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Pancreatic and Duodenal Invasion in Distal Bile Duct Cancer: Paradox in the Tumor Classification of the American Joint Committee on Cancer

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Abstract
Background Distal bile duct cancer often invades the pancreas and/or duodenum. Invasion of the pancreas is defined as a T3 and that of the duodenum as a T4 tumor in the T classification of the American Joint Committee on Cancer (AJCC). The aim of this study was to assess whether this T classification is rational from the viewpoint of prognostic power.
Method Ninety-five patients with distal bile duct cancer were retrospectively analyzed according to the current T classification of the AJCC.
Results The main determinant of pT3 (n = 32) and pT4 (n = 30) was pancreatic and duodenal invasion, respectively, and the survival rates for patients with pT3 and pT4 are similar (p = 0.595). Duodenal invasion was present in 39% of the patients with pancreatic invasion, whereas pancreatic invasion was observed in 86% of those with duodenal invasion. The survival for patients with pancreatic invasion was not significantly different (p = 0.283) whether or not there was concomitant duodenal invasion (n = 19 and n = 37, respectively). Multivariate analysis identified venous invasion, distant metastasis, histologic grade, and pancreatic invasion as independent prognostic factors.
Conclusion Although duodenal invasion usually occurs after pancreatic invasion, it is not a significant prognostic factor while pancreatic invasion is. The current T classification should be revised since it expresses tumor extension but does not reflect a survival in distal bile duct cancer.

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In 2002, the American Joint Committee on Cancer (AJCC) published the sixth edition of the AJCC cancer staging manual in which the tumor (T)-node (N)-metastasis (M) classification and stage grouping of extrahepatic bile duct carcinoma was revised rather substantially [1]. With respect to T category, T3 was defined in the fifth edition [2] as tumor invading the liver, pancreas, duodenum, gallbladder, and stomach. In the sixth edition, the previous T3 classification was divided into a new T3 (tumor invading the liver, pancreas, gallbladder, and unilateral portal vein or hepatic artery) and T4 category (tumor invading the duodenum, colon, stomach, abdominal wall, and bilateral/main portal vein or common hepatic artery) [1, 2]. This reclassification, however, was not based on clinical evidence, except for portal vein invasion [3]. In our experience, distal bile duct cancer often invades the pancreas and/or duodenum because these two organs are adjacent to the distal bile duct.

The surgical strategy for cholangiocarcinoma is based largely on tumor location; therefore, cholangiocarcinoma is generally divided into three types: intrahepatic, perihilar, or distal tumor [4, 5]. However, many studies investigating the prognostic factors or TNM staging categories combined both distal and hilar cholangiocarcinomas because both carcinomas belong to the same disease entity, i.e., "extrahepatic bile duct cancer" [6–11]. To accurately estimate prognostic factors, it is important to analyze tumors that are as much alike as possible; in other words, to group tumors located at the same site and which were resected by the same surgical procedure. We hypothesized that invasion of the pancreas and of the duodenum have equivalent prognostic significance and

that it would be better if they had the same T classification. This study was conducted to investigate this issue in patients with distal bile duct cancer who underwent pancreatoduodenectomy (PD).

Patients and methods

Patient population

A total of 100 patients with distal bile duct cancer underwent PD at the First Department of Surgery at Nagoya University Hospital from October 1975 to December 2005. During this study period, the surgical strategy or procedure for distal bile duct cancer had not been very different. In this study distal bile duct cancer was defined as a middle- or lower-third bile duct cancer, according to a report by Nakeeb et al. [5]. Seven patients who underwent bile duct resection during this period were not included because the surgical procedure was selected as a result of the patient's poor general condition, the patient's advanced age, and/or the histologic assessment of the pancreas was impossible. Five patients were excluded because they died of intra-abdominal hemorrhage (n = 3), respiratory failure (n = 1), or bacteremia (n = 1), 8, 12, 30, 33, or 72 days after surgery in the early study period. The remaining 95 patients formed the basis of this retrospective study. There were 55 men and 40 women with a median age of 67 years (range = 39–86 years). Eighty-nine patients were jaundiced at admission; 87 of them had received percutaneous transhepatic (n = 77) or endoscopic (n = 10) biliary drainage before surgery. Percutaneous transhepatic cholangioscopy was performed in 65 patients to make an accurate assessment of the longitudinal extent of cancer [12].

