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The Anatomical Pattern of the Proximal Jejunal Vein as a Prognostic Factor in Patients With Pancreatic Head Cancer Treated With Preoperative Chemoradiation Therapy

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Abstract. *Background/Aim: The significance of the anatomical variations of proximal jejunal vein [the so-called 1st jejunal vein (J1v)] has been reported from a technical standpoint. The aim of this study was to retrospectively investigate the prognostic impact of the anatomical variations of J1v in the surgical treatment of resectable pancreatic cancer (PC). Patients and Methods: A total of 49 patients with resectable PC located in the uncinate process were included in this study. The J1v converging pattern was divided into 2 groups in terms of its relation to the SMA (i.e., the J1v status): i) group D: the J1v travels posterior to the SMA; ii) group V: the J1v travels anterior to the SMA. The associations between the J1v status and surgical outcome were assessed. Results: The 5-year survival rate after resection in group V (35%) was significantly lower than that in group D (70%) (p=0.029), and the J1v status of group V was the only independent negative prognostic factor (HR=5.49; 95% CI=1.69-19.3; p=0.005). Conclusion: The J1v converging pattern is a significant prognostic variable in patients with PC located in the uncinate process: the J1v status of group V was significantly associated with impaired survival.*

Tumor invasion of major vascular systems is one of the significant factors of a poor prognosis in the treatment of pancreatic cancer (PC) (1-3). PC located in the head of the pancreas, especially in the uncinate process, frequently involves the mesenteric vasculature due to the anatomical proximity of the uncinate process and the root of the mesentery (4-6). The mesenteric vasculature in the root of the mesentery consists of the superior mesenteric vein (SMV), superior mesenteric artery (SMA), and the tributaries of these major vessels. A variety of anatomical variations of these vessels have been previously reported, and those variations could potentially have a significant influence on the pattern of locoregional tumor extension and thereby might have prognostic significance in terms of the surgical treatment of PC located in the uncinate process (7). The anatomy of the SMA and its tributaries has been well investigated from a surgical (technical), as well as from an oncological (prognostic) viewpoint in performing pancreaticoduodenectomy (PD) (8, 9). It is well known that tumor extension around the SMA is associated with significantly impaired surgical outcomes in patients with PC treated with the surgery-first strategy, and it has also been reported that anatomical variations of the tributaries of the SMA, for example, the replaced right hepatic artery arising from the SMA, could potentially have a significant impact on the short- and long-term outcomes after PD (7, 10). In this context, we have also previously reported that tumor extension around the SMA negatively impacts the prognosis of patients treated with preoperative chemoradiation therapy (CRT) for PC (11).

Recently, several authors have reported the clinical significance of anatomical variations of the SMV and its tributaries, such as the most proximal jejunal vein or the first jejunal vein (J1v), in association with technical approaches during PD (8, 12-14). The J1v is one of the major tributaries of the SMV, and its converging pattern has been previously reported to be variable and complicated (8, 12-16). Typically, the J1v converges into the right posterolateral aspects of the

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main trunk of the SMV after traveling transversely, posterior to the SMA ("dorsal J1v", Figure 1a). In this pattern, the J1v is located between the SMA and the uncinate process. Additionally, it has been reported that the J1v sometimes drains into anterior aspects of the main trunk of the SMV after running transversely, anterior to the SMA ("ventral J1v", Figure 1b). In this case, the uncinate process is located directly next to the SMA (Figure 1b). Ishikawa *et al*. noted that a ventral J1v was observed in 21% of patients who underwent PD and tended to form a large trunk of jejunal veins; in addition, the injury or ligation of those large draining veins from the upper mesentery potentially caused severe and massive congestion of the elevated jejunum during PD (16). However, there have been no reports on assessing the oncological (prognostic) impact of anatomical variations of the J1v in the surgical treatment of pancreatic head cancer (PHC).

In light of the anatomical proximity and complexity of the SMV-J1v-SMA bundle and PC in the uncinate process and the robust negative prognostic impact of tumor extension around the SMA, anatomical variations of the SMV-J1v in relation to the relative location of the SMA (dorsal *vs*. ventral J1v) and the PC in the uncinate process could potentially have prognostic significance in the surgical treatment of PC. We hypothesized that in patients with PC located in the uncinate process and a ventral J1v (Figure 1b), the tumor is predisposed extension toward the surroundings of the SMA because PC in the uncinate process is located closely and directly next to the SMA. Consequently, poorer outcomes may be achieved by the surgical treatment of patients with PC in the uncinate process and with a ventral J1v than in those with a dorsal J1v (Figure 1a). Thus, we conducted this retrospective study with the aim of investigating the prognostic impact of the anatomical relationship between the SMV-J1v-SMA bundle and PC located in the uncinate process with respect to the preoperative treatment strategy.

