

Comparison of oncologic outcomes of extrahepatic cholangiocarcinoma according to tumor location: perihilar cholangiocarcinoma versus distal bile duct cancer

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Purpose: Extrahepatic cholangiocarcinoma is distinguished into perihilar cholangiocarcinoma (PHC) and distal bile duct cancer (DBC). The studies for each subtype have been conducted separately. This study compared oncological outcomes between PHC and DBC.

Methods: From 2001 to 2017, patients who underwent surgery at Seoul National University Hospital for PHC or DBC were enrolled. T stage was reclassified for tumor extent as 'confined to' or 'beyond' the bile duct (BD). In survival analysis, stage matching was performed based on tumor extent and lymph node (LN) metastasis.

Results: There were 680 patients enrolled: 295 with PHC and 385 with DBC. The R0 resection rate was higher in DBC (77.3% vs. 89.9%, $P = 0.001$). Tumors confined to BD were more common in PHC (61.7% vs. 37.7%, $P = 0.001$). The 5-year survival rate (5YSR) was higher in DBC patients (30.8% vs. 47.8%, $P = 0.001$). After stage matching, DBC patients showed better 5YSR for tumors confined to BD/LN(-) (47.1% vs. 64.3%), confined to BD/LN(+) (22.0% vs. 35.0%), beyond BD/LN(-) (21.9% vs. 49.8%), and beyond BD/LN(+) (9.6% vs. 26.9%). The overall recurrence rate was higher in PHC (59.7% vs. 51.9%, $P = 0.045$), with no difference in the recurrence types between two groups. Radiation therapy was effective for patients with advanced stage disease (5YSR: 35.8% vs. 29.5%, $P = 0.022$); adjuvant chemotherapy was effective for patients receiving R1 resection (5YSR: 37.3% vs. 13.2%, $P = 0.040$).

Conclusion: Differences were identified in oncological outcomes between PHC and DBC, including pathologic findings and survival outcomes.

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Key Words: Bile duct neoplasms, Cholangiocarcinoma, Klatskin tumor, Pathology, Survival analysis

INTRODUCTION

Cholangiocarcinoma can be divided into intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma (EHC) depending on the anatomical location [1]. EHC is not a common disease, especially in Europe and Western countries;

however, the incidence of EHC has gradually increased worldwide [2,3]. In the United States, the age-adjusted incidence rate of EHC has increased for the last 4 decades; the incidence of intrahepatic cholangiocarcinoma has remained stable [4]. On the other hand, since EHC is a relatively common disease in Asia, many studies have been conducted [5-7]. The highest

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incidence rate for EHC was found in Korea [8].

EHC can be further distinguished into perihilar cholangiocarcinoma (PHC) and distal bile duct cancer (DBC) [9]. Although PHC and DBC share the same extrahepatic bile duct (BD) origin, there are differences in surgical treatment and prognosis. Major hepatic resections, including hemihepatectomy and trisectionectomy, are performed for PHC; pancreaticoduodenectomy is typically performed for DBC [10]. In addition, the cancer staging systems of PHC and DBC are different according to the 7th edition of the American Joint Committee on Cancer (AJCC) guidelines [11]. Therefore, PHC and DBC are currently considered as distinct entities based on differences in their tumor biology rather than the anatomical location of the tumor [12].

Previous studies have reported that the prognosis is similar depending on the location of tumor in cholangiocarcinoma [13-15]. On the other hand, there are also studies showing that PHC has a worse prognosis than DBC [16-18]. Prognostic factors of each subtype are also different according to other studies [19-21]. However, small cohort sizes in previous studies prevent meaningful comparison between PHC and DBC. A comprehensive analysis between these subtypes should be based on a well-established database that includes radiologic findings, surgical outcomes, pathological reports, and records of adjuvant treatment. Therefore, the purpose of this study was to compare oncological outcomes between PHC and DBC based on data from a single large institute.

METHODS

Patients and data

This study was a retrospective cohort study with prospectively collected data. Patients who were pathologically diagnosed with EHC and underwent curative intent surgery at Seoul National University Hospital (Seoul, Korea) from 2001 to

2017 were reviewed for inclusion in the current study. Patients with distant metastasis, who received palliative surgery or neoadjuvant treatment, were excluded. Patients were classified into the PHC and DBC group.

The baseline characteristics were investigated and included age, sex, body mass index, American Society of Anesthesiologists physical status, and underlying disease. Tumor markers that included CA 19-9 and CEA were also checked before surgery. The type of operation, operation time, and estimated blood loss (EBL) were investigated. Data from after the surgery, including the hospital stay duration, the number of patients with complications above Clavien-Dindo classification grade III, and the efficacies of adjuvant chemotherapy and radiation therapy were also investigated.

This study was approved by the Institutional Review Board of our hospital (No. SNUH-2104-123-1213). This study was performed in accordance with the Declaration of Helsinki and written informed consent was waived due to its retrospective nature.

