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Current Surgical Concepts and Future Perspectives in the Treatment of Borderline Resectable and Potentially Resectable Locally Advanced Pancreatic Cancer

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Rezumat

Concepte chirurgicale actuale și perspective de viitor în tratamentul cancerului pancreatic la limita rezecabilității și cancerului pancreatic local avansat potențial rezecabil

Adenocarcinomul ductal pancreatic (ADP) reprezintă o tumoră agresivă, cu o rată de supraviețuire la cinci ani mai mică de 10%. Se estimează că doar 20% dintre pacienți sunt eligibili pentru rezecția curativă în momentul prezentării. Prognosticul grupului de cancere pancreatice la limita rezecabilității (borderline resectable BPRC) şi local avansate (LAPC) era mult mai rezervat în trecut. Deşi terapia multimodală a ADP a fost îmbunătățită, intervenția chirurgicală rămâne singurul tratament cu viză curativă. Combinată cu tratamentul adjuvant şi/sau neoadjuvant, chirurgia pancreatică poate creşte supraviețuirea la cinci ani cu până la 20%. Cu toate acestea, rezecția pancreatică este frecvent asociată cu un risc crescut de complicații şi este considerată una dintre cele mai complexe proceduri chirurgicale. Operația TRIANGLE ar trebui adăugată la arsenanul de intervenții chirurgicale pancreatice ca o procedură cheie, având potențialul de a creşte numărul de ganglioni limfatici recoltați şi de a reduce rata complicațiilor, cu o eficacitate mai bună ca tratament curativ al BRPC şi LAPC convertite la rezecabilitate după terapia neoadjuvantă (NAT). Pancreatectomia din ce în ce mai agresivă a devenit justificată în contextul NAT. Standardizarea suplimentară a tehnicii şi terapia neoadjuvantă optimă sunt obligatorii pentru diseminarea globală a pancreatectomiilor agresive. Acest articol rezumă tratamentul chirurgical al BRPC şi al LAPC potențial rezecabil pe baza literaturii actuale, concentrându-se pe conceptul „TRIANGLE” al chirurgiei pancreatice.

Cuvinte cheie: cancer pancreatic, cancere pancretice la limita rezecabilității, cancer pancreatic local avansat, pancreatectomie, operația TRIANGLE

Abstract

Pancreatic ductal adenocarcinoma (PDAC) represents an aggressive tumor with a low five-year survival rate of less than 10%. Only 20% of patients are estimated to be eligible for upfront curative resection at the time of presentation. The larger group of borderline resectable (BRPC) and locally advanced pancreatic cancers (LAPC) had much poorer outcomes in the past. Although there are improvements for the multimodal therapy of PDAC, surgery remains the single hope for a cure. Combined with adjuvant and/ or neoadjuvant treatment, pancreatic surgery can enhance five-year survival by up to 20%. However, pancreatic resection is widely associated with a high risk of complications and is regarded as one of the most complex surgical procedures. TRIANGLE operation should be added to pancreatic surgery armamentarium as a key procedure, with the potential to increase the number of harvested lymph nodes, reduce the complications rate, and better radical treatment efficacy for BRPC and LAPC be converted to resectability after neoadjuvant treatment (NAT). More and more aggressive pancreatectomy has become justified in the context of NAT. Further technical standardization and optimal neoadjuvant strategy are mandatory for the global dissemination of aggressive pancreatectomies. This review summarizes the surgical treatment for BRPC and potentially resectable LAPC based on the current literature, focusing on the "TRIANGLE "concept of pancreatic surgery.

Key words: pancreatic cancer, borderline resectable pancreatic cancer, locally advanced pancreatic cancer, pancreatectomy, TRIANGLE operation

Introduction

Surgery is the only potential curative treatment for pancreatic ductal adenocarcinoma (PDAC) and is recommended to be combined with adjuvant chemotherapy or other multimodal treatments. Besides the advances in the multimodal approaches, surgical techniques have substantially progressed, particularly in addressing advanced resections (1).

The definition of borderline resectable pancreatic cancer (BRPC) and locally advanced pancreatic cancer (LAPC) is based on the relationship between the tumor and its nearby main blood vessels (2). Previous classifications made by AHPBA/SSO/SSAT were further clarified by the National Comprehensive Cancer Network (NCCN) and the International Study Group of Pancreatic Surgery (ISGPS) (3,4). Only 20% of patients diagnosed with PDAC are estimated to be eligible for upfront curative resection at the presentation time. The larger group of BRPC and LAPC had much poorer outcomes in the past. Over the years, improvements have been made to the chemotherapy regimens and surgical approach for treating PDAC such that more of these patients now have a chance of disease cure.

The positive impact of adjuvant chemotherapy on survival after resection of PDAC has been shown during the last two decades (5). Few recent studies reported median survival times between 30 and 54 months and 5-year survival of 30%, which reflects the need for adjuvant systemic treatment after PDAC resection (5,6).

While neoadjuvant therapies (NAT) are necessary for LAPC to achieve a chance of conversion surgery afterward, its benefits in BRPC and especially resectable PDAC are currently under debate.

Radical resection is now regarded as the only possible way to cure PDAC (3). However, the role of surgical resection in BRPC is still controversial: Indications for resection in PDAC largely depend on preoperative imaging diagnosis, which unfortunately cannot always provide real resectability (7) and can not accurately distinguish true tumor invasion from fibrosis caused by inflammation (8).