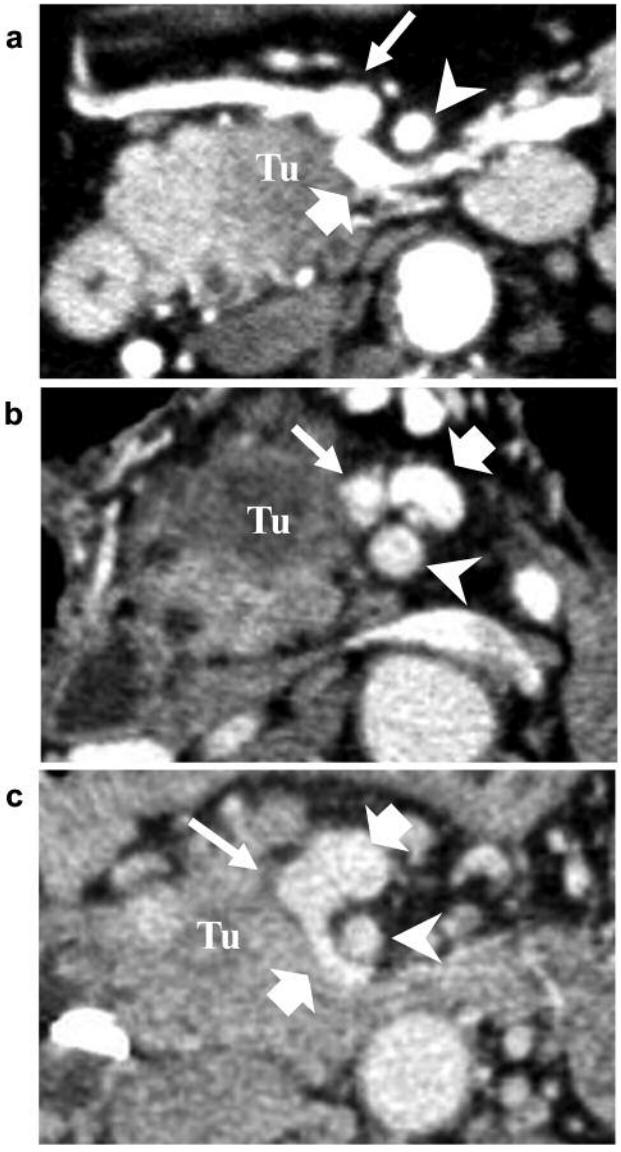

Figure 1. *Anatomical pattern of J1v location. The first jejunal branching pattern of the superior mesenteric vein (SMV) (white thin arrow) travels posterior to the superior mesenteric artery (SMA). That is, first jejunal vein (white thick arrow) runs between pancreatic head tumor (Tu) and SMA (white arrow head) (a). The first jejunal branching pattern of the SMV (white thin arrow) travels anterior to the SMA. That is, pancreatic head tumor (Tu) is located just next to SMA (white arrow head) (b). The SMA (white arrow head) is sandwiched between 2 isolated proximal jejunal veins (white thick arrow) converging from SMV (white thin arrow). That is, one vein runs between pancreatic head tumor (Tu) and SMA (white arrow head) and another vein travels anterior to the SMA (c).*

Patients and Methods

Patients. Between 2006 and 2015, a total of 266 treatment-naive patients with resectable and borderline resectable PHC underwent preoperative gemcitabine-based CRT and subsequent surgery as a part of a prospective phase II clinical trial at Osaka International Cancer Institute (UMIN-CTR: UMIN000001804) (17, 18). All protocols were conducted after obtaining written informed consent from all patients in accordance with the approved procedures at our hospital. Among these 266 patients, 183 with resectable PHC according to the National Comprehensive Cancer Network (NCCN) guidelines Version 2.2017 were identified and included them in this study, whereas the remaining 83 patients with borderline resectable PHC were excluded from this study (Figure 2) (19). Therefore, for the 183 patients included in this study, the following radiographical findings were confirmed before initiation of the preoperative CRT: (i) no evidence of distant metastasis (M0); (ii) definite radiographic evidence of tumor extension beyond the pancreatic confines (T3 disease according to the 7th version of the UICC classification); (iii) no evidence of tumor abutment to the SMA, common hepatic artery (CHA), or celiac axis (CA); (iv) either no evidence of solid tumor contact of >180˚ of the circumference of the SMV/portal

