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ORIGINAL ARTICLE

Clinical impact of pancreatic invasion in T1-stage distal bile duct cancer and prognostic factors associated with long-term survival: A multicenter study

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Abstract

Background/Purpose: The eighth edition of the AJCC staging system introduced a shift in the staging of distal bile duct cancer (DBC), emphasizing the depth of invasion over adjacent organ invasion. This study aimed to evaluate the clinical impact of pancreatic invasion in pT1-stage DBC and identify prognostic factors for long-term survival.

Methods: This multicenter retrospective analysis encompassed DBC patients who underwent pancreaticoduodenectomy between 2009 and 2019 in six Korean tertiary centers, specifically those with final pathology confirming AJCC eighth edition T1 stage and intrapancreatic bile duct tumor origin. Primary endpoints were five-year recurrence-free survival (RFS) and overall survival (OS). Secondary objectives included the identification of prognostic determinants.

Results: This study involved 287 patients, comprising 190 without and 97 with pancreatic invasion. Pancreatic invasion did not significantly influence five-year OS and RFS rates (OS: without pancreatic invasion 69.9% vs. with pancreatic

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invasion 54.1%, $p = .25$; RFS: 56.3% vs. 55.4%, $p = .97$). Multivariate analysis highlighted male gender, age, lymphovascular invasion, and N stage as significant OS determinants. Notably, male gender, ampulla of Vater invasion, lymphovascular invasion, and N1 stage were also associated with RFS.

Conclusions: In pT1 DBC, pancreatic invasion demonstrates no substantial impact on long-term prognosis, in accordance with the depth-based paradigm of the eighth edition AJCC staging system. The prognostic factors influencing OS were identified as male gender, age, lymphovascular invasion, and nodal metastasis.

KEYWORDS

distal bile duct cancer, pancreatic invasion, prognostic factor, pT1, survival analysis

1 | INTRODUCTION

Cholangiocarcinoma, or biliary tract carcinoma, refers to a variety of invasive adenocarcinomas that develop in the intrahepatic, perihilar, or distal biliary tree. Bile duct carcinomas account for 3% of all gastrointestinal malignancies globally and are more common in Eastern Asian nations including Korea, China, and Thailand.[1] According to 2019 nationwide cancer statistics in Korea, 7300 cases of biliary tract cancer and gallbladder cancer are newly diagnosed every year, with a crude incidence rate of 14.4 per 100 000. However, the survival rate was the second lowest, at 28.5%, after pancreatic cancer (13.9%).[2] Bile duct cancer is categorized based on the location of the tumor. Distal bile duct cancer (DBC), or distal cholangiocarcinoma, which comprises 20%–40% of identified cholangiocarcinomas, is a tumor that develops in the common bile duct below the junction of the cystic duct and above the ampulla of Vater.[3] DBC accounts for 11%–20% of periampullary tumors, the standard treatment for which is pancreaticoduodenectomy (PD). Resectability at DBC presentation is as low as 35%, and even after curative surgery, the 5-year overall survival (OS) is only 40%, with a median OS time 35–48 months.[4]

DBC is staged according to the American Joint Committee on Cancer (AJCC) cancer staging manual. From the seventh to the eighth edition of the AJCC, published in 2016, the T staging system of DBC was completely revised. The seventh edition used an anatomic layer-based approach, which was criticized for vague descriptions, such as "confined to the bile duct" and "beyond the wall of the bile duct", resulting in interobserver variation and inaccurate classification for predicting the survival of patients with DBC.[5–8] To overcome these problems, the eighth edition of the AJCC staging manual classifies the T stage according to depth-based approach, which considers the depth of invasion (DOI) and better determines prognosis compared to the previous edition.[5,6,9–11]

Despite this change, studies have reported that organ invasion in the previous, seventh edition, system still has an impact on prognosis.[10,12] Especially in clinical practice, tumors with a depth of <5 mm but with pancreatic invasion were downstaged from T3 to T1 between the seventh and eighth edition. In these cases, it is not yet known whether surrounding organ involvement is still a prognostic factor in patients with stage T1 disease. This study focused on eighth T1 stage patients only since they underwent the greatest change in staging, and aimed to find out if chemotherapy could be skipped in patients with T1 stage but pancreatic invasion. Therefore, this study analyzed whether pancreatic invasion, which was a criterion in the seventh edition of T staging, affected the prognosis of patients with DBC who had undergone radical surgery and had T1 disease according to the AJCC eighth edition. In addition, we also explored what other factors affected the prognosis in T1 DBC and what factors were necessary for staging.

2 | MATERIALS AND METHODS

2.1 | Study population

To calculate the number of required subjects, we used a 5-year survival of stage I (T1N0M0) of 69.3% based on the AJCC eighth edition and stage IIA (T3N0M0) of 53.5% based on data from a tertiary center in Korea.[5,10] With an alpha of .05, a beta of .2, and a survival improvement of 0.15, a total of 219 patients were calculated to be required. The study used a multicenter retrospective design to ensure adequate participant recruitment and a total of six tertiary centers in Korea (Asan Medical Center [AMC], Samsung Medical Center [SMC], Seoul National University Hospital [SNUH], Seoul National

University Bundang Hospital [SNUBH], Yonsei University Health System [YUHS], and the National Cancer Center [NCC]) participated in this study. The Institutional Review Board of AMC approved this study (registration no: 2022-1658).

