Tanno S, Nakano Y, Nishikawa T, et al. Natural history of branch duct intraductal papillary-mucinous neoplasms of the pancreas without mural nodules: long-term follow-up results. Gut. 2008;57(3):339–43.

Tanno S, Nakano Y, Sugiyama Y, et al. Incidence of synchronous and metachronous pancreatic carcinoma in 168 patients with branch duct intraductal papillary mucinous neoplasm. Pancreatology. 2010a;10(2–3):173–8.

Tanno S, Nakano Y, Koizumi K, et al. Pancreatic ductal adenocarcinomas in long-term follow-up patients with branch duct intraductal papillary mucinous neoplasms. Pancreas. 2010b;39(1):36–40.

Uehara H, Nakaizumi A, Ishikawa O, et al. Development of ductal carcinoma of the pancreas during follow-up of branch duct intraductal papillary mucinous neoplasm of the pancreas. Gut. 2008;57(11):1561–5.

Uehara H, Ishikawa O, Katayama K, et al. Size of mural nodule as an indicator of surgery for branch duct intraductal papillary mucinous neoplasm of the pancreas during follow-up. J Gastroenterol. 2011;46(5):657–63.

Yamaguchi K, Ohuchida J, Ohtsuka T, et al. Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinoma of the pancreas. Pancreatology. 2002;2(5):484–90.

Yamaguchi K, Kanemitsu S, Hatori T, et al. Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN. Pancreas. 2011;40(4):571–80.

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ORIGINAL ARTICLE

A replaced right hepatic artery adjacent to pancreatic carcinoma should be divided to obtain R0 resection in pancreaticoduodenectomy

Ken-ichi Okada · Manabu Kawai · Seiko Hirono · Motoki Miyazawa · Atsushi Shimizu · Yuji Kitahata · Masaji Tani · Hiroki Yamaue

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Abstract
Background The aim of the present study was to clarify the optimal surgical strategy in the patients with right hepatic artery (RHA) variation undergoing pancreaticoduodenectomy (PD) based on the tumor position and the R1 resection rate.
Methods A total of 180 consecutive patients who underwent PD for pancreatic ductal adenocarcinoma between January 2000 and May 2013 were evaluated for RHA variation, surgical outcome, and the R1 resection rate retrospectively. In this study, we defined three types of tumors: (i) the resectable type, where tumors were situated more than 10 mm away from the root of the replaced right hepatic artery (rRHA)/replaced common hepatic artery (rCHA); (ii) the adjacent type, where tumors were situated within 10 mm from the root of the rRHA/rCHA without tumor abutment of the superior mesenteric artery (SMA); and (iii) the borderline resectable type, where the tumor abuts the SMA, but does not to exceed 180° of the circumference of the vessel wall.
Results Twenty-five patients were identified to have a RHA variation in preoperative imaging studies. There were 16 patients with resectable type tumors, five with adjacent type tumors, and four with borderline resectable tumors. The rRHA/rCHA was preserved in 14 (88 %) patients with the resectable type, all of the patients with the adjacent type and none of the patients with the borderline type pancreatic carcinomas. The R1 resection rates were significantly higher in patients with adjacent/borderline resectable type tumors (78 %) compared to those with resectable type tumors (6 %) (p=0.001).
Conclusion The rRHA of the adjacent type pancreatic carcinoma should be divided to improve the rate of R0 resection.

Keywords Replaced right hepatic artery · Pancreaticoduodenectomy · Borderline resectable disease

K.-i. Okada · M. Kawai · S. Hirono · M. Miyazawa · A. Shimizu · Y. Kitahata · M. Tani · H. Yamaue (✉)
Second Department of Surgery, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-8510, Japan
e-mail: yamaue-h@wakayama-med.ac.jp

K.-i. Okada
e-mail: okada@wakayama-med.ac.jp

M. Kawai
e-mail: kawai@wakayama-med.ac.jp

S. Hirono
e-mail: seiko-h@wakayama-med.ac.jp

M. Miyazawa
e-mail: mo-0702@wakayama-med.ac.jp

A. Shimizu
e-mail: atsus28@wakayama-med.ac.jp

Y. Kitahata
e-mail: yuji-kh@wakayama-med.ac.jp

M. Tani
e-mail: matani@wakayama-med.ac.jp

Introduction

Most cases of pancreatic carcinoma are discovered at an advanced stage. Among these cases, the radical resection rate remains less than 23 % [1]. In the current therapeutic strategy for pancreatic ductal adenocarcinoma, radical resection with a sufficient dissection margin is given priority [2–5]. Pancreatic surgeons sometimes encounter right hepatic artery (RHA) variations, including a replaced right hepatic artery (rRHA) or replaced common hepatic artery (rCHA), which have been reported to be present in 19–24 % of patients who undergo pancreaticoduodenectomy (PD) [6–9].

A recent study reported that the presence of RHA variation in patients with pancreatic carcinoma did not affect the resectability [7–9], although the relationship between the resectable/borderline resectable category and the risk of an R1 resection in patients with RHA variation has not been well discussed [10, 11]. Therefore, more precise classification for patients with rRHA based on the National Comprehensive Cancer Network (NCCN) criteria should be developed, and the indications for preservation of the rRHA/rCHA should be investigated in detail to avoid R1 resection. Although the definition of R0 has been controversial [12–14], the distance between the tumor and the vascular structures directly influences the local radicality of the resection. One of the main reasons for R1 resection is the presence of tumor abutment of a major artery. The aim of the present study was to clarify the optimal resection strategy in patients with RHA variation undergoing PD based on the tumor position and the R1 resection rate.

Patients and methods

Patient characteristics and perioperative therapy Between January 2000 and May 2013, 180 consecutive patients underwent pancreaticoduodenectomy (PD) with D2 node dissection, including 155 (86 %) with a normal right hepatic artery (RHA) and 25 (14 %) with RHA variations, including 23 replaced right hepatic arteries (rRHA) and two replaced common hepatic arteries (rCHA), for invasive ductal adenocarcinoma in the pancreatic head at Wakayama Medical University Hospital. We have performed PD with antecolic duodenojejunostomy since April 2004, with pylorus-resecting fashion since April 2009 based on the results of our two prospective, randomized, controlled trials [15, 16]. The patients with invasive ductal carcinoma derived from an intraductal papillary mucinous neoplasm (IPMN) were excluded from this study. All of the patients with tumor encasement of the rRHA were expected to undergo preoperative coil embolization of the rRHA to enlarge the collateral pathways and prevent ischemia-related complications, regardless of the diameter of the rRHA. In this period, the indication of preoperative coil embolization for rRHA was tumor encasement of the rRHA. We did not resect the para-aortic lymph nodes, but did perform D2 lymph node dissection along the hepatic artery, celiac axis, and superior mesenteric artery (SMA), with semicircumferential dissection of the right/posterior-sided nerve plexuses around the SMA in the present study [17].

Among the patients with a normal RHA, there were five patients with Stage IA, two with Stage IB, 49 with Stage IIA, 94 with Stage IIB, one with Stage III, and four with Stage IV disease; among the patients with RHA variation, one patient had Stage IA, one had Stage IB, three had Stage IIA, 18 had Stage IIB, and two had Stage IV disease [18] (Table 1).

During the period between January 2000 and April 2010, no patients with pancreatic carcinoma received neoadjuvant therapy; patients were recommended to receive postoperative adjuvant chemotherapy using systemic intravenous gemcitabine since January 2002. The dose and schedule were based on the CONKO-001 study [19]. During the period between May 2010 and December 2011, the patients with borderline resectable [10] pancreatic head carcinoma were planned to receive S-1 standard-dose chemotherapy for nine weeks and multifield radiotherapy focused on the retropancreatic tissue for a total of 50 Gy over a five-week period. After three weeks of rest for both therapies, the patients without progression of disease or new distant metastasis underwent PD. Since January 2012, the patients with borderline resectable pancreatic head carcinoma were planned to receive S-1 standard-dose/gemcitabine 800 mg/m^2 chemotherapy preoperatively.

The safety and outcomes of the operation in patients with rRHA/rCHA are discussed in terms of the stage, curability, complications, and survival compared with the patients without rRHA. All tissue specimens were reviewed after resection. The microscopically positive sites of the peripancreatic tissue margin were identified by macroscopic/microscopic histopathological examinations of the pathological specimens. Every patient was followed up in the outpatient clinic every one to three months. The clinical data and follow-up information for each patient were obtained from the medical records.

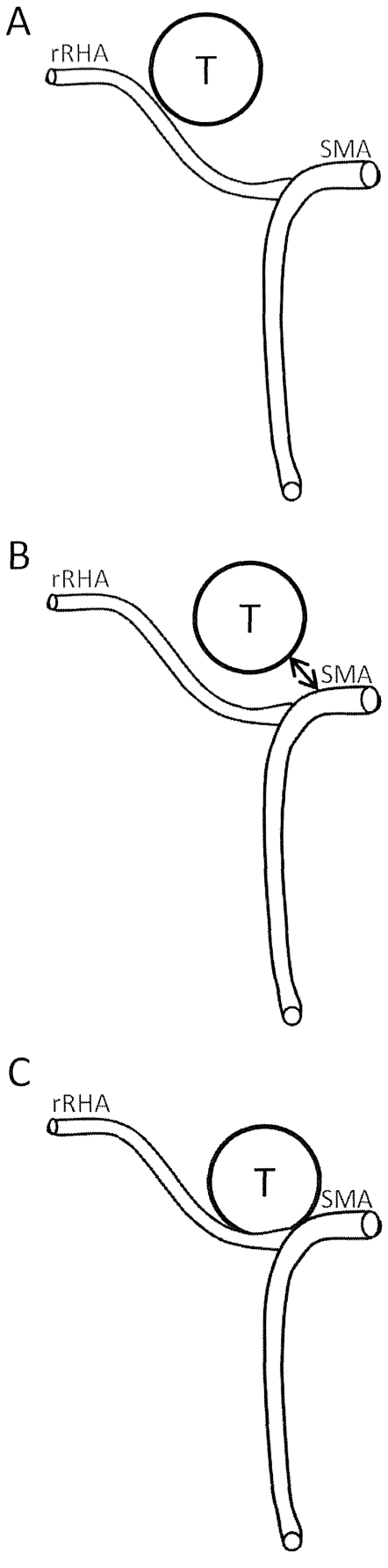
The types of relationships between the tumor and RHA variation The following terminology was used to define and classify three patterns of radicality in terms of the relationship between the tumor and the root of the rRHA/rCHA retrospectively. Resectable type: the patients with tumors situated more than 10 mm away from the root of the rRHA, with or without involvement of the rRHA (Fig. 1a). The patients with tumors situated within 10 mm from the root of the rRHA without tumor abutment of the SMA, who were not classified as having the borderline resectable type, were classified as having the adjacent type in this study (Fig. 1b). Borderline resectable type: the patients with tumor abutment of the SMA that did not exceed 180° of the circumference of the vessel wall, according to NCCN criteria (Fig. 1c) [10]. In patients with RHA variation, the distances between the proximal edge of the tumor and the root of the rRHA/rCHA were measured on computed tomography (CT) images.

