Case reports of interest

Pancreatic invasion is a prognostic indicator after radical resection for carcinoma of the ampulla of Vater

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Abstract: Sixty-three patients who had undergone pancreatoduodenectomy for carcinoma of the ampulla of Vater were analyzed with respect to tumor extent and prognosis. The postoperative mortality rate was 3% and overall survival rates 3 and 5 years after surgery were 55% and 46%, respectively. pTNM stage did not reflect prognosis after resection in patients at stages 2 and 3, while pancreatic invasion and regional lymph node metastasis clearly reflected prognosis after resection. Of the 26 patients who had no pancreatic invasion, regional lymph node metastasis was seen in only 19%, whereas of the 37 patients with pancreatic invasion, 62% exhibited lymph node metastasis. These factors were significantly correlated ($P < 0.001$). Pancreatic invasion appeared to be an indirect indicator of regional lymph node metastasis. We conclude that, to improve prognosis for patients with pancreatic invasion, extended resection including extended lymphadenectomy, is a preferable additional procedure.

Key words: carcinoma of the ampulla of Vater, pancreatoduodenectomy, pancreatic invasion of carcinoma of the ampulla of Vater, lymph node metastasis of carcinoma of the ampulla of Vater, prognosis of carcinoma of the ampulla of Vater

Introduction

The prognosis for carcinoma of the ampulla of Vater, with a reported 5-year survival rate after radical operation of 34%–61%,[1-11] is relatively good in comparison with prognoses for other periampullary malignancies for which; 4%–19% has been reported for pancreatic cancer[11-14] and 16%–33% for distal bile duct cancer.[11,14] This relatively favorable outcome for carcinoma of the ampulla of Vater is due, in part, to recent advances in

endoscopic diagnosis,[15,16] and in part to the clinical characteristics of the tumor, which sometimes exhibits signs or symptoms e.g., obstructive jaundice, hepatic dysfunction, pancreatitis, melena, or abdominal pain, in the early period of the disease. Once the disease is advanced, however, prognosis is poor, even after radical resection of the tumor.[17] In the present study, an attempt was made to identify an indicator that would precisely reflect prognosis after radical resection and that would suggest how surgeons should conduct the operation. The experience of 63 consecutive patients who had undergone pancreatoduodenectomy for carcinoma of the ampulla of Vater was analyzed retrospectively with respect to tumor extent and prognosis. Our results suggest that pancreatic invasion of the tumor is a good prognostic indicator and, for those patients with pancreatic invasion, further resection, including extended lymphadenectomy, is the procedure of choice to improve prognosis.

Patients and methods

Between 1983 and 1994, 98 patients with carcinoma of the ampulla of Vater were surgically treated at the Department of General Surgery, University of Ulm, Germany. Sixty-three of the 98 patients underwent radical resection of the tumor; 37 patients had the Kausch-Whipple operation (partial pancreatoduodenectomy; PD) and 26 had a pylorus-preserving pancreatoduodenectomy (PPPD). Nine patients had a wide resection of the ampulla (ampullectomy) and 26 had a palliative bypass operation. The 63 patients who had undergone PD or PPPD were selected for this study. Thirty-four were men and 29 were women; the median age of all patients was 63 years (range, 28–82 years).

The resected specimens were submitted to pathological examination and classified based on the pTNM clas-

sification.[18] The patients were divided into two groups based on pT, pT1,2 being considered a tumor negative for pancreatic invasion and pT3,4 as a tumor positive for pancreatic invasion. The patients were also divided into two groups based on pN, pN0 being considered as negative for lymph node metastasis and pN1 to be positive for lymph node metastasis. The survival rates of these groups after surgery were assessed. The prognosis for PD and PPPD was also evaluated. The survival rate was calculated by the Kaplan-Meier method. For the statistical analyses, the generalized Wilcoxon test and Fisher's exact test were used. Statistical significance was taken as $P < 0.05$.

Results

Of the 63 patients who received radical resection of the tumor, there was no residual tumor (R0) in 61 patients (97%) and 2 patients died of causes related to the operation (operative mortality rate, 3%). The survival rates 3 and 5 years after the radical resection were 55% and 46%, respectively (Table 1). Of the 9 patients who had the ampullectomy, the operation resulted in R0 in 2 (22%) and the 3-year survival rate was 54%. Two of the patients who had the ampullectomy are still alive and cancer free, and 1 is alive with tumor recurrence. None of the patients who had the bypass operation survived for more than 17 months.

pTNM stage and prognosis

When the patients were classified according to pTNM stage, 11% were stage 1, 43% were stage 2, 37% were stage 3, and 9% were stage 4. No patient had a distant metastasis at operation. The survival rate at 5 years was 100% for patients at stage 1, decreasing to 47% for stage 2 and 42% for stage 3, no stage 4 patient survived for more than 1 year after the operation (Fig. 1). The differences in survival rates between stages 1 and 2 ($P = 0.04$) and stages 3 and 4 ($P = 0.006$) were significant, whereas no significant difference in survival rate was found between stages 2 and 3.

