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ORIGINAL ARTICLE

Sub-adventitial divestment technique for resecting artery-involved pancreatic cancer: a retrospective cohort study

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Abstract

Purpose To introduce sub-adventitial divestment technique (SDT), a procedure to remove the tumor while preserving the artery during curative pancreatectomy. Peri-operative safety profile was also evaluated.

Methods In a single center consecutive series of pancreatectomy for pancreatic cancer, the outcome of patients who had pancreatectomy with SDT was compared to standard pancreatic surgery.

Results From June 2014 to June 2016, 72 patients had pancreatectomy with SDT and 235 had standard surgery. Tumor stage was T4 in all 72 (100%) tumors removed using SDT compared to four (2%) with standard pancreatectomy ($p < 0.001$). All 72 (100%) tumors in the SDT group were stage III compared to 24 (10%) in the standard surgery group ($p < 0.001$). Both groups had a high proportion of poorly differentiated tumors (52 (72%) and 163 (69%) respectively) and perineural tumor invasion (62 (86%) and 186 (79%) respectively). R1 (< 1 mm) was found in 24 (86%) of 28 tumors in the SDT group, and in 72 (60%) out of 120 standard pancreatectomy tumors ($p = 0.01$). Complications occurred in 29 (40%) of the SDT group and in 88 (37%) of the standard group. The in-hospital mortality was four (6%) in the SDT group and one (0.4%) in the standard group ($p = 0.01$), with a 90-day mortality of 5 (8%)/60 and 6 (3%)/209 ($p = 0.07$) respectively.

Conclusions The sub-adventitial divestment technique appeared to be an effective surgical technique to remove the tumor while preserving the artery. This approach warrants further validation in prospective studies.

Keywords Pancreatic neoplasms · Pancreatectomy · Arterial resection · Venous resection · Artery preservation

Introduction

Surgery with modern adjuvant chemotherapy offers the prospect of increased 5-year survival to around 30% in patients with resected pancreatic cancer [1], and even to 40–50% in selected patients with more potent regimen [2]. In the adjuvant setting, an R0 resection is associated with a median overall survival of 39.5 months and 40% 5-year survival rate in unselected pancreatic cancer patients, significantly greater compared to R1 resections [1, 3, 4]. For patients with locally advanced pancreatic cancer, neoadjuvant chemotherapy can result in resection rates of 50–65% with median survival rates of 15.3–31.4 months, exceeding that of palliative chemotherapy without resection [5, 6]. R0 resection rates of 31.3–69.0% have been reported with an improved overall survival rate compared to R1, which in turn are associated with improved survival compared to an R2 resection [5, 6].

Baobao Cai and Zipeng Lu contributed equally to this work. Markus W. Büchler and Yi Miao shared the correspondence authorship.

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Pre-operative resectability of pancreatic cancer in the head of the pancreas is defined by the extent of involvement of key vessels including the hepatic portal vein (HPV) and superior mesenteric veins (SMV), the celiac axis (CA), the common and proper hepatic arteries (CHA/PHA), and the superior mesenteric artery (SMA) [7–12]. Standard surgical approaches have been developed for resectable and borderline resectable pancreatic cancer that may require partial or complete venous resection [11, 13, 14]. Resection of locally advanced pancreatic cancer in the head of the pancreases encasing major arteries is much more challenging, and usually involves advanced surgical techniques including arterial resection with or without graft replacement [15–19] and periarterial dissection [20–22], as well as the Heidelberg Triangle Operation [23]. The plane of dissection between the tumor mass and the artery is either just external to the arterial lymphatic network covering the artery circumferentially, and sometimes within the network but external tunica externa. This is also known as the tunica adventitia and consists of a collagen and elastin matrix, which contains the nervi vasorum and vasa vasorum.

In a series of 52 patients who had resection for locally advanced pancreatic cancer reported by Bachellier et al. [24], 26 patients had an arterial resection of whom 21 also had an HPV resection, and 26 patients who did not have an arterial resection of whom 20 also had an HPV resection. On histological examination, only four (15.4%) of the 26 resected arterial segments were found to have vascular cancer invasion, compared to venous wall invasion in 29 (70.7%) of the 41 venous resected specimens [24]. Moreover, in series of 20 patients who had a left pancreata-splenectomy for pancreatic cancer, Watanabe et al. [25] identified arterial involvement in eleven of the resected splenic arteries but this was entirely limited to the tunica adventitia in 10 (90.9%) with deeper involvement in only one case. Based on these observation, we developed a standardized technique to separate the tumor from the artery by dissecting into the plane between the external elastic of tunica adventitia and the tunic media of the involved artery [26, 27]; we present the report of the sub-adventitial divestment technique (SDT), in a single-center series of 72 patients with pancreatic cancer who had this procedure.

