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Improved prognostic predictability of the latest Japanese TNM Classification in patients undergoing resection for distal cholangiocarcinoma

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Abstract: In March 2021, the Japanese TNM Classification for Cancer of the Biliary Tract (JCCB) was revised. This study aimed to validate the 7th edition of JCCB based on long-term outcomes after resection for distal cholangiocarcinoma (DCC). We retrospectively reviewed 107 patients with resected DCC without distant metastasis between 2007 and 2019. Survival curves according to TNM factors were compared between the 6th and 7th editions. The 5-year overall survival (OS) and recurrence-free survival rate (RFS) were 43.4% and 35.5%, respectively. Significant differences in OS were observed between T categories in the 7th edition (T1 *vs.* T2, $p = 0.049$; T2 *vs.* T3, $p = 0.027$), but not in the 6th. The N classification also showed better prognostic discrimination in both editions, with more refined stratification in the 7th. Stage grouping in the 6th edition failed to show significant OS differences, while the 7th edition demonstrated clear stratification (*e.g.*, Stage I *vs.* IIA, $p = 0.0274$; StageIIA *vs.* StageIIB, $p = 0.0043$; StageIIB *vs.* StageIIIA, $p = 0.0108$). These findings indicate that the revised T and N classifications in the 7th edition more accurately reflect postoperative prognosis for resected DCC. Overall, our results support the clinical validity and improved prognostic utility of the 7th edition compared with the 6th edition.

Keywords: overall survival, invasive tumor thickness, depth of invasion

1. Introduction

Bile duct cancer (BCC) accounts for 3% of all gastrointestinal cancers (*1*), and its incidence is gradually increasing worldwide, particularly in East Asia (*2,3*). Meanwhile, distal cholangiocarcinoma (DCC) accounts for 20% to 30% of all BCCs (*4*). The only curative treatment for DCC is surgery, with a 5-year survival rate of 22–47% (*5-7*).

The Japanese TNM Classification for Cancer of the Biliary Tract (JCCB) has been mainly used in Japan. In March 2021, it was revised from the 6th to the 7th edition, following the revision of the Union for the International Cancer Control (UICC) staging system from the 7th to the 8th edition (*8,9*). The 7th edition of JCCB exhibited close similarity to the 8th edition of the UICC and the 6th edition of JCCB to the 7th edition. Regarding the T factor, the classification in the 6th edition — based on the extent of tumor invasion — was revised in the 7th edition to reflect the depth of invasion (DOI) or invasive tumor thickness (ITT) in case the DOI could not be measured. As for the N factor, the previous classification in the 6th edition according to the presence or absence of lymph node metastasis (LNM) was changed into the latest classification in the 7th edition according to the number of lymph node metastasis (N0: 0 N1: 1–3 nodes N2: more than 4 nodes).

The present study aimed to validate the prognostic performance of the 7th edition of the JCCB by comparing survival outcomes according to the T, N, and stage categories defined in the 6th and 7th editions.

2. Patients and Methods

2.1. Study participants

A total of 109 patients who underwent surgical resection for DCC at Osaka Metropolitan University Hospital between January 1, 2007, and December 31, 2019, were initially identified. The inclusion criteria were: *i*) histologically confirmed DCC, *ii*) curative-intent surgical resection with available pathological assessment, and *iii*) complete clinical, pathological, and follow-up data. The exclusion criteria were: *i*) presence of distant metastasis

at the time of surgery, *ii*) recurrent or remnant bile duct cancer, *iii*) synchronous malignancies, and *iv*) insufficient clinical or pathological information.

Based on these criteria, two patients with distant metastasis were excluded, leaving 107 patients for the final analysis. All patients were followed for survival outcomes, with a median follow-up duration of 33.1 months (range, 3.4–132.2 months). Recurrence was defined as radiologic detection of new lesions consistent with tumor relapse on contrast-enhanced computed tomography or other imaging modalities.

2.2. Data collection

The demographic and clinical variables collected included age, sex, preoperative cholangitis, biliary drainage, serum albumin level, modified Glasgow prognostic score, serum carbohydrate antigen 19-9, operative procedure, presence or absence of portal vein and hepatic artery resections, surgical duration, intraoperative blood loss, DOI or ITT, histological grade, lymphatic invasion, venous invasion, perineural invasion, postoperative hospital length of stay, postoperative complications, and receipt of adjuvant chemotherapy.