Pathologic findings with T stage reclassification

All specimens were examined pathologically after surgery and were reported based on the AJCC 7th edition guidelines. They were classified into PHC or DBC based on the gross findings of the specimen and pathological reports. Patients with tumor invading the first confluence of common BD were classified as PHC group, while patients with tumor invading distal BD were classified as DBC group. The pathological reports included resection status, tumor size, T stage, and metastatic status of harvested lymph nodes (LN). In addition, the status of cell differentiation, angiolymphatic invasion, venous invasion, and perineural invasion were reported.

Pathological T stage had to be unified because there were differences between PHC and DBC in the cancer staging systems of the AJCC 7th edition guidelines. Therefore, all lesions were

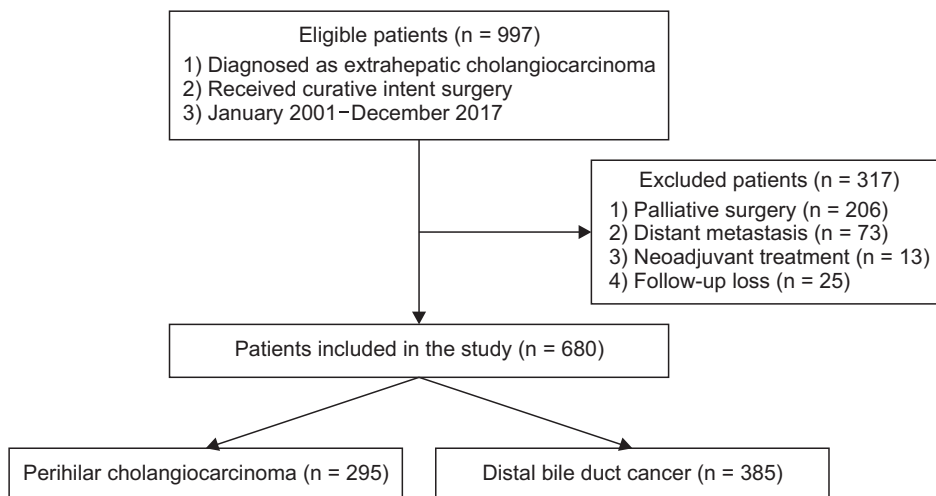


Fig. 1. Flow chart of patient selection.

defined relative to the BD as 'confined to BD' or 'beyond BD.' In PHC, stage T1 and T2a were defined as tumors confined to BD; stage T2b, T3, and T4 were defined as tumors beyond BD. In PHC cases, stage T1 and T2a tumors were classified as confined

to BD because they infiltrate the surrounding adipose tissue; stage T2b, T3, and T4 were classified as beyond BD because they infiltrate the hepatic parenchyma. In DBC cases, stage T1 and T2 could be classified as confined to BD because they infiltrated

Table 1. Baseline demographics and clinicopathologic outcomes

Variable	Total	PHC group	DBC group	P-value
No. of patients	680	295	385	
Age (yr)	65.5 ± 9.1	65.3 ± 9.0	65.5 ± 9.1	0.789
Male sex	475 (69.9)	204 (69.2)	271 (70.4)	0.728
Body mass index (kg/m ²)	23.3 ± 2.8	23.1 ± 2.7	23.4 ± 2.9	0.269
ASA physical status				0.545
I	141 (20.7)	57 (19.3)	84 (21.8)	
II	453 (66.6)	182 (61.7)	271 (70.4)	
III	44 (6.5)	14 (4.7)	30 (7.8)	
Underlying disease				
Hypertension	271 (39.9)	120 (40.7)	151 (39.2)	0.700
Diabetes mellitus	154 (22.6)	67 (22.7)	87 (22.6)	0.972
Previous abdominal operation history	139 (20.4)	44 (14.9)	95 (24.7)	0.002
Preop CA 19-9, >37 U/mL	387 (56.9)	183 (62.0)	204 (53.0)	0.018
Preop CEA, >5 ng/mL	52 (7.6)	26 (8.8)	26 (6.8)	0.321
Operation name				0.001
PPPD/Whipple's operation	381 (56.0)	0 (0.0)	375 (97.4)	
Major hepatectomy	183 (26.9)	183 (62.0)	0 (0)	
Hilar resection	100 (14.7)	95 (32.2)	5 (1.3)	
HPD	13 (1.9)	11 (3.7)	2 (0.5)	
Total pancreatectomy	3 (0.4)	0 (0.0)	3 (0.8)	
Operation time (min)	339.2 ± 107.9	342.8 ± 127.5	336.5 ± 90.3	0.470
EBL (mL)	571.0 ± 511.3	690.7 ± 625.4	479.2 ± 378.6	0.001
Resection status				0.001
R0	574 (84.4)	228 (77.3)	346 (89.9)	
R1	106 (15.6)	67 (22.7)	39 (10.1)	
Tumor size (cm)	3.1 ± 1.4	3.2 ± 1.6	2.9 ± 1.3	0.011
Extent of tumor				0.001
Confined to BD	327 (48.1)	182 (61.7)	145 (37.7)	
Beyond BD	353 (51.9)	113 (38.3)	240 (62.3)	
LN metastasis (+)	225 (33.1)	107 (36.3)	118 (30.6)	0.123
No. of harvested LNs	13.2 ± 8.4	9.7 ± 6.0	15.9 ± 9.0	0.001
No. of metastatic LNs	0.9 ± 1.8	1.1 ± 2.1	0.7 ± 1.4	0.005
LN positive ratio	0.16 ± 0.21	0.25 ± 0.24	0.12 ± 0.21	0.001
Differentiation				0.335
WD	110 (16.2)	53 (18.0)	57 (14.8)	
MD	437 (64.3)	181 (61.4)	256 (66.5)	
PD	93 (13.7)	36 (12.2)	57 (14.8)	
Invasion				
Angiolymphatic	218 (32.1)	90 (30.5)	128 (33.2)	0.448
Venous	136 (20.0)	67 (22.7)	69 (17.9)	0.112
Perineural	515 (75.7)	218 (73.9)	297 (77.1)	0.328
Complication, CD grade ≥ IIIa	145 (21.3)	33(11.2)	112 (29.1)	0.001
Postoperative hospital stay (day)	20.6 ± 20.4	18.2 ± 11.2	22.5 ± 25.1	0.006
Adjuvant chemotherapy	373 (54.9)	154 (52.2)	219 (56.9)	0.224
Adjuvant radiation therapy	368 (54.1)	151 (51.2)	217 (56.4)	0.179

