World J Surg (2019) 43:626–633
https://doi.org/10.1007/s00268-018-4791-7

ORIGINAL SCIENTIFIC REPORT

Risk Factors for Late-Onset Gastrointestinal Hemorrhage After Pancreatoduodenectomy for Pancreatic Cancer

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Published online: 17 September 2018

Abstract

Background Late-onset gastrointestinal hemorrhage after pancreatoduodenectomy (PD) occasionally occurs repeatedly or leads to a serious condition. This retrospective study aimed to clarify its frequency and pathogenesis.

Methods A total of 147 consecutive patients who underwent PD for pancreatic cancer between 2006 and 2014 were evaluated. Patients were divided into two groups according to the occurrence of late-onset gastrointestinal hemorrhage on postoperative day 100 or later. Furthermore, recurrence and portal vein (PV) hemodynamics were thoroughly reevaluated by computed tomography.

Results Eleven patients experienced late-onset gastrointestinal hemorrhage. The bleeding sites were gastrojejunostomy in four patients, choledochojejunostomy in two, transverse colic marginal vein in one, and unknown in four. The median occurrence time of late-onset gastrointestinal hemorrhage was 13.3 months after PD. PV occlusion (63.6 vs. 8.9%; $p < 0.001$), no patency of PV–splenic vein (SPV) confluence (54.5 vs. 12.7%; $p = 0.002$), and SPV ligation (36.4 vs. 9.6%; $p = 0.025$) were found to be significant risk factors for late-onset gastrointestinal hemorrhage. Among 11 patients who experienced late-onset gastrointestinal hemorrhage, 7 had PV occlusion and 6 had local recurrence.

Conclusions Our data suggested for the first time that both oncologic and non-oncologic factors might contribute to late-onset gastrointestinal hemorrhage after PD for pancreatic cancer. Furthermore, PV occlusion, no PV–SPV patency, and SPV ligation were found to be significant risk factors for late-onset gastrointestinal hemorrhage. Therefore, to prevent late-onset gastrointestinal hemorrhage, we must consider various approaches to maintain the patency of the PV and SPV.

Introduction

Pancreatic resection is one of the most technically complex surgical procedures. Even at well-experienced institutions, the postoperative complications occur with an incidence of 30–60% after pancreatoduodenectomy (PD) [1–3]. Complication such as pancreatic fistula, intra-abdominal abscess, delayed gastric emptying, bile leak, and postoperative hemorrhage are reported early complication after PD [4–8], while exocrine pancreatic insufficiency, non-alcoholic fatty liver disease, and refractory diarrhea are reported late complication [9, 10]. We sometimes experience late-onset gastrointestinal hemorrhage (GH) after PD. However, the etiology and frequency of late-onset GH after PD are largely unknown [6, 7, 11].

Pancreatic cancer is one of the most refractory cancers. It often recurs at wide intervals, even after curative surgery for many patients [12–14]. Once patients develop recurrence, they need to be treated with chemotherapy. Several

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new anticancer drugs and regimens for pancreatic cancer have recently been introduced and helped improve the prognosis. However, if gastrointestinal hemorrhage occurs in patients with recurrence, the treatment for recurrent cancer may be interrupted. Furthermore, if gastrointestinal hemorrhage happens repeatedly, recurrent patients may not be able to receive sufficient anticancer treatment. Thus, the prevention of late-onset gastrointestinal hemorrhage may help improve not only the quality of life but also the prognosis of patients with pancreatic cancer.

Several studies on early (≤24 h after the end of the operation) or late (>24 h after the end of the operation) perioperative postpancreatectomy hemorrhage (PPH) have been reported [6, 7, 11]. PPH was defined and graded according to the International Study Group of Pancreatic Surgery (ISGPS) definition [4]. Many factors, such as pancreatic fistula, pancreatoduodenectomy, age, nutritional risk index chronic renal insufficiency, blood loss, and operation time, have been reported as risk factors for perioperative PPH. However, to our knowledge, no studies have addressed the risk factors for late-onset (postoperative day 100 or later) gastrointestinal hemorrhage Therefore, the etiology and clinical characteristics are largely unknown.