Contrast-enhanced computed tomography is the primary approach for diagnosis and resectability evaluation (1). However, magnetic resonance is superior to ductal anatomy evaluation and liver metastases detection (9,10). Although a multidisciplinary treatment for PDAC is widely used (11), sometimes it can happen to lose the opportunity of surgery for a resectable tumor, or there is a fear of excision of a tumor in which R0 resection can not be achieved. For example, patients who are considered initially unresectable because of celiac artery (CA), common hepatic artery (CHA), or superior mesenteric artery (SMA) encasement (no more than half in circumference) can get an R0 resection with a surgeon's effort after NAT. For treating BRPC, NAT is highly recommended in guidelines, especially in Europe and the USA (12,13). Few studies have shown improvements in the resection rate and prognosis of BRPC and LAPC with NAT (14,15).

The Heidelberg group initially proposed the TRIANGLE operation in 2017 (16) as a novel approach for patients with potentially resectable LAPC after the NAT. Afterward, the TRIANGLE technique was also extended to BRPC and localized PDAC. The superior mesenteric/ portal vein (SMV/PV), CA/CHA, and SMA define the triangle area.

The rationale of TRIANGLE operation in BRPC or potentially resectable LAPC is based on the observation that after NAT, conventional imaging might not be able to distinguish between real tumor encasement or abutment and fibrotic only residual tissue at the arterial level (16). Thus, for patients without a radiological response (no downsizing/staging) after NAT, there is a potential not to undergo radical resection of the tumor. For patients with artery encasement, resection with extensive dissection of the TRIANGLE region, including CA, CHA, SMA, PV, and SMV, and complete skeletonization of these vessels may allow an R0 resection and decrease the local recurrence. The study of Zhai et al. has shown no local recurrence even after upfront resection with the TRIANGLE technique for BRPC (12). A few other studies also demonstrated the safety of TRIANGLE operation for BRPC (12,17). TRIANGLE operation has been proven safe in a total pancreatectomy (TP), increasing the number of harvested lymph nodes, reducing complications, and improving radical treatment efficacy for BRPC (12).

Total Mesopancreas Excision (TMpE) in PDAC

Gockel et al. introduced the term mesopancreas and complete removal of the mesopancreas in PDAC as an analogy to the mesorectum and to the technique of total mesorectum excision known to increase local control after resection for rectal cancer (18). This retropancreatic perineural and lymphatic tissue, which is also named the "retroportal lamina," "pancreatic head plexus," "PA ligament," or "mesopancreas," remains poorly known to many surgeons performing PDAC resections (19).

The mesopancreas has the following boundaries: laterally, the medial and posterior aspect of the uncinate process and pancreatic head; medially, the right aspect of the SMV and SMA; proximally (cephalic), the origin of the CA; distally (caudal), the beginning of the mesenteric root and posteriorly, the left renal vein (*Fig. 1*) (19).

The TMpE concept includes resectioning the lymphatic structures on the SMA's right side and along the pancreatic head's neuronal plexus. The perineural tumor invasion rate in PDAC is up to 75%.

The mesopancreas is considered the primary site of a positive resection margin, and it was suggested that en bloc resection of this structure during pancreatoduodenectomy (PD) would reduce local recurrence (20-22). Complete clearance of this area may increase

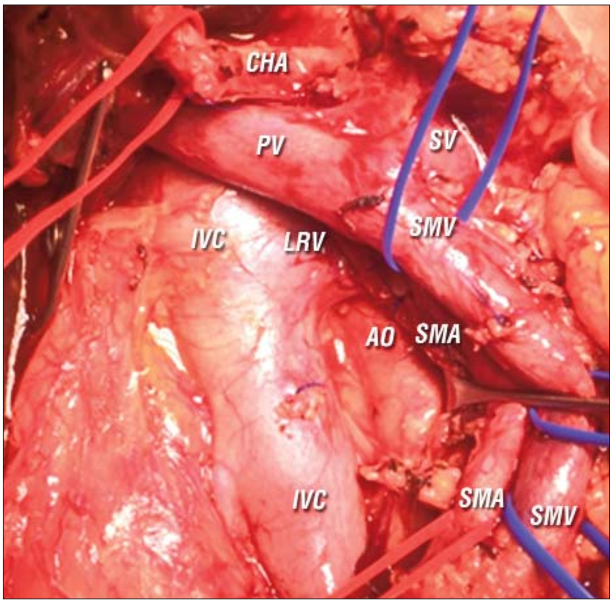

Figure 1. Pancreatectomy with complete circumferential vascular clearance and total mesopancreas excision (TMpE)

(PV-portal vein; SMV-superior mesenteric vein; IVC-inferior vena cava; LRL-left renal vein; AO-aorta; SMA-superior mesenteric artery; CHA-common hepatic artery; SV-splenic vein)

the R0 resection rate in patients with PDAC. R status independently predicts overall survival, and R0 resection is a crucial prognostic factor. However, even patients with R0 resection experience retropancreatic recurrence. Moreover, if circumferential margins are thoroughly evaluated using an axial slicing protocol for pathological assessment, high rates of R1 are observed, especially at the retroperitoneal margin (23,24). The high rate of non-curative resections in patients with PDAC is mainly related to the close anatomical relationship of the tumor with the SMV and SMA as well as with the CA. Medial/ SMA margins significantly impact recurrence and overall survival rates (19,25).

