

ORIGINAL ARTICLE

Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in 150 evaluable specimens

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Abstract

Objectives: This study aimed to determine the impact of a standardized pathological protocol on resection margin status after pancreaticoduodenectomy (PD) for ductal adenocarcinoma.

Methods: A total of 150 patients operated during 2008–2010 were included in a prospective multicentre study using a 'quality protocol'. Multicolour inking by the surgeon identified three resection margins: the portal vein–superior mesenteric vein margin (PV-SMVm) or mesenterico–portal vein groove; the superior mesenteric artery margin (SMAm), and the posterior margin. Resection margins were stratified by 0.5-mm increments (range: 0–2.0 mm). Pancreatic neck, bile duct and intestinal margins were also analysed. Correlations between histopathological factors and survival in the 0-mm resection margin group were analysed.

Results: Thirty-six patients (24%) had a PV-SMV resection (PV-SMVR). An analysis of resections categorized according to margin distances of 0 mm, <1.0 mm, <1.5 mm and <2.0 mm confirmed R1 resections in 35 (23%), 91 (61%), 94 (63%) and 107 (71%) patients, respectively. The most frequently invaded resection margin was the PV-SMVm (35% of all patients) and PV-SMVR was the only factor correlated with a higher risk for at least one 0-mm positive resection margin on multivariate analysis ($P < 0.001$). Two-year progression-free survival (PFS) and median PFS time in patients with R0 and R1 resections (at 0 mm), respectively, were 42.0% and 26.5%, and 19.5 months and 10.5 months, respectively ($P = 0.02$). A positive PV-SMVm and SMAm had significant impact on PFS, whereas a positive posterior margin had no impact.

Conclusions: Pancreaticoduodenectomy requiring PV-SMVR was associated with a higher risk for R1 resection. The standardization of histopathological analysis has a clinically relevant impact on PFS data.

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Introduction

With more than 278 000 new diagnoses each year worldwide, pancreatic ductal adenocarcinoma (PDAC) accounts for 10% of all

digestive system cancers.¹ Some 266 000 of these newly diagnosed patients will die.^{1,2} The annual incidence rate approximates the mortality rate, which exceeds annual prevalence. Curative resection with negative resection margins (R0 resection) represents the only chance of cure, but the rate of such resections is remarkably low as a result of the lack of early specific biological markers, non-specific symptoms at presentation, delayed diagnosis and early

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metastasis.^{2–4} The prognosis remains extremely poor, with 5-year survival rates of <5% in the EU and USA.^{2–4} As a generally accepted oncological principle after the resection of a solid tumour, microscopic resection margin involvement (R1) has been reported as an independent predictor of poor long-term survival following pancreaticoduodenectomy (PD) for PDAC in several studies,^{5–21} but not in others.^{22,23} Underreporting of microscopic margin involvement may cause some discrepancy between margin status and clinical outcome, and hence the clinical significance of R1 resection remains unclear.^{24,25} There has recently been increased interest in resection margin involvement in PDAC, as well as in its prognostic and therapeutic implications. The standardization of pathological examination increased the rate of R1 resections after PD from 20% to 50%^{10,12} and to >70% when an intensified histopathological workup was applied.^{20,26–34}

Adjuvant chemotherapy after PD for PDAC is presently the standard of care in the EU.^{6,35} Significant progress has been made in preoperative imaging, and major improvements have been achieved surgically in terms of postoperative morbidity and mortality.³⁶ However, assessment of the quality of histopathological reporting on margin status, as well as the quality of the resection, should represent a crucial step towards patient stratification. The results of randomized multicentre trials evaluating adjuvant therapy for PDAC should be interpreted according to those settings.³⁷ In the present study, a surgical quality protocol and a standardized pathological workup were applied prospectively to 150 consecutive pancreatic head resections for PDAC performed in French tertiary referral centres.

Materials and methods

Patient series

A prospective French multicentre study approved by the National Cancer Institute (INCA) commenced in August 2008 (ClinicalTrials.gov identifier: NCT00918853). Enrolment closed in May 2010. The collection of data for primary outcome measures was completed in May 2012. A total of 214 patients with periampullary tumours provided informed consent to their inclusion in the study before laparotomy, and 150 patients (70%) with true macroscopically margin-free PDAC underwent PD and entered the present study. Exclusion criteria applied after surgery included findings of macroscopic residual tumour in the operative field (R2 resection), non-adherence to the surgical protocol, non-ductal adenocarcinoma, and margin analysis performed without using the predefined criteria. Sixty-four (30%) patients with distal bile duct cancers, ampullary tumours, neuroendocrine tumours, non-invasive intraductal papillary mucinous neoplasm (IPMN) and periampullary tumours of various aetiologies were excluded after histopathological review. Any doubtful diagnosis led to the exclusion of that patient from the study.

Standardized PD by ‘quality protocol’

Circumferential dissection of the portal vein–superior mesenteric vein (PV-SMV) axis and dissection of the right hemi-

circumference of the superior mesenteric artery (SMA) to the right of the coeliac trunk were required to obtain a good medial clearance (Fig. 1). The dissection of the SMA removed all soft tissue to the right of the adventitia, which corresponded to the SMA margin (SMAM) on the specimen.^{22,38–40} This technique obviated the need for intraoperative frozen-section analysis of the SMAM. A standard lymphadenectomy plus resection of lymph nodes to the right of the coeliac trunk, hepatic artery and hepato-duodenal ligament were carried out in all patients.⁴¹ The pancreatic neck transection margin and the common bile/hepatic duct transection margins were evaluated using frozen-section analysis and, if results were positive, additional tissue was resected to achieve negative margins at these two sites. En bloc resection of the SMV, PV or PV-SMV confluence was performed in 36 patients (PV-SMVR: 24%); PV-SMVR was planned in half of these patients and performed in the other half in response to intraoperative suspicion of venous wall invasion. Four patients were subjected to combined arterial resection as a result of the abutment or encasement of a short segment of the hepatic artery. Three patients underwent en bloc right colectomy for invasion of the mesocolon.

The surgeon clearly identified the margins in the operative room with multicolour coded inking of: (i) the mesenterico-portal vein groove or PV-SMV margin (PV-SMVM); (ii) the SMA margin (SMAM), and (iii) the posterior margin (Fig. 2). In cases of PV-SMVR, the venous segment was clearly identified on the specimen (Fig. 3). The anterior surface was not considered as a transection margin and was not inked.