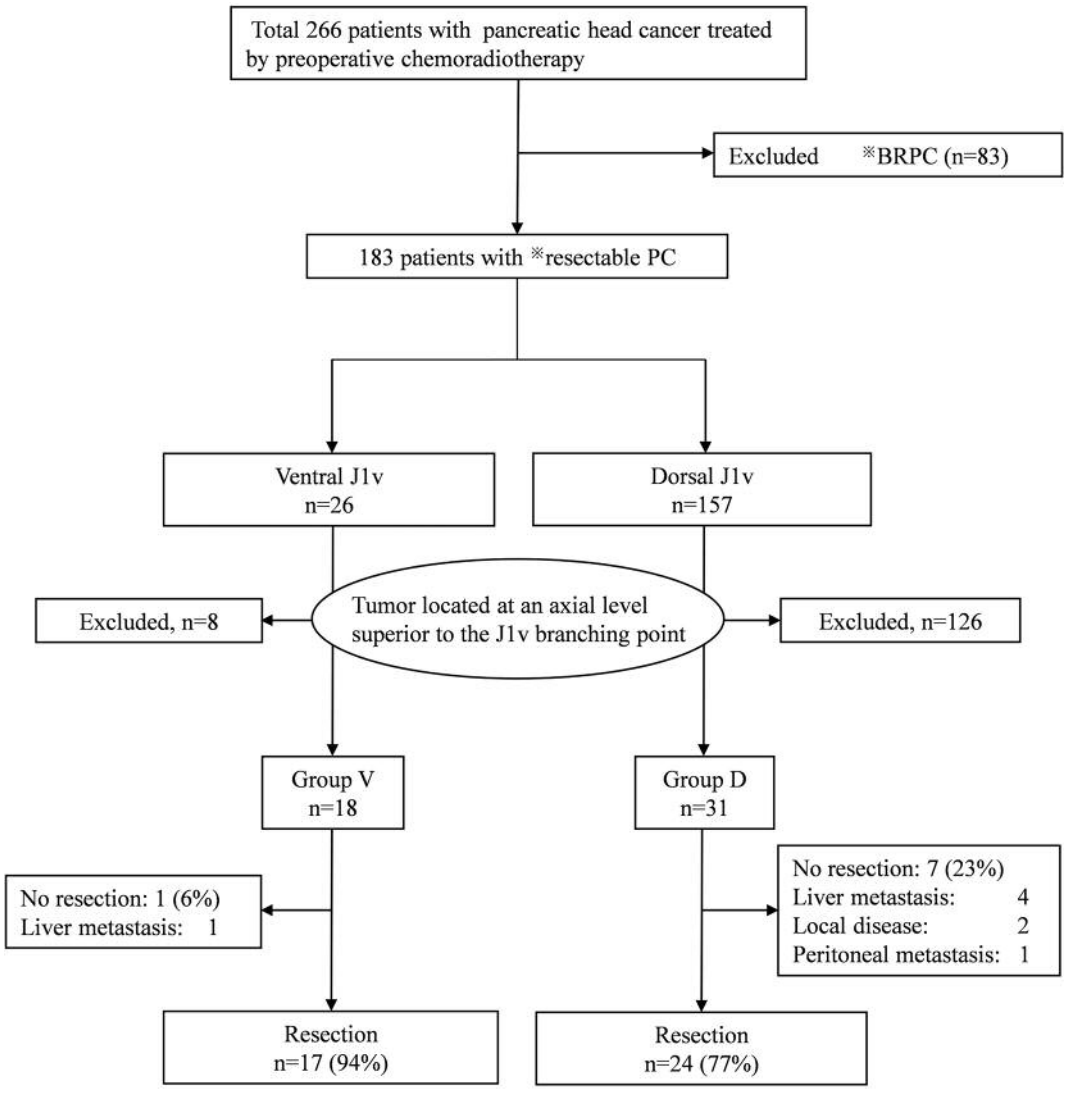

Figure 2. *Algorithm of the clinical process according to J1v status. *Pancreatic cancer was graded according to the guidelines from the National Comprehensive Cancer Network (NCCN) Version 2.2017 (19). J1v, the most proximal jejunal vein or the first jejunal vein; BRPC, borderline resectable pancreatic cancer.*

vein (PV) or contour irregularity of the SMV/PV due to tumor invasion. We reviewed the computed tomography (CT) images before initiation of the preoperative CRT and assessed the anatomical pattern of the SMV tributaries with special reference to the locational relationships among the J1v, SMA, and PHC, as described below in detail.

