Risk Factors of Positive Resection Margin Differ in Pancreaticoduodenectomy and Distal Pancreatosplenectomy For Pancreatic Ductal Adenocarcinoma: A Study Based On Leeds Pathology Protocol

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Research

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Abstract

Background: Positive resection margin indicates worse prognosis. The present study identified the independent risk factors of R1 resection in pancreaticoduodenectomy (PD) and distal pancreatosplenectomy (DP) for patients with pancreatic ductal adenocarcinoma (PDAC).

Methods Consecutive patients who were operated from 1st December 2017 to 30th December 2018 were analyzed retrospectively. A standardized pathological examination with digital whole-mount slide images (DWMSIs) was utilized for evaluation of resection margin status. R1 was defined as microscopic tumor infiltration within 1 mm to the resection margin. The potential risk factors of R1 resection for PD and DP were analyzed separately by univariate and multivariate logistic regression analyses.

Results For the 240 patients who underwent PD, and the 146 patients who underwent DP, the R1 resection rates were 30.8% and 35.6 %, respectively. Univariate analysis on risk factors of R1 resection for PD were tumor location, absence of tumor necrosis, N staging, and TNM staging; while those for DP were perineural invasion, T staging, and TNM staging. Multivariate logistic regression analysis showed the location of tumor in the neck and uncinate process, and N1/2 staging were independent risk factors of R1 resection for PD; while those for DP were T3/4 staging.

Conclusions The clarification of the risk factors of R1 resection might clearly make surgeons take reasonable decisions on surgical strategies for different surgical precedures in patients with PDAC, so as to obtain the first attempt of R0 resection.

Introduction

Pancreatic cancer is a lethal disease, being characterized by increasing incidences and mortality rates, and with a dismayed 5-year survival rate of <10% [1]. Currently, radical surgery with adjuvant chemotherapy is the only potentially curative therapy for pancreatic ductal adenocarcinoma (PDAC) [2]. However, only about 15-20% of patients are eligible for upfront radical resection at the time of diagnosis [3, 4]. Even when surgery is followed by chemotherapy or radiotherapy, the majority of patients develop tumor recurrence within 2 years after surgery [5]. Tumor relapse can occur either locally or as a metastatic disease [6]. Recurrence relating to microscopic positive resection margins (R1) is common, accounting for 46.7% of patients with pancreatic body/tail and 8.2% with pancreatic head PDAC [7]. Recent studies showed that the R1 margin status significantly lowered the disease-free survival (DFS) and the overall survival (OS) compared to the clear resection (R0) margin status after pancreaticoduodenectomy (PD) [8-10] or distal pancreatosplenectomy (DP) [11]. Moreover, positive resection margins associated with a more aggressive biology for PDAC[12]. However, a research reported that even for patients who underwent PD for PDAC with positive resection margins shown on frozen section, further surgical resection to achieve R0 did not have any significant positive impact on OS [13].

Thus, to achieve first attempt of R0 resection is critical to prognosis of PDAC. Whereas, the definition of R1 and the protocol on pathological examination of resected specimens have not been standardized [14-16], and standardized histopathological reporting for resection margin should be agreed upon [9, 17, 18]. In our high volume pancreatic center, R1 is defined as detection of any cancer cells within 1 mm of one or more surfaces or margins in the resected specimens. Meanwhile, the Leeds Pathology Protocol (LEEPP) was used since November 2016 in our high volume center. The pathological reports were rigorously filed according to the latest National Comprehensive Cancer Network (NCCN) guidelines (Version 3, 2021) for pancreatic adenocarcinoma. Moreover, the R status has since been

assessed by digital whole-mount slide images (DWMSIs) [19] which has the advantages of identifying the R status more accurately and comprehensively compared to the conventional methods[20]. Based on a standardized protocol of pathological examination and R1 definition, we hypothesized that risk factors of R1 resection differed in PD and DP for patients with PDAC. Therefore, the aim of the present study was to identify independent risk factors of R1 resection in PD and DP for PDAC respectively and to help surgeons make better decisions on resection strategies for the first attempt of R0 resection.