Imaging diagnosis of arterial anatomy and resectability Between January 2000 and May 2005, all patients were expected to undergo angiography to obtain more detailed information of arterial anatomy prior to PD in addition to the CT scan. Based on the findings, we performed preoperative coil embolization for patients with rRHA encasement. Since June 2005, we have used plain/dynamic

Table 1 The patient characteristics and surgical outcomes

	Without a replaced RHA (n=155) (86 %)	With a replaced RHA (n=25) (14 %)	p value
Age at surgery (years)	68±10	68±9	0.896
Gender (n)			
Male	88	11	0.281
Female	67	14	
BMI (kg/m^2)	22±3	23±4	0.227
Tumor size (cm)	26±8	28±6	0.134
Stage (n)			
IA	5 (3.2 %)	1 (4.0 %)	0.999
IB	2 (1.3 %)	1 (4.0 %)	0.363
IIA	49 (31.6 %)	3 (12.0 %)	0.056
IIB	94 (60.6 %)	18 (72.0 %)	0.375
III	1 (0.7 %)	0	0.999
IV	4 (2.6 %)	2 (8.0 %)	0.196
Neoadjuvant therapy (n)	12 (7.7 %)	4 (16.0 %)	0.245
Adjuvant therapy (n)	129 (83.2 %)	20 (80.0 %)	0.775
Portal vein resection (n)	61 (39.4 %)	10 (40.0 %)	0.999
SMA plexuses hemidissection (n)	151 (97.4 %)	23 (92.0 %)	0.196
Length of operation (min)	417±86	420±74	0.865
EBL (ml)	997±1008	1046±762	0.778
Transfusion (+) (n)	62 (40.0 %)	11 (44.0 %)	0.827
Residual tumor (n)			
R0	125 (80.6 %)	17 (68.0 %)	0.185
R1	30 (19.4 %)	8 (32.0 %)	

RHA right hepatic artery, *BMI* body mass index, *Stage* the stage based on the TNM classification, *SMA* superior mesenteric artery, *EBL* estimated blood loss



◀ **Fig. 1** A schematic drawing showing the relationship between the tumor and the root of the replaced right hepatic artery (rRHA). **a** Resectable type: a potentially resectable tumor with/without rRHA involvement. **b** Adjacent type: a tumor situated within 10 mm from the root of the rRHA without tumor abutment of the superior mesenteric artery. **c** Borderline resectable type: a tumor that abuts the superior mesenteric artery but not exceeding 180 ° of the circumference of the vessel wall according to NCCN guidelines *Double-headed arrows* indicate that the distance between the tumor and the root of the rRHA is ≤10 mm. *T* pancreatic carcinoma, *SMA* superior mesenteric artery, *rRHA* replaced right hepatic artery

multidetector computerized tomography (MD-CT) with 3D-CT image as a substitute for the angiography. The conditions for dynamic MD-CT imaging were as follows: contrast material injection: 99 ml/60 kg, 4 ml/s (0–25 s), shooting on 30 s (early arterial phase), 45 s (late arterial phase), 65 s (portal venous phase), and 180 s (equilibrium phase), 1.25-mm thick from the neck to the pelvis (GE Healthcare, Light Speed VCT).

Definition of postoperative complications We evaluated the liver ischemia with the hypodensity area on enhanced CT with elevated aminotransferase. Delayed gastric emptying (DGE) was defined according to a consensus definition and the clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery (ISGPS) [20]. A pancreatic fistula was defined by the International Study Group of Pancreatic Fistula (ISGPF) guidelines [21]. Intra-abdominal hemorrhage was defined by the ISGPS [22]. Biliary fistulae were defined as the presence of bile in the drainage fluid that persisted on postoperative day 4. Surgical site infections included surgical wounds or intra-abdominal abscesses with positive cultures. An intra-abdominal abscess was defined as intra-abdominal fluid collection with positive cultures, identified by ultrasonography or CT that was associated with a persistent fever and elevation of the white blood cell count. The global morbidity rate and the type of complications were evaluated by Dindo's classification [23]. Patients were discharged only when they fulfilled the following criteria: they could return to their preoperative activities of daily living, they had no drains, no deep-site infections, normal laboratory data, and the possibility for oral nutrition above the basal metabolic level. Mortality was defined as death within 30 days after surgery.

Pathological work-up Macroscopically identified dissected surface was examined microscopically regarding the presence of tumor cells. We defined the R1-status as the presence of tumor cells at the resection margin.

Statistical analysis Descriptive statistics were employed to examine the demographic characteristics of the study population. Statistical comparisons between two groups were made

using the Chi-square statistic, Fisher's exact test or the Mann–Whitney *U* test, where appropriate. The baseline characteristics, surgical outcomes, and postoperative complications were compared between the patients with and without RHA variation by means of the Chi-square test for continuous and categorical variables. A value of $p<0.05$ was considered to indicate a statistically significant difference. All of the analyses were performed using the statistical software package SPSS II (version 20.0; SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics In the present study, 25 patients were identified to have RHA variation by preoperative imaging studies. The variations of the RHA included 22 rRHA from the superior mesenteric artery (SMA), two rCHA from SMA and one RHA directly branched from the aorta. Cases of accessory RHA were excluded from this study, and those were treated as normal variation [24]. The accuracy to identify vascular anomalies by the two independent attending radiologists was 100 %, and all rRHAs were identified preoperatively. Figure 2 presents a diagnostic and therapeutic flowchart of 180 patients. There were no patients with occlusion of the rRHA due to the tumor ingrowth, but six patients were diagnosed to have the rRHA encasement on CT (Fig. 3a, b). Two patients in the resectable type and all of the borderline resectable type were diagnosed to have encasement of rRHA. These six patients underwent preoperative coil embolization for the rRHA (Fig. 3c) and PD combined with rRHA resection. Nineteen patients underwent PD that preserved the rRHA ($n=17$)/rCHA ($n=2$). A histopathological examination revealed an R1 site in three patients (50 %) in the rRHA resection group and five patients (26 %) in the rRHA/rCHA preservation group ($p=0.344$). The median number of resected and infiltrated lymph nodes were 22 (4–64) and 2 (0–26). Table 1 shows the characteristics and surgical outcomes of 180 consecutive patients with/without rRHA/rCHA. There were no significant differences between the two groups, including the R0 resection rates. In this series, the number of patients who received systemic gemcitabine given by intravenous infusion postoperatively was 144 (80 %), four patients with arterial variants received both neoadjuvant and adjuvant therapies, and 20 received only adjuvant therapies. One patient refused to receive both neoadjuvant and adjuvant therapy (Table 1.). Eighty-nine of 180 patients finished adjuvant chemotherapy as scheduled; the others refused because of poor general condition, early recurrence, and prolonged hospitalization.

The radicality in terms of the types of relationships between the tumor and RHA variation There were 16 patients with resectable type tumors, five with adjacent type tumors, and four with borderline resectable type tumors; the R1 resection rates were 6 % ($n=1$), 80 % ($n=4$), and 75 % ($n=3$), respectively (Fig. 4), i.e., the accuracy of preoperative prediction for R0 resection was 94 % in resectable type, and 20 % of adjacent type. The R1 resection rates were significantly higher in patients with adjacent/borderline resectable type tumors (78 %) compared to those with resectable type tumors (6 %) ($p=0.001$). The rRHA was preserved in 14 (88 %) patients with the resectable type tumors, all of the patients with the adjacent type ($n=5$) and none of the patients with the borderline type pancreatic carcinoma. The histopathological examination revealed positive margins for tumor infiltration in eight patients (32 %) with right hepatic artery variation. Microscopically positive margins were identified frequently in two

