Is there a Role for the Appleby Procedure in 2020? Results from a Matched-Pair-Analysis

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Abstract. *Background/Aim:* Locally advanced pancreatic cancer (LAPC) of the pancreatic body involving the celiac axis requires specialized treatment, including a subtotal distal pancreatectomy (SDP) with resection of the celiac axis (Appleby procedure). This study aimed to examine the value of the Appleby procedure, in current individualized treatment approaches, and to define its possible therapeutic impact for patients with LAPC. *Patients and Methods:* 20 consecutive patients who underwent SDP with resection of the celiac axis between January 2005 and December 2018 were identified from a prospectively collected database and were matched with 20 patients experiencing SDP without resection of the celiac axis. Both perioperative parameters, as well as the overall postoperative course, were evaluated. *Results:* The rate of perioperative complications in both groups was comparable ($p=0.744$). The rate of severe type C postoperative pancreatic haemorrhages (PPH) was significantly lower in patients with resection of the celiac axis compared to those without ($p=0.035$). *Conclusion:* The Appleby procedure may be considered as a safe and feasible treatment option with favorably fewer postoperative severe bleeding complications. Besides surgical expertise, such procedures, however, require an experienced interventional radiologist and should thus only be performed in high-volume centers.

Systemic treatment options, such as neoadjuvant chemotherapy (NAC), are available for the treatment of pancreatic ductal adenocarcinoma (PDAC) and can improve overall survival rates. The only curative treatment strategy, however, still includes a radical surgical resection (1). Current definitions of resectability, defining PDAC subgroups of i) potentially resectable (RPC), ii) borderline resectable (BRPC) and iii) locally advanced types (LAPC), such as the NCCN guidelines for the definition of BRPC (2), mainly rely and focus on vessel involvement. Vessel involvement is nevertheless not always the limiting factor in therapeutic decision making, although it influences resectability. PDAC of the pancreatic body is often associated with the involvement of the celiac axis (CA) as well as a late point of diagnosis. Symptoms are unspecific and mainly consist of back pain, weight loss, and unspecific abdominal pain (3). LAPC of the pancreatic body is associated with a reduced resection rate of 10% and a mean overall survival of 3-4 months (4). One possible treatment option, a subtotal distal pancreatectomy (SDP) with simultaneous CA resection, was initially described in 1976 (5). The first-ever illustrated resection of the celiac axis was performed in 1953 during an extended resection of gastric carcinoma and was named after the first surgeon to describe as the Appleby Procedure (6).

As the blood supply to the common hepatic artery (CHA) is maintained through collateral pathways over the gastroduodenal artery (GDA), and the stomach is supplied by the right gastric artery and gastroepiploic arteries fed by collaterals with the GDA over the superior mesenteric artery (SMA), resection of the CA has become a feasible treatment option for patients with advanced tumour infiltration. Favorable median survival times of 21 and 26 months have been described (7, 8). Nevertheless, liver necrosis and consecutive liver abscesses as well as gastric ulceration, necrosis, and perforation, have been described as the main procedure-related complications (9). Prior angiography with selective embolization of the CA can decrease the incidence

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of such complications by preoperatively conditioning the collateral pathways (10). To examine the value of the Appleby procedure, we performed a one-to-one matched-pair analysis with patients who underwent SDP without CA resection.

Patients and Methods

Data collection and matching criteria. Our retrospective single-center analysis was conducted at the Charité–Universitätsmedizin Berlin, Campus Virchow-Klinikum in Berlin, Germany. Data of all patients undergoing pancreatic resections between January 2005 and December 2018 were entered into a prospective database. All patients obtained a written informed consent, and an independent ethics committee approved the study design. Patients' characteristics were extracted from our medical records and further analyzed. All patients undergoing SDP with CA resection for PDAC were included. A one-to-one matched-pair analysis was performed by age, sex, and tumor entity with patients who underwent SDP without CA resection.

SDP was defined as a resection proximal to the superior mesenteric vessels. Patients undergoing distal pancreatectomy with a resection line distal to the superior mesenteric vessels as well as patients undergoing resection for other tumor entities were excluded.

