yes *versus* no)	0.95 (0.47,1.90)	0.879	0.70 (0.32,1.53)	0.368	1.05 (0.59,1.86)	0.874	0.97 (0.46,2.06)	0.944
Perineural (unknown *versus* no)	6.71 (1.74,25.9)	0.006	15.5 (1.48,161)	0.022	11.9 (2.51,56.0)	0.002	2.80 (0.38,20.8)	0.315
Angioinvasion (yes *versus* no)	1.20 (0.78,1.86)	0.410	1.05 (0.60,1.85)	0.861	1.04 (0.73,1.48)	0.822	0.71 (0.42,1.19)	0.195
Angioinvasion (unknown *versus* no)	2.94 (1.54,5.57)	0.001	1.51 (0.58,3.91)	0.400	2.63 (1.43,4.84)	0.002	1.49 (0.68,3.25)	0.316
Differentiation stage (3–4 *versus* 1–2)	1.94 (1.25,3.00)	0.003	2.29 (1.33,3.95)	0.003	1.17 (0.86,1.61)	0.321	1.23 (0.89,1.89)	0.350
Differentiation stage (unknown *versus* 1–2)	4.48 (1.87,10.7)	<0.011	1.20 (0.33,4.34)	0.786	4.49 (1.41,14.4)	0.011	3.45 (0.77,15.8)	0.107
Adjuvant therapy* (yes *versus* no)	0.37 (0.20,0.69)	0.002	0.31 (0.15,0.62)	<0.001	0.48 (0.33,0.69)	<0.001	0.47 (0.30,0.72)	<0.001
Adjuvant therapy* (unknown *versus* no)	0.36 (0.14,0.90)	0.029	0.19 (0.06,0.57)	0.003	0.82 (0.42,1.59)	0.556	0.71 (0.33,1.55)	0.389
SMV margin status* (>0.5 *versus* ≤0.5 mm)	0.79 (0.46,1.34)	0.381	0.84 (0.45,1.56)	0.572	0.99 (0.59,1.65)	0.954	–	–
No cancer in the vein specimen	1.17 (0.57,2.42)	0.675	1.86 (0.81,4.28)	0.144	0.90 (0.54,1.49)	0.671	–	–
Cancer in the vein specimen	0.52 (0.28,0.96)	0.037	0.47 (0.24,0.93)	0.030	1.22 (0.75,1.99)	0.422	–	–

*Centre adjusted. CA19-9, carbohydrate antigen 19-9.

Another challenge regarding resection classification is how to define the margin clearance when a venous resection is performed. The invasion of the SMV-facing margin, especially beyond the adventitia of the PV, has been reported to be associated with a poorer prognosis[16], although the margin itself is wider after the venous resection. A study by Kleive *et al.*[17] demonstrated that the margin clearance at the SMV-facing margin was frequently less than or equal to 1 mm, especially for large tumours with a broad invasive front, and concluded that it is not feasible to achieve a margin clearance greater than 1 mm. The SMV margin analysis showed that a positive margin on the vein specimen was associated with longer OS among stage IIB patients. This result may be explained by a potentially more aggressive oncological approach among these patients.

This study demonstrated that evaluation of venous infiltration intraoperatively can be difficult and inaccurate, showing that