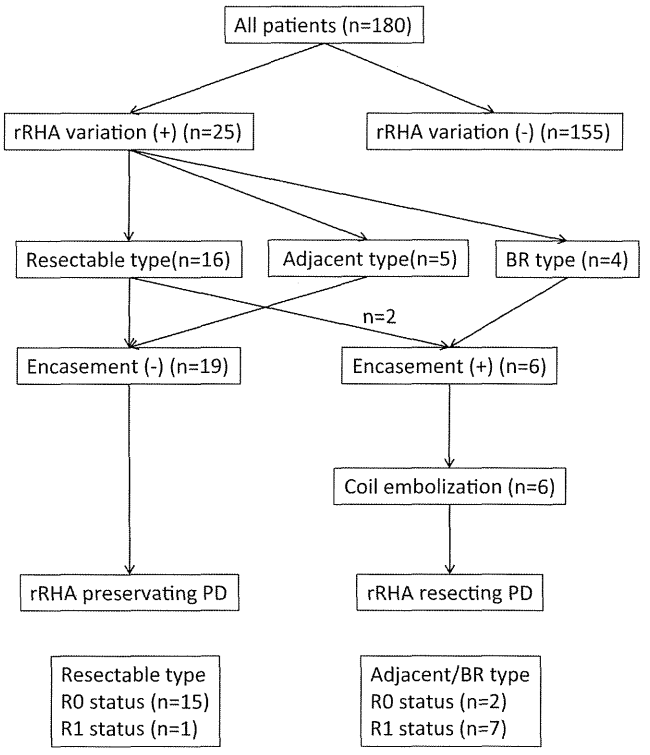


Fig. 2 A diagnostic and therapeutic flowchart of 180 patients with pancreatic ductal adenocarcinoma. Resectable type: the patients with tumors situated more than 10 mm away from the root of the replaced right hepatic artery (rRHA), with or without involvement of the rRHA. The patients with tumors situated within 10 mm from the root of the rRHA without tumor abutment of the SMA, who were not classified as having the borderline resectable type, were classified as having the adjacent type. Borderline resectable type: the patients with tumor abutment of the SMA that did not exceed 180° of the circumference of the vessel wall, according to NCCN criteria. Two patients in the resectable type were diagnosed to have encasement in the distal side of rRHA. All patients in the borderline resectable type were diagnosed to have encasement in the root of rRHA. Six patients underwent preoperative coil embolization for the rRHA and pancreaticoduodenectomy (PD) combined with rRHA resection. Nineteen patients underwent rRHA preserving PD. The R1 resection rates were significantly higher in patients with adjacent/borderline resectable type tumors (78 %) compared to those with resectable type tumors (6 %) ($p=0.001$). *BR* borderline resectable

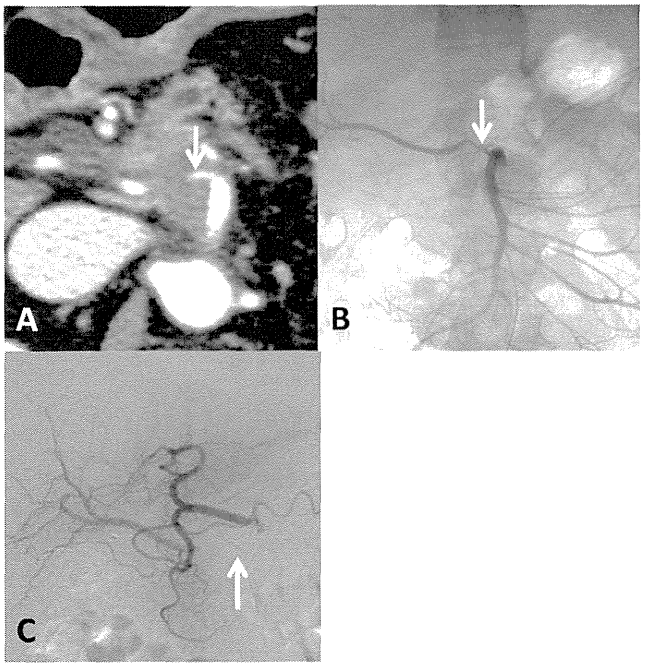


Fig. 3 **a**, **b** The images of computed tomography (**a**)/angiography (**b**) showed the tumor encasement (*arrow*) in the root of replaced right hepatic artery (rRHA) of a patient with borderline resectable type pancreatic ductal carcinoma. The patient underwent preoperative coil embolization after neoadjuvant chemoradiation therapy prior to pancreaticoduodenectomy with rRHA combined resection. **c** Immediately after the embolization of the root of the rRHA with two microcoils (*arrow*), the vascular flow in distal rRHA from intrahepatic communication artery was confirmed

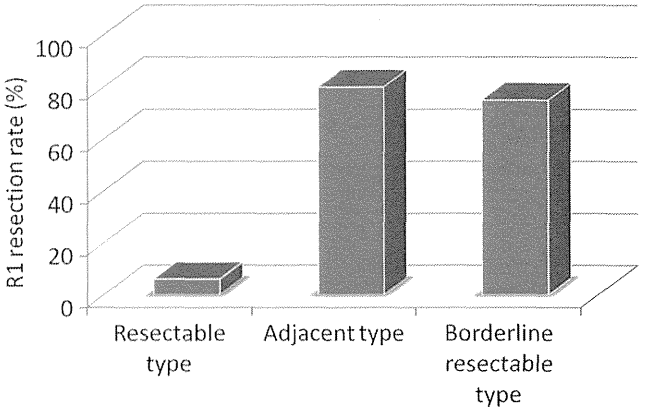


Fig. 4 The R1 resection rates for the three types of relationships between the tumor and the replaced right hepatic artery. The rates were 6 % (n=1), 80 % (n=4), and 75 % (n=3), respectively, for resectable, adjacent, and borderline resectable type tumors

dissected sites. The root of rRHA/rCHA in the periarterial nerve plexuses around SMA was involved in three patients, and the retropancreatic tissue adjacent to the periarterial nerve plexuses around the rRHA/rCHA was involved in five patients. In resectable/adjacent type cases, all positive margins (n=5) were identified in the retropancreatic tissue adjacent to the periarterial nerve plexuses around the rRHA/rCHA. All positive margins were identified at the dissection surface, and there was no histopathological evidence of tumor cell infiltration into the artery.

Postoperative complications Table 2 shows the postoperative complications in patients with a normal RHA and RHA variation. There were no cases of hepatic infarction or hepatic abscess in patients who underwent preoperative coil embolization in this series. Postoperative cholangitis due to arterial devascularization was not found in this series. The incidence of postoperative pancreatic fistula development, DGE, and intra-abdominal hemorrhage revealed no significant differences between the two groups. The grading of the overall postoperative complications evaluated by Dindo's classification also revealed no significant differences between the groups. Four patients underwent reoperation due to an early intra-abdominal hemorrhage (n=1), non-occlusive mesenteric ischemia (n=1), necrosis of the transverse colon (n=1), and abdominal compartment syndrome after intra-abdominal hemorrhage (n=1). One patient died on postoperative day 22 due to non-occlusive mesenteric ischemia.

Survival The median follow-up for all patients was 15 (0–119) months. The estimated one-year survival rate was 63.2 %, the estimated two-year survival rate was 35.5 %, and the estimated median survival time was 17 months in all patients. The patients who underwent R0 resections (n=17) showed a better survival than those with R1 resections (n=8) in the RHA variation group (p=0.073, log-rank test).

The distance between the edge of the tumor and the root of the replaced right/common hepatic artery The relationship between the radicality of the resection and the distance between the edge of the tumor and the rRHA/rCHA root in patients who underwent PD is shown in Fig. 5. Microscopically positive margins were detected more frequently in the patients with tumors situated ≤10 mm from the rRHA/rCHA (n=8) than in those with tumors >10 mm from the rRHA/rCHA (n=17) (p=0.001, $\chi 2$ test).

Discussion

Although recent studies have reevaluated or redefined the R1 resection in pancreatic carcinoma, R0 resection is still an essential and surgical requirement for long-term survival [12–14]. In this study, the investigation of the histopathological features of the risk of R1 surgery of all cases revealed that only serosal and retropancreatic tumor invasion increased the risk of R1 resection. The presence of an RHA variation itself did not affect the R1 resection rate. On the other hand, the previous literature indicated that the invasion of the artery is a

Table 2 The postoperative complications and outcomes

	Without a replaced RHA (n=155)	With a replaced RHA (n=25)	p value
Liver ischemia	0	0	
Pancreatic fistula[a]	19	3	0.999
Grade A	10	2	0.675
Grade B	5	1	0.999
Grade C	4	0	0.999
Delayed gastric emptying[b]	14	2	0.999
Grade A	6	0	0.999
Grade B	6	2	0.307
Grade C	2	0	0.999
Intra-abdominal hemorrhage[c]	6	0	0.999
Grade A	1	0	0.999
Grade B	0	0	
Grade C	5	0	0.999
Dindo's classification			
0, I, II	135	24	0.316
IIIa	8	1	0.999
IIIb	5	0	0.999
IVa	4	0	0.999
IVb	2	0	0.999
V	1	0	0.999
Reoperation	4	0	0.999
Mortality	1	0	0.999

RHA right hepatic artery

[a] Pancreatic fistula was defined according to the International Study Group of Pancreatic Surgeons

[b] Delayed gastric emptying was defined according to the International Study Group of Pancreatic Surgeons

[c] Intra-abdominal hemorrhage was defined according to the International Study Group of Pancreatic Surgeons

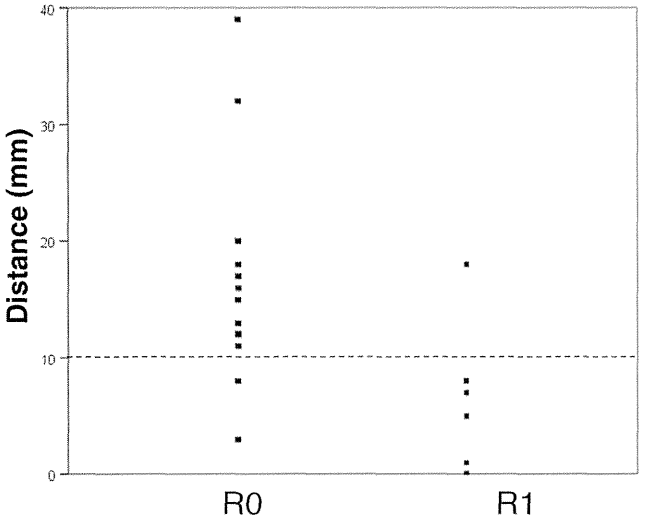


Fig. 5 The patients with tumors situated ≤10 mm from the replaced right hepatic artery had a greater incidence of R1 resection (p=0.001, χ2 test)

crucial prognostic factor for pancreatic carcinoma [25]. The proximity between the tumor and a major artery makes it difficult to obtain sufficient surgical margins. Therefore, the proximity of the pancreatic carcinoma to the right hepatic artery variations would be expected to correlate with a poor prognosis due to an increased R1 resection rate or the invasion of the rRHA/rCHA.