The aim of this study was to evaluate the factors influencing late-onset gastrointestinal hemorrhage after PD.

Materials and methods

Patients

In this study, patients who underwent PD for pancreatic cancer at Nara Medical University Hospital between 2006 and 2014 were evaluated. We excluded patients with benign diseases and malignant diseases other than pancreatic cancer, as these were considered to influence the tumor factors and behavior of pancreatic cancer. Patients provided their written informed consent before treatment according to the rules and regulations of our institution.

Operative procedure and follow-up

All patients underwent subtotal stomach-preserving pancreatoduodenectomy (SSPPD) or pancreatoduodenectomy. If pancreatic cancer invaded the portal vein (PV) or superior mesenteric vein (SMV), we performed combined resection and reconstruction of the PV or SMV. However, no patients underwent reconstruction of the PV–splenic vein (SPV) in this series. The anastomosis between the SMV and PV was fashioned using a 5/0 non-absorbable running suture impregnated with a growth factor. When we were unable to preserve the inferior mesenteric vein (IMV), we ligated and cut it. After surgery, we performed adjuvant chemotherapy to prevent recurrence, as previously described [15, 16]. Patients were examined by computed tomography (CT) or magnetic resonance imaging (MRI) every three to six months after operation to assess recurrence and PV hemodynamics.

A comprehensive review of the medical records was performed to evaluate various clinicopathological factors for our analysis, including patient demographics, preoperative laboratory values, the tumor pathological diagnosis, and perioperative data. The institutional review board at our institution verified the appropriateness of the study from ethical, scientific, and medical perspectives.

The definition and diagnosis

We defined the presence of hematemesis or/and melena as gastrointestinal hemorrhage. We defined late-onset gastrointestinal hemorrhage as gastrointestinal bleeding that occurred on day 100 or later after PD. We confirmed the source of bleeding by gastroenterology endoscopy, contrast-enhanced computed tomography, or bleeding scintigraphy. We assessed the hemodynamics, including disruption or overswelling of blood vessels, by CT or MRI. Patients were divided into two groups according to the occurrence of late-onset gastrointestinal hemorrhage. We defined the complete obstruction of the PV or SMV as "PV occlusion." We also defined the lack of any blood flow between the SPV and PV as "no PV–SPV patency."

The incidence of postoperative early complication (those that occurred within 30 days after surgery) was evaluated in this study, and the severity of complications was defined according to the Clavien–Dindo classification [17]. If more than one complication occurred in a single patient, the most severe grade was considered for the present analysis. In this study, severe complications were defined as complications of grade III or greater. Pancreatic fistula was defined according to the definition of the International Study Group on Pancreatic Fistula (ISGPF) [18]. We further evaluated various outcome parameters, including the patency of the PV or SMV or SPV on follow-up CT.

Statistical analysis

The parameters were compared using Student's t test, the Chi-squared test, or Fisher's exact test as appropriate. Continuous variables were expressed as the mean and standard deviation (SD). $P < 0.050$ was considered statistically significant, and confidence intervals were calculated at the 95% level. All statistical analyses were performed using the SPSS software program, version 19.0 (SPSS, Chicago, IL, USA).

Results

A total of 147 consecutive patients who underwent PD for pancreatic cancer at Nara Medical University Hospital between 2006 and 2014 were evaluated. Eleven patients (7.5%) had late-onset gastrointestinal hemorrhage. These patients were 7 males and 4 females with a median age 66 years (range 47–82 years).

