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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Cholangiographic Tumor Classification for Simple Patient Selection Prior to Hepatopancreatoduodenectomy for Cholangiocarcinoma

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ABSTRACT

Background. Hepatopancreatoduodenectomy (HPD) is employed for patients with laterally advanced cholangiocarcinoma. However, the survival benefit of this extended approach remains controversial. The aim of this study is to identify a tumor feature benefiting from HPD from the standpoint of long-term survival.

Patients and Methods. Patients with cholangiocarcinoma who underwent HPD with curative intent between 2001 and 2017 were retrospectively analyzed. Tumors were radiologically classified by preoperative cholangiogram. Diffuse type was defined as significant tumor/stricture located from the hilar to intrapancreatic duct; localized type was defined as tumor otherwise. Univariable and multivariable analyses were performed to identify prognostic indicators.

Results. Of 100 study patients, 28 (28%) patients had diffuse tumor type, while the remaining 72 (72%) patients had localized tumors. The former group showed significantly longer lateral length (43 versus 22 mm, $P < 0.001$) and more frequent pancreatic invasion (50% versus 32%, $P = 0.110$), advanced T classification (64% versus 49%, $P = 0.185$), and nodal metastasis (57% versus 47%, $P = 0.504$), compared with the latter group. The survival for patients with diffuse tumor type was significantly worse than that for patients with localized tumor type, with 5-year survival rates of 59.0% versus 26.3%, respectively ($P = 0.003$). Multivariable analysis identified four independent factors deteriorating long-term survival: cholangiographic diffuse tumor ($P = 0.021$), higher age ($P = 0.020$), percutaneous biliary drainage ($P = 0.007$), and portal vein resection ($P = 0.007$).

Conclusions. Presurgical cholangiographic classification, diffuse or localized type, is a tumor-related factor closely associated with survival probability; therefore, it may be a useful feature for patient selection prior to HPD for cholangiocarcinoma.

Hepatopancreatoduodenectomy (HPD) is a multivisceral resection that includes a hepatectomy and a pancreatoduodenectomy for treatment of advanced biliary tract cancers that are otherwise unresectable.[1,2] Although a high HPD-associated mortality of over 10% reported in the 1990s had made it unfeasible as a surgical practice,[3,4] the risk gradually reduced with the subsequent increase in HPD.[2,5,6] However, recent nationwide surveys still demonstrated a mortality of 7.6% in Japan,[7] 18.2% in the USA,[8] and 34.2% in Brazil.[9] This fact indicates a persisting, high-risk nature at present for HPD. Meanwhile, several studies have shown 5-year survival rates ranging from 37 to 50% after HPD,[2,10,11] suggesting the need for an appropriate patient selection process to warrant the long-term oncologic benefits that would outweigh the perioperative risks. We attempted to classify tumor morphologies using preoperative cholangiogram and to evaluate its prognostic impacts, which have not yet been addressed. The aim of this study is to identify a tumor feature benefiting from HPD from the standpoint of long-term survival.

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PATIENTS AND METHODS

Study Population

Data from patients who underwent HPD with curative intent for primary cholangiocarcinoma at the First Department of Surgery, Nagoya University Hospital between 2001 and 2017 were collected from the prospective database. This study was approved by the Human Research Review Committee of Nagoya University Hospital (Approval Number: 2017-0478).

Preoperative Tumor Work-Up

A contrast-enhanced computed tomography (CT) scan was performed for the whole lung and abdomen to evaluate local tumor extension, metastatic status, vascular anatomy, and liver volume. An endoscopic or percutaneous cholangiography was also performed to diagnose the extension of the tumor along the biliary tree, which was then followed by biliary drainage in patients with dilatations of the intrahepatic biliary tree.[12] Biopsy samples were taken from the main tumor stricture with forceps to histologically confirm malignancies, and from the seemingly benign surrounding bile duct to define the lateral tumor extension as far as possible.[13] Magnetic resonance cholangiopancreatography (MRCP) and positron emission tomography imaging were utilized in select patients.

