

TRIANGLE operation for borderline resectable pancreatic cancer in total pancreatectomy

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Background: Pancreatic cancer is a highly aggressive cancer featured by early metastasis and multiple chemoresistance. Surgical resection remains the only way for the radical cure of pancreatic cancer. The aim of this study was to assess the safety, feasibility and oncological effect of the Heidelberg TRIANGLE operation in total pancreatectomy (TP) for borderline resectable pancreatic cancer (BRPC).

Methods: Patients with BRPC eligible for TP were selected and underwent total pancreatectomy with Heidelberg TRIANGLE operation. Sharp dissection was applied to separate tumor and involved artery. Then we completely dissected the soft tissues surround celiac axis (CA) and superior mesenteric artery (SMA) in each case. If superior mesenteric vein (SMV) or portal vein (PV) were invaded by the tumor, resection and reconstruction of veins were performed. Operation time, blood loss, post-operative complications, perioperative mortality, number of lymph node examined and R0 resection rate were collected and analyzed.

Results: Nine BRPC patients underwent TRIANGLE operation in TP. No perioperative death occurred. 3 cases developed postoperative complications: biliary leakage and colon fistula in 1 case and lymphatic leakage in 2 cases. The R0 resection rate of operation was 88.89% (8/9).

Conclusions: For patients with BRPC, upfront surgery should be encouraged when they were unwilling or unable to received neoadjuvant therapy. Especially for those patients with artery involvement eligible for TP, TRIANGLE operation can help to achieve arterial sparing resection. Thus, the risk of postoperative hemorrhage for vascular reconstruction and skeletonization can be reduced. After postoperative adjuvant therapy, the prognosis is acceptable.

Keywords: Pancreatic cancer; general surgery; pancreatectomy

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Introduction

Due to its location depth and asymptomatic feature in early stage, pancreatic cancer has often developed into advanced stage when diagnosed (1). Therefore, the treatment of borderline resectable or locally advanced pancreatic cancer is of great importance. The definition of borderline resectable pancreatic cancer (BRPC) and locally advanced

pancreatic cancer (LAPC) is based on the relationship of tumor and its nearby main blood vessels (2,3).

This study was conducted for patients with BRPC that required total pancreatectomy (TP) and combined a previously reported surgical procedure, TRIANGLE operation (4), to evaluate its perioperative clinical outcomes, effectiveness of radical resection and prognosis of patients.

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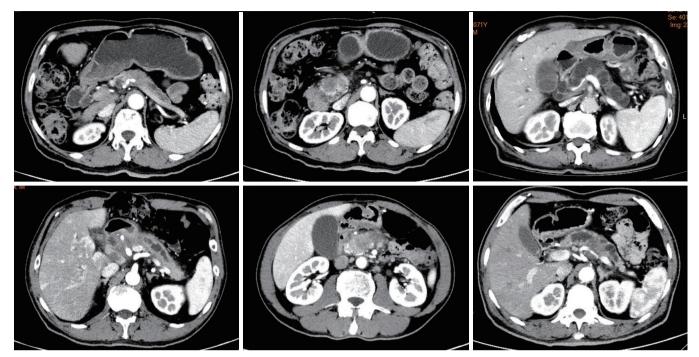


Figure 1 CT scan of patients eligible for TRIANGLE operation.

Methods

Patients

Patients who met the following criteria were collected and retrospectively analyzed: (I) Diagnosed as BRPC by multidisciplinary treatment (MDT) (5). (II) Refused to receive the neoadjuvant therapy and asked for surgery due to the unwillingness to take the risk of down-staging failure after neoadjuvant therapy. (III)Without distant metastasis. (IV) Diagnosed by CT scan (Figure 1) as large malignant tumor (postoperative pathological diagnosis of pancreatic ductal adenocarcinoma, PDAC) that has invaded pancreatic neck, intraductal papillary mucinous tumor (IPMT) involved the whole pancreas, multifocal and multi-segment pancreatic cancer, and other situations which were eligible for TP (6).

Surgery procedure

Resectability assessment: Explore the abdominal cavity to exclude distant metastasis and make the Kocher maneuver. Then, we cut off the gastrocolic ligament and dissect the inferior border of pancreas. When we found SMV, separate its left side and then explore the SMA and CA. Resectability was evaluated according to NCCN

guidelines (version 3.2017) (7).