We previously reported that the patients with pancreatic body/tail carcinoma located within 10 mm from the root of the splenic artery had a greater incidence of R1 resection [26]. In the present study, we examined the impact of three different types of tumors, in terms of the distance between the tumor and the root of the rRHA/rCHA and the presence of arterial abutment of the SMA. Not only the borderline type but also the adjacent type showed a high R1 resection rate, and R1 resection correlates with a poor survival rate in patients without lymph node metastasis.

To improve the R0 rate (68 %) in patients with RHA variation, we investigated the positive surgical margins from resected specimens in patients who underwent PD. Eight of the 25 patients who underwent PD had microscopically positive margins at the nerve plexuses of the root of the rRHA/rCHA. In this series, five of the eight cases (63 %) who were positive for infiltration at the surgical margins were in the artery preservation group, and microscopically positive margins were frequently identified in the retropancreatic tissue adjacent to the periarterial nerve plexuses around the rRHA/rCHA in patients with the resectable or adjacent type pancreatic carcinoma. This result suggests that it is technically and oncologically difficult to achieve sufficient surgical margins for pancreatic carcinoma in patients with right hepatic artery variation who undergo PD, regardless of whether there is tumor abutment. In fact, we had made a decision to preserve an rRHA/rCHA for each case with the adjacent type of potentially resectable pancreatic carcinoma preoperatively. Therefore, we suggest that en bloc resection of the rRHA should be performed to obtain an R0 resection in patients with adjacent type pancreatic carcinoma who would otherwise undergo preservation of the rRHA [27].

The patients with rCHA which has to be preserved should be carefully selected for PD, as should the patients with borderline resectable/unresectable pancreatic carcinoma. In addition, our results also showed that the patients with tumors located within 10 mm from the root of the rRHA, i.e., adjacent/borderline resectable type pancreatic carcinoma, had a greater incidence of R1 curability. In particular, the R1 rate in the patients with the adjacent type pancreatic carcinoma, who tended to be treated the same as those with resectable type pancreatic carcinoma, was 80 %. Therefore, preoperative therapy may offer a better R0 resection rate for the patients with tumors located within 10 mm from the root of the rRHA, including cases of adjacent type pancreatic carcinoma.

More effective regimens of neoadjuvant chemotherapy should be established for unresectable pancreatic carcinoma in the future [28, 29] because the rRHA resection strategy did not increase the R0 resection rate in patients with borderline resectable type tumors in this study.

The major limitation of this study was that the survival rates between the patients who underwent R0 and R1 resection were not significantly different due to the small numbers of patients and the shorter follow-up period in patients with RHA variations. Although the small number in the subgroups, in particular adjacent and borderline may not be sufficient to draw any strong conclusion, the adjacent type would be a distinct pitfall for pancreatic surgeons. Additional studies in a larger number of patients and with a longer follow-up period are warranted to confirm our present findings.

In conclusion, PD is a feasible and safe surgical modality in patients with rRHA similar to patients with normal variants. The R1 resection rate in patients who underwent rRHA preserving PD was high in patients with adjacent type pancreatic carcinoma. rRHA resecting PD of the patients with adjacent type pancreatic carcinoma would improve the R0 resection rate.

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Conflicts of interest None.

References

1. Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Castillo CF, Deshpande V et al (2013) Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? Ann Surg 257: 731–736

2. Motoi F, Ishida K, Fujishima F, Ottomo S, Oikawa M, Okada T et al (2013) Neoadjuvant chemotherapy with gemcitabine and S-1 for resectable and borderline pancreatic ductal adenocarcinoma: results from a prospective multi-institutional phase 2 trial. Ann Surg Oncol
3. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB et al (2008) Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg 206:833–846
4. Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H et al (2006) Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol 13:1035–1046
5. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC (2009) Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 16:1727–1733
6. Hiatt JR, Gabbay J, Busuttil RW (1994) Surgical anatomy of the hepatic arteries in 1000 cases. Ann Surg 220:50–52
7. Turrini O, Wiebke EA, Delpero JR, Viret F, Lillemoe KD, Schmidt CM (2010) Preservation of replaced or accessory right hepatic artery during pancreaticoduodenectomy for adenocarcinoma: impact on margin status and survival. J Gastrointest Surg 14:1813–1819
8. Kim PT, Temple S, Atenafu EG, Cleary SP, Moulton CA, McGilvray ID et al (2013) Aberrant right hepatic artery in pancreaticoduodenectomy for adenocarcinoma: impact on resectability and postoperative outcomes. HPB (Oxford). doi:10.1111/hpb.12120
9. Eshuis WJ, Olde Loohuis KM, Busch OR, van Gulik TM, Gouma DJ (2011) Influence of aberrant right hepatic artery on perioperative course and longterm survival after pancreatoduodenectomy. HPB (Oxford) 13:161–167
10. Tempero MA, Arnoletti JP, Behrman S, Ben-Josef E, Benson AB 3rd, Berlin JD et al (2010) Pancreatic adenocarcinoma. J Natl Compr Cancer Netw 8:972–1017
11. Tempero MA, Arnoletti JP, Behrman SW, Ben-Josef E, Benson AB 3rd, Casper ES et al (2012) National Comprehensive Cancer Networks. Pancreatic adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines. J Natl Compr Cancer Netw 10:703–713
12. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A (2006) Redefining the R1 resection in pancreatic cancer. Br J Surg 93:1232–1237
13. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H et al (2008) Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 15:1651–1660
14. Rau BM, Moritz K, Schuschan S, Alsfasser G, Prall F, Klar E (2012) R1 resection in pancreatic cancer has significant impact on long-term outcome in standardized pathology modified for routine use. Surgery 152:S103–S111
15. Tani M, Terasawa H, Kawai M, Ina S, Hirono S, Uchiyama K, Yamaue H (2006) Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. Ann Surg 243:316–320
16. Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, Uchiyama K, Yamaue H (2011) Pylorus ring resection reduces delayed gastric emptying in patients undergoing pancreatoduodenectomy: a prospective, randomized, controlled trial of pylorus-resecting versus pylorus-preserving pancreatoduodenectomy. Ann Surg 253:495–501
17. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, Pancreas Cancer Working Group et al (2005) A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surg 138:618–628
18. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (2010) AJCC Cancer Staging Manual, 7th edn. Springer, New York
19. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K et al (2007) Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 297:267–277
20. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR et al (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 142:761–768
21. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, International Study Group on Pancreatic Fistula Definition et al (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 138:8–13
22. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ et al (2007) Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 142:20–25
23. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
24. Winston CB, Lee NA, Jarnagin WR, Teitcher J, DeMatteo RP, Fong Y, Blumgart LH (2007) CT angiography for delineation of celiac and superior mesenteric artery variants in patients undergoing hepatobiliary and pancreatic surgery. AJR Am J Roentgenol 189:W13–W19
25. Kanda M, Fujii T, Sahin TT, Kanzaki A, Nagai S, Yamada S et al (2010) Invasion of the splenic artery is a crucial prognostic factor in carcinoma of the body and tail of the pancreas. Ann Surg 251:483–487
26. Okada K, Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A et al (2013) Surgical strategy for patients with pancreatic body/tail carcinoma: who should undergo distal pancreatectomy with en-bloc celiac axis resection? Surgery 153:365–372
27. Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK et al (2008) En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. Ann Surg 247:300–309
28. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Groupe Tumeurs Digestives of Unicancer, PRODIGE Intergroup (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
29. Mahaseth H, Brutcher E, Kauh J, Hawk N, Kim S, Chen Z et al (2013) Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas 42:1311–1315

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PHASE II STUDIES

Phase II trial of combination therapy of gemcitabine plus anti-angiogenic vaccination of elpamotide in patients with advanced or recurrent biliary tract cancer

Masato Matsuyama · H. Ishii · J. Furuse · S. Ohkawa · H. Maguchi · N. Mizuno · T. Yamaguchi · T. Ioka · T. Ajiki · M. Ikeda · K. Hakamada · M. Yamamoto · H. Yamaue · K. Eguchi · W. Ichikawa · M. Miyazaki · Y. Ohashi · Y. Sasaki

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Summary *Background* Elpamotide is an HLA-A*24:02-restricted epitope peptide of vascular endothelial growth factor receptor 2 (VEGFR-2) and induces cytotoxic T lymphocytes (CTLs) against VEGFR-2/KDR. Given the high expression of VEGFR-2 in biliary tract cancer, combination chemoimmunotherapy with elpamotide and gemcitabine holds promise as a new therapy. *Patients and Methods* Patients with unresectable advanced or recurrent biliary tract cancer were included in this single-arm phase II trial, with the primary endpoint of overall survival. Survival analysis was performed in comparison with historical control data. The patients concurrently received gemcitabine once a week for 3 weeks (the fourth week was skipped) and elpamotide once a week for 4 weeks. *Results* Fifty-five patients were registered, of which 54 received the regimen and were included in the full analysis set as well as the safety analysis set. Median survival was 10.1 months, which

M. Matsuyama (✉) · H. Ishii
Gastroenterological Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: mahsanmahsan2000@yahoo.co.jp

J. Furuse
Department of Medical Oncology, Kyorin University School of Medicine, Tokyo, Japan

S. Ohkawa
Division of Hepatobiliary and Pancreatic Oncology, Kanagawa Cancer Center Hospital, Kanagawa, Japan

H. Maguchi
Center for Gastroenterology, Teine-Keijinkai Hospital, Hokkaido, Japan

N. Mizuno
Department of Gastroenterology, Aichi Cancer Center Hospital, Aichi, Japan

T. Yamaguchi
Department of Gastroenterology, Chiba Cancer Center, Chiba, Japan

T. Ioka
Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

T. Ajiki
Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, Hyogo, Japan

M. Ikeda
Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Chiba, Japan

K. Hakamada
Department of Surgery, Hirosaki University Graduate School of Medicine, Aomori, Japan

M. Yamamoto
Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

H. Yamaue
Second Department of Surgery, Wakayama Medical University, Wakayama, Japan

K. Eguchi
Division of Medical Oncology, Teikyo University School of Medicine, Tokyo, Japan

W. Ichikawa · Y. Sasaki
Division of Medical Oncology, Showa University School of Medicine, Tokyo, Japan

M. Miyazaki
Department of General Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

Y. Ohashi
Department of Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo, Japan

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was longer than the historical control, and the 1-year survival rate was 44.4 %. Of these patients, injection site reactions were observed in 64.8 %, in whom median survival was significantly longer (14.8 months) compared to those with no injection site reactions (5.7 months). The response rate was 18.5 %, and all who responded exhibited injection site reactions. Serious adverse reactions were observed in five patients (9 %), and there were no treatment-related deaths. *Conclusion* Gemcitabine and elpamotide combination therapy was tolerable and had a moderate antitumor effect. For future development of therapies, it will be necessary to optimize the target population for which therapeutic effects could be expected.

