Assessment of Standardization Circumferential Resection Margin Status Influence Survival following Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma

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Abstract

Background: Not only to assess the prognostic influence on standardization circumferential resection margin R0 and R1 Status but also to research the prognostic influence on adjuvant chemotherapy to PV/SMV, SMA resection margins≤1mm. The SMV and SMA resection margins had an important prognostic influence to PDAC patients, and the survival prognosis of R1 status(resection margin≤1mm) was poor.

Methods: A total of 228 patients performed PD between 2015 and 2019 were included, which was assessment of standardization circumferential resection margin status and survival prognosis. There were cancer cells within 1mm clearance of PV/SMV and SMA resection margins named $R1_{PV/SMV, SMA}$, and no cancer cells named $R0_{PV/SMV, SMA}$.

Results: The resection margin 1mm clearance of PV/SMV, SMA (P=0.010) and postoperative adjuvant chemotherapy (P=0.001) were prognostic independent predictors. The median survival time was 22 months of 166 $R0_{PV/SMV, SMA}$ patients (73%) compared to 15 months of 62 $R1_{PV/SMV, SMA}$ patients (27%) (*P*=0.005). There was the statistical significance of survival time between the adjuvant chemotherapy group and the none-adjuvant chemotherapy group (*P*=0.000). In the $R1_{PV/SMV, SMA}$ group, there was no statistical significance of survival time between the adjuvant chemotherapy patients and the none-adjuvant chemotherapy patients (*P*=0.208).

Conclusions: Patients undergoing PD for PDAC, postoperative adjuvant chemotherapy could not improve the poor survival prognosis of $R1_{PV/SMV, SMA}$ resection patients. The resection margins of PV/SMV, SMA had a greater prognostic influence on survival than postoperative adjuvant chemotherapy.

Trial registration: Clinicaltrials.gov/ct2/show/NCT02928081

Background

Pancreatic ductal adenocarcinoma (PDAC) is the malignant tumor of the digestive system with a poor prognosis. The latest research report showed that the annual incidence of PDAC was 12.9/100000, and the death rate was 11/100000[1]. In the last 20 years, because of progression the comprehensive treatment, the 5-year survival rate of PDAC was higher than before[2, 3]. Compared to the other malignant tumor, however, the 5-year survival rate of PDAC was only 8% and it was still lower [4]. The 5-year survival rate of PDAC patients who had received surgical treatment would reach 12.4%, and the 5-year survival rate of PDAC patient who was metastatic disease could only be 2.9%[3, 4]. And the latest studies predict that the pancreatic adenocarcinoma will be the second most fatal malignancy in 2030[5]. Nowadays, surgical treatment was still the only radical cure method for PDAC[6–8].

The 90% of PDAC located in pancreatic head. Previous studies had shown that resection margin was an independent prognostic factor affecting the prognosis of pancreatic head adenocarcinoma [9–15].

However, some studies had shown that the resection margin was not the independent prognostic factor [16–19]. The reasons caused those results might be none standardized definition of resection margins or none standardized pancreaticoduodenectomy(PD). Then, the Royal College of Pathologists (RCP) had recommended the definition of R1 status was that there were the cancer cells within the 1 mm clearance of the circumferential margin of pancreatic surgical specimen[20, 21]. After that, the International Study Group of Pancreatic Surgery (ISGPS) and College of American Pathologists (CAP) also recommended whether there were cancer cells within the resection margin 1 mm to define the R0 status or R1 status [22, 23].

With the standard of pathological examination for the pancreatic resection margins, many studies had begun to focus on prognostic influence of pancreatic resection margins [10, 11, 14, 24]. Those studies had revealed that in resectable pancreatic head carcinoma patients (exclude vascular invasion patients) who the cancer cells were not microscopic examined within 1 mm clearance of resection margins, the 5-year survival rate could reach 48%. However, in the patients who the cancer cells were microscopic examined within 1 mm clearance of resection margins, the 5-year survival rate was only 14% [10, 11, 14, 24]. Those studies also revealed that the resection margins were an independent risk factor for survival prognosis, and the R1resection status had had a poor survival prognosis. And there were multiple resection margins of PD. Whether each resection margin had the same effect on survival prognosis? And, whether it was prognostic significance to study each resection margin? Those questions were controversial. Previous studies had suggested that each resection margin of PDAC had the same effect on survival prognosis [25–29].In 2020, a study in < Pancreatology > had revealed that not all resection margin positivity had the same prognostic significance, and superior mesenteric artery(SMA) and superior mesenteric vein(SMV) margin positivity had a worse survival impact [30].

In the previous studies, the SMV and SMA resection margins had an important prognostic influence to PDAC patients, and the survival prognosis of R1 status(resection margin≤1 mm) was poor. However, the previous results had not analyzed the prognostic influence of adjuvant chemotherapy on the R1 status patients. Whether efficacy of adjuvant therapy could improve the survival prognosis of R1 status patients? And whether the R1 status patients who had received adjuvant chemotherapy could be the same survival rate to the R0 status patients? If so, then the patients of resectable pancreatic head carcinoma would perform PD first and then received adjuvant chemotherapy.

In this study, we had examined all the resection margins of PD and assessed the Port Vein/SMV, SMA resection margins. We defined the microscopic examined cancer cells within 1 mm clearance of PV/SMV, SMA resection margins as R1 resection(resection margins≤1 mm), and none microscopic examined cancer cells within 1 mm clearance of PV/SMV, SMA resection margins as R0 resection(resection margins>1 mm). Consequently, we not only assessed the prognostic influence on R0 and R1 status but also researched the prognostic influence on adjuvant chemotherapy to PV/SMV, SMA resection margins≤1 mm.

Methods

Patients

This study was a retrospective cohort study (Clinicaltrials.gov/ct2/show/NCT02928081), which was approved by the Ethics Committee of Sichuan University West China Hospital (No.2016:122). All patients underwent surgical treatment in the Department of Pancreatic Surgery, Sichuan University West China Hospital, during a 4-year period (January 1, 2015 to March 31, 2019). The decision to perform surgical treatment was made by a multidisciplinary team (MDT) including radiologists, surgeons, pathologists and oncologists. All patients were performed classic PD by 2 surgeons (XB.L and NW.K). This study was limited to patients undergoing PD for resection of pancreatic head adenocarcinoma which all the pathological diagnosis was PDAC. And other lesions such as ampullary, intraductal papillary mucinous neoplasms (IPMN), mucinous cystadenocarcinomas, duodenal or distal bile duct adenocarcinomas and were excluded. And we also had excluded: (a) the patients had received neoadjuvant therapy, (b) the pathological report had not clearly defined the distance between the circumferential margin (CRM) and the tumor.