Surgical procedures

Pylorus-preserving PD was performed in 50 patients, standard PD (Whipple procedure) in 26, and subtotal stomach-preserving PD in 19. Dissection of the regional lymph nodes (the pericholedocal, retroportal, cystic duct, hepatic artery, right celiac, pancreatoduodenal, and the right side of the superior mesenteric nodes groups) was performed in all patients, 43 of whom underwent additional para-aortic node clearance. Portal vein resection with reconstruction was performed in ten patients, three of whom also underwent hepatic artery resection. The remaining pancreas, bile duct, and stomach/duodenum were anastomosed to a jejunal limb in this order (a modified Child's method).

Postoperative complications occurred in 51 patients (54%). Pancreatic fistula was the most common (n = 42), followed by delayed gastric emptying (n = 8), intra-abdominal bleeding (n = 5), severe wound infection (n = 4), intra-abdominal abscess (n = 4), pneumonia (n = 3), leakage of the choledochojejunostomy (n = 3), bacteremia (n = 2), gastrointestinal bleeding (n = 1), liver abscess (n = 1), and hepatic insufficiency (n = 1).

Pathologic assessment

We routinely performed specimen cholangiopancreatogram by injecting the contrast agent into the cut stumps of bile duct and main pancreatic duct. The entire bile duct with the surrounding tissue, including the duodenum and pancreas, was sectioned serially at 5-mm intervals. All sections were carefully inspected and embedded in paraffin and stained with hematoxylin and eosin. The epicenter of the tumor was located at the lower third of the bile duct in 58 patients and at the middle third in 37 patients. More exactly, the tumor involved the intrapancreatic bile duct in 48 patients, the suprapancreatic duct in 16 patients, and both in 31 patients. Histologically, the outer border of the bile duct wall was defined as the outermost part of dense fibromuscular tissue in cases of mild fibrosis or as the line of large arteries or nerves in cases of severe fibrosis [13]. Pancreatic invasion was defined as evident tumor cell infiltration in the pancreatic parenchyma, irrespective of the length of infiltration; therefore, tumor invasion of the fibroadipose tissue between the bile duct and the pancreatic capsule was not considered pancreatic invasion. Cystic duct invasion (n = 12) was not considered to be gallbladder invasion because the cystic duct continues and often runs parallel to the bile duct and is not defined as the gallbladder in the AJCC staging manual [1]. Perineural, lymphatic, or venous invasion as well as invasions of the duodenum and portal vein were also documented. Based on these considerations, the tumors were classified as tumor confined to the bile duct (T1, n = 9), tumor beyond the wall of the bile duct (T2, n = 24), tumor invading the pancreas (T3, n = 32), and tumor invading the portal vein, duodenum, or hepatic artery (T4, n = 30).

Nodal involvement was present in 36 of 95 patients (38%), of whom five had involvement of the para-aortic lymph nodes, classified as pathologic distant metastasis (pM1). The other five patients with single liver metastasis or limited peritoneal dissemination in the specimen were also classified as pM1, although these lesions were removed.