Table 4 Disease-free survival analysis: without venous resection

	Stage IIB				Stage III			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% c.i.)	P	HR (95% c.i.)	P	HR (95% c.i.)	P	HR (95% c.i.)	P
Age (>65 *versus* ≤65 years)	0.98 (0.72,1.33)	0.875	–	–	1.27 (0.87,1.84)	0.211	–	–
Sex (female *versus* male)	0.96 (0.71,1.29)	0.785	–	–	0.81 (0.57,1.15)	0.235	–	–
BMI >25 kg/m^2 (yes *versus* no)	0.89 (0.59,1.13)	0.225	–	–	0.69 (0.49,0.99)	0.044	0.61 (0.42,0.90)	0.012
ASA grade (III–IV *versus* I–II)	0.99 (0.70,1.39)	0.943	–	–	1.39 (0.95,2.04)	0.095	1.52 (1.00,2.31)	0.050
ASA grade (unknown *versus* III–IV)	3.57 (0.50,25.8)	0.207	–	–	5.69 (0.78,41.7)	0.087	2.89 (0.38,21.9)	0.306
CA19-9 (per 100 kU/l increase)	1.01 (1.00,1.02)	0.037	1.01 (1.00,1.03)	0.035	1.01 (1.00,1.02)	0.003	1.02 (1.01,1.03)	<0.001
Tumour size (per cm increase)	1.18 (1.05,1.32)	0.004	1.33 (1.15,1.55)	<0.001	1.05 (0.92,1.20)	0.513	–	–
T stage (T3 *versus* T1–2)	2.20 (1.58,3.06)	<0.001	–	–	1.04 (0.72,1.50)	0.839	–	–
T stage (T3 *versus* unknown)	0.60 (0.19,1.89)	0.382	–	–	0.72 (0.23,2.29)	0.579	–	–
Perineural invasion (yes *versus* no)	1.60 (1.04,2.46)	0.034	1.06 (0.59,1.88)	0.856	0.73 (0.42,1.28)	0.276	–	–
Perineural invasion (unknown *versus* no)	1.22 (0.55,2.71)	0.634	0.94 (0.34,2.63)	0.903	1.43 (0.51,4.00)	0.492	–	–
Angioinvasion (yes *versus* no)	1.22 (0.89,1.67)	0.214	–	–	1.15 (0.69,1.93)	0.589	–	–
Angioinvasion (unknown *versus* no)	1.46 (0.88,2.42)	0.145	–	–	1.76 (0.86,3.60)	0.124	–	–
Differentiation stage (3–4 *versus* 1–2)	1.14 (0.83,1.56)	0.409	–	–	1.11 (0.77,1.60)	0.575	–	–
Differentiation stage (unknown *versus* 1–2)	1.69 (0.78,3.63)	0.184	–	–	1.51 (0.65,3.48)	0.337	–	–
Adjuvant therapy* (yes *versus* no)	0.88 (0.59,1.30)	0.511	0.68 (0.43,1.08)	0.105	0.38 (0.25,0.57)	<0.001	0.35 (0.23,0.55)	<0.001
Adjuvant therapy* (unknown *versus* no)	0.43 (0.18,1.03)	0.058	0.38 (0.16,0.93)	0.034	0.29 (0.14,0.59)	<0.001	0.31 (0.154,0.64)	0.001
MRM cut-off >0 mm* (yes *versus* no)	1.07 (0.67,1.72)	0.767	–	–	1.05 (0.67,1.67)	0.824	–	–
MRM cut-off >0 mm* (unknown *versus* no)	1.21 (0.60,2.41)	0.596	–	–	1.68 (0.82,3.4)	0.153	–	–
MRM cut-off >0.5 mm* (yes *versus* no)	0.94 (0.64,1.40)	0.777	–	–	0.97 (0.63,1.49)	0.883	–	–
MRM cut-off >0.5 mm* (unknown *versus* no)	0.95 (0.48,1.88)	0.881	–	–	1.60 (0.80,3.17)	0.183	–	–
MRM cut-off >1 mm* (yes *versus* no)	0.97 (0.69,1.35)	0.837	–	–	1.09 (0.72,1.65)	0.617	–	–
MRM cut-off >2 mm* (yes *versus* no)	1.03 (0.65,1.63)	0.903	–	–	1.59 (0.81,3.12)	0.176	–	–
MRM cut-off >2 mm* (unknown *versus* no)	0.97 (0.56,1.67)	0.911	–	–	1.08 (0.66,1.73)	0.774	–	–

*Centre adjusted. CA19-9, carbohydrate antigen 19-9; MRM, minimum reported margin.

Table 5 Disease-free survival analysis: SMV margin analysis

	Stage IIB				Stage III			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% c.i.)	*P*	HR (95% c.i.)	*P*	HR (95% c.i.)	*P*	HR (95% c.i.)	*P*
Age (>65 *versus* ≤65 years)	0.92 (0.58,1.47)	0.739	–	–	0.78 (0.54,1.12)	0.179	–	–
Sex (female *versus* male)	0.65 (0.42,1.00)	0.049	0.59 (0.36,0.96)	0.032	1.28 (0.90,1.81)	0.170	–	–
BMI >25 kg/m^2 (yes *versus* no)	0.98 (0.60,1.62)	0.947	–	–	1.36 (0.94,1.96)	0.104	–	–
ASA grade (III–IV *versus* I–II)	0.95 (0.57,1.58)	0.852	–	–	0.90 (0.59,1.36)	0.631	1.26 (0.78,2.20)	0.341
ASA grade (unknown *versus* I–II)	3.12 (0.43,23.0)	0.263	–	–	7.65 (1.03,56.8)	0.047	5.28 (0.64,43.9)	0.124
CA19-9 (per 100 kU/l increase)	1.01 (1.00,1.02)	0.127	–	–	1.01 (1.00,1.02)	0.060	1.01 (1.00,1.02)	0.008
Tumour size (per cm increase)	1.21 (1.05,1.39)	0.007	0.82 (0.62,1.09)	0.171	1.00 (0.90,1.11)	0.978	–	–
T stage (T3 *versus* T1–2)	3.24 (1.90,5.55)	<0.001	8.01 (3.35,19.2)	<0.001	1.10 (0.76,1.58)	0.62	–	–
T stage (unknown *versus* T1–2)	0.65 (0.09,4.73)	0.670	0.21 (0.02,2.45)	0.215	0.35 (0.09,1.43)	0.144	–	–
Perineural invasion (yes *versus* no)	1.12 (0.49,2.59)	0.786	–	–	1.48 (0.72,3.05)	0.291	1.44 (0.53,3.96)	0.477
Perineural (unknown *versus* no)	3.00 (0.60,15.1)	0.182	–	–	15.6 (3.09,78.5)	<0.001	6.32 (0.69,57.8)	0.10
Angioinvasion (yes *versus* no)	1.08 (0.68,1.74)	0.739	0.90 (0.48,1.67)	0.736	1.19 (0.79,1.77)	0.410	0.46 (0.25,0.85)	0.013
Angioinvasion (unknown *versus* no)	2.26 (1.11,4.60)	0.025	1.76 (0.70,4.47)	0.23	1.82 (0.83,4.22)	0.075	0.45 (1.01,24.0)	0.113
Differentiation stage (3–4 *versus* 1–2)	1.32 (0.84,2.09)	0.235	1.53 (0.84,2.79)	0.165	0.90 (0.62,1.29)	0.556	1.83 (1.09,3.08)	0.023
Differentiation stage (unknown *versus* 1–2)	2.90 (1.14,7.39)	0.026	3.88 (1.23,12.3)	0.021	6.73 (2.05,22.1)	0.002	4.93 (1.01,24.0)	0.048
Adjuvant therapy* (yes *versus* no)	0.79 (0.39,1.62)	0.524	0.62 (0.28,1.38)	0.242	0.57 (0.36,0.89)	0.013	0.60 (0.36,0.98)	0.041
Adjuvant therapy* (unknown *versus* no)	0.36 (0.12,1.08)	0.067	0.38 (0.11,1.32)	0.126	0.30 (0.12,0.75)	0.009	0.17 (0.06,0.50)	0.001
SMV margin status* (>0.5 *versus* ≤0.5 mm)	0.51 (0.28,0.92)	0.024	0.35 (0.17,0.69)	0.002	0.66 (0.36,1.20)	0.174	–	–
No cancer in the vein specimen	0.91 (0.44,1.88)	0.911	0.72 (0.31,1.67)	0.446	1.26 (0.70,2.28)	0.437	–	–
Cancer in the vein specimen	0.63 (0.33,1.21)	0.166	0.65 (0.33,1.30)	0.222	1.52 (0.89,2.60)	0.126	–	–