The inclusion criteria were: (a) age 18–75 years, (b) the computed tomography (CT) showed the tumor had localized in the head of the pancreas, (c) there was no greater than 180° circumferential involvement of SMV and no overt arterial involvement [14], (d) follow-up data were completed.

No patients got neoadjuvant therapy. Postoperatively, some patients did not choose to receive chemotherapy. Follow-up which was up to December 4, 2019, comprised the out-patient and telephone reviews. When the Carbohydrate antigen19-9 (CA19-9) was high, CT scans were given to the postoperative patients.

Pathology Assessment

Measurement, stained and fixation of the surgical specimen and definition of the resection margins, pathological examination, and pathological report were all based on the guidelines of the RCPath. (https://www.rcpath.org/profession/guidelines/cancer-data sets-and-tissue-pathways.html)

We had paid particular attention to the CRM definition of the postoperative specimens, which included surface of anterior, posterior, SMV, and SMA (FIGURE 1A). And also, we had examined the transection margins which consisted of the corpus/neck margin, proximal and distal gastric/ jejunum margins and the bile duct margin. Then we had stained the PV/SMV and SMA resection margins(FIGURE 1B), with glacial acetic acid strengthened. The standard of choosing a transverse plane was not only to show the relationship between tumor and adjacent tissues but to show the distance between tumor and resection margin. Thereafter 3 cuts were made from the tumor in head of pancreas. Then the specimens were fixed with 10% neutral formalin solution for 24 to 48 hours. After that, the specimen was further microscopic

examined as follows: the tumor, anterior margin, posterior margin, PV/SMV and SMA margin, proximal gastric margin, distal jejunum margin, common bile duct margin and gallbladder, corpus/neck margin [26].

In microscopic assessment, each resection margin was measured at 1/10 mm intervals up to 5 mm which the blocks of resection margins were cut. And the standard pathological report included as follows: maximum tumor diameter and extent; tumor grade and location of local spread; lymphatic, venous and perineural invasion; total number of lymph nodes examined; number positive lymph nodes. We had performed Tumor Node Metastasis (TNM) which corresponded to the staging system of Union for International Cancer Control (UICC) or American Joint Commission on Cancer (AJCC).

In this study, we had microscopically assessed the R0 or R1 status according to the RCPath criteria. And we had defined the microscopically positive margin as<1 mm when there were cancer cells within 1 mm clearance of PV/SMV and SMA resection margins, and the other margins were not. Those formed the PV/SMV and SMA resection margins>1 mm group($R1_{PV/SMV, SMA}$). Also, we had defined the microscopically negative margin as>1 mm when there were no cancer cells within 1 mm clearance of PV/SMV and SMA resection margins, and the other margins were not as well. And those formed the PV/SMV and SMA resection margins>1 mm group($R0_{PV/SMV, SMA}$).

Statistical Analysis

All statistical analyses were processed by SPSS version 20.0 (SPSS Inc. Chicago, IL). The χ^2 test was used for counting data, and Fisher's exact test was used for frequency which was less than 5. Shapiro-Wilk test analyzed the normal distribution of data, and the Levebe test analyzed the homogeneity of variance. The T-test was used for Gaussian distribution, which was expressed as mean ± standard deviation, and the statistical value was *t*. And the Mann-Whitney U test was used for the abnormal distribution, which was expressed as M (P25, P75), and the statistical value was *Z*. Kaplan-Meier survival analysis analyzed the overall survival withdrawing a survival curve. The Log-Rank test was used for univariate analysis. The proportional hazards regression (Cox regression) model was used for multi-factor analysis. Statistical significance was set at a $P<0.05$.

Results

Different Resection Margin Status of the Patient Cohort from Pathological Report

Patients whose resection margins were not clearly indicated in the pathological report were excluded. There were a total of 228 patients performed PD between 2015 and 2019 in this study. (FIGURE 2)According to the Pathological report: there were no cancer cells in anterior margin, posterior margin, proximal gastric margin, distal jejunum margin, common bile duct margin and gallbladder, corpus/neck margin of the all the 228 patients. 62 (27%) patients had histologically positive which there were cancer

cells within 1 mm (<1 mm) in PV/SMV and SMA margins and were $R1_{PV/SMV, SMA}$ resections group. The others 166(73%) patients which there were no cancer cells within 1 mm (>1 mm) were $R0_{PV/SMV, SMA}$ resections group.

Clinico-pathologic Characteristics Of Different Resection Margin Status Groups

In this study, tumor grade is categorized into poorly differentiated tumors, poorly- moderately differentiated tumors, moderately differentiated tumors, moderately-well differentiated tumors and well differentiated tumors. All patients were tumor stage T1, T2 or T3. And the AJCC criteria of TNM staging were applied. The clinico-pathologic characteristics of the different resection margin status groups are summarized in Table 1.

Table 1
Clinico-Pathologic Characteristics of Different Resection Margin Status Groups

		Total patients **228 (100%)**	**$R0_{PV/SMV, SMA}$** **166 (73%)**	**$R1_{PV/SMV, SMA}$** **62 (27%)**	$\chi^2/t/Z$	*P*
Age, year	M (P25,P75)	60.5 (53, 68.25)	61 (53, 69)	57 (52,66.25)	-1.467	0.142
Gender					0.006	0.938
Male	n (%)	137(60)	100(60)	37(60)		
Female	n (%)	91(40)	66(40)	25(40)		
BMI, kg/m^2	M (P25,P75)	21.495 (19.53,23.83)	21.53 (19.38,23.72)	21.485 (19.99,23.97)	-0.661	0.509
Diameter, cm	M (P25,P75)	3 (2.5,3.825)	3 (2.475,4)	3 (2.5,3.8)	-0.890	0.373
CA19-9, U/ml	M (P25,P75)	102.75 (16.14,309.35)	106.3 (18.83,334.9)	83.785 (6.125,271.55)	-0.605	0.545
HGB, g/L	M (P25,P75)	123.5 (113,133.25)	124 (113,135)	123 (113,132)	-0.143	0.887
TBIL, μmol/L	M (P25,P75)	106.9 (12.75,223.08)	95.4 (12.75,209)	139.95 (11.75,232.95)	-0.818	0.413
ALT, U/L	M (P25,P75)	86(26,187)	82 (23.5,209)	97 (41,160.75)	-0.407	0.684
AST, U/L	M (P25,P75)	59 (28,140.5)	57.5 (24,142.75)	59 (38.75,132.5)	-0.451	0.652
ALB, g/L	M (P25,P75)	40.05 (37.08,43.43)	39.9 (37.13,43.25)	40.55 (37.08,43.98)	-0.690	0.490
GLU, mmol/L	M (P25,P75)	5.81 (5.09,7.10)	5.845 (5.25,7.44)	5.65 (4.94,6.71)	-1.390	0.165
Adjuvant Chemotherapy					0.063	0.801
Yes	n(%)	95(42)	70(42)	25(40)		

