

En bloc vascular resection for the treatment of borderline resectable pancreatic head carcinoma

HIROHISA KITAGAWA¹, HIDEHIRO TAJIMA¹, HISATOSHI NAKAGAWARA¹, ISAMU MAKINO¹,
TOMOHARU MIYASHITA¹, MASATOSHI SHOJI¹, SHINICHI NAKANUMA¹, NORIHIRO HAYASHI¹,
HIROYUKI TAKAMURA¹, TETSUO OHTA¹ and HIROSHI OHTAKE²

Departments of ¹Gastroenterologic Surgery and ²Cardiovascular Surgery, Graduate School of Medical Science,
Kanazawa University, Kanazawa, Ishikawa 920-8641, Japan

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Abstract. Borderline resectable (BR) pancreatic head carcinoma (PhC) is an advanced disease, presenting with infiltration of major vessels. Major vascular resection (VR), particularly arterial resection, to achieve microscopic no residual tumor (R0) is a controversial approach, due to the potential complications. In this study, we aimed to clarify the benefit of en bloc R0 resection with VR for PhC by retrospectively evaluating 78 PhC patients who underwent pancreatoduodenectomy at our institute. The patients were divided into 4 groups as follows: R, resectable (n=20); BR-V, BR involving the superior mesenteric vein or portal vein (PV) (n=28); BR-SMA, BR involving the superior mesenteric artery (n=21); and BR-HA, BR involving the hepatic artery (n=9). In total, 65 patients underwent VR, with 63, 21 and 9 patients undergoing PV, SMA and HA resection, respectively. The R0 rates were as follows: R group, 85%; BR-V, 82%; BR-SMA, 71%; and BR-HA, 33%. The median survival time and 5-year survival rate for R0 resection were 31 months and 25% in the R group, 22 months and 28% in the BR-V group, 17 months and 27% in the BR-SMA group and 10 months and 0% in the BR-HA group, respectively. The prognosis was comparable among the BR-V, BR-SMA and R groups, but was significantly poorer in the BR-HA group. In total, 5 patients (6.4%) died perioperatively (4 from postoperative hemorrhage and 1 from suffocation due to failure of expectoration, without pneumonia or asthma). Of the 4 patients who succumbed to hemorrhage, 3 had undergone

arterial resection. Therefore, en bloc resection with major VR for R0 may be suitable for BR-V and BR-SMA PhC patients.

Introduction

Borderline resectable (BR) pancreatic adenocarcinoma is an advanced disease and conventional resection has been proven to be inadequate for improving patient prognosis. The criteria of the resectability status are defined by the National Comprehensive Cancer Network guidelines as tumor infiltration into nearby major vessels (1). A combination of vascular resection (VR) is required to achieve no microscopic residual tumor (R0) resection for BR pancreatic head carcinoma (PhC). The principle underlying our surgical strategy for resectable (R) PhC is total excision of the lymphatic basin of the pancreatic head, which is termed meso-pancreatoduodenum (meso-pd). For BR PhC, additional venous and/or arterial resection may be required for R0 resection. In the present study, 78 patients with PhC were evaluated, including 65 patients who underwent VR and were consecutively treated at our institute between 2002 and 2012, in order to clarify the benefit of the en bloc VR technique for R0 resection of BR PhC.

Patients and methods

Diagnostic procedures and staging. The PhCs were classified as follows: R; BR-V, BR involving the superior mesenteric vein (SMV) or portal vein (PV); BR-SMA, BR involving the superior mesenteric artery; and BR-HA, BR involving the hepatic artery. The classification was performed on the basis of the extent of the cancer nest, which was determined by multi-detector row computed tomography (MDCT). The extent of nerve plexus (PLX) invasion was determined by either the coarse reticular pattern or the mass and strand pattern connected to the main lesion of the carcinoma (2). Abutment or near abutment of the SMV/PV, SMA or HA by the cancer nest was considered an indication for en bloc resection of these vessels.

The resected specimens were serially sliced into 5-mm stepwise sections along the axial plane. The tumor stage and grade were classified according to the 7th edition of the tumor-node-metastasis classification system of the International

Correspondence to: Professor Hirohisa Kitagawa, Department of Gastroenterologic Surgery, Graduate School of Medical Science, Kanazawa University, 13-1 Takara machi, Kanazawa, Ishikawa 920-8641, Japan
E-mail: kitagawa@staff.kanazawa-u.ac.jp

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Union against Cancer (UICC) (3). Tumor-node-metastasis staging was performed in accordance with the UICC/American Joint Commission on Cancer staging system (4), which corresponds to the histopathological reporting of pancreatic cancer of the Royal College of Pathologists (5). Margin positivity was defined as tumor clearance of <1 mm.