Clinical characteristics of 11 cases with late-onset gastrointestinal hemorrhage

Table 1 shows the details of 11 cases with late-onset gastrointestinal hemorrhage. Bleeding sites were gastrojejunostomy in four cases, and cholangiojejunostomy in two cases, and ascending colonic varicose vein in one case. In the other four cases, the bleeding sites were unclear. The median occurrence time of first late-onset gastrointestinal hemorrhage was 13.3 months after PD (range 3.6–83.2 months). The median time from PV occlusion on CT images to clinical bleeding was about 5 months, ranging from 3.6 to 55.0 months. Regarding the frequency of gastrointestinal hemorrhage, the average was 4 times, and the maximum was 16 times. Four patients only experienced hemorrhage once, and seven suffered from repeated bleeding. The interval between bleedings ranged from as short as a few weeks to as long as approximately a year. Ten out of eleven patients required blood transfusions. A median of 6 units of red blood cells were used for each episode, and the maximum was 36 units. To arrest hemorrhage, we treated 2 cases with interventional radiology (IVR) (case Nos. 1 and 4). The coil embolization for gastrointestinal hemorrhage around cholangiojejunostomy was used for case No. 1. PV stent insertion and partial splenic embolization (PSE) were used for case No. 4. Both of them were effective. Furthermore, we treated 2 cases with endoscopic interventions (case Nos. 6 and 11). Endoscopic coagulation therapy was used for case Nos. 6 and 11. For case No. 11, it was successfully completed. For case No. 6, the first intervention was insufficient. Two more endoscopic interventions including clipping and endoscopic variceal ligation were needed. Six patients had local recurrence, and seven had PV occlusion. Two patients (case Nos. 5 and 6) had PV occlusion without local recurrence. No patient died from blood loss. Nine patients (all but case Nos. 2 and 5) died due to recurrence of pancreatic cancer. Case No. 2 died caused from other malignant disease, and case No. 5 is alive without recurrence. Case No. 5 has also not experienced gastrointestinal hemorrhaging for 1 year after suffering from repeated gastrointestinal hemorrhaging for 3.3 years. The

Table 1 Clinical features of eleven cases with late gastrointestinal hemorrhage

Case	Gender	Age	Recurrence	PV occlusion	Local recurrence	PV–SPV no patency	SPV ligation	PV resection	IMV ligation	LGV ligation	Bleeding site	Time after PD (mo)	No. of bleeding
1	F	66	LN	–	–	+	+	–	+	+	Cholangiojejunostomy	22.5	7
2	M	74	–	–	–	–	–	–	–	–	Gastrojejunostomy	3.6	1
3	M	71	Liver	–	–	+	+	+	+	+	Unclear	17.2	2
4	M	65	Local, LN	–	+	+	+	+	–	+	Gastrojejunostomy	9.1	3
5	F	54	–	+	–	+	–	–	–	+	Cholangiojejunostomy	10.7	16
6	M	69	Liver	+	–	–	–	+	–	–	Gastrojejunostomy	7.2	8
7	F	47	Local	+	+	+	–	+	–	–	Ascending colonic varices	83.2	1
8	M	68	Local	+	+	+	+	+	+	+	Unclear	8.8	1
9	F	61	Local, P	+	+	–	–	+	–	–	Unclear	13.3	3
10	M	82	Local	+	+	–	–	+	+	+	Unclear	58.4	2
11	M	62	Local, LN	+	+	–	–	+	–	–	Gastrojejunostomy	14.7	1

PV portal vein, *SPV* splenic vein, *IMV* inferior mesenteric vein, *LGV* left gastric vein, *PD* pancreatoduodenectomy, *M* male, *F* female, *LN* lymph node, *P* peritoneum