Keywords Biliary tract cancer · Immunotherapy · Cancer vaccines · Phase II clinical trial · VEGFR2

Introduction

In Japan, the incidence of biliary tract cancer (BTC) was ranked the sixth leading cause of cancer death in 2012. Although BTC is rare in Europe and America, it is highly prevalent in Japan, Chile, and East Asia [1, 2], presenting a serious health concern. The only hope for a complete cure is early-stage surgical resection. However, many BTC cases are unresectable due to locally advanced or distant metastasis. Moreover, recurrence after curative resection is not rare. Therefore, effective pharmacotherapies must be developed.

Vascular endothelial growth factor (VEGF)-A and its receptor, VEGF receptor (VEGFR), is highly expressed in many tumors including BTC [3]. VEGFR-2/KDR strongly promotes tumor angiogenesis, and active immunization against VEGFR-2/KDR has been reported to inhibit tumor growth and metastasis [4]. Thus, VEGFR-2/KDR holds hope as a target for tumor immunotherapy. Elpamotide, an HLA-A*24:02-restricted epitope peptide derived from VEGFR-2/KDR (KDR169), induces cytotoxic T lymphocytes (CTLs) that specifically recognize VEGFR-2/KDR169. These CTLs target tumor vascular endothelial cells that express KDR169-presenting HLA molecules, i.e., VEGFR-2/KDR expressing cells.

In this study, we assessed the efficacy and safety of combination immunotherapy with gemcitabine (Gem) and elpamotide in patients with BTC.

Methods

Study design

This multicenter, open-labeled, single-arm, phase II trial, which recruited patients via central registration, was conducted in accordance with the Declaration of Helsinki and the Standards for the Implementation of Clinical Trials on Pharmaceutical Products. The primary endpoint was overall survival, and secondary endpoints included progression-free survival and tumor regression. Sixteen facilities participated in this trial. This study was registered with UMIN, Clinical Trials Registry before the enrollment of the first subject (Registration number: UMIN000002500). Inclusion criteria of this trail were shown in Table 1.

Study treatment

One course of elpamotide (4 weeks) consisted of a single weekly subcutaneous injection (2.0 mg/mL/body) on day 1, day 8, day 15, and day 22. One course of Gem (4 weeks) consisted of a single weekly mediation (1000 mg/m^2/30 min) on day 1, day 8, and day 15 (day 22 was skipped). Criteria for discontinuation were shown in Table 1.

Efficacy and safety

Restaging CT was performed every 6 weeks and evaluated according to RECIST criteria version 1.1. The final tumor regression effect was determined by consensus of the image evaluation committee. Overall survival was defined as time

Table 1 Criteria of this trial

Inclusion criteria
a) pathologically diagnosed adenocarcinoma or adenosquamous carcinoma with bile duct origin (extrahepatic bile duct, intrahepatic bile duct, gallbladder, or vater papilla)
b) unresectable or recurrent disease
c) HLA-A*24:02 positive
d) aged ≥20 years and <75 years
e) ECOG performance status of 0 or 1
f) expected to live for ≥3 months
g) adequate organ function meeting the following criteria: white blood cell count ≥3500/mm^3 and ≤12,000/mm^3, neutrophil count ≥2000/mm^3, hemoglobin ≥9.0 g/dL, platelet count ≥100,000/mm^3, total bilirubin ≤2.0 mg/dL, aspartate aminotransferase ≤150 IU/L, alanine aminotransferase ≤150 IU/L, and serum creatinine ≤1.5 mg/dL;
h) no previous history of chemotherapy, radiotherapy, or immunotherapy for BTC (eligible if adjuvant therapy with S-1 was performed ≥6 months before registration)
i) if underwent laparotomy, it was performed ≥2 weeks before registration
j) provision of written informed consent.
Criteria for discontinuation
a) when the primary disease observably worsened
b) when dose reduction of Gem was required for more than two stages
c) when adverse events made continuation difficult
d) when treatment was postponed for more than 28 days
e) when 1.5 years had passed from registration

from the day of registration to the day of death from any cause or 1.5 years afterwards. Progression-free survival was counted from the day of registration to the day of progressive disease by clinical evaluation or imaging diagnosis, whichever was earlier.

Adverse events were evaluated at each hospital visit and graded according to the Common Toxicity Criteria version 3 (CTCAE v3). Adverse events which could not be ruled out as being related to the trial therapy were reported as adverse drug reactions (ADRs). For each adverse event, we documented the worst grade for each patient, and confirmed the incidence of each by grade.

Exploratory assessment

Induction of VEGFR-2-specific CTLs and serum concentrations of VEGFR-2 were analyzed only in subjects who provided specific consent to receive these assessments at some of the participating medical institutions.

The induction of VEGFR-2-specific CTLs was evaluated by an enzyme-linked immunospot assay. CTL positivity was defined as when the calculated value (average spot number in the peptide pulse group - average spot number in the negative control group/average spot number in the peptide pulse group × 100) by time was greater than that of day 1, and further when the average spot number in the peptide pulse group was greater than the average spot number and standard deviation range in the negative control group.

Serum concentrations of VEGFR-2 were measured before drug administration on day 1, day 8, and day 29, using Quantikine® Human Soluble VEGFR-2 Immunoassay (R&D Systems, Inc).

Statistical analysis

Overall survival, 1-year survival and progression-free survival were estimated with the Kaplan-Meier method. To assess differences in overall survival between the elpamotide and historical control groups [5, 6], log-rank tests and the Harrington-Fleming, in which time is weighted and was used in anticipation that the effects of the vaccine would present with time, were used.

Calculation of sample size was based on an additional treatment effect of 15 % in the elpamotide group compared with the 1-year survival rate in the historical control group, which was derived from previous reports [5, 6]. The null hypothesis was "no extension of 1-year survival" to achieve a one-sided type I error of <10 % and a power of >80 %. We estimated that the 1-year survival rate of the historical control group based on patients with BTC was 15–30 %, and expected elpamotide to add a treatment effect of 15 %. When the historical control group was set at 200 patients, the sample size needed for the elpamotide group was calculated to be 45–60 patients. Accordingly, we aimed to select a total of 50 patients.

Serum concentrations of VEGFR-2 were analyzed by post-hoc test. All statistical analyses were conducted with SAS software, version 9.1.3 (SAS Institute).

Results

Patient characteristics

Of the 55 patients registered from October 2009 to June 2011, 54 who underwent the trial therapy were included in the full analysis set and safety analysis set. Patient characteristics are summarized in Table 2. Compared to the historical control group, the present trial had higher proportions of patients without gallbladder cancer (66.7 % vs. 45–50.7 %) and those having a performance status of 0 (90.7 % vs. 60 %).

Survival and response rate

Fourteen patients (25.9 %) survived ≥1.5 years, and two completed the 1.5-year trial therapy. The median number of courses of study treatment was 4.5 (range: 1–20), and the dose intensity of elpamotide and Gem was 90.0 and 82.7 %,

Table 2 Patient characteristics (N _54)*

Characteristics	No. of patients	%
Age, years		
<65	27	50
≥65	27	50
Sex		
Male	30	55.6
Female	24	44.4
Primary tumour site		
Intrahepatic bile duct	20	37
Gallbladder	18	33.3
Extrahepatic bile duct	13	24.1
Ampulla of vater	3	5.6
Extent of disease		
Metastatic	34	63
Locally advaced	20	37
Resection		
No	37	68.5
Yes	17	31.5
Lymphocyte		
≥18 %	45	83.3
<18 %	9	16.7
PS (ECOG)		
0	49	90.7
1	5	9.3

Clinical characteristics of the 54 patients who received elpamotide+GEM

PS (*ECOG*) Performance status (Eastern Cooperative Oncology Group)

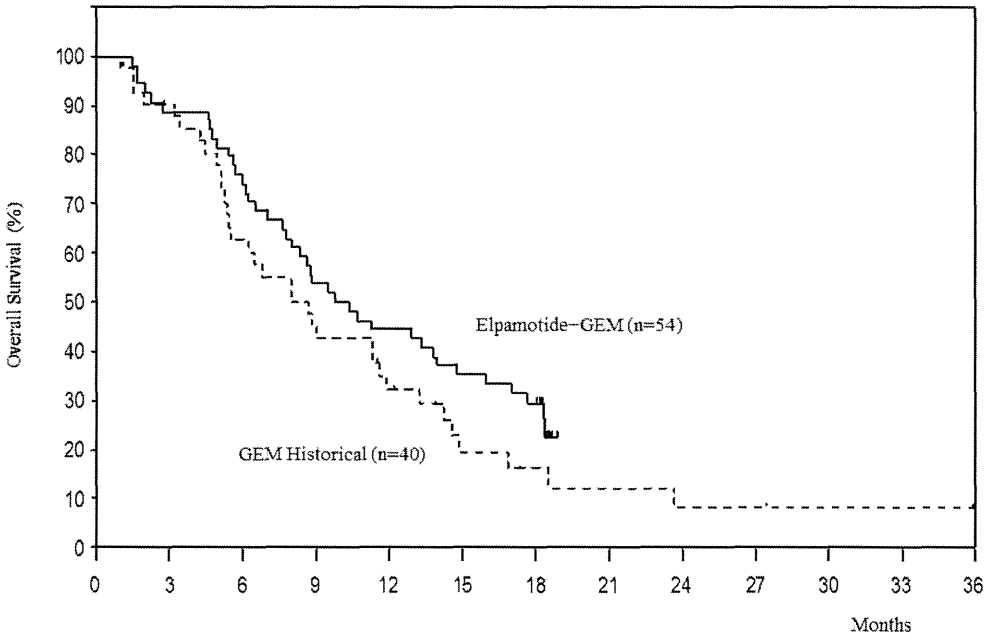

Fig. 1 Overall survival

respectively. Main reasons for discontinuation were exacerbation of primary disease (34 cases) and adverse event-related reasons (6 cases).