Patients with T1 DBC according to the eighth edition of the AJCC staging manual and who underwent PD between January 2009 and December 2019 were identified. In addition, only patients with an epicenter of tumor in the intrapancreatic bile duct were included to confirm pancreatic invasion. To evaluate T staging in both the seventh and eighth editions, patients with pathological reports on DOI and adjacent organ invasion were included. Patients who underwent bile duct resection (BDR) and hepatopancreaticoduodenectomy (HPD) were excluded from the study. In the case of BDR, the surgical specimen does not include the pancreas and duodenum, making it difficult to properly evaluate the involvement of other organs surrounding the biliary tract. In the case of HPD, differentiation from perihilar cholangiocarcinoma is necessary and HPD itself increases surgical mortality. Patients who underwent R2 resection and had distant metastases were also not included in the study since these are known confounding variables for oncological outcomes.

2.2 | Surgical procedure and postoperative adjuvant therapy

Standard PD (Whipple procedure), pylorus-preserving PD with preservation of the entire stomach, and pylorus-resecting PD with resection of only the pyloric ring with preservation of nearly all the stomach were performed according to the preference of each surgeon [25, 26]. After surgery, some patients received adjuvant therapy. Adjuvant chemotherapy was administered using various regimens, including six cycles of uracil-tegafur with or without leucovorin (LV), six cycles of LV plus 5-fluorouracil (LV/5-FU), six or eight cycles of gemcitabine/cisplatin, and 12 cycles of 5-FU/levofolic acid/cisplatin. Adjuvant chemoradiotherapy was administered in combination, including LV/5-FU-chemoradiotherapy (CRT) (LV/5-FU with 5400 cGy/30 Fx) or concurrent chemoradiotherapy (CCRT)-Xeloda (capecitabine with 5040 cGy/30 Fx). All patients were followed up postoperatively according to their respective institutional protocols.

2.3 | Clinicopathological findings

Clinical and pathological data were collected based on the electronic medical records (EMR) system of each center. Data were collected on patient sex; age; operative details; and survival status and tumor recurrence; histological subtype; differentiation; DOI; invasion of adjacent organs including the duodenum, ampulla of Vater, pancreas, gallbladder, and cystic duct; lymphovascular invasion; perineural invasion; nodal metastasis; resection margin status; eighth AJCC stage; and adjuvant therapy. R1 resection was defined as invasive adenocarcinoma, high-grade dysplasia, or biliary intraepithelial neoplasia 3 observed at the resection margin.

We analyzed the pathological outcomes of the patients based on DOI, encompassing all six participating institutions. The definition of depth of invasion on the pathological slides was set from the mucosal surface to the point of deepest infiltration.[5] Specifically, we measured the distance from the basal lamina to the tumor cells that penetrated the most deeply, even along the irregular bile duct wall, by using an imaginary curved baseline to the deepest invaded tumor cell. In cases where the depth of invasion was less than 1 mm, we assumed that it had infiltrated beyond CIS (carcinoma in situ) but did not reach 1 mm.

2.4 | Outcomes

The primary outcomes of this study were OS and recurrence-free survival (RFS) according to pancreatic invasion. OS was measured from the date of surgery to the date of death from any cause and RFS was measured from the date of the surgery to the date of the first recurrence. Recurrence was confirmed by radiological imaging or histopathological findings. The secondary outcome was the prognostic factors associated with survival in stage pT1 DBC. Additionally, this study conducted survival analysis by reclassifying the T1 stage based on DOI, aiming to establish a refined and comprehensive definition of the T1 stage.

2.5 | Statistical analysis

Sample size calculation and statistical analyses were carried out in R (version 4.1.1). Baseline variables of clinicopathological data are presented as absolute numbers, percentages, or medians with interquartile range (IQR), using Pearson's chi-squared test, Wilcoxon rank sum test and Fisher's exact test. Survival outcomes were calculated using the Kaplan–Meier method and compared using log-rank tests according to the status of pancreatic invasion, AJCC seventh edition T staging, and adjuvant therapy. Cox proportional hazard regression analyses were used for the multivariate analysis of

TABLE 1 Clinicopathological characteristics of the study patients.

Characteristics	Overall, $N=287$		
	Pancreatic invasion (−), $N=190$	Pancreatic invasion (+), $N=97$	p-value[a]
Sex			.056
Female	48 (25%)	35 (36%)	
Male	142 (75%)	62 (64%)	
Age	67 (61, 73)	69 (62, 76)	.2
Type of operation (1)			.13
PD	21 (11%)	4 (4.1%)	
PPPD	140 (74%)	79 (81%)	
PrPD	29 (15%)	14 (14%)	
Type of operation (2)			.4
Open	159 (84%)	86 (89%)	
Laparoscopic	16 (8.4%)	7 (7.2%)	
Robotic	15 (7.9%)	4 (4.1%)	
Histological subtype			>.9
Adenocarcinoma	184 (97%)	95 (98%)	
Adenosquamous carcinoma	3 (1.6%)	2 (2.1%)	
Intraductal papillary neoplasm	2 (1.1%)	0 (0%)	
Signet ring cell carcinoma	1 (0.5%)	0 (0%)	
Differentiation			.011
Well	38 (20%)	10 (11%)	
Moderate	122 (66%)	60 (63%)	
Poor	26 (14%)	24 (25%)	
Undifferentiated	0 (0%)	1 (1.1%)	
Not available	4	2	
Beyond the bile duct			<.001
Absent	62 (33%)	0 (0%)	
Present	128 (67%)	97 (100%)	
Duodenum invasion			.4
Absent	181 (95%)	90 (93%)	
Present	9 (4.7%)	7 (7.2%)	
Ampulla of Vater invasion			.2
Absent	163 (86%)	78 (80%)	
Present	27 (14%)	19 (20%)	
Gallbladder invasion			>.9
Absent	183 (96%)	94 (97%)	
Present	7 (3.7%)	3 (3.1%)	
Cystic duct invasion			>.9
Absent	160 (84%)	82 (85%)	
Present	30 (16%)	15 (15%)	
Lymphovascular invasion			.024
Absent	135 (71%)	56 (58%)	
Present	55 (29%)	41 (42%)	
Perineural invasion			<.001
Absent	99 (52%)	19 (20%)	
Present	91 (48%)	78 (80%)	