Total pancreas resection: For resectable tumor, without dissecting pancreatic neck, free the pancreatic head and duodenum following the procedure of pancreaticoduodenectomy (PD), Then, according to distal pancreatectomy (DP), free the spleen and pancreatic body and tail from distal to proximal till meet the pancreatic head. At the same time, the surrounding lymph nodes were dissected.

Clearance of Heidelberg triangle (4): a complete skeletonization of artery was required. The surgery should be performed in the adventitial level. Arterial skeletonization was performed, which included the excision of the sheath of SMA, CA, abdominal aorta and root of common hepatic artery (CHA), and the dissection of lymphoid and fat tissue along the arterial adventitia. The resection and reconstruction of SMV or PV could be done when either of them was invaded by tumor, vein reconstruction including direct anastomosis or artificial vascular bypass. At last, the complete dissection of lymphoid and fat tissue, as well as nerve tissue in Heidelberg triangle was accomplished—complete skeletonization around CA, the origin of SMA, PV/SMV and CHA (Figure 2).

Anastomosis: choledochojejunostomy and gastrojejunostomy were performed. When operation

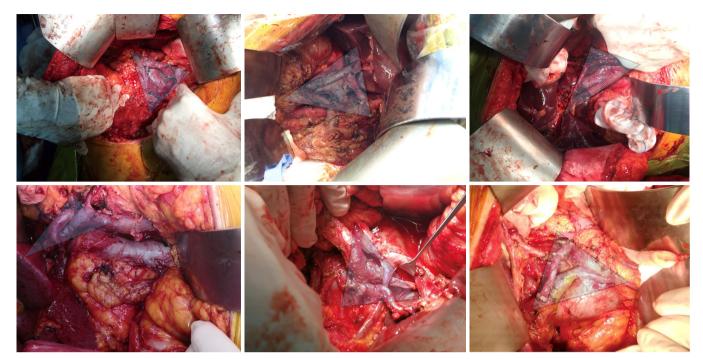


Figure 2 Pictures taken during surgery. The triangle indicates CA, SMA and PV/SMV, which are involved in TRIANGLE operation. CA, celiac axis; SMA, superior mesenteric artery; SMV, superior mesenteric vein; PV, portal vein.

finished, drainage tubes were placed beside the bilioenteric anastomosis and in splenic fossa respectively.

Surgerical specimen management: The surgical margin of bile duct, uncinate process, retroperitoneum, stomach and jejunum, along with the location of lymph nodes, were marked. The posterior peritoneal resection margin was defined as the intraoperative removal of a piece of connective tissue closely adjacent to the celiac trunk. All specimens received pathological examination (8).

Patient data

Age, sex, body mass index (BMI), American Society of Anesthesiologist's classification (ASA) and Eastern Cooperative Oncology Group (ECOG) stages were collected as baseline parameters. All patients received CT and MRI scan before surgery. Operative parameters included operation time, blood loss and details of the surgical procedure. International Study Group of Pancreatic Surgery (ISGPS) (9,10) and the Clavien-Dindo classification (11) were used to classify the postoperative morbidity. Leeds protocol, in which R0 resection is defined as a minimum distance of 1 mm of tumor cells to the resection margin (8), was used to perform histopathological examination of the

samples. Informed consent from all participating patients and approval from the Ethics Committee of Shanghai Ruijin Hospital (No.172 in 2018) were obtained to conduct this research.

Statistics

Results are presented in the form of mean ± SD, including perioperative parameters, postoperative parameters and postoperative complications. Data was analyzed using GraphPad Prism 7.

Results

From Aug 2017 to Jun 2018, 9 patients with BRPC underwent TRIANGLE operation in TP (*Table 1*). 8 patients underwent one step TP. 1 patient underwent TP of the remnant pancreas after DP due to local recurrence. According to imaging examination, SMA or CA was encased by the tumor less than half in circumference in 5 patients. The mean age of the patients was 63.3 years old and 7 of them were male. Six patients were defined as ASA 1, the rest 3 patients as ASA 2. The mean BMI was 21.5. ECOG performance status was 0 or 1 for all patients. Four patients

Table 1 Baseline parameters

Characteristics	Number			
Age	63.33±10.1			
Sex (M/F)	7:2			
BMI	21.57±2.568			
ASA class ≤2	9			
ECOG ≤1	9			
Diabetes mellitus	4			
Hypertension	3			
Cardiopulmonary dysfunction	0			

BMI, body mass index; ASA, American Society of Anesthesiologist; ECOG, Eastern Cooperative Oncology Group.

had diabetes history and 3 suffered hypertension. No one had cardiopulmonary dysfunction.