TRIANGLE Operation in PDAC

Surgical resection is the mainstay of a potential cure for patients with PDAC. However, local recurrence is a frequent event after pancreatectomies for PDAC (26). Hackert et al. initially described the TRIANGLE operation, an extended resection technique for PD aiming at a more radical resection of the nerve and lymphatic tissue between CA, CHA, SMA, and SMV-PV axis, for patients with potentially resectable locally advanced PDAC after NAT and stable disease. One of the main goals was to increase the resection rates even after arterial encasement (1,16).

The technique implies the removal of all soft tissue along the CA, SMA, SMV, and PV. During the resection, it is mandatory to show that the periarterial tissue does not include viable tumors by frozen section; afterward, a radical artery-sparing approach can be performed (1). Complete skeletonization of the regional vasculature is required. The surgery should be performed at the adventitial level. Arterial circumferential skeletonization is mandatory, including a complete clearance of the sheath of the proper vasculature..

The post-resectional result is an anatomic TRIANGLE bordered by the CA/ CHA, SMA, and PV/SMV revealed by the dissection, indicating the comprehensive removal of all soft tissue contained within these borders of fibrotic, neural, and lymphatic tissue (*Fig. 2*). In cases with associated SMV/ PV invasion, the venous resection and reconstruction can be done either with direct anastomosis or using the artificial vascular graft (*Fig. 2*). TRIANGLE TP offers a good space for the operator to perform the veins resection and reconstruction, lowering the time of PV obstruction. Moreover, it appears that TP with TRIANGLE technique significantly impacts the radical resection, the rate of negative resection margins, and the prognosis of patients with PDAC (12,16, 27). The coronary vein is usually divided during the TP, and reinsertion is impossible in most patients due to resection. Therefore, the stomach perfusion must be critically evaluated at the end of the operation. A distal or subtotal gastric resection may be required to avoid congestion-related ischemia (28).

Above all, the TRIANGLE technique allows patients with PDAC after NAT to have the chance to obtain a complete tumor removal. Furthermore, a significant advantage of the technique is the no need for arterial resection and reconstruction (1). However, in particular

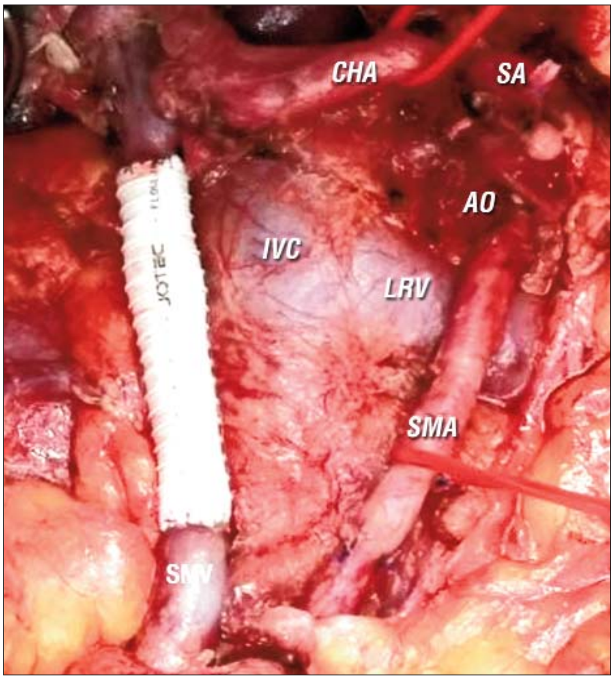

Figure 2. TRIANGLE total pancreatectomy with "en bloc "porto mesenteric vein resection: intraoperative view after complete dissection of the TRIANGLE region, including circumferential skeletonization of the CA/ CHA, SMA (red tape), and PV/ SMV resection and reconstruction with ringed PTFE allograft interposition

(SMV-superior mesenteric vein; IVC-inferior vena cava; LRV-left renal vein; AO-aorta; SMA-superior mesenteric artery; CHA-common hepatic artery; SA-splenic artery)

cases, the TRIANGLE operation can be associated with arterial resection and reconstruction; a venous resection is frequently needed.

Zhai et al. (12) and Rosso et al. (17) have shown the safety and efficiency of the TRIANGLE operation for BRPC. The TRIANGLE operation for BRPC can be safely performed also by laparoscopy in carefully selected patients (17).

Recently, the Heidelberg group published the data of 165 patients with PD or TP with the TRIANGLE technique. The outcomes were compared to a matched historic cohort with standard resections. In the TRIANGLE group, there were an increased number of harvested lymph nodes compared to the standard resection group, but statistical significance was reached only in the PD groups of patients (PD: 27.5 (21–35) versus 31.5 (24–40), p=0.0187; TP: 33 (28–49) versus 44 (29–53), p=0.3174). It also appears that the tumor-positive resections margins, R1 (direct), dropped in the TRIANGLE group. However, longer operative times and increased blood loss were observed in the TRIANGLE group compared to the standard resection group. Postoperative mortality and complications rates did not differ significantly between the groups concluding that the TRIANGLE pancreatectomy can be performed without increased morbidity and mortality at a high-volume center. Long-term survival and quality of life need to be investigated in prospective clinical trials with an adequate sample size (27).

According to Pengfei et al., in a retrospective and descriptive study of clinicopathological data of 30 patients with PDAC, TRIANGLE operation was associated with high radicality rates and low postoperative local recurrence rates, at the expense of slightly high morbidity and mortality rates. The long-term efficacy of such a procedure needs to be further evaluated. The authors recommend that this procedure be performed for selected patients after NAT in high-volume pancreatic surgery centers (29).