Standardization of the protocol for pathological examination

Serial slicing of the entire pancreatic head specimen was performed in a single axial plane (i.e. perpendicular to the longitudinal axis of the duodenum) according to the guidelines of the Royal College of Pathologists and the Leeds Pathology Protocol.^{26,27,29,40,42} Thus, large slices were obtained (median number: 12), allowing a precise study of each inked margin in increments of 0.5 mm from 0 mm to 2.0 mm. Margin involvement (R1) was defined for the 0-mm margin if tumour cells were present at the inked margin; R1 was also defined for each margin width if tumour cells were present within the margin, independently of the mode of tumour spread. The ‘vascular’ margin was defined as the PV-SMVM plus SMAM inked margins. Patients undergoing PV-SMVR for local invasion were considered to have a positive PV-SMVM if tumour was present at the resection margin, not simply intraluminally. The resection was considered as curative (R0) if no tumour cells were identified at any of the resection margins (including bile duct and pancreatic neck non-inked transection margins), again for each margin width (see Appendix). The pathological protocol also included the maximal transverse diameter of the tumour, the tumour–node–metastasis (TNM) classification, the grade of differentiation, the presence or absence of perineural, lymphatic and/or vascular spread, and the

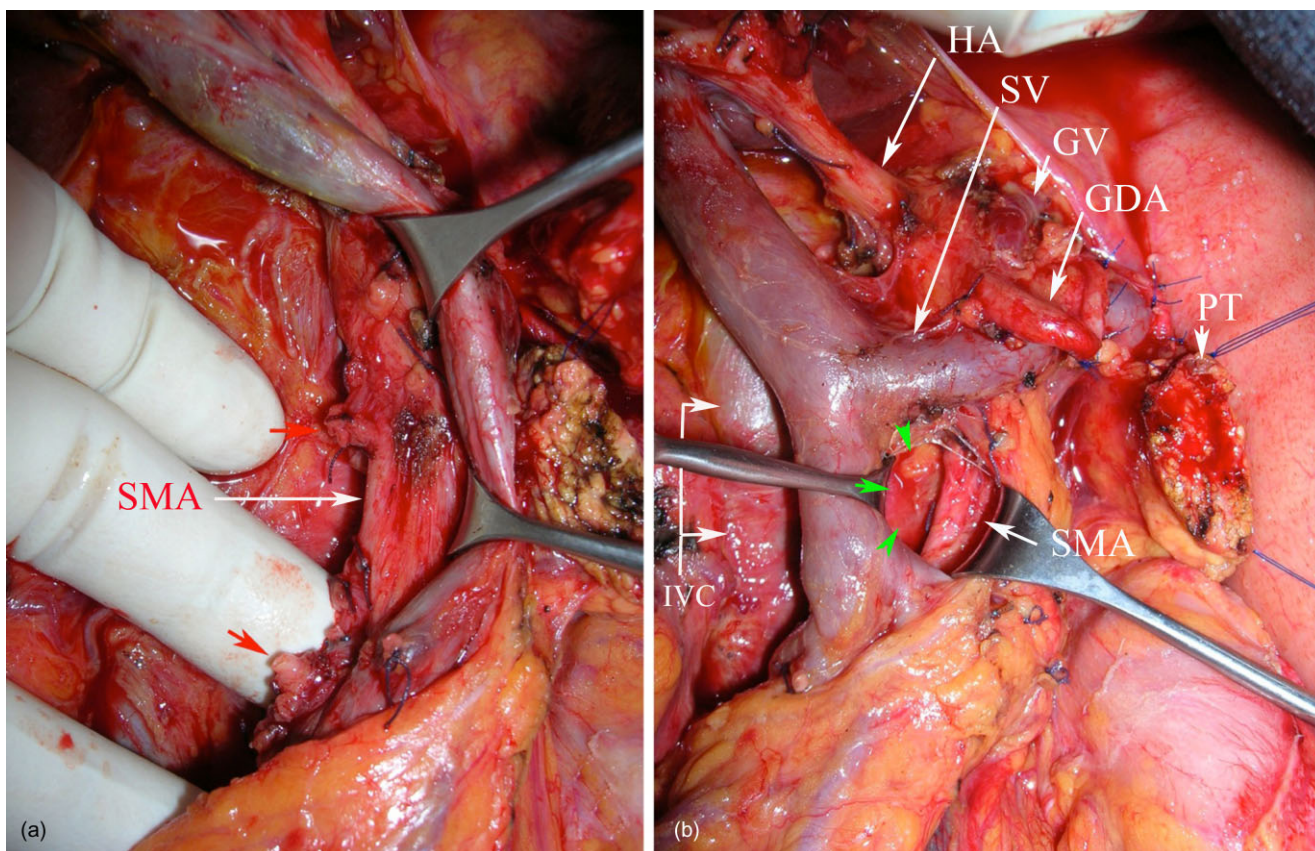


Figure 1 Standardized pancreaticoduodenectomy. Operative view showing: (a) the dissection of the right hemi-circumference of the superior mesenteric artery (SMA) with elective division of the pancreaticoduodenal arteries (red arrows); (b) clearance of the medial margin (green arrows) with no residual soft tissue to the right of the SMA. Note the circumferential dissection of the mesenterico–portal venous axis. HA, hepatic artery; SV, splenic vein; GV, gastric vein; GDA, stump of the gastroduodenal artery; PT, pancreatic transection; IVC, inferior vena cava

number of lymph nodes retrieved from the specimen, enabling the calculation of the lymph node ratio (LNR). The presence and grading of pre-neoplastic lesions were also recorded. In PV-SMVR, the length of the resection was recorded and the margins of the vessel segment were examined; if the vein was invaded, the depth of invasion was specified (invasion of adventitia, media or intima). Pathological data for PD specimens with PV-SMVR were compared with data for PD specimens without PV-SMVR.

Power and sample size considerations

The primary objective of this prospective multicentre study was to confirm the negative impact on longterm clinical outcome of resection margin involvement (R1 or R0) in patients with PDAC who underwent PD according to a standardized protocol. As defined in the protocol, the main evaluation criterion was overall survival (OS): a minimum of 87 deaths were required to reach 90% power using a two-sided 0.05-level log-rank test to detect a significant difference in hazard ratio (HR) between R1 and R0

status, assuming a true HR difference ($HR = 2.0$). In response to an unexpectedly low 2-year death rate, the initial sample size ($n = 156$) was increased. A total of 214 patients were recruited prior to laparotomy, of whom 150 with proven macroscopically margin-free PDAC entered this prospective 2-year follow-up study period. The first patient was accrued in August 2008 and the last in May 2010.

Follow-up

According to the protocol, patients were scheduled to be followed for a 2-year fixed period. Postoperative mortality was defined as in-hospital mortality or mortality within 30 days of discharge (five patients). Patients were followed every 4 months after discharge and evaluated using computed tomography (CT) and carbohydrate antigen 19-9 (CA 19-9) levels, or reviewed for any abnormal symptom. If an isolated elevation of CA 19-9 occurred [i.e. without documented CT or positron emission tomography (PET)-CT recurrence], the patient was followed every 2 months.