Methods

Patients

This was a retrospective single series cohort study of 328 consecutive patients with histologically confirmed pancreatic ductal adenocarcinoma (PDAC) treated at the Pancreas Center, The First Affiliated Hospital Nanjing Medical University, from 1 June 2014 to 30 June 2016. The medical records and operation notes were reviewed for demographic, intra- and post-operative data and pathological variables of all the patients who underwent a partial pancreata-duodenectomy, left pancreatectomy, or total pancreatectomy with curative intent. Patients who had laparoscopic surgery or metastasectomy were excluded. Patients who had a sub-adventitial divestment technique (SDT) procedure were compared with the remainder who had standard surgery [13, 14]. Informed consent was obtained from all patients for the utilization of their data for research purposes. None of the patients had neoadjuvant therapy.

Sub-adventitial divestment technique

The artery-first approach was routinely used in all patients undergoing the sub-adventitial divestment technique (SDT) procedure [28, 29]. The plane between the tunica adventitia and the white glossy external elastic lamina was identified using careful dissection with an electrocautery or ultrasonic scalpel at a site of an uninvolved segment of the involved or encased artery (CA, CHA, PHA, and/or SMA) just proximal or distal to the area of tumor involvement. Blunt dissection using the tip of right-angled arterial clamp is used to proceed along the plane above the external elastic lamina towards the tumor from either one or both directions. The non-working tip of an ultrasonic scalpel was also sometimes used. Dissection is continued along the plane above the external elastic lamina to begin to separate the tumor from the artery. The plane is developed both longitudinally and circumferentially until artery has been freed from any tumor (Figs. 1 and 2). A vascular loop is usually deployed to improve control and provide countertraction. Bleeding from any vasa vasorum can be controlled by cautious electrocoagulation. Small arterial branches must be ligated then divided. Tumor involvement can be cleared from multiple arteries such as the CA, CHA, and SMA (Fig. 3). If the dissection plane cannot be clearly identified and cleanly developed as required, the dissection should be stopped and artery resection would be considered or the curative intended resection should be ceased, as this usually means that the tumor has invaded the external elastic lamina into the smooth muscle of the tunica media.

Methodology

Extended pancreatectomy and surgical complications including post-operative pancreatic fistula (POPF), delayed gastric emptying (DGE), post-operative hemorrhage (PPH), and chyle leakage were defined and graded according to the recommendations from the International Study Group on Pancreatic Surgery (ISGPS) [13, 30–33]. Pre-operative physical status was graded according to the American Society of Anesthesiologists (ASA) guidelines [34]. Pre-operative contrast-enhanced computed tomography (CECT) scans, in cases in which these were available, were also retrospectively