Methods

Study population

This retrospective study included consecutive patients who were diagnosed to have PDAC by pathological examination after pancreatic resectional surgery between 1st December 2017 to 30th December 2018. The inclusion criteria were: (1) PD or DP with curative intention, and (2) underwent a standardize pathological protocol for the resected specimen and a standard reporting record for resection margin (R) status according to the NCCN guidelines for pancreatic cancer. The exclusion criteria were: (1) total pancreatectomy (TP); (2) macroscopic evidence of margin involvement (R2); (3) patients received neoadjuvant chemotherapy; (4) resection for metastatic disease. The Changhai Hospital Review Board approved the study, and no additional informed consent was required to review the patients' medical records.

Routines of surgical procedures

As a high volume center for pancreatic surgery, we have standardized the surgical approach based on the guidlines and the updated papers[21, 22]. In our cohort, the indication for upfront surgery was resectable patients evaluated by radiologist and surgeon and borderline resectabe patients elected by a robust and nuanced multidisciplinary discussion [23]. The surgical technique for PD and DP conformed with our institution's standard practice protocol. Both pylorus-preserving and Whipple PDs were underwent. For DP, the types of approach included minimally invasive pancreatic surgery (MIPS, either laparoscopic or robot-assisted[24]) and open DP. The level of the transection line for PD was at the left of the portal vein axis, which was cut by the harmonic mainly and the scalpel for the area of Wirsung duct. The level of the transection line for DP was at the level of the pancreatic body-tail or at the pancreatic neck which was cut by the linear stapler. Besides, the surgical procedures of the present study were almost done by senior surgeons in our center to avoid the bias.

Pathological Examination

The Leeds Pathology Protocol (LEEPP) was routinely used [25, 26] for the pathological examination.

For PD specimens: Briefly, after multicolor inking of the posterior, medial margin, and anterior surfaces of the pancreatic head, the specimen of PD was serially sliced in an axial plane, perpendicular or paralleled to the longitudinal duodenal axis. For DP specimens: After multicolor inking of the posterior and anterior surfaces of the pancreatic body and tail, the specimen of DP was serially sliced in a plane parallel to the main pancreatic duct or the pancreatic transection margin when the tumor invades to the surface of the pancreas according to the NCCN guidelines.

The entire specimen was sliced in 5-mm-thick sections, which resulted in 10–35 (average 24.5±6.7) formalin-fixed paraffin-embedded (FFPE) block for each specimen. Then, each FFPE block was cut in 4-mm-thick sections on

whole-tissue glass slides measuring 7.8 × 5.4 cm^2. These slides were scanned by the Hamamatsu S60 Whole Slide Scanner (Hamamatsu Photonics, Hamamatsu city, Japan) to obtain the DWMSIs with an average of 6.47 GB in file size [27]. The DWMSIs can also be observed by the NanoZoomer Digital Pathology (NDP) viewer2 version 2.7.25 (Figure 1), and the distance between the resection margins and the tumor cells can be measured precisely down to 0.01 mm on the screen (Supplementary Figure 1).

Classification and Defining of the R Status

The pathological reports on a detailed form were reassessed retrospectively. The slides were rechecked if the reports were not clearly depicted. According to the NCCN guidelines, the R status records for PD were comprised of the transection margin, the anterior surface, the posterior margin, the bile duct margin, the enteric margin, and the medial margin, which included the SMV (superior mesenteric vein)/PV (portal vein) resection margin and the SMA (superior mesenteric artery) (Figure 2) . There were just three margins for DP (Figure 2). R1 was defined as one or more cancer cells within 1 mm of one or more surfaces or margins (R1<1 mm) or at the surface or margin (R1-directed). R0 was defined as >1 mm from any surface or margin (R0 >1 mm). The R status were classified by two senior pathologists majored in pancreatic pathology and the discordance was discussed.

Variables Analyzed

For all the patients, the following demographic, clinical, and pathological variables, including sex, age, preoperative carbohydrate antigen (CA) 19-9, tumor location (head, neck, or uncinate process for PD; neck and body, or body and tail for DP), necrosis, perineural invasion, lymphovascular invasion, duodenal papilla invasion, tumor grade (G1/2 or G3/4), vascular resection. The TNM staging was also recorded using the 8^{th} edition of the AJCC Cancer Staging Manual for Pancreatic Cancer. Resectability status was recorded according to the NCCN guideline for pancreatic adenocarcinoma (version 3. 2021).