Values are presented as number only, mean ± standard deviation, or number (%).

PHC, perihilar cholangiocarcinoma; DBC, distal bile duct cancer; ASA, American Society of Anesthesiologists; Preop, preoperative; PPPD, pylorus preserving pancreaticoduodenectomy; HPD, hepatopancreaticoduodenectomy; EBL, estimated blood loss; BD, bile duct; LN, lymph node; CD, Clavien-Dindo classification.

only the surrounding soft tissue, as listed in the pathology report; stage T3 and T4 were considered as tumors beyond BD.

Long-term oncological outcomes with stage matching

Overall survival of the PHC and DBC groups was evaluated by the Kaplan–Meier estimator for the 5-year survival rate (5YSR). Univariate and multivariate analyses were performed to identify prognostic factors for each group. Additional analysis was performed in 4 groups by stage matching using combinations of the tumor extent and status of LN metastasis. Recurrence rates and recurrence patterns were also investigated.

Statistical analysis

Continuous variables were calculated as the mean and standard deviation and were analyzed with Student t-test or the Mann–Whitney U-test, as appropriate. Categorical variables were compared using the chi-square test or Fisher exact test.

Survival analysis was performed using the Kaplan–Meier estimator. Statistical significance was defined as $P < 0.05$. To determine the independent prognostic factors for survival outcomes, multivariate analysis was performed using a Cox proportional hazards model. All statistical calculations were performed using IBM SPSS Statistics ver. 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients and clinicopathologic findings

There were 997 patients confirmed pathologically as EHC who underwent curative intent surgery between January 2001 and December 2017. Excluded from the study were 206 patients who underwent palliative surgery, 73 patients who had distant metastasis, and 13 patients who received neoadjuvant therapy; 25 patients were missed during the follow-up period. Consequently, 680 patients were enrolled in this study, of whom 295 (43.4%) were diagnosed as PHC and 385 (56.6%) were diagnosed as DBC (Fig. 1).

The baseline demographics and clinicopathological outcomes of each group are shown in Table 1. The demographics were comparable between the PHC and DBC groups. Patients with a CA 19-9 level of >37 U/mL were more frequent in the PHC group than in the DBC group.

For the type of operation according to the location of lesion, major hepatectomy was the most common operation in the PHC group (62.0%) and pancreaticoduodenectomy was the most common in the DBC group (97.4%). Most of the operations were performed by open method (98.7%). Operation time was comparable between the 2 groups; however, EBL was much more prevalent in the PHC group.

The R0 resection rate was higher in the DBC group than in

the PHC group (77.3% vs. 89.9%, $P = 0.001$). Patients in the PHC group demonstrated larger mean tumor sizes than those in the DBC group (3.2 cm vs. 2.9 cm, $P = 0.011$). However, tumors confined to the BD were more frequent in the PHC group than in the DBC group (61.7% vs. 37.7%, $P = 0.001$). The ratio of patients with LN metastasis in each group was comparable. Although patients in the PHC group demonstrated fewer harvested LNs (9.7 vs. 15.9, $P = 0.001$), the number of metastatic LNs was higher than that in the DBC group (1.1 vs. 0.7, $P = 0.005$).