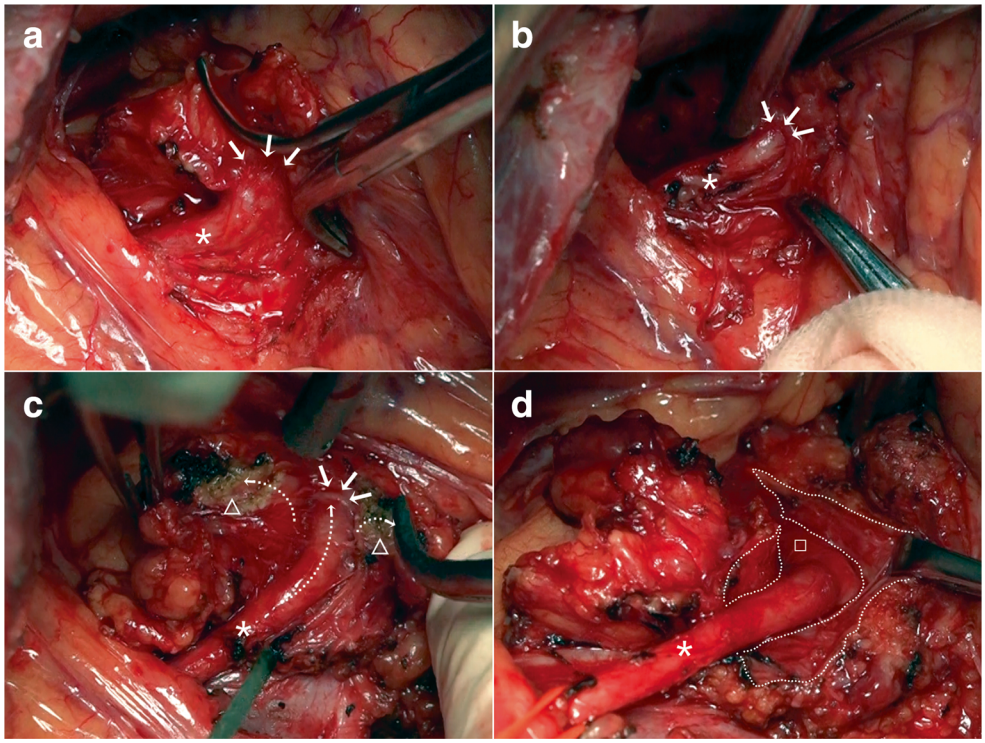

Fig. 1 The technique of sub-adventitial divestment in a patient with tumor involvement of the celiac axis and the common hepatic artery. **a** Tumor invasion of the proximal CHA shown after dissection of lymph node station 8a (Japan Pancreas Society Classification). Sub-adventitial divestment of the artery was started at the uninvolved segment, which showed normal soft pink-colored vascularized connective tissue surrounding this. **b** The white glossy external elastic lamina was exposed after dissection of the adventitia demonstrating the tumor invasion boundary. **c** Dissection of the tumor-involved adventitia using blunt dissection along the plane external to the external elastic lamina of the CHA towards its origin at CA. **d** The encased CHA was released from tumor-involved adventitia of the CHA and the CA was exposed after sub-adventitial dissection. CA celiac axis, CHA common hepatic artery, EEL external elastic lamina.Asterisk = CHA; triangle = tumor-invaded adventitia separated from the tunica media; square = CA; solid arrows = tumor invasion boundary; dotted arrows = dissection direction; dotted area = dissected tumor-involved adventitia

reviewed and assessed according to the radiology reporting template jointly recommended by the Society of Abdominal Radiology and the American Pancreatic Association [12]. Until February 2015, a positive resection margin (R1) was defined as R1-direct with cancer cells present at one more transection margins of the pancreatic neck, the distal main bile duct, and the proximal and distal gastrointestinal transection margins. From February 2015, a standardized pathologic examination protocol was introduced, which comprised inking and evaluating the major surfaces (the anterior surface, posterior surface, medial HPV/SMV groove margin, and the uncinate margin for partial pancreata-duodenectomy; the anterior and posterior margins for left pancreatectomy; and all of the former for total pancreatectomy) as well as including all of the transection margins. Primary tumor, TNM overall staging, lymph node status, and resection margin status were classified according to the AJCC Cancer Staging Manual (8th Edition) [35]. A negative resection margin (R0) was defined as no residual tumor cells within 1 mm to any margin/surface; otherwise, the margin was recorded as positive (R1 < 1 mm) [1, 35]. In accordance with AJCC Cancer Staging Manual (8th Edition), primary tumors were graded as T4 if (1) preoperative imaging showed tumor abutment or encasement of the SMA, the CA, and/or the CHA [12] and (2) if at operation there was tumor invading the SMA, the CA, and/or the CHA with SDT and/or arterial resection was warranted [35]. The lymph node ratio (LNR) was defined as the percentage of detected positive lymph nodes on all harvested lymph nodes.

Statistics analysis

Continuous variables were expressed as median and range and/or inter-quartile range (IQR). Categorical variables were presented as frequency (percentage). Categorical variables were compared using the χ^2 or Fisher's exact tests and the Wilcoxon rank-sum test was used to compare continuous variables. A logistic regression model was utilized to identify risk factors for 90-day mortality among all the cases included. Univariate risk factors ($p \leq 0.1$) were inputted into multivariate logistic regression model. A secondary analysis was also undertaken by tertials of the total number of patients with completed 90-day follow-up comprising 90, 89, and 90 patients respectively. All tests were two sided and p values $\leq$ 0.05 were considered as statistically significant. R Studio