Statistical Analysis

Categorical data were presented as percentage proportion, and continuous data were transformed into categorical data by the median value. For incomplete data, a dummy variable classified as “missing” was included in the analysis. To compare the differences in the categorical data between the two groups, the Fisher’s exact test or the c^2 test was used as appropriate. All variables found to be statistically significant (P<0.1) on univariate analysis were subsequently included in a multivariate binary logistic regression model to determine the independent risk factors associated with R1 resection. For all the analyses, a two-tailed P<0.05 was considered as statistically significant. The analyses were performed using the SPSS version 25.0 (SPSS, Chicago, IL, USA).

Results

Patient Characteristics

From 1^{st} December 2017 to 30^{th} December 2018, 457 patients underwent pancreatic surgery and were diagnosed to have PDAC on pathological examination. A total of 71 (15.5%) patients were excluded: 6 patients because of TP, 7 patients due to a lack of standard records for the R status, 9 patients because of R2, 41 patients because of neoadjuvant chemotherapy before surgery, and 8 patients because of resection for metastatic disease, which were discovered during the operations. The remaining 386 patients were included in this study (M:F=1.47:1; age range 28-83, mean age 61.9±9.5 years), with 240 patients underwent PD and 146 patients underwent DP (Figure 3). The R

status of the two groups of patients was assessed using DWMSIs. No significant differences were detected in the baseline data between R0 and R1 resections in the patients who underwent PD and DP, respectively.

Distribution of the R Status (margins)

For all the patients, 260 (67.4%) patients had a R0 margin, 77 (19.9%) patients a R1<1 mm margin, and 49 (12.7%) patients a R1-directed margin (Table 1). Table 1 also showed that for the 240 patients who underwent PD, 74 (30.8%) patients had R1 resections (either R1<1 mm or R1-directed). A single positive margin was found in 52 (21.7%) patients, two positive margins in 14 (5.8%) and ≥ 3 positive margins in 8 (3.3%). The R1 resection incidence rates of the six specific margins in PD were 19.6% in the medial margin, 10.5% in the anterior surface, 9.6% in the posterior margin, 3.8% in the transection margin of pancreas, 0.8% in the bile duct margin, and none in the enteric margin. The R1 resection in the medial margin of the PD was maximal (44.3%) of the total R1 resection margins, followed by the anterior surface (23.6%) and the posterior margin (21.7%). For the 146 patients who underwent DP, 52 had R1 resections (35.6%). A single positive margin was found in 35 patients (24.0%) and two positive margins in 17 patients (11.6%). The R1 resection incidence rates of the anterior surface was 26.0%, the posterior surface 19.2%, and the transection margin of pancreas 2.1%. In DP, the R1 resection of the anterior surface was maximal (55.1%), followed by the posterior margin (40.6%) (Table 1).

Univariate Analysis of Risk Factor for R1 Resection

Univariate analysis on demographics and potential risk factors between the R0 and R1 resection groups of patients who underwent PD are shown in Table 2. Patients with R1 resection had a higher incidence of tumor localization in the neck and uncinate process (40.5% *vs*. 16.3%, P<0.001) and lymphovascular invasion (50% *vs*. 36.7%, P=0.054). Duodenal papilla invasion were common in patients with R0 and R1 resections (28.3% *vs*. 17.6%, P=0.076). N1/2 cancer (83.8% *vs*. 57.2%, P<0.001) and TNM III cancer (48.6% *vs*. 21.7%, P<0.001) were significantly higher in the R1 resection group as compared to the R0 group. Univariate analysis on demographics and potential risk factors between the R0 and R1 resection groups of patients who underwent DP are also shown in Table 2. Patients with R1 resection had a high incidence of perineural invasion (96.2% *vs*. 85.1%, P=0.041). The prevalence of T3 cancer (76.9% *vs*. 42.6%, P<0.001) and TNM stage III cancer (34.6% *vs*. 19.1%, P=0.038) were significantly higher in the R1 resection group as compared to the R0 group. The prevalence of N1/2 cancer (69.2% *vs*. 56.4%, P=0.095) was higher in the R1 resection group.