		Total patients 228 (100%)	$R0_{PV/SMV, SMA}$ 166 (73%)	$R1_{PV/SMV, SMA}$ 62 (27%)	$\chi^2/t/Z$	*P*
No	n(%)	133(58)	96(58)	37(60)		
Grade					1.410	0.842
poorly	n (%)	28(12)	22(13)	6(10)		
poorly-moderately	n (%)	101(44)	70(42)	31(50)		
moderately	n (%)	81(36)	61(37)	20(32)		
moderately-well	n (%)	15(7)	11(7)	4(6)		
well	n (%)	3(1)	2(1)	1(2)		
T					1.346	0.510
1	n (%)	40(18)	31(19)	9(15)		
2	n (%)	153(67)	112(67)	41(66)		
3	n (%)	35(15)	23(14)	12(19)		
N					2.645	0.448
x	n (%)	42(18)	28(17)	14(23)		
0	n (%)	108(47)	84(51)	24(39)		
1	n (%)	62(28)	43(26)	19(31)		
2	n (%)	16(7)	11(6)	5(7)		
TNM					2.923	0.571
IA	n (%)	27(12)	22(13)	5(8)		
IB	n (%)	71(31)	53(32)	18(29)		
IIA	n (%)	12(5)	10(6)	2(10)		
IIB	n (%)	69(31)	48(29)	21(34)		
III	n (%)	49(21)	33(20)	16(19)		

BMI = Body Mass Index, HGB = Hemoglobin, TBIL = Total bilirubin, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, ALB = Albumin, GLU = Glucose

Table 2
A. Result of Log-Rank in Prognostic Factors

Characteristics	N	Survival Rate%			χ^2	*P*
		1-Year	2-Year	3-Year		
Resection margin					7.871	0.005
$R0_{PV/SMV, SMA}$	166	73%	37%	25%		
$R1_{PV/SMV, SMA}$	62	61%	13%	10%		
Adjuvant Chemotherapy					12.759	0.000
Yes	95	83%	56%	31%		
No	133	65%	30%	14%		
Gender					0.607	0.436
Male	137	72%	44%	20%		
Female	91	75%	44%	20%		
Age					0.418	0.518
≤ 60 year	111	74%	31%	24%		
60 year	117	71%	41%	16%		
BMI					0.376	0.540
Normal	139	74%	36%	18%		
Abnormal	89	68%	32%	20%		
CA19-9					1.159	0.282
Normal	59	71%	43%	25%		
Abnormal	169	69%	39%	19%		
HGB					1.407	0.236
Normal	183	74%	38%	23%		
Anemia	45	69%	21%	8%		
TBIL					0.125	0.724
Normal	82	75%	38%	19%		
Jaundice	146	68%	35%	17%		
ALT					0.636	0.425

Characteristics	N	Survival Rate%			χ^2	*P*
		1-Year	2-Year	3-Year		
Normal	82	71%	37%	23%		
Abnormal	146	68%	30%	10%		
AST					2.247	0.134
Normal	73	77%	38%	26%		
Abnormal	155	71%	33%	15%		
ALB					1.239	0.266
Normal	194	71%	36%	21%		
Hypoalbuminemia	34	64%	26%	14%		
GLU					1.375	0.241
Normal	168	71%	36%	22%		
Hyperglycemia	60	70%	26%	15%		
Maximum Diameter of Tumor					1.364	0.505
≤ 2 cm	98	76%	39%	19%		
>2cm,≤4 cm	81	70%	38%	18%		
>4 cm	49	68%	32%	16%		
Grade					4.199	0.380
poorly	28	70%	41%	0		
poorly-moderately	101	65%	31%	16%		
moderately	81	79%	39%	17%		
moderately-well	15	79%	63%	47%		
well	3	99%	0	0		
TNM					3.064	0.547
IA	27	80%	46%	25%		
IB	71	75%	43%	7%		
IIA	12	61%	61%	30%		
IIB	69	64%	32%	15%		
III	49	68%	21%	17%		

Characteristics	N	Survival Rate%			χ^2	*P*
		1-Year	2-Year	3-Year		

Table 2B. **Result of Multivariate Analysis in Prognostic Factors**

Characteristics	HR	95%C.I		P
Resection Margin	1.649	1.126	2.415	0.010
Adjuvant Chemotherapy	1.896	1.303	2.758	0.001

Survival Prognostic Factors By Univariate And Multivariate Analysis

The results of the Log-rank test showed that resection margins status (*P* = 0.005) and adjuvant chemotherapy (*P* = 0.000) were associated with survival prognosis (Table 2A). The results of Cox regression showed that resection margins status (*P* = 0.010) and adjuvant chemotherapy (*P* = 0.001) were independent risk factors for survival prognosis (Table 2B).

Relationship Between Survival And Resection Margin Status

In a total of 228 patients, 215(94.3%) patients were followed up after surgical. 152(91.6%) patients were followed up in the R0 $_{PV/SMV, SMA}$ group. And 57(91.9%) patients were followed up in the R1 $_{PV/SMV, SMA}$ group. The follow-up time ranged 6–60 months, and the median follow-up time was 20 months (Table 3)

Table 3
Survival Analysis between Resection Margin Status and Adjuvant Chemotherapy

	Survival time (M)	Median survival time (M)	Mean survival time (M)	1-Year	2-Year	3-Year	*P*
Total patients 228 (100%)	0.3–52	21	15.75 ± 8.90	73%	40%	19%	-
Resection margin (228)							
$R0_{PV/SMV, SMA}$ 166 (73%)	0.3–52	22	16.98 ± 8.99	73%	37%	25%	0.005
R1 $_{PV/SMV, SMA}$ 62 (27%)	0.6–42	15	13.22 ± 8.21	61%	13%	10%	
Adjuvant chemotherapy (228)							
Yes 95(42%)	6–43	24	17.28 ± 8.48	83%	56%	31%	0.000
No 133(58%)	0.3–52	17	14.59 ± 9.08	65%	30%	14%	
None-adjuvant chemotherapy group (133)							
$R0_{PV/SMV, SMA}$ 96 (72%)	0.3–52	19	15.7 ± 9.53	69%	36%	15%	0.074
R1 $_{PV/SMV, SMA}$ 37 (28%)	0.6–35	15	12.66 ± 8.00	54%	11%	0%	
Adjuvant chemotherapy group (95)							
$R0_{PV/SMV, SMA}$ 70 (74%)	6–43	26	18.42 ± 8.22	84%	63%	35%	0.025
R1 $_{PV/SMV, SMA}$ 25 (26%)	2–42	16	14.11 ± 8.61	79%	25%	13%	