Patient follow-up after operation

Postoperative adjuvant treatment was not performed. Patients were followed regularly in outpatient clinics every

Table 1 Survival of the 95 study patients according to the latest AJCC cancer staging classification

Variable	No. of patients	Survival rate (%)			MST (95% CI)	
		1-year	3-year	5-year	(months)	*p*
pT classification						<0.001
pTl	9	89	89	89	–	
pT2	24	95	73	55	–	
pT3	32	63	31	21	18 (6–26)	
pT4	30	65	29	16	19 (8–31)	
pN classification						0.001
pNO	59	86	60	46	55 (29–81)	
pNl	36	57	25	19	14 (9–20)	
pM classification						<0.001
pMO	85	80	52	39	38 (17–59)	
pMl	10	25	0		7 (2–12)	
Stage grouping						<0.001
Stage IA	7	100	100	100	–	
Stage IB	18	100	82	58	–	
Stage IIA	19	78	53	36	38 (17–71)	
Stage IIB	17	56	19	19	13 (11–15)	
Stage III	24	78	37	21	23 (12–34)	
Stage IV	10	25	0		7 (2–12)	

AJCC = American Joint Committee on Cancer; MST = median survival time; 95% CI = 95% confidence interval; pT classification = pathologic primary tumor classification; pN classification = pathologic lymph node classification; pM classification = pathologic distant metastasis classification

three to six months with a median follow-up period of 26 months (range = 3–136) and all survival data were obtained. At the time of assessment of the disease status, 58 patients had died of tumor recurrence and 9 patients had died from other causes with no evidence of recurrence. Two patients were alive with recurrent disease and the remaining 26 were alive without disease.

Statistics

The follow-up period was defined as the interval between the date of surgery and that of the last follow-up. Deaths from cancer were considered treatment failures, while those from other causes were considered censored cases. Categorical data were compared using the χ^2 test. Postoperative survival curves were generated by the Kaplan-Meier method, and differences in survival were compared with the log-rank test. The variables identified as potentially significant on univariate analysis were subsequently chosen for multivariate analysis with the Cox proportional hazards model to identify independent predictors of survival. In this model, a stepwise forward selection was used with entry and removal limits of $p < 0.1$ and $p > 0.15$, respectively. When a variable had three or more categorical parts, the parts were coded as dummy variables. All tests were two-sided and $p < 0.05$ was considered statistically significant. All statistical calculations were performed using the SPSS 11.0 J software package (SPSS Japan Inc., Tokyo, Japan).

Results

Patient survival according to T classification

The overall postoperative survival rates for the 95 study patients were 75% at 1 year, 47% at 3 years, 35% at 5 years, and 26% at 10 years, with a median survival time of 30 months. Twenty-three patients have lived more than five years after surgery. The survival rates and median survival time according to TNM classifications and stage grouping are summarized in Table 1. Survival was associated with the pT classifications (Fig. 1). The 1-, 3-, and 5-year survival rates were all 89% in patients with pT1 tumor and were 95%, 73%, and 55%, respectively, in those with pT2 tumor ($p = 0.1473$). Among the nine patients with pT1 tumor, only one patient, who had undergone resection but had a nodal metastasis and a positive surgical margin, died of tumor recurrence 11 months after surgery and the other eight patients had no recurrent disease, while 12 of 24 patients with pT2 tumor had recurrent disease. The survival curve for patients with pT3 tumor was similar to that for patients with pT4 tumor ($p = 0.595$). There was a significant difference in survival between the following pT classifications: pT1 vs. pT3 ($p = 0.003$), pT1 vs. pT4 ($p < 0.0003$), pT2 vs. pT3 ($p = 0.003$), and pT2 vs. pT4 ($p < 0.001$). The survival curve of 19 patients with pT3N0M0 and that of 14 patients with pT4N0M0 were not statistically different ($p = 0.058$), when the patients without nodal involvement were selected. Thus, irrespective of status of