Anatomical definition of the J1v and classification of the J1v converging pattern toward the main SMV trunk. Although there is no consensus regarding the anatomical definition of the J1v, in this study, we designated the J1v as follows based on the classification schemes presented in previous reports (15, 16): i) the primary jejunal vein emerging from the SMV, excluding the small direct venous branches into the proximal small bowel; ii) the vein accompanying the first jejunal artery; iii) the vein draining the small venous tributaries from the uncinate process. The J1v sometimes forms a venous trunk with the second jejunal vein, middle colic vein and inferior mesenteric vein; in such cases, this venous trunk was defined as a part of the J1v in this study (15, 16).

The J1v converging pattern (J1v status) was divided into two groups according to its location relative to the SMA; the dorsal J1v group, in which the J1v converges with the right posterolateral aspects of the main trunk of the SMV after traveling transversely, posterior to the SMA (Figure 1a), and the ventral J1v group, in which the J1v enters the anterior aspects of the main trunk of the SMV after running transversely, anterior to the SMA (Figure 1b). In the case that 2 isolated proximal jejunal veins converged into the main trunk of the SMV after coursing transversely, posterior to and anterior to the SMA, the J1v was considered dorsal in this study (Figure 1c).

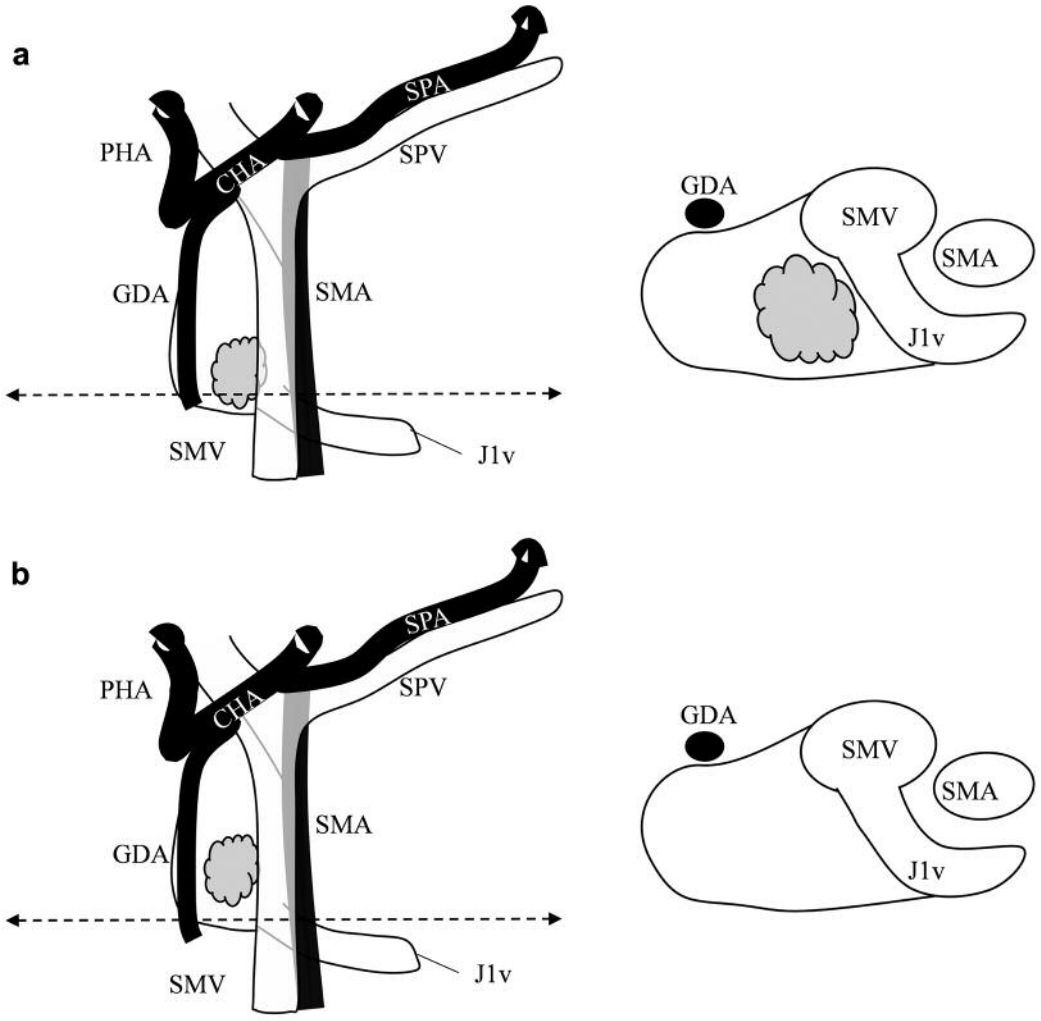

Figure 3. *Criteria for anatomical relationship between tumor and J1v around the uncinate process. Anatomic drawing depicts uncinate process derived from ventral pancreatic bud. J1v converged from SMV in a level below the inferior margin of tumor site (shaded area) (a). Tumor site (shaded area), with inferior margin, which we defined as the same axial level of the J1v branching, was found on the same plane as J1v converging point from SMV, as to the tumor images on preoperative CT from axial viewing (b). CHA, Common hepatic artery; SPA, splenic artery; PHA, proper hepatic artery; SMV, superior mesenteric vein; SMA, superior mesenteric artery; J1v, first jejunal vein; GDA, gastroduodenal artery; SPV, splenic vein.*

Protocol for pre-operative gemcitabine-based CRT. The details of the protocol for preoperative gemcitabine-based CRT have been previously described (17, 18). In brief, 3D radiation was administered at a total dose of 50 Gy (a 2-Gy daily fraction 5 times per week for 4 weeks) targeting the following fields: the primary pancreatic tumor, the celiac artery and SMA, the retroperitoneal soft tissue, and the para-aortic region. The intravenous administration of gemcitabine (1,000 mg/m^2) was concurrently initiated on days 1, 8, and 15 during each 4-week cycle; this procedure was performed repeatedly for 3 cycles, such that preoperative CRT was completed approximately 3 months after initiation. Restaging of the tumor was performed at the time of preoperative CRT completion and laparotomy, and a pancreatectomy was performed on patients who did not reveal disease progression (*i.e.*, no manifestations of distant metastasis) during pre-operative CRT. After surgical resection of the PC, each patient underwent post-operative liver perfusion chemotherapy (previously described in detail) (17, 18) and the standard post-operative follow-up examinations.