Median survival was 10.1 months (95 % confidence interval (CI): 8.0–14.0 months), which was longer than that of the historical control (7.6 months) (P=0.079; Harrington-Fleming method; P=0.043, log-rank test; Fig. 1). One-year survival rate was 44.4 %, and median progression-free survival was 4.5 months (95 % CI: 2.8–7.1 months).

Median overall survival by site of origin was as follows: intrahepatic bile duct (11.6 months), extrahepatic bile duct (18.3 months), gallbladder (8.4 months), and vater papilla (9.8 months). These were superior to the 8.7, 10.1, 6.5, and 9.3 months, respectively, in the historical control.

None of the patients achieved complete response, while 10 achieved partial response, with the imaging response rate of 18.5 %. Stable disease was maintained for ≥6 months in 8 of 28 patients (14.8 %).

Toxicity

Major hematologic ADRs included decreased white blood cell counts (75.9 %), decreased platelet counts (72.2 %), and decreased neutrophil counts (64.8 %). Major non-hematologic ADRs included injection site reaction (68.5 %), induration and erythema (64.8 and 27.8 %), nausea (51.9 %), and decreased appetite and malaise (37.0 %). Severe adverse effects were observed in five patients as follows: pneumocystis pneumonia, loss of appetite, thrombotic microangiopathy, interstitial lung disease, and fever. ADRs of grade 3 or higher are summarized in Table 3. There were no treatment-related deaths.

Subgroup analysis

Among 37 patients who developed injection site reactions (ulcer, induration, or erythema), tumor regression was observed in 10 (27 %) during the study period. Moreover, the median overall survival of the 37 patients was significantly longer (14.8 months) compared to that of the remaining 17 who developed no injection site reactions (5.7 months; Table 4 and Fig. 2).

Table 3 Adverse drug reactions

Adverse drug reactions	Grade 3		Grade 4	
	N	%	*N*	%
Hematological				
Decreased neutrophil count	16	29.6	3	5.6
Decreased lymphocyte count	9	16.7	0	0.0
Decreased white blood cell count	5	9.3	0	0.0
Decreased platelet count	4	7.4	1	1.9
Anemia	2	3.7	0	0.0
Non-hematological				
Pneumocystis jiroveci pneumonia	1	1.9	0	0.0
Thrombotic microangiopathy	1	1.9	0	0.0
Decreased appetite	1	1.9	0	0.0
Interstitial lung disease	1	1.9	0	0.0
Elevated alanine aminotransferase level	1	1.9	0	0.0
Elevated aspartate aminotransferase level	1	1.9	0	0.0
Elevated blood glucose level	1	1.9	0	0.0
Elevated gamma-glutamyltransferase level	1	1.9	0	0.0
Elevated hepatic enzyme level	1	1.9	0	0.0

Table 4 Relationship between the efficacy and injection site reactions

	With ISR (n=37) N (%)	Without ISR (n=17) N (%)	P-value
Response			
Complete response (CR)	0 (0.0)	0 (0.0)	
Partial response (PR)	10 (27.0)	0 (0.0)	
Stable disease (SD)	20 (54.1)	8 (47.1)	
Progressive disease (PD)	7 (18.9)	7 (41.2)	
Not evaluable (NE)	0 (0.0)	2 (11.8)	
Overall survival			
Median survival (95 % CI)	14.8 months (9.8, 18.4)	5.7 months (4.6, 8.6)	0.002 (H-F), <0.001 (log-rank)

CI confidence interval, *ISR* injection site reaction

Exploratory analysis

The induction of VEGFR2-specific CTLs was assessed in nine patients; six were positive (66.7 %). There was no clear association between CTL positivity with treatment survival, response rate, or ADRs.

Serum concentrations of VEGFR-2 were evaluated in 43 patients, and found to be significantly increased from baseline (day 1) to day 8 (P=0.015), and significantly decreased from day 8 to day 29 (P=0.010); there was no significant difference from baseline to day 29. Response rate in the 31 patients (72 %) with an elevated serum VEGFR-2 concentration at day 8 was 19 %, and median survival was 13.3 months. There was no apparent association between serum VEGFR-2 concentration and efficacy or ADRs.

Discussion

Tumor immunotherapy has recently gained much attention, and there are currently more than 100 clinical studies in progress around the world. As a results, some immunotherapeutic drugs already approved [7, 8], and such approval reflects the findings that immunotherapy activates the immune response in cancer patients and is clinically effective.

The present trial was planned and conducted before Gem plus cisplatin therapy became the standard chemotherapy for BTC based on results of the ABC-02 [9] and BT-22 [10] trials. The reliable reference data at the time of planning this trial were only the retrospective data from two studies [5, 6]. Based on results from those studies, we set the threshold 1-year survival rate at 15–30 %, and expected to add a 15 % treatment effect. The result was a 44.4 % 1-year survival rate, which was in line with this prediction. However, the proportion of good performance status cases and of those without gallbladder cancer were high in this trial. Thus, in the comparison with the historical control, improved survival may have been related to patient background, rather than the vaccine's additive effects. Median survival with the standard Gem plus cisplatin

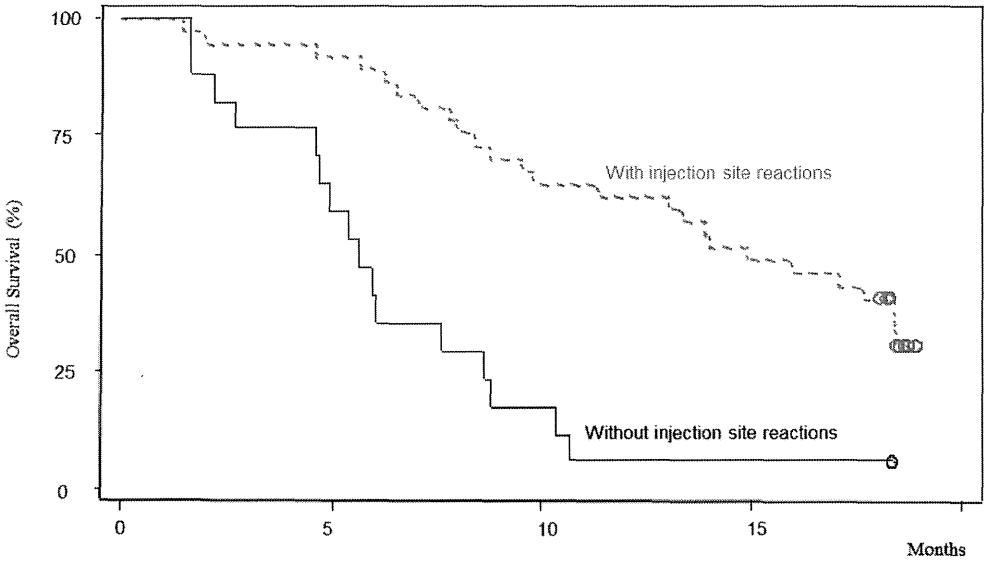

Fig. 2 Overall survival with or without injection site reactions

therapy in the ABC-02 and BT22 trials was 11.7 and 11.2 months, respectively. Based on the median survival of 10.1 months in the present trial, single-agent Gem chemotherapy clearly lacks power as a platform for additive effects over elpamotide.

Survival curves for subgroups of patients who did and did not exhibit injection site reactions differed substantially. The fact that those who exhibited injection site reactions showed better long-term results suggests that it can be used as an indicator for early determination of those likely to benefit from therapy. This phenomenon was also observed in the Gem ± elpamotide trial (PEGASUS-PC Study), which targeted advanced pancreatic cancer patients, and although primitive, it may serve as a highly reliable indicator.

In conclusion, combined immunotherapy with Gem and elpamotide was well-tolerated and showed moderate antitumor effects. For future development of therapies, it will be necessary to optimize the target population for which therapeutic effects could be expected.