Median blood loss was 633 mL (range, 200–1,500 mL), median operation time was 383 min (range, 240–660 min) and packed red blood cells (2–6 units) or fresh frozen plasma (4–10 units) was transfused to 8 patients during surgery. Median tumor diameter was 7 cm (range, 3.3–8 cm). The perioperative data was listed in *Table 2*. Compared to the perioperative data from surgery without TRIANGLE operation in recent years, despite longer operating time and more blood loss, much more lymph nodes and positive lymph nodes were collected (*Figure 3*).

In histopathological examination, 8/9 patients got an R0 resection. One case of positive resection margin was found in retroperitoneal resection margin. Perineural and lymphovascular invasion were observed in all of the 9 patients. The number of lymph node collected in surgery ranged from 19 to 44. N1 stage was found in 4 patients, N2 in 5 patients.

As is shown in *Table 3*, median postoperative hospital stay was 29 days (range, 17–42 days). Two patients suffered diarrhea after surgery. No one had postoperative bleeding, pancreatic fistula or hypokalemia. No postoperative mortality occurred, surgical morbidity was observed in 3/9 patients, include 2 cases of chyle leak (n=2), and 1 case of bile leakage combined with colon fistula who received re-operation. Complication of 2 patients was classified as Clavien-Dindo grade 2 and 1 patient as grade 4 with the need for ICU care. No readmission occurred.

The median follow-up days was 8.9 months (range, 5–10 months). Two patients suffered tumor recurrence (1 patient with liver metastases, 1 with lung recurrence)

after 4 months. Five patients have been dead until now. The median survival was 205 days (range, 130–309 days).

Discussion

The morbidity of pancreatic cancer has been increasing in recent years. Many patients are diagnosed with vascular invasion or distant metastasis. How to effectively treat BRPC is a breakthrough point in improving the overall therapeutic effect of PDAC, and also should be a priority for doctors (12). Radical resection is now regarded as the only way to possibly cure the pancreatic cancer (13), but surgical resection of BRPC is still controversial: (I) Whether to resect the tumor largely depends on preoperative imaging diagnosis, which unfortunately cannot always provide real resectability (14) and can not distinguish tumor invasion from fibrosis caused by inflammation (15). Despite the wide application of MDT in the treatment of pancreatic cancer (16), there is still a dilemma where you may lose the opportunity of surgery for a resectable tumor or excise an unresectable tumor for which R0 resection can not be achieved. For example, especially those patients who are considered unresectable because of CA, CHA or SMA encasement (no more than half in circumference) can get R0 resection with surgeon's effort. (II) For the treatment of BRPC, neoadjuvant therapy is highly recommended in guidelines especially in Europe and America (17). Some treatment reported has greatly improved the resection rate and prognosis of these two types of tumor (18-21).

However, some patients, whose tumor fails to downstage but develops after neoadjuvant therapy, lose the opportunity to undergo radical resection of the tumor. In addition, unlike patients in Europe and America, many Asian patients cannot tolerate chemotherapy, and cannot endure a complete neoadjuvant therapy. Secondly, this study comes from China, and patients are more willing to receive traditional Chinese medicine treatment. Finally, most patients are unable to afford the high cost of neoadjuvant therapy. Hence, many patients have a strong wish of receive "surgery first" treatment. For those patients with artery encasement, when they choose "surgery first", the dissection of the triangle region including CA, SMA and PV (Heidelberg triangle) and skeletonization of these vessels may decrease the local recurrence. In fact, those patients in the study do not appear local recurrence after surgery.

