Clinical Significance of Portal-Superior Mesenteric Vein Resection in Pancreatoduodenectomy for Pancreatic Head Cancer

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Objectives: The purpose of this study was to determine the significance of portal vein–superior mesenteric vein (PV-SMV) invasion on survival in patients who underwent margin-negative pancreatoduodenectomy (PD) with PV-SMV resection for pancreatic adenocarcinoma. **Methods:** We retrospectively reviewed the records of 60 patients who underwent margin-negative PD with or without PV-SMV resection for pancreatic adenocarcinoma between August 2001 and December 2007. The depth of vessel invasion was investigated and was categorized into 3 groups: tunica adventitia, media, and intima. Clinicopathologic factors and survival were analyzed.

Results: Portal vein–superior mesenteric vein resection was performed on 19 patients, but only 15 patients (78.9%) had histologically true invasion and showed poorer survival (median survival, 14 vs 9 months; P < 0.05). Univariate analysis revealed that poorly differentiated tumor, lymphatic invasion, endovascular invasion, PV-SMV invasion, and invasion into the intima of PV-SMV were statistically significant. Poorly differentiated tumor and invasion into the intima of PV-SMV were significant in multivariate analysis.

Conclusions: Aggressive surgical resection should be attempted in cases with suspected PV-SMV invasion because 21.1% of patients had no true invasion and showed better survival than those with true invasion. However, invasion into the tunica intima may be a poor prognostic factor for survival even after margin-negative PD for pancreatic adenocarcinoma.

Key Words: pancreatic cancer, portal–superior mesenteric vein invasion, survival

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D espite the advances in surgical management and chemotherapeutic agents, the treatment outcome of pancreatic cancer is very poor because only 15% to 20% of the tumors are found to be resectable when they are diagnosed.¹ The reason for this is that this tumor easily metastasizes to the liver and infiltrates into the surrounding major vessels such as portal vein (PV), superior mesenteric vein (SMV), hepatic artery, or superior mesenteric artery. With the advances in surgical technique and accumulation of experiences, PV-SMV invasion is not considered to be a contraindication to resection, and synchronous PV-SMV resection is recommended during pancreatoduodenectomy (PD) with or without pylorus-preserving procedures to obtain a tumor-free margin in the absence of metastatic disease.² From the sixth American Joint Committee on Cancer/ International Union Against Cancer stage, PV-SMV invasion is

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categorized as the same stage as peripancreatic infiltration (T3), which is different from the fifth edition (T4).

However, PV directly enters the liver, which is the most common site of metastasis of pancreatic cancer. This means that there is a possibility of tumor spreading from the invaded focus of the PV-SMV to the liver. We can find early liver metastasis (within 6 months of margin-negative surgery) not infrequently in patients with a huge mass with PV-SMV total obliteration. Fortner et al³ reported that a tumor bigger than 5 cm receive no benefit from surgery even after regional pancreatectomy. We can hypothesize that if the PV-SMV is invaded by the tumor, the prognosis is poor. There are many reports regarding whether there are benefits from synchronous PV-SMV resection during PD.^{2,4-13} However, these reports have shown contradictory results. The reason for this is that many authors focused mainly on the PV-SMV "resection" but not on the PV-SMV "invasion." Thus, there are few reports dealing with histologically true invasion cases separately from simple adhesion cases. 14,15 Even though pancreatic cancer frequently develops systemic disease after R0 resection, the only way for cure is the complete resection of the tumor. This is the purpose of PV or splenic vein resection. However, unlike the splenic vein resection in distal pancreatectomy, the PV-SMV resection may impose additional morbidity on the high-morbidity operation of PD. Therefore, we need to ascertain who benefits from PV-SMV resection in PD for pancreatic head cancer.

The purpose of this study was to determine the significance of PV-SMV invasion on survival in patients who underwent margin-negative PD (R0) with PV-SMV resection for pancreatic adenocarcinoma.