Histological pancreatic invasion and prognosis

In the 26 patients without pancreatic invasion, the survival rate was 87% at 3 years and 79% at 5 years. Among the 37 patients with pancreatic invasion, however, the 3- and 5-year survival rates were 40% and 24% (Fig. 2). The differences in survival rates between these two groups were significant ($P < 0.002$).

Histological regional lymph node metastasis and prognosis

Thirty-five patients had no regional lymph node metastasis and 28 patients were positive for regional lymph node metastasis. The prognosis of the patients without lymph node metastasis was significantly better (with 3-year and 5-year survival rates being 72% and 57%, respectively), than that of the patients with lymph node metastasis, whose survival rates at 3 and 5 years were both 35% ($P = 0.01$) (Fig. 3).

Correlation between histological pancreatic invasion and regional lymph node metastasis

In the 26 patients who had no pancreatic invasion, regional lymph node metastasis was seen only in 19%, whereas 62% of the patients with pancreatic invasion exhibited lymph node metastasis (Table 2). Statistical analysis revealed a significant correlation between pancreatic invasion and regional lymph node metastasis ($P < 0.001$).

Prognosis after PD or PPPD

Before 1990, PD was employed for all patients with carcinoma of the ampulla of Vater, in our institute, however, since 1990, PPPD has been employed. pTNM stage in the patients who underwent PD or PPPD is shown in Table 3; there were no significant differences in the background of the two groups. The survival rate at 3 years was 82% in the patients with PPPD and 50% in those with PD (Fig. 4).

Table 1. Degree of residual tumor, mortality rate, and survival rate according to operative procedure

|	Number of patients	Residual tumor[b]			Mortality rate	Survival rate[c]	
		R0	R1	R2		3-Year	5-Year
Radical resection[a]	63	61	2	0	3%	55%	46%
Ampullectomy	9	2	7	0	0%	54%	0%
Bypass operation	26	0	0	26	19%	0%	0%