	Survival time (M)	Median survival time (M)	Mean survival time (M)	1-Year	2-Year	3-Year	*P*
The Relationship between R0$_{PV/SMV, SMA}$ Patients and Adjuvant chemotherapy (166)							
Adjuvant chemotherapy							
Yes 70(42%)	6–43	26	18.42 ± 8.22	84%	63%	35%	0.001
No 96(58%)	0.3–52	19	15.7 ± 9.53	69%	36%	15%	
The Relationship between R1$_{PV/SMV, SMA}$ Patients and Adjuvant chemotherapy (62)							
Adjuvant chemotherapy							
Yes 25(40%)	2–42	16	14.11 ± 8.61	79%	25%	13%	0.208
No 37(60%)	0.6–35	15	12.66 ± 8.00	54%	11%	0%	

In a total of 228 patients, the survival time ranged 0.3–52 months, the median survival time was 21 months, the mean survival time was 15.75 ± 8.90 months and the 1-year, 2-year, and 3-year survival rates were 73%, 40%, and 19%, respectively. In the R0 $_{PV/SMV, SMA}$ group, the survival time ranged 0.3–52 months, the median survival time was 22 months, the mean survival time was 16.98 ± 8.99 months and the 1-year, 2-year, and 3-year survival rates were 73%, 37%, and 25%, respectively. In the R1 $_{PV/SMV, SMA}$ group, the survival time ranged 0.6–42 months, the median survival time was 15 months, the mean survival time was 13.22 ± 8.21 months, and the 1-year, 2-year, and 3-year survival rates were 61%, 13%, and 10%, respectively. There was statistical significance of survival time between R1 $_{PV/SMV, SMA}$ group and R0 $_{PV/SMV, SMA}$ group (P = 0.005)(Table 3)(FIGURE 3 A).

Survival Relationship Between Adjuvant Chemotherapy And Resection Margin Status

Postoperatively, 95 (42%) patients had received adjuvant chemotherapy. 24 patients were treated with Gemcitabine, 57 patients were treated with Tegafur Gimeracil Oteracil Potassium Capsule, 4 patients were treated with Tegafur Gimeracil Oteracil Potassium Capsule combined Gemcitabine. 4 patients were treated with FOLFIRINOX and 6 with Doxifluridine. In addition to this, 133 (58%) patients had not received any adjuvant therapy.

There was the statistical significance of survival time between the adjuvant chemotherapy group and the none-adjuvant chemotherapy group (P = 0.000), (Table 3)(FIGURE 3B). In the none-adjuvant chemotherapy group, there was no statistical significance of survival time between R0 $_{PV/SMV, SMA}$ patients and R1 $_{PV/SMV, SMA}$ patients(P = 0.074) (Table 3) (FIGURE 3C). In the adjuvant chemotherapy

group, there was statistical significance of survival time between R0 $_{PV/SMV, SMA}$ group and R1 $_{PV/SMV, SMA}$ group(P = 0.025). (Table 3) (FIGURE 3D)

In the R0 $_{PV/SMV, SMA}$ group, there was the statistical significance of survival time between the adjuvant chemotherapy patients and the none-adjuvant chemotherapy patients (P = 0.001) (Table 3) (FIGURE 3E). In the R1 $_{PV/SMV, SMA}$ group, there was no statistical significance of survival time between the adjuvant chemotherapy patients and the none-adjuvant chemotherapy patients (P = 0.208) (Table 3) (FIGURE 3F).

Discussion

The previous study had suggested that the patients of R1$_{PV/SMV, SMA}$ resection had a poor survival prognosis. And in this study, resection margin (P = 0.010) and postoperative adjuvant chemotherapy (P = 0.001) were independent risk factors of survival prognosis. We had researched the survival prognosis of PV/SMV and SMA resection margins. Except the PV/SMV and SMA resection margins, the other resection margins in PD were R0 status according to the 1 mm clearance principle of RCPath. For many of the previous studies had failed to demonstrate that adjuvant chemotherapy influenced the outcome of R1 status. And specific details of relationship between the PV/SMV and SMA resection margins and the adjuvant chemotherapy were lacking in previous studies. Then, we had not only analyzed the survival prognosis of R1 $_{PV/SMV, SMA}$ status but analyzed whether the adjuvant chemotherapy could improve the survival prognosis of R1 $_{PV/SMV, SMA}$ status.

Previous studies had revealed that smoking and obesity were modifiable risk factors for PDAC, and that was to say, smoking cessation and diet could reduce the risk of PDAC [31]. Male had nearly 30% more than women for the incidence of PDAC [32]. In our study, 137 (60%) patients were male, and 91 (40%) patients were female, which was consistent with previous studies. The cause of difference in incidence might be male's preference for alcohol, smoking and obesity. However, the gender, age and BMI were not the independent prognostic factors in this study, which might relate to the small sample and PDAC had caused patients to lose weight quickly.

A series of previous studies on resection margins in which the standardized histopathological examination had reported that the resection margins had prognostic influence on survival. Popescu I *et al* had reported that R0 resection of PD in PDAC could improve overall postoperative survival rate [33]. Tummers W.S *et al* had researched the relationship between the R0 and (or) R1 resection and postoperative local recurrence, overall survival, which had reported that the R status of resection margin was associated with the postoperative local recurrence, overall survival of PDAC patients [34]. Especially in N1staging patients, there were having similar recurrence characteristics between R0 and R1 resection [34]. Demir I.E *et al* had reported that the PD for advanced PDAC was more likely to be R1 resection, and the resection margins could be independent risk factor for survival prognosis [35]. In a prospective randomized controlled study, Delpero J.R *et al* had also reported that the R status of resection margin was associated with the survival prognosis, and they further reported that resection margins < 1 mm was

independent risk factor for survival prognosis [36]. After standardized histopathological examination on the resection margins of specimen, Hank T *et al* had reported that the resection margins 1 mm was independent risk factor for survival prognosis [37]. In this study, there was statistical significance between R1 $_{PV/SMV, SMA}$ group and R0 $_{PV/SMV, SMA}$ group (P = 0.005). And the 1, 2, 3-year survival rate of R0 $_{PV/SMV, SMA}$ group patients were significantly better than that of R1 $_{PV/SMV, SMA}$ group(73% *VS* 61%、40% *VS* 13%、19% *VS* 10%). Therefore, the resection margin 1 mm clearance of PV/SMV, SMA was the independent risk factor for survival prognosis in this study.