Statistical analysis. Correlations between the J1v status and the clinicopathological factors were determined using the chi-squared test. Survival rates were estimated using the Kaplan-Meier method, and the differences in survival according to the J1v status were analyzed by log-rank test. Univariate and multivariate analyses were performed to determine significant prognostic factors using Cox regression models. The presence of a statistically significant difference was denoted by $p<0.05$. All analyses were performed using JMP Pro version 13.0.0 software (JMP, SAS Institute, Cary NC).

Results

One hundred fifty-seven of 183 patients (86%) had a dorsal J1v, whereas the remaining 26 patients had a ventral J1v (14%) (Figure 2). Among those 183 patients, we identified 49 patients (18 in group V and 31 in group D, Figure 2) with PHC primarily located in the uncinate process and at the same axial level as the J1v branching point (Figure 3a), whereas the remaining 134 patients (8 in group V and 126 in group D, Figure 2) had PHC located at an axial level superior to the J1v branching point (Figure 3b). In this study, we focused on former 49 patients (Figure 3a) to assess the prognostic impact of the locational relationship between PHC and the SMV-J1v-SMA bundle.

Table I summarizes the pretreatment clinical characteristics of the 49 patients used for the prognostic analyses. Forty-one patients underwent subsequent pancreatectomy, including PD (n=39) and total pancreatectomy (n=2) (resection rate: 84%) (Figure 2 and Table I). Eight patients failed to undergo pancreatectomy because of liver metastasis (n=5), local disease (n=2) or peritoneal metastasis (n=1) (Figure 2). Table II summarizes the histopathological variables of all the patients who underwent resection (n=41). The rate of positive nodal involvement was 29%, and a major histological response [*i.e.*, a histological appearance of grade III and IV, as proposed by Evans *et al*. (20)] was observed in 8 cases (20%). Pathological margin-negative (R0) resection was achieved in all of the patients in both groups. The 5-year survival rate among the 41 patients who underwent resection was 53%, whereas the median survival of those who did not was 11 months (Figure 4a).

Thirty-one of the 49 patients had a dorsal J1v (group D), and the remaining 18 had a ventral J1v (group V) (Figure 2 and Table I). Table I also shows a comparison of the pretreatment patient demographics between groups D and V. There were no significant differences in the pretreatment patient demographics between groups D and V or in the resection rate (77% *vs*. 94%, respectively, p=0.096) (Table I). Differences in the histopathological variables of patients who underwent resection were evaluated between groups D and V (Table II). No significant difference was observed in the histopathological variables, including nodal involvement, nerve plexus involvement, and vascular invasion, between the 2 groups (Table II).