The Role of Total Pancreatectomy in PDAC

The forward steps of surgical techniques, glycemic control, and the development of synthetic insulin and pancreatic enzymes for postoperative treatment have made TP a safe procedure with increasing indications (30).

The first successful TP for PDAC was performed by Rockey (31) in 1943. TP was attempted in patients requiring total resection of their pancreatic diseases to reduce the incidence of morbidity and mortality, avoid anastomosis complications related to pancreatic fistulae after PD, and reduce tumor recurrence rates as an extension of oncological radicality (32). TP also strongly influences the patient quality of life (QOL) compared to organ preserving pancreatectomy because it causes volatile and difficult-to-control blood sugar levels (33). After advances in surgical techniques, glycemic monitoring, and the development of synthetic insulin and pancreatic enzymes, the medical management after TP has improved. Few studies have demonstrated acceptable QOLs after TP for neoplastic disease (32-34). With growing experience, technical improvement, and perioperative care advancement, the mortality after TP is less than 3%, and morbidity rates are around 40% in high-volume centers (35,36). Schmidt et al. reported significant improvements in the prognosis after TP for pancreatic neck cancers, showing a median survival time of 18 months (37). After 2010, a large series comprising 289 patients with TP for PDACs documented a median survival time of 18.1 months (38). Accordingly, TP was re-introduced step by step as a reliable option to achieve a cure for selected patients with PDAC (38,39,40).

TP has been reevaluated as an effective option to balance local control and postoperative safety. Furthermore, an arterial resection with TP in the surgical treatment of LAPC has been encouraged thanks to the latest chemotherapy regimens such as FOLFIRINOX or Gemcitabine and nab-paclitaxel, which have provided adequate patient selection and local tumor regression, justifying an extensive local surgical approach (41).

The techniques of arterial resection or TP have developed and become a routine among experienced pancreatic surgical teams. However, pancreatectomies with major arterial resection with or without TP are still controversial because it appears that the prognosis is not considered worthy of assuming the potential operative complications for patients with PDAC (38,39,40-42).

Indications for TP

Even if the number of TP performed has decreased over time, this procedure still plays a role in pancreatic surgery (26).

Indications for TP can be classified into four "T "groups (43,44): tumors of advanced stage or specific localization, technical problems due to soft pancreatic tissue or small pancreatic duct, troubles due to perioperative surgical complications after PD, and refractory therapy pain due to chronic pancreatitis. The most frequent indication for TP is advanced or multifocal pancreatic tumors (44). Recurrent pancreatic carcinoma, intraductal papillary mucinous neoplasms (IPMN), and extensive neuroendocrine tumors are also tumor-related indications for TP (45-47).

TP in main-duct IPMN and mixed-type IPMN cases is conducted either as a primary en bloc resection when IPMN extends throughout the entire pancreas or as a sequential operation when frozen section analysis reveals IPMN on the resection margin after partial resection (48). The intraoperative frozen section should always examine the resected IPMN to confirm its benign nature. In the case of unexpected malignancy, a more extended oncological resection must be chosen.

Managing a branch-duct IPMN is even more challenging and controversial regarding indications, correct timing, and extent of surgical interventions (48). Based on the "Fukuoka" criteria, the risk of malignancy in these lesions has been described (49). AAccording to these guidelines, resection of a lesion greater than 3 cm in diameter should be performed. Smaller ones should be resected, but only if "high-risk" stigmata are present (mural nodules, positive cytology, symptoms, or a synchronously dilated main duct). Still, remaining concerns are, among all IPMN smaller than 3 cm, that in the resected ones, there were observed malignancies rates of 25%. The standard approach for all suspected malignant branch-duct IPMN is adequate resection with lymphadenectomy, similar to the approach in a main-duct IPMN (48).

Technical problems due to soft pancreatic tissue do not represent an uncommon indication for TP. In this situation, carrying out a safe pancreatic anastomosis is not feasible due to vulnerable and soft pancreatic remnants being unable to hold sutures (44). When faced with the pancreatic remnant of poor quality, pancreatic fistula, sepsis, and life-threatening hemorrhage can occur if pancreaticojejunostomy is conducted. That is why elective TP must be a preferred choice since emergency completion of pancreatectomy is associated with high mortality rates (44).

It is worth mentioning that in patients with associated CHA or SMA resection and reconstruction, TP is generally performed and recommended (50,51). The complete resection of the pancreas reduces the rate of morbidity and mortality by eliminating the incidence of pancreatic fistula and its potentially fatal effect on arterial anastomosis (52). Following "partial" pancreatic resection, a pancreatic fistula can be complicated by acute bleeding and/ or sepsis. In these cases, TP is indicated as a salvage procedure (43).

When the indication for resection is PDAC, the first question is: what is resectable? In patients undergoing pancreatectomy for PDAC, TP provided chances of R0 resections in isolated neck margin-positive patients and was associated with a survival benefit. TP is recommended for cancer patients spread to the left part of the pancreas (37,52). According to Zhai, TP has an essential role in the treatment of PDAC for several reasons: (1) TP is the only surgical option for the radical resection of PDAC, which cannot be entirely resected by PD or distal pancreatectomy; (2) Multifocal and multi-segment pancreatic cancer, as well as IPMN that involves the entire pancreas, require TP; (3) TP is helpful to the dissection of surrounding lymph nodes and nerves, and might improve the long-term prognosis of PDAC; (4) Fistula of the pancreatic stump and anastomotic leak can be prevented by TP (12).