Cholangiographic Tumor Classification

On the cholangiograms, the extrahepatic biliary tree was anatomically classified into three segments: the hilar, middle, and lower bile ducts. The hilar duct was defined as the right or left hepatic duct, the confluence, and the hepatic duct above the orifice of the cystic duct. The middle duct was defined as the bile duct between the orifice of the cystic duct and the pancreatic entry. The lower bile duct was defined as the intrapancreatic bile duct above the papilla of Vater. The level of the cystic duct and the pancreatic entry was determined with reference to the CT images, as needed. The latter two sections were considered as the distal bile ducts. Cholangiocarcinomas were radiologically classified on the basis of the location of significant tumor masses/structures (Fig. 1). Diffuse tumors were defined as tumors involving the three segments of the extrahepatic biliary tree. Localized tumors were defined as tumors invading one or two of the three segments and were further divided into either perihilar or distal tumors based on the predominance of the epicenter of the main tumor.[14]

Surgery

HPD was indicated as a treatment for various modes of cholangiocarcinoma spreads that otherwise could not be completely removed. The type of hepatectomy was chosen based on the balance of tumor extents with the functional reserves of the future liver remnant. Exceptionally, the initial surgical plan of hepatectomy or pancreatoduodenectomy was revised to HPD on the basis of intraoperative findings including frozen-section histology. A vascular resection was performed when macroscopic vascular invasion was confirmed during the surgery.[15,16] Detailed techniques and perioperative managements were previously reported.[1,2] Three senior hepatobiliary surgeons (T.E., T.M., and N.M.) among the nine authors exclusively performed HPD.

Chemotherapy and Radiotherapy

Unresected patients received chemotherapy with gemcitabine hydrochloride, cisplatin, or tegafur–gimeracil–oteracil potassium (S-1) since 2006. Postoperative adjuvant chemotherapy was performed in patients with nodal metastasis and/or a positive surgical margin according to the institutional guideline, where gemcitabine hydrochloride or S-1 was given for at least 6 months after surgery.[17,18] Postoperative radiotherapy combined with chemotherapy was used in selected patients with a positive surgical margin. For patients with relapsed disease, any of the above-mentioned regimes were initiated, if possible.

Pathological Assessment

The whole bile duct with the surrounding tissue was extensively sampled and stained with hematoxylin–eosin in a previously described manner. [19] The gross tumor morphology was classified into two broad categories: papillary and nonpapillary tumors.[20,21] The pathological findings and tumor–node–metastasis classifications were determined according to the American Joint Committee on Cancer (AJCC) staging manual, 7th edition,[14] in which the distal and perihilar cholangiocarcinomas were classified and staged under the discrete framework. Superficial spreading was defined as presence of extensive (usually more than 20 mm) carcinoma in situ (CIS) around the main tumor.[20,22] For residual disease (*R*) status, ductal involvement with CIS was considered to be negative in the survival analysis because it has no impact on survival.[20,23]

Statistical Analysis

Continuous data are expressed as median (range). Variables were compared between groups using the χ^2 test

