pISSN: 2508-5778 • eISSN: 2508-5859
Ann Hepatobiliary Pancreat Surg 2023;27:251-257
https://doi.org/10.14701/ahbps.22-134

AHBPS
Annals of Hepato-Biliary-Pancreatic Surgery

Original Article

Retrospective analysis of 8th edition American Joint Cancer Classification: Distal cholangiocarcinoma

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Backgrounds/Aims: This is a retrospective analysis of whether the 8th edition American Joint Committee on Cancer (AJCC) was a significant improvement over the 7th AJCC distal extrahepatic cholangiocarcinoma classification.
Methods: In total, 111 patients who underwent curative resection of mid-distal bile duct cancer from 2002 to 2019 were included. Cases were re-classified into 7th and 8th AJCC as well as clinicopathological univariate and multivariate, and Kaplan-Meier survival curve and log rank were calculated using R software.
Results: In patient characteristics, pancreaticoduodenectomy/pylorus preserving pancreaticoduodenectomy had better survival than segmental resection. Only lymphovascular invasion was found to be significant (hazard ratio 2.01, $p = 0.039$) among all clinicopathological variables. The 8th edition AJCC Kaplan Meier survival curve showed an inability to properly segregate stage I and IIA, while there was a large difference in survival probability between IIA and IIB.
Conclusions: The 8th distal AJCC classification did resolve the anatomical issue with the T stage, as T1 and T3 showed improvement over the 7th AJCC, and the N stage division of the N1 and N2 category was found to be justified, with poorer survival in N2 than N1. Meanwhile, in TMN staging, the 8th AJCC was able differentiate between early stage (I and IIA) and late stage (IIB and III) to better explain the patient prognosis.

Key Words: Bile duct cancer; TNM classification; Prognosis; Cholangiocarcinoma

INTRODUCTION

Cholangiocarcinoma is a cluster of tumors that can be classified into three clinical types: intrahepatic, perihilar, and distal. Cases of cholangiocarcinoma have been increasing worldwide. Currently, these tumors account for 15% of all primary liver cancers and less than 3% of gastrointestinal malignancies [1]. Unfortunately, the early stage of this cancer is typically asymptomatic, which leads to late diagnosis and higher rates of morbidity and mortality.

In the last decade, the American Joint Committee on Cancer (AJCC) has made several revisions to the distal cholangiocarcinoma classification. In 2017, the 8th edition the AJCC proposed an alternative method of TNM staging. This classification measured the depth of tumor invasion from the basal lamina of the adjacent normal epithelium to the deepest infiltrating tumor cells. The lymph node classification was also changed: N0 means no metastasis is noted in the examined lymph nodes, N1 means metastasis in 1 to 3 regional lymph node(s), and N2 means metastasis in ≥ 4 regional lymph nodes (Table 1). These changes enabled a more objective diagnosis and thus assisted in finding an improved method of the treatment outcome for this cancer. This study focuses on the efficacy of the 8th version of AJCC staging against the 7th edition in the prediction of prog-

Received: December 21, 2022, **Revised:** February 6, 2023,
Accepted: February 14, 2023, **Published online:** May 2, 2023

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Table 1. American Joint Committee on Cancer (AJCC) distal cholangiocarcinoma

AJCC 7th edition	AJCC 8th edition
T category (pT)	
T1 tumor confined to the bile duct histologically	T1 depth of invasion < 5 mm
T2 tumor invades beyond the wall of the bile duct	T2 depth of invasion 5–12 mm
T3 tumor invades gallbladder, pancreas, duodenum or other adjacent organs without involvement of celiac axis or superior mesenteric artery	T3 depth of invasion > 12 mm
T4 tumor involves celiac axis, superior mesenteric artery and/or common hepatic artery	T4 involves the celiac axis, or the superior mesenteric artery
N category (pN)	
N0 no regional lymph node metastasis	N0 no regional lymph node metastasis
N1 regional lymph node metastasis	N1 metastasis in 1–3 regional lymph nodes
	N2 metastasis in 4 regional lymph nodes

nosis of patients with distal cholangiocarcinoma.