The Surgical Procedure of TP

TP can be performed in two different situations, namely:

1. TP as a second step after PD: due to technical reasons, early septic and bleeding complications or neoplastic infiltration of the pancreatic resectional margin found in the frozen section. In such cases, a left pancreatectomy is performed after PD.
2. TP as an "at once" procedure. In this case, an en bloc resection of the entire pancreas, part of the stomach, duodenum, jejunum, common bile duct, gallbladder, and spleen is performed.

An initial right subcostal or limited upper midline incision is made. A thorough exploration is performed, focusing on all peritoneal and visceral surfaces. In the absence of metastatic disease, the subcostal incision is extended to the left or the midline incision. The resectability of a patient with PDAC proposed for a pancreatectomy should be evaluated according to the NCCN guidelines (version 2. 2017.) (53).

Opening the lesser omentum and retracting downward the lesser gastric curvature allow good exposure of the celiac region and anterior surface of the pancreas.

Kocher's maneuver to lift the head of the pancreas and the duodenum and exposure of the SMA origin

The pancreatic head and the duodenum are reclined to the left upper side, the right renal vein, right genital vein, and inferior vena cava are exposed, and then leftwards, assess the area in the background of the pancreatic head and PV. After the left renal vein and the abdominal aorta are exposed, show the root of SMA (artery first approach). The origin of SMA is isolated from a right posterior side (54) just above the aorta and left renal vein; after that, the intrapancreatic portion of SMA is taped using the mesenteric approach proposed by Nakao (55). The concept of artery first approaches is to show a potential tumor adherence to the SMA at the early stage of the surgical procedure and either abort resection or plan an arterial resection.

Skeletonizing the hepatoduodenal ligament

The elements of the hepatic pedicle are skeletonized by cutting the serosa above the hepatoduodenal ligament and duodenum to identify CHA and the root of the splenic artery. The right gastric artery is ligated proximal to expose the proper hepatic artery. After removing the gallbladder, the common hepatic duct is transected over the cystic duct, and the gastroduodenal artery is divided and ligated.

Mobilization of the spleen and the body and tail of the pancreas

The body-tail of the pancreas is mobilized from left to right to dissect and isolate the splenopancreatic complex from left to right till they reach the pancreatic isthmus and head. This procedure is more effortless if started with the ligation and section of the splenic artery at its origin, thus reducing bleeding and decongesting the spleen. The mesenteric–portal venous trunk is freed by sectioning the splenic vein, located on the posterior side of the pancreatic body, upstreaming its connection to the superior and inferior mesenteric vein. Then, the pancreatic head and duodenum are freed following the procedure of PD without dissecting the pancreatic neck.

Clearance of TRIANGLE

After assessment of the resectability and dissection of the hepatoduodenal ligament, the SMA, CA, CHA, PV, and SMV are exposed, combined with dissection of putatively tumor-infiltrated lymphatic and neural tissue from the triangular space. During the TRIANGLE operation, it is required to at least finish the skeletonization of the right semi-circumference of the SMA and CA in cases of PD, whereas the left semi-circumference in distal pancreatectomy. In principle, both SMA and CA are circumferentially skeletonized for cases of TP, with complete dissection of lymphatic, neural, and fibrous tissues, following the adventitial plane of the whole mesopancreas from the triangular space delimited by the borders of SMA, CHA and PV-SMV (17,29). At the time of resection, it must be shown that the periarterial tissue does not include viable tumors by frozen section; afterward, an artery-sparing approach can be performed (1).

Detachment of the cephalic duodenopancreatic complex, dividing the gastric antrum, transecting jejunum

Once the left splenopancreatic complex has been entirely mobilized, and the retropancreatic vessels have been freed, the procedure is completed with the detachment of the cephalic duodenopancreatic complex as in extended PD. Section of the gastric antrum between the body and the antrum allows total mobilization of the upper part of the duodenopancreatic complex. Inferiorly, the mobilization of the angle of Treitz and the first jejunal loop allow the mesenteric complex to be detached.

Bilio-digestive and gastro-jejunal reconstructions

The most straightforward technique consists of using a single jejunal loop to perform transmesocolic bilio-digestive anastomosis and, subsequently, transmesocolic gastro-jejunal anastomosis to restore digestive continuity (26).

Periarterial Divestment in PDAC

There are still controversies regarding major arterial resection, particularly for the SMA. Even in highly selected patients, the SMA resection is considered complex. To obtain both surgical and oncological safety, the arterial divestment technique has been proposed as an alternative for SMA resection. The meaning of "divestment" is "undressing" or "circumferential dissection" (*Fig. 3*) (41). The precise technique and outcomes of arterial divestment were described in recent reports from the Heidelberg group (27,56).

Based on the increasing application of NAT in PDAC, particularly in LAPC, surgical strategies and concepts have gradually evolved, and resection techniques, particularly for the down-staged or stable disease cases. There is still a question if it is mandatory to perform arterial resection in PDAC. An alternative approach has been proposed as the "periarterial divestment" technique. It is of utmost importance for this artery "sparing "surgery to be performed on the adventitial or sub-adventitial layer, which opens longitudinally and allows circumferential lymphadenectomy and complete soft tissue removal of the respective area (56,57). This technique implies radical tumor removal without required arterial resection. Due to the inability to detect actual arterial involvement and real arterial invasion by modern imaging, surgical exploration is indicated (1).

