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ORIGINAL SCIENTIFIC REPORT

Surgical Indications of Distal Pancreatectomy with Celiac Axis Resection for Pancreatic Body/Tail Cancer

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Abstract

Background The survival impact of distal pancreatectomy (DP) with celiac axis resection for locally advanced pancreatic body/tail cancer remains unclear.

Methods A total of 16 patients underwent DP with celiac axis resection, while 76 underwent standard DP for pancreatic body/tail cancer. The indications for DP with celiac axis resection included: (a) tumor invasion of either the celiac axis or common hepatic artery or both [CA/CHA (+)] and (b) tumor invasion of the root of the splenic artery, which is difficult to dissect without securing an adequate surgical margin [CA/CHA (−)].

Results DP with celiac axis resection presented longer operative time and greater amount of blood loss than DP. The median survival time was 17.5 months in the DP with celiac axis resection group and 43.1 months in the DP group ($p = 0.040$). Among the patients who underwent DP with celiac axis resection, the median survival time was 35.1 months in the CA/CHA (−) group and 13.2 months in the CA/CHA (+) group ($p = 0.001$). Comparing the patients undergoing standard DP and DP with celiac axis resection with a CA/CHA (−) status, there were no significant differences in either disease-free or overall survival times. The CA19-9 value, CA/CHA (+) status, and microscopic venous infiltration were revealed independent significant prognostic factors.

Conclusions DP with celiac axis resection should therefore be indicated in patients with a CA/CHA (−) status. However, it is difficult to justify the use of DP with celiac axis resection in patients with CA/CHA (+) status due to the poor survival.

Introduction

Despite the development of various modalities for diagnosing pancreatic disease, pancreatic body/tail cancer continues to be a disease with a dismal prognosis. Due to the lack of specific signs and symptoms, most patients miss the opportunity for surgical resection as a result of the development of distant metastasis or the involvement of major vessels [1]. Tumor extension to the celiac axis and/or common hepatic artery (CHA) is one of the main factors preventing the use of surgical resection.

The extension of surgical indications for treating locally advanced disease using distal pancreatectomy (DP) with en bloc celiac axis resection makes the procedure challenging. Appleby reported a technique that involved the use of en bloc resection of the celiac axis combined with DP and total gastrectomy for locally advanced gastric cancer in 1953 [2]. Thereafter, Nimura first applied this technique to resect tumors of the body and tail of the pancreas in 1976 [3]. Since then, several authors have reported their experience with DP with celiac axis resection with and without arterial reconstruction [4–15]. These reports proved that the

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use of DP with celiac axis resection could increase the resectability with an acceptable postoperative complication rate, but their results were inconsistent, with an R1 resection rate of 9–69 % and a median survival time of 9.3–26 months [4–11]. These inconsistencies seem to have been caused by differences in the precise indications for DP-CAR determined by each author.

In this study, we reviewed our experience with the aim of clarifying the survival impact of and appropriate indications for DP with celiac axis resection in patients with locally advanced pancreatic body/tail cancer.

Methods

Between October 2002 and June 2014, a total of 420 patients underwent pancreatectomy for invasive ductal carcinoma of the pancreatic body and tail (322 pancreatoduodenectomies, 92 distal pancreatectomies, and six total pancreatectomies). Among the 92 patients undergoing distal pancreatectomies, 16 underwent DP with celiac axis resection and 76 underwent standard DP. All tumors were considered to be technically resectable. No patients underwent preoperative chemo- and chemoradiotherapy. All patients were followed for at least 18 months after resection or until death. The median follow-up period for the censored patients was 36 months. The indication for DP with celiac axis resection was determined based on the findings of computed tomography (CT): (a) tumor invasion of the celiac axis and/or CHA [CA/CHA (+)] (Fig. 1a, b) and (b) tumor invasion of the root of the splenic artery, which is difficult to ligate and divide without securing an adequate surgical margin [CA/CHA (−)] (Fig. 2a, b). Tumor invasion of the superior mesenteric artery (SMA) was considered to be a contraindication. Among the patients treated with DP with celiac axis resection, CT findings of CA/CHA (−) and CA/CHA (+) were detected in seven and nine patients, respectively. In seven patients with a CA/CHA (−) status, the distance between the right edge of the tumor and the origin of the splenic artery was measured by computed tomography. The pathological findings were described according to the UICC TNM classification system [16]. The standardization of the R status has been described previously [17]. The short- and long-term surgical results were compared between the patients treated with DP and DP with celiac axis resection and between those with a CA/CHA (−) and CA/CHA (+) status. Prognostic factors after surgical resection for pancreatic body/tail cancer were also evaluated.