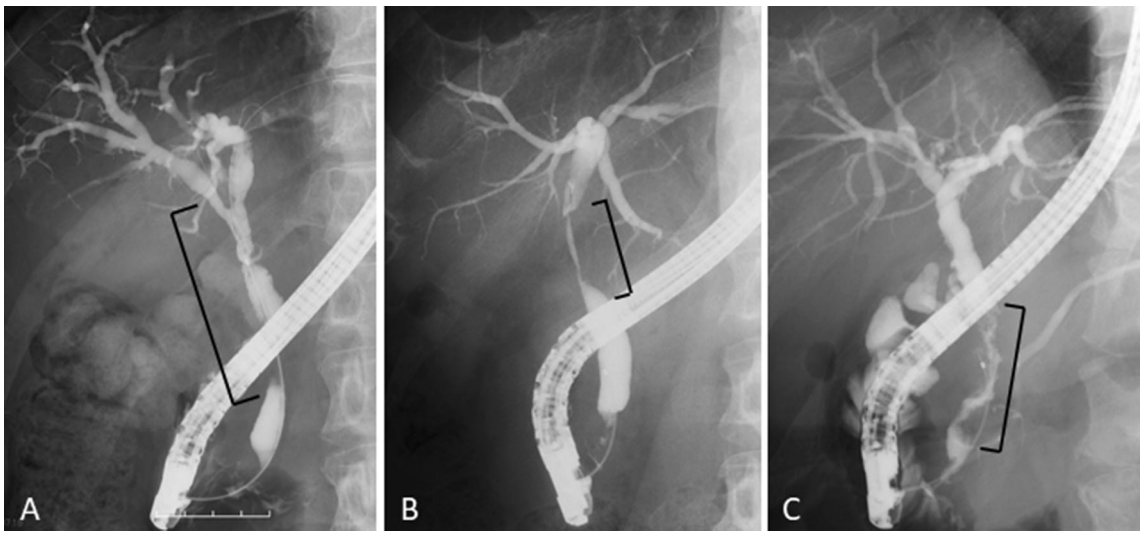

FIG. 1 Cholangiographic tumor classification. A diffuse tumor type defined as cholangiocarcinoma invading all three segments of the extrahepatic bile duct, including the hilar, middle, and lower segments (**a**). A localized tumor type defined as a tumor invading one or two segments of the bile duct, which was further divided into a perihilar tumor (**b**) and a distal tumor (**c**) on the basis of the predominant location. Brackets indicate main tumor location

or Mann–Whitney *U* test, as appropriate. Survival curves were calculated using the Kaplan–Meier method and compared with the log-rank test. Variables identified as potentially significant on univariable analyses were subsequently chosen for multivariable analysis by using the Cox proportional hazards model. All reported *P* values are two-sided, with $P < 0.05$ considered statistically significant. All statistical calculations were performed using IBM SPSS Statistics® version 24 (IBM Japan Inc., Tokyo, Japan).

RESULTS

During the study interval, 104 consecutive patients underwent HPD with curative intent for cholangiocarcinomas. Excluding 4 (3.8%) patients who died of surgical complications, the remaining 100 patients were enrolled in this retrospective study. There were 72 men and 28 women with median age of 69 years (range 36–82 years). Clinical backgrounds are summarized in Table 1. Median body mass index was 21.9 kg/m^2 (range 15.3–34.9 kg/m^2). Median operative time was 715 min (range 519–1012 min). Postoperative adjuvant chemotherapy was given in 33 patients, 2 of whom received preoperative chemotherapy. Postoperative radiotherapy was performed in three patients.

Cholangiographic Spectrum and Indication for HPD

According to the cholangiographic classification, diffuse and localized tumors were found in 28 (28%) and 72 (72%) patients, respectively. The latter tumor classification included 37 perihilar tumors and 35 distal tumors. One patient had a double tumor with a predominant perihilar tumor and an extra small papillary tumor at the distal end of the lower duct; this double tumor was treated in the localized perihilar category.

Of the cohort, 89 patients were initially scheduled for HPD based on the preoperative tumor staging (Supplemental Fig. 1). The remaining 11 (11%) patients underwent conversion surgeries from either a hepatobiliary resection ($n = 10$) or pancreatoduodenectomy ($n = 1$) to HPD due to the following intraoperative findings: a positive distal ductal margin ($n = 8$), a bulky nodal metastasis around the pancreatic head ($n = 1$), an unexpectedly discovered papillary cholangiocarcinoma in the lower bile duct during a hepatobiliary resection for perihilar cholangiocarcinoma ($n = 1$), and a positive proximal ductal margin ($n = 1$). Thus, the tumors exhibited the following heterogeneous modes of spread: a distal tumor that exhibited upward superficial spreading ($n = 34$), a perihilar tumor that exhibited downward superficial spreading ($n = 31$), a diffusely infiltrating tumor of the whole extrahepatic bile duct ($n = 28$), a bulky mass formation that approximated the pancreatic entry in perihilar tumor ($n = 3$) and the right hepatic artery in distal tumor ($n = 1$), a perihilar tumor with a bulky nodal metastasis of the pancreatoduodenal region ($n = 2$), and a double cholangiocarcinoma ($n = 1$).