MATERIALS AND METHODS

Study population

All cases of surgically resected primary distal cholangiocarcinoma were collected between May 2002 and March 2019 from a hospital database. The information on the 115 patients that was collected in this way was reclassified into TNM according to the 7th and 8th edition classifications. We excluded four patients with inadequate data on depth, margins, lymph node status, and perineural invasion (PNI). Hence, a total of 111 patient cases were ultimately considered to be suitable for this study.

The informed consent was waived by Gangnam Severance Hospital IRB (No. 3-2019-0282).

Clinical variables

The clinical variables for the selected cases were age, sex, preoperative bile drainage, operation type, complications, postoperative adjuvant chemotherapy or concurrent chemoradiation therapy (CCRT), tumor size, tumor differentiation, portal vein invasion, lymphovascular invasion (LVI), PNI, tumor invasion depth, positive lymph node count, and tumor stage as per the 7th and 8th editions of the AJCC classifications (Table 2).

Statistical analysis

For statistical analyses, the R software was used. The univariate and multivariate cox proportional hazard model was used to analyze various clinicopathological factors, and a p-value < 0.05 was considered to denote statistical significance. The life table, the Kaplan-Meier curve, and the log rank test were used to compare the 7th and 8th AJCC TNM staging.

Table 2. Patient characteristics (n = 111)

Data	Differentiation	Total no.	Percentage (%)
Age (yr)	< 70	55	49.5
	≥ 70	56	50.5
Sex	Male	69	62.2
	Female	42	37.8
Method of bile drainage before surgery	No drainage	17	15.3
	ERBD/ENBD	72	64.9
	PTBD	18	16.2
	Combined	4	3.6
Operation type	PD/PPPD[a)]	95	85.6
	Segmental resection	16	14.4
Histological differences	G1	20	18.0
	G2	71	64.0
	G3	20	18.0
Portal vein resection	Yes	12	10.8
	No	99	89.2
Lymphovascular invasion	Yes	29	26.1
	No	82	73.9
Perineural invasion	Yes	77	69.4
	No	34	30.6
Complications	Yes	35	31.5
	No	76	68.5
Postoperative adjuvant chemo/CCRT	No	64	57.7
	Yes	47	42.3
T stage (7th AJCC)	T1	17	15.3
	T2	44	39.6
	T3	50	45.0
N stage (7th AJCC)	N0	75	67.6
	N1	36	32.4
T stage (8th AJCC)	T1	47	42.3
	T2	55	49.5
	T3	9	8.1
N stage (8th AJCC)	N0	75	67.6
	N1	25	22.5
	N2	11	9.9

ERBD, endoscopic retrograde biliary drainage; ENBD, endoscopic nasobiliary drainage; PTBD, percutaneous transhepatic bile drainage; PD, pancreaticoduodenectomy; PPPD, pylorus preserving pancreaticoduodenectomy; CCRT, concurrent chemoradiation therapy; AJCC, American Joint Committee on Cancer.

[a)]Total pancreatectomy was included for convenient statistical analysis (n = 1).

RESULTS

Patient characteristics

Out of 111 cases, 69 patients were male and 42 were female, and the mean age during the surgery was 68 years. Of all 111 patients, 96 underwent a drainage procedure prior to their surgery. The most common drainage was endoscopic retrograde biliary drainage (ERBD/ENBD), which was done for 72 of the patients.

Pyloric preserving pancreaticoduodenectomy (PPPD) was performed in 95 patients. Most patient had G2 histological differentiation (adenocarcinoma, moderately differentiated), 29 patients had LVI positive and 77 patients had PNI positive on final histopathology report. Postoperatively adjuvant treatment with either chemotherapy or CCRT was conducted in 47 of the patients that were enrolled in the study.

Table 3. Staging wise reclassification from 7th edition to 8th edition (n = 111)

Staging	8th AJCC					
	I	IIA	IIB	IIIA	IIIB	Total
7th AJCC						
IA	13	3				16
IB	19	15				34
IIA	7	13	2			22
IIB	1	9	18	10		38
III			1			1
Total	40	40	21	10		111

AJCC, American Joint Committee on Cancer.