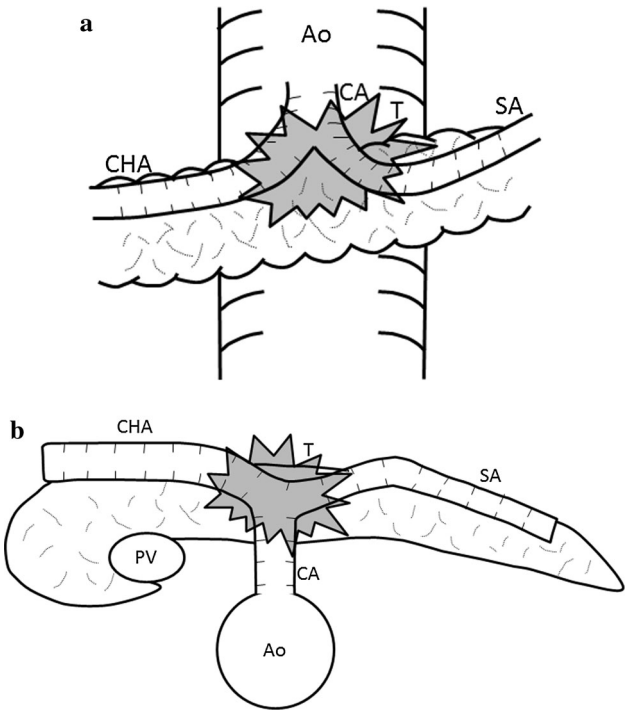

Fig. 1 CT findings of CA/CHA (+). Tumor invades the celiac axis and common hepatic artery. **a** Anteroposterior view, **b** axial view. *CA* celiac axis, *CHA* common hepatic artery, *SA* splenic artery, *Ao* aorta, *PV* portal vein

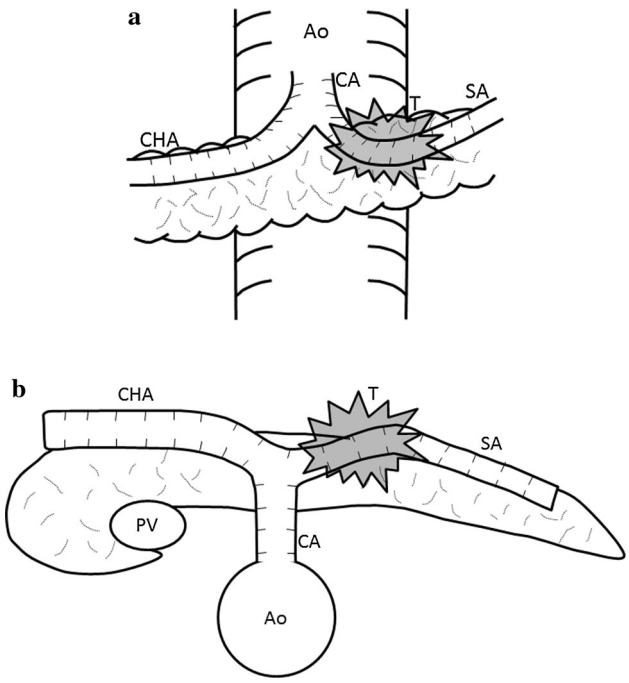

Fig. 2 CT findings of CA/CHA (−). Tumor is adjacent the root of the splenic artery. It is difficult to divide the splenic artery without securing an adequate surgical margin. **a** Anteroposterior view, **b** axial view. *CA* celiac axis, *CHA* common hepatic artery, *SA* splenic artery, *Ao* aorta, *PV* portal vein

Table 1 Comparison of the patients' characteristics according to the surgical procedure