Postoperative complications were more common in the DBC group (11.2% vs. 29.1%, $P = 0.001$). In DBC group, the most common complication was postoperative pancreatic fistula ($n = 47$, 42.0%), followed by wound-related complications ($n = 23$, 20.5%) and intraabdominal fluid collection ($n = 20$, 17.9%). In PHC group, the most common complication was intraabdominal fluid collection ($n = 13$, 39.4%), followed by wound-related complications ($n = 9$, 27.3%) and pleural effusion ($n = 5$, 15.2%). Patients in the PHC group demonstrated a shorter duration of hospital stay than those in the DBC group (18.2 vs. 22.5 days, $P = 0.006$). After recovery from surgery and discharge from the hospital, the ratio of patients who received adjuvant chemotherapy or radiation therapy in each group were comparable. There was also no difference in chemotherapy regimen between DBC and PHC groups (5-fluorouracil, 74.0% vs. 75.3%, respectively; gemcitabine, 15.1% vs. 15.6%, respectively; $P = 0.659$). Radiation up to 55 Gy was used for more than 4 weeks in all patients who received adjuvant radiation therapy.

Long-term oncological outcomes

The 5YSR of the entire study cohort was 40.4%. The 5YSR of

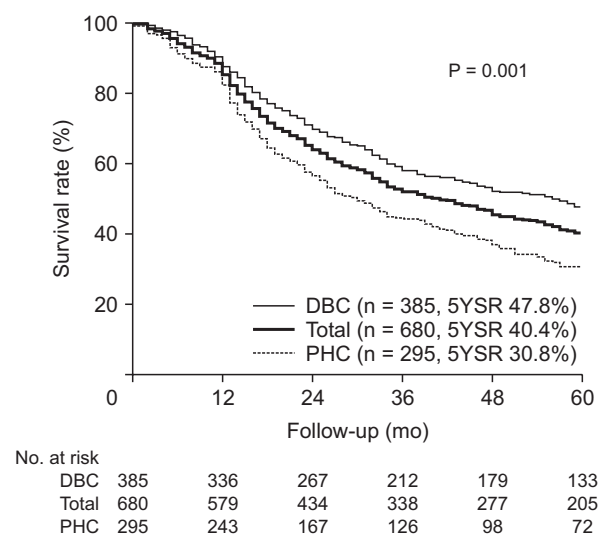


Fig. 2. Overall survival of extrahepatic cholangiocarcinoma according to tumor location. The overall survival of perihilar cholangiocarcinoma (PHC) was worse than distal bile duct cancer (DBC). 5YSR, 5-year survival rate.

the PHC group was worse than that of the DBC group (30.7% vs. 47.8%, $P = 0.001$) (Fig. 2). After stage matching into 4 subgroups based on combinations of tumor extent and LN metastasis, the patients of the PHC group showed worse survival outcomes than those of the DBC group in 3 subgroups; the exception was for the subgroup with tumors confined to the BD and positive

LN metastasis (Fig. 3).

The recurrence patterns are shown in Table 2. The overall recurrence rate was higher in the PHC group than in the DBC group (59.7% vs. 51.9%, $P = 0.045$). However, when recurred patients were divided into local and systemic recurrences, there was no difference in the type of recurrence between the 2