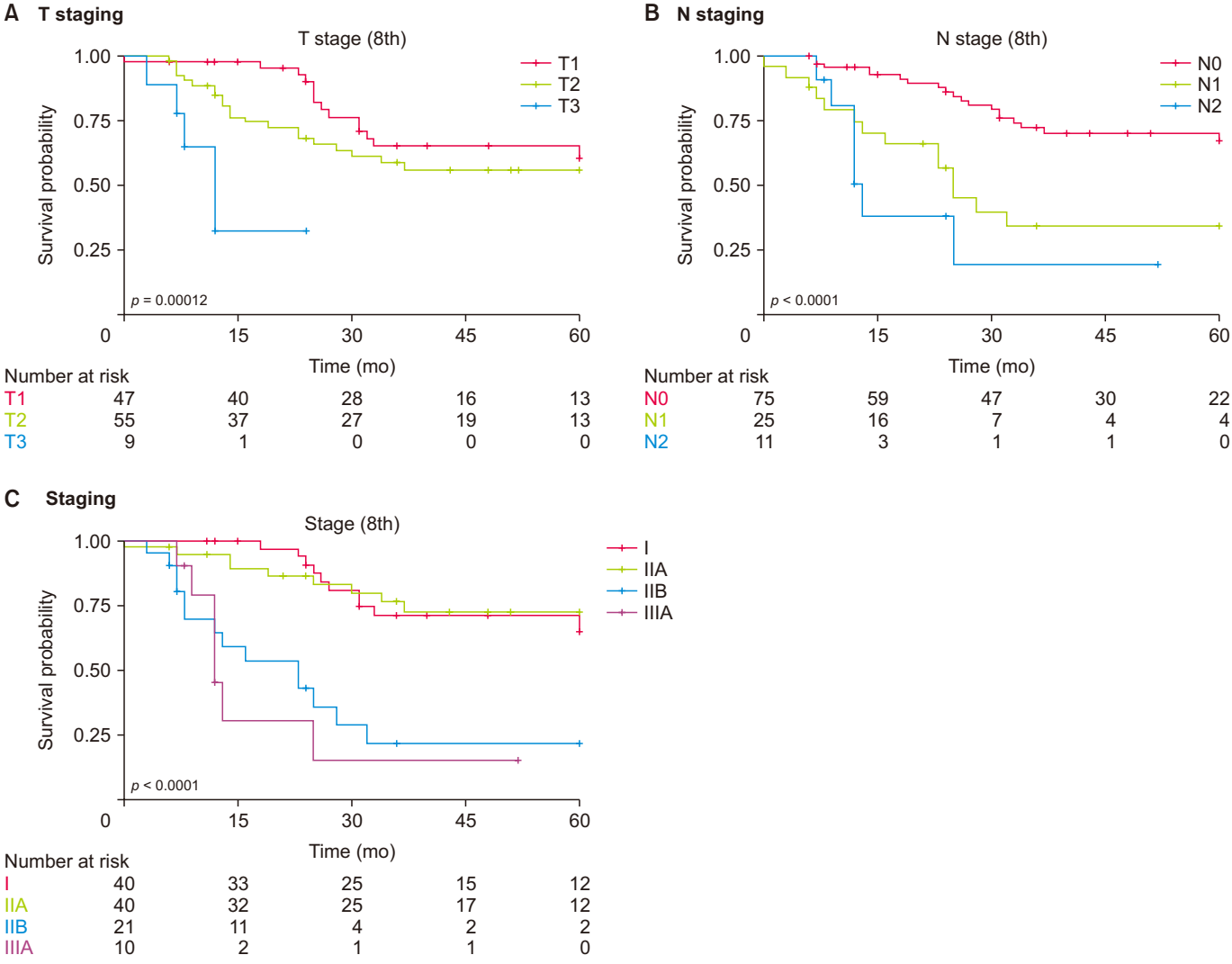

Fig. 1. Kaplan-Meier survival curve according to 8th American Joint Committee on Cancer (AJCC) staging (n = 111): (A) T staging, (B) N staging, and (C) Kaplan-Meier survival staging. In the 8th Kaplan-Meier survival staging shows an intercrossing of I and IIA in 30 months onward with similar survival till 5 years with a huge gap between IIB and IIIA.

Stage reclassification from the 7th edition to the 8th edition

After reclassification from the 7th edition to 8th edition AJCC, 40 patients were in stage I, 40 were in stage IIA, 21 were in stage IIB, 40 were in stage IIIA, and none were in either stage IIB or stage IV (Table 3).