Preoperative assessment, preconditioning, and surgical procedure. A multimodal therapeutic approach was individually formulated following initial diagnosis for every oncologic patient by a multidisciplinary tumor board, which consisted of medical oncologists, specialized radiation therapists, radiologists, and surgeons. Multiphase computed tomography (CT), or magnetic resonance imaging (MRI) with contrast agents were routinely used for radiological diagnostics and planning. An MRI showing an encased CA is shown in Figure 1.

Patients were excluded from exploration in the presence of widespread metastatic disease. Preoperatively, the clinical diagnostic tests included standard physical examination and routine laboratory testing as well as measuring CA19-9 serum levels. When preoperative CT or MRI showed tumor involvement of the CA and CHA but no impairment of the SMA and GDA, we evaluated patients for an Appleby procedure. Preoperative embolization of the CA and the CHA was executed if further diagnostics revealed appropriate conditions for resection without distant metastasis. All patients in our case group underwent preresectional embolization. After preparation, a selective angiography was performed. CA and SMA were catheterized simultaneously and following a temporary blocking of the CHA with a balloon, digital subtraction angiography of the SMA was performed to demask proper collateralization. If collateralization was judged as appropriate, coil or Amplatzer vascular plug occlusions of the CHA, left gastric artery and splenic artery as well as – if technically feasible – CA were performed. With this, the direct arterial blood supply from the CA to the liver and stomach was interrupted. Through collateral pathways over the pancreatoduodenal arcade to the GDA, the arterial blood supply was enhanced to the proper hepatic artery (PHA) and the gastroeiploic artery, as previously described (10). Radiographic imaging of balloon occlusion, coiling and collateralization are demonstrated in Figures 2-4. Following a short in-hospital stay, patients were sent home and returned for subsequent resection.

Experienced surgeons performed all procedures according to international standards at that time. Somatostatin analogs were not prescribed. Dissection of the pancreas was either done using electrocautery or a stapling device. In cases of pancreatic resections performed by electrocautery, a subsequent closure of the main pancreatic duct of the pancreatic remnant was achieved by a stitch ligation using 4-0 polypropylene sutures, followed by single U-shaped 4-0 polypropylene sutures (Prolene, Johnson & Johnson Medical GmbH, Norderstedt, Germany). Distal closure of the pancreatic remnant by stapler was performed using linear stapling devices armed with a black 60-mm cartridge (EndoGIA™, Auto-Suture, Covidien). Cartridges were reinforced by a bioabsorbable mesh (SEAMGUARD®, W.L. Gore, Flagstaff, AZ, USA). CA-resection was secured using both ligature and suture in all open surgery cases. In the case of robotic-assisted surgery a vascular stapler was used. All included patients underwent a simultaneous splenectomy and received at least one intra-abdominal drain (Degania Silicone Europe GmbH, Regensburg, Germany) to measure the postoperative lipase levels, while the drain output was placed directly at the pancreatic resection line.

Postoperative evaluation. Following surgery, all patients were monitored at a specialized surgical intensive care unit for at least one day. The lipase levels were repeatedly assessed and measured in the serum and in the intraoperatively placed abdominal drains to identify postoperative pancreatic fistula. In the absence of signs of POPF and DGE, oral food intake was started depending on the clinical presentation and tolerance. The Clavien-Dindo (CD) classification was used to grade postoperative complications (11). Major complications were defined as CD≥3a. All resected specimens were histologically examined to identify the underlying tumor entity and completeness of resection by an attending pathologist. Postoperative application of chemotherapy and radiotherapy was considered case-by-case, based on factors, such as i) the completeness of the resection, ii) local histopathological tumor stage, iii) response to prior therapy, and iv) the patient's condition.

Data collection. Collected and reviewed data included preoperative ASA, BMI, demographics, time from embolization to resection, application of neoadjuvant chemotherapy as well as postoperative local histopathological tumor stage (TNM) and infiltration of resection margins. Furthermore, postoperative morbidity and mortality were recorded: POPF, PPH, SSI, DGE, in-hospital stay, ICU-stay, the requirement of reoperation or intervention, mortality within 30 days, and readmission within 90 days.