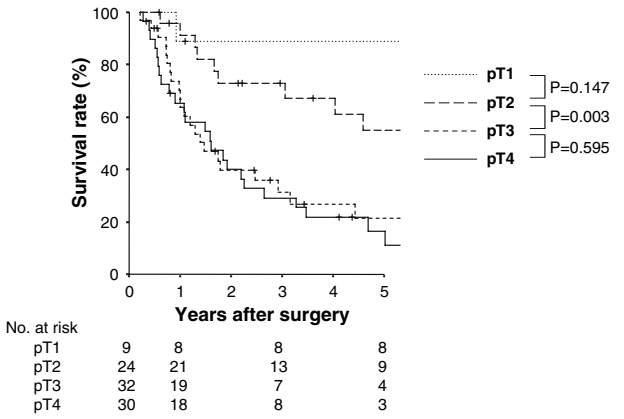

Fig. 1 Kaplan-Meier survival curves of the 95 patients with distal bile duct cancer, divided according to their pathologic tumor (pT) classifications. Cross marks in the curves indicate censored cases

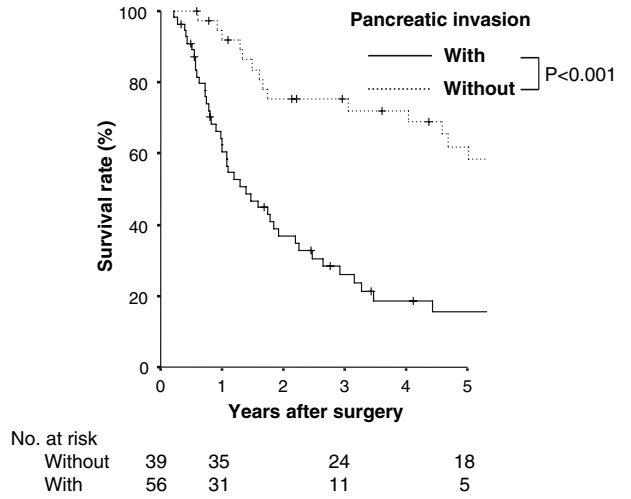

Fig. 2 Kaplan-Meier survival curves of the 95 patients with distal bile duct cancer, divided according to the presence or absence of pancreatic invasion. Cross marks in the curves indicate censored cases

nodal metastasis, survival of the patients with pT3 tumor and that of the patients with pT4 tumor was similar.

Correlation of determinants betweenT3 and T4 tumors

Pancreatic invasion, the single T3 determinant found in our series, was observed in 56 patients, 24 of whom had pT4 tumors, because of simultaneous duodenal invasion (n = 17), portal vein invasion (n = 5), or both (n = 2). On the other hand, duodenal invasion, portal vein invasion, or both was present in 20, 8, and 2 patients (i.e., 30 patients with pT4 tumor) of 95 patients, respectively; therefore three patients with duodenal invasion and three patients with portal vein invasion did not have pancreatic invasion. With respect to the correlation between pancreatic and duodenal invasion, duodenal invasion was present in 19 (34%) of 56 patients who had pancreatic invasion, whereas pancreatic invasion was present in 19 (86%) of 22 patients who had duodenal invasion (p = 0.003).

Survival of patients with pancreatic and duodenal invasion

The survival rate of patients with pancreatic or duodenal invasion was significantly worse than that of the patients without invasion (Figs. 2 and 3). The survival curves of the 56 patients with pancreatic invasion and also with (n = 19) or without (n = 37) duodenal invasion were not significantly different (Fig. 4): 1-year survival, 55% vs. 63%; 3-year survival, 18% vs. 30%; 5-year survival, 12% vs. 17%; median survival, 13 months vs. 17 months, respectively (p = 0.283). The presence of duodenal invasion did not significantly worsen the survival of the patients with pancreatic invasion.

Prognostic factors

Twelve pathologic variables were analyzed as potential prognostic factors (Table 2). Univariate analysis revealed that tumor configuration, pancreatic invasion, duodenal invasion, lymphatic vessel invasion, venous invasion, perineural invasion, histologic grade, nodal metastasis, and distant metastasis were significantly associated with survival. Multivariate analysis was performed incorporating these nine potential variables, and venous invasion, distant metastasis, histologic grade, and pancreatic invasion were identified as independent predictors of survival in patients with distal bile duct cancer who underwent PD.