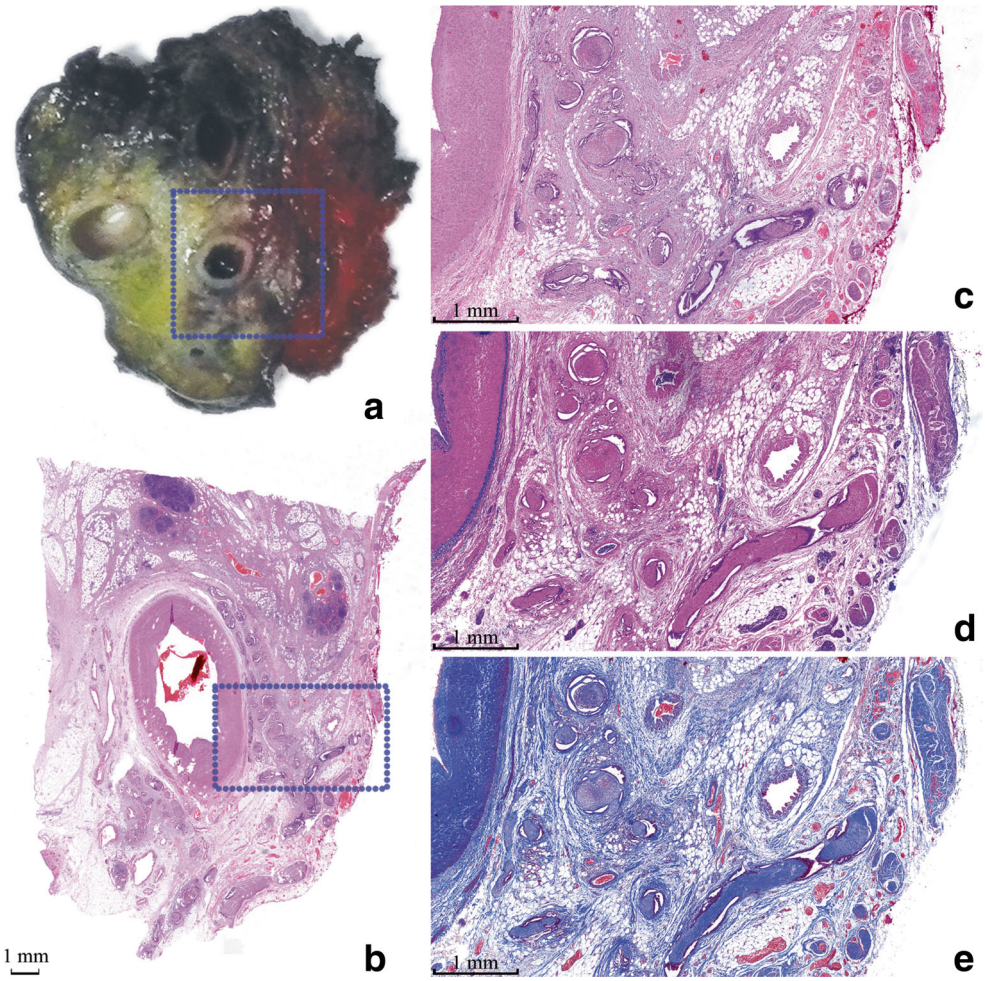

Fig. 2 Pathology and histopathology of a left pancreatectomy that included an SDT of the celiac axis. **a** Posterior-anterior section slicing of a left pancreatectomy specimen containing the splenic artery and the divestment margin of the celiac axis (inked red). **b** Overview of the section with hematoxylin and eosin staining (dotted frame showing the area in inset **c**–**e**); **c** tumor invading nerve fiber distributed in soft connective tissue; **d** external elastic lamina of the encased splenic artery was intact, and no external elastic lamina at the CA divestment margin (Victoria blue staining); **e** perineural and peri-vasa-vasorum desmoplasia (Masson staining). Scale bars in panels **b**–**e** represent 1 mm

software version 1.2.5033 with R version 3.6.2 was utilized for data process and statistical analysis.

Results

Pre-operative findings

After review of 328 operation notes, 12 laparoscopic cases and 9 resections with M1 disease were excluded. Of the remaining 307 patients, 72 had SDT resections, and 235 patients had standard surgery. There were 131 women and 176 men in the cohort, with a median (IQR) age of 64 (54–70) years. There were no significant differences between the two groups in terms of age, sex distribution, ASA grades, serum bilirubin, and obstructive jaundice and serum CA19-9 levels (Table 1).

Pre-operative CECT images were reviewed in 175 patients, of which 42 had SDT (58% of all SDT cases), and 133 had standard surgery (57% of all standard procedures) ($p = 0.79$). Patients in the SDT group had bigger tumors than that of the standard surgery group (maximum axial diameter, 37.7 versus 30.9 mm; $p = 0.001$), and also more arterial involvement overall, and specifically of the SMA (36 (86%) versus 33 (25%); $p < 0.001$), the CA (20 (48%) versus 14 (11%); $p < 0.001$), and the CHA/PHA (19 (45%) versus 26 (20%); $p < 0.001$) (Table 1).

Intra-operative procedures

In the entire cohort, a total of 218 pancreaticoduodenectomies (47 SDT versus 171 standard), 86 left pancreatectomies (22 SDT versus 64 standard), and 3 total pancreatectomies (3 SDT versus 0 standard) were performed. Patients in the SDT group underwent significantly more extended pancreatectomies (26 (36%) versus 53 (23%); $p = 0.02$) and extended lymphadenectomy (11 (15%) versus 7 (3%); $p < 0.001$) including combined arterial resections (5 (7%) versus 4 (2%) cases; $p = 0.04$) compared to the standard surgery group, while combined venous resections (18 (25%) versus 39 (17%); $p = 0.11$) and additional organ resections (6 (8%) versus 12 (5%); $p = 0.390$) were not significantly different between the two groups (Table 2).