MATERIALS AND METHODS

Patients

Between August 1, 2001, and December 31, 2007, a total of 204 patients underwent PD (including pylorus-preserving PD [PPPD], total pancreatectomy, and hepatopancreatoduodenectomy) at the National Cancer Center of Korea. We retrospectively reviewed the medical records of patients with pancreatic ductal adenocarcinoma (n = 70) and excluded 10 patients with resection margin involvement (R1 or R2) to avoid the effect of the residual disease on survival after resection. We checked the margin of the resected PV-SMV and obtained the negative margin in all the resected PV-SMV cases and analyzed the surgical outcome after margin-negative (R0) resection (n = 60). We planned marginnegative resection if metastatic disease was not identified in preoperative patient workup. History taking, physical examination, liver function tests with tumor marker (carbohydrate antigen 19-9), and abdominal computed tomography (CT) were used for diagnostic and staging workup. Whole-body positron emission tomography was added if necessary. If the tumor encases the vessel more than 180 degrees, or there is luminal narrowing of the vessel on CT scan, it was considered as a tumor invasion. The

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FIGURE 1. Microscopic features of the 4 different categories of vascular invasion. A, Simple adhesion case with intact 3 layers of the vessel. B, Invasion to the tunica adventitia with an intact media and intima. C, Invasion to the tunica media with an intact intima. D, Intimal invasion with an exposed cancer gland into the lumen. Ad indicates tunica adventitia; Ca, cancer; In, tunica intima; Md, tunica media (hematoxylin-eosin stain, original magnification ×40).

median age of 60 patients was 63 years (range, 42–83 years), with a male-female ratio of 1.14:1 (32:28). Patient demographics and clinical and histological factors were evaluated to determine the prognostic significance after resection.

Operative Procedures

Pylorus preservation was attempted in all cases unless severe duodenal ischemia, duodenal ulcer, or cancer infiltration into the duodenal bulb was present. Combined resection of the PV-SMV was performed if pancreas was not separated from the vessel. Lymph node dissection included removal of the regional lymph nodes to the right side of the celiac and superior mesenteric artery and removal of all the lymphatic and nerve tissues in the hepatoduodenal ligament. Aortocaval lymph node (a2, b1) dissection was also performed. The mean number of harvested lymph nodes was 31.4 per patient.

Adjuvant Therapy

After surgery, we performed concurrent chemoradiation (CCRT) on all patients without severe medical comorbidities and poor physical status. Thirty-seven patients (61.6%) underwent postoperative CCRT via linear accelerators using multiple-field techniques. The median interval between CCRT and surgery was 6 weeks (range, 4–10 weeks). The initial irradiated field, which was defined as the tumor bed plus regional nodes, was usually administered at 45 Gy in 25 fractions of a 4-field technique (anteroposterior, posteroanterior, and paired laterals) using 15-MV x-rays. The tumor bed boost field received an additional 5.4 to 10.8 Gy in 3 to 6 fractions of 1.8 Gy. Concomitant 5-fluorouracil–based chemotherapy during radiation therapy was recommended for all patients.

Statistical Analysis

The following factors were analyzed: age, sex, tumor marker, operation modality, blood transfusion, tumor size, tumor

stage, lymph node metastasis, histological differentiation, lymphatic invasion, perineural invasion, and vascular invasion including PV-SMV invasion. The cumulative survival rate was calculated by the Kaplan-Meier method. Factors associated with cumulative survival in both univariate and multivariate analyses were identified by the Cox proportional hazard regression analysis. P < 0.05 was considered statistically significant.

RESULTS

Operative Outcomes

Operative procedures included 16 cases of PD (26.7%), 40 cases of PPPD (66.7%), and 4 cases of total pancreatectomy



FIGURE 2. Overall survival for 60 patients who underwent curative resection of pancreatic ductal adenocarcinoma.

(6.6%). The mean operation time was 8.3 hours (range, 5.0– 13.5 hours), and intraoperative transfusion was required in 17 patients (28.4%). Median postoperative hospital stay was 23 days, and 20 patients (33.3%) developed postoperative complications. Nineteen patients (31.7%) underwent PV-SMV resection including segmental resection with end-to-end anastomosis (n = 17) or wedge resection (n = 2). One patient developed PV-SMV resection–related complication, which was PV thrombosis, and she recovered after stent insertion with thrombolysis. There were 2 hospital mortalities (3.3%); 1 patient died on postoperative day 16 due to superior mesenteric artery pseudoaneurysm rupture, and the other died on postoperative day 279 due to superior mesenteric artery stenosis that resulted in small bowel necrosis followed by sepsis and multiorgan failure.