With the standardized histopathological examination on the specimen, most R0 resection of PD in the past was actually R1 resection, which the reason might be that the PV/SMV, SMA resection margins were nonstandardized of radical resection. For this cohort of patients, neoadjuvant therapy and adjuvant chemotherapy might have been critical to improving survival prognosis. NCCN had recommended adjuvant chemotherapy following resection of PDAC as standard treatment since 2000. Postoperatively, however, less than 50% of patients received adjuvant chemotherapy [38]. In a retrospective study of PDAC, Shaib W.L *et al* had reported that the adjuvant chemotherapy could prolong survival time [39]. In the same study, Nagrial A.M *et al* had reported that the elder PDAC patients who had received postoperative adjuvant chemotherapy could live longer [40]. This study had provided adjuvant chemotherapy evidence for elderly PDAC patients after PD. In a study of adjuvant chemotherapy with Gemcitabine, Oettle H *et al* had reported that the PDAC patients who had received standardized treatment of Gemcitabine for 6 months would live longer and get higher disease-free survival [41]. Then in the study of system evaluation in PDAC patients, Parmar A *et al* had not only confirmed that postoperative adjuvant chemotherapy could significantly improve the survival prognosis but also had recommended the mFOLFIRINOX as the preferred adjuvant chemotherapy regimen [42]. And in our study, there was statistical significance of survival time between the adjuvant chemotherapy group and the none-adjuvant chemotherapy group (P = 0.000). The adjuvant chemotherapy group patients had higher 1-year, 2-year, and 3-year survival rates than the none-adjuvant chemotherapy group (83% *vs* 65%, 56% *vs* 30%,31% *vs* 14%), which was consistent with previous studies.

When we had analyzed the survival time of subgrouping of the R0 $_{PV/SMV, SMA}$ group, and R1 $_{PV/SMV, SMA}$ group separately by comparison of adjuvant chemotherapy and none- adjuvant chemotherapy. In R0 $_{PV/SMV, SMA}$ group, and adjuvant chemotherapy patients had a longer mean survival time (18.42 ± 8.22 m *vs* 15.7 ± 9.53 m) and a higher 1-year, 2-year, and 3-year survival rates(86%vs68%、63%vs36%、35%vs15%) than none-adjuvant chemotherapy patients. However, in R1 $_{PV/SMV, SMA}$ group, though the adjuvant chemotherapy patients had a higher 1-year, 2-year, and 3-year survival rates than none-adjuvant chemotherapy patients(75%vs54%、25%vs11%、35%vs0%), there was no statistical significance in survival analysis between the adjuvant chemotherapy patients and none-adjuvant chemotherapy patients (P = 0.208). In this study, if the R1$_{PV/SMV, SMA}$ patients would not receive adjuvant chemotherapy, and the 3-year survival rate was 0. And the postoperatively adjuvant chemotherapy could not improve survival

prognosis of R1 $_{PV/SMV, SMA}$ patients which survival prognosis was very poor. To this cohort of patients, it was insignificance to perform surgical treatment.

Conclusion

In conclusion, we had demonstrated that in this cohort of 228 patients undergoing PD for PDAC, the R0$_{PV/SMV, SMA}$ rate was 73% and the R1 $_{PV/SMV, SMA}$ rate was 27%, and the resection margin 1 mm clearance of PV/SMV, SMA was prognostic independent predictor. And the R0$_{PV/SMV, SMA}$ patients had a better survival prognosis. Furthermore, postoperative adjuvant chemotherapy was also prognostic independent predictor in this cohort of 228 patients. However, postoperative adjuvant chemotherapy could not improve the poor survival prognosis of R1 $_{PV/SMV, SMA}$ patients. This result had suggested that the resection margins of PV/SMV, SMA had a greater prognostic influence on survival than postoperative adjuvant chemotherapy. This was small sample and single-center research but should future validation in big data and multiple centers study. It is possible to improve prognostication and efficacy of R1 $_{PV/SMV, SMA}$ patients by early treatment intervention such as neoadjuvant therapy.

Abbreviations

PDAC
Pancreatic ductal adenocarcinoma
PD
Pancreaticoduodenectomy
RCP
Royal College of Pathologists
ISGPS
International Study Group of Pancreatic Surgery
CAP
College of American Pathologists
SMA
Superior Mesenteric Artery
SMV
Superior Mesenteric Vein
PV
Port Vein
MDT
Multidisciplinary Team
IPMN
Intraductal Papillary Mucinous Neoplasms
CRM
Circumferential Margin

CT
Computed Tomography
CA19-9
Carbohydrate antigen19-9
TNM
Tumor Node Metastasis
UICC
Union for International Cancer Control
AJCC
American Joint Commission on Cancer

Declarations

Ethics approval and consent to participate

This study was a prospective cohort study (Clinicaltrials.gov/ct2/show/NCT02928081), which was approved by the Ethics Committee of Sichuan University West China Hospital (No.2016:122).

Consent for publication

Consent for publication had be obtained from all patients.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JHL and YTW contributed equally to this study.