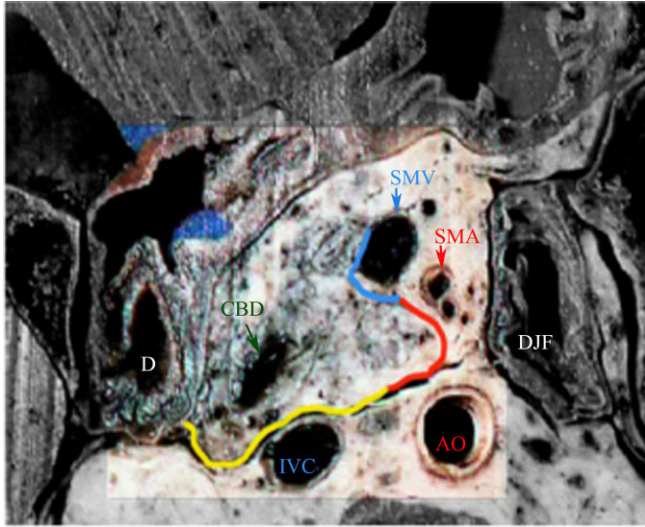


Figure 2 Cross-section of the pancreatic head showing the inked margins: the mesenterico-portal vein groove (medial circumferential resection margin) in blue, the superior mesenteric artery (SMA) margin (uncinate margin) in red and the posterior margin in yellow. D, duodenum; DJF, duodenojejunal flexure; CBD, common bile duct; AO, aorta; IVC, inferior vena cava; SMV, superior mesenteric vein

Recurrences were defined as locoregional or metastatic (including peritoneal carcinomatosis) events or both.

As of May 2012, when data collection was completed, all demographic clinical and histological characteristics were monitored and centrally reviewed; however, longterm clinical outcome data collection remains ongoing or under resolution. According to these preliminary longterm data, 66 patients died and 71 (47%) demonstrated disease progression. To preserve the power of this prospective study, the time to progression or death was defined as the primary evaluation criterion in a revised statistical analysis plan issued in blind conditions.

Statistical analysis

Descriptive statistics were used to summarize the clinical and histological characteristics of the full cohort of patients who entered the prospective follow-up study period ($n = 150$). Two groups of patients were first considered: patients who underwent standard PD ($n = 114$), and patients who underwent PD with PV-SMVR ($n = 36$). Differences between the groups in patient characteristics were assessed using the chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. The main objective of this study was to evaluate microscopic involvement on at least one of the inked resection margins and to identify factors correlated with resection margin involvement. A selection of factors that may influence microscopic involvement were established prior to data analysis and then categorized using predefined cut-offs [age, sex, body mass index (BMI), Karnowsky index, conventional pathological factors,

venous resection, preoperative treatments]. Factors correlated with positive margins at each increment were identified using the non-parametric Fisher's (exact) chi-squared test. All factors found to be significant at the 0.05 level or to be of borderline significance at the 0.15 level in univariate analysis were entered into a multivariate logistic regression model to identify independent factors correlated with microscopic involvement at each margin increment. Similar univariate and multivariate analyses were carried out for each category of margin involvement defined according to the presence of tumour cells at the inked margin and within resection margins in 0.5-mm increments. Preliminary longterm clinical outcome data were used to measure the prognostic impact of microscopic involvement on at least one inked margin. Median survival, OS and progression-free survival (PFS) were calculated for the 0-mm margin. Thus, the following results are preliminary data because the positive margin is defined by the presence of tumour cells at 0 mm.^{38,39} Patients alive without disease progression and patients alive at the end of follow-up were considered as censored on the right at the date of last contact. Time to progression or death (PFS) and time to death (OS) defined from the date of PD to the date of the event analysed were summarized using the Kaplan-Meier method and comparisons were made using the log-rank test. All statistical analyses were carried out using SAS Version 9.3 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was accepted at the 5% level with no adjustment for multiple testing.

Results

Demographics are shown in Table 1. The study group included 95 men and 55 women, with a median age of 63 years (range: 41–84 years). Twenty-two (15%) patients had IPMN with invasive cancer. Twenty-nine (19%) patients received neoadjuvant treatment (FOLFIRINOX: $n = 12$; gemcitabine or 5-fluorouracil and platinum-based chemoradiation: $n = 17$), mostly for suspicion of involvement of more than half of the circumference of the venous axis on the portal phase of the preoperative CT. Nine of the 36 PV-SMVRs and all four arterial resections were performed after neoadjuvant treatment.

Clinicopathological data for the entire cohort are reported in Table 1. A total of 78% of the tumours were classified as T3 tumours (T1: 8%; T2: 9%; T4: 5%). More than half of the tumours were moderately differentiated (grade 1: 30%; grade 2: 52%; grade 3: 19%). Significantly more poor prognostic factors were observed in the PD with PV-SMVR group (Table 1).

Margin status

The mean and median distances separating tumour cells from each inked margin are reported in Table 2. Microscopic involvement was present on at least one of the inked margins in 35 patients (23%) at the 0-mm margin and in 91 (61%), 94 (63%) and 107 (71%) patients at the 1.0-mm, 1.5-mm and 2.0-mm margins, respectively (Table 1). The number of patients in whom two or three margins were involved increased from 14 for the