	DP ($n = 76$)	DP-CAR ($n = 16$)	p
Age (y.o)	71 (45–85)	70 (32–85)	0.691
Gender			
Male	44	10	0.734
Female	32	6	
CA19-9 (U/ml)	230 (2–2857)	279 (1–1739)	0.248
Operation time (min)	263 (129–557)	338 (259–507)	<0.001
Blood loss (ml)	460 (76–2716)	902 (461–1893)	0.001
Portal vein resection	5 (7 %)	5 (31 %)	0.004
Pancreatic fistula	31 (41 %)	7 (44 %)	0.827
Morbidity[a]	48 (63 %)	14 (88 %)	0.059
Hospital stay (days)	21 (8–86)	26 (15–39)	0.131
Differentiation			
Well	25 (33 %)	3 (19 %)	0.566
Mode	40 (53 %)	9 (56 %)	
Poor	4 (5 %)	1 (6 %)	
Asc	7 (9 %)	3 (19 %)	
Lymph node metastases	42 (55 %)	14 (88 %)	0.016
UICC stage			
I	9 (12 %)	0	<0.001
IIA	28 (37 %)	1 (5 %)	
IIB	37 (49 %)	8 (50 %)	
III	0	7 (44 %)	
IV	2 (3 %)	0	
Positive surgical margin	9 (12 %)	6 (38 %)	0.012
Adjuvant chemotherapy	43 (57 %)	9 (56 %)	0.981

[a] Clavien–Dindo classification (>IIIa)

Surgery

All of the pancreatectomies, including standard DP and DP with celiac axis resection, were planned before surgery according to the preoperative imaging evaluation. Our standard DP procedure consisted of en bloc resection of the distal pancreas and spleen. The splenic artery was divided at the origin. The cut margin of the pancreas was examined using frozen sections. If the resected margin was positive, then additional resection of the pancreatic neck was performed when possible. The regional and peripancreatic lymph nodes, including those along the CHA, and the celiac axis were routinely dissected. The left half of the SMA nerve plexus and lymph nodes along the SMA were also dissected. Our DP with celiac axis resection procedure included additional en bloc resection of the celiac axis, CHA and left gastric arteries, the celiac nerve plexus, and the anterior to left-sided nerve plexus along the SMA. No patients underwent arterial reconstruction.

Statistical analysis

All statistical analyses were performed using the SPSS, version 19.0. Continuous variables were expressed as medians with ranges. The Chi-square test or Fisher's exact test were performed for categorical variables where appropriate. The Mann–Whitney U test was used for continuous variables. The Kaplan–Meier method was used to calculate the overall survival rates. Univariate analyses were performed to determine which variables were associated with survival according to the log-rank test. The variables that were found to be significant in