Therefore, even in LAPC, a viable tumor is not necessarily remaining after NAT, and a radical resection may be possible in a relatively

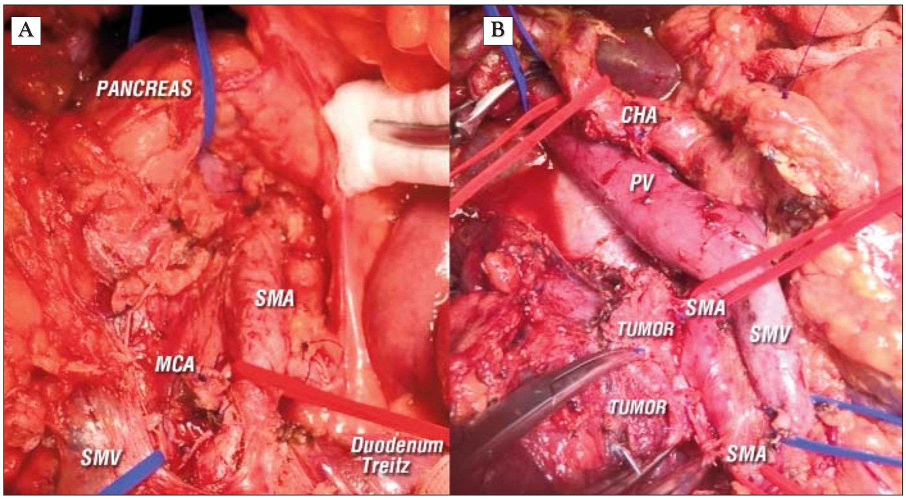

Figure 3. TRIANGLE operation with periarterial divestment (PAD): the artery-first Nakao mesenteric approach **(A)** and complete circumferential adventitial clearance of SMA up to the aorta **(B)**.
(SMV-superior mesenteric vein; SMA-superior mesenteric artery; MCA-middle colic artery; PV- portal vein; CHA-common hepatic artery)

high proportion of patients without an arterial resection. The technique applied is comparable to a "level 3" dissection as described for the upfront surgery by Inoue et al. (58), which implies carrying out the preparation on the adventitial layer of the arterial vessel, presuming that no viable tumor is found in frozen section during exploration. Periadventitial dissection (PAD) of the SMA was proposed to obtain the local control of the peri-SMA region. Inoue et al. proposed a specific operative technique of SMA-PAD using the supracolic anterior artery-first approach. Thus, no mortality was obtained in 158 patients, with an R0 rate of 74% (58,59). However, the safe utilization of this technique has never been widely spread. An artery-first approach is mandatory to select the following options: divestment, arterial resection, or aborting resection before the point of no return.

Vascular Resection in PDAC

The TRIANGLE operation can be combined with venous and arterial resections.

The first case of PD with mesenterico-portal vein resection was reported by Moore et al. (60) in 1951 and then by Asada et al. (61) in 1963. In 1973, Fortner (62) proposed "regional pancreatectomy," involving a systematic en bloc resection of the major peripancreatic vessels and wide soft-tissue clearance to achieve R0 resection to improve prognosis.

Venous resections are nowadays routine surgical procedures in high-volume centers (1,63). The ISGPS strongly recommends surgical exploration and resection if suspected mesenterico-portal axis involvement. According to recommendations, a venous resection is considered to be taken into consideration if complete tumor resection (R0) is possible, although this may lead to higher intraoperative and postoperative complication rates (3). ISGPS also published a classification of venous resections and distinguished four types of venous resections (3). Different vascular reconstructions were proposed using primary venous closure, end-to-end anastomosis, autologous, allogenous, or prosthesis grafts (*Fig. 4*). The patency rate of the reconstructions mentioned above varies between 70 and 90% (64,65). Each technique has its advantages and disadvantages. Therefore, the best venous reconstruction is still unclear (66).

According to many authors, the highest patency rate is observed after primary venorraphy, followed by segmental resection, the interposition of autologous vein grafts, and synthetic grafts. The option of partial venous resection with primary vein closure or segmental resection with primary end-to-end anastomosis depends on the length and circumference of tumor infiltration, which determines venous resection type. Primary vein closure is feasible when a tumor infiltrates the vascular lumen

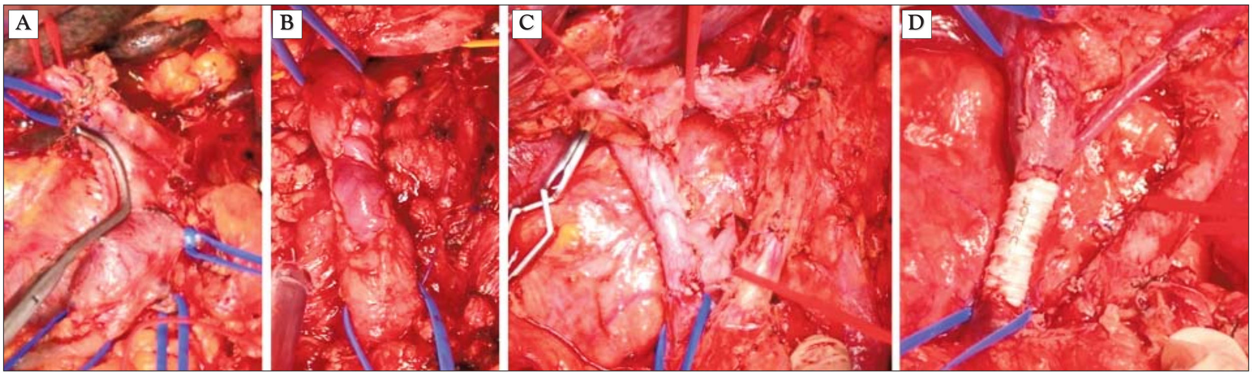

Figure 4. TRIANGLE pancreatectomy with different types of resected porto-mesenteric trunk vein reconstruction: **(A)** Lateral venorrhaphy. **(B)** Autologous peritoneal patch "plasty." **(C)** Direct end-to-end porto-mesenteric venous anastomosis. **(D)** PTFE ringed graft interposition