Most of the findings were not significantly different between the patients with diffuse tumors and those with localized tumors (Table 2), except for lateral tumor length (43 versus 22 mm, $P = 0.001$). However, pancreatic

TABLE 1 Clinical characteristics of 100 study patients

	Total (n = 100)	
Age, years (range)	69	(36–82)
Gender, male/female	72/28	
Body mass index (range), kg/m^2	21.9	(15.3–34.9)
Serum CA 19-9, U/ml (range)	44	(2–2792)
Preoperative workup, n (%)		
MRCP	33	(33%)
Cholangiography	100	(100%)
Biliary drainage	98	(98%)
Percutaneous	35	(35%)
Endoscopic[a]	63	(63%)
Biliary tissue sampling	74	(74%)
Portal vein embolization	75	(75%)
Type of hepatectomy[b], n (%)		
S1, 5, 6, 7, 8	57	(57%)
S1, 4, 5, 6, 7, 8	4	(4%)
S1, 2, 3, 4	20	(20%)
S1, 2, 3, 4, 5, 8	18	(18%)
S1	1	(1%)
Portal vein resection, n (%)	30	(30%)
Hepatic artery resection, n (%)	11	(11%)
Operative time, min (range)	715	(519–1012)
Operative blood loss, ml (range)	1791	(316–5315)
Complications ≥ Clavien grade III, n (%)	81	(81%)
Pancreatic fistula ≥ grade B[c]	67	(67%)
Bile leakage ≥ grade B[d]	22	(22%)
Liver failure ≥ grade B[d]	50	(50%)
Delayed gastric emptying ≥ grade B[e]	19	(19%)
Intraabdominal bleeding	5	(5%)
Reoperation, n (%)	3	(3%)
Postoperative hospital stay, days (range)	39	(16–218)

CA carbohydrate antigen, *MRCP* magnetic resonance cholangiopancreatography

[a]Nasobiliary tube (n = 58), plastic stent (n = 3), and self-expandable metallic stent (n = 2)

[b]Expressed as Couinaud's hepatic segments resected

[c]According to definition of International Study Group of Pancreatic Fistula

[d]According to definition of International Study Group of Liver Surgery

[e]According to definition of International Study Group of Pancreatic Surgery

invasion, advanced T classification, and nodal metastasis were more often found in the former group.

Survival Analysis

The postoperative survival rate for the entire cohort was 62.3% at 3 years, 49.2% at 5 years, and 32.3% at 10 years, with median survival time (MST) of 4.03 years (Fig. 2a). According to the cholangiographic tumor classification (Fig. 2b), patients with a localized tumor had better survival than those with a diffuse tumor: 59.0% versus 26.3% at 5 years with MST of 5.80 versus 2.27 years, respectively (P = 0.003). Among the 72 patients with localized tumors, survival rates were not significantly different between the perihilar and distal groups (P = 0.700).

Univariable analyses followed by multivariable analysis demonstrated that diffuse tumor, age of 70 years or older, percutaneous biliary drainage, and portal vein resection were independent predictors deteriorating survival (Table 3). The number of these four risk factors significantly stratified survival (Fig. 3). The survival for patients with zero or one risk factor was significantly better than that for patients with two risk factors: 71.5% versus 36.2% at 5 years, with MST of 11.5 versus 2.38 years, respectively ($P < 0.001$). In contrast, all of the patients with three or four risk factors died within 4 years after HPD, with MST of 1.52 years.

DISCUSSION

Due to the rarity of HPD usage, disease-specific prognostic factors after HPD remain unclear. In this challenging setting, the present study first analyzed the prognostic factors of cholangiocarcinoma requiring HPD by using a large sample size of 100 individuals. Although over half of the present cohort overlapped the cohort that was used in the previous institutional study,[2] the main focus differed between the two studies.

The present study failed to demonstrate significant effects of pathologic vascular invasion, pancreatic invasion, nodal metastasis, and margin status that were shown to be prognostic factors in previous studies.[2,6,24] This difference may be explained by the multiple factors that are associated with the nature of a retrospective study: differences in the collection period, sample sizes, and the definition of the analysis set. The type of biliary drainage was included in this study because several recent studies have demonstrated that the percutaneous approach significantly raised the risk of postoperative disseminated disease and subsequently reduced the survival probability. [25–27] In addition, a novel variable (the cholangiographic tumor classification) was included for the first time in the current study, and this classification was associated with pancreatic invasion, advanced tumor classification, and nodal metastasis, although not significantly so. Therefore, potential confounding function of the cholangiographic classification may mask the effect of these pathologic parameters. Institutional indication for postoperative chemotherapy also may have affected the results.