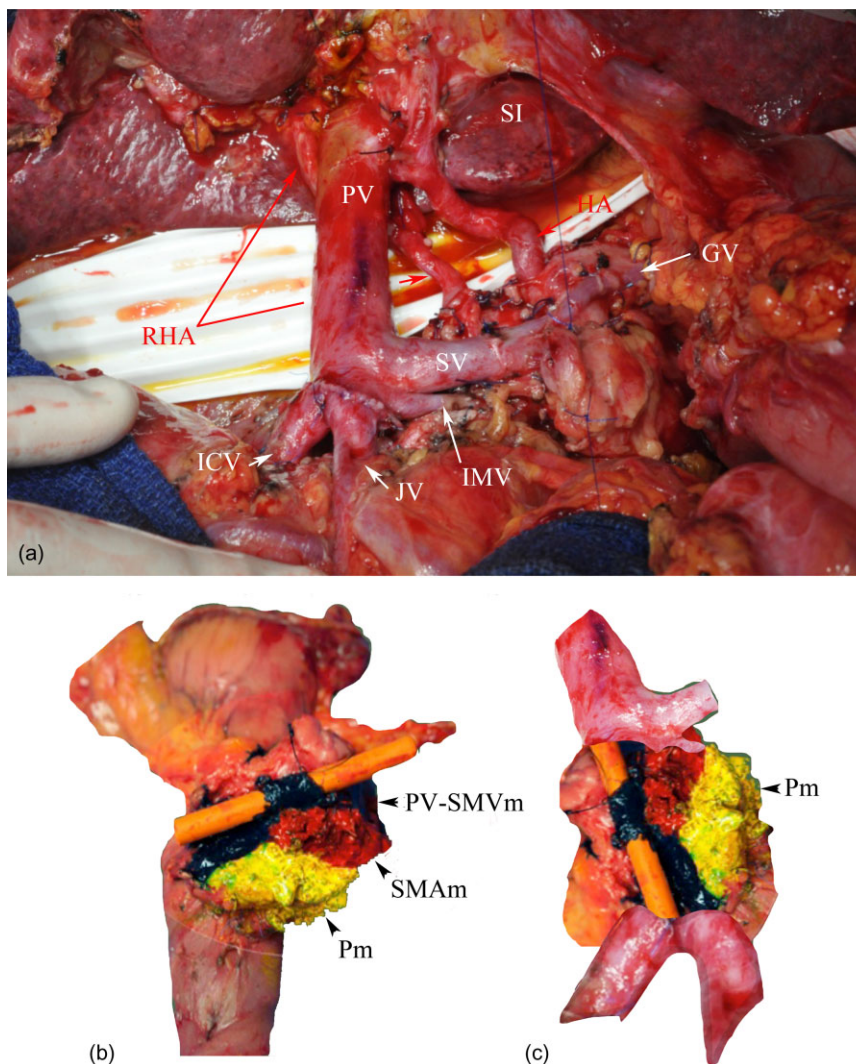


Figure 3 Pancreaticoduodenectomy with venous resection. (a) Operative view of venous confluence reconstruction. (b) A simple trick to identify the vein for the pathologist: a small drain is gently inserted into the venous lumen; the vein is inked to show the portal vein groove (PV-SMVm). (c) Photographic reconstruction of the venous axis with a medial and posterior view of the specimen. RHA, right hepatic artery; PV, portal vein; SI, liver segment I; GV, gastric vein; ICV, ileo-colic vein; JV, jejunal vein; SV, splenic vein; IMV, inferior mesenteric vein; SMAm, superior mesenteric artery margin; Pm, posterior margin

0-mm margin (14/35, 40%) to 40 (40/91, 44%), 43 (43/94, 46%) and 66 (66/107, 62%) for the 1.0-mm, 1.5-mm and 2.0-mm margins, respectively (Table 3).

The rates of positive inked margins within each increment are reported in Table 1. More invaded margins were observed in the PV-SMVR group (Table 1). The most frequently invaded margin was the PV-SMVm.

Invasion of the 'vascular' margin (PV-SMVm plus SMAm) was present in 23% of specimens at the 0-mm margin and in close to 50% at the 1.0-mm and 1.5-mm margins. Despite the intraoperative frozen-section analysis, 1% ($n = 2$) of bile duct transections and 5% ($n = 8$) of pancreatic neck transections were found to be invaded on final examination.

In summary, if R1 resection is defined by a positive margin of 0 mm,^{38,39,43,44} 23% of the present patients achieved R1 resection. If R1 resection is defined by the presence of tumour cells within 1.0 mm^{40,42,45} or 1.5 mm,⁴⁶ 61% and 63%, of the present patients achieved R1 resection. Bile duct and pancreatic neck transection invasion resulted in an additional 7% of R1 resections for any definition of R1 on the inked margins. Thus, the rate of R1 resections was 30% when R1 was defined according to the 0-mm rule and 68% when R1 was defined according to the 1.00-mm rule (ratio: 2.3).

Univariate and multivariate analyses of factors associated with the risk for a positive inked margin at each increment are shown in Tables 4 and 5.

Table 1 Comparison of clinicopathological data for the entire cohort and in the standard pancreaticoduodenectomy (PD) group and the PD with portal vein–superior mesenteric vein resection (PV-SMVR) group

	All patients (n = 150)	Standard PD (n = 114)	PD with PV-SMVR (n = 36)	P-value (χ^2 or Wilcoxon test)
Age, years, median (range)	63 (41–84)	64 (41–84)	62 (41–78)	0.135
Male, n (%)	95 (63%)	72 (63%)	23 (64%)	0.909
Female, n (%)	55 (37%)	42 (37%)	13 (36%)	
pT3, n (%)	111 (74%)	80 (70%)	31 (86%)	0.057
pN1, n (%)	108 (72%)	78 (68%)	30 (83%)	0.417
Grade 3, n (%)	24 (19%)	14 (15%)	10 (28%)	0.037
Tumour size, cm, median (range)	3.5 (0.21–12)	3 (0.21–9)	4 (1.5–12)	<0.001
LN retrieved, n, median (range)	23 (3–80)	19 (3–55)	37 (7–80)	<0.001
Disease-positive LN, n, median (range)	3 (0–50)	2 (0–16)	3 (0–50)	0.211
LNR, median (range)	0.11 (0–0.75)	0.12 (0–0.75)	0.08 (0–0.72)	0.552
	42 (29%)	34 (32%)	8 (22%)	0.785
Neoadjuvant treatment, n (%)	29 (19%)	20 (18%)	9 (25%)	0.323
Positive margin status for the 0-mm margin				
At least one positive margin, n (%)	35 (23%)	17 (15%)	18 (50%)	<0.001
Pm, n (%)	11 (7%)	4 (4%)	7 (19%)	0.009
PV-SMVM, n (%)	27 (18%)	12 (11%)	15 (42%)	<.001
SMAM, n (%)	15 (10%)	6 (5%)	9 (25%)	<.001
Vascular margin ^a , n (%)	34 (23%)	16 (14%)	18 (50%)	<.001
Positive margin status for the 1.0-mm margin				
At least one positive margin, n (%)	91 (61%)	63 (55%)	28 (78%)	0.016
Pm, n (%)	52 (37%)	35 (31%)	17 (47%)	0.069
PV-SMVM, n (%)	61 (41%)	39 (34%)	22 (61%)	0.004
SMAM, n (%)	37 (25%)	24 (21%)	13 (36%)	0.067
Vascular margin ^a , n (%)	73 (49%)	48 (42%)	25 (69%)	0.004
Positive margin status for the 1.5-mm margin				
At least one positive margin, n (%)	94 (63%)	66 (58%)	28 (89%)	0.031
Pm, n (%)	40 (27%)	21 (18%)	19 (53%)	0.131
PV-SMVM, n (%)	62 (41%)	40 (35%)	22 (61%)	0.006
SMAM, n (%)	40 (27%)	26 (23%)	14 (39%)	0.057
Vascular margin ^a , n (%)	74 (49%)	49 (43%)	25 (69%)	0.006
Positive margin status for the 2.0-mm margin				
At least one positive margin, n (%)	107 (71%)	76 (67%)	31 (86%)	0.025
Pm, n (%)	54 (36%)	34 (30%)	20 (56%)	0.187
PV-SMVM, n (%)	78 (52%)	54 (47%)	24 (67%)	0.043
SMAM, n (%)	54 (36%)	36 (32%)	18 (50%)	0.045
Vascular margin ^a , n (%)	87 (58%)	59 (52%)	28 (78%)	0.006

^aVascular margin: SMAM + PV-SMVM.

LN, lymph node; LNR, lymph node ratio; Pm, posterior margin; PV-SMVM, portal vein–superior mesenteric vein margin; SMAM, superior mesenteric artery margin (uncinate margin).