This retrospective study was approved by the appropriate Institutional Review Board, and informed consent was obtained from each patient.

Surgical procedures. The basic and standard protocol for the treatment of PhC was total meso-pd resection, en bloc resection of the pancreatic head and the lymphatic basin. The lower dissection limit of the mesentery was above the third duodenal portion and the posterior dissection plane included the anterior renal fascia. The PLX surrounding the SMA was not included in the meso-pd. VR was optional, depending on the extent of tumor infiltration. All the SMV/PV resections were performed using the sleeve resection technique. The preferred reconstruction technique following segmental resection was primary end-to-end anastomosis; however, interpositioning of the autologous venous graft from the external iliac vein was completed to provide a tension-free anastomosis, when necessary. Following venous confluence resection, the splenic vein stump was closed and the inferior mesenteric vein was preserved, if possible. SMA resection was performed in 21 cases, from its origin until the infiltration-free portion (6). In the first 17 cases, we performed interpositioning of the autologous venous graft of the saphenous vein for reconstruction with a tension-free, end-to-end anastomosis. For the following 4 cases, we performed a direct anastomosis of the aorta inferior to the origin of the inferior mesenteric artery, using an autologous venous graft of the saphenous vein, via side-to-end anastomosis for the proximal site and end-to-side anastomosis for the distal site. Prior to SMV/PV or SMA resection and reconstruction, occlusion of the SMA was repeated 3 times to induce ischemic preconditioning in the mesentery. HA resection was performed in 7 cases. End-to-end reconstruction was performed in 5 cases to restore the arterial blood supply to the liver, whereas in the remaining 2 cases it was unnecessary. An autologous venous graft of the saphenous vein was used for reconstruction in 1 case. Vascular reconstruction following SMA or HA resection was performed using a 2-step method. Arterial reconstruction and reperfusion were performed, followed by SMV/PV reconstruction. The specimen was mobilized prior to VR, resulting in en bloc resection that included the involved vessel as the last step of the surgical procedure.

In-hospital parameters. The following patient parameters were routinely assessed, included in an online prospective database and analyzed: Perioperative morbidity, particularly surgical complications (occurrence of postpancreatectomy hemorrhage; thrombosis of the PV, SMV, SMA or HA in patients undergoing VR; abdominal or liver abscess formation and duodenal ulcer) and perioperative mortality, defined as in-hospital mortality or death within the first month following discharge from the hospital.

Follow-up. The routine postoperative evaluation included a regularly scheduled physical examination, measurement

of carcinoembryonic antigen and carbohydrate antigen 19-9 levels and imaging studies with MDCT every 3 months.

Statistical analysis. The associations between categorical variables were assessed using the Fisher's exact test or the χ^2 test. The Kaplan-Meier method was used to estimate survival probability at 24 and 60 months after surgery. The differences between patient groups with respect to survival were assessed using log-rank tests. $P < 0.05$ was considered to indicate a statistically significant difference. SPSS software for Windows®, version 13 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Procedures and perioperative patient characteristics. The patient characteristics, surgical procedures and perioperative outcomes of the entire study cohort are summarized in Table I. Of the 78 patients who underwent pancreatoduodenectomy for PhC, 20 patients had R PhC, 28 had BR-V PhC, 21 had BR-SMA PhC and 9 had BR-HA PhC. Of the 20 patients with R PhC, 10 underwent SMV/PV resection. Of the 28 patients with BR-V PhC, 25 underwent SMV/PV resection and 3 underwent synchronous resection of the SMA. In the BR-SMA group, all 21 patients underwent SMV/PV resection, with synchronous resection of the SMA in 17 patients. In the BR-HA PhC group, all 9 patients underwent SMV/PV resection, with 7 patients undergoing synchronous resection of the HA and 1 patient undergoing resection of the SMA. Total pancreatectomy was performed in the remaining 2 BR-HA PhC patients who exhibited extensive involvement of the splenic artery beyond the bifurcation of the common hepatic and splenic arteries.