TABLE 1 (Continued)

Characteristics	Overall, $N=287$		
	Pancreatic invasion (−), $N=190$	Pancreatic invasion (+), $N=97$	p-value[a]
Resection margin status			>.9
R0	178 (94%)	91 (94%)	
R1	12 (6.3%)	6 (6.2%)	
T stage (AJCC 7th edition)			<.001
T1 (confined to the bile duct)	48 (25%)	0 (0%)	
T2 (beyond the bile duct)	82 (43%)	0 (0%)	
T3 (invasion of adjacent organs)	60 (32%)	97 (100%)	
N stage (AJCC 8th edition)			.2
N0	158 (83%)	79 (81%)	
N1	29 (15%)	13 (13%)	
N2	3 (1.6%)	5 (5.2%)	
M stage (AJCC 8th edition)			
M0	190 (100%)	97 (100%)	
Stage (AJCC 8th edition)			.2
I	158 (83%)	79 (81%)	
IIA	29 (15%)	13 (13%)	
IIIA	3 (1.6%)	5 (5.2%)	
Adjuvant treatment			.8
None	128 (67%)	62 (64%)	
CTx	42 (22%)	23 (24%)	
CCRT	20 (11%)	12 (12%)	

Abbreviations: AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; CTx, chemotherapy; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; PrPD, pylorus-resecting pancreaticoduodenectomy.

[a]Pearson's chi-squared test, Wilcoxon rank sum test; Fisher's exact test.

factors associated with OS and RFS. Statistical significance was defined as $p < .05$.

3 | RESULTS

3.1 | Patient clinicopathological characteristics

During the study period, a total of 2531 patients underwent PD surgery for DBC across the participating centers (AMC, $n=685$; SMC = 572; YUHS, $n=419$; SNUBH; $n=278$; SNUH, $n=398$; NCC, $n=179$). Among them, 287 patients with T1 stage tumors fulfilled the study's inclusion criteria, and were included in the analysis (AMC, $n=130$; SMC, $n=75$; YUHS, $n=30$; SNUBH, $n=22$; SNUH, $n=21$; NCC, $n=9$) (Table 1). Patients were divided into two groups according to the presence of pancreatic involvement. There were 190 patients without pancreatic invasion and 97 patients with pancreatic invasion. Clinical characteristics did not differ between the two groups. Most patients were male, and the median age was 67, 69 years for each group. The most common type of surgery was pylorus-preserving pancreaticoduodenectomy (PPPD) using an open approach. The median operation time was 318, 310 min, respectively.

Several pathological features were statistically significantly different between the two groups. Differentiation was worse in the group with pancreatic invasion ($p=.011$), and lymphovascular invasion and perineural invasion were more common ($p=.024$, <.001, respectively). Otherwise, there were no differences in histological type, node stage, or other organ invasion. There were no differences in postoperative complication rates or adjuvant treatment between two groups.

The relationship between DOI and the T stage, as outlined in the seventh edition of the staging guidelines, is depicted in a dot plot (Figure 1). This distribution indicates that the DOI values for patients classified within the T1 stage are lower than those observed for patients in the T2 and T3 stages. Additionally, it