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References

1. Sheth S, Bedford A, Chopra S (2000) Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. Am J Gastroenterol 95(6):1402–1410
2. Matsukura N, Yokomuro S, Yamada S et al (2002) Association between Helicobacter bilis in bile and biliary tract malignancies: H. bilis in bile from Japanese and Thai patients with benign and malignant diseases in the biliary tract. Jpn J Cancer Res 93(7):842–847
3. Tian Y, Ding R, Zhi Y et al (2005) Analysis of P53 and Vascular endothelial growth factor and its receptor Flk-1Expression in human gallbladder carcinoma for determination of tumor vascularity. Chin J Cancer Res 17(4):273–277
4. Niethammer AG, Xiang R, Becker JC et al (2002) A DNA vaccine against VEGF receptor 2 prevents effective angiogenesis and inhibits tumor growth. Nat Med 8(12):1369–1375
5. Yonemoto N, Furuse J, Okusaka T et al (2007) A Multi-center retrospective analysis of survival benefits of chemotherapy for unresectable biliary tract cancer. Jpn J Clin Oncol 37(11):843–851
6. Okusaka T, Ishii H, Fukutomi A et al (2006) Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer. Cancer Chemother Pharm 57(5):647–653
7. Kantoff PW, Higano CS, Shore ND et al (2010) Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363(5):411–422
8. Ledford H (2011) Melanoma drug wins US approval. Nature 471(7340):561
9. Valle J, Wasan H, Palmer DH et al (2010) Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362(14): 1273–1281
10. Okusaka T, Nakachi K, Fukutomi A et al (2010) Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 103(4):469–474

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TECHNICAL VIEW

Tips and tricks of the surgical technique for borderline resectable pancreatic cancer: mesenteric approach and modified distal pancreatectomy with en-bloc celiac axis resection

Seiko Hirono · Hiroki Yamaue

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Abstract Borderline resectable (BR) pancreatic cancer involves the portal vein and/or superior mesenteric vein (PV/SMV), major arteries including the superior mesenteric artery (SMA) or common hepatic artery (CHA), and sometimes includes the involvement of the celiac axis. We herein describe tips and tricks for a surgical technique with video assistance, which may increase the R0 rates and decrease the mortality and morbidity for BR pancreatic cancer patients. First, we describe the techniques used for the "artery-first" approach for BR pancreatic cancer with involvement of the PV/SMV and/or SMA. Next, we describe the techniques used for distal pancreatectomy with en-bloc celiac axis resection (DP-CAR) and tips for decreasing the delayed gastric emptying (DGE) rates for advanced pancreatic body cancer. The mesenteric approach, followed by the dissection of posterior tissues of the SMV and SMA, is a feasible procedure to obtain R0 rates and decrease the mortality and morbidity, and the combination of this aggressive procedure and adjuvant chemo(radiation) therapy may improve the survival of BR pancreatic cancer patients. The DP-CAR procedure may increase the R0 rates for pancreatic cancer patients with involvement within 10 mm from the root of the splenic artery, as well as the CHA or celiac axis, and preserving the left gastric artery may lead to a decrease in the DGE rates in cases where there is more than 10 mm between the tumor edge and the root of the left gastric artery. The development of safer surgical procedures is necessary to improve the survival of BR pancreatic cancer patients.

Keywords Borderline resectable pancreatic cancer · Mesenteric approach · Modified distal pancreatectomy with en-bloc celiac axis resection

S. Hirono · H. Yamaue (✉)
Second Department of Surgery, Wakayama Medical University School of Medicine, 811-1 Kimiidera, Wakayama 641-8510, Japan
e-mail: yamaue-h@wakayama-med.ac.jp

Instructions

Complete surgical resection is the sole curative treatment for pancreatic cancer patients; however, only 15–20% of the pancreatic patients are eligible for surgery [1, 2]. Therefore, aggressive surgical procedures, including concomitant portal vein and/or superior mesenteric vein (PV/SMV) resection and/or resection of major arteries during pancreatectomy, have been performed for advanced pancreatic cancer patients [3, 4] since Fortner et al. reported these aggressive surgical procedures in 1973 [5]. Nevertheless, these aggressive procedures have been considered to be contraindicated because of the high associated morbidity and mortality rates [4]. Recently, the surgical techniques, perioperative management and adjuvant chemotherapy or chemoradiation therapy have improved, and the national consensus of "borderline resectable (BR) pancreatic cancer" has widely been used worldwide [6–8].

BR pancreatic cancer involves the PV/SMV and/or major arteries (determined based on computed tomography [CT]) and is associated with a high risk of harboring radiographically occult metastases. Therefore, it is difficult for BR pancreatic cancer patients to obtain pathologically negative surgical margins to obtain survival benefits even if they undergo extended surgical resection. The definition of the National Comprehensive Cancer Network (NCCN) guideline 2013 described that: (1) no distant metastasis; (2) venous involvement of the PV/SMV with distortion or narrowing of the vein or occlusion of the vein with suitable vessels proximal and distal, allowing for safe resection and replacement; (3) gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the celiac axis; and (4) tumor abutment of the superior mesenteric artery not to exceed more than 180 degrees of the circumference of the vessel wall [9]. However, the definitions of BR pancreatic cancer have subtle differences, and vary by institution [9–11]. For example, distal pancreatec-

tomy with en-bloc celiac axis resection (DP-CAR) has been widely performed for BR pancreatic cancer patients with radiological abutment of the celiac axis in Japan [12–15].

Although some studies have reported the advantages and disadvantages of aggressive surgical procedures for a small number of BR pancreatic cancer patients, it has not been known whether these aggressive surgical procedures, including concomitant dissection of the nerve plexus along major arteries and the resection of major vessels, lead to improvements in the survival of patients with BR pancreatic cancer. Recently, neoadjuvant therapy has been recommended for BR pancreatic cancer; however, it is unknown what regimen is the most effective and safest, and whether the neoadjuvant therapy could impact the survival [16–19].

The aim of this article is to suggest surgical techniques that can be used to increase the R0 rates and survival benefits, as well as to decrease the morbidity and mortality rates for BR pancreatic cancer using surgical videos.

Methods

We selected two operative procedures for BR pancreatic cancer patients in this article: one was mesenteric approach during pancreaticoduodenectomy (PD) for pancreatic head cancer, and another was DP-CAR with preservation of the left gastric artery (modified DP-CAR) for pancreatic body cancer, and trimmed each operation videos. The tips and tricks of the two operative procedures will be introduced with videos assistance and some published research in this article.

Results

Mesenteric approach for BR pancreatic cancer located in the pancreatic head (Video S1)

In Video S1, the patient was a 50-year-old male, and had the cancer located in the head of the pancreas with abutment of the SMA with 90 degrees of the circumference. Therefore, he was diagnosed as BR pancreatic cancer, and underwent neoadjuvant chemotherapy using gemcitabine and S-1.

First, the mesentery of the jejunum is incised at the line between the Treiz ligament and the third portion of the duodenum in order to identify the SMV and SMA at the line. Next, the J1 and J2 arteries are approached at the root of the SMA (Fig. 1), and the inferior pancreaticoduodenal artery (IPDA) is also identified. After the J1 artery and IPDA are ligated and divided, the posterior tissues of the SMA and SMV are dissected completely (Fig. 2). In cases with the involvement of the SMA, right side semicirumferential dissection of the nerve plexus of the SMA may be required in addition to this procedure in order to obtain negative surgical margins. The dissection of the tissues along the SMV and SMA is promoted cephalad toward the inferior border of the pancreatic body.

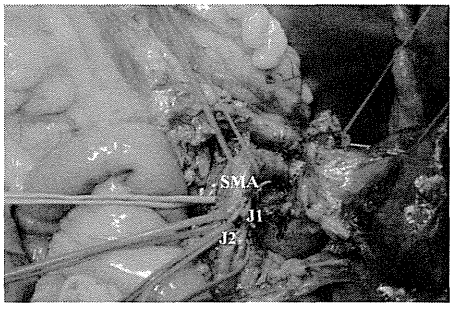

Fig. 1 After identification of the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV) at the line between the Treiz ligament and the third portion of the duodenum, we approached the J1 and J2 arteries at the roots of the SMA to proceed with the posterior approach for the SMA

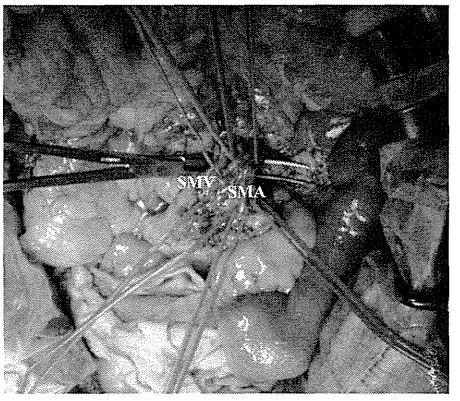

Fig. 2 The dissection of the posterior fat tissues of the superior mesenteric artery (SMA) and superior mesenteric vein (SMV) is completed via the mesenteric approach

After transection of the stomach or duodenum, the lymph node dissection around the common hepatic artery and hepatoduodenal ligament is performed. The dissection of the nerve plexus around the common hepatic artery may sometimes be required for pancreatic cancer with involvement of the common hepatic artery and/or the root of the gastroduodenal artery, especially for pancreatic neck cancer. After the dissection around the common hepatic artery and the hepatoduodenal ligament, the bile duct and the pancreas are transected. In cases of pancreatic neck cancer, the invasion of the confluence of the PV and SMV and even splenic vein invasion are sometimes found behind the tumor, and a procedure is needed that allows the range of the tumor to be cleared by intraoperative ultrasound and dissection of the posterior tissues between the pancreas and splenic artery from the PV toward the left side of the tumor [20].

Next, the dissection of the nerve plexus from the celiac trunk and the root of the SMA at the aorta to the pancreatic head is performed, and the pancreatic head is dissected

from the retroperitonum by the Kocher maneuver. After transection of the jejunum, the pancreatic head is connected with only the PV/SMV, if the tumor involves the PV/SMV. After the specimen is removed with the resection of the PV/SMV, PV/SMV reconstruction is performed. If the length of the resected PV/SMV is long, the splenic vein should be divided and/or an autologous graft should be interposed for a tension-free anastomosis in order to prevent the development of vessel thrombosis after reconstruction [21].

Modified DP-CAR procedure for BR pancreatic cancer located in the pancreatic body and/or tail (Video S2)

The patient was a 72-year-old male, and had the cancer located in the body of the pancreas with radiographic invasion of nerve plexus around the confluence of splenic artery and common hepatic artery and celiac axis. Therefore, he was diagnosed as having BR pancreatic cancer, and underwent neoadjuvant chemotherapy using gemcitabine and S-1. After neoadjuvant treatment, the tumor was stable disease, and his common hepatic artery was preoperatively embolized by angiographic coiling to increase arterial blood flow to the liver via the pancreatoduodenal arcades from the SMA.