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Figures

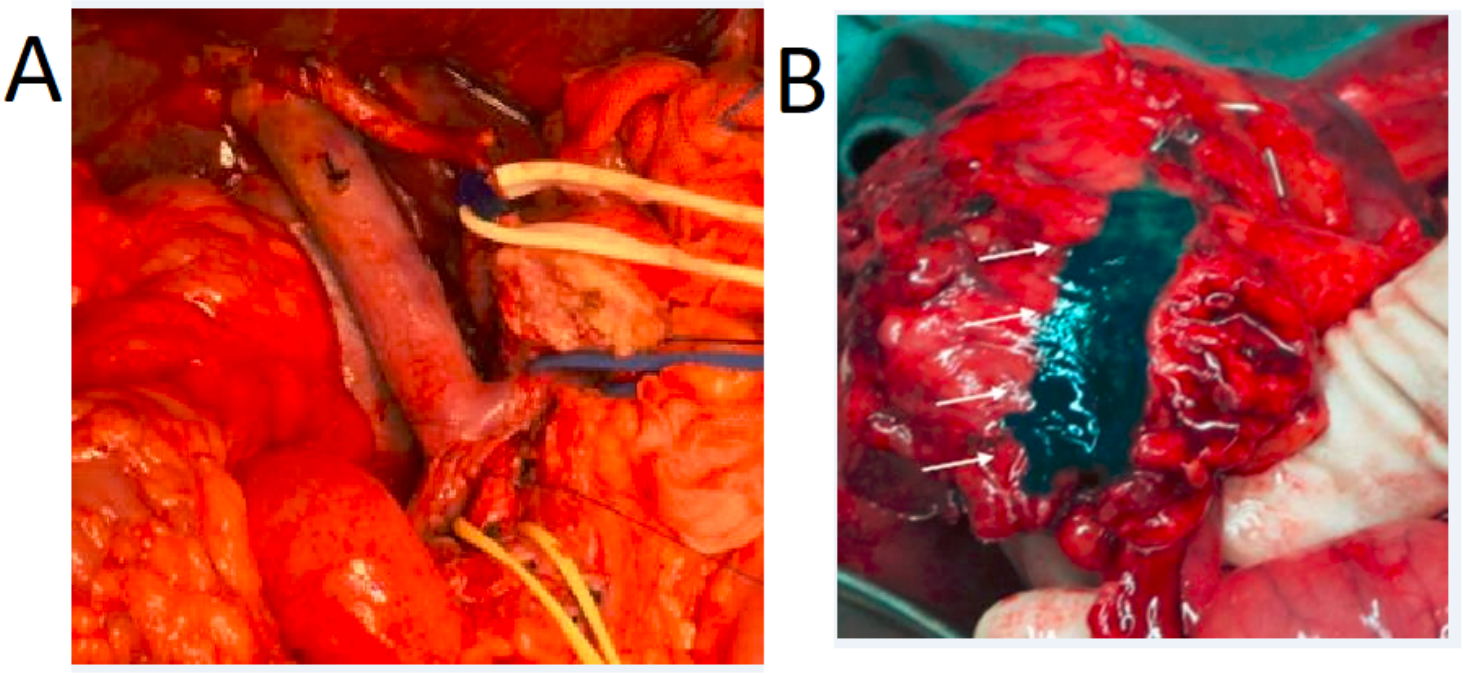
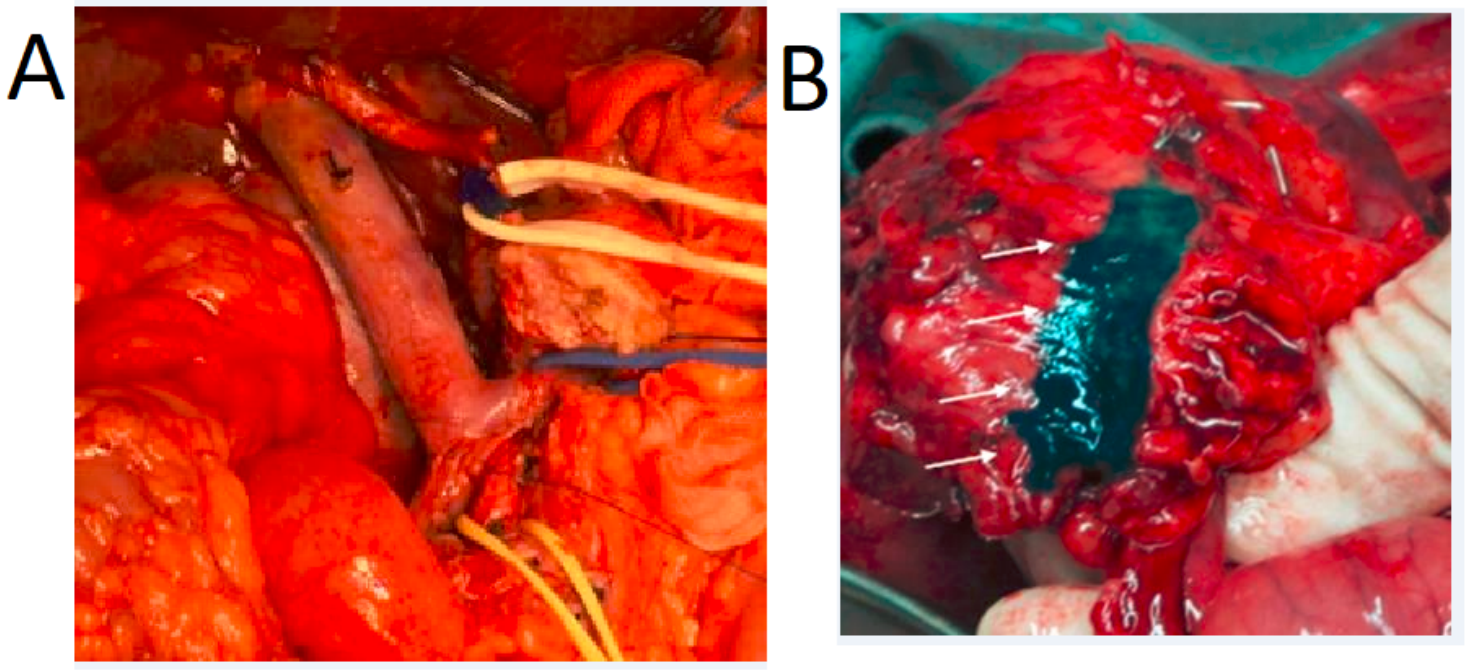


Figure 1

The resection margin of PV/SMV, SMA: (A) The PV/SMV, SMA surface after radical pancreaticoduodenectomy. (B)Stained the PV/SMV, SMA groove of the pancreaticoduodenectomy resection specimen.