Clinical impact of resection margin status

The median follow-up was 24.1 months (range: 23.7–24.8 months). Six (4%) patients were lost to follow-up (median follow-up: 7.5 months; range: 1.4–16.1 months). During the follow-up period, 66 (44%) patients died and disease progression was observed in 71

(47%) patients; five (3%) patients died from perioperative causes. A total of 54 (37%) patients developed one or more metastases, with ($n = 15$, 10%) or without ($n = 39$, 27%) local recurrence. In 16 (11%) patients, local recurrence was isolated. Eight patients with isolated local recurrence had R0 resections.

Table 2 Mean and median clearances observed for each inked margin. In some patients the margin status was specified as positive or negative for each of the increments, but the precise distance between the margin and the tumor cells was not clearly specified

Inked margins (number of patients with a specified distance in mm)	Mean clearance (mm \pm SD)	Median clearance (mm; range)
Pm (129/150)	5.6 (7)	3.00 [0.10–35.00]
PVSMVm (115/150)	6.8 (6.9)	3.00 [0.10–20.00]
SMAm (123/150)	9.0 (9.6)	5.00 [0.20–30.00]
«Vascular» margin (PVSMVm + SMAm; 106/150)	5.8 (6.6)	2.25 [0.10–20.00]

Table 3 R1 resection rate for each margin increment (0–2.0 mm) and proportions of patients with at least one, two or three positive margins, respectively. R1 resection rates were comparable across the 1.0-mm and 1.5-mm margin widths

Margin widths, mm	R1 resections, n/n (%)	One positive margin, n/n (%)	Two positive margins, n/n (%)	Three positive margins, n/n (%)
0	35/150 (23%)	21/35 (60%)	10/35 (29%)	4/35 (11%)
1.0	91/150 (61%)	51/91 (56%)	21/91 (23%)	19/91 (21%)
1.5	94/150 (63%)	51/94 (54%)	23/94 (24%)	20/94 (21%)
2.0	107/150 (71%)	41/107 (38%)	38/107 (36%)	28/107 (26%)

Median OS in the 150 patients was 20 months [95% confidence interval (CI) 16.4–22.6]. Patients with at least one positive inked margin had median survival of 17.7 months (11.7–36.4), whereas patients with R0 resections had a median survival of 32.9 months [$P = 0.10$; 95% CI 22.7 – not reached (NR)]. Two-year OS rates in patients with R0 and R1 resections were, respectively, 59.3% (95% CI 48–69) and 44.6% (95% CI 27–61) ($P = 0.106$; HR = 0.64, 95% CI 0.37–1.11) (Fig. 4). Median and 2-year rates of PFS by margin status are shown in Fig. 5 and Table 6. The relationship between margin status at each increment and survival is yet to be determined.

Discussion

This study is the first prospective multicentre study of resection margins in PDAC specimens to use a surgical quality protocol and a standardized pathological workup. Despite recommendations published since 1996,^{47–51} there is no consensus today on PD specimen handling and the assessment of resection margins. There is also a lack of consensus regarding the definition of microscopic margin involvement. However, this topic has recently attracted increasing interest.^{20,21,26–34,46}

There is marked heterogeneity in published rates of R1 resection. Most series have reported rates well below 20–40%, by contrast with those that report rates of >70% in series using a standardized protocol for the pathological examination of PD specimens.^{24,28–34} These discrepancies are mainly caused by differences in pathological assessment rather than in surgical procedure and patient selection,^{26–28,30–34} although outcomes in low-volume centres negatively affect the rate of positive resection margins.⁵² The Leeds²⁴ and Heidelberg²⁸ groups were the first to demonstrate that the standardization of histopathological study resulted in a significant increase in R1 resection rates, without requiring any change in surgical technique (respectively, from 53% to 85%²⁴ and

14% to 76%²⁸). Thus, a high rate of R1 resection in PDAC is clearly a marker of high-quality pathology and depends firstly on the number of peri-pancreatic soft tissue resection margins examined, secondly on the number of blocks analysed,^{27,42} and thirdly on the minimum clearance in millimetres used to define microscopic margin involvement (R1).

In a study published recently by Campbell *et al.*, tumour involvement within 1.0 mm of, but not directly reaching, one or more resection margins represented 45% of the 79% of resection margins identified as positive.³⁰ In the most recent series, comparisons of R1 rates achieved using the Union for International Cancer Control (UICC) criteria (R1: 0 mm definition), which are commonly used in North America,^{22,38,39,43,44} and those achieved using the UK Royal College of Pathologists (RCPath) criteria (R1: 1.0 mm definition)⁴² show ratios ranging from 1.3 to 1.8.^{28,30–32,34} The ratio was 2.3 in the present study. Katz *et al.* reported a ratio of 5.5 (4–22%) in a study in which only the SMAm was assessed and in which 76% of patients had received preoperative radiochemotherapy; this study also showed that preoperative CT overestimated the SMAm in 73% of patients.⁵³ Hartwig *et al.* reported a maximum ratio of 8.4 in a study comparing the 0 mm definition to the revised ‘R1 = 1.0 mm’ definition (4.8–40.5%).¹⁵

The confusing terminology used to define resection margins, which is sometimes ambiguous, makes it difficult to compare rates of microscopic invasion for each of the margins²⁷ (see Appendix). The assessment of resection margins is often limited to those of the pancreatic neck and bile duct transections and the SMAm or medial margin.^{12,22,37,47–49} However, the medial circumferential resection margin (CRM),²⁶ which faces the superior mesenteric vessels, and the posterior soft tissue margins were the most frequently involved.^{8,12,18,20–22,26–34} In the present study, assessments of the SMAm and SMVm were clearly distinct,^{8,40} and these medial resection margins, which represent true transection resection

Table 4 Univariate analysis of factors associated with at least one positive margin for each of the margins at each width from 0 mm to 2.0 mm. Three non-pathological factors were significantly associated with a positive margin: male sex; portal vein–superior mesenteric vein resection (PV-SMVR), and neoadjuvant treatment. Values in bold refer to factors that reached significance at a *P*-value of <0.05; values in italics refer to factors that did not reach significance at a *P*-value of <0.05, but tended towards significance at a *P*-value of <0.10