[a] Radical resection, i.e., partial pancreato duodenectomy (PD) and pylorus-preserving pancreato duodenectomy (PPPD).
[b] R0, No residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor.
[c] Survival calculations done by the Kaplan-Meier method.
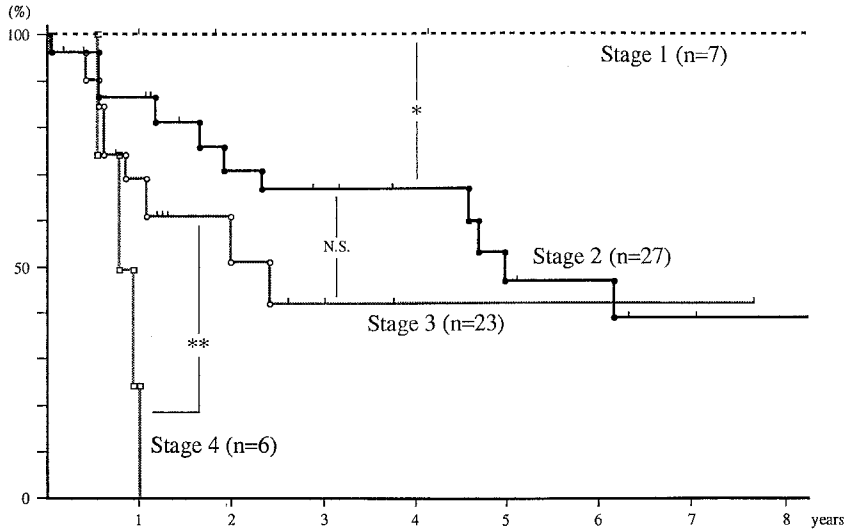
Fig. 1. Survival rates after radical resection for carcinoma of the ampulla of Vater according to stage (Kaplan-Meier method). $*P = 0.04$; $**P = 0.006$
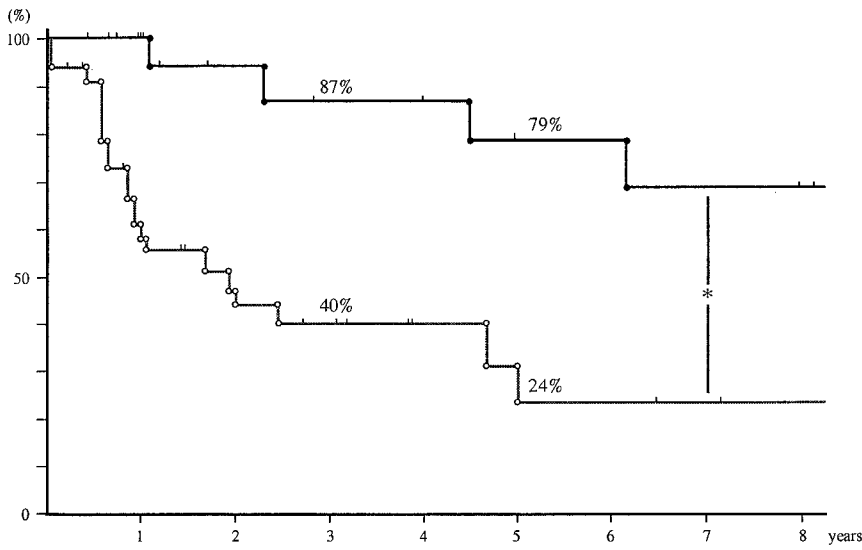
Fig. 2. Survival rates after radical resection for carcinoma of the ampulla of Vater according to pancreatic invasion (Kaplan-Meier method). *Dots*, Negative for pancreatic invasion ($n = 26$); *circles*, pancreatic invasion ($n = 37$). $*P = 0.002$
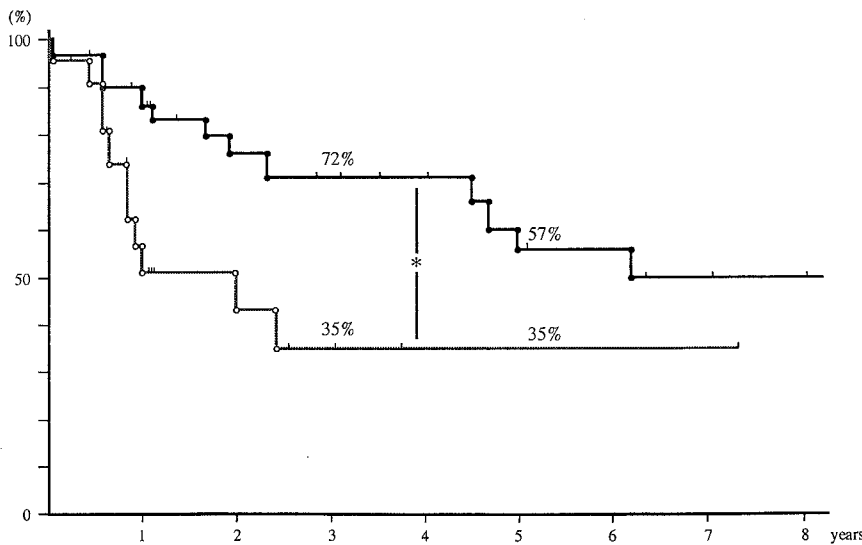
Fig. 3. Survival rates after radical resection for carcinoma of the ampulla of Vater according to regional lymph node metastasis (Kaplan-Meier method). *Dots*, No lymph node metastasis ($n = 35$); *circles*, lymph node metastasis ($n = 28$). $*P = 0.01$
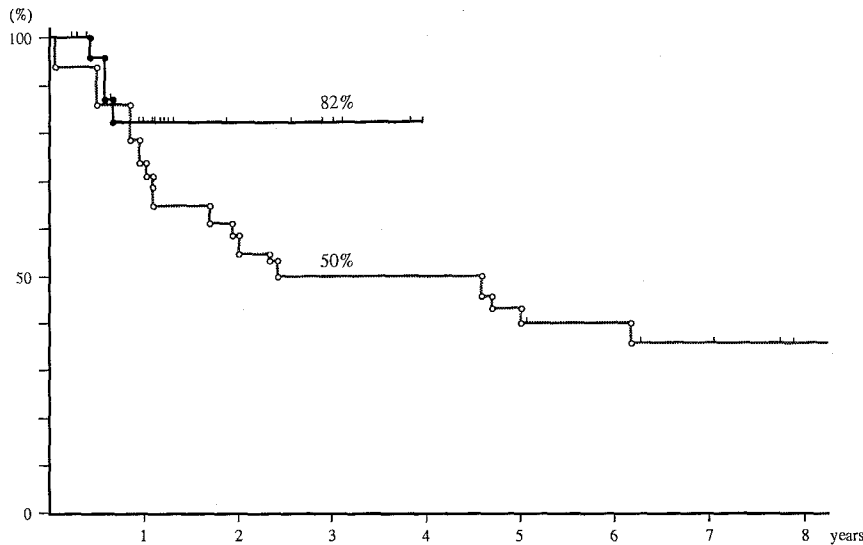
Fig. 4. Survival rates after partial pancreatoduodenectomy (*circles, n = 37*) or pylorus-preserving pancreatoduodenectomy (*dots, n = 26*) for carcinoma of the ampulla of Vater (Kaplan-Meier method)