The pathological T, N, and stage classifications were recorded according to both the 6th and 7th editions of JCCB (*10,11*). The 6th edition defines the T category based on the anatomic extent of tumor invasion into adjacent structures, whereas the 7th edition incorporates DOI or ITT as quantitative, measurement-based criteria. Similarly, the N category in the 6th edition is determined by the presence or absence of LNM, while the 7th edition classifies N status according to the number of metastatic lymph nodes (0, 1–3, or ≥ 4). These classification systems were systematically applied to each patient to enable direct comparison of staging between the two editions.

Tumor differentiation was classified according to the World Health Organization criteria as well-, moderately-, or poorly differentiated, as well as undifferentiated adenocarcinoma (*12*).

2.3. Statistical analysis

Survival rate was calculated using the Kaplan–Meier method, and the log-rank test was employed to compare the groups. Comparisons were made for T, N, and stage categories according to both the 6th and 7th editions of the JCCB. $P < 0.05$ was considered to indicate statistical significance. JMP® version 12 (SAS Institute, Cary, NC, United States) was used to conduct all statistical analyses.

2.4. Ethical approval

All patients provided informed consent for using their data in this study according to the institutional regulations of the study sites. This study was approved by the Ethics Committees of Osaka Metropolitan University (approval No.2020-241) and was performed in compliance with the Declaration of Helsinki.

3. Results

3.1. Patient characteristics

The baseline characteristics of the 107 patients are summarized in Table 1. The median age was 70 years (range, 30–86), and 74 patients (69.2%) were male. Preoperative cholangitis occurred in 27 patients (25.2%), and 103 patients (96.3%) underwent biliary drainage. Regarding surgical procedures, subtotal stomach-preserving pancreaticoduodenectomy was the most frequently performed (n = 75), followed by classical pancreaticoduodenectomy (n = 19) and bile duct resection (n = 8). A total of 36 patients (33.6%) received adjuvant chemotherapy after surgery, with S-1 being the most commonly administered regimen (n = 36), followed by gemcitabine (n = 9), tegafur–uracil (n = 6), and gemcitabine plus cisplatin (n = 6). Decisions regarding adjuvant chemotherapy were made at the discretion of the treating physicians.

3.2. Overall survival and relapse-free survival for resected distal cholangiocarcinoma

Patients who underwent DCC resection demonstrated a 5-year overall survival (OS) rate of 43.4% and a median survival time of 47.7 months (Figure 1A) as well as a 5-year relapse-free survival (RFS) rate of 35.5% and a median RFS of 29.2 months (Figure 1B).

3.3. Distribution of the 7th edition T factor in the 6th edition T factor

Table 2 presents the distribution of the 7th edition T factor in the 6th edition T factor. According to the 6th edition, 1/11/30/57/7/1 patients were classified into pTis/T1b/T2/T3a/T3b/T4, respectively. When the 7th edition was applied, distributions of pTis/T1/T2/T3/T4 changed to 1/40 (15 downgraded from T2, 16 downgraded from T3a in the previous edition)/37 (2 upgraded from T1b, 22 downgraded from T3a)/21 (2 patients upgraded from T2)/8 (7 patients upgraded from T3b).

3.4. Lymph node metastasis rate according to the T factor of the 6th and 7th editions

Table 3 presents LNM rate according to the T factor of the 6th and 7th editions. As can be seen from the table, LNM rates increased as the T factor increased in the 7th edition.

3.5. Survival curve according to T factor of the 6th and 7th editions

Table 1. Patient characteristics (*n* = 107)

Characteristics	Number
Age	
Median (range)	70 (30–86)
Sex	
Male	74
Female	33
Preoperative BMI[*]	
Median (range)	22.9 (15.2–35.6)
Preoperative cholangitis	
Absent	80
Present	27
Preoperative biliary drainage	
None	4
PTBD[†]	13
EBD[‡]	90
Preoperative serum Alb level median (range)	3.8 (2.7–4.8)
Preoperative mGPS[§]	
0	78
1	21
2	8
Preoperative CA19-9	
Normal	61
Elevated	46
Surgery	
PD[ǁ]	19
PpPD[¶]	4
SSPPD[**]	75
HPD[††]	1
BDR[‡‡]	8
Portal vein resection	
Present	8
Absent	99
Hepatic artery resection	
Present	3
Absent	104
Operation time (minutes), median (range)	500 (289–838)
Intraoperative blood loss volume (mL), median (range)	700 (210–4000)
DOI[§§] (ITT[ǁǁ]) (mm), median (range)	6 (0.5–28.0)
Histological grade	
pap	7
well	25
mod	63
por	11
Sig	1
T factor (6th edition)[¶¶]	
Tis	1
T1a	0
T1b	11
T2	30
T3a	57
T3b	7
T4	1
T factor (7th edition)[***]	
Tis	1
T1	40
T2	37
T3	21
T4	8
N factor (7th edition)[***]	
N0	65
N1	34
N2	8
Lymph node metastasis count median (range)	0 (0-10)
Stage (6th edition)[¶¶]	
0	1
IA	9
IB	24
IIA	31
IIB	41
III	1
Stage (7th edition)[***]	
0	1
I	30
IIA	30
IIB	30
IIIA	8
IIIB	8
Residual tumor	
R0	78
R1	18
R2	11
Lymphatic invasion (ly)	
0	42
1	38
2	18
3	4
X	5
Venous invasion (v)	
0	76
1	21
2	5
3	0
X	5
Perineural invasion (ne)	
0	19
1	32
2	30
3	22
X	4
Postoperative length of stay (day) median (range)	33 (12–225)
Postoperative complication (≥ CDIIIa)[†††]	
0	4
I	13
II	23
IIIa	58
IIIb	4
IVa	4
IVb	0
V	1
Adjuvant chemotherapy	
yes	36
no	71