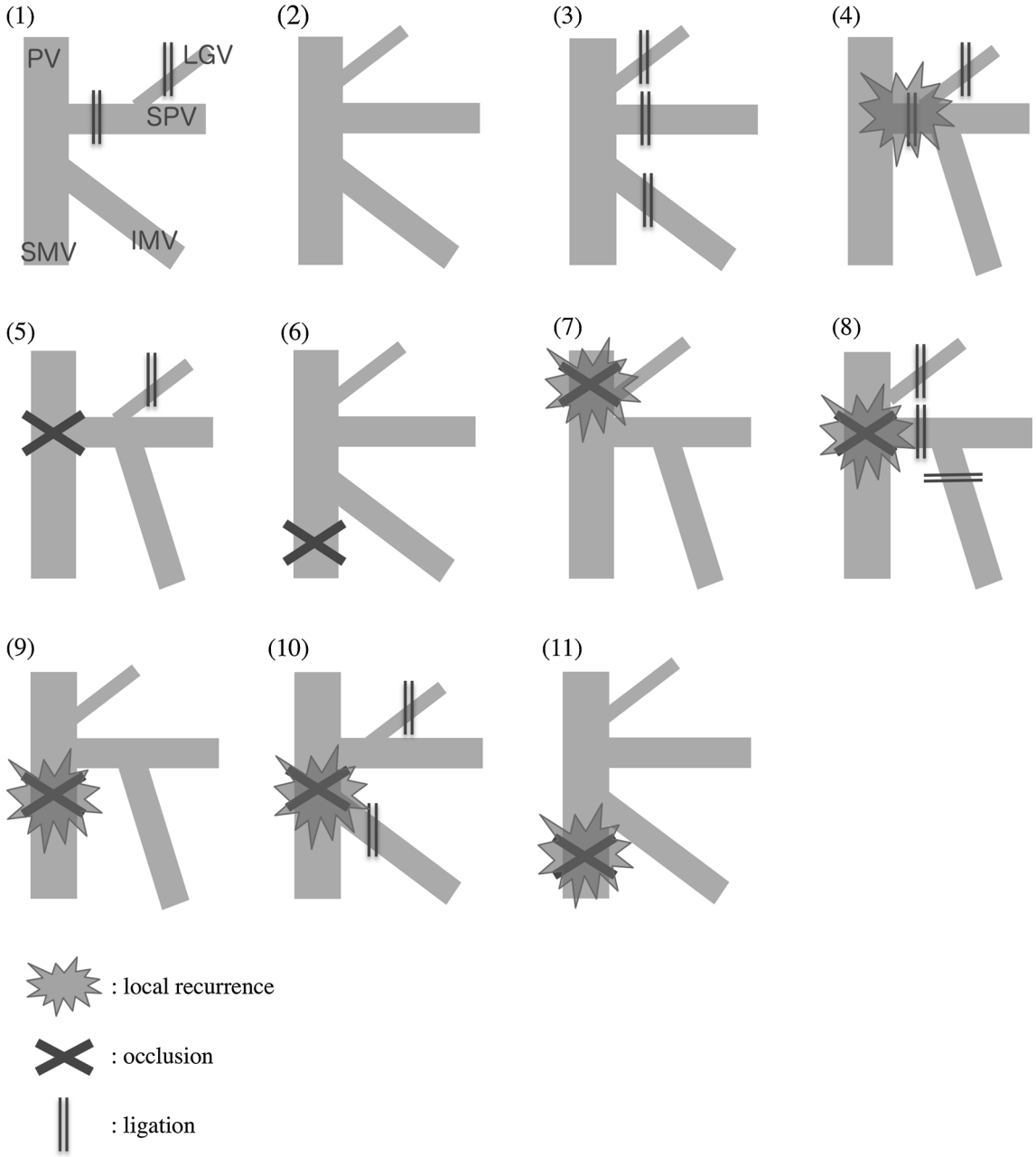

Fig. 1 The hemodynamic status of 11 cases with late-onset gastrointestinal hemorrhage. *PV* portal vein, *SMV* superior mesenteric vein, *SPV* splenic vein, *IMV* inferior mesenteric vein, *LGV* left gastric vein

hemodynamic status, including the point of PV occlusion and local recurrence site, of all cases is shown in Fig. 1.