Table 2. Correlation between pancreatic invasion and regional lymph node metastasis

	Lymph node metastasis		
	(−)	(+)	Total
Pancreatic invasion (−)	21	5 (19%)	26
Pancreatic invasion (+)	14	23 (62%)	37
Total	35	28	63

$P < 0.001$

Table 3. pTNM stage in patients who underwent PD or PPPD

	pTNM stage				
	1	2	3	4	Total
PD (1983–1990)	5	19	8	5	37
PPPD (1990–1994)	2	8	15	1	26
Total	7	27	23	6	63

Discussion

Recent advances in diagnostic techniques such as endoscopic ultrasonography (EUS) make it possible to provide precise preoperative diagnosis with regard to the extent of the tumor. In carcinoma of the ampulla of Vater, EUS has a particular advantage for the detection of pancreatic invasion of the tumor and regional lymph node metastasis. Accuracy rates of 78%–87% have been reported for the diagnosis of pancreatic invasion and 54%–83% for the diagnosis of regional lymph node metastasis.[15,16] Because of this marked progress, surgeons have been able to obtain useful information concerning resection margins.

As shown in this report, the prognosis of stage 1 patients was excellent, with a 5-year survival rate of 100%, while the prognosis of stage 4 patients was ex-

tremely poor, similar to that for patients who had the palliative bypass operation. No significant difference in survival rate was noted between stages 2 and stage 3, however. In the present series of patients, the classification of stages 2 and 3 did not indicate prognosis after surgery, so that it is unclear what operative course surgeons should take for these patients. When we analyzed differences in survival rate after surgery between two groups classified on the basis of pancreatic invasion or regional lymph node metastasis, these factors clearly reflected prognosis, and the two factors were significantly correlated. Regional lymph node metastasis was seen in only 19% of the patients who had no pancreatic invasion, whereas the proportion rose to 62% in patients with pancreatic invasion. These findings suggest that pancreatic invasion indirectly indicates the status of regional lymph node metastasis. It is also possible that, once the tumor invades the pancreatic parenchyma, cancer cells easily spread to the regional lymph nodes. The prognostic significance of pancreatic invasion in carcinoma of the ampulla of Vater has been reported by other investigators.[4,8,9] Imaizumi et al.[4] reported that the incidence of lymph node metastasis around the superior mesenteric artery (SMA) was 15.8% in 38 patients who had received radical resection accompanied by extended lymphadenectomy, while the recurrence rate around the SMA in patients who did not have

lymphadenectomy was higher (25%). Kayahara et al.[19,20] reported the incidence of lymph node metastasis around the SMA to be 15.6% in carcinoma of the ampulla of Vater, and they showed the lymphatic pathway from posterior pancreatoduodenal lymph nodes to para-aortic lymph nodes via lymph nodes around the SMA. In 1995, Hanyu et al.[21] reported that extended lymphadenectomy improved prognosis, showing a higher 5-year survival rate (81%) in patients who had undergone complete lymphadenectomy around the SMA compared with 40% in patients who had received incomplete lymphadenectomy around the SMA. In light of these findings, as well as our own, it would appear that an extended lymphadenectomy should be performed as an additional procedure for patients with pancreatic invasion, as positive regional lymph node metastasis predicts possible further lymph node metastases.

With respect to the results of PPPD in the present series, the survival rate at 3 years was 82% for patients who received PPPD and 50% for those who received PD. While these findings are not strictly comparable because of differences between operative periods, the results demonstrate that, at least to date, PPPD has not had unfavorable effects on prognosis. Nakasako et al.[22] investigated the incidence of lymph node metastasis in 54 patients who had undergone PD for carcinoma of the ampulla of Vater, finding the incidence of infrapyloric lymph node metastasis to be 3.7%, this value was the highest for lymph nodes around the stomach. Accordingly, if no metastasis is confirmed in the infrapyloric lymph node by intraoperative frozen section examination, PPPD can be employed for carcinoma of the ampulla of Vater.

We conclude that pancreatic invasion is a good prognostic indicator after radical resection for carcinoma of the ampulla of Vater. To improve the prognosis for patients with pancreatic invasion, further resection that includes extended lymphadenectomy is a recommended additional procedure.

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