In the SDT group, 33 (46%) patients received divestment of SMA and/or its branches (jejunum artery and replaced right hepatic artery (RRHA)), 11 (15%) received divestment of CA and/or its branches, and 23 (32%) patients received combined SDT of both SMA and CA. Among 5 patients with combined

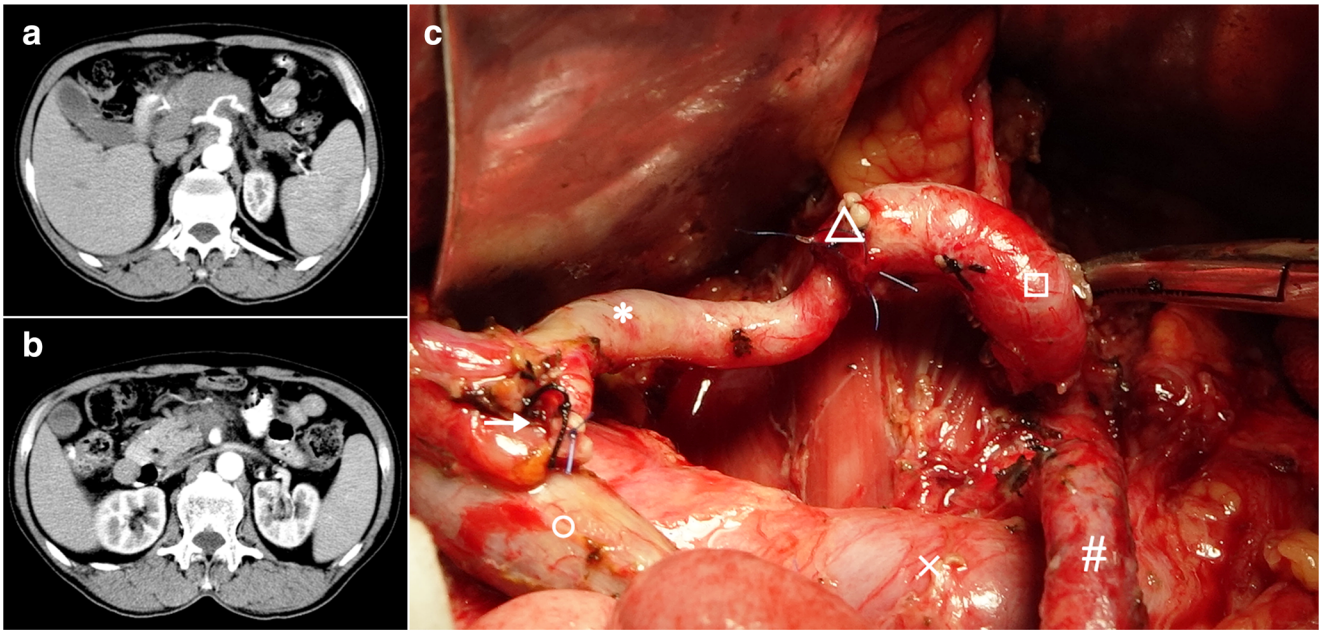

Fig. 3 Sub-adventitial divestment in a patient with multiple arterial involvement. **a** and **b** Contrast-enhanced CT showed tumor involvement of the CA, CHA, and the SMA. **c** View of the resection bed after tumor removal showing the divested arteries resection. CA celiac axis, CHA common hepatic artery, SMA superior mesenteric artery, HPV hepatic portal vein. Asterisk = CHA; number sign = SMA; square = CA; circle = HPV; multiplication sign = left renal vein. triangle = splenic artery remnant; solid arrow = gastroduodenal artery remnant

SDT and artery resection, 2 patients had modified Appleby procedures with SDT of SMA, 2 received RRHA resection with SMA or CA sub-adventitial divestment respectively, and 1 received left gastric artery resection with SDT of hepatic artery and gastroduodenal artery.

For all 72 patients who had pancreatectomy with SDT, the median (IQR) duration of surgery was 242 (210–308) min, which was significantly longer compared to the standard surgery group (210 (180–270) min; $p < 0.001$). Patients in the SDT group had a blood transfusion more frequently than the standard surgery group (20 (28%) versus 37 (16%) respectively; $p = 0.02$), but the overall median (IQR, range) estimated blood loss was not significantly different between the two groups (300 (50–500, 50–1400) compared to 200 (50–400, 50–2000) mL respectively; $p = 0.15$).

Pathology and staging

The median (IQR) maximum tumor diameter in the SDT group was (4.0 (2.5–4.5) compared to 3.0 (2.5–4.0) cm in the standard surgery group ($p = 0.002$). Tumor stage was T4 in all 72 (100%) of the resected specimens in the SDT group compared to only four T4 (2%) tumors in the standard surgery group ($p < 0.001$) (Table 1). The four T4 tumors found in the standard surgery group were only identified during exploration and therefore these patients underwent a standard procedure all with a combined artery resection. The N stage distribution was not different between the two groups. All 72 (100%) tumors in the SDT group were stage III compared to 24 stage III (10%) tumors in the standard surgery group. Both groups had a high proportion of poorly differentiated tumors (52 (72%) and 163 (69%) respectively; $p = 0.82$) and a high proportion with perineural tumor invasion (62 (86%) and 186 (79%) respectively; $p = 0.19$). R1 (< 1 mm) was found in 24 tumors (86%) of 28 who had a pancreatectomy with SDT, which was significantly higher than the 72 (60%) out of 120 tumors removed by standard surgery ($p = 0.01$).