Statistics. Statistics present mean (range) or numbers (%). Two-tailed Pearson's chi-square test and Friedman-test were used to compare ordinal or nominal scaled variables, respectively. Significance tests were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses, as well as initial matching of cases and controls, were performed using SPSS, version 25.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics. An overall of 40 patients was included in this study. Twenty patients underwent SDP with additional resection of the CA, and the other 20 patients

Figure 1. Survival curves. Overall survival (OS) for patients undergoing subtotal distal pancreatectomy with resection of the celiac axis (Appleby) and for patients undergoing subtotal distal pancreatectomy without resection of the celiac axis with no significant difference ($p=0.433$).

experienced SDP without resection of the CA. Out of all the patients, 45% were female, and 55% male. The mean age was 62.9 years (37-79 years). Preoperative ASA scores and BMI were comparable. One patient underwent SDP with simultaneous CA resection with the use of the DaVinci robotic system. Table I indicates patient characteristics.

Perioperative parameters. The postoperative histopathological tumor stage was comparable in both groups (Table II). The most common T stage was T3 (69.2%), while nodal positivity was found in 55% of the patients in our case group and in 50% of the patients in the control group ($p=0.949$). The largest tumor diameter was comparable between the two groups as well, with a mean of 30.94 mm (18-59) in the case group and 27.9 mm (12-56) in the control group ($p=0.443$). From the case group, 25% of the patients underwent neoadjuvant treatment with either FOLFIRINOX or Gemcitabine/nabPaclitaxel compared to 20% of the patients from the control group. The same amount (25%) of patients in the case group, went under an additional portal vein resection, whereas in our control group, only 5% underwent an additional portal vein resection. Direct anastomosis or a patch plastic using a falciform ligament, VMI patch or Vascu Guard Patch achieved vascular reconstruction. Additional partial gastric resections were performed in 10% of the patients in our case group and in 20% of the patients in our

Table I. Patient characteristics.

Characteristics N (%)	All patients (N=40)	Appleby procedure (N=20)	Subtotal distal pancreatectomy (N=20)	p-Value
Gender N (%)				1.0
Male	22 (55)	11 (55)	11 (55)	
Female	18 (45)	9 (45)	9 (45)	
Age (years)				0.37
Mean	62.9	60.75	65.05	
Minimum	37	37	46	
Maximum	79	77	79	
ASA Score N (%)				0.384
1	4 (10)	3 (15)	1 (5)	
2	21 (52.5)	8 (40)	13 (65)	
3	10 (25)	4 (12.5)	6 (30)	
4	0 (0)	0 (0)	0 (0)	
BMI N (%)				0.603
Mean	25.7	25.5	25.9	
Minimum	19.8	19.8	19.8	
Maximum	36.9	35.5	36.9	

ASA: American Society of Anesthesiologists; BMI: body mass index.

control group. In our case group, resection was performed after a mean of 11.2 (4-20) days after selective angiography and embolization.

SDP including CA resection with the use of a robotic system. One patient in our case group, a 58-year-old male without any prior abdominal operations, underwent resection using the DaVinci robotic system six days after embolization. No further vessel resections were necessary. He underwent NAC with FOLFIRINOX before embolization and resection. The tumour diameter was 55 mm, and the histopathological TNM stage was ypT3 ypN1 G2 R0 L0 V0. The in-hospital stay was nine days, including one day in the intensive care unit. No postoperative complications occurred during the in-hospital stay, and no readmission was necessary.

Complications. Overall, complications were comparable in both groups. In our case group a rate of 60% overall complications, and in our control group a rate of 65% overall complications appeared ($p=0.744$). Significant complications, classified as CD $\geq$ 3a, appeared in 50% of the patients in our case group and in 55% of the patients in our control group. Complications, such as POPF, SSI, DGE, and others, including cardiovascular, pulmonary, and urinary tract complications, appeared in a comparable number in both groups (Table III). However, as the overall appearance of PPH was similar in both groups ($p=0.1$), the severity was significantly higher in the control compared to the case group, with no type C bleeding in our case group and four type C

Table II. Perioperative parameters.