Margins	Variables	Margin widths, mm				
		0	0.5	1.0	1.5	2.0
At least one positive inked margin	Tumour size	0.018 3.5 (1.2–9.7)	–	0.005 2.8 (1.4–6)	0.005 3 (1.4–6.3)	<i>0.051</i> 2.2 (1–5)
	T stage	0.029 9.7 (1.2–74)	–	0.003 4 (1.6–10)	0.018 2.94 (1.2–7)	0.007 3.6 (1.4–9)
	N stage	0.018 4.5 (1.3–16)	0.009 3.2 (1.3–7.7)	0.004 3.2 (1.4–7)	0.005 3 (1.4–7)	–
	LNR>0.2	–	0.017 2.5 (1.2–5.2)	0.040 2.4 (1–5.6)	–	–
	PV-SMVR	<0.001 5 (2.2–12)	0.012 2.7 (1.2–6)	–	–	–
Posterior margin	N-stage	–	–	0.012 3.45 (1.3–9)	0.043 2.49 (1–6)	0.035 2.42 (1–5.5)
	LNR >0.2	<i>0.075</i> 3.1 (0.9–11)	0.029 2.5 (1.1–5.6)	0.005 2.9 (1.4–6)	0.015 2.5 (1.2–5.2)	0.022 2.4 (1.1–5)
	PV-SMVR	0.007 6.0 (1.7–22)	–	–	–	–
	Neoadjuvant treatment	–	–	0.045 0.4 (0.1–1)	–	<i>0.077</i> <i>0.464 (0.2–1.1)</i>
PV-SMVm	Tumour size	<i>0.053</i> 3.1 (1.0–9.6)	–	0.001 3.7 (1.6–8.4)	0.001 3.9 (1.7–8.8)	0.002 3.2 (1.5–6.7)
	T-stage	–	0.049 4.5 (1.0–20)	0.007 4.8 (1.5–15)	0.016 3.6 (1.3–10)	–
	N-stage	–	0.042 3.2 (1.0–9.8)	0.032 2.5 (1.1–5.9)	0.026 2.6 (1.1–6)	–
	PV-SMVR	<0.001 5.6 (2.3–14)	0.011 2.9 (1.3–6.5)	0.012 2.7 (1.2–5.8)	0.016 2.6 (1.2–5.6)	–
SMAm	Tumour size	–	–	0.023 3.0 (1.16–8.06)	0.009 3.6 (1.4–9.3)	<0.001 5.4 (2.2–13)
	N-stage	–	–	–	0.038 2.99 (1.06–8.39)	–
	LNR >0.2	0.010 4.3 (1.4–13)	0.014 3.6 (1.3–9.9)	0.004 3.2 (1.4–7)	0.013 2.7 (1.2–5.8)	–
	Grade 3	0.050 3.6 (0.8–16)	0.002 4.39 (1–19)	0.014 4.83 (1.5–16)	0.008 5.7 (1.74–18.8)	0.002 8.00 (2.44–26.2)
	PV-SMVR	0.002 5.8 (1.9–18)	0.011 3.8 (1.4–11)	–	–	–
	Male versus female	–	0.024 0.2 (0.04–0.8)	<i>0.054</i> <i>0.4 (0.2–1.0)</i>	–	–
Vascular margin PV-SMVm + SMAm	Tumour size	0.009 4.4 (1.4–14)	0.027 2.7 (1.1–6.4)	<0.001 4.47 (2.0–9.8)	<0.001 4.7 (2.1–10)	<0.001 4.2 (1.9–8.9)
	T-stage	0.033 9.2 (1.2–71)	0.042 3.7 (1.0–13)	0.002 5.3 (1.8–15)	0.005 4.2 (1.5–11)	0.009 3.4 (1.3–8.4)
	N-stage	0.022 4.3 (1.2–15)	0.018 3.4 (1.2–9.6)	0.011 2.9 (1.3–6.6)	0.001 3.0 (1.3–6.8)	0.043 2.2 (1.0–4.9)
	LNR >0.2	–	0.016 2.56 (1.2–5.5)	0.015 2.6 (1.2–5.6)	0.020 2.5 (1.1–5.3)	0.043 2.4 (1.0–5.4)
	Grade 3	–	–	0.049 4.0 (1.3–12)	<i>0.067</i> <i>3.6 (1.1–11)</i>	–
	PV-SMVR	<0.001 5.5 (2.4–13)	0.006 3.0 (1.4–6.6)	0.018 2.6 (1.2–6)	0.023 2.5 (1.1–5.7)	0.028 2.7 (1.1–6.4)
	Male versus female	–	–	0.022 0.45 (0.22–0.88)	0.037 0.48 (0.24–0.95)	–

LNR, lymph node ratio; PV-SMVm, portal vein–superior mesenteric vein margin; SMAm, superior mesenteric artery margin (uncinate margin).

Table 5 Multivariate analysis of factors associated with at least one positive margin for each of the margins at each width from 0 mm to 2.0 mm. Values in bold refer to factors that reached significance at a *P*-value of <0.05; values in italics refer to factors that did not reach significance at a *P*-value of <0.05, but tended towards significance at a *P*-value of <0.10

Margins	Variables	Margin widths, mm				
		0	0.5	1.0	1.5	2.0 mm
At least one positive inked margin	Tumour stage	–	–	<i>0.073</i> 2.5 (1.0–6.9)	–	0.039 2.8 (1.0–7.3)
	PV-SMVR	<0.001 4.7 (2.0–12)	0.016 2.8 (1.2–6.4)	–	–	–
Posterior margin	LNR >0.2	0.036 4.4 (1.10–17.7)	<i>0.053</i> 2.2 (0.989–5.13)	<i>0.059</i> 2.2 (0.968–5.12)	–	–
	PV-SMVR	0.005 7.5 (1.8–31)	–	–	–	–
PV-SMVm	Tumour size	–	–	–	<i>0.066</i> 2.2 (1.0–5.0)	<i>0.055</i> 2.1 (1.0–4.4)
	PV-SMVR	0.001 4.5 (1.8–11)	0.035 2.5 (1.0–5.7)	–	–	–
SMAm	Tumour size	–	–	–	–	0.020 3.0 (1.2–8.0)
	Grade 3	–	–	0.049 4.05 (1.1–14)	0.046 4.39 (1.2–16)	0.032 5.5 (1.5–20)
	LNR >0.2	0.019 5.8 (1.3–25)	–	–	–	–
	PV-SMVR	0.009 6.8 (1.6–28)	0.047 3.9 (1.0–15)	–	–	–
Vascular margin PV-SMVm + SMAm	Tumour size	–	–	<i>0.065</i> 2.2 (0.97–5.1)	0.034 2.5 (1.0–5.7)	0.017 2.6 (1.2–5.6)
	LNR >0.2	–	<i>0.065</i> 2.3 (0.95–5.5)	–	–	<i>0.099</i> 2.17 (0.86–5.47)
	PV-SMVR	<0.001 5.2 (2.0–13)	0.012 3.06 (1.3–7.4)	–	–	<i>0.080</i> 2.31 (0.91–5.88)

^aVascular margin: SMAm + PV-SMVm.

PV-SMVR, portal vein–superior mesenteric vein resection; LNR, lymph node ratio; PV-SMVm, portal vein–superior mesenteric vein margin; SMAm, superior mesenteric artery margin (uncinate margin).