Surgical morbidity and mortality

The overall complication rates in the SDT and standard surgery group were not significantly different (29 (40%) versus 88 (37%) respectively; $p = 0.67$) (Table 2). There were also no significant differences between the groups with respect to POPF (10 (14%) versus 25 (11%) respectively; $p = 0.45$), DGE (13 (18%) versus 38 (16%) respectively; $p = 0.71$), and chyle leakage (4 (6%) versus 15 (6%) respectively; $p = 1.0$). Post-operative pancreatic hemorrhage occurred significantly more frequently after the SDT procedure compared to standard surgery (12 (17%) versus 15 (6%) respectively; $p = 0.01$). SDT was also associated with an increased in-hospital mortality rate with four deaths (6%) compared to only one death (0.4%) in the standard surgery group ($p = 0.01$). Two of the four patients who died in the SDT group died of early severe hemorrhage, and the other two died of sepsis. Both of the two patients who demised with severe

Table 1 Baseline demographic, pre-operative findings, and TNM staging

	SDT surgery	Standard surgery	*p* value
Demographics	*n*=72	*n*=235	
Age (median, range) years	62 (31–80)	64 (28–87)	0.18
Men	39 (54%)	137 (58%)	0.54
Diabetes mellitus	19 (26%)	32 (14%)	0.01
Hypertension	16 (22%)	81 (34%)	0.05
ASA			
I and II	55 (76%)	187 (80%)	0.56
III and IV	17 (24%)	48 (20%)	
Total bilirubin (median, IQR) μmol/L	16.1 (11.6–108.6)	19.6 (10.9–133.0)	0.37
Obstructive jaundice (bilirubin > 17 μmol/L)	34 (47%)	125 (53%)	0.38
CA 19-9 (median, IQR) KU/L	257 (84–627)	209 (44–702)	0.45
CA 19-9			
≤ 37 KU/L	9 (13%)	55 (23%)	0.11
38–1000 KU/L	49 (68%)	132 (56%)	
≥ 1000 KU/L	14 (19%)	48 (20%)	
Pre-operative CECT	*n*=42	*n*=133	
Maximum diameter (median, IQR) mm	37.7 (29.1–48.8)	30.9 (24.8–37.6)	0.001
HPV/SMV involvement	23 (55%)	63 (47%)	0.43
Arterial involvement			
Artery-tumor contact	35 (83%)	42 (32%)	< 0.001
Artery-tumor stranding	7 (17%)	7 (5%)	0.04
SMA involvement	36 (86%)	33 (25%)	< 0.001
> 180°	20 (56%)	14 (42%)	0.28
Solid/stranding contact	27/9	26/7	0.71
Celiac axis involvement	20 (48%)	14 (11%)	< 0.001
>180°	15 (75%)	7 (50%)	0.16
Solid/stranding contact	14/6	12/2	0.42
CHA/PHA involvement	19 (45%)	26 (20%)	< 0.001
> 180°	12 (63%)	13 (50%)	0.38
Solid/stranding contact	19/0	25/1	1.0
Staging	*n*=72	*n*=235	
Maximum tumor diameter (median, IQR) cm	4.0 (2.5–4.5)	3.0 (2.5–4.0)	0.002
T stage			
T1	0	47 (20%)	< 0.001
T2	0	149 (63%)	
T3	0	35 (15%)	
T4	72 (100%)	4 (2%)	
Differentiation			
Well	0 (0%)	1 (0.4%)	0.82
Medium	20 (28%)	71 (30%)	
Poor	52 (72%)	163 (69%)	
Perineural invasion	62 (86%)	186 (79%)	0.19
Positive lymph node ratio (median, IQR)	0.14 (0–0.25)	0.11 (0–0.28)	0.36
N stage			
N0	25 (35%)	112 (48%)	0.07
N1	35 (49%)	102 (43%)	
N2	12 (17%)	21 (9%)	
TNM stage			
I A	0	23 (10%)	< 0.001
I B	0	69 (29%)	
II A	0	18 (8%)	
II B	0	101 (43%)	
III	72 (100%)	24 (10%)	
*R1 (< 1 mm) margin status	24/28 (86%)	72/120 (60%)	0.01

*Only cases with tumor specimens were examined with standardized pathological protocol from February 2015, standardized to AJJC 8th Edition (2018)

hemorrhage were after pancreaticoduodenectomy with only dissection at the SMA. Among them, one patient had pseudoaneurysm of SMA as suggested by angiography, while the other patient experienced massive intraabdominal bleeding and subsequent clinical deterioration in a short period without clear demonstration of the bleeding site. The death in the one patient in the standard surgery was also due to PPH from SMA. Two hundred and sixty-nine (88%) patients were followed-up for a minimum of 90 days with five (8%) deaths out of 60 patients in the SDT group and six (3%) deaths out of 209 patients in the standard surgery group ($p = 0.07$).