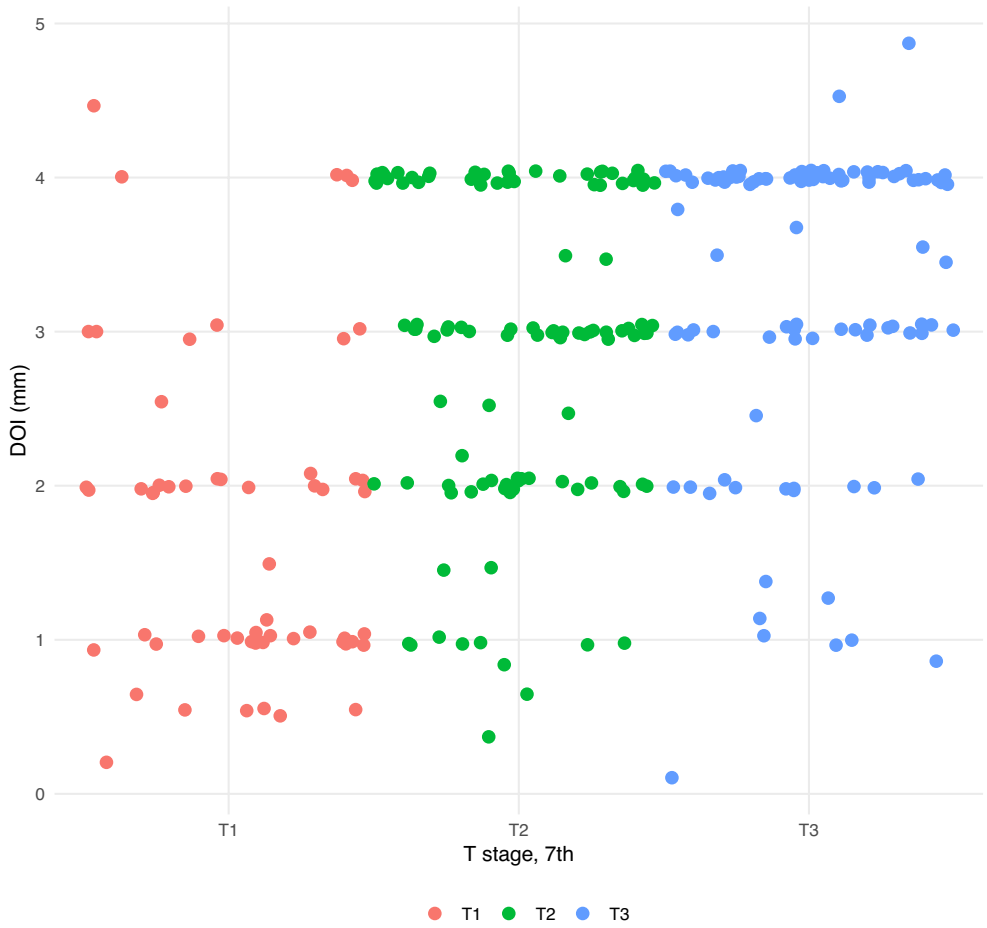

FIGURE 1 Dot distribution of depth of invasion (DOI) according to T stage of seventh edition of AJCC.

indicates that patients classified under the T3 stage, according to the seventh edition, exhibit the highest DOI values, suggesting an increase in DOI with advancing T stage.

3.2 | Oncological outcomes: 5-year OS and RFS

Among the 287 patients, 114 (40%) died and 118 (41%) experienced relapses (83 systemic and 54 locoregional recurrences) during the observation period.

The 5-year OS and RFS rates in the total patient population were 63.9% (95% confidence interval [CI]: 58.2%–70.2%) and 56.2% (95% CI: 50.2%–62.9%), respectively (Figure S1). Comparison of the survival outcome between the two groups according to pancreatic invasion showed no differences in the 5-year OS (without, 69.9%, 95% CI: 63.4%–77.2% vs. with, 54.1%, 95% CI: 44.5%–65.6%; $p = .25$) and RFS (without, 56.3%, 95% CI: 48.8%–65.0% vs. with, 55.4%, 95% CI: 45.9%–66.8%; $p = .97$) rates (Figure 2a,b). When the survival rate was further divided into N− and N+ groups according to the absence or presence of metastatic lymph nodes, the survival rate changed according to the status of lymph node metastasis ($p < .0001$) (Figure 2c,d). In the N− group, the 5-year OS and RFS rates for patients without pancreatic invasion were 74.8% (95% CI: 67.9%–82.4%) and 61.2% (95% CI: 53.2%–70.4%), respectively, while those for patients with pancreatic invasion were 61.1% (95% CI: 50.8%–73.6%) and 62.8% (95% CI: 52.6%–74.9%). The 5-year OS and RFS rates of the N+ group were significantly lower in cases without pancreatic invasion (without: 46.7%, 95% CI: 32.2%–67.7% and 26.4%, 95% CI: 10.5%–66.5%, $p < .0001$; with: 22.5%, 95% CI: 8.8%–57.7% and 19.3%, 95% CI: 6.3%–58.5%, $p < .0001$).

According to the AJCC seventh edition T staging criteria, this study included 62 patients with T1, T2, and T3 stage disease (Figure 2). The 5-year OS rates were 75.1% (95% CI: 64.8%–86.9%), 67.3% (95% CI: 58.6%–77.4%), and 55.1% (95% CI: 46.1%–65.9%) for T1, T2, and T3-stage patients, respectively. Similarly, the 5-year RFS rates were 65.3% (95% CI: 53.4%–79.9%), 51.3% (95% CI: 41.6%–63.2%), and 55.4% (95% CI: 46.4%–66.0%) for T1, T2, and T3 stage patients, respectively. The 5-year OS ($p = .25$) and 5-year RFS ($p = .97$) rates did not differ significantly between patients based on the seventh edition T staging of the AJCC.