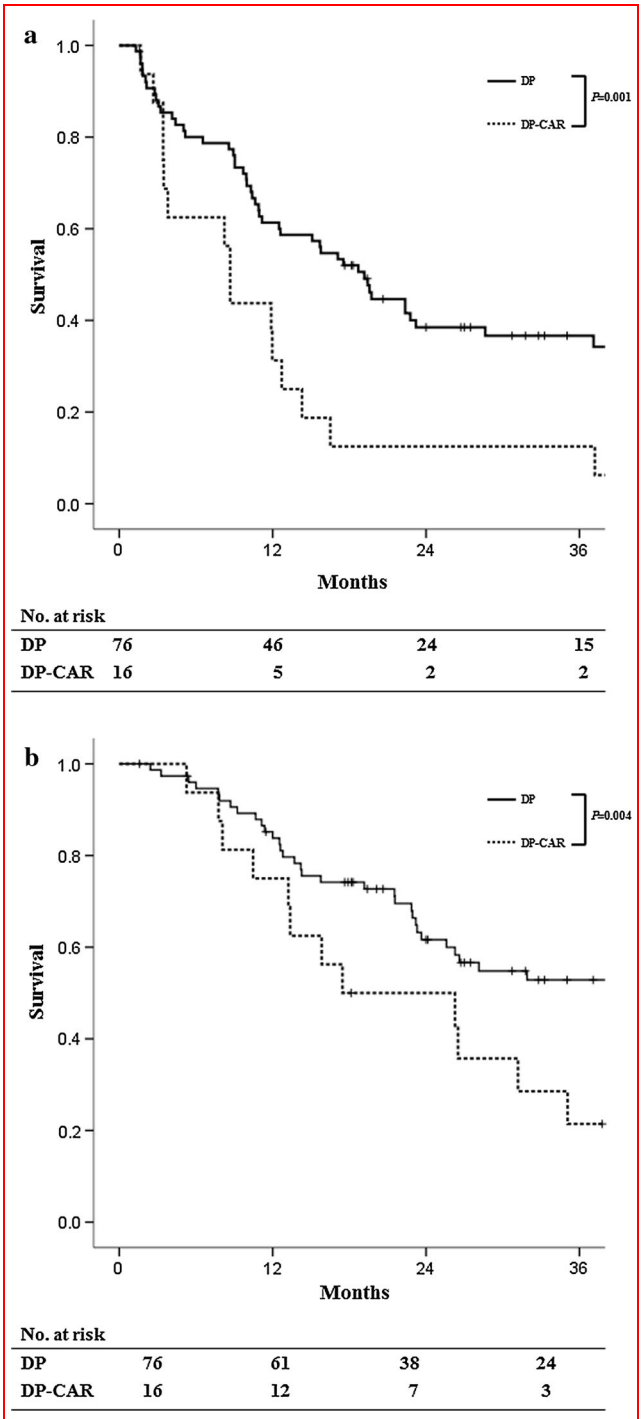

Fig. 3 Survival curve according to surgical procedure. **a** Disease-free survival, **b** overall survival

the univariate analysis were subjected to a multivariate Cox proportional hazards regression analysis. A value of $p < 0.05$ was considered to be statistically significant.

Results

The patient's characteristics according to the surgical procedure are presented in Table 1. DP with celiac axis resection was associated with a significantly longer operative time (338 vs. 263 min, $p < 0.001$) and greater amount of blood loss (902 vs. 460 ml, $p = 0.001$) than DP. Combined portal vein resection and reconstruction was performed more frequently in the DP with celiac axis resection group than in the DP group (31 vs. 7 %, $p = 0.004$). However, the rates of morbidity were almost identical (81 vs. 67 %, $p = 0.059$). There were no arterial resection-related complications such as liver abscess and gastric ischemia, and no hospital deaths occurred in either group. According to the UICC TNM classification system [16], the majority of patients undergoing standard DP had stage IIA or IIB disease, whereas stage IIB and III diseases were dominant in the patients undergoing DP with celiac axis resection. The microscopic positive margin (R1) resection rate was significantly higher in the DP with celiac axis resection group than in the standard DP group (38 vs. 12 %, $p = 0.012$). The 1- and 3-year disease-free survival rates and median disease-free survival time were 31.3, 12.5 %, and 8.7 months in the DP with celiac axis resection group and 61.3, 36.7 %, and 19.2 months in the DP group ($p = 0.001$) (Fig. 3a). The 1- and 3-year overall survival rates and median overall survival time were 75.0, 21.4 %, and 17.5 months in the DP with celiac axis resection group and 85.2, 52.9 %, and 43.1 months in the DP group ($p = 0.040$) (Fig. 3b).

Table 2 shows a comparison of the patient characteristics according to tumor extension among the patients who underwent DP with celiac axis resection. In patients with CA/CHA (−) status, the median distance between the right edge of the tumor and the origin of the splenic artery was 3 mm (range 2–7 mm). Pathologically, six of seven patients with a CA/CHA (−) status had stage IIB disease, whereas seven of nine patients with a CA/CHA (+) status had stage III disease. There were no significant differences regarding the perioperative outcomes between the CA/CHA (−) and CA/CHA (+) groups.

The 1- and 3-year disease-free survival rates and median disease-free survival time were 71.4, 28.6 %, and 14.3 months in the patients with a CA/CHA (−) status and 0, 0 %, and 8.2 months in the patients with a CA/CHA (+) status ($p = 0.011$) (Fig. 4a). All patients with a CA/CHA (+) status developed recurrence within 12 months after undergoing resection. The 1- and 3-year overall survival rates and median overall survival time were 100, 42.9 %, and 35.1 months in the patients with a CA/CHA (−) status and 55.6, 0 %, and 13.2 months in the patients with a CA/

Table 2 Comparison of the patients' characteristics among those who underwent DP-CAR according to the degree of tumor extension