Multivariable Analysis of Risk Factor for R1 Resection

Multivariable analyses showed that neck tumors (odds ratio (OR)=9.549, P=0.001) uncinate process tumor (OR=3.311, P=0.002), and N1 (OR=2.406, P=0.031) and N2 (OR=6.430, P<0.001) staging were independent risk factors of R1 resection in patients who underwent PD. Multivariable analyses showed that T3 staging (OR=5.26, P<0.001) was an independent risk factor of R1 resection in patients who underwent DP (Table 3).

Discussion

With accurate assessment of resection margins by a standardized pathological examination protocol using LEEPP and DWMSIs, our study supported neck/uncinate tumor, and N1/2 stage were independent risk factors of R1 resection for PD, and T3 was independent risk factors for DP. Previous studies reported R1 resection was frequently present in PV/SMV margins [28] and SMA margins[29], which was closely related to prognosis [30]. Our data also showed similar results in PD. Other studies who demonstrated lesions in the neck (OR=5.48) or uncinate process

(OR=2.996) [14], tumor size >30 mm (OR=1.13) [15] or large tumor size [31], positive lymph nodes [31] and grade 3 tumors (OR=4.05) [28] were independent risk factors of R1 resection. However, there were no studies to clarify independent risk factors separately for R1 in PD and DP.

Patients with tumor located in neck and uncinate are more likely with positive margin attributed to the anatomical features. The pancreatic neck is a narrow anatomical region between the pancreatic head and body, lying just anterior to the PV, gastroduodenal artery, and common hepatic artery [32]. The uncinate process is closely related to the SMA and the SMV [33]. As a consequence, pancreatic neck or uncinate process cancer are prone to invade these major vessels to become either a borderline or unresectable tumor. R0 resection is technically difficult with involvement of theses vessels. In our study, neck tumor had the highest R1 resection rate, followed by uncinate process tumors. In addition, the most frequently R1 invaded margin in PD was the medial margin which included the SMA margin and SMV/PV margin. When the R status of different tumor locations in PD was analyzed (Supplementary Table 1), neck tumors had a significantly higher rate of positive resection margin in the transection margins (38.5%) and medial margins (53.8%). These results suggested that the R0 resection rate of neck tumor was extremely low (3/13 or 23.1%). Our results suggested that surgeons should resect more pancreatic tissues towards the pancreatic tail to obtain first attempt of R0. To decrease R1 resection in the medial margin, the alternative treatment for patients with pancreatic neck tumor should undergo neoadjuvant therapy followed by surgery [34]. Supplementary Table 1 also showed that uncinate process tumors had a high frequency (31.8%) of positive medial margins. Besides, it may explain that the pancreatic tumor cells are characterized by neurotropic features[35], and the tumor located in uncinate process are more likely invaded the neural structures.

In further, the regional lymph nodes are mainly distributed along vasculature, and tumor cells can easily invade lymph nodes along the lymphatic drainage pathway. This explain why the N stage is an independent risk factor of R1 resection in PD. In further analysis showed that tumors with N2 stage had a higher frequency (32.9%) of positive medial margins compared with N0 (10.8%) or N1 (17.2%), so as posterior margin with 22.9% of R1 in N2 stage (Supplementary Table 1), which were also matched with pathway of lymph nodes metastasis.

Pancreatic body and tail tumors present late as they do not have symptoms in the early stages [36]. Thus, the pancreatic body and tail tumors are likely to invade beyond the pancreas. Our study suggested that T3 was an independent risk factor of R1 resection. And the anterior surface is more vulnerablely invaded by the tumor with R1 resection rate of 36.3% in T3 stage (Supplementary Table 2), which may indicate that the surgical procedure related with anterior surface of pancreas should exclusively fit the principles of an-neoplasia surgical operation and an-touch radical excision [37], in order to avoid the implantation metastasis during the operation.