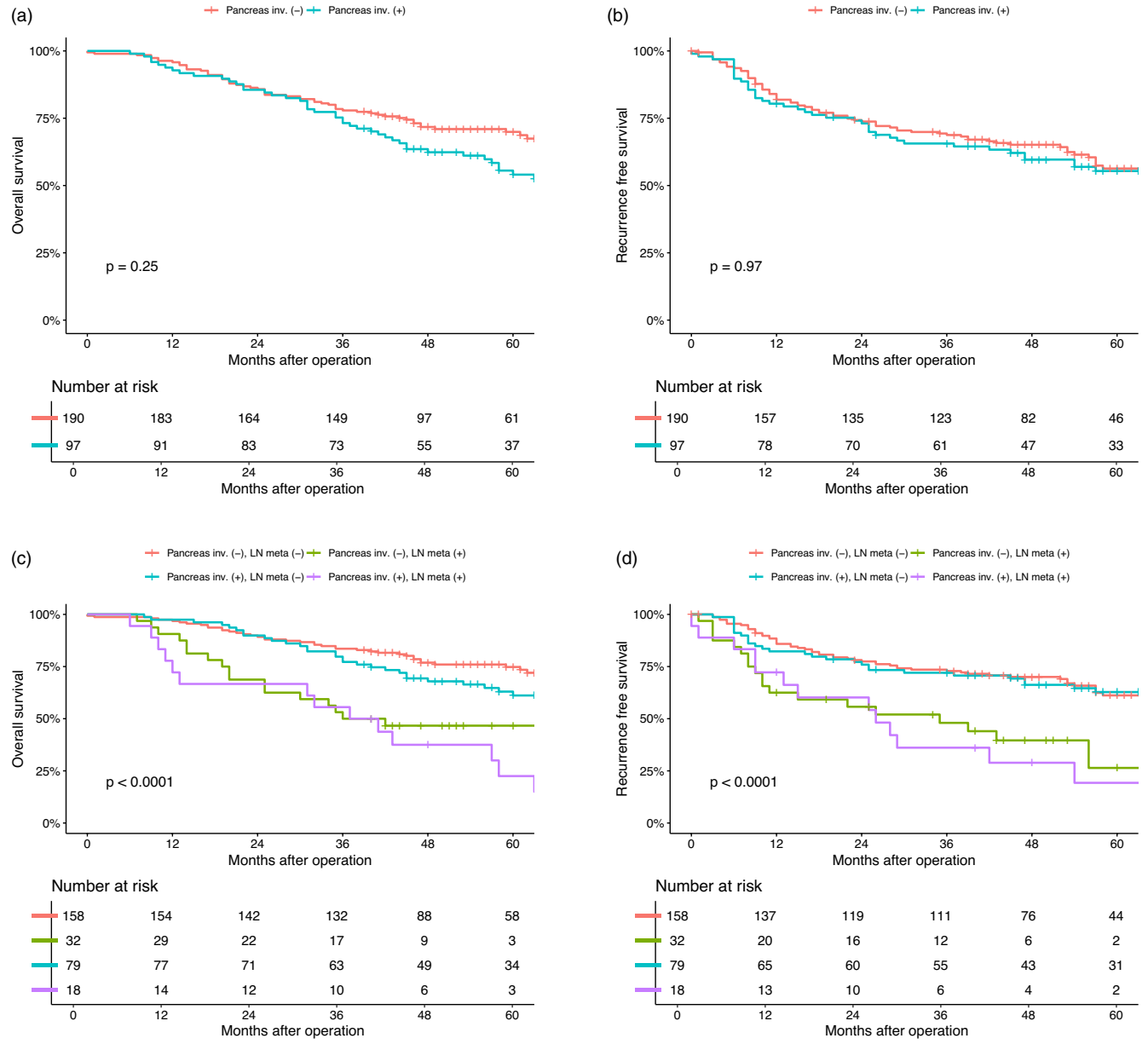

FIGURE 2 Kaplan–Meier survival curve of the oncological outcomes of the patients. (a) Overall survival (OS) according to the pancreatic invasion. (b) Recurrence-free survival (RFS) according to the pancreatic invasion. (c) OS according to the pancreatic invasion and lymph node metastasis. (d) RFS according to the pancreatic invasion and lymph node metastasis.

3.3 | Risk factors associated with OS and RFS

In univariate analysis, the risk factors associated with OS were male sex (hazard ratio [HR]: 1.62, $p = .031$), age (HR: 1.03, $p = .025$), poor differentiation (HR: 2.30, $p = .005$), lymphovascular invasion (HR: 2.79, $p < .001$), and N stage (N1, HR: 2.53, $p < .001$; N2, HR: 5.24, $p < .001$) (Table 2). In multivariate analysis, male sex (HR: 1.92, 95% CI: 1.23–3.01, $p = .004$), age (HR: 1.03, 95% CI: 1.01–1.06, $p = .007$), lymphovascular invasion (HR: 2.15, 95% CI: 1.43–3.23, $p < .001$), R1 resection (HR: 2.09, 95% CI: 1.07–4.10, $p = .031$), and N stage (N1, HR: 2.09, 95% CI: 1.28–3.42, $p = .003$; N2, HR: 4.94, 95% CI: 2.14–11.4, $p < .001$) were associated with OS. Invasion of the ampulla of Vater was the only factor associated with a reduced HR (HR: 0.49, 95% CI: 0.27–0.90, $p = .020$). Invasion of the duodenum, pancreas, and gallbladder, which were all classed as T3 in the seventh edition staging, did not show any significant p-values in either univariate or multivariate analyses.

Both univariate and multivariate analyses of risk factors for RFS were performed (Table 3). Male sex (HR: 1.65, $p = .024$), poor differentiation (HR: 2.05, $p = .020$), lymphovascular invasion (HR: 2.42, $p < .001$), and N stage (N1, HR: 2.69, $p < .001$; N2, HR: 2.60, $p = .039$)

TABLE 2 Risk factors associated with overall survival.