Intraoperative parameters, morbidity and mortality. The operative time was significantly longer in patients with BR-V, BR-SMA and BR-HA PhC, compared to that in patients with R PhC ($P < 0.001$) and the intraoperative blood loss was significantly greater for BR-SMA and BR-HA PhC compared to that for R and BR-V PhC ($P < 0.001$). Overall, 6 patients experienced postoperative hemorrhage. In the BR-V PhC group, postoperative hemorrhage occurred in 2 patients, 1 due to failure of the anastomosis of the SMA and the other due to rupture of the ligated stump of the right gastric artery. Both hemorrhages were induced by abdominal abscess without pancreatic fistula, and the latter was fatal. In the BR-SMA PhC group, postoperative hemorrhage occurred in 3 patients, 1 due to rupture of a pseudo-aneurysm induced by a pancreatic fistula, 1 due to rupture of an old aortic aneurysm induced by an abdominal abscess and 1 due to failure of the SMA anastomosis induced by an abdominal abscess. The resulting hemorrhage in the former 2 patients was fatal. In the BR-HA PhC group, postoperative hemorrhage occurred at the HA anastomosis site in 1 patient with severe arterial sclerosis. Although hemostasis was achieved, the patient succumbed to rapid recurrence of liver and lung metastases. Overall, there were 5 cases (6.4%) of perioperative mortality, with 4 deaths due to postoperative hemorrhage and 1 due to suffocation by failure of expectoration, without pneumonia or asthma.

Table I. Characteristics of the study population (n=78).

Characteristics	Resectable n=20	BR-V n=28	BR-SMA n=21	BR-HA n=9	P-value
Gender (M/F)	(13/7)	(14/14)	(15/6)	(7/2)	0.316
Age, years (range)	66 (52-77)	64 (44-78)	60 (38-78)	65 (53-79)	0.295
Operative time, min (range)	648 (422-811)	750 (528-1,015)	850 (690-1,045)	829 (580-1,110)	<0.001
PPPD/PD	6/14	6/22	4/17	1/8 ^a	<0.001
Vascular resection					
SMV/PV	10	25	21	9	
SMA	0	3	17	1	
HA	0	0	0	7	
Blood loss, ml (range)	662 (115-1,840)	883 (210-3,510)	2768 (250-8,880)	2981 (1,170-5,640)	<0.001
Surgical morbidity (major)	4 (20%)	3 (11%)	8 (38%)	3 (33%)	0.126
Hemorrhage	0	2	3	1	
Pancreatic fistula (grade B,C)	3	2	2	0	
PV thrombosis	0	0	1	0	
Arterial thrombosis	0	0	0	0	
Abdominal abscess	0	2	2	1	
Liver abscess	0	0	0	1	
Duodenal ulcer	0	0	1	0	
Perioperative mortality	0	1	2	2	0.120

^aTwo patients with total pancreatectomy were included. PD, pancreatoduodenectomy; PPPD, pylorus-preserving PD; SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery; HA, hepatic artery; BR, borderline resectable; BR-V, BR involving the SMV or PV.

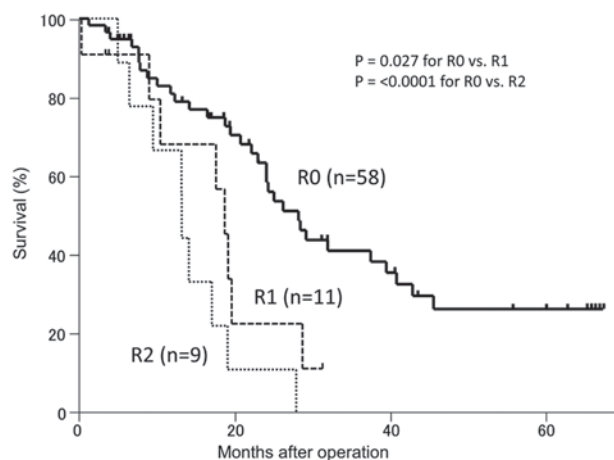


Figure 1. Kaplan-Meier survival curves for 78 patients with pancreatic ductal adenocarcinoma grouped according to their resectability status. The differences were statistically significant (log-rank test). R, resectable; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor.