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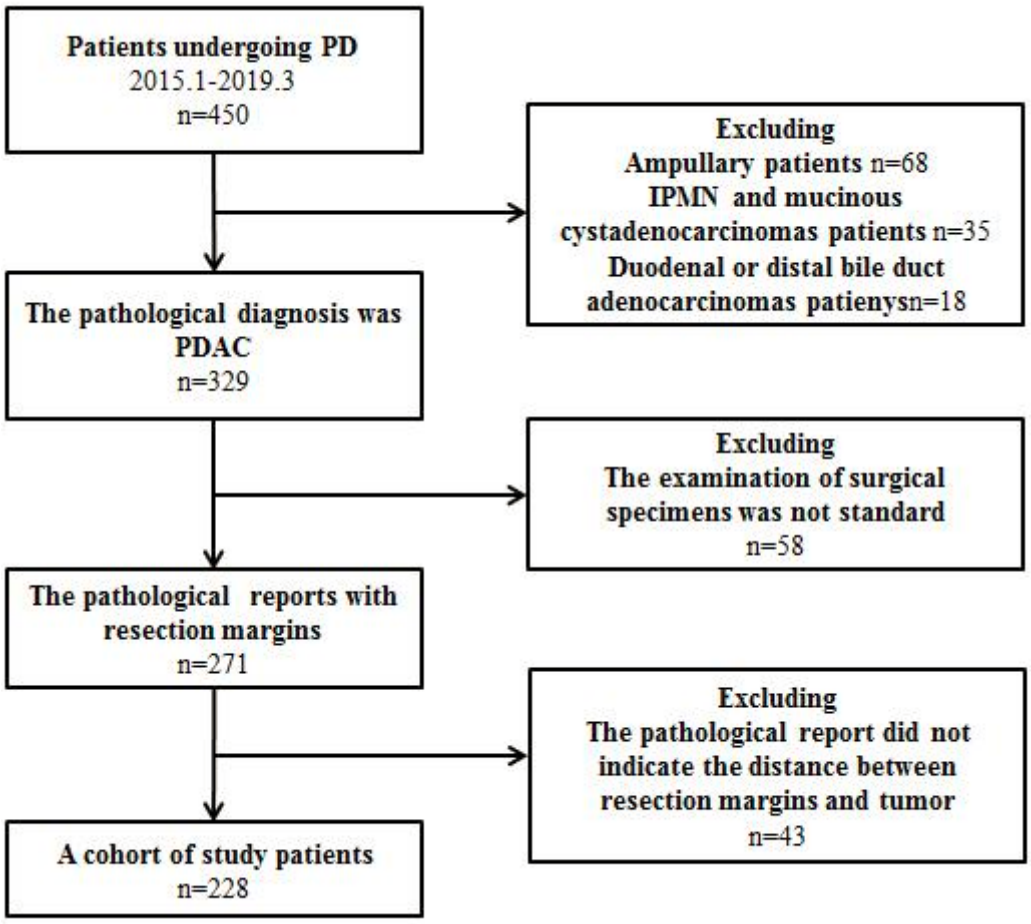
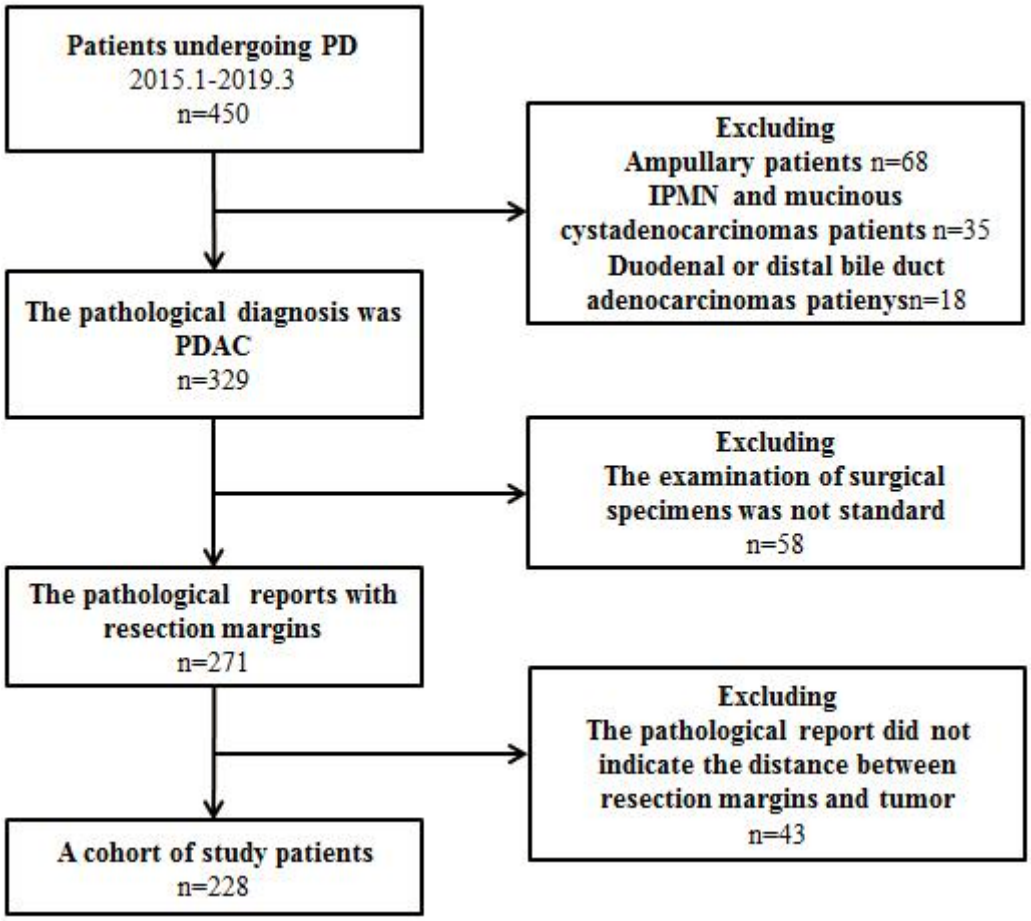


Figure 2

Flow chart of screening patients.