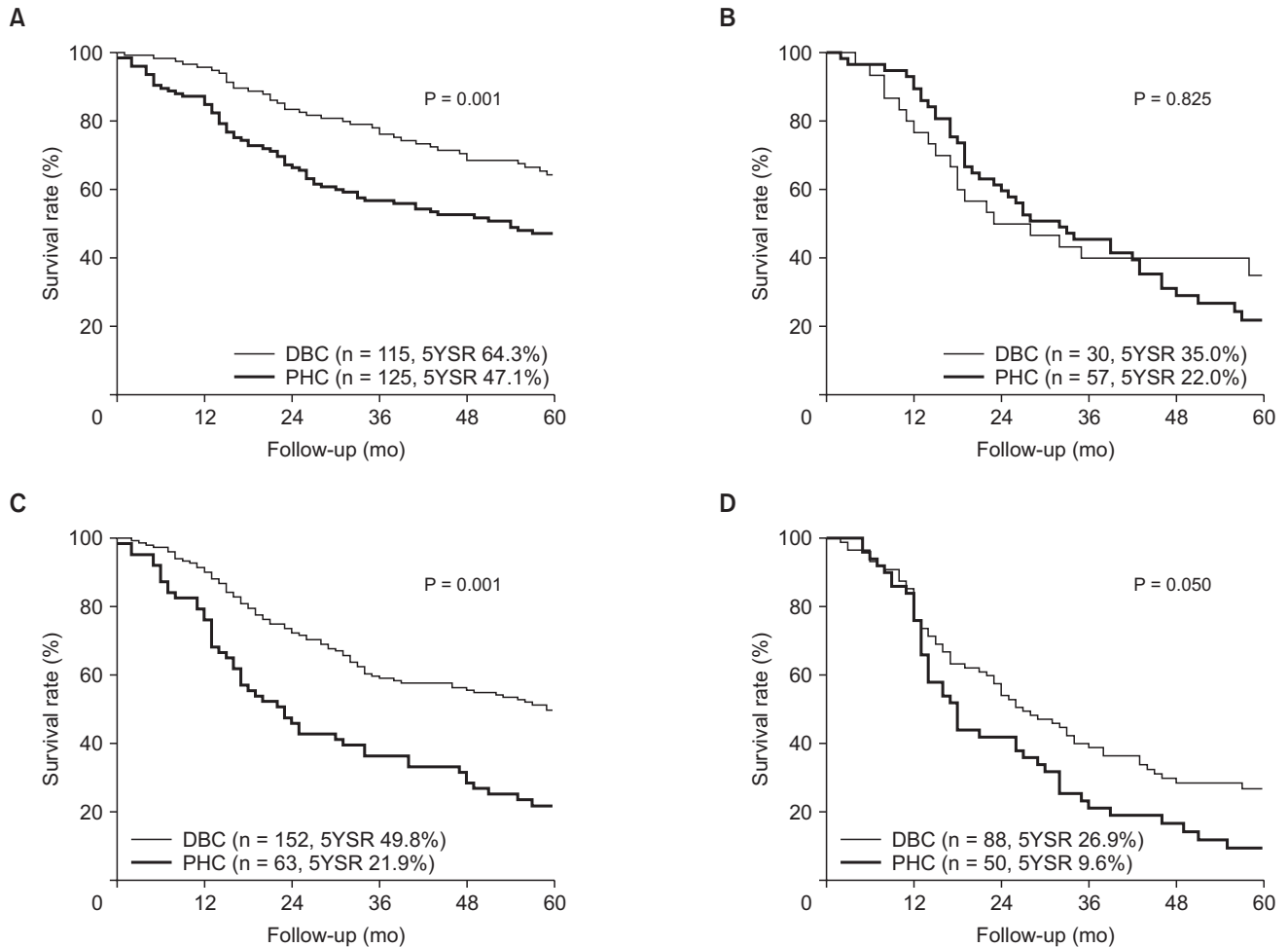


Fig. 3. Overall survival between perihilar cholangiocarcinoma (PHC) and distal bile duct cancer (DBC) after stage matching. (A) The overall survival of PHC was worse in patients with tumors confined to bile duct (BD) and without lymph node (LN) metastasis. (B) The overall survival of PHC was comparable with DBC in patients with tumors confined to BD and LN metastasis. (C) The overall survival of PHC was worse in patients with tumors beyond BD and without LN metastasis. (D) The overall survival of PHC was worse in patients with tumors beyond BD and LN metastasis. CTx, chemotherapy; RTx, radiation therapy; 5YSR, 5-year survival rate.

Table 2. Recurrence patterns between PHC and DBC groups

Variable	Total (n = 680)	PHC group (n = 295)	DBC group (n = 385)	P-value
Overall recurrence	376 (55.3)	176 (59.7)	200 (51.9)	0.045
Recurrence type				0.455
Local	100 (26.6)	50 (28.4)	50 (25.0)	
Systemic	276 (73.4)	126 (71.6)	150 (75.0)	

Values are presented as number (%).

PHC, perihilar cholangiocarcinoma; DBC, distal bile duct cancer.

Table 3. Prognostic factors of extrahepatic cholangiocarcinoma

Variable	Univariate analysis			Multivariate analysis		
	No. of patients	5YSR (%)	P-value	HR (95% CI)	P-value	
Age (yr), ≤65/>65	335/345	42.0/38.7	0.041	1.190 (0.98–1.44)	0.074	
Preop CA 19-9 (ng/mL), ≤37/>37	620/52	40.8/34.6	0.040	0.967 (0.68–1.37)	0.848	
Preop CEA (IU/mL), ≤5/>5	288/387	54.5/32.5	0.001	1.433 (1.17–1.75)	0.001	
R0/R1	574/106	42.7/29.7	0.001	1.617 (1.56–2.08)	0.001	
Tumor location, distal/perihilar	385/295	47.8/30.8	0.001	1.555 (1.27–1.90)	0.001	
Extent of tumor, BD/>BD	327/353	47.9/33.5	0.001	1.316 (1.07–1.61)	0.008	
LN metastasis, –/+	455/225	48.8/22.8	0.001	1.531 (1.25–1.87)	0.001	
Differentiation, WD/MD/PD	110/437/93	54.2/38.6/27.1	0.001		0.006	
WD/MD				1.186 (0.90–1.57)	0.233	
WD/PD				1.711 (1.21–2.42)	0.002	
Angiolymphatic invasion, –/+	462/218	45.5/29.4	0.001	1.150 (0.93–1.42)	0.198	
Venous invasion, –/+	544/136	43.5/26.4	0.001	1.026 (0.81–1.31)	0.834	
Perineural invasion, –/+	165/515	59.6/34.1	0.001	1.246 (0.97–1.61)	0.091	
Complication, –/+	535/145	39.9/42.1	0.303			
Adjuvant chemotherapy, –/+	307/373	44.8/36.6	0.120			
Adjuvant radiotherapy, –/+	312/368	43.7/37.5	0.460			