Comparison of Kaplan-Meier survival according to the different variables

The stage grouping of the 8th edition was found to be a stronger predictor of long-term outcome ($p < 0.0001$) (Fig. 1C). In terms of the Kaplan-Meier survival curve pairwise comparisons, the 5year patient survival at 30, 45, and 60 months was similar between patients in stages I and IIA; in a comparison of stage IIA and IIB, the survival of IIA patients was drastically better than IIB survival, and for IIIA, more than 80% of patients did not survive beyond 12 months. The total percentages of patient survival at 5 years were 30%, 30%, 9.5%, and 0% for patients with tumors at stages I, IIA, IIB, and IIIA, accordingly (Fig. 1C).

Upon analyzing the previous 7th AJCC model tumor staging, the results were statistically significant at $p < 0.0001$. At the end of 5 years, there were 4 patients with stage IA tumors who survived, 12 with stage IB, 5 with stage IIA, 6 with stage IIB, and no survivors with stage III after 10 months (Fig. 1, 2).

Univariate analysis of factors associated with overall survival

In the univariate model, females were found to be at more risk than males, and patients who were over 70 years were also at a higher risk (hazard ratio [HR] 1.12, $p = 0.717$). Another high-risk factor was patients who underwent combined drain-

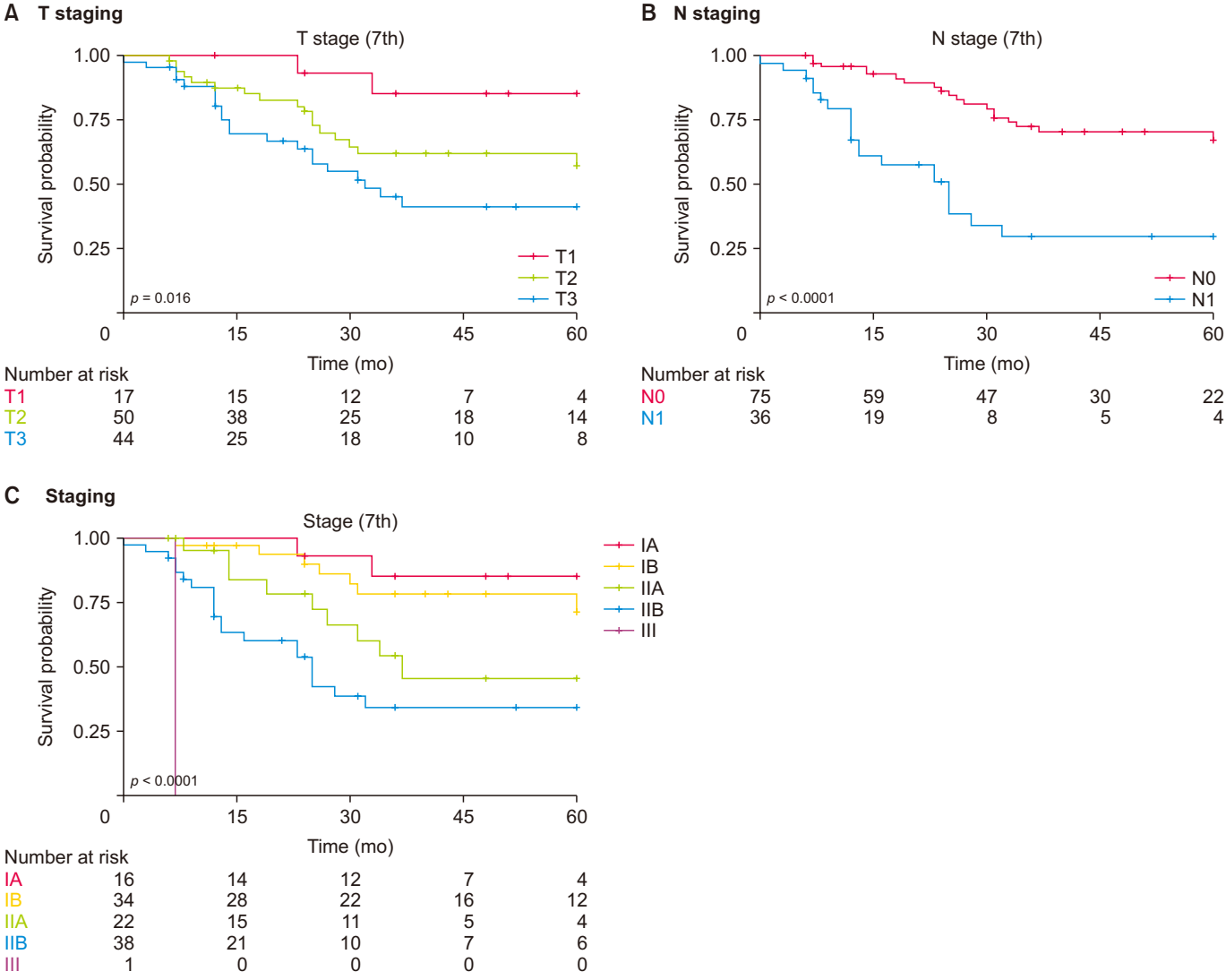

Fig. 2. Kaplan-Meier survival curve according to 7th American Joint Committee on Cancer (AJCC) staging (n = 111): (A) T staging, (B) N staging. (C) In the 7th Kaplan-Meier survival curve, IA and IB were closely graphed with stage III poor survival.

age rather than other drainage procedures (HR 6.07, $p = 0.050$), and PD/PPPD surgery had better survival rates than segmental resection surgery. Similarly, G3 grade tumors had bad prognosis compared to G2 and G1 grade tumors, while LVI present at final histopathology was found to be higher risk (HR 2.01, $p = 0.039$) in a statistically significant finding (Table 4).

Univariate analysis of T and N staging according to 7th and 8th AJCC