For patients of BRPC who received "surgery first" treatment, En-bloc resection, R0 resection, complete lymph nodes and nerves dissection, good postoperative recovery,

Table 2 Perioperative and pathological data

No.	1	2	3	4	5	6	7	8	9
Vascular invasion	SMA/SMV	SMV/PV	SMV/PV	SMV/PV/SV	CA/PV/PA	SMA/PV	SMA/PV	SMV/PV	PV/SMA
Surgery	One-step TP	Remnant TP							
Operating time (min)	240	420	660	200	420	300	550	240	420
Blood loss (mL)	200	300	1,500	600	400	500	800	200	1,200
Reoperation	No	No	No	No	No	Yes	No	No	No
Pathological classification	PDAC	PDAC	PDAC	PDAC	IPMT	PDAC	IPMT	PDAC	PDAC
Tumor size (cm)	8.1	8.4	6.1	3.8	13.5	3.5	8.6	5.6	4.2
LNR	2/22	4/39	7/38	7/24	4/19	2/35	2/27	10/44	3/22
Margin	R0	R0	R0	R0	R0	R0	R1	R0	R0
Perineuronal invasion	Yes	Yes							
TNM stage (AJCC 8 th)	III	III							
Vein resection and reconstruction		PV	PV		PV	PV	PV	PV	PV
Postoperative adjuvant therapy	TCM	GS	GS	GEM	GS	TCM	S-1	GS	TCM

SMA, superior mesenteric artery; SMV, superior mesenteric vein; PV, portal vein; SV, splenic vein; CA, celiac axis; PDAC, pancreatic ductal adenocarcinoma; IPMT, intraductal papillary mucinous tumor; LNR, lymph node ratio; AJCC, The American Joint Committee on Cancer. GEM, Gemcitabine, 1,000 mg/m² (i.v.) at 1st, 8th, 15th day of chemotherapy; GS, Gemcitabine + S-1, 1,000 mg/m² gemcitabine (i.v.) at 1st, 8th day of chemotherapy and 60 mg/m² S-1 (po, bid) from 1st to 14th day of chemotherapy; S-1, 60 mg/m² S-1 (po, bid) from 1st to 14th day of chemotherapy.

appropriate and timely adjuvant therapy are beneficial to patients' survival. Our study was aimed at patients with BRPC eligible for TP, and based on surgical skills such as vascular skeletonization and vessel reconstruction. Therefore, we suggest that the "Heidelberg TRIANGLE operation" should be added to TP as a key procedure, which will help to increase the number of lymph nodes examined, reduce complications rate and have better radical treatment efficacy for BRPC.

TP plays an important role in the treatment of pancreatic cancer for several reasons: (I) TP is the only surgery for the radical resection of pancreatic cancer, which cannot be achieved by PD or DP. (II) Multifocal and multi-segment pancreatic cancer, as well as IPMT that involves the entire pancreas, require TP. (III) TP is helpful to the dissection of surrounding lymph nodes and nerves, and improves the long-term prognosis of pancreatic

cancer. (IV) Fistula of pancreatic stump and anastomotic leak can be prevented by TP.

When Heidelberg TRIANGLE operation is performed in TP, the tissue around SMA, CA, PV and CHA can be fully exposed (*Figure 2*). Also we can control the potential of bleeding when dissecting near the vessels, which helps to open the arterial sheath and strip the lymphoid tissue, soft tissue and nerves along the adventitia. Besides, this operation provides enough space for operator to reconstruct the veins and reduces the time of portal vein occlusion. Moreover, it exerts great impact on the radical resection the negative rate of surgical margin and long-time survival of patients of pancreatic cancer (4,6).

This group of patients did not receive neoadjuvant therapy. As a result, there is less fibrosis of tissue and adventitia induced by chemotherapy, which can help us prevent unintended arterial injuries. The second remarkable

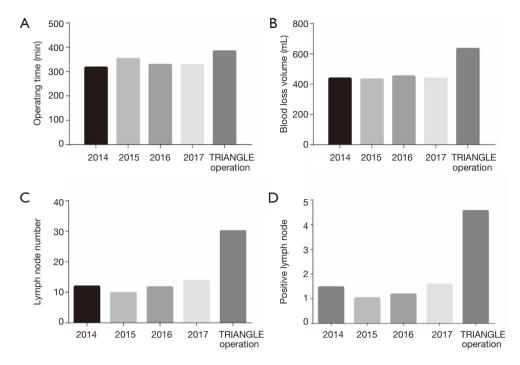


Figure 3 Perioperative data collected in recent years and in TRIANGLE operation. (A) Operating time, (B) blood loss, (C) lymph node number and (D) number of positive lymph node.