TABLE 2 Pathological characteristics of patients according to cholangiographic tumor classification

Variable	Cholangiographic tumor classification				*P*
	Diffuse (*n* = 28)		Localized (*n* = 72)		
Gross tumor morphology, *n* (%)					1.000
Papillary	3	(10.7%)	10	(13.9%)	
Nonpapillary	25	(89.3%)	62	(86.1%)	
Lateral tumor length, mm (range)	43	(24–94)	22	(8–56)	0.003
Histologic grade, *n* (%)					0.801
Well differentiated	8	(28.6%)	18	(25.0%)	
Moderately/poorly differentiated	20	(71.4%)	54	(75.0%)	
Pancreas invasion, *n* (%)	14	(50.0%)	23	(31.9%)	0.110
Liver invasion, *n* (%)	15	(53.6%)	31	(43.0%)	0.378
Arterial invasion, *n* (%)	5	(17.9%)	13	(18.1%)	1.000
Portal vein invasion, *n* (%)	8	(28.6%)	19	(26.4%)	0.807
Microscopic perineural invasion, *n* (%)	24	(85.7%)	65	(90.3%)	0.496
Microscopic lymphatic invasion, *n* (%)	21	(75.0%)	56	(77.8%)	0.795
Microscopic venous invasion, *n* (%)	13	(46.4%)	32	(44.4%)	1.000
AJCC T classification, 7th, *n* (%)					0.185
pT1/2	10	(35.7%)	37	(51.4%)	
pT3/4	18	(64.3%)	35	(48.6%)	
Nodal metastasis, *n* (%)	16	(57.1%)	34	(47.2%)	0.504
Positive surgical margin, *n* (%)	11	(39.3%)	21	(29.2%)	0.491
With carcinoma in situ	5	(17.9%)	11	(15.3%)	0.766
With invasive cancer	6	(21.4%)	12	(16.7%)	0.573

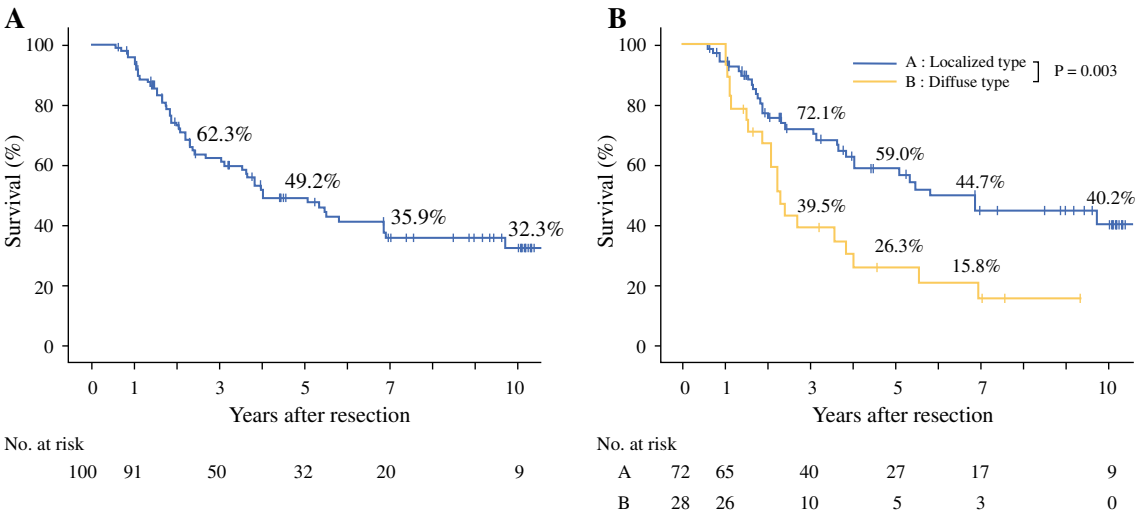

FIG. 2 **a** Overall survival of all study patients. **b** Overall survival according to cholangiographic tumor classification

The cholangiographic tumor classification was determined based on the main tumor location in the standard biliary anatomy, as defined by the AJCC system. Although the availability of this system could not be validated in the MRCP due to the low executing rate of 32% in the present cohort, the MRCP clearly depicts the main lesion of cholangiocarcinoma within the whole biliary tree.[28,29] Therefore, the simple tumor classification, diffuse versus localized type, can be applied in MRCP. The median tumor length significantly differed between the diffuse (43 mm) and localized types (22 mm), suggesting that the measured tumor length can be used as an alternative to the present approach. However, as the length of the extrahepatic bile duct depends on the body size,[30] the tumor length requires a correction for body size because reliable metrics and cutoff values that are sought in Japanese patients, generally