The DP-CAR procedure includes en-bloc resection of the celiac axis, common hepatic artery and left gastric artery, in addition to the distal pancreatectomy. The nerve plexus and ganglions around the celiac axis and the SMA, and the retroperitoneal fat tissues, are also dissected. No reconstruction of the arterial system is required because of the development of the collateral arterial pathways via the pancreatoduodenal arcades from the SMA. Preoperative coil embolization of the common hepatic artery is often performed in order to enlarge the collateral pathways and prevent ischemia-related complications. Moreover, the right gastric vein, which usually joins to the portal vein, should be preserved for the prevention of the congestive gastropathy. If PV/SMV invasion is found and resection is required, the use of an autologous graft should be considered for a tension-free anastomosis after PV/SMV reconstruction to prevent thrombosis in the reconstructed PV/SMV [21].

Furthermore, we reported DP-CAR with preservation of the left gastric artery, named "modified DP-CAR", and found that the incidence of postoperative delayed gastric emptying was lower in the modified DP-CAR than standard DP-CAR. Therefore, we recommend the modified DP-CAR procedure over the standard DP-CAR, if the length between the edge of the tumor and the root of the left gastric artery is longer than 10 mm [15].

Discussion

Some artery-first approaches have been reported for PD [22], including the right posterior approach [23, 24], left posterior approach [25] and mesenteric approach [26, 27]. BR pancreatic cancer located in the pancreatic head has often required PV/SMV resection and lymph node dissection along the SMV and the SMA, and/or the dissection of the nerve plexus along the SMA, in order to obtain negative surgical margins. Therefore, the combination of the mesenteric approach and the left posterior approach to the SMA may be the most appropriate procedure for BR pancreatic cancer patients, because this approach makes it easy to dissect the lymph nodes and nerve plexus along the SMA, even for BR pancreatic cancer with PV/SMV involvement. This approach also makes it easy to determine the resectability at the beginning of the operation. However, there is currently no evidence whether the mesenteric approach and/or left posterior approach have clinical and survival benefits for BR pancreatic cancer patients. Therefore, further large studies, including randomized clinical trials, are needed to confirm the optimal approach.

Distal pancreatectomy with en-bloc celiac axis resection is sometimes performed to obtain R0 resection for pancreatic cancer with involvement of the celiac axis and/or common hepatic artery [12–15], although the NCCN guidelines classify pancreatic cancers with involvement of the celiac axis as unresectable [9]. Some studies have reported that DP-CAR is a safe and feasible procedure, and this procedure may have survival benefits for patients with pancreatic body and/or tail cancer [13–15]. Furthermore, our data showed that the DP-CAR procedure might lead to increased R0 rates and improve survival for patients with pancreatic body/tail cancer within 10 mm from the root of the splenic artery [14]. However, further large studies are needed to determine whether this aggressive surgery has survival benefits.

We also reported that the incidence of postoperative delayed gastric emptying was lower in the modified DP-CAR, which means DP-CAR with preservation of the left gastric artery, than standard DP-CAR [15]. Therefore, the pancreatic body/tail cancer, where the length between the edge of the tumor and the root of the left gastric artery is longer than 10 mm may be indicated for the modified DP-CAR, because it is important to decrease morbidity rate and postoperative adjuvant therapy starts as soon as possible for advanced pancreatic cancer.

To obtain negative surgical margins for BR pancreatic cancer, these aggressive surgical procedures are often required. However, it remains unknown whether these aggressive procedures improve the clinical and survival benefits. Recent studies have reported the effectiveness of neoadjuvant therapy to decrease the rates of the lymph node metastasis, and the activity of the tumor cells [16–19, 28]; however, it is also controversial what regimen is the most appropriate as neoadjuvant therapy, and whether chemotherapy or chemoradiation therapy is better for the BR pancreatic cancer patients.

In conclusion, the combination of safe R0 surgical resection and adjuvant therapies, including preoperative and postoperative chemo(radiation) therapy, is essential to improve the survival of the BR pancreatic cancer patients. The development of safer and more effective multimodality treatments is necessary for the BR pancreatic cancer patients.

Conflict of interest None declared.

References

1. World Health Organization: Regional Office for Europe. The European health report 2012: charting the way to well-being. 2012.
2. Howlader NNA, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. SEER cancer statistics review, 1975–2009 posted to the SEER web site, April 2012. Bethesda, MD: National Cancer Institute; 2011.
3. Amano H, Miura F, Toyota N, Wada K, Katoh K, Hayano K, et al. Is pancreatectomy with arterial reconstruction a safe and useful procedure for locally advanced pancreatic cancer? J Hepatobiliary Pancreat Surg. 2009;16:850–7.
4. Nakao A, Takeda S, Inoue S, Nomoto S, Kanazumi N, Sugimoto H, et al. Indications and techniques of extended resection for pancreatic cancer. World J Surg. 2006;30:976–82.
5. Fortner JG. Regional resection of cancer of the pancreas: a new surgical approach. Surgery. 1973;73:307–20.
6. Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, et al. Borderline resectable pancreatic cancer: definitions, management and role of preoperative therapy. Ann Surg Oncol. 2006;13:1035–46.
7. Evans DB, Farnell MB, Lillemore KD, Vollmer C, Strasberg SM, Schulick RD. Surgical treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. Ann Surg Oncol. 2009;16:1736–44.
8. Calley MP, Chang KJ, Fishman EK, Talamonti MS, William TL, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16:1727–33.
9. National Comprehensive Cancer Network. NCCN practice guidelines for pancreatic cancer, version 2. Available at http://www.nccn.org/professionals/physician_gls/recently_updated.asp.
10. Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. Clin Gastroenterol Hepatol. 2008;6:1301–8.
11. Li H, Zeng MS, Zhou KR, Jin DY, Lou WH. Pancreatic adenocarcinoma: the different CT criteria for peripancreatic major arterial and venous invasion. J Comput Assist Tomogr. 2005; 29:170–5.
12. Kondo S, Katoh H, Hirano S, Ambo Y, Tanaka E, Okushiba S, et al. Results of radical distal pancreatectomy with en bloc resection of the celiac artery for locally advanced cancer of the pancreatic body. Langenbecks Arch Surg. 2003;388:101–6.
13. Hirano S, Kondo S, Hara T, Ambo Y, Tanaka E, Shichinohe T, et al. Distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic body cancer. Ann Surg. 2007;246:46–51.
14. Okada K, Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, et al. Surgical strategy for patients with pancreatic body/tail carcinoma: who should undergo distal pancreatectomy with en-bloc celiac axis resection? Surgery. 2013;153:365–72.
15. Okada K, Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, et al. Preservation of the left gastric artery on the basis of anatomical features in patients undergoing distal pancreatectomy with celiac axis en-bloc resection (DP-CAR). World J Surg. 2014;38:2980–5.
16. Christians KK, Tasi S, Mahmoud A, Ritch P, Thomas JP, Wiebe L, et al. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? Oncologist. 2014;19:266–74.
17. Lee JL, Kim SC, Kim JH, Lee SS, Kim TW, Park H, et al. Prospective efficacy and safety study of neoadjuvant gemcitabine with capecitabine combination chemotherapy for borderline-resectable or unresectable locally advanced pancreatic adenocarcinoma. Surgery. 2012;152:851–62.
18. Barugola G, Partelli S, Crippa S, Capelli P, D'Onofrio M, Pederzoli P, et al. Outcomes after resection of locally advanced or borderline resectable pancreatic cancer after neoadjuvant therapy. Am J Surg. 2012;203:132–9.
19. Stokes JB, Nolan NJ, Stelow EB, Walters DM, Weiss GR, Lange EE, et al. Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. Ann Surg Oncol. 2011;18:619–27.
20. Strasberg SM, Sanchez LA, Hawkins WG, Fields RC, Linehan DC. Resection of tumors of the neck of the pancreas with venous invasion: the "Whipple at the splenic artery (WATSA)" procedure. J Gastrointest Surg. 2012;16:1048–54.
21. Hirono S, Kawai M, Tani M, Okada K, Miyazawa M, Shimizu H, et al. Indication for the use of an interposed graft during portal vein and/or superior mesenteric vein reconstruction in pancreatic resection based on perioperative outcomes. Langenbecks Arch Surg. 2014;399:461–71.
22. Sanjay P, Takaori K, Govil S, Shrikhande SV, Windsor JA. "Artery-first" approaches to pancreatoduodenectomy. Br J Surg. 2012;99:1027–35.
23. Ohigashi H, Ishikawa O, Eguchi H, Yamada T, Sasaki Y, Noura S, et al. Early ligation of the inferior pancreaticoduodenal artery to reduce blood loss during Pancreaticoduodenectomy. Hepatogastroenterology. 2004;51:4–5.
24. Pessaux P, Varma D, Arnaud J. Pancreatoduodenectomy: superior mesenteric artery first approach. J Gastrointest Surg. 2006; 10:607–11.
25. Kurosaki I, Minagawa M, Takano K, Takizawa K, Hatakeyama K. Left posterior approach to the superior mesenteric vascular pedicle in Pancreaticoduodenectomy for cancer of the pancreatic head. JOP. 2011;12:220–9.
26. Nakao A, Takagi H. Isolated pancreatectomy for pancreatic head carcinoma using catheter bypass of the portal vein. Hepatogastroenterology. 1993;40:426–9.
27. Weiz J, Rahbari N, Koch M, Büchler MW. The artery first approach for resection of pancreatic head cancer. J Am Coll Surg. 2010;210:e1–e4.
28. Kang CM, Chung YE, Park JY, Sung JS, Hwang HK, Choi HJ, et al. Potential contribution of preoperative neoadjuvant concurrent chemoradiation therapy on margin-negative resection in borderline resectable pancreatic cancer. J Gastrointest Surg. 2012;16:509–17.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Video S1 Mesenteric approach for BR pancreatic cancer located in the pancreatic head.
Video S2 Modified DP-CAR procedure for BR pancreatic cancer located in the pancreatic body and/or tail.