with narrowing less than 30%. In other cases, a segmental resection followed by end-to-end anastomosis is necessary. According to many authors, a primary end-to-end anastomosis is an option in resection involving <2–3 cm of the venous length. An interposition graft should be performed when primary vein closure or end-to-end anastomosis is impossible. Nowadays, there is no consensus or guidelines regarding perioperative anticoagulation in patients with pancreatectomy and associated venous resections (66).

The latest meta-analysis showed that patients with pancreatectomy and venous resection seemed to have different features such as larger tumor size, positive lymph nodes, microscopic positive margins rates, and higher 30-day mortality (67). However, no substantial differences were observed in the overall complication rates. In the odds of the observed poor survival after venous resection, a late propensity score-matched analysis demonstrated the same survival for the patients with and without venous resection (68).

If a vein resection is relatively widely accepted, an artery resection is more controversial for its increased morbidity and mortality and is mainly considered an individual decision (68,69). There is no good evidence that arterial resections during PD are associated with patient benefits. Patients categorized as BRPC based on features of arterial involvement on imaging must have surgical exploration to verify any arterial infiltration.

The "artery-first" approach, SMA intra-operatively, is a valuable procedure (70). Currently, resection is not indicated in verifying arterial involvement (3,66). Until late, a large series of SMA resections for PDACs was quite limited, and mortality after SMA resection had been reported to be higher than standard pancreatectomies, which discouraged the aggressive resection of LAPCs involving the SMA (41).

From the technical point of view, when arterial resection is performed, resection without reconstruction has to be differentiated from resection with direct anastomosis or graft insertion to replace the resected vessel. An essential aspect of LAPC surgery is avoiding arterial resection and reconstruction without constraining margin clearance. The CA might be resected to its aortal orifice in PD and distal pancreatectomy or TP (41). This operation is often called an Appleby procedure or distal pancreatectomy with celiac axis resection (DP-CAR). DP-CAR is a rare procedure indicated in a tiny number of patients (71). The advantages of this operation are that the redundancy of the blood supply to the liver and stomach through the gastroduodenal artery obviates the need for arterial reconstruction.

Hirano et al. were the first to show the early- and long-term outcomes of the DP-CAR. Their study included 23 patients with DP-CARs; no mortality was noted, and an acceptable overall survival was observed, with a 42% five-year survival rate and median survival time of 21 months (41,72).

Resection without hepatic artery reconstruction, potentially after preoperative embolization, has been described in a Japanese 21-patients series by Miyazaki et al. (73) for partial and TP. Miyazaki et al. have shown particular management of hepatic artery resection with preoperative embolization to enhance the collateral hepatic arterial inflow. In this study report, 20/21 patients underwent hepatic artery resection without reconstruction. Twelve of these patients had received a preoperative embolization of the CHA with the aim of collateral vessel formation. Except for a temporary postoperative increase of liver enzymes, there was no mortality or relevant morbidity associated with this procedure (73).

From the technical point of view, there are various possibilities for arterial reconstruction after resection, including direct anastomosis, insertion of allografts, and replacement by autologous bridging or interposition (73). In all situations of major arterial resection and reconstruction, the possibility of a TP should be critically considered to avoid pancreatic fistula, a well-known and potentially fatal complication in arterial erosional bleeding (74).

Advanced cancers of the pancreatic neck often extend to the common and proper hepatic artery and the gastroduodenal artery. In these particular situations, the hepatic artery's segmental resection, including the gastroduodenal artery's root, is proposed. An end-to-end anastomosis is usually feasible if there is a limited tumoral invasion and the resected arterial segment is short (74). Amano H et al. first reported a series of hepatic artery resections that described the techniques and outcomes of arterial reconstruction. The in-hospital mortality rate was 7%, with an R0 rate of 80% and a median survival time of 12 months. The authors considered that hepatic artery resection is justified only when an R0 resection can be obtained for selected patients with PDAC (41).

Furthermore, in recent years, the techniques of replacement applied for the hepatic artery or the SMA have been improved, and procedures such as splenic artery use have been described for restoration of hepatic or small-bowel perfusion (50). According to our policy, we have performed arterial resection only if the tumor infiltrated the right hepatic artery origin from the SMA (*Figs. 5, 6*). A meta-analysis showed that patients with pancreatectomies and artery resection had increased risks of postoperative mortality, morbidity, and worse three-year survival (75). Specific complications, the length of hospital stay, and the margins positive rates were not significantly different compared to patients without artery resection. Another study, including approximately 40 years of experience, has also shown the safety and efficacy of arterial resection for patients with LAPC, suggesting preoperative NAT with artery resection as a valuable tool for LAPC (76). A single-center cohort study reported that pancreatectomy with artery resection could