To our knowleges, this is the first report for independent risk factors of R1 resection in PD and DP for PDAC respectively. The present results may guide the surgeons to optimize the surgical indication and the surgical strategy. A research indicated that microscopic margin positivity is not associated with recurrence and survival in localized PDAC patients resected after treatment with neoadjuvant chemotherapy[38], so the patients with high risk of R1 resection in upfront surgery may benefit from neoadjuvant chemotherapy followed by surgery. Meanwhile, margin positivity may be a surrogate for biologic aggressiveness [39] and seleceted patients with severe aggressiveness may not profit from surgical resection bacause of the early metastasis.

The present study has several limitations. First, this retrospective study has the intrinsic defects of any retrospective study. Second, the definition of R1 resection margin and the standard procedure for pathological examination of resection margin used in this study made it difficult to compare our results with other published studies. Third, long-term surgical outcomes could not be obtained due to the short study period. Fourth, we used harmonic and surgical

knife to cut the pancreatic tissue in the transection line for PD, whereas the stapler was applied to cut in the transection line for DP. And the different processing of pancreatic transection margin may influenced R status evaluation. The staples were all removed before the pathological examination for R status, which may not influence the evaluation of R status compared with transectin margin conducted by surgical knife. However, the heat produced by the harmonic may ruin the margin cells, which may lead underestimation of R1 status. Fifth, due to the disconsensus on evaluation of R status of pancreatic cancer following neoadjuvant therapy [38, 40, 41], the present study have ruled out the patients with neoadjuvant chemotherapy. So the independent risk factors of R1 resection for patients with neoadjuvant therapy still need further investigate.

Conclusions

A standardized pathological examination using the LEEPP, DWMSIs and the definition of R1 resection margin within 1 mm to the tumor were used in this study to analyze independent risk factors for PD and DP separately. The clarification of the risk factors of R1 resection might clearly make surgeons take reasonable decisions on surgical strategies for different surgical procedures of PDAC, so as to obtain the first attempt of R0 resection.

Declarations

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Authors' contributions

LB,GSW and YXY contributed to analysis and interpretation of data, drafting the article and final approval of the version to be published. SXH, NCM, GSZ, LG and NCR contributed to conception and design of data, revising the article critically for important intellectual content and final approval of the version to be published. JH, LWY and JG contributed to analysis and interpretation of data, drafting the article and final approval of the version to be published. All authors read and approved the final manuscript.

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Availability of data and materials

Please contact the corresponding authors for data requests.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Changhai Hospital (Shanghai Changhai Hospital Ethics Committee, reference number: CHEC2020-043).

Consent for publication

All patients enrolled in the study signed the consent for publication. The written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Distribution of the R status in patients who underwent PD and DP

(%)	R status of PD			Total	R status of DP			Total
	R0	R1<1mm	R1-Directed		R0	R1<1mm	R1-Directed	
	166(69.2)	42(17.5)	32(13.3)	240(100)	94(64.4)	35(24.0)	17(11.6)	146(100)
Number of R1 Margin								
0	166(100)	0(0)	0(0)	166(69.2)	94(100)	0(0)	0(0)	94(64.4)
1	0(0)	33(78.6)	19(59.4)	52(21.7)	0(0)	23(65.7)	12(70.6)	35(24.0)
2	0(0)	9(21.4)	5(15.6)	14(5.8)	0(0)	12(34.3)	5(29.4)	17(11.6)
≥3	0(0)	0(0)	8(25.0)	8(3.3)				
Transection margin								
R0	166(100)	38(90.5)	27(84.4)	231(96.3)	94(100)	34(97.1)	15(88.2)	143(97.9)
R1<1mm	0(0)	4(9.5)	0(0)	4(1.7)	0(0)	1(2.9)	0(0)	1(0.7)
R1-Directed	0(0)	0(0)	5(15.6)	5(2.1)	0(0)	0(0)	2(11.8)	2(1.4)
Anterior surface								
R0	166(100)	29(69.0)	20(62.5)	215(89.6)	94(100)	8(22.9)	6(35.3)	108(74)
R1<1mm	0(0)	13(31.0)	2(6.3)	15(6.3)	0(0)	25(71.4)	0(0)	25(17.1)
R1-Directed	0(0)	0(0)	10(31.3)	10(4.2)	0(0)	2(5.7)	11(64.7)	13(8.9)
Posterior margin								
R0	166(100)	32(76.2)	19(59.4)	217(90.4)	94(100)	16(45.7)	8(47.1)	118(80.8)
R1<1mm	0(0)	10(23.8)	5(15.6)	15(6.3)	0(0)	19(54.3)	0(0)	19(13.0)
R1-Directed	0(0)	0(0)	8(25.0)	8(3.3)	0(0)	0(0)	9(52.9)	9(6.2)
Medial margin								
R0	166(100)	18(42.9)	9(28.1)	193(80.4)				
R1<1mm	0(0)	24(57.1)	5(15.6)	29(12.1)				
R1-Directed	0(0)	0(0)	18(56.3)	18(7.5)				
Bile duct margin								
R0	166(100)	42(100)	30(93.8)	238(99.2)				
R1<1mm	0(0)	0(0)	1(3.1)	1(0.4)				
R1-Directed	0(0)	0(0)	1(3.1)	1(0.4)				
Enteric								