5YSR, 5-year survival rate; HR, hazard ratio; CI, confidence interval; Preop, preoperative; BD, bile duct; WD, well differentiated; MD, moderate differentiated; PD, poorly differentiated.

groups ($P = 0.455$).

Prognostic factors according to anatomical location

Further analysis was performed to identify prognostic factors that affect the survival outcomes. In multivariate analysis, the preoperative CEA level (hazard ratio [HR], 1.433; 95% confidence interval [CI], 1.17–1.75; $P = 0.001$), R0 resection (HR, 1.617; 95% CI, 1.56–2.08; $P = 0.001$), tumor extent (HR, 1.316; 95% CI, 1.07–1.61; $P = 0.008$), LN metastasis (HR, 1.531; 95% CI, 1.25–1.87; $P = 0.001$), and cell differentiation (HR, 1.711; 95% CI, 1.21–2.42; $P = 0.002$) were identified as prognostic factors for 5YSR in patients with resected EHC (Table 3). The tumor location was also identified as an independent prognostic factor in multivariate analysis (HR, 1.555; 95% CI, 1.27–1.90; $P = 0.001$).

To compare prognostic factors between PHC and DBC, multivariate analysis was performed in each group (Table 4). In the PHC group, the preoperative CA 19-9 level, R0 resection, and the tumor extent were revealed as independent prognostic factors. The most powerful risk factor of PHC was the preoperative CA 19-9 level (HR, 1.844; 95% CI, 1.37–2.48; $P = 0.001$). In the DBC group, age, R0 resection, LN metastasis, cell differentiation, and perineural invasion were revealed as important prognostic factors. The most powerful risk factor of DBC was poor cell differentiation (HR, 2.634; 95% CI, 1.62–4.28; $P = 0.001$).

Effect of adjuvant treatment in extrahepatic cholangiocarcinoma

For patients with advanced-stage tumors (above stage 2), adjuvant radiation therapy affected the survival outcome, but there was no effect for adjuvant chemotherapy (Supplementary Fig. 1A, B). The 5YSRs of patients who received or did not receive radiation therapy were 35.8% and 29.5%, respectively (P

$= 0.022$). In addition, adjuvant chemotherapy was effective for patients with R1 resection (Supplementary Fig. 1C). The 5YSRs of patients who received or did not receive chemotherapy were 37.3% and 13.2%, respectively ($P = 0.040$). Adjuvant radiation therapy was statistically not important in R1 patients, but the 5YSR of patients who received or did not receive it differed by 35.2% and 15.7% (Supplementary Fig. 1D). For patients with R1 status, PHC group showed better 5YSR when they received chemotherapy (37.4% vs. 10.7%, $P = 0.100$; Supplementary Fig. 2A) or radiation therapy (33.6% vs. 13.5%, $P = 0.586$; Supplementary Fig. 2B). In the DBC group, although there was no statistical difference in overall survival, chemotherapy (37.0% vs. 20.0%, $P = 0.367$; Supplementary Fig. 2C), and radiation therapy (37.9% vs. 20.8%, $P = 0.697$; Supplementary Fig. 2D) were effective in increasing 5YSR for patients with R1 status.

DISCUSSION

PHC and DBC are classified as EHC because they have the same origin in the mucous membrane of the extrahepatic biliary tract. However, the cancer staging system and surgical treatment of each group are different according to their anatomical location. Therefore, they are treated as different types of carcinoma and studied separately. The epidemiological, pathological, and oncological differences between the 2 groups are not well studied. This study compared the oncological outcomes according to the tumor location between the 2 groups to improve survival rates by identifying factors that influence the prognosis.