Table 3 Postoperative outcomes

Table 5 Tostoperative dateomes					
Characteristics	Number				
Postoperative stay	29 [17–42]				
Abnormal blood sugar after medication	0				
Diarrhea	2				
POPF	0				
PPH	0				
Hypokalemia	0				
Lymphatic leak	2				
Biliary fistula	1				
Reoperation	1				
Colon fistula	1				

POPF, postoperative pancreatic fistula; PPH, postoperative hemorrhage.

feature of this approach is the increased number of lymph nodes dissected in surgery and the positive lymph nodes among then. With the publication of the eighth edition of AJCC (22), biological behavior of tumor was addressed and N stage was revised. Patients with different number of

positive lymph nodes have different prognosis. According to Figure 3, compared to the cases in 2014–2017 at our center, despite an increase in operating time and blood loss, the application of TRIANGLE operation results in more dissected lymph nodes and examining more positive lymph nodes. Recent evidence suggests that the detection rate of positive lymph node of pancreatic cancer is based on certain amount of lymph nodes dissected in surgery (23,24). The clearance of lymph nodes, though it remains controversial in improving patients' prognosis, has more practical application in judging the stage of cancer and predicting the prognosis (25-27). Our postoperative hospital stay is longer because: (I) patients were discharged when they were fully recovered (absence of fever >48 h; able to take solid food; passage of normal stools; adequate mobilization; no drainage tube; acceptance of discharge by the patient). (II) patients would not be referred to community hospital.

The overall complication rate of resection of BRPC is high (28), but not in our approach which often requires vascular resection and reconstruction and excision of arterial sheath, which dramatically increase the risk of surgery. The common complications of pancreatic surgery are postoperative pancreatic fistula (POPF) and postoperative hemorrhage (PPH), which usually come together and have

a causal relationship. POPF, intraperitoneal infection and PPH are regarded as lethal triad of pancreatic surgery. Fortunately, TP can prevent POPF, which is helpful to reduce the risk of hemorrhage caused by vascular resection, reconstruction and skeletonization. This approach has a large scale of lymph node dissection, so the incidence of lymphatic leak is higher. We have summarized two points on how to prevent lymphatic leak in this approach: (I) Protect the visible lymphatic vessels. (II) Every lymphatic leak should be ligated when we are checking after resecting.

The effect of TP on endocrine and exocrine function cannot be neglected. Patients who have an exocrine function disorder often suffer varying degrees of diarrhea, mostly fatty diarrhea. The reasons can be listed as follows: (I) The loss of exocrine function results in lack of multiple digestive enzymes. (II) The digestive tract is shortened by the excision of upper gastrointestinal tract and the time to digest is shortened accordingly. (III) The cut-off of autonomic nerves leads to hypersensitivity of digestive tract. All structures of the autonomous nerve system as well as all lymphatic tissue are dissected in the surgery, postoperative diarrhea or chyle leaks may occur. The complete dissection of nerves around SMA could result in refractory diarrhea which may reduce patient's quality of life. Thus, digestive enzymes and antidiarrheal should be provided. At present, this symptom is under good control through the internal medicine treatment. After TP, patients also will be devoid of insulin, the main hormones to regulate blood sugar, and present symptom of diabetes. It should be controlled with long-acting insulin, and strict diet, blood sugar monitoring also cannot be neglected. The glycemic control scheme in our study: 6-8 unit of long-acting insulin before sleep adjust with everyday blood sugar monitoring, is effective. Although TP results in the loss of endocrine and exocrine function, the modification of insulin preparation and application of pancreatin can dramatically improve the quality of life after surgery. Therefore, TP is not supposed to be restricted as it used to be, but to enlarge its scope of indication in pancreatic disease.

The perioperative outcomes of these 9 patients collected in the present study was good, in which there was no mortality and the morbidity rate was within acceptable limits. There was only one R1 resection which could not be avoided unless arterial resection and reconstruction was performed. Since arterial resection can be very risky and the application of adjuvant therapy in R1 situation may provide better outcomes than a merely palliative treatment (29), whether to routinely perform such operation, due to the

high morbidity and mortality, has not reached an agreement (25,30). Therefore, more investigations are needed to further assess the reliability and feasibility of TRIANGLE operation.

Conclusions

TRIANGLE operation is a possible method to achieve the radical resection of BRPC in patients who have not received neoadjuvant therapy. With TRIANGLE operation, arterial sparing resection can be achieved and the postoperative risk of POPF and PPH can be reduced. However, more studies are needed to further assess the reliability, feasibility and long-term effect of this operation.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tcr.2019.09.50). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent from all participating patients and approval from the Ethics Committee of Shanghai Ruijin Hospital (No.172 in 2018) were obtained to conduct this research.

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