margins				
R0	166(100)	42(100)	32(100)	240(100)

Table 2 Univariate analysis of risk factors for R1 resection

	PD			DP		
	R status		*P*	R status		*P*
	R0	R1		R0	R1	
Total (%)	166(69.2)	74(30.8)		94(64.4)	52(35.6)	
Gender			0.237			0.489
Male(%)	101(60.8)	39(52.7)		56(59.6)	34(65.4)	
Female(%)	65(39.2)	35(47.3)		38(40.4)	18(34.6)	
Age			0.896			0.799
60years(%)	53(31.9)	23(31.1)		40(42.6)	21(40.4)	
≥60years(%)	113(68.1)	51(68.9)		54(57.4)	31(59.6)	
Preoperative CA19-9			0.415			0.351
223U/mL(%)	110(66.3)	45(60.8)		65(69.1)	32(61.5)	
≥223U/mL(%)	56(33.7)	29(39.2)		29(30.9)	20(38.5)	
Location			**<0.001**			0.214
Head(%)	139(83.7)	44(59.5)				
Neck(%)	3(1.8)	10(13.5)				
Uncinate (%)	24(14.5)	20(27.0)				
Neck and body (%)				11(11.7)	10(19.2)	
Body and tail (%)				83(88.3)	42(80.8)	
Resectability status			0.529			0.996
Resectable(%)	131(78.9)	61(82.4)		56(59.6)	31(59.6)	
Borderline resectable(%)	35(21.1)	13(17.6)		38(40.4)	21(40.4)	
Vascular resection			0.934			0.211
Without(%)	142(85.5)	63(85.1)		77(81.9)	38(73.1)	
With (%)	24(14.5)	11(14.9)		17(18.1)	14(26.9)	
Necrosis			0.050			0.466
Without(%)	18(10.8)	15(20.3)		15(16.0)	6(11.5)	
With (%)	148(89.2)	59(79.7)		79(84.0)	46(88.5)	
Perineural invasion			0.100			**0.041**
Without(%)	14(8.4)	2(2.7)		14(14.9)	2(3.8)	
With (%)	152(91.6)	71(97.3)		80(85.1)	50(96.2)	
Lymphovascular invasion			**0.054**			0.617

Without(%)	105(63.3)	37(50)		67(71.3)	35(67.3)	
With (%)	61(36.7)	37(50)		27(28.7)	17(32.7)	
Duodenal papilla invasion			**0.076**			
Without(%)	119(71.7)	61(82.4)				
With (%)	47(28.3)	13(17.6)				
G			0.374			0.714
G1/2(%)	134(80.7)	56(75.7)		66(70.2)	38(73.1)	
G3/4(%)	32(19.3)	18(24.3)		28(29.8)	14(26.9)	
T stage			0.404			**<0.001**
1/2(%)	134(80.7)	54(73.0)		54(57.4)	12(23.1)	
3(%)	32(19.3)	20(27.0)		40(42.6)	40(76.9)	
N stage			**<0.001**			**0.095**
0(%)	71(42.8)	12(16.2)		41(43.6)	16(30.8)	
1(%)	60(36.1)	27(36.5)		39(41.5)	21(40.4)	
2(%)	35(21.1)	35(47.3)		14(14.9)	15(28.8)	
TNM stage			**<0.001**			**0.038**
□/□(%)	130(78.3)	38(51.4)		76(80.9)	34(65.4)	
□(%)	36(21.7)	36(48.6)		18(19.1)	18(34.6)	