	CA/CHA (−) ($n = 7$)	CA/CHA (+) ($n = 9$)	p
Age (y.o)	72 (32–78)	69 (60–85)	0.671
Gender			
Male	5	5	0.632
Female	2	4	
CA19-9 (U/ml)	183 (11–457)	375 (1–1739)	0.832
Distance (mm)[a]	3 (2–7)	–	–
Operation time (min)	322 (259–507)	406 (305–504)	0.186
Blood loss (ml)	913 (464–1607)	815 (461–1893)	0.874
Portal vein resection	1 (14 %)	4 (44 %)	0.308
Pancreatic fistula	3 (43 %)	4 (44 %)	1
Morbidity[b]	6 (86 %)	8 (89 %)	1
Hospital stay (days)	23 (16–33)	30 (15–39)	0.595
Differentiation			
Well	2 (29 %)	1 (11 %)	0.670
Mode	4 (57 %)	5 (56 %)	
Poor	0	1 (11 %)	
Asc	1 (14 %)	2 (22 %)	
Lymph node metastases	6 (86 %)	8 (89 %)	1
UICC stage			
I	0	0	0.007
IIA	1 (14 %)	0	
IIB	6 (86 %)	2 (22 %)	
III	0	7 (78 %)	
IV	0	0	
Lymphatic infiltration	6 (86 %)	8 (89 %)	1
Venous infiltration	3 (43 %)	8 (89 %)	0.106
Positive surgical margin	2 (29 %)	4 (44 %)	0.632
Adjuvant chemotherapy	5 (71 %)	5 (56 %)	0.633

[a] Distance between the proximal edge of the tumor and the root of the splenic artery

[b] Clavien–Dindo classification (>IIIa)

well, mode, and poor; well, moderately, and poorly differentiated adenocarcinoma

asc, adenosquamous carcinoma

CHA (+) status ($p = 0.001$) (Fig. 4b). Comparing the patients undergoing standard DP and DP with celiac axis resection with a CA/CHA (−) status, there were no significant differences in either the disease-free or overall survival times (Fig. 4a, b).

Table 3 presents the pattern of first recurrence in the patients undergoing DP with celiac axis resection. Although there were no significant differences, liver metastasis tended to occur more frequently in the patients with a CA/CHA (+) status.

The results of the univariate and multivariate survival analyses are listed in Table 4. The multivariate analysis showed that preoperative value of CA19-9, CT findings of celiac axis and/or common hepatic artery invasion defined as CA/CHA (+), and microscopic venous infiltration were proven to be independent significant prognostic factors.

Discussion

Since Hirano et al. [4] reported their series of DP with celiac axis resection with a lower R1 resection rate and acceptable survival, with a median survival time of 21 months, DP with celiac axis resection has been expected to improve the survival of patients with locally advanced pancreatic body/tail cancer. However, subsequent reports have shown inconsistent results with this challenging procedure, with a median survival time ranging from 9.3 to 26 months [5–10]. Therefore, it remains unclear whether DP with celiac axis resection truly achieves favorable survival outcomes in patients with locally advanced pancreatic body/tail cancer.

We noted that there are two indications for DP with celiac axis resection. One is cancer invasion of celiac axis