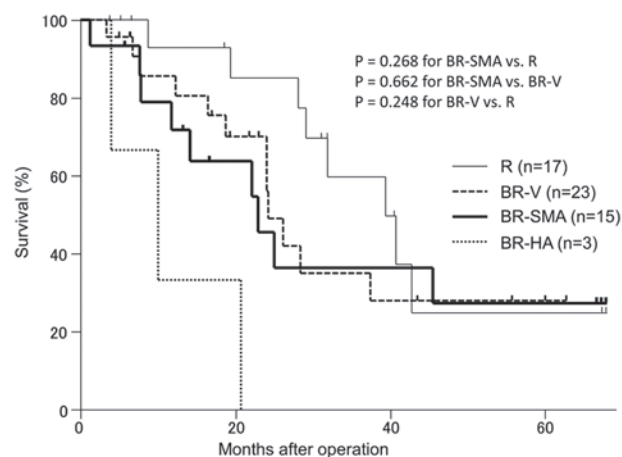


Figure 2. Kaplan-Meier survival curves for 58 patients who achieved R0 resection according to the vascular infiltrations (logrank test). R, resectable; BR, borderline resectable; SMA, superior mesenteric artery; HA, hepatic artery; BR-V, BR involving the superior mesenteric or portal vein.

Histopathology. The histopathological results of the patients are summarized in Table II. All the patients had histopathologically confirmed pancreatic ductal adenocarcinoma. The microscopic R0 rates were 85% (17/20), 82% (23/28), 71% (15/21) and 33% (3/9) in the R, BR-V, BR-SMA and BR-HA PhC groups, respectively. Vascular infiltration was defined as tumor clearance of <1 mm. The histopathological analysis of the BR-SMA or BR-HA PhC groups revealed evidence of SMA or HA infiltration in 20 (95%) and 9 (100%) patients, respectively (Table II).

Survival. The median survival time (MST) and the 5-year survival rate were 22 months and 26% for the R0 patients, respectively (Fig. 1). No patients with microscopic residual tumor (R1) or macroscopic residual tumor (R2) remained alive at 3 years postoperatively. For the R0 cases, the MSTs and 5-year survival rates were 31 months and 25% for the R PhC group, 22 months and 28% for the BR-V PhC group and 17 months and 27% for the BR-SMA PhC group, respectively (Fig. 2), with no statistically significant difference among these

Table II. Histopathology.

Tumor characteristics and resectability	R (n=20)	BR-V (n=28)	BR-SMA (n=21)	BR-HA (n=9)	P-value
T stage					<0.001
T1	3	2	0	0	
T2	0	0	0	0	
T3	17	25	11	2	
T4	0	1	10	7	
N stage					0.069
N0	9	6	6	0	
N1	11	22	15	9	
Grade					0.651
G1	6	5	4	1	
G2	12	18	16	6	
G3	2	5	1	2	
Resectability status (%)					0.062
R0	17 (85)	23 (82)	15 (71)	3 (33)	
R1	2 (10)	3 (11)	2 (10)	2 (22)	
R2	1 (5)	2 (7)	4 (19)	4 (45)	
Vascular infiltration ^a					
SMV/PV	2	17	19	9	
SMA	0	0	20	1	
HA	0	1	0	9	

^aVascular infiltration positivity was defined as tumor clearance of <1 mm. R, resectable; R0, no residual microscopic tumor; R1, residual microscopic tumor; R2, residual macroscopic tumor; SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery; HA, hepatic artery; BR, borderline resectable; BR-V, BR involving the SMV or PV.

groups. Overall, 7 patients remained alive at 5 years postoperatively (2 patients in the R PhC group, 2 patients in the BR-V PhC group and 3 patients in the BR-SMA PhC group).

Discussion

Surgical resection is the only potentially curative approach for the management of PhC. Our strategy for surgical extirpation of PhC comprised total meso-pd resection, as a primary lymphatic basin resection, and VR for R0 resection margins, when necessary. In selected patients with arterial involvement, arterial en bloc resection for PhC may result in an overall survival comparable to that obtained with standard resection for R PhC and improved compared to that obtained with palliative bypass for BR PhC (7,8). In the present study, the prognoses of the BR-V and BR-SMA PhC groups were comparable to that of the R PhC group; however, the BR-HA PhC group had a significantly worse prognosis. For BR-HA PhC, it was difficult to perform R0 resection and hepatic recurrences developed within 1 year postoperatively in 6 of the 9 cases.