Table 3 Multivariate analysis of risk factors for R1 resection

	PD		DP	
	OR(95% CI)	*P*	OR(95% CI)	*P*
T stage				
T1/2 v.s. T3			5.26(2.36-11.73)	**<0.001**
N stage				
N1 v.s. N0	2.41(1.08-5.35)	**0.031**		
N2 v.s. N0	6.43(2.85-14.50)	**<0.001**		
Location				
Neck v.s. head	9.55 (2.39-38.20)	**0.001**		
Uncinate v.s. head	3.31(1.58-6.94)	**0.002**		

Figures

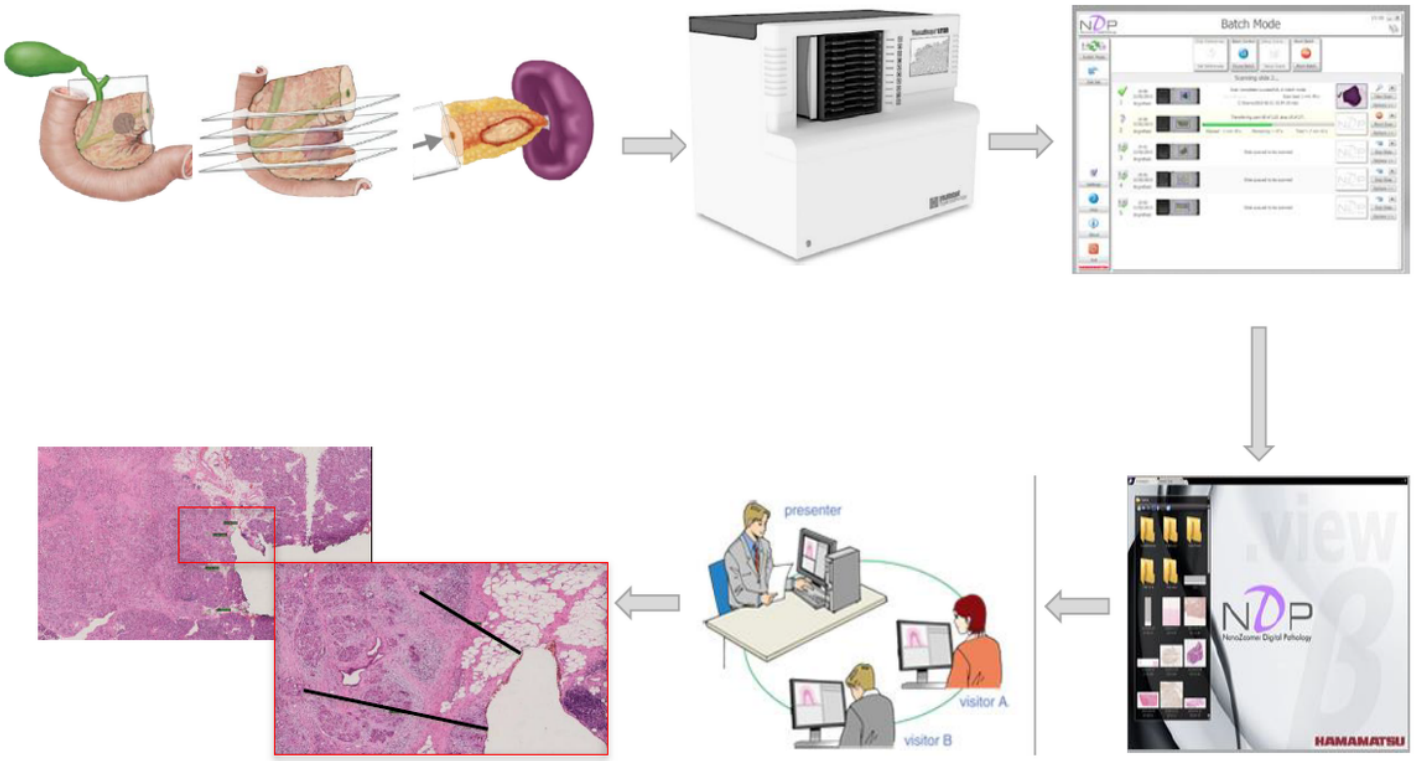

Figure 1

Schematic representation of a standardized pathological examination for the R status which includes: the entire specimen being sliced and made into whole-tissue glass slides, the whole-tissue glass slides area then scanned by the Hamamatsu S60 whole slide scanner. The software NDP viewer is then used to obtain the DWMSIs, which is viewed by the NDP viewer. The pathologists view the DWMSIs on the screen, and measure the distance between the margins and the tumor cells to identify the R status. NDP: NanoZoomer Digital Pathology, DWMSIs: digital whole-mount slide images.