In the univariate analysis of the postoperative survival of the patients who underwent resection, a ventral J1v was identified as a statistically significant adverse prognostic factor (p=0.033, Table III). In a multivariate analysis with a stepwise regression model, a ventral J1v was an independent prognostic factor of impaired survival [hazard ratio (HR)=5.49, p=0.005; Table III]. The Kaplan-Meier curves of the post-operative survival according to the J1v status showed that the 5-year survival rate in group V was significantly lower than that in group D (35% *vs*. 70%; p=0.029) (Figure 4b). Table IV summarizes the location of the initial recurrence [local *vs*. distant: distant recurrence included the liver (n=7), lungs (n=3), peritoneum (n=2), and remote lymph nodes (n=3)]. Although the frequency of local recurrence in group V was comparable to that in group D (12% *vs*. 8%, p=0.555), the frequency of distant recurrence was marginally higher in group V than in group D (53% *vs*. 25%, p=0.067) (Table IV).

Discussion

A detailed understanding of the local anatomy of major vascular systems is important for safety in performing various surgeries. Previous reports have usually described the clinical significance of anatomical variations of the mesenteric vasculature from surgical aspects related to technical pitfalls during PD (12, 16, 21, 22). Certainly, separation of the uncinate process from the root of the mesentery is a technically demanding process during PD. In addition, PC, especially PC located in the uncinate process, has a strong tendency to infiltrate the locoregional area along the mesenteric vasculature in the root of the mesentery; thus, appropriate management of the SMV, SMA, and their tributaries is a key for the oncologically successful resection of PC (8, 9, 23, 24). In this regard, anatomical variations of the major vascular systems in the root of the mesentery could potentially have a significant impact from an oncological (prognostic) perspective as well.

Our current study first demonstrates the oncological impact of anatomical variations of the tributaries of SMV (J1v) in the treatment of PHC located in the uncinate process. In the current study, 49 of 183 patients with PHC had tumors primarily located at the same axial level as the J1v branching point, and 37% of these patients had a ventral J1v (group V), which was concordant with the results of previous reports (ranging from 11% to 31%); additionally, the survival rate among those patients was significantly lower than that among patients with a dorsal J1v (group D) (Figure 4b) (8, 13, 15, 16). The difference in the anatomical features of the SMV-J1v-SMA bundle between patients with a ventral and dorsal J1v could be translated in relation to the PC in the uncinate process, as follows: the PC in the uncinate process in patients with a ventral J1v is located directly abutting the connective tissues and/or nerve plexus surrounding the SMA, while in patients with a dorsal J1v is located directly abutting the SMV and its tributaries. Based on these concepts, there are two important points to be noted in interpreting the results of the current study. First, all the patients included in this study had T3 disease according to the 7th version of the UICC classification, which is categorized as resectable PHC, *i.e.*, a tumor showing definite radiological findings of extension beyond the pancreatic confines without radiographically evident nerve plexus invasion around the SMA before the

Table I. *Patient demographics before the initiation of preoperative treatment according to the J1v status.*

	Total (n=49) n (%)	J1v Status		*p*-Value
		Group D* (n=31) n (%)	Group V** (n=18) n (%)	
Gender				0.326
Male	34 (69)	20 (65)	14 (78)	
Female	15 (31)	11 (35)	4 (22)	
Age				0.110
≤65	29 (59)	21 (68)	8 (44)	
>65	20 (41)	10 (32)	10 (56)	
Size(mm)				0.812
≤20	18 (37)	11 (35)	7 (39)	
>20	31 (63)	20 (65)	11 (61)	
Pancreatectomy				0.096
Yes	41 (84)	24 (77)	17 (94)	
No	8 (16)	7 (23)	1 (6)	

*J1v branching posterior to the superior mesenteric artery (SMA) (Dorsal J1v cases). **J1v branching anterior to the SMA (Ventral J1v cases).