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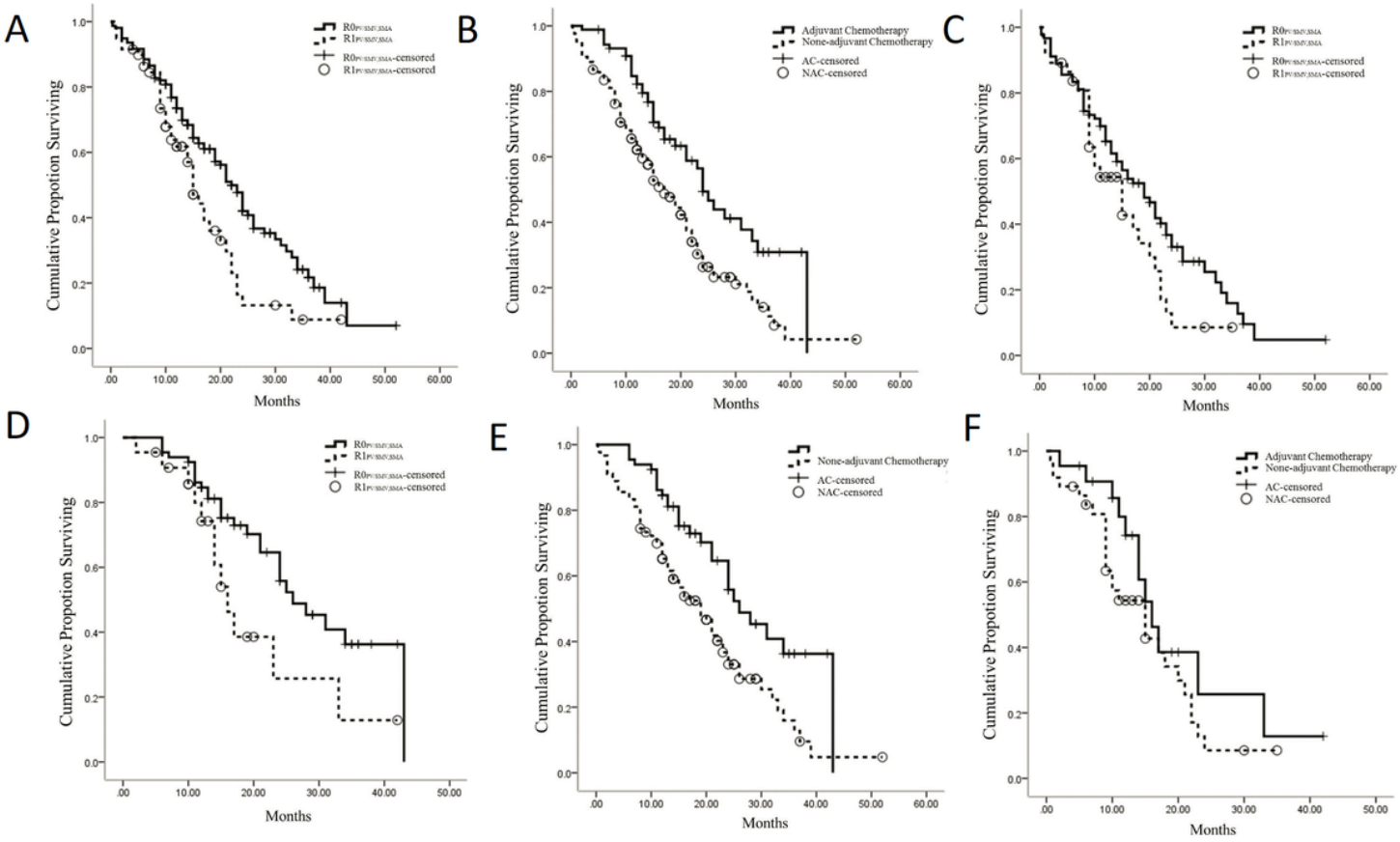
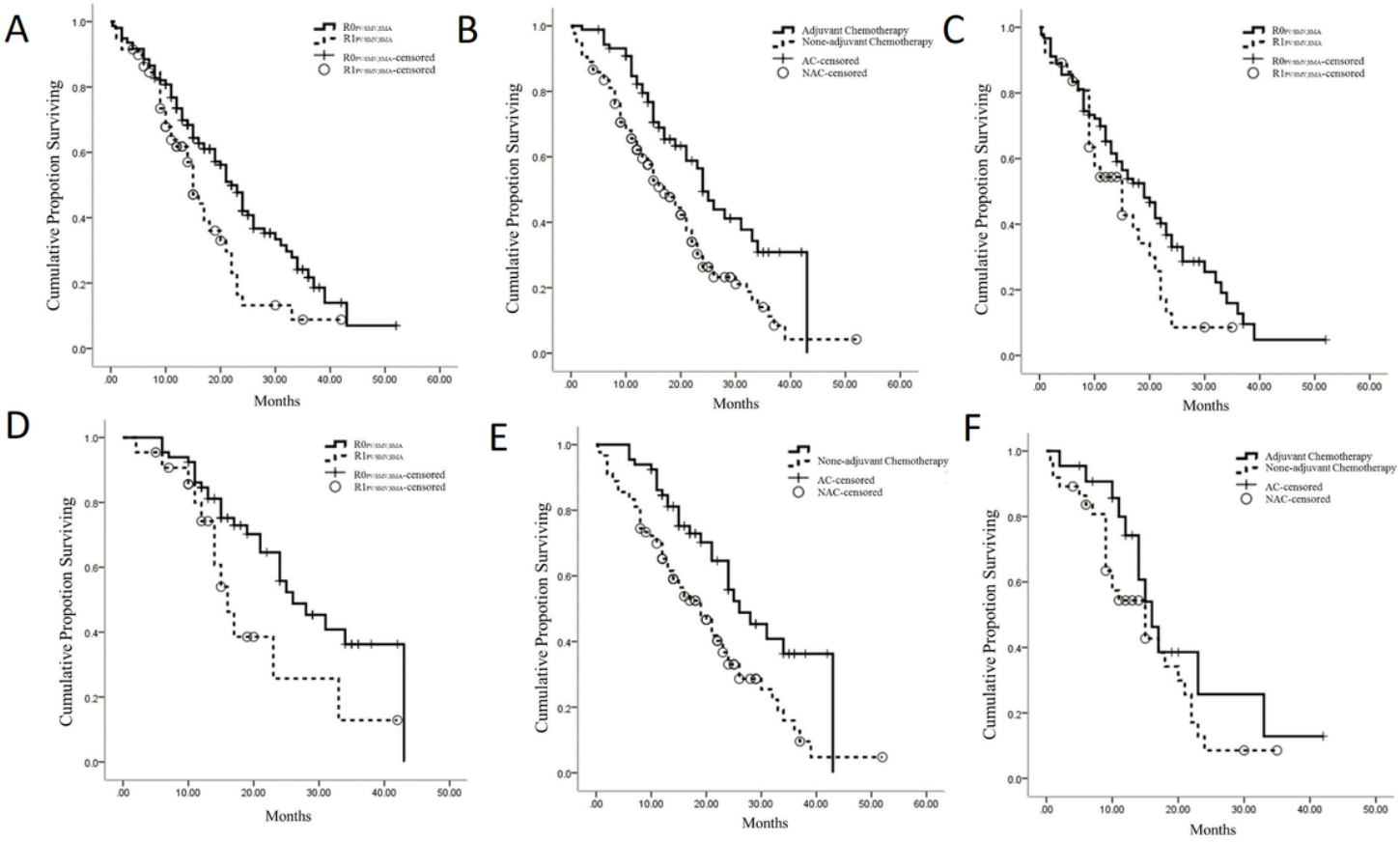


Figure 3

Kaplan-Meier Survival Curves for the cohort of patients: (A) The median survival time of 166 R0PV/SMV, SMA patients was 22 months compared with 15 months of 62 R1 PV/SMV, SMA patients (P=0.005).(B) The median survival time of 95 adjuvant chemotherapy patients was 24 months compared with 17 months of 133 none-adjuvant chemotherapy patients(P=0.000). (C) In the 133 none-adjuvant chemotherapy patients, the median survival time of 96 R0PV/SMV, SMA patients was 19 months compared with 15 months of 37 R1 PV/SMV, SMA patients (P=0.074). (D) In the 95 adjuvant chemotherapy patients, the median survival time of 70 R0PV/SMV, SMA patients was 26 months compared with 16 months of 25 R1PV/SMV, SMA patients (P=0.025). (E) In the 166 R0PV/SMV, SMA patients, the median survival time of 70 adjuvant chemotherapy patients was 26 months compared with 19 months of 96 none-adjuvant chemotherapy patients(P=0.001). (F) in the 62 R1 PV/SMV, SMA patients, the median survival time of 25 adjuvant chemotherapy patients was 16 months compared with 15 months of 37 none-adjuvant chemotherapy patients(P=0.001).



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