	Univariate analysis			Multivariate analysis		
Characteristic	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Sex						
Female	–	–		–	–	
Male	1.62	1.04, 2.51	.031	1.92	1.23, 3.01	.004
Age	1.03	1.00, 1.05	.025	1.03	1.01, 1.06	.007
Pathology						
Adenocarcinoma	–	–				
Adenosquamous carcinoma	1.04	0.26, 4.19	>.9			
Intraductal papillary neoplasm	3.03	0.42, 21.8	.3			
Signet ring cell carcinoma	0.00	0.00, Inf	>.9			
Differentiation						
Well	–	–				
Moderate	1.05	0.63, 1.76	.8			
Poor	2.30	1.28, 4.12	.005			
Undifferentiated	0.00	0.00, Inf	>.9			
Invasion beyond the bile duct						
Absent	–	–				
Present	1.35	0.83, 2.18	.2			
Duodenum invasion						
Absent	–	–				
Present	1.50	0.70, 3.23	.3			
Ampulla of Vater invasion						
Absent	–	–		–	–	
Present	0.59	0.33, 1.06	.076	0.49	0.27, 0.90	.020
Pancreas invasion						
Absent	–	–				
Present	1.25	0.85, 1.82	.3			
Gallbladder invasion						
Absent	–	–				
Present	0.84	0.27, 2.66	.8			
Cystic duct invasion						
Absent	–	–				
Present	1.51	0.94, 2.44	.088			
Lymphovascular invasion						
Absent	–	–		–	–	
Present	2.79	1.92, 4.04	<.001	2.15	1.43, 3.23	<.001
Perineural invasion						
Absent	–	–		–	–	
Present	1.43	0.97, 2.12	.070	1.39	0.92, 2.09	.11
Resection status						
R0	–	–		–	–	
R1	1.75	0.91, 3.36	.091	2.09	1.07, 4.10	.031
N stage						
N0	—	—		—	—	

TABLE 2 (Continued)

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
N1	2.53	1.60, 4.00	<.001	2.09	1.28, 3.42	.003
N2	5.24	2.40, 11.5	<.001	4.94	2.14, 11.4	<.001
Adjuvant treatment						
None	—	—				
CTx	0.89	0.56, 1.42	.6			
CCRT	1.28	0.72, 2.26	.4			

Abbreviations: CCRT, concurrent chemoradiotherapy; CI, confidence interval; CTx, chemotherapy; HR, hazard ratio.

were associated with RFS in univariate analysis. After multivariate analysis, the only variables still contributing to RFS were male sex (HR: 1.87, 95% CI: 1.20–2.92, $p = .005$), lymphovascular invasion (HR: 2.07, 95% CI: 1.39–3.06, $p < .001$), and N1 stage (HR: 2.23, 95% CI: 1.39–3.56, $p < .001$). As in OS, the multivariate analysis also revealed that invasion of the ampulla of Vater was related to a reduced HR in RFS (HR: 0.50, 95% CI: 0.29–0.87, $p = .015$). The factors that were the basis for the seventh edition staging such as invasion beyond the bile duct and of adjacent organs were not significant risk factors for RFS.

3.4 | Refined classification of T1 tumors based on DOI

Based on DOI, T1 stage tumors were further divided, and a survival analysis was conducted. Tumors with a DOI of less than 1 mm were classified as T1a, representing the earliest subset of T1 tumors, while those with a DOI greater than 1 mm but less than 5 mm were categorized as T1b, indicating a slightly more advanced level of invasion within the T1 stage. Out of the 287 patients analyzed in this study, 18 patients with DOIs smaller than 5 mm, but lacking precise DOI values, were excluded. Consequently, 269 patients were reclassified according to the aforementioned definitions, with 13 patients classified as T1a and 256 as T1b. Survival analyses for OS and RFS were conducted based on these categories, with the results depicted in Figure 3. The survival analysis did not show a significant difference in the 5-year OS rates; T1a had a survival rate of 76.9% (95% CI 57.1%–100.0%), and T1b had 63.3% (95% CI 57.2%–70.0%), with a *p*-value of .38 (Figure 3a). Also, there was no significant difference in 5-year RFS rates between T1a (53.8%, 95% CI: 32.6%–89.1%) and T1b (56.55%, 95% CI: 50.24%–63.65%) subcategories of T1 tumors with a *p*-value of .45 (Figure 3b).

4 | DISCUSSION

In cases of DBC with a depth of tumor invasion <5 mm, even if they had pancreatic involvement classified as stage IIA (T3N0M0) according to the AJCC seventh edition, no significant difference in the 5-year survival rate was observed compared to cases without such involvement. Additionally, postoperative adjuvant treatment in patients with T1-stage disease without lymph node metastases did not show a survival benefit. In patients with T1-stage disease, the prognostic factors for 5-year OS included male sex, advanced age, lymphovascular invasion, R1 resection, and nodal metastasis, while factors for 5-year RFS included male sex, lymphovascular invasion, and nodal metastasis. Invasion of the ampulla of Vater was associated with a lower risk of survival and recurrence.

The anatomy and histology of the distal bile duct is unique. Grossly, it forms a complex anatomical structure with various organs such as the pancreas and duodenum. Microscopically, the bile duct wall lacks a well-defined muscular layer and leads to the periductal tissue without a clear demarcation.[13] Furthermore, the invasion of bile duct carcinoma causes a desmoplastic stromal reaction in the bile duct wall, making it difficult to determine whether it is confined within the bile duct or has extended beyond.[9] When peripheral pancreatic acinar cells are observed within the lower portion of the bile duct wall, it may be difficult to distinguish between the pancreas and bile duct wall in the intrapancreatic portion.[14] To overcome the ambiguous characteristics of distal bile duct cancer (DBC), Aoyama and Zhao have advocated for the concept of invasive tumor thickness (ITT).[15,16] They report that in more than half of the cases, the basal lamina cannot be identified, making it impossible to accurately measure the DOI. However, a recent paper by Jun et al., conducted a comparative study on ITT and DOI. It was demonstrated that DOI is a superior grading system in relation to patient survival compared to ITT.[17] This paper precisely describes the method of measuring DOI according to the growth patterns and addresses the criticism regarding

TABLE 3 Risk factors associated with recurrence-free survival.