*Centre adjusted. CA19-9, carbohydrate antigen 19-9; SMV, superior mesenteric vein.

nearly 40% of venous specimens had no malignancy during the final pathological examination. These data are concordant with the results of a large study by Delpero *et al.*[18], which reported that 46% of patients with a venous resection had no vein infiltration.

In this study, adjuvant therapy was associated with longer OS in the multivariable analysis of both stage IIB and stage III patients. The DFS analysis showed a beneficial effect of adjuvant therapy on DFS for stage III patients, but not for stage IIB patients. This may be explained by varying follow-up schemes in the participating centres when the date of the detection of local recurrence or distant metastasis is associated with the follow-up intervals.

The main strength of this study is the use of the standardized histological, axial slicing protocol (LEEPP). Moreover, patients were recategorized according to the eighth edition of TNM classification by the AJCC to stage IIB and stage III PDAC subgroups. The new categories take into consideration the effect of the nodal involvement on survival. Thus, the application of the eighth edition of TNM classification decreased the potential bias caused by the nodal status in the results. In addition, data on a 1 mm margin clearance were available in all reports, which enabled the analysis of the current R0 definition among patients who underwent a pancreatic resection without a venous resection. The exclusion of patients who underwent neoadjuvant therapy allowed direct evaluation of the effect of surgical radicality on survival. The analysis was centre adjusted to decrease the impact of centre-related differences.

Some limitations need to be acknowledged. The retrospective and multicentre nature of the study challenged data recording completeness. This might have led to an underpowered analysis, especially with regard to the SMV margin analysis. During recent years, preoperative neoadjuvant therapy has become a common strategy when there is a suspicion of any vessel involvement in the preoperative imaging. The effect of margin clearance on survival after neoadjuvant therapy could not be determined in this study due to the limitations in the dataset. Despite the standardized histopathological protocol, the majority of the pathology reports contained incomplete data on the margin clearance for different margin sites. This is most likely due to a clinical policy not to report the margin widths when the margin clearance was less than 1 mm for one margin, as that held no clinical relevance for the current R0 or R1 definition.

In conclusion, adjuvant therapy plays an essential role in the prognosis among patients with PDAC with nodal involvement. The margin clearance greater than 1 mm showed no significant association with OS in this study. As earlier studies have reported, true margin clearance analysis requires meticulous sampling of the specimens and, without this, the microscopic spread of PDAC may not be noticed. Whether the same quality of margin clearance evaluation can be achieved in clinical work as in a research setting is uncertain. On the other hand, challenges exist regarding how to interpret margin clearance after a vein resection and/or when a greater than 1 mm margin is impossible to achieve due to tumour location. This study emphasizes the role of postoperative oncological therapy and diminishes the role of 1 mm margin clearance as a prognostic factor. In the future, neoadjuvant therapy may decrease infiltrative growth and systemic spread and improve OS, especially in borderline resectable PDAC patients.

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Disclosure

The authors declare no conflicts of interest.

Data availability

Data were handled according to personal data legislation and individual data are not available.

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