Table 2 Operative procedures and intra- and post-operative complications in the SDT surgery group and the standard surgery group

	SDT surgery	Control group	*p* value
Operative procedures	*n*=72	*n*=235	
Resection type			
Pancreaticoduodenectomy	47 (65%)	171 (73%)	0.01
Left pancreatectomy	22 (31%)	64 (27%)	
Total pancreatectomy	3 (4%)	0 (0%)	
Extended pancreatectomy	26 (36%)	53 (23%)	0.02
Artery resection	5 (7%)	4 (2%)	0.04
HPV/SMV resection	18 (25%)	39 (17%)	0.11
Additional organ resections	6 (8%)	12 (5%)	0.39
Extended LN dissection	11 (15%)	7 (3%)	< 0.001
Surgical duration (median, IQR) min	242 (210–308)	210 (180–270)	< 0.001
Intra-operative blood transfusion	20 (28%)	37 (16%)	0.02
Estimated blood loss (median, IQR) mL	300 (50–500)	200 (50–400)	0.15
Post-operative complications	*n*=72	*n*=235	
Overall complications	29 (40%)	88 (37%)	0.67
POPF	10 (14%)	25 (11%)	0.45
Grade B	8 (11%)	25 (11%)	0.08
Grade C	2 (3%)	0 (0%)	
Biological leakage	6 (8%)	15 (6%)	0.60
PPH	12 (17%)	15 (6%)	0.01
Grade A	3 (4%)	4 (2%)	0.02
Grade B	4 (6%)	8 (3%)	
Grade C	5 (7%)	3 (1%)	
DGE	13 (18%)	38 (16%)	0.71
Grade A	5 (7%)	18 (8%)	0.48
Grade B	5 (7%)	7 (3%)	
Grade C	3 (4%)	13 (6%)	
Chyle leakage	4 (6%)	15 (6%)	1.0
Biliary leakage	2 (3%)	1 (0.4%)	0.14
Re-operation	1 (1%)	3 (1%)	1.0
Admission to the intensive care unit	18 (25%)	36 (15%)	0.06
Post-operative hospital stay (median, IQR) days	13 (10–23)	13 (10–17)	0.32
In-hospital mortality	4 (6%)	1 (0.4%)	0.01
90-day mortality	5/60 (8%) [missing data=12]	6/209 (3%) [missing data=26]	0.07

The associations between post-operative 90-day mortality and multiple pre- and intra-operative variables including utilization of the divestment technique were evaluated with a logistic regression model involving the whole cohort. In univariant analysis, tumor size (odds ratio = 1.41; $p = 0.04$) and SDT (odds ratio = 3.08; $p = 0.07$) were identified as potential risk factors for 90-day post-operative mortality (Table 3). In multivariate regression, however, there were no significant independent risk factors for 90-day mortality, including the different tertial periods of the study (Table 3).

Discussion

Arterial resection with reconstruction is being increasingly adopted as a surgical option for arteries involved by pancreatic cancer [15, 18, 23–25, 36, 37]. However, peri-operative mortality after arterial resection and reconstruction has always been relatively high ranging from 5 to 18.5% even in recent studies [19, 38, 39]. The Mayo Clinic Rochester reported on 111 patients who underwent pancreatectomy with arterial resection (from July 1990 to July 2017) with a 90-day morbidity of 54% and mortality of 13%, but with a significant decrease

Table 3 Univariant logistic regression and multi-variant risk factor analysis or post-operative 90-day mortality

Variables	Odds ratio	*p* value	Variables	Odds ratio	*p* value
Univariant logistic regression for post-operative 90-day mortality					
Age	0.98	0.47	Operation tertial (comparator period 1)		
Male	1.43	0.58	Period 2	0.12	0.04
Diabetes	< 0.1	0.99	Period 3	0.23	0.07
Hypertension	0.46	0.33	Surgical duration	1.00	0.13
ASA (comparator ASA I)			Extended pancreatectomy	2.42	0.15
II	> 10	0.99	Combined organ resection	3.60	0.12
III	> 10	0.99	Combined arterial resection and reconstruction	3.13	0.30
IV	1.00	1.00	Combined vein resection	0.97	0.97
Total bilirubin>21 μmol/L	0.20	0.04	Extended LN dissection	< 0.1	0.99
CA 19-9	1.00	0.29	Estimated blood loss	1.00	0.40
Surgical procedures (comparator partial pancreato-duodenectomy)			Intra-op. blood product transfusion	0.82	0.80
Left pancreatectomy	0.90	0.88	Intra-op. RBC transfusion	0.95	0.95
Total pancreatectomy	< 0.1	0.99	Tumor size	1.41	0.04
SDT	3.08	0.07			
Multi-variant risk factor analysis for 90-day post-operative mortality					
Operation date (comparator period 1)					
Period 2	0.1476	0.0817			
Period 3	0.2599	0.1042			
Tumor size	1.1155	0.5379			
Total Bilirubin>21 μmol/L	0.2253	0.0672			
SDT	2.1651	0.2412			