	Univariate analysis			Multivariate analysis		
Characteristic	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Sex						
Female	–	–		–	–	
Male	1.65	1.07, 2.55	.024	1.87	1.20, 2.92	.005
Age	0.99	0.97, 1.01	.5			
Pathology						
Adenocarcinoma	–	–				
Adenosquamous carcinoma	1.60	0.51, 5.04	.4			
Intraductal papillary neoplasm	2.33	0.32, 16.7	.4			
Signet ring cell carcinoma	0.00	0.00, Inf	>.9			
Differentiation						
Well	–	–				
Moderate	1.17	0.70, 1.96	.6			
Poor	2.05	1.12, 3.75	.020			
Undifferentiated	0.00	0.00, Inf	>.9			
Invasion beyond the bile duct						
Absent	–	–				
Present	1.33	0.83, 2.14	.2			
Duodenum invasion						
Absent	–	–				
Present	1.28	0.59, 2.74	.5			
Ampulla of Vater invasion						
Absent	–	–		–	–	
Present	0.65	0.38, 1.11	.12	0.50	0.29, 0.87	.015
Pancreas invasion						
Absent	–	–				
Present	1.01	0.69, 1.48	>.9			
Gallbladder invasion						
Absent	–	–				
Present	1.19	0.44, 3.22	.7			
Cystic duct invasion						
Absent	–	–				
Present	1.30	0.81, 2.08	.3			
Lymphovascular invasion						
Absent	–	–		–	–	
Present	2.42	1.69, 3.48	<.001	2.07	1.39, 3.06	<.001
Perineural invasion						
Absent	–	–				
Present	1.27	0.87, 1.86	.2			
Resection status						
R0	–	–				
R1	1.48	0.75, 2.91	.3			
N stage						
N0	–	–		–	–	

TABLE 3 (Continued)

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
N1	2.69	1.74, 4.16	<.001	2.23	1.39, 3.56	<.001
N2	2.60	1.05, 6.44	.039	1.79	0.70, 4.58	.2
Adjuvant treatment						
None	–	–				
CTx	1.14	0.74, 1.75	.6			
CCRT	1.28	0.73, 2.23	.4			

Abbreviation: CCRT, concurrent chemoradiotherapy; CI, confidence interval; CTx, chemotherapy; HR, hazard ratio.

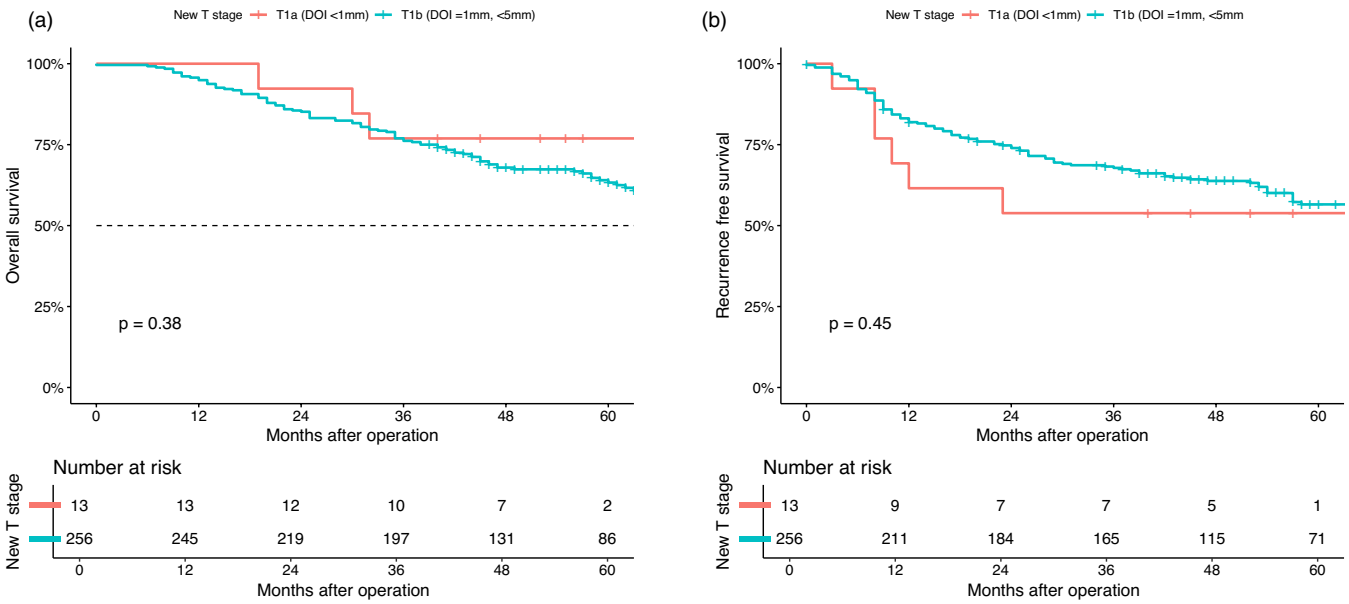

FIGURE 3 Kaplan–Meier survival curve of T1a (depth of invasion [DOI] <1 mm), T1b (DOI ≥1 mm, <5 mm). (a) Overall survival. (b) Reccurrence-free survival.

the difficulty of identifying the basal lamina. By using the right measuring technique, DOI can be measured in over 90% of cases. It also showed that the measurements of DOI and ITT nearly coincide in sclerosing type cases where the basal lamina is not clearly visible. Furthermore, it validated the current cutoff values of 5 mm and 12 mm.[11,17] Therefore, our study evaluated the T stage based on DOI.