Postoperative T-Stage N (%)				0.443
T1	5 (12.8)	1 (10.5)	3 (15)	
T2	5 (12.8)	3 (15.8)	2 (10)	
T3	27 (69.2)	12 (63.2)	15 (75)	
T4	2 (5.1)	2 (10.5)	0 (0)	
Postoperative N-Stage N (%)				0.949
N0	19 (47.5)	9 (45)	10 (50)	
N1	19 (47.5)	10 (50)	9 (45)	
N2	2 (5)	1 (5)	1 (5)	
Postoperative L-Stage N (%)				0.736
L0	27 (67.5)	14 (70)	13 (65)	
L1	13 (32.5)	6 (30)	7 (35)	
Postoperative V-Stage N (%)				0.311
V0	27 (67.5)	12 (60)	15 (75)	
V1	13 (32.5)	8 (40)	5 (25)	
Tumour Diameter (mm)				0.443
Mean	29.34	30.94	27.9	
Minimum	12	18	12	
Maximum	59	59	56	
Grading N (%)				0.691
G1	3 (7.7)	1 (5.3)	2 (10)	
G2	25 (64.1)	13 (68.4)	12 (60)	
G3	11 (28.2)	5 (26.3)	6 (30)	
Postoperative resection stage N (%)				0.342
R0	19 (47.5)	8 (40)	11 (55)	
R1	21 (52.5)	12 (60)	9 (45)	
Neoadjuvant treatment N (%)	9 (22.5)	5 (25)	4 (20)	0.705
Additional vessel resection N (%)				
Portal vein resection	6 (15)	5 (25)	1 (5)	0.212

bleedings in our control group ($p=0.035$). In our case group, two patients developed gastric complications, including a gastric perforation and gastric ischemia with the need for reoperation. There was no 30-day mortality in our case group, but there was an in-hospital mortality within 30 days in two cases of our control group ($p=0.147$). The in-hospital stay was comparable in both groups, with a mean of 29.45 days (7-162) in our case group and 31.65 days (11-93) in our control group ($p=0.409$) (Table III). Survival curves for both groups did not reveal any significant differences between the groups ($p=0.433$; Figure 1).

Discussion

LAPC of the pancreatic body has a sparse prognosis and is described with a resectability rate of 10% and a mean survival of 3-4 months (4). The ability of additional CA resections in the case of CA involvement has led to a favorable median survival of 24.1 months following resection (12).

Pain release after resecting the infiltrated retroperitoneal nerval plexus may lead to an additional improvement of life quality (8). SDP with additional CA resection appears to be a safe treatment option with a comparable overall complication

Table III. Complications.

Characteristics	All patients (N=40)	Appleby procedure (N=20)	Subtotal distal pancreatectomy (N=20)	p-Value
Overall complications N (%)	25 (62.5)	12 (60)	13 (65)	0.744
Clavien/Dindo classification N (%)				0.319
0	14 (35)	8 (40)	6 (30)	
1	3 (7.5)	1 (5)	2 (10)	
2	2 (5)	1 (5)	1 (5)	
3a	8 (20)	6 (30)	2 (10)	
3b	5 (12.5)	2 (10)	3 (15)	
4a	4 (10)	0 (0)	4 (20)	
4b	1 (2.5)	1 (5)	0 (0)	
5	3 (7.5)	1 (5)	2 (10)	
POPF N (%)				0.619
Biochemical leak	3 (7.5)	1 (5)	2 (10)	
B	16 (40)	7 (35)	9 (45)	
C	1 (2.5)	1 (5)	0 (0)	
PPH N (%)				0.1
A	0 (0)	0 (0)	0 (0)	
B	3 (7.5)	2 (10)	1 (5)	
C	4 (10)	0 (0)	4 (20)	0.035
SSI N (%)	2 (5)	1 (5)	1 (5)	1.0
DGE N (%)	1 (2.5)	1 (5)	0 (0)	0.311
Other complications N (%)	11 (27.5)	5 (25)	6 (30)	0.723
Gastric ischemia	1 (2.5)	1 (5)	0 (0)	
Gastric perforation	1 (2.5)	1 (5)	0 (0)	
Reoperation rate N (%)	8 (20)	3 (15)	5 (25)	0.429
30-day mortality N (%)	2 (5)	0 (0)	2 (10)	0.147
90-day readmission rate N (%)	6 (15)	3 (15)	3 (15)	1.0
Inhospital stay (days)				0.409
Minimum	7	7	11	
Maximum	162	162	93	
Mean	30.55	29.45	31.65	
ICU stay (days)				0.281
Minimum	1	1	1	
Maximum	130	130	81	
Mean	13.05	10.3	15.8	

POPF: Postoperative pancreatic fistula; PPH: postoperative pancreatic haemorrhage; SSI: surgical site infection; DGE: delayed gastric emptying; ICU: intensive care unit.