Achievement of an R0 resection margin status following surgery is essential for the prolonged survival of patients with PhC. Although the demarcation of the dissection line for R0 resection using preoperative imaging is carefully performed, local recurrence due to microscopically positive margins is common, particularly at the SMA (4,9,10). The

involvement of the SMA in PhC is termed extrapancreatic PLX invasion and is an indicator of poor prognosis (11-18). The majority of PhCs are scirrhous and are characterized by a fibrous stroma with scattered carcinoma cells. The normal PLX is almost always composed of adipose tissue, with a low computed tomography (CT) number, whereas PLX invasion is fibrous and imaged by MDCT as a coarse reticular pattern or a mass and strand pattern connecting to the main lesion of the carcinoma (2). The extent of the cancer nest is assessed by the fibrous changes connected to the main tumor. Histologically, these fibrous changes consist of desmoplastic tissue with scattered carcinoma cells and have been described as 'peritumoral inflammation' or 'mimicking tumor invasion', according to the low density of the carcinoma cells. To avoid an R1 resection margin during curative surgery, the desmoplastic cancer nest should be resected en bloc, with a macroscopic safety margin of 5 mm. The extent of this safety margin remains controversial, but a microscopic margin of >1 mm on histological examination is recommended (19-25). As preoperative demarcation of the dissection line is assessed by MDCT, which is a crucial decision and must include an adequate safety margin macroscopically. At our institution, VR was defined as abutment or near abutment of the aforementioned vessels by the cancer nest. Therefore, careful review of CT images is crucial in determining the extent of PLX invasion. A window level and width of 40 and 350 HU, respectively, are recommended.

The mesentery is a fan-shaped fold of the peritoneum through which the blood vessels, lymph vessels and nerves of the abdominal visceral organs pass. Therefore, the mesentery corresponds to the initial field of infiltration of carcinoma (26). Our 'meso-pd' concept refers to the mesentery of the pancreatic head and the duodenum, which is a firm and well-vascularized perineural lymphatic layer located dorsal to the pancreas that reaches behind the mesenteric vessels and has been described as the 'mesopancreas' (27). However, the term mesopancreas is insufficient, as this mesentery is common to the pancreatic head and the duodenum. Therefore, we considered the term 'meso-pd' to be more descriptive of this mesentery. The meso-pd is fan-shaped and its trunk is the inferior pancreatoduodenal artery, which is a tributary of the SMA. The meso-pd is a counterpart of the mesocolon and the mesentery, including the meso-pd, rotates between the 6th and 12th week of the prenatal period. The envelope of fibrous sheath or fascia enclosing the meso-pd is invisible (28), since the original fascia is fused and lost during embryonal development. Therefore, a total meso-pd resection was performed with respect to the PLX surrounding the SMA and including the anterior renal fascia. The caudal border of the meso-pd is the lower level of the third duodenal portion, where tiny lymphatic emboli were observed (29).

We determined the manner of lymphatic extension and PLX infiltration of the PhC depending on whether the tumor originated from the embryonic dorsal or ventral pancreatic bud (30,31). Tumors confined to the ventral pancreas extend toward the SMA, whereas tumors confined to the dorsal pancreas extend towards the common HA or hepatoduodenal ligament. If the tumor infiltrates deeply into both areas, the cancer is likely to extend in both directions. Therefore, the meso-pd was considered to be the mesentery of the embryonic ventral pancreas and total meso-pd resection would be essential for PhC confined to the ventral pancreas. We developed an aggressive surgical method termed 'augmented regional pancreatoduodenectomy (ARPD)' in 2002 for the resection of the pancreatic head together with the SMA and SMV/PV for cases of PhC (6). This procedure was performed in 21 patients: 3 with BR-V PhC, 17 with BR-SMA PhC and 1 with BR-HA PhC. The 3 patients with BR-V and the patient with BR-HA were 'nearly BR-SMA cases'; therefore, ARPD was performed. ARPD has theoretical advantages for en bloc and curative resection of carcinomas of the ventral pancreas. By contrast, the mesentery corresponding to the embryonic dorsal pancreas is currently unclear, although it is associated with the HA. Survival following HA resection was poor in our study and our procedure, which focuses on the meso-pd, was shown to be insufficient for the treatment of carcinomas of the dorsal pancreas.

Intraoperative blood loss during ARPD was higher in patients with BR-SMA PhC compared to that in patients with R or BR-V PhC; this difference was most likely due to the improvement in the operative technique with increased experience, with an estimated blood loss of 615 ± 273 ml in the last 4 patients. All the reported deaths occurred in patients who were operated on within the first 3 years. Postoperative hemorrhage was fatal, particularly when induced by a pancreatic fistula or intra-abdominal infection. Failure of the arterial anastomosis occurred in 3 patients, with 1 patient successfully treated by arterial re-anastomosis. The results of the present study indicate that the en bloc resection of the meso-pd with major VR for R0

may be suitable for patients with BR-V PhC and BR-SMA PhC, but not for those with BR-HA PhC.

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