Figure 2

R status identification for specific cases. A-C show a tumor located in the uncinate process and the medial margin was identified as R1-directed. D-F show a tumor located in the head and the posterior margin was identified as R0. H-I show a specimen obtained from posterior RAMPS (black arrow shows the adrenal gland in the specimen in H) and the tumor cells had infiltrated into the left adrenal gland (black arrowhead). Slides B,C,E,F,H and I are stained with hematoxylin-eosin. Scale marker, 3 mm. RAMPS: radical antegrade modular pancreatosplenectomy.

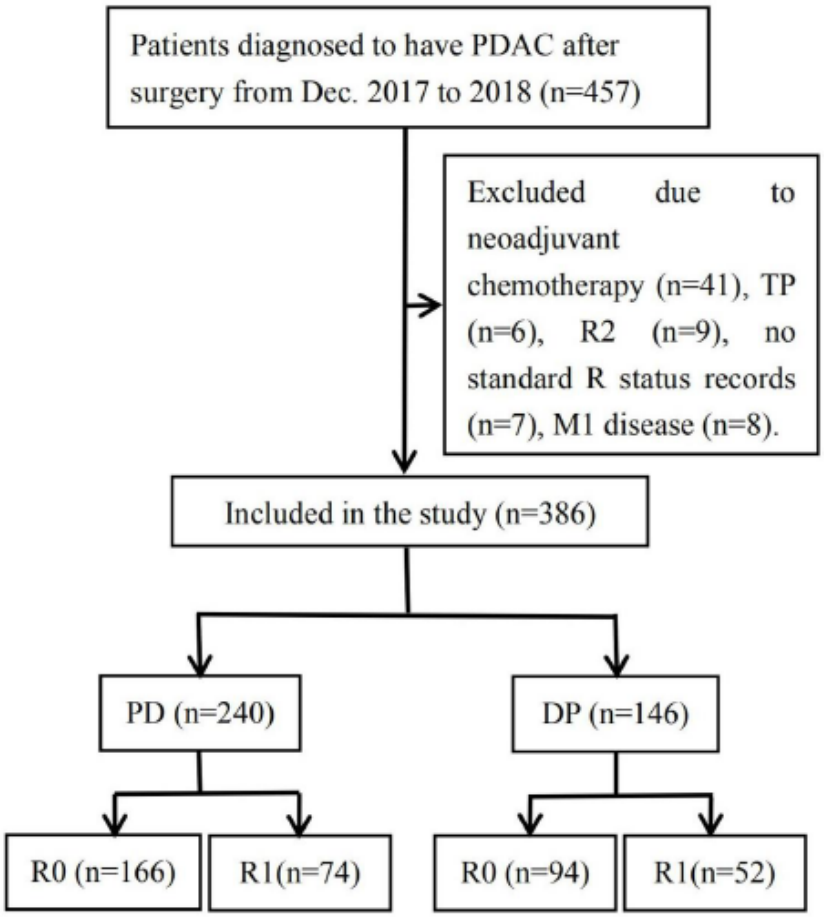

Figure 3

Flowchart of patient selection in the study. DP: distal pancreatosplenectomy, PD: pancreaticoduodenectomy, TP: total pancreatectomy.

Supplementary Files

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- SupplementryFigure1.png
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