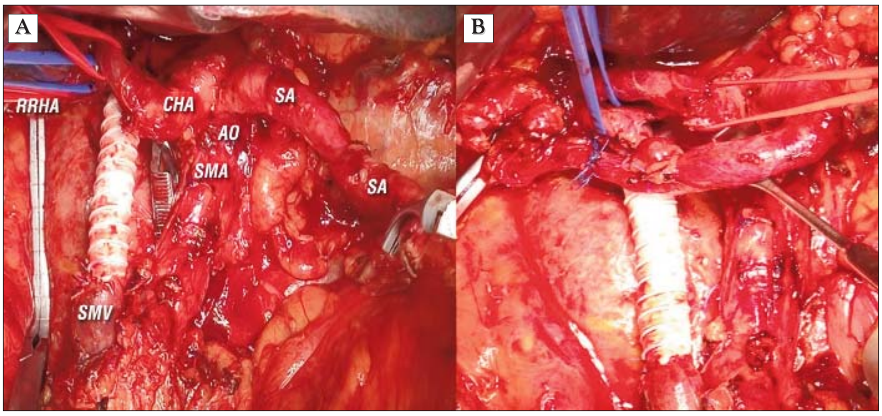

Figure 5. TRIANGLE total pancreatectomy with combined vascular resections (PTFE graft interposition with SA transposition in reconstruction): Venous resection of PV/SMV trunk and arterial RRHA from SMA resection (SA prepared for transposition and RRHA reconstruction) **(A)**; PTFE ringed allograft interposition used for PV/SMV reconstruction, while SA was transpositioned and anastomosed for the RRHA reconstruction **(B)**

(SMV-superior mesenteric vein, AO-aorta, SMA-superior mesenteric artery, CHA-common hepatic artery, SA-splenic artery)

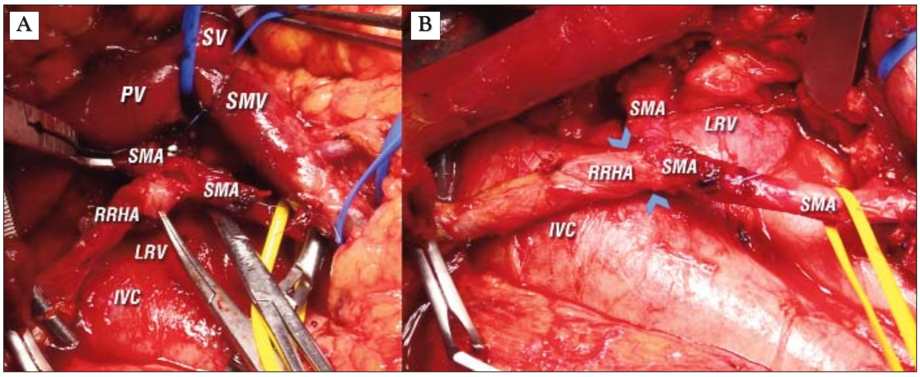

Figure 6. TRIANGLE total pancreatectomy with arterial resection: Clearance of TRIANGLE space with concomitant resection of RRHA arising from SMA: direct "side-to-end" SMA-RRHA arterial reconstruction **(A)** and copleted SMA-RRHA arterial reconstruction (blue arrowheads marks the anastomosis) **(B)**

(PV-portal vein; SMV-superior mesenteric vein; IVC-inferior vena cava; LRL-left renal vein; SMA-superior mesenteric artery; RRHA-replaced right hepatic artery from SMA)

obtain better one-, three-, and five-year survival rates compared to palliation for patients with LAPC (77). According to the authors, the TRIANGLE procedure should be performed without arterial resection. Loss et al. (78) and Schneider et al. (79) recently observed that arterial resection is effective in patients with LAPC after NAT, with better long-term survival than the palliative treatment. However, this procedure should be performed in experienced pancreatic centers. After NAT, in centers with expertise in pancreatic resection, arterial resection is possible with acceptable morbidity and mortality (80).

Conclusions

TRIANGLE operation is a possible method to achieve radical resection of BRPC in patients who have received or not NAT or in LAPC patients after NAT. With TRIANGLE operation, arterial sparing resection can be achieved, and the postoperative risk of pancreatic fistula can be reduced. Thus, the risk of postoperative hemorrhage for vascular reconstruction and skeletonization can be reduced. After postoperative adjuvant therapy, the prognosis is acceptable (12). However, more studies are needed to assess further this operation's reliability, feasibility, and long-term effect (12).

Even though surgeons have performed fewer TP for treating pancreatic diseases in recent years, there are few limited indications for this procedure. TP is supported for treating PDAC in appropriately selected patients because the long-term survival rates were comparable to those for patients who underwent PD (30). The similar 3- and 5-year survival rates in patients who underwent TP vs. those who underwent PD suggested that the glycemic issues were not significant determinants of death in the long term (81). The patients referred to the endocrinology unit after TP for education purposes can have reasonable glycemic control and self-management (82).

Given the advanced technology and comprehensive strategies, curative resections and the quality of perioperative management have improved. As a result, the mortality rate after pancreatic surgery has reduced to a current rate of less than 5% in specialized centers (82).

Looking at the outcomes of PDAC surgery, the anatomical classification we are using today to define who should or should not receive surgery seems to be misaligned with the biology of the disease. Therefore, the problem is not the role of vascular resections in PDAC but the role of surgery in PDAC. In an era where medical treatment has improved significantly, we should shift from anatomical classification of resectability to more prognostic and biological classifications (83).

Conflicts of Interests

The authors declare that they have no conflict of interest.

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