Comparisons between the gastrointestinal hemorrhage group and no hemorrhage group

The clinical characteristics are compared between the gastrointestinal hemorrhage group and the no hemorrhage group in Table 2. There were no significant differences between the two groups in various factors, including neoadjuvant chemoradiotherapy (NACRT) and preoperative biliary drainage. There were no significant differences between the two groups in several perioperative data, including operating time, estimated blood loss, blood transfusion, portal vein resection, dissection of nerve plexuses around the superior mesenteric artery (SMA), and the R0 status (Table 3). However, the SPV ligation rate was 36.4% in the late-onset gastrointestinal hemorrhage

Table 2 Clinical characteristics of patients

Variables	GH (n = 11)	No GH (n = 136)	P
Age (years) [mean (SD)]	65.4 (9.5)	67.6 (9.7)	0.455
Gender			
Male [n (%)]	7 (63.6)	78 (57.4)	0.471
Female [n (%)]	4 (36.4)	58 (42.6)	
Diabetes mellitus [n (%)]	4 (36.4)	45 (33.3)	0.538
CRP[a] (mg/dl) [mean (SD)]	1.6 (2.1)	0.8 (1.6)	0.153
Albumin[a] (g/dl) [mean (SD)]	3.8 (0.5)	3.8 (0.5)	0.744
CEA[a] (ng/ml) [mean (SD)]	5.8 (5.8)	4.8 (5.2)	0.544
CA 19-9[a] (U/ml) [mean (SD)]	190.2 (337.4)	248.7 (664.7)	0.774
Neoadjuvant CRT [n (%)]	4 (36.4)	61 (44.9)	0.414
Preoperative biliary drainage [n (%)]	7 (63.6)	80 (58.8)	0.509

GH gastrointestinal hemorrhage, *SD* standard deviation, *CRP* C-reactive protein, *CEA* carcinoembryonic antigen, *CA* carbohydrate antigen, *CRT* chemoradiotherapy

[a]Data at the time before surgery of the primary tumor

Table 3 Perioperative data

Variables	GH (n = 11)	No GH (n = 136)	P
Operating time (min) [mean (SD)]	363 (55)	342 (83)	0.410
Estimated blood loss (ml) [mean (SD)]	1293 (728)	889 (2240)	0.554
Blood transfusion [n (%)]	6 (54.5)	51 (37.5)	0.212
Operative procedure [n (%)]			
PD combined PV resection	8 (72.7)	77 (56.6)	0.238
SPV ligation	4 (36.4)	13 (9.6)	0.025
Dissection of nerve plexuses around SMA	10 (90.9)	122 (89.7)	0.688
R0 resection [n (%)]	10 (90.9)	117 (86.0)	0.542

GH gastrointestinal hemorrhage, *PD* pancreatoduodenectomy, *PV* portal vein, *SPV* splenic vein, *SMA* superior mesenteric artery

group, which was significantly higher than in the control group (vs. 9.6%; $p = 0.025$).

Postoperative data are shown in Table 4. There were no significant differences between the two groups in the postoperative early complications, including pancreatic fistula, intra-abdominal abscess, and delayed gastric emptying. Furthermore, there were no significant differences between the two groups in the severity of complications or pathological findings. However, the incidence of no PV–SPV patency (54.5 vs. 12.7%; $p = 0.002$, respectively), PV occlusion (63.6 vs. 8.9%; $p < 0.001$, respectively), and collateral vessels formation (63.6 vs. 19.9%; $p = 0.003$) were significantly higher in the late-onset gastrointestinal hemorrhage group than in the control group.

Risk factors for late-onset gastrointestinal hemorrhage

We analyzed the risk factors for late-onset gastrointestinal hemorrhage and found that SPV ligation, no PV–SPV patency, and PV occlusion were significant factors associated with late-onset gastrointestinal hemorrhage (Table 5).