The perioperative short-term outcomes are different between PHC and DBC because of the different methods of surgical treatment. PHC shows more EBL due to bleeding during liver resection as compared with DBC. After surgery, complications

Table 4. Difference of prognostic factor between PHC and DBC

Variable	PHC		DBC	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr), $\leq 65 / > 65$			1.344 (1.03–1.75)	0.028
Preop CA 19-9 (ng/mL), $\leq 37 / > 37$	1.844 (1.37–2.48)	0.001	1.220 (0.93–1.60)	0.151
R0/R1	1.593 (1.16–2.18)	0.004	1.737 (1.16–2.60)	0.007
Extent of tumor, BD/ $>$ BD	1.487 (1.13–2.00)	0.005	0.949 (0.71–1.26)	0.722
LN metastasis, $- / +$	1.115 (0.81–1.53)	0.505	2.062 (1.57–2.71)	0.001
Differentiation, WD/MD/PD	1.270 (0.76–2.13)	0.632		0.001
WD/MD			1.405 (0.93–2.13)	0.110
WD/PD			2.634 (1.62–4.28)	0.001
Angiolymphatic invasion, $- / +$	1.152 (0.82–1.63)	0.423	1.209 (0.91–1.60)	0.183
Venous invasion, $- / +$	1.001 (0.70–1.42)	0.998	1.122 (0.79–1.59)	0.518
Perineural invasion, $- / +$	1.069 (0.74–1.56)	0.726	1.543 (1.09–2.19)	0.039

PHC, perihilar cholangiocarcinoma; DBC, distal bile duct cancer; HR, hazard ratio; CI, confidence interval; Preop, preoperative; BD, bile duct; WD, well differentiated; MD, moderate differentiated; PD, poorly differentiated.

are more frequent in the DBC group than in the PHC group because of postoperative pancreatic fistulae. In the DBC group, intraabdominal fluid collection related to a postoperative pancreatic fistula was the most common complication, followed by wound complications. In the PHC group, intraabdominal fluid collection around the liver resection site was the most common complication, also followed by wound complications. Consequently, more complications led to longer hospital stays in the DBC group.

In 2015, Ercolani et al. [13] reported pathologic differences between subtypes of cholangiocarcinoma; however, the differences in the cancer staging systems between subtypes were not considered. To compare pathological findings and long-term survival outcomes between PHC and DBC, T stage reclassification and stage matching using tumor extent and LN metastasis status were performed in our study. The 5YSR of the PHC group was worse than the DBC group. In 2011, Murakami et al. [16] reported similar overall survival between the PHC and DBC groups (5YSR of 37% vs. 43%, respectively). In 2017, Waseem and Tushar [14] reported better median survival for the DBC group, although overall survival was not significantly different between the 2 groups. However, the results of these previous studies were limited by small sample sizes and different cancer stage proportions between the PHC and DBC groups. The number of patients in our study was 608, whereas the number of patients in the studies mentioned above was between 106 and 152.

There was also a difference in prognostic factors between the 2 groups. In 2018, Bird et al. [22] performed meta-analysis of prognostic factors for overall survival in patients with resected PHC. They reported T stage, LN involvement, microvascular invasion, perineural invasion, and cell differentiation as significant prognostic factors. However, in our study, the preoperative CA 19-9 level, resection margin status, and T stage were identified as prognostic factors for PHC. In addition, in 2016, Wellner et al. [23] performed a meta-analysis and reported that perineural invasion, LN metastasis, positive resection margin status, and not-well-differentiated adenocarcinoma were associated with shorter survival times in DBC patients. These results were consistent with the findings of our study. Achieving R0 resection could be very important, since it was a significant prognostic factor for both groups.

The role of adjuvant treatment in EHC remains unclear. In 2015, Hoehn et al. [24] reported that there was no benefit from adjuvant treatment in patients with resected EHC (median survival for surgery only, 2.8 years; surgery with adjuvant treatment, 2.76 years). However, they reported adjuvant chemotherapy and radiation therapy improved survival outcomes of patients with LN metastasis or positive surgical margins. In 2012, our institution also reported beneficial effect of adjuvant radiation therapy in patients with microscopic

residual disease after surgical resection for EHC [25]. There was no difference in overall survival between patients with R0 and R1 status who received adjuvant radiation therapy (5YSR: R0, 46.3% vs. R1, 41.4%; $P = 0.664$). In current study, patients with advanced disease above stage 2 who received radiation therapy showed better 5YSR (35.8% vs. 29.5%, $P = 0.022$). In addition, patients who received adjuvant chemotherapy or radiation therapy in R1 status showed better 5YSR than who did not (chemotherapy: 37.3% vs. 13.2%, $P = 0.040$; radiation therapy: 35.2 vs. 15.7%, $P = 0.448$). Therefore, it is important to select the target for adjuvant chemotherapy and radiation therapy appropriately.

The present study has some limitations. First, since it was a retrospective study, the patients with missing data had to be excluded. Second, only patients who underwent surgery were included in our study, and patients with advanced disease that could not undergo surgery were excluded. Therefore, there was a limit to describing the entity of the entire disease. Last, there were changes in treatment methods over time because of the long study period. In particular, adjuvant chemotherapy and radiation therapy showed differences according to time and physician.

In conclusion, there were differences in oncological outcomes between PHC and DBC patients, including pathologic findings, survival outcomes, and prognostic factors. Therefore, it is important to plan a treatment strategy with consideration of the exact tumor location.