rate and rate of major complications ($CD\geq 3a$) between our case and control cohort. Mortality and morbidity of patients undergoing SDP with CA resection have been described with 0% and 47.1%, 2.1% and 40.6%, and 0% and 62%, respectively in three studies, comparable with 0% and 60% found in our study (8, 13, 9). PPH is one of the most common and threatening complications in pancreatic surgery and one of the most important reasons for reoperation and mortality. The most common bleeding source in cases of SDP is the

splenic artery (14, 15). In our case group, following embolization and CA resection, no PPH type C were observed, whereas four type C bleedings occurred in our control group. The Appleby procedure appears to decrease the risk of severe PPH significantly. A combination of embolization and consecutive CA resection may serve as an explanation. After resection of the nerval plexus, a higher incidence of postoperative and persistent diarrhea has been described (16). In our cohort, no increased incidence of diarrhea appeared; postoperative diarrhea was mainly caused by transient or persistent exocrine insufficiency and was successfully treated with the substitution of pancreatic enzymes.

Current definitions of PDAC subtypes are based on vessel involvement or encasement, and mainly rely on anatomical rather than on clinically relevant parameters (17). The Appleby procedure may serve as an example for the need of redefining the PDAC subtypes and the resectability criteria as it is a safe treatment option with favorable survival rates. In our cohort, patients both undergoing or not undergoing CA resection had comparable survival rates. If indicated, CA resection should, thus, be performed regardless of anatomically defined classifications. Typical complications related to CA resection are gastric or hepatic ischemia. Gastric ischemia has been described to occur in 12.87% of all patients, whereas prior embolization can lead to a favorable incidence of 10.74% compared to 14.38% in cases without prior embolization (12). Our case cohort had a comparable frequency of 5% gastric ischemia and 5% gastric perforation in all patients undergoing prior selective embolization. Resectability can, in each patient, only be finally evaluated during exploration. This is even enhanced by the fact that regression following NAC can be hardly distinguished radiographically from vital tumor tissues. Therefore, embolization can, from time to time, be done unnecessarily (18).

PDAC, however, should be considered as a systemic disease, with the main life-threatening issues being recurrence and metastasis (8). In our cohort, we found a rate of R0 resections of 40% in our case group and 55% in our control group. A meta-analysis has previously found a R0 rate of 72.79% (30.8-100%) (12). Performing the Appleby procedures following neoadjuvant chemotherapy has resulted in an R0 resection rate of 91% (18). Infiltrated resection margins can be correlated with the deterioration of prognosis, whereas NAC is correlated with a higher amount of R0 resections (19). Resectability of LAPC of the pancreatic body with infiltration of the CA is often limited by simultaneous SMA infiltration, because both vessels cannot be resected at the same time (20).

Another point in the current field of LAPC treatment is the use of laparoscopy and robotic systems. In our case, the use of a robotic system was a feasible treatment option. Its value in the individualized treatment of LAPC, however, needs further assessment.

The strengths of our study include: i) the case-matched study design, and ii) the homogeneity within both groups. The present study is limited by common biases that are mainly due to the retrospective character of this analysis. Precision and completeness of data acquisition are tough to control, especially over such an extended study period. To encounter this condition, we used a carefully matched control group. In conclusion, CA resection in patients with LAPC of the pancreatic body appears to be a safe treatment option increasing a favorable outcome with few severe bleeding complications. It, nevertheless, requires an experienced interdisciplinary treatment team and should thus only be performed at a high volume centre. At times of individualized treatment approaches tailored to the patient's needs, NAC appears to further improve R0 resection rates and survival time. Also, the use of minimally invasive treatment options, such as the use of a robotic system in the treatment of LAPC, needs further assessment in prospective trials.

Conflicts of Interest

All Authors declare no commercial associations that might represent conflicts of interest with this article and have nothing to disclose.

Authors' Contributions

Substantial contributions to the conception or design of the study were done by TM, LT, FK, DG, JP, MB. Acquisition, analysis, or interpretation of data for the study was done by TM, LT, FK, JP, MB. Drafting the work or revising it critically for intellectual content was done by TM, LT, FK, DG, JP, MB. Final approval of the version to be published was done by TM, LT, FK, DG, JP, MB.

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