in mortality post-2010 of 9% versus 29% before this date [19]. Klompmaker et al. [38] reported on a European multicenter experience of 191 patients who had left (distal) pancreatectomy with celiac axis resection with a 90-day mortality rate of 5.5% at five high-volume and 18% at 18 low-volume centers. Hartwig et al. [39] reported 12 (19%) deaths out of 65 arterial resections performed for borderline and locally advanced pancreatic cancer. PPH is the most worrisome complication when surgical dissection involves the major arteries. Tee et al. [19] reported a post-operative PPH rate of 17.1% after pancreatectomy with arterial resection, with grades B and C counting for 89.5% of all PPH cases, while in SDT cohort in our study, the overall PPH rate was 17% and 75% cases which were grades B and C.

The results from pancreatectomy using SDT compared favorably with these reported studies in terms of morbidity and mortality. In our study, 29 (40%) out of the 72 patients who had SDT had one or more complications which was not significant from the 88 (37%) out of the 235 patients that had standard surgery. The in-hospital mortality was 4 (6%) in the SDT group and one (0.4%) in the standard surgery group with a 90-day mortality 5 (8%)/60 and 6 (3%)/209 respectively. PPH in the SDT group was more frequent occurring in 12 (17%) patients compared to 15 (6%) in those with standard resections but tended to be less severe. It needs to be considered however that all 72 (100%) patients in the SDT group had stage III tumors compared to 24 (10%) in the standard surgery group. Since the minimally invasive pancreatectomies are ever evolving recently, it would be interesting to validate the safety profile of laparoscopic or robotic SDT in experienced hands in the future.

During sub-adventitial divestment, one potential critical risk is massive hemorrhage due to iatrogenic damage to the artery. There were two critical technical points we followed to prevent this surgical scenario. One was to dissect along the right plane along the surface of EEL, and once the dissection plane could not be established safely, radical intention surgery would be abandoned, or arterial resection would be considered. When tumor invasion to EEL was suspected intra-operatively, sub-adventitial dissection was not technically feasible. The other rule was to deal with the branches of the dissected artery with extra patience, as these tumor-invaded branching points of the artery were more vulnerable to violate dissection; once damaged, it would lead to tearing up of the artery truck and massive bleeding. Once the integrity of tunica media was incidentally disrupted, repair with 5-0/6-0 Prolene for minor injuries or artery resection

for major injuries (did not happen in current cohort) would be considered. Prophylactic intraluminal placement of covered stent could also be helpful.

The present study is a preliminary cohort of sub-adventitial divestment technique, and we reported this approach for cancer surgery and it appears to be relatively safe without excessive mortality compared to arterial resection and reconstruction [21]. However, retrospective data collection resulted in the incompletion of radiology review and heterogeneous margin evaluation as well as lack of long-term follow-up on survival and recurrence. Thus, oncological benefit of SDT could not be properly evaluated so far. Furthermore, SDT group was constructed with more complicated cases, with 36% extended pancreatectomy, 25% combined PV/SMV resection, and even 7% AR&R, which was difficult to control to evaluate surgical security. Prospective and controlled studies were needed in the future [20, 22]. The third limitation of current study was that all the patients followed the surgery-first approach, which was a routine practice in China during the study period. The feasibility and oncological outcomes of SDT in neoadjuvant setting need to be tested in future. The fourth is limited pathology evaluation on SDT margins and its correlation study with pre-operative imaging, which will provide critical information for pre-operative evaluation and surgical planning for SDT. Habib et al. [20] reported peri-arterial pathologic changes in surgical specimens after peri-adventitial dissection and the "halo sign" on pre-operative CT, providing us more detailed insights in artery invasion by pancreatic cancer.

Conclusion

The sub-adventitial divestment technique appeared to be an effective surgical technique to remove the tumor while preserving the artery. Further studies are needed to evaluate the longer-term oncological results after SDT and to identify potential subgroups of patients who could benefit.

Code availability Not applicable.

Authors' contributions Baobao Cai and Zipeng Lu collected the data and drafted the manuscript; John P. Neoptolemos interpreted data of the cohort and made critical review of the work; Lingdi Yin and Yong Gao acquired informed consent from patients and collected the data; Mingna Li, Markus K. Diener, Jishu Wei, Jianmin Chen, Feng Guo, Min Tu, and Chunhua Xi reviewed and analyzed data and contributed to draft revision; Junli Wu, Wentao Gao, and Cuncai Dai performed the procedure and interpreted the data; Kuirong Jiang performed and developed the procedure and refined the design of this study; Markus W. Büchler and Yi Miao designed, performed, and developed the procedure, conducted this study, and refined and determined the final submitted version of manuscript

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Data availability All data and material used or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Publication has been approved by all co-authors.

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