According to the 7th AJCC edition, T2 patients were 3.5 times more at risk than T1 patients whereas T3 patients were 5 times more at risk than T1 patients. Meanwhile, in the 8th AJCC edition, T2 patients had 50% more risk than T1 patients (HR 1.49, $p = 0.245$), and T3 was 8 times more at risk than T1 patients (HR 8.43, $p < 0.001$). There were no T4 patients in our study (Table 4).

The results of the univariate model showed 5-year survival of 8th stage N1 (HR 3.38, $p < 0.001$) N2 (HR 6.08, $p < 0.001$), and 7th N staging model N1 (HR 3.93, $p < 0.001$).

Multivariate analysis of T and N staging 7th and 8th AJCC

In the 7th AJCC, 5-years survival showed T2 (HR 2.56, $p =$

Table 4. Univariable analysis of factors associated with overall survival (n = 111)

Variable	Categorization	Univariable analysis	
		HR (95% CI)	*p*-value
Sex	Female	1	
	Male	0.84 (0.43–1.63)	0.607
Age (yr)	< 70	1	
	≥ 70	1.12 (0.60–2.08)	0.717
Drainage	No drainage	1	
	ERBD/ENBD	2.35 (0.71–7.73)	0.157
	PTBD	2.17 (0.54–8.70)	0.271
	Combined	6.07 (0.99–37.15)	0.050
Operation type	PD/PPPD	1	
	Segmental resection	1.32 (0.61–2.88)	0.473
Histological differences	G1	1	
	G2	1.99 (0.76–5.17)	0.156
	G3	2.28 (0.72–7.20)	0.160
Portal vein resection	Yes	1	
	No	0.76 (0.26–2.15)	0.606
Lymphovascular invasion	No	1	
	Yes	2.01 (1.03–3.92)	0.039
Perineural invasion	No	1	
	Yes	1.93 (0.92–4.08)	0.081
Complication	Yes	1	
	No	0.78 (0.40-1.49)	0.2456
Postoperative treatment	No	1	
	Yes	1.69 (0.9–3.1)	0.096
T stage (7th AJCC)	T1	1	
	T2	3.51 (0.81–15.21)	0.090
	T3	5.89 (1.38–25.18)	0.016
N stage (7th AJCC)	N0	1	
	N1	3.93 (2.09–7.38)	< 0.001
T stage (8th AJCC)	T1	1	
	T2	1.49 (0.75–2.93)	0.245
	T3	8.43 (2.79–25.48)	< 0.001
N stage (8th AJCC)	N0	1	
	N1	3.38 (1.68–6.78)	< 0.001
	N2	6.08 (2.47–14.91)	< 0.001

HR, hazard ratio; CI, confidence interval; ERBD, endoscopic retrograde biliary drainage; ENBD, endoscopic nasobiliary drainage; PTBD, percutaneous transhepatic bile drainage; PD, pancreaticoduodenectomy; PPPD, pylorus preserving pancreaticoduodenectomy; AJCC, American Joint Committee on Cancer.