Discussion

Several studies have described the risk factors for PPH [2, 4–7]. However, almost all of them reported on perioperative hemorrhage, and few reports have described the details of late-onset gastrointestinal hemorrhage. Ricci et al. reported that the severity of postoperative pancreatic fistula and pancreatic anastomosis independently increased the risk of late PPH [6]. Darnis et al. reported that the predictors of PPH were pancreatic fistula, pancreatoduodenectomy, age, and the nutritional risk index [7]. Other studies also have reported the risk factors for perioperative PPH [1–4, 19–23]. However, we considered that late-onset gastrointestinal hemorrhage was not induced as an acute effect of the operation. Furthermore, the risk factors for late-onset gastrointestinal hemorrhage might differ from those for perioperative PPH. In the present study, we

Table 4 Postoperative outcomes

Variables	GH (n = 11)	No GH (n = 136)	P
Postoperative early complication [n (%)]	363 (55)	342 (83)	0.573
Pancreatic fistula[a] [n (%)]			
Grade 0/A	11 (100)	129 (94.9)	0.793
Grade B/C	0 (0)	7 (5.1)	
Intra-abdominal abscess [n (%)]	0 (0)	3 (2.2)	0.622
Delayed gastric emptying [n (%)]	1 (9.1)	11 (8.1)	0.650
Severity of complication[b] [n (%)]			
Grade 0–II	9 (81.8)	110 (80.9)	0.650
Grade IIIa–V	2 (18.2)	26 (19.1)	
Pathological findings[c] [n (%)]			
T factor			
pT 0-2	0 (0)	16 (11.8)	0.268
pT 3-4	11 (100)	12 (88.2)	
Lymph node metastasis [n (%)]	5 (45.5)	71 (52.2)	0.452
Stage			
0–IIB	10 (90.9)	119 (87.5)	0.599
III–IV	1 (9.1)	17 (12.5)	
Recurrence [n (%)]	9 (81.8)	84 (62.7)	0.329
PV–SPV no patency [n (%)]	6 (54.5)	17 (12.7)	0.002
PV occlusion [n (%)]	7 (63.6)	12 (8.9)	<0.001
Collateral vessels formation [n (%)]	7 (63.6)	27 (19.9)	0.003
Conversion surgery [n (%)]	1 (9.1)	3 (2.2)	0.270
Adjuvant chemotherapy [n (%)]	11 (100.0)	126 (92.6)	0.448

GH gastrointestinal hemorrhage, *PV* portal vein, *SPV* splenic vein

[a]Defined according to International Study Group of Postoperative Pancreatic Fistula

[b]Defined according to Clavien–Dindo classification

[c]Defined according to Union for International Cancer Control, values in parentheses are percentages

defined late-onset gastrointestinal hemorrhage as that occurring more than 100 days after operation and investigated the risk factors.

Our data indicated that PV occlusion was a risk factor for late-onset gastrointestinal hemorrhage. PV occlusion is known to cause sinistral portal hypertension, thereby leading to collateral vein formation, including esophageal and gastric varicose veins, colonic varicose veins, or varicose veins around cholangiojejunostomy anastomosis. We suspected that bleeding around cholangiojejunostomy, gastrojejunostomy, or colonic veins might occur during this process of collateral formation [5, 21]. In most cases, the bleeding will spontaneously resolve according to the degree of collateral vein formation. However, there are refractory patients who require repeated transfusions. For such cases, we may consider IVR, such as PV stent or PSE, depending on the patient's symptoms and conditions. As previously noted, in the present study, we performed PV stent insertion and PSE for only one case (case No. 4). That patient had not suffered from bleeding after IVR for 6 months, until he died of pancreatic cancer. Since IVR can be a technically challenging procedure with a potential risk of severe morbidity, its indication should be carefully considered.