Histopathologic Findings

In all 60 patients, a tumor-free resection margin (R0) was obtained. The mean tumor size was 3.1 cm (range, 1.5–7.0 cm),

ABLE 1. Univariate Analysis of Clinicopathologic Factors for Overall Survival					
Factors	Number	Median Survival, mo	HR (95% CI)	Р	
Age, y					
≤65	34	14.0	1	0.117	
>65	26	9.0	1.591 (0.890-2.841)		
Sex					
Male	32	15.0	1	0.439	
Female	28	10.0	1.260 (0.701-2.265)		
CA-19-9, U/mL					
≤37	12	16.0	1	0.061	
>37	48	10.0	2.164 (0.964-4.857)		
Operation modality					
PD/PPPD	56	11.0	1	0.470	
TP	4	3.0	1.544 (0.475-5.017)		
Blood transfusion					
No	42	13.0	1	0.644	
Yes	18	8.0	1.160 (0.618-2.176)		
Tumor size, cm					
≤3	31	14.0	1	0.585	
>3	29	9.0	1.176 (0.657-2.105)		
LN metastasis			· · · · ·		
_	15	16.0	1	0.153	
+	45	11.0	1.705 (0.820-3.548)		
Perineural invasion					
_	6	11.0	1	0.957	
+	54	11.0	1.026 (0.404-2.602)		
Differentiation*			· · · · ·		
WD/MD	45	15.0	1	0.014	
PD	10	5.0	1.376 (1.066-1.775)		
Lymphatic invasion					
_	11	33.0	1	0.032	
+	49	10.0	2.782 (1.090-7.099)		
Endovascular invasion					
_	29	21.0	1	0.004	
+	31	9.0	2.501 (1.337-4.677)		
PV-SMV invasion					
_	45	14.0	1	0.045	
+	15	9.0	1.937 (1.013-3.702)		
Depth of PV/SMV invasion			(,)		
No invasion	45	13	1	0.068	
Ad/Md	10	10	1.646 (0.774-3.499)		
Intima	5	6	2.888 (1.095–7.619)		
Intima invasion	č	2			
_	55	12.0			
	- -				

*Data on tumor differentiation of 5 patients were not available.

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Ad/Md indicates adventitia/media; CA-19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; LN, lymph node; MD, moderately differentiated; PD, poorly differentiated; TP, total pancreatectomy; WD, well differentiated.

6.0

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0.032

2.852 (1.097-7.413)

and lymph node metastasis was observed in 45 cases (75%). Tumor classification according to the seventh AJCC/UICC staging system in the 60 patients was as follows: T1/T2/T3 were 3 (5%)/1 (1.7%)/56 (93.3%). The histopathologic differentiation was as follows: 5 (8.3%) had the well-differentiated type; 40 (66.7%), the moderately differentiated type; and 10 (16.7%), the poorly differentiated type. The data on tumor differentiation were not available in 5 patients. Perineural, lymphatic, and blood vessel invasions were detected in 54 (90.0%), 49 (81.7%), and 33 patients (55.0%), respectively. Among the 19 patients who underwent PV-SMV resection, histologically true tumor invasion of PV-SMV was observed in 15 patients (78.9%), and the remaining 4 patients (21.0%) proved to have only fibrous adhesion. The depths of tumor invasion of the PV-SMV were divided into 3 groups: tunica adventitia (n = 3), tunica media (n = 7), and tunica intima (n = 5) (Fig. 1).

Survival and Prognostic Factors

The overall 1- and 3-year survival rates in 60 patients who underwent R0 surgical resection were 55.2% and 33.0%, respectively (Fig. 2), and the median survival was 14 months. Clinicopathologic factors were analyzed as variables possibly affecting prognosis. Univariate analysis revealed that poorly differentiated tumor, lymphatic invasion, endovascular invasion, PV-SMV invasion, and PV-SMV intima invasion were statistically significant (Table 1; Fig. 3). The depth of PV-SMV invasion showed a deeper invasion led to a poorer survival rate, but had only a marginal significance. By multivariate analysis, poorly differentiated tumor and PV-SMV intima invasion turned out to be independent poor prognostic factors (Table 2). We had 39 patients with recurrence, and 32 (82%) of them had systemic recurrence such as liver metastasis, peritoneal seeding, or lung metastasis. Among the 39 recurred patients, 28 patients were in PV-SMV noninvasion group and 11 in PV-SMV invasion group. Liver metastasis was found in 14 patients in PV-SMV noninvasion group (50%) and 5 in PV-SMV invasion group (45.5%). There was no significant difference between 2 groups.

DISCUSSION

Portal vein–superior mesenteric vein invasion by pancreatic cancer is down-staged from T4 to T3 in the sixth AJCC/UICC stage based on the concept that PV-SMV invasion is not the result of aggressive behavior but the result of tumor location. However, since the 1990s, there have been many reports showing that PV-SMV invasion has resulted in poor survival. Nakao et al¹⁴ demonstrated that the 1-year survival rate was 5.5% in



FIGURE 3. Survival difference between PV-SMV invasion–positive (+) group and –negative (–) group.