Table 5. Multivariable analysis of factors associated with overall survival (n = 111)

Variable	Categorization	7th AJCC staging		8th AJCC staging	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
T stage (7th AJCC)	T1	1			
	T2	2.56 (0.58–11.32)	0.213		
	T3	3.73 (0.84–16.53)	0.082		
N stage (7th AJCC)	N0	1			
	N1	3.20 (1.68–6.11)	< 0.001		
T stage (8th AJCC)	T1			1	
	T2			1.34 (0.68–2.66)	0.391
	T3			3.90 (1.18–12.84)	0.025
N stage (8th AJCC)	N0			1	
	N1			3.10 (1.53–6.29)	0.001
	N2			4.36 (1.60–11.83)	0.003

AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval.

0.213), T3 (HR 3.73, $p = 0.082$), and N1 (HR 3.20, $p < 0.001$) compared to 8th AJCC T2 (HR 1.34, $p = 0.391$), T3 (HR 3.90, $p = 0.025$), N1 (HR 3.10, $p = 0.001$), and N2 (HR 4.36, $p = 0.003$) (Table 5).

DISCUSSION

Previous research proved that the 7th AJCC classification for distal cholangiocarcinoma had inadequate T staging [2]. That combined with the lack of a precise histological definition of the bile duct anatomy [3] led to the creation of the 8th AJCC classification. The 8th edition's advantage in terms of T classification is that it eliminates the subjectivity in determining the edge of invasion by using histological means and the variability of tissue constituents around the bile duct [3-5]. It also helped elucidate the prognosis of the patients and create a tailor-made treatment regimen for them.

In this analysis, only the LVI in the final histopathology report was found to be statistically significant in terms of *p*-value, whereas other variables (age, sex, drainage, portal/superior mesenteric vein resection, operation performed, histological differences, PNI, complication, and postoperative treatment) showed increased HR, but were not statistically significant in terms of *p*-value.

When the Kaplan-Meier survival curve was chartered, T1 and T3 and N stage of 8th AJCC all showed better patient survival probability than 7th AJCC, but T2 of the 7th edition was found to have a better survival rate than the 8th edition. While the 8th stage Kaplan-Meier survival analysis shows stage I and IIA having nearly the same survival months, at between 30 months to 60 months. Meanwhile, stage I survival probability was lower than that of stage IIA at the end of 5 years. There was a huge survival difference between IIA and IIB. While there have been multiple studies in recent years in T and N categories from the 8th edition of AJCC staging to predict patient prognosis [6], tumor depth was a better indicator than if anatomically confined to bile duct or spread [5,7], and dual organ invasion is associated with a lower survival rate than single organ invasion in a distal duct cancer study [8]. Reappraisals of the classification of distal cholangiocarcinoma are based on tumor depth [9] or a proposed modification of staging for distal cholangiocarcinoma based on lymph node ration using the Korean multicenter database [10], which sought to validate or suggest necessary changes in the 8th AJCC.

In our retrospective analysis, the 8th AJCC classification did resolve the anatomical issue within the T stage, and there were also improvements in T1 and T3. The N stage division of the N1 and N2 category was justified as there was poorer survival probability in N2 than N1. Meanwhile, in TMN staging, the 8th AJCC was able to differentiate between early stage (I and IIA) and late stage (IIB and III) to better explain the patient prognosis. However, the similarity between the Kaplan-Meier survival curve after 30 months in stage I and IIA and the big disparity in the survival curve between IIA and IIB suggests that the 8th AJCC edition still requires another revision.

It is to be duly noted that this paper has limitations, as this case study was conducted with data collected from a single institution that had 111 viable cases. A much larger multi-institution or multi-national study with a higher number of cases and a longer follow-up period with the inclusion of an unresected T4 group would be ideal for a stronger statistical study.

FUNDING

None.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: JSP. Data curation: ADB, KP. Methodology: SS, JHN. Visualization: HSK. Writing - original draft: ADB. Writing - review & editing: JSP.

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