SUPPLEMENTARY MATERIALS

Supplementary Figs. 1 and 2 can be found via <https://doi.org/10.4174/astr.2022.102.2.100>.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

- Razumilava N, Gores GJ. Classification, diagnosis, and management of cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2013;11:13-21.
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
- Ke Q, Wang B, Lin N, Wang L, Liu J. Does high-grade dysplasia/carcinoma in situ of the biliary duct margin affect the prognosis of extrahepatic cholangiocarcinoma? A meta-analysis. *World J Surg Oncol* 2019;17:211.
- Tyson GL, Ilyas JA, Duan Z, Green LK, Younes M, El-Serag HB, et al. Secular trends in the incidence of cholangiocarcinoma in the USA and the impact of misclassification. *Dig Dis Sci* 2014; 59:3103-10.
- Akamatsu N, Sugawara Y, Hashimoto D. Surgical strategy for bile duct cancer: advances and current limitations. *World J Clin Oncol* 2011;2:94-107.
- Jang JY, Kim SW, Park DJ, Ahn YJ, Yoon YS, Choi MG, et al. Actual long-term outcome of extrahepatic bile duct cancer after surgical resection. *Ann Surg* 2005; 241:77-84.
- Seyama Y, Makuuchi M. Current surgical treatment for bile duct cancer. *World J Gastroenterol* 2007;13:1505-15.
- Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang Y, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma: focus on East and South-Eastern Asia. *Asian Pac J Cancer Prev* 2010;11:1159-66.
- Esnaola NF, Meyer JE, Karachristos A, Maranki JL, Camp ER, Denlinger CS. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. *Cancer* 2016;122:1349-69.
- Reding R, Buard JL, Lebeau G, Launois B. Surgical management of 552 carcinomas of the extrahepatic bile ducts (gallbladder and periampullary tumors excluded). Results of the French Surgical Association Survey. *Ann Surg* 1991;213:236-41.
- Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17:1471-4.
- Blechacz B. Cholangiocarcinoma: current knowledge and new developments. *Gut Liver* 2017;11:13-26.
- Ercolani G, Dazzi A, Giovinazzo F, Ruzzenente A, Bassi C, Guglielmi A, et al. Intrahepatic, peri-hilar and distal cholangiocarcinoma: three different locations of the same tumor or three different tumors? *Eur J Surg Oncol* 2015;41:1162-9.
- Waseem D, Tushar P. Intrahepatic, perihilar and distal cholangiocarcinoma: management and outcomes. *Ann Hepatol* 2017;16:133-9.
- Al Mahjoub A, Bouvier V, Menahem B, Bazille C, Fohlen A, Alves A, et al. Epidemiology of intrahepatic, perihilar, and distal cholangiocarcinoma in the French population. *Eur J Gastroenterol Hepatol* 2019;31:678-84.
- Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Kondo N, et al. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. *Ann Surg Oncol* 2011;18:651-8.
- DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007;245:755-62.
- Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996;224:463-73.
- Yoshida T, Matsumoto T, Sasaki A, Morii Y, Aramaki M, Kitano S. Prognostic factors after pancreatoduodenectomy with extended lymphadenectomy for distal bile duct cancer. *Arch Surg* 2002;137:69-73.
- Sakamoto Y, Kosuge T, Shimada K, Sano T, Ojima H, Yamamoto J, et al. Prognostic factors of surgical resection in middle and distal bile duct cancer: an analysis of 55 patients concerning the significance of ductal and radial margins. *Surgery* 2005;137:396-402.
- Hu HJ, Mao H, Shrestha A, Tan YQ, Ma WJ, Yang Q, et al. Prognostic factors and long-term outcomes of hilar cholangiocarcinoma: a single-institution experience in China. *World J Gastroenterol* 2016;22:2601-10.
- Bird N, McKenna A, Dodd J, Poston G, Jones R, Malik H. Meta-analysis of prognostic factors for overall survival in patients with resected hilar cholangiocarcinoma. *Br J Surg* 2018;105:1408-16.
- Wellner UF, Shen Y, Keck T, Jin W, Xu Z. The survival outcome and prognostic factors for distal cholangiocarcinoma

- following surgical resection: a meta-analysis for the 5-year survival. *Surg Today* 2017;47:271-9.
24. Hoehn RS, Wima K, Ertel AE, Meier A, Ahmad SA, Shah SA, et al. Adjuvant chemotherapy and radiation therapy is associated with improved survival for patients with extrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2015;22 Suppl 3:S1133-9.
25. Kim K, Chie EK, Jang JY, Kim SW, Han SW, Oh DY, et al. Adjuvant chemoradiotherapy after curative resection for extrahepatic bile duct cancer: a long-term single center experience. *Am J Clin Oncol* 2012;35:136-40.