TABLE 3 Univariable and multivariable analyses of survival

Variables	No.	Survival rate (%)		Univariable	Multivariable	*P*
		3-Year	5-Year	*P*	RR (95% CI)	
Age				0.017		0.020
< 70 years	52	71.7	61.8		1.00	
≥ 70 years	48	52.3	35.2		2.00 (1.19–3.58)	
Gender				0.773		
Male	72	62.9	48.0			
Female	28	61.0	51.9			
Type of biliary drainage				0.003		0.007
Endoscopic	63	73.3	59.8		1.00	
Percutaneous	35	44.7	32.8		2.24 (1.24–4.03)	
Serum CA19-9 level				0.062		
< 100 U/ml	69	68.9	54.0			
≥ 100 U/ml	31	46.1	31.4			
Cholangiographic tumor classification				0.003		0.021
Diffuse	28	39.5	26.3		2.00 (1.11–3.60)	
Localized	72	72.1	59.0		1.00	
Gross tumor morphology				0.097		
Papillary	13	83.3	63.5			
Nonpapillary	87	59.1	47.0			
Portal vein resection				< 0.001		0.007
Absent	70	73.9	58.6		1.00	
Present	30	37.4	28.9		2.50 (1.29–4.84)	
Histologic grade				0.021		0.109
Well	26	79.4	62.0		1.00	
Moderately/poorly	74	56.0	44.5		0.56 (0.28–1.14)	
Pancreas invasion				0.137		
Absent	63	69.3	55.5			
Present	37	51.2	38.7			
Liver invasion				0.862		
Absent	54	59.6	51.8			
Present	46	65.3	46.7			
AJCC T classification (7th)				0.003		0.906
pT1/2	47	81.1	65.0		1.00	
pT3/4	53	46.0	35.3		0.96 (0.46–1.99)	
Nodal metastasis				0.004		0.339
Absent	50	76.4	64.1		1.00	
Present	50	47.6	32.5		1.38 (0.72–2.64)	
Surgical margin status				0.002		0.349
Negative[a]	82	66.5	57.0		1.00	
Positive	18	41.7	9.3		1.42 (0.68–3.00)	
Adjuvant chemotherapy				0.736		
Absent	67	61.0	48.5			
Present	33	64.7	50.1			

CA carbohydrate antigen

[a]Included positive ductal margin with carcinoma in situ

small, cannot be extrapolated to other races. Therefore, tumor length, despite being an objective value, has a critical limitation for global use.

Interestingly, localized-type cholangiocarcinoma was common, accounting for over two-thirds of the present cohort. Most (65 out of 72) patients with this tumor type

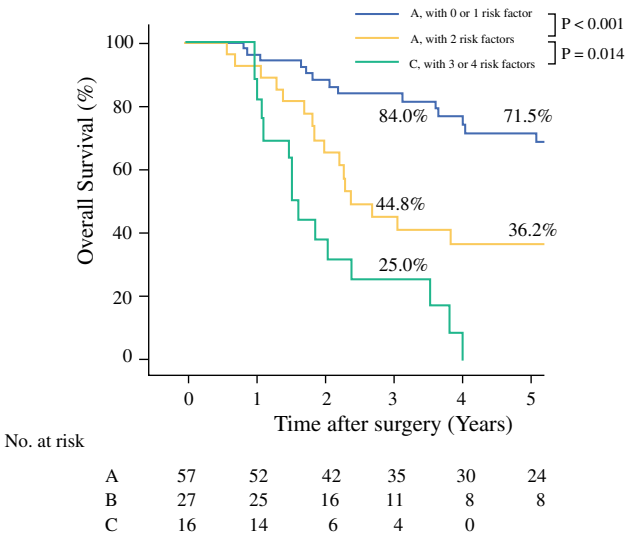

FIG. 3 Overall survival stratified according to the matching number of four risk factors (diffuse tumor, of 70 years or older, percutaneous biliary drainage, and portal vein resection)