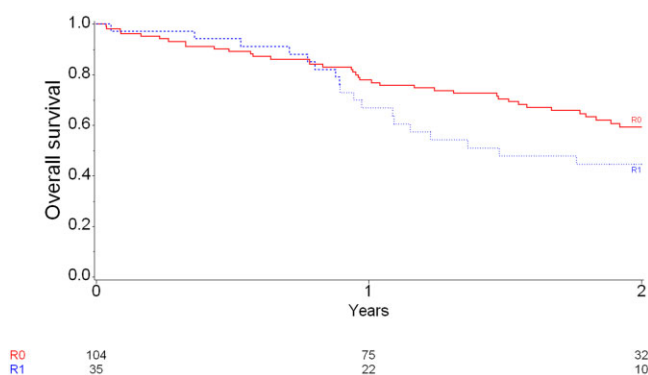


Figure 4 Overall survival in 139 patients for whom data were available at the time of the study. Hazard ratio: 0.64, 95% confidence interval 0.37–1.11; *P* = 0.106

margins,³⁴ were distinguished from the posterior margin. For the 0-mm and 1.0-mm margin definitions, the SMV_m was the most commonly involved (18% and 41%, respectively), as in the study by Pingpank *et al.*,⁸ which contrasts with the particularly low rates of 3–10% reported by others.^{21,46} For the 0-mm and 1.0-mm margin definitions, the SMAm was invaded in 10% and 25% of specimens, respectively, and the vascular resection margin was invaded in 23% and 49% of specimens, respectively. In the present study, no significant difference in R1 rates emerged between the 1.0-mm and 1.5-mm margins. The median and mean clearances were lower for the PV-SMV_m than for the SMAm. The assessment of resection margins along both vessels gives an accurate picture of resection margin status because these areas represent the most critical part of the CRM in terms of the occurrence of microscopic residual disease. Optimization of this crucial resection margin using the artery-first approach has been advocated,⁵⁴ and the issue of a systematic en bloc PV-SMVR after a first SMA approach was addressed recently by Turrini *et al.*⁵⁵

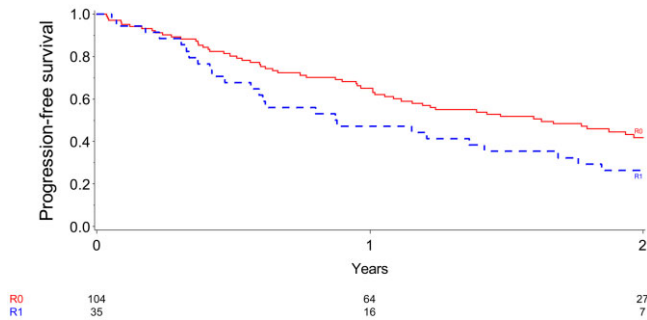


Figure 5 Progression-free survival in 139 patients for whom data were available at the time of the study. Cases of postoperative mortality were excluded ($n = 5$). Numbers of events were, respectively, 57 in the R0 group and 27 in the R1 group. Patients in whom an R0 resection was achieved had a significantly better outcome than those in whom an R1 resection was performed (at least one positive margin according to the 0-mm definition). Hazard ratio: 0.59, 95% confidence interval 0.37–0.94; $P = 0.023$

In the present study, the anterior surface of the specimen (anterior part of the whole CRM) was not inked. Assessment of the anterior resection margin as a part of the CRM was recommended several years ago in Japan,⁵⁶ and subsequently in Europe²⁷ and more recently in North America.^{40,43} Invasion of the anterior surface has been reported as marking a margin relevant to the definition of ‘radicality’ in the Japanese pancreatic cancer registry.⁵⁷ However, the anterior/serosal margin has not been considered as a transection margin.^{28,34,46} Invasion has been reported in 7–15% of patients,^{26–28} but isolated infiltration of the anterior surface is unusual²⁸ and has sometimes not been considered as indicating R1 resection.³⁰ It was therefore proposed that assessment of this margin should be excluded from a standardized pathological protocol,²⁸ or that the 0-mm clearance rule should be used.^{27,29} In the current study, despite the lack of inking of the anterior surface of the specimen, nearly 70% of patients were found to have at least one positive margin according to the 1.00-mm clearance rule, which is closest to the rates reported in recent series using a standardized pathological protocol.^{26,28,30–32,34}

In the present study, the fact that 19% of patients had received neoadjuvant treatment, including irradiation in nearly 60%, may have biased the evaluation of resection margins. Low rates of R1 resection are usually observed after neoadjuvant radiochemotherapy, especially for the SMAm^{8,22,58,59} and SMVm.⁸ However, neoadjuvant therapy has been reported as a non-significant predictor of SMAm status.^{22,58} In the present study, neoadjuvant treatment was correlated with a reduced risk for a positive posterior margin at only the 1.0-mm definition in univariate analysis.

What constitutes an adequate margin in PDAC resection specimens was recently discussed by Verbeke *et al.*⁶⁰ Indeed, the 1.0-mm margin rule⁴² has been extrapolated from the circumferential margin recognized as discriminant of recurrence in rectal cancer, but has never been validated for PDAC. Its relevance is

questionable because of the infiltrative, dispersed and discontinuous growth pattern of PDAC.^{24,60} Chang *et al.* reported that a minimum clearance of 1.5 mm was an independent predictor of survival in multivariate analysis.⁴⁶ A revision of the current 0-mm and 1.0-mm definitions of R1 resection should be considered for PDAC, as for rectal cancer.^{32,60,61}

Curative resection (R0) is one of the key factors influencing survival after PD for PDAC.^{3,5–7,9,15} However, as in the present study, positive margins are often correlated with other strong pathologically prognostic factors that may be potential confounding variables in an assessment of the correlation of a positive resection margin with local recurrence and survival.

Numerous published multivariate analyses have emphasized the prognostic value of tumour size,^{7,10,22,34,46} tumour stage,³⁴ grade 3,^{7,10,15,34,62,63} lymph node involvement,^{10,16,21,46} LNR^{15,64,65} and vascular invasion.⁴⁶ Regardless of pre- or postoperative treatment, other clinical and biological variables have been reported as prognostic factors, including preoperative variables such as insulin-dependent diabetes and a CA 19-9 level of ≥ 400 U/ml,¹⁵ surgical variables such as blood loss^{7,22,53} and postoperative complications,^{11,63} and postoperative variables such as persistently elevated levels of CA 19-9.⁶⁶ In the present study, patients with a PV-SMVR had more negative histological factors, including more positive margins, although they had more often received neoadjuvant treatment. An increased frequency of positive resection margins has been reported in patients who required PV-SMVR.^{21,58} As in the present study, a recent report by Gnerlich *et al.* showed that the invasion of at least one margin was significantly more frequent (34% versus 22%), and the PV-SMVM was more often invaded (52% versus 24%) in patients who required PV-SMVR.²¹ However, Tseng *et al.* reported that the significantly increased risk for a microscopically positive SMAm in patients who required PV-SMVR was associated with tumour size and not with vascular resection.⁵⁸

Thus, the effect of positive resection margins *per se* remains controversial,²⁵ and some authors consider the finding of a positive margin to represent a function of tumour size and anatomical location,²² rather than a surrogate marker of tumour biology.^{5,16,46}