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TABLE 2.	Significant Factors for Overall Survival by
Multivaria	te Analysis

	1
1	0.001
2.863 (1.509-5.434)	
1	0.036
2.817 (1.069-7.420)	
	1 2.863 (1.509–5.434) 1 2.817 (1.069–7.420)

*Data on tumor differentiation of 5 patients were not available.

CI indicates confidence interval; HR, hazard ratio; MD, moderately differentiated; PD, poorly differentiated; WD, well differentiated.

tumors that invaded the tunica intima and that the survival rate can be predicted by preoperative angiography. They insisted that aggressive surgical resection is not indicated for patients with marked stenosis or obstruction of PV-SMV with collateral vessels. Recently published systematic review of 52 studies with 1646 patients revealed that the median survival time and 5-year survival rate of patients with PV-SMV invasion were 12 months and 5.8%, respectively.7 They also showed a high rate of lymph node metastasis (67.4%), which implies that, by the time a pancreatic cancer involves the PV-SMV, the risk of metastasis is high. Therefore, PV-SMV invasion is not simply a matter of location, but also the location itself is important because the vessel directly enters the liver, which is the most common site of metastasis of pancreatic cancer. However, there are still many other opinions that PV-SMV resection could achieve better survival.^{2,4} The reason for these contradictory results is that these reports have mainly focused on PV-SMV "resection" but not on "invasion." Because they focused on patients with PV-SMV resection, they analyzed data on both patients with true invasion and those with simple adhesion. In addition, even after PV-SMV resection, they still had R1 resection patients. As the rationale for PV-SMV resection is to obtain a tumor-free margin, which is known to be a significant prognostic factor, the clinical benefit of PV-SMV resection should be evaluated in patients undergoing R0 resection and in patients with true invasion. In this study, we performed PV-SMV resection when pancreas was not separated from the tumor and examined the specimen to determine whether there was a histologically true invasion.

Because pancreatic cancer induces a severe desmoplastic reaction with the surrounding tissue, in some cases, pancreas was not separated from the vessel as if there is cancer invasion. In this study, 21.1% of the suspected invasion cases had no evidence of histological invasion, and they showed better survival than cases of true invasion. In addition a deeper invasion led to a poorer survival rate. The median survival of patients with intima invasion was only 6 months, which is similar to that of resection margin-positive (R1 or R2) patients or metastatic disease.¹⁶ If we could have clearly predicted the depth of invasion preoperatively, we could have avoided the operation in patients with poorer survival. There have been several attempts to find out predictable findings on angiography or CT. Radiologists usually evaluate vascular invasion, depending on the degree of vascular encasement by the tumor on preoperative imaging studies.¹⁷ If the tumor encases the vessel more than 180 degrees, it is considered as a tumor invasion.¹⁸ Some surgeons used intraportal ultrasonography or angiography to evaluate vascular invasion intraoperatively or preoperatively. They

suggested that, in cases of severe vascular invasion, aggressive surgery should be avoided because survival was even poorer than in unresectable cases.^{19,20}

Recent reports by the MD Anderson Cancer Center group mentioned the term *borderline resectable* pancreatic cancer.^{21,22} They consistently proposed neoadjuvant chemoradiation in patients with suspected vascular invasion or liver metastasis before surgery, which implies that, when advanced disease is suspected, surgery should be reserved to identify the subset of patients who were most likely to benefit from surgery.

Although we included various clinicopathologic factors to evaluate the prognostic significance, we obtained significance in tumor differentiation, lymphatic invasion, endovascular invasion, PV-SMV invasion, and intima invasion after univariate analysis. We could not identify the significance in some well-known prognostic factors such as tumor stage or perineural invasion, because 93.3% of the patients were at T3 (peripancreatic invasion), and 90% of the patients had perineural invasion. This means that it is not appropriate to gain significance through statistical analysis. Blood transfusion may play a role in the prognosis. In our results, transfusion group showed poorer median survival rate than the nontransfusion group (8 vs 13 months). However, it failed to gain statistical significance.

In summary, even though radical surgery is the only way to give the chance of a cure to patients, the role of surgery might be minimal by the time a pancreatic cancer invades the PV-SMV, especially to the tunica intima. However, we should not easily give up aggressive surgical resection unless there is definite evidence of invasion because 21.1% of the PV-SMV resection cases had only fibrous adhesion and showed better survival than true invasion cases. The results of this study suggest that PV-SMV invasion by pancreatic cancer is not a matter of tumor location but of prognosis.

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