Table II. *Histopathological variables of resected cases.*

	Total (n=41) n (%)	J1v Status		*p*-Value
		Group D* (n=24) n (%)	Group V** (n=17) n (%)	
Nodal involvement				0.477
Negative	29 (71)	18 (75)	11 (65)	
Positive	12 (29)	6 (25)	6 (35)	
Extra pancreatic nerve plexus invasion				0.803
Negative	39 (95)	23 (95)	16 (94)	
Positive	2 (5)	1 (5)	1 (6)	
Vascular invasion				0.360
Negative	38 (93)	23 (95)	15 (88)	
Positive	3 (7)	1 (5)	2 (12)	
Intrapancreatic perineural invasion				0.938
Negative	22 (54)	13 (54)	9 (52)	
Positive	19 (46)	11 (46)	8 (47)	
Lympho-vascular invasion				0.160
Negative	29 (71)	19 (79)	10 (59)	
Positive	12 (29)	5 (21)	7 (41)	
Histological appearance***				0.799
I/II	33 (80)	19 (79)	14 (82)	
III/IV	8 (20)	5 (21)	3 (18)	

*J1v branching posterior to the superior mesenteric artery (SMA). **J1v branching anterior to the SMA. ***The evaluation of the histopathological response to preoperative chemoradiation therapy (CRT) was performed based on a grading scheme described by Evans *et al.* (20).

initiation of preoperative CRT. However, previous reports have also indicated the difficulty of accurately diagnosing pathological nerve plexus invasion by preoperative radiographic evaluations (27-29). Yamamoto *et al.* reported that pathological nerve plexus invasion was observed in more than 50% of patients with PC who had only minimal increased hazy density around the SMA without direct abutment to its circumference (*i.e.*, resectable disease), and that those patients had significantly impaired post-operative survival (29). In the current study, we speculate that the patients in group V would be predisposed to subclinical tumor infiltration around the SMA, because T3 tumors located in the uncinate process directly abut the connective tissues and/or nerve plexus surrounding the SMA. Consequently, the survival rate in the

Table III. *Univariable and multivariable analyses of 41 patients in resected case.*

	Univariable analysis			Multivariable analysis		
Variables	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Clinical variables						
Gender (male)	1.14	0.36-5.07	0.834			
Age (>65)	0.60	0.16-1.78	0.366	0.31	0.08-1.05	0.061
Tumor size (>20 mm)	1.13	0.37-3.25	0.826			
J1v status of group V	3.19	1.10-10.43	0.033	5.49	1.69-19.32	0.005
Histopathologic variables						
Nodal involvement	2.00	0.65-5.86	0.205			
Vascular invasion	3.03	0.47-11.26	0.206			
Extra pancreatic nerve plexus invasion	3.03	0.47-11.32	0.206			
Perineural invasion	1.94	0.67-5.95	0.223			
Lympho-vascular invasion	2.24	0.73-6.51	0.151			
Histologic appearance (I/II)*	3.70	0.73-67.5	0.130	4.45	0.85-82.0	0.083

HR, Hazard ratio; CI, confidence interval. *The evaluation of the histopathological response to preoperative chemoradiation therapy (CRT) was performed based on a grading scheme described by Evans *et al*. (20).

patients in group V was unfavorable compared with that in group D. Second, all the patients included in the current study were treated in the context of a pre-operative CRT strategy. Theoretically, PC in the uncinate process is more likely to involve the SMV and/or its tributaries (*e.g.*, the J1v) in patients in group D than in those in group V, because in patients with a dorsal J1v the PC is located directly next to those vessels (Figure 1a). However, in our previous report, we demonstrated that PV/SMV involvement was not a significant prognostic factor in patients with PC treated with pre-operative CRT (18). In this regard, the prognostic impact of potential SMV invasion in patients in group D was minimized in the context of pre-operative CRT, and as a consequence, the prognostic significance of subclinical tumor infiltration around the SMA may become more evident in the patients in group V. Additionally, the locoregional effect of preoperative CRT may explain the observation that the incidence of pathological extra-pancreatic nerve plexus invasion was quite low in both patients with a ventral and dorsal J1v, and that no significant difference was observed in any of the histopathological factors, including nerve plexus invasion, between groups D and V (Table II).

Another interesting finding drawn from our current study is that the frequency of distant recurrence was higher (marginally) in group V than in group D. This observation might support the speculation regarding the negative prognostic impact of a ventral J1v mentioned above. Namely, previous reports have indicated that the axonal flow within the perineural space around the major arteries is one of the significant pathways for lymphatic involvement in PC, and tumor infiltration of the dense network of nerves surrounding the SMA may facilitate systemic tumor spreading (18). Therefore, a possible higher incidence of subclinical tumor spreading around the SMA in the patients in group V might explain the higher incidence of distant recurrence in these patients than in those in group D. Considering the negative prognostic impact of a ventral J1v due to the increased rate of distant recurrence, preoperative treatment utilizing a more potent systemic chemotherapy [*e.g.*, FOLFIRINOX (combination chemotherapy with leucovorin, fluorouracil, irinotecan and oxaliplatin) and gemcitabine combined with nab-paclitaxel] might improve the surgical outcome in the patients with a ventral J1v (30-33). Further investigation is required to address the pathophysiological mechanism of the prognostic significance of anatomical variations of the J1v in patients with PC located in the uncinate process.