The suggestion that positive margins may be predictive of the risk for local recurrence makes sense.^{13,20,21,28,53} The rate of local recurrence after resection of PDAC based on autopsy findings⁶⁷ seems to be at odds with the R1 rate reported in series using a standardized pathological protocol for the examination of PD specimens.²⁷ However, the rate of isolated local recurrence is usually below 25%, and in clinical practice, the majority of patients had metastases at the time of diagnosis of local recurrence and died of metastases.^{13,21} In the present study, in which follow-up was relatively short, 16 of 31 instances of local recurrence were isolated and, as previously reported, resection margin status did not affect the pattern of first recurrence.⁵⁸

Microscopic resection margin involvement (R1) has been reported as an independent predictor of poor longterm survival following PD for PDAC in several studies,^{5–21,63} but R1 status was

Table 6 Median length and rate of 2-year progression free-survival for each 0-mm positive margin

	Margin status (n assessed)	Months, median (95% CI)	2-year, % (95% CI)	P-value (log-rank test)
At least one positive margin	R0 (n = 104)	19.5 (13.0–NR)	42% (32–52)	0.023
	R1 (n = 35)	10.5 (5.6–20.3)	27% (13–42)	
PV-SMVm	R0 (n = 114)	17.0 (12.7–23.6)	40% (30–49)	0.051
	R1 (n = 27)	10.5 (5.0–21.0)	27% (12–45)	
SMAm	R0 (n = 122)	19.5 (13.8–24.0)	42% (33–51)	0.017
	R1 (n = 15)	9.6 (3.7–17.0)	13% (2–35)	
PV-SMVm + SMAm (vascular margin)	R0 (n = 105)	19.5 (13.4–24.5)	41% (31–51)	0.026
	R1 (n = 34)	10.5 (5.6–20.3)	27% (14–43)	
Posterior margin	R0 (n = 128)	16.7 (12.2–22.5)	39% (30–47)	0.281
	R1 (n = 11)	16.4 (0.9–21.2)	20% (3–48)	

95% CI, 95% confidence interval; NR, not reached; PV-SMVm, portal vein–superior mesenteric vein margin; SMAm, superior mesenteric artery margin (uncinate margin).

not identified as a significant factor for survival in a meta-analysis of data collected from randomized controlled trials (RCTs) of adjuvant treatment.²³ In some studies, R1 resection was found to correlate with poorer survival on univariate but not multivariate analysis.^{26,30} In other studies, as in the present study, median OS did not differ significantly, whereas survival time of patients with R0 resections varied by ≥ 6 months,^{22,28} which may be considered a substantial difference in PDAC. The ‘vascular’ margins (medial part of the CRM) seem to be the most important.^{8,21,26,28,31,34} As Jamieson *et al.* have reported, the involvement of ‘transection’ margins was an independent predictor of poor outcome even in patients with node-negative disease; by contrast, outcomes in patients with posterior margin and anterior surface involvement (‘mobilization’ margins) were similar to those in patients with R0 resections.³⁴ In the present study, the median and 2-year PFS were significantly worse in patients with at least one 0-mm positive margin; positive vascular margins significantly decreased PFS, but a positive posterior margin had no impact. Pingpank *et al.* reported a significant decrease in disease-free survival in patients with SMVm and SMAm involvement, but not in those with posterior margin or pancreatic margin involvement.⁸ Furthermore, multiple margin involvement, which has been reported in 20–45% of PD specimens,^{21,26,28,30,34,68} significantly increased the risk for local recurrence²¹ and was correlated with a significantly worse outcome.^{34,68} In the current study, the impacts of R1 status (defined as a 0-mm invasion of at least one margin) on PFS and OS estimated by the Cox model are close (HR = 0.59 and 0.64, respectively): this suggests that the non-significance of the impact of R1 status on OS is related to the lack of power of the study (resulting from an insufficient number of observed deaths).

Adjuvant chemotherapy is currently the standard treatment for patients following a potentially curative PD for PDAC in Europe.^{5,6,35} It is noteworthy that the R1 rates in RCTs that have led to changes in clinical practice were very low (19% in ESPAC-1⁵ and 17% in CONKO-001⁶). Two recent meta-analyses and a large,

prospective monocentre database have suggested that in patients with R1 status, postoperative radiochemotherapy may be useful and probably better than chemotherapy alone.^{23,63,69} Thus, postoperative radiotherapy may be considered if radiotherapy has not been administered before the intervention. Neoadjuvant treatment is promising⁷⁰ and may decrease the rate of microscopically positive resection margins and the rate of local recurrence.^{22,58,59} However, there is currently a lack of randomized trials showing that neoadjuvant treatment abrogates the adverse effect of R1 status and results in a significant increase in disease-free or overall survival.^{8,59} In any case, the use of a standardized pathological protocol for the stratification of patients in clinical trials of adjuvant treatment is relevant today.³⁷

Conclusions

The present prospective study shows that recently reported results of positive margins are reproducible in a multicentre trial and that rates obviously depend on the definitions of microscopic invasion used. Achieving better understanding of the biology of pancreatic cancer will undoubtedly represent the most important step towards improving survival. Meanwhile, the standardization of histological examination is not only necessary to provide accurate prognostic information, but may represent a significant step forward in the design of future RCTs and the optimization of adjuvant treatment strategies.

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Conflicts of interest

None declared.

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Appendix

Correspondence between terms used to define resection margins in pancreatoduodenectomy specimens according to the Royal College of Pathologists (RCPATH) (UK) (<http://www.rcpath.org>) and the College of American Pathologists (CAP) (<http://www.cap.org/>)^a

Terminology	RCPATH, ⁴² Verbeke <i>et al.</i> ²⁶	AJCC, CAP ^{38,39}	Jamieson <i>et al.</i> ³⁴
CRM	Anterior, medial and posterior RMs		Transection versus mobilization margins
SMAm	SMAm + Pm = posterior CRM	Mesenteric or uncinat ^c	Transection
SMVm	Medial part of the CRM ^p		Transection
Vascular margin ^d	SMAm + SMVm		Medial transection margin
Pm	Part of the posterior CRM	Deep radial posterior margin	Posterior mobilization
Anterior surface	Anterior CRM		Anterior mobilization

^aIn the present study, the superior mesenteric artery margin (SMAm) and the mesenterico–portal vein groove or superior mesenteric vein margin (SMVm) were assessed separately.

^bSurface of the pancreatic head that faces the SMV and separates the anterior from the posterior CRM.²⁸

^cThe soft tissue adjacent to the right lateral border of the proximal 3–4 cm of the SMA. The term ‘retroperitoneal margin’, commonly used in place of SMAm or uncinat margin, should be abandoned.

^dIn the present study, the SMAm and SMVm were assessed separately; they both define the vascular margin (or medial transection margin³⁴ of the mesopancreas^{31,34}).

The section of the pancreatic neck, which is not included in this table, is a transection margin.

AJCC, American Joint Committee on Cancer; RM, resection margin; CRM, circumferential resection margin; SMAm, superior mesenteric artery margin; SMVm, superior mesenteric vein margin (or mesenterico–portal vein groove); Pm, posterior margin.