underwent HPD due to superficial spreading, i.e., CIS of 2 cm or more beyond the extent of the main tumor, which has been reported as a disease-specific feature with incidence of 6–15% among all extrahepatic cholangiocarcinomas.[19,20] Importantly, the very minute configuration of CIS complicates the clinical diagnosis by use of a cholangiogram alone; therefore, a biliary biopsy with the use of forceps will be required, particularly with a seemingly naïve surrounding bile duct. Among 11 patients with the localized tumor type who received a conversion surgery to HPD, an extensive biliary biopsy was completed in only 1 patient, whereas 49 (80.3%) patients received this biopsy among the 61 patients with localized tumor type who were initially planned for HPD. These findings suggest a clinical utility for a mapping biliary biopsy in cholangiocarcinoma, in order to survey for superficial spreading, as has been already stressed by Aoki et al.[6] Therefore, when considering cholangiocarcinoma, an endoscopic cholangiography followed by biliary tissue sampling should be performed for tumor staging as far as possible, which may partly conflict with the popular strategy of performing no preoperative biliary drainage.[31] At present, we perform "multistep biliary biopsy" as preoperative routine work-up; samples are taken from the lower bile duct, main tumor, hepatic duct confluence, right hepatic duct, right posterior duct, right anterior duct, left hepatic duct, or left medial duct, depending on the main tumor location or planned hepatectomy type.

Regarding a surgical indication for HPD, Aoki et al. highlighted a node-negative widespread cholangiocarcinoma.[6] However, this indication has less clinical value on making a presurgical decision for patient selection because the lymph node status is hard to preoperatively confirm with the usual CT imaging techniques.[32] The present study specified a localized tumor as a tumor feature that benefitted most from HPD, which may explain a difference in the long-term survival rates among studies. Thus, a considerable proportion of localized tumors with superficial spreading potentially boosted the overall survival in the present study. The diffuse versus localized tumor classification should be clearly shown in further oncological studies concerning HPD. The present study identified another three independent predictors of survival (age, type of biliary drainage, and portal vein resection). Portal vein resection literally represents a surgical factor. However, recent technology, in the form of multidetector-row computed tomography, can yield an accuracy of 94% for presurgical diagnosis of portal vein resection.[33] Therefore, portal vein resection can be replaced by radiologic portal vein invasion. Thus, all four independent prognostic factors are nonpathologic parameters. The matching number of the four unfavorable factors significantly stratified survival. Patients with zero or one risk factors showed the most favorable survival, indicating that HPD is strongly recommended for this subset of patients. In contrast, patients with three or four factors had dismal prognosis, with MST of only 1.52 years. Compared with the MST of 0.83–0.98 years in patients with unresectable tumor,[34,35] the survival benefit from HPD is too small to justify the surgical risk of HPD. Thus, indication of HPD should be carefully considered in this subgroup. Patients with two risk factors showed an intermediate outcome, suggesting that adjuvant/neoadjuvant therapy should be considered. This three-tier clinical classification can guide clinicians in selecting ideal candidates for HPD in the presurgical setting.

There were some limitations to the present retrospective study. First, the study was conducted at a single Japanese center, which suggests that the present results may not be simply extrapolated in Western institutions. Although the authors realize that an internal or external validation study is needed, a limited sample number of approximately 100 individuals impeded this attempt. Second, the study cohort data were collected during as long a time period as 17 years, due to the rarity of HPD for cholangiocarcinoma. Therefore, the bias stemming from this long collection period potentially affected the present results, and further multi-institutional study is needed to confirm applicability. Third, although patient selection using the four prognostic indicators may maximize the survival benefit from HPD, it cannot be used for the sake of surgical safety. Importantly, mortality after HPD varies among centers or regions. The low mortality in Japan is possibly explained by low body mass index and liberal use of biliary drainage and portal vein embolization.[2,6] In our center, very limited surgeons

who have high expertise with surgical management for perihilar cholangiocarcinoma perform HPD,[36] which may lead to the low mortality. Further study is necessary in order to establish another patient selection method for HPD-associated mortality with a multiinstitutional approach.

CONCLUSIONS

Presurgical cholangiographic tumor classification (diffuse versus localized types of tumors) was closely associated with survival, which suggests that this label potentially works as a tumor-related prognostic feature in HPD. This simple tumor classification along with age, type of biliary drainage, and portal vein resection may form a key to enhance long-term survival probability in patients who are to undergo the challenging HPD for cholangiocarcinoma.

DISCLOSURE The authors declare that they have no conflict of interest of this work.

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