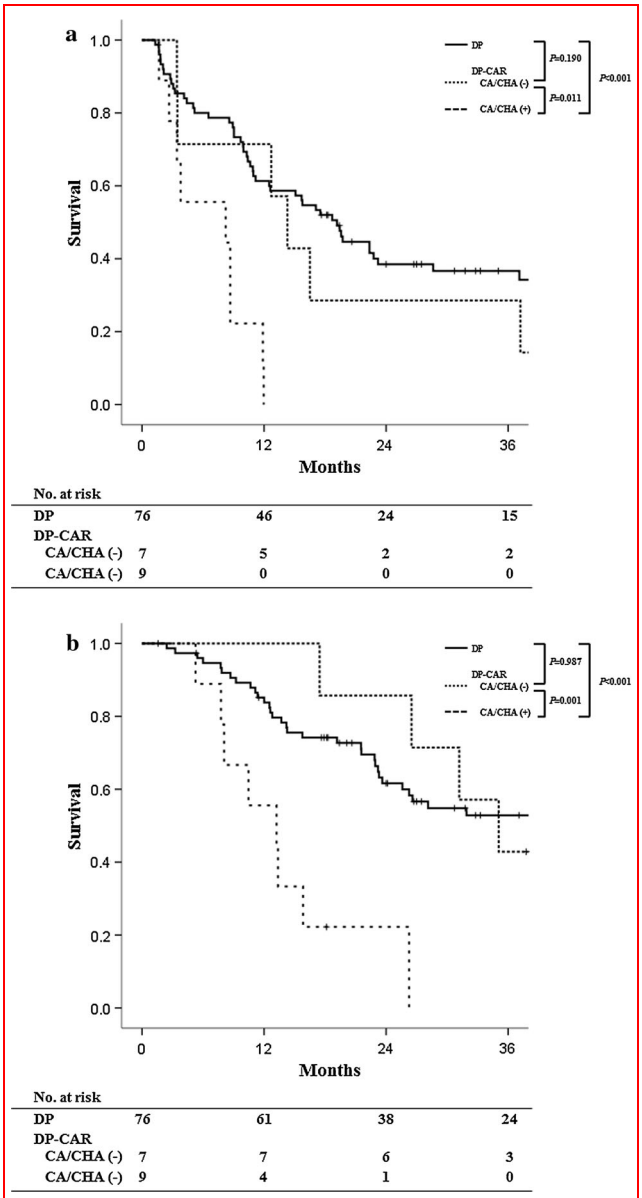

Fig. 4 Survival curve according to three groups. **a** Disease-free survival, **b** overall survival

and/or CHA, and the other is invasion of the root of the splenic artery without involvement of celiac axis or CHA. The former [CA/CHA (+) in the current study] is clinically classified as T4, resulting in at least stage III, according to the UICC classification [16], and the latter [CA/CHA (−)] is classified as T3, resulting in stage IIA or IIB. We considered that the existence of two indications and the intermixture of cancer stages may be causes of the inconsistency in survival outcomes of DP with celiac axis resection.

In the current series, neither the overall nor disease-free survival of the patients with a CA/CHA (−) status were significantly different from that observed in the DP group. For such patients, the performance of DP with celiac axis resection might be controversial. Among the patients with a CA/CHA (−) status, the median distance between the origin of the splenic artery and the border of the cancerous mass was only 3 mm (range 2–7 mm). We experienced some patients who underwent standard DP despite the tumor being adjacent to the root of the splenic artery; this resulted in an R1 resection and subsequent local recurrence. Tsuchikawa et al. [12] clarified that the celiac axis was frequently involved from the neural plexus around the splenic artery; however, making a preoperative diagnosis based on imaging findings alone is difficult. They, therefore, recommended DP with celiac axis resection in cases where the cancer extended close to celiac artery (root of splenic artery). Although they did not describe the long-term outcome, their concept is almost identical with our protocol. Okada et al. [9] also reported that patients with tumors located within 10 mm from the root of the splenic artery exhibit a greater incidence of R1 curability with standard DP. It is therefore necessary to perform DP with celiac axis resection in patients with a CA/CHA (−) status in order to obtain an adequate surgical margin. Although the impact of the margin status on survival remains controversial [17–23], the principle of curative surgical resection for pancreatic cancer should involve the complete clearance of cancer cells. The use of DP with celiac axis

Table 3 Site of first recurrence

	CA/CHA (−) ($n = 7$)	CA/CHA (+) ($n = 9$)	p
Liver	3 (43 %)	7 (78 %)	0.302
Peritoneum	1 (14 %)	2 (22 %)	1
Lymph node	1 (14 %)	2 (22 %)	1
Local	2 (29 %)	2 (29 %)	1
Other distant[a]	1 (14 %)	3 (33 %)	0.585

Numbers include overlap in patients

[a] Other than liver or peritoneum

Table 4 Prognostic factors for postoperative survival

	Univariate			Multivariate		
	n	MST	*p*	HR	95 % CI	*p*
Operative procedure						
DP	76	43	0.04			
DP-CAR	16	17				
CA/CHA invasion[a]						
−	83	41	<0.001			
+	9	13		3.63	1.60–8.23	0.002
Margin status						
R0	77	43	0.002			
R1	15	23				
Lymph node metastases						
−	36	–	0.001			
+	56	23				
Lymphatic infiltration						
−	24	–	0.007			
+	68	26				
Venous infiltration						
−	39	78	<0.001			
+	53	23		2.91	1.52–5.53	0.004
Perineural invasion						
−	11	–	0.019			
+	81	26				
Differentiation						
Well	28	72	0.103			
Others	64	26				
Serosal invasion						
−	58	45	0.001			
+	34	23				
Retroperitoneal invasion						
−	17	–	0.001			
+	75	23				
Nerve plexus invasion						
−	68	52	0.001			
+	24	23				
Portal/splenic vein invasion						
−	47	46	0.002			
+	45	23				
Arterial invasion						
−	66	45	0.002			
+	26	23				
CA19-9 (U/ml)						
<250	70	45	<0.001			
≥250	22	13		3.99	2.03–7.84	<0.001
Postoperative chemotherapy						
−	40	27	0.873			
+	52	32				

[a] CT findings of celiac axis or common hepatic artery invasion

resection in patients with a CA/CHA (−) status can be justified from both a theoretical point of view and a standpoint of survival following surgery.