Discussion

Bile duct cancer is histologically characterized as an aggressive locoregional tumor with a high incidence of nodal metastasis, wide extent of neurovascular invasion, and frequent microscopic infiltration beyond the main tumor mass [14–18]. These characteristics have lead biliary surgeons to perform extensive surgery to achieve curative resections [16, 19–24]. In distal bile duct cancer, the incidence of lymph node metastasis along the superior mesenteric artery is 20% and invasion of the extrapancreatic nerve plexus is 14% [16]. Therefore, a PD with regional lymph node dissection is indicated for most distal bile duct carcinomas [8, 16, 22, 25, 26]. Since recent randomized controlled trials have proven that the differences in the PD, ranging from a pyrolus-preserving to a Whipple procedure, did not influence long-term survival in periampullary cancer [27, 28], we grouped the patients

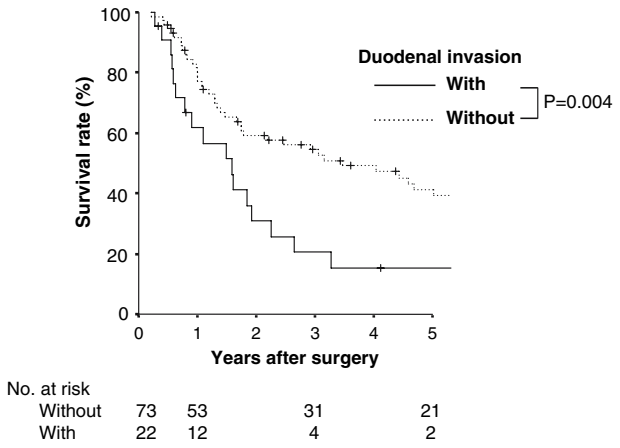

Fig. 3 Kaplan-Meier survival curves of the 95 patients with distal bile duct cancer, divided according to the presence or absence of duodenal invasion. Cross marks in the curves indicate censored cases

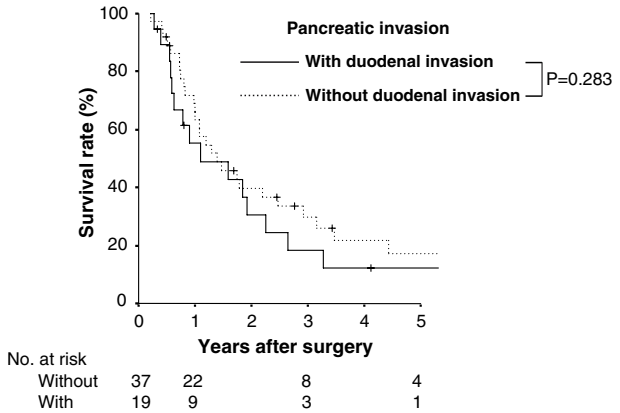

Fig. 4 Kaplan-Meier survival curves of the 56 patients who had pancreatic invasion, divided according to the presence or absence of duodenal invasion. Cross marks in the curves indicate censored cases

according to type of PD received. In addition, the specimens obtained after PD are suitable to make histologic slides of both the bile duct and the pancreas, which is necessary for an accurate evaluation of pancreatic invasion. In other studies that involved patients who underwent bile duct resection or hepatectomy as well as PD, the histologic diagnosis of pancreatic invasion may have been inaccurate. To our knowledge this is the first report to verify the clinical value of the current AJCC staging system, focusing on distal bile duct cancer.