Late-onset gastrointestinal hemorrhage can occur due to oncological as well as non-oncological conditions. Among oncological factors, the majority of cases of PV occlusion are associated with local recurrence. Local recurrence is often observed after pancreatectomy or lymph node dissection. It induces the stenosis or occlusion of the PV, SPV, or SMV. In addition, it affects the hemodynamics and leads to sinistral portal hypertension. In this study, 5 cases, representing about 45% of the 11 late-onset gastrointestinal hemorrhage cases, had PV occlusion caused by local recurrence. Therefore, we believe that it is very important to control local recurrence in order to prevent late-onset gastrointestinal hemorrhage. NACRT, which can lead to R0 resection, may be a potent therapeutic option [14, 24].

Table 5 Risk factors for late gastrointestinal hemorrhage after PD

Variables	Odds ratio	95% CI	*P*
Neoadjuvant CRT	0.703	0.20–2.51	0.414
PD combined PV resection	2.043	0.52–8.04	0.238
SPV ligation	5.407	1.40–20.96	0.025
Dissection of nerve plexuses around SMA	1.148	0.14–9.64	0.688
Pancreatic Fistula Grade B/C[a]	0	–	0.573
Intra-abdominal abscess	0	–	0.791
Sevier complication (Grade IIIa–V)[b]	0.940	0.19–4.61	0.650
T 3–4	0	–	0.268
Lymph node metastasis	0.763	0.22–2.62	0.452
R1 resection	0.616	0.08–5.09	0.542
Recurrence	1.042	0.29–3.74	0.611
PV–SPV no patency	8.259	2.27–30.04	0.002
PV occlusion	17.938	4.59–70.17	<0.001

CI confidence interval, *CRT* chemoradiotherapy, *PD* pancreatoduodenectomy, *PV* portal vein, *SPV* splenic vein, *SMA* superior mesenteric artery

[a]Defined according to International Study Group of Postoperative Pancreatic Fistula

[b]Defined according to Clavien–Dindo classification

However, NACRT can also cause PV occlusion. Since NACRT might induce changes in the tissue around the tumor, such as a fibrosing reaction or inflammatory change, it might influence the hemodynamics in some way. Tsuruga et al. reported that a relationship between PV stenosis and NACRT is suspected [22]. Mitsunaga et al. suggested that the development of extrahepatic PV occlusion after intraoperative radiation therapy (IORT) is associated with the periportal changes induced by IORT [25]. However, whether or not radiation, such as NACRT or IORT, influences PV stenosis or occlusion is unclear. Our data indicated that NACRT was a significant risk factor for neither late-onset gastrointestinal hemorrhage nor PV occlusion.

Among non-oncological factors, anastomotic stenosis or thrombus formation may be associated with late-onset gastrointestinal hemorrhage, as the majority of cases of PV occlusion occurred near the PV reconstruction site. Therefore, we should try to maintain PV patency and PV–SPV patency during the operation. Furthermore, it may be best to consider the reconstruction of the SPV to prevent late-onset gastrointestinal hemorrhage after PD. In addition, if PV stenosis or occlusion is noted on CT during the postoperative course after PD, it may be best to consider administering anticoagulant drugs and sometimes IVR, such as PV stents. However, the best approach to managing PV stenosis or occlusion remains controversial. Further studies are needed to establish the best care for the prevention of late-onset gastrointestinal hemorrhage.

In conclusion, we reported for the first time that PV occlusion, SPV ligation, and no PV–SPV patency were risk factors for late-onset gastrointestinal hemorrhage after PD. Both oncologic and non-oncologic factors may contribute to PV occlusion and no PV–SPV patency. Furthermore, gastrointestinal hemorrhage can occur after postoperative day 100 or later in PD procedures for pancreatic cancer. Therefore, we need not only perioperative but also long-term follow-up after PD while taking into account late-onset gastrointestinal hemorrhage.

Acknowledgements This study was supported in part by Nara Medical University Grant-in-Aid for Collaborative Research Projects.

Funding Sources of funding for research and/or publication: This study was supported in part by Nara Medical University Grant-in-Aid for Collaborative Research Projects.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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