Table IV. *Pattern of recurrence.*

	Group D* (n=24) n	Group V** (n=17) n	*p*-Value
Local	2	2	0.555
Distant	6	9	0.067

*J1v branching posterior to the superior mesenteric artery (SMA) (Dorsal J1v cases). **J1v branching anterior to the SMA (Ventral J1v cases.

There are several limitations in our current study. This study consisted of a small number of patients at a single institution, and the prognostic analyses were performed retrospectively. Further prospective studies with a larger number of patients are necessary to assess the prognostic significance of anatomical variations of the J1v without unexpected biases.

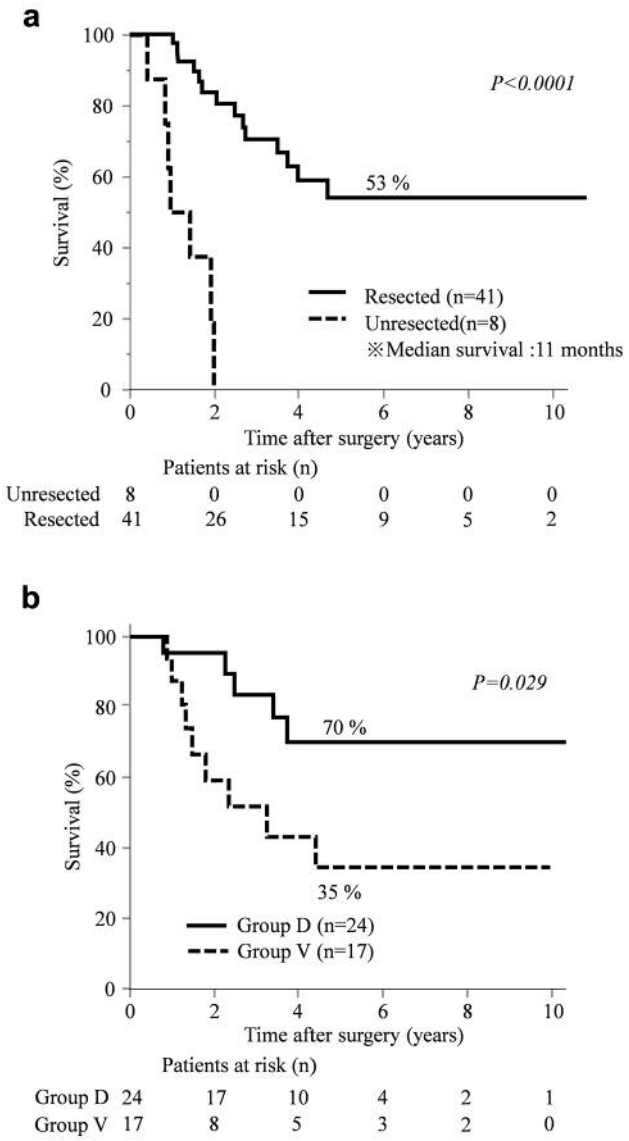

Figure 4. *Survival curve of resected and unresected cases in 49 patients. The 5-year survival rate of the resected cases was 53%, whereas the median survival time of unresected cases was 11 months (a). Survival curve of the postoperative cases according to J1v status. The 5-year survival rates of patients in group D and group V were 70% and 34.6%, respectively (p=0.029) (b).*

In conclusion, the results of the current study indicate that anatomical variation of the J1v converging pattern in relation to the location of the SMA is a significant prognostic factor in patients with PC located in the uncinate process. Specifically, the presence of a ventral J1v was significantly associated with impaired survival possibly because the proximity of PC located in the uncinate process to the SMA in patients with a ventral J1v predisposes the tumor to subclinical locoregional spreading surrounding the SMA.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

SN contributed to study conception and design, acquisition of data, analysis and interpretation of data, drafting manuscript. HT contributed to study conception and design, acquisition of data, analysis and interpretation of data, drafting manuscript. Drafting and revisiting manuscript, and interpretation of the results were performed by HA, KA, SH, DY, HW, HH, NS, HU, NH, KS, KY, JN, MY, TO, HM, MO, MY, MS, OI.

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