In this study the patients with pT1 tumor had a very favorable prognosis with a 5-year survival rate of 89%, and those with pT2 tumor had the second most favorable survival with a 5-year survival rate of 73%, although there was no statistical difference between the two groups, possibly because of the small number of pT1 tumors ($n = 9$) in our series. The patients with pT1 tumor had no recurrent disease, except for one patient described above; this differed from those with pT2 tumor. Albores-Saavedra et al. [29] and Yamaguchi [30] also reported nine and seven patients with pT1 tumor, respectively, and concluded that pT1 tumor is associated with an excellent long-term survival and a low incidence of reccurence. Therefore, the pT1 tumor may represent early-stage disease in the current staging system. In contrast, the survival curves of patients with pT3 and pT4 tumors were poor and almost similar with 5-year survival rates of 31% and 29%, respectively. The current T classification might divide the study patients into three groups, i.e., pT1, pT2, and pT3/4, from the standpoint of survival. The main determinant of pT3 status was pancreatic invasion while that of pT4 was duodenal invasion. In our series duodenal invasion and portal vein invasion were present in 22 (39%) and 10 (18%), respectively, of the 56 patients who had pancreatic invasion; pancreatic invasion was present in 19 (86%) of the 22 patients who had duodenal invasion and in 7 (70%) of 10 the patients with portal vein invasion. These incidences suggest that distal bile duct cancer, irrespective of the middle or distal tumor, extends progressively to the pancreas, followed by the duodenum or the portal vein. The current classifications of T3 and T4 may express tumor extension from an anatomic viewpoint but not reflect a patient's survival.

Multivariate analysis revealed that the independent prognostic factors were venous invasion, histologic grade, pancreatic invasion, and distant metastasis. Importantly, only pancreatic invasion was a variable that is included in the determinants of T classification. Other authors also have reported that pancreatic invasion, not duodenal invasion, had a negative survival impact in bile duct cancer [10, 11, 31]. In pancreatic invasion, the incidence of nodal metastasis and perineural invasion increased progressively, and these two factors have been reported to be negative factors of survival [10, 11, 16]. The additional presence of duodenal invasion did not worsen survival for the patients with pancreatic invasion (Fig. 4) and portal vein invasion had no significant impact on survival (Table 2). In short, the survival of patients with pT4 tumor is determined predominantly by the presence of pancreatic invasion, not by duodenal invasion or portal vein invasion. This result illustrates the overlapping survival curves of the patients with pT3 and pT4 tumors. In this context, the pancreas is a key organ and is a major determinant of T classification in distal bile duct cancer.

Nishio et al. [32] reported that in perihilar cholangiocarcinoma, the current T classification did not clearly stratify the postoperative survival of the patients with pT1, pT2, and pT3 tumors, but it could discriminate between pT1-3 and pT4 tumors. In their series, the main determinant of T3 was liver invasion and that of T4 was

Table 2 Univariate and multivariate analyses of survival, according to pathologic factors

Variable	No. of patients	Survival rate (%)		Univariate analysis	Multivariate analysis	
		3-year	5-year	*p* value	Relative risk (95% CI)	*p* value
Location				0.361		
Middle	37	45	27			
Lower	58	48	42			
Tumor configuration				0.010		
Papillary	23	71	60			
Nodular	59	37	25			
Infiltrating	13	49	39			
Pancreatic invasion				<0.001		0.002
Absent	39	75	62		1.00	
Present	56	26	15		2.72 (1.46–5.12)	
Duodenal invasion				0.004		
Absent	73	54	41			
Present	22	21	15			
Portal vein invasion				0.075		
Absent	85	47	38			
Present	10	40	15			
Lymphatic vessel invasion				0.001		
Absent	28	74	61			
Present	67	34	24			
Venous invasion				<0.001		<0.001
Absent	66	61	46		1.00	
Present	29	17	14		3.83 (2.20–6.69)	
Perineural invasion				0.002		
Absent	26	67	63			
Present	69	38	23			
Histologic grade				0.024		0.003
Well differentiated	25	73	64		1.00	
Moderately differentiated	54	42	28		2.95 (1.40–6.20)	
Poorly differentiated	16	20	20		3.55 (1.44–8.74)	
Nodal metastasis				0.001		
Absent	59	60	46			
Present	36	25	19			
Distant metastasis				<0.001		0.001
Absent	85	52	39		1.00	
Present	10	0			3.72(1.72–8.03)	
Surgical margin status				0.145		
Negative	85	48	37			
Positive	10	34	17			