In contrast, both the overall and disease-free survival of the patients with a CA/CHA (+) status were significantly more deteriorated than those observed in the DP group and the patients with a CA/CHA (−) status. The median disease-free and overall survival times of the CA/CHA (+) status patients were only 8.2 and 13.2 months, respectively. Some authors have stressed that the use of DP with celiac axis resection to treat advanced (T4) pancreatic body/tail cancer is justified because the prognosis of patients who undergo DP with celiac axis resection is significantly better than that of patients with unresectable disease [5, 7]. However, with advances in chemo- and chemoradiotherapy, the survival of patients with locally advanced unresectable pancreatic cancer has improved. A recently introduced regimen with gemcitabine and/or S-1 has been reported to achieve a median survival time of up to 15.9 months [24]. Another study demonstrated that capecitabine-based chemoradiotherapy also offers a median survival time of 15.2 months [25]. The survival data for DP with celiac axis resection in patients with a CA/CHA (+) status are even worse than those for patients treated with chemo- or chemoradiotherapy. Therefore, it is difficult to justify the use of DP with celiac axis resection in pancreatic cancer patients with a CA/CHA (+) status.

Although a CA/CHA (+) status indicates the presence of locally advanced disease, it is associated with a higher incidence of liver metastasis in the early postoperative period. It has been reported that even if a portion of the celiac axis is resected, the majority of patients with locally advanced disease already have potential systemic metastases, although such lesions are not always apparent on preoperative imaging studies [26, 27]. In the current study, pathological examinations revealed microscopic venous infiltration in eight of the nine CA/CHA (+) patients. Looking at the very short disease-free survival, high rate of liver metastasis at the first recurrence site, and the pathologic findings, a CA/CHA (+) status can be considered to potentially indicate the presence of systemic disease.

Recently, preoperative treatments, such as neoadjuvant chemoradiotherapy, for borderline resectable or advanced pancreatic cancer have been applied [8, 28, 29]. Baumgartner et al. [8] reported the use of DP with en bloc celiac axis resection following neoadjuvant chemoradiotherapy for locally advanced pancreatic cancer of the neck and body. The authors achieved higher local control, with an R0 resection rate of 91 % and a median overall survival time of 26 months. Cesaretti et al. [11] reported that five of seven cases with borderline resectable/locally advanced pancreatic cancer could undergo DP with en bloc celiac axis resection after neoadjuvant chemotherapy, and they demonstrated a median overall survival time of 24 months. The advantages of this approach are considered to include the following: (1) the preoperative downstaging of the disease to achieve an R0 resection, (2) the early treatment of micrometastases that are already present before surgery, and (3) the discrimination of patients who are likely to benefit from subsequent surgery. Although the efficacy of this strategy is uncertain, it appears to represent one option for treating advanced pancreatic cancer, as our results clarified that DP with celiac axis resection alone does not achieve satisfactory survival outcomes in patients with a CA/CHA (+) status. Once we became aware of this result, we changed the treatment strategy for patients with CA/CHA (+) pancreatic cancer from surgery first to neoadjuvant chemoradiotherapy prior to DP with celiac axis resection. The accumulation of cases and long-term follow-up will be necessary for the evaluation of this strategy.

A limitation of this study is its retrospective nature of the study and the small number of the patients. However, the number of patients who meet the criteria for DP with celiac axis resection is limited. Therefore, multicenter studies are needed to analyze the role of DP with celiac axis resection on a large scale.

In conclusion, there were different indications for DP with celiac axis resection: namely CA/CHA (−) and CA/CHA (+). DP with celiac axis resection brought acceptable survival, which was equivalent to that of the DP group, for patients with a CA/CHA (−) status. However, it was difficult to justify DP with celiac axis resection for patients with a CA/CHA (+) status because such patients showed a worse survival.

Compliance with ethical standards

Conflict of interest The authors declare no financial or any other type of support.

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