Even after the change to the eighth edition, studies still report that adjacent organ invasion affects prognosis. Kang et al. demonstrated that the eighth edition predicted survival outcomes better for T1 and T2 compared to the seventh edition, which the authors attributed to the small number of cases with T1 and T2 stage disease in the study and the downstaging of T3 disease in the seventh edition to T2 in the eighth edition.[10] The authors found that the predictive power of the eighth edition was not statistically significantly higher than that in the seventh edition. They also suggested that the tumor aggressiveness may be underestimated because the DOI alone does not reflect the overall morphologies of the tumor. Min et al. showed that patients with organ invasion have poorer RFS and OS than patients without organ invasion, with significant differences in RFS and OS between single- and dual-organ invasion.[12] Tamura et al. suggested a new tumor classification system combining both layer-based and depth-based systems, indicating the invasion of the duodenum or pancreas as a significant independent factor for recurrence.[13] According to their findings, adjacent organ invasion could enhance prognosis prediction in advanced T stages. The present study including only patients with early-stage (T1) disease found that involvement of the pancreas did not affect prognosis, as did duodenum or gallbladder involvement.

In this study, lymphovascular invasion and lymph node metastasis significantly negatively impacted the prognosis of T1-stage DBC. These factors were considered prognostic factors in previous studies. Lymph node

metastasis is among the strongest reported predictors of survival.[4,7,8,18,19] However, several studies have demonstrated different results regarding the predictive value of the presence of lymphovascular invasion in DBC.[7,8] Kim et al.[7] showed no statistically significant difference in OS between patients with and without lymphovascular invasion in intrapancreatic cholangiocarcinoma after PD. In their investigation of the prognostic factors for middle and distal bile duct cancer after BDR or PD, Kwon et al. found that lymphovascular invasion was associated with the DOI and the presence of lymphovascular invasion affected survival in patients without nodal metastasis.[8] Prognostic factors such as the presence of perineural invasion, poor differentiation, and high tumor grade were also reported to lower the survival outcome of DBC.[4,19]

Among the risk factors for survival, R0 resection is the only variable that can be controlled through clinical practice. Several studies have shown that R0 resection is not associated with survival.[20,21] One included cases with mixed tumor biology, with only 38% of patients undergoing PPPD for DBC[20]; the other study reported that additional resection margins for R0 resection in lymph node-positive cases did not provide a survival benefit.[21] However, most current research has emphasized the importance of R0 resection in DBC.[8,22,23] R0 resection, even after further resection for a negative resection margin, significantly impacts survival.[14] The results of the present study, which included only patients with T1 DBC, showed that R1 resection significantly impacted survival, with an HR of 2.09 in multivariate analysis. Therefore, R0 resection should be a priority goal for surgeons.

Unexpectedly, invasion of the ampulla of Vater was associated with significantly lower HRs for 5-year OS and RFS of 0.49 and 0.50, respectively, in multivariate analysis. Cases with such invasion would presumably be diagnosed earlier because symptoms such as jaundice are more readily apparent. This could be associated with a higher survival rate as these patients receive appropriate treatment before further disease progression.

Taking advantage of a relatively large sample of 287 T1 tumor patients, this study attempted to subdivide the T1 stage, enhancing our understanding of T1 DBC. We introduced a new classification into T1a, for tumors with less than 1 mm invasion, clearly indicating infiltration beyond CIS but not reaching 1 mm, signifying extremely minimal invasion. However, no significant differences were observed in OS and RFS. The absence of significant differences is attributed to the small sample size, with only 13 patients having a T1a tumor. Moreover, in the early stage of DOI of less than 5 mm, prognostic factors other than DOI might be relevant. Particularly, this study lacks data on growth patterns (e.g., papillary, nodular, sclerosing type), which could be histological factors influencing prognosis in minimal invasion DBC. For an accurate categorization of the T1 tumor, further research including larger sample sizes, particularly focusing on tumors with DOI < 1 mm and exploring histopathological or molecular predictors is deemed necessary.

The limitations of this study include its retrospective design, which is subject to selection bias. To overcome this limitation, we retrospectively collected only patients with T stage disease according to both the seventh and eighth editions of the AJCC staging manual and excluded patients with only one or the other. Since this study was based only on EMR data, central pathological review was not available. Additionally, as insufficient data were available on the gross morphology of the tumor such as size or type, they were not included in the analysis. Moreover, the number of patients with stage N2 disease and radiation therapy was insufficient for statistical analysis. In addition, the lack of standardized adjuvant therapy for T1-stage DBC has led to a diversity of regimens and modalities across multiple centers, presenting a limitation in the analysis of adjuvant treatment outcomes.

Despite these limitations, the present study was significant as it was a multicenter trial that overcame the rarity of DBC to collect data from a sizable patient population with T1 stage disease. Previous studies focused on the biliary tract cancer patient population, showing the heterogeneous nature of perihilar cholangiocarcinoma and DBC; however, this study included only DBC. Additionally, the results of this study demonstrated that adjuvant therapy at the T1 stage had no survival benefit in DBC after curative-intent surgery.

In summary, the results of this study showed no survival impact of pancreatic invasion in patients with T1-stage DBC. These findings are consistent with the depth-based system of staging system of the eighth edition of the AJCC staging manual.

CONFLICT OF INTEREST STATEMENT

The authors confirm there are no conflicts of interest.

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