95% CI = 95% confidence interval

contralateral/main portal vein invasion. Independent prognostic indicators were histologic grade, nodal involvement, and portal vein invasion [3]. Therefore, portal vein invasion is a key prognostic factor in perihilar cholangiocarcinoma, and survival for the patients with pT4 tumor was strikingly worse. These results were largely different from the results in this study, which suggests that perihilar cholangiocarcinoma and distal bile duct cancer may need to be staged differently. On the other hand, Hong et al. [6] reported that there was no significant difference in survival between patients with pT2 tumors and those with pT3 tumors in extrahepatic bile duct cancer. This is probably the result of their inclusion of both hilar and distal bile duct cancers and the inclusion of relatively few T4 tumors.

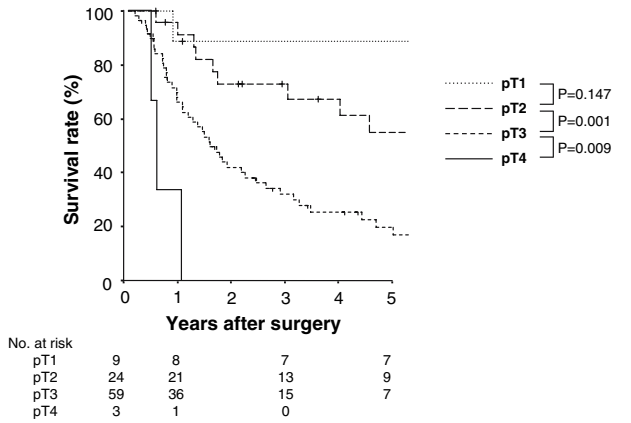

Fig. 5 Kaplan-Meier survival curves of the 95 patients with bile duct cancer, divided according to our proposed T classification

Overall, it does not seem logical to apply the same T classifications to both hilar and distal bile duct cancers, and different T classifications are probably required.

We propose here a new T classification for distal bile duct cancer, i.e., T1 (confined within the bile duct), T2 (beyond the bile duct), T3 (other organ invasion, except the hepatic artery), and T4 (hepatic artery invasion). These definitions of T1, T2, and T3 exactly correspond to the T classification of the previous edition of the AJCC manual [2]. In general, the T4 tumor symbolizes an unresectable tumor due to locally advance disease [1]. However, patients with the current T4 distal bile duct tumors due to duodenal and portal vein invasion are good candidates for resection, at least in leading centers. Therefore, T4 should be defined as positive direct or perineural invasion of the hepatic artery, which is a local factor leading to irresectability. According to the above definitions, 9 patients in this study had pT1, 24 had pT2, 59 had pT3, and 3 had pT4 tumors. The survival curves of each T category were considerably different (Fig. 5). In our series, three patients with hepatic artery invasion (proposed pT4 disease) exceptionally underwent PD with hepatic artery resection and reconstruction, but they died of disease 6, 7, and 13 months after surgery, not significantly different from the survival of 21 patients with unresectable distal bile duct cancer during the same study period (19% at 1 year and 0 at 2 years, with a median survival time of 4.9 months, $p = 0.854$). This suggests that the proposed T4 tumor symbolizes a locally advanced distal bile duct cancer that may be unsuitable for definite resection. Because our study is retrospective with a limited number of patients, large pooled data should be used to assess the predictive accuracy of the staging scheme.

In conclusion, although duodenal invasion usually occurs after pancreatic invasion in distal bile duct cancer, the most significant prognostic factor is not duodenal invasion but pancreatic invasion. The current AJCC T classification for extrahepatic bile duct cancer should be revised since the T classification is not satisfactory for distal bile duct cancer: it expresses tumor extension but does not reflect survival in distal bile duct cancer.

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