[*]BMI: body mass index. [†]PTBD: percutaneous transhepatic biliary drainage.[‡]EBD: endoscopic biliary drainage. [§]mGPS: Modified Glasgow Prognostic Score. [ǁ]PD: pancreatoduodenectomy. [¶]PpPD: pylorus-preserving pancreaticoduodenectomy. [**]SSPPD: subtotal stomach-preserving pancreaticoduodenectomy. [††]HPD: hepatopancreatoduodenectomy. [‡‡]BDR: bile duct resection. [§§]DOI: depth of invasion. [ǁǁ]ITT: invasion of tumor thickness. [¶¶]by the 6th edition of the Japanese TNM Classification for Cancer of the Biliary Tract (JCCB). [***]by the 7th edition of the Japanese TNM Classification for Cancer of the Biliary Tract (JCCB). [†††]CD: Clavien–Dindo classification.

Figure 2A presents the survival curve according to the 6th edition T factor. The 5-year survival rates of pTis/T1b/T2/T3a/T3b/T4 were 100%/71.6%/56.2%/29.7%/13.1%/100%, respectively. A significant difference was observed in OS between pT3a and T3b ($p = 0.002$). In contrast, there was no significant difference in OS between the other groups (pTis *vs.* T1b, $p = 0.57$; pT1b *vs.* T2, $p = 0.39$; pT2 *vs.* T3a, $p = 0.68$; pT3b *vs.* T4, $p = 0.21$).

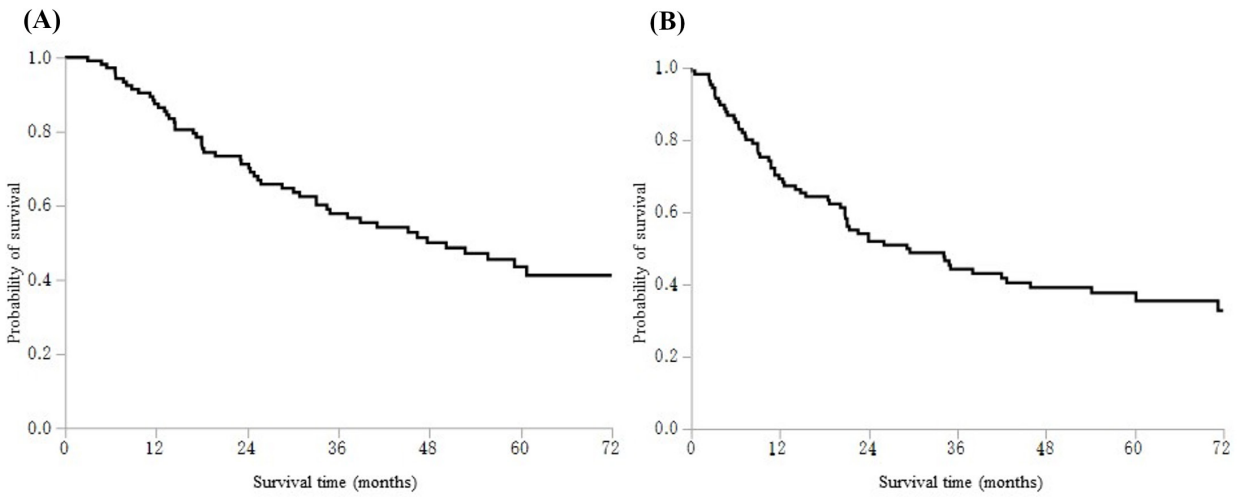

Figure 1. Survival curve of the resected distal cholangiocarcinoma (*n* = 107). (A) Overall survival 5-survival year rate: 43.4%, median survival time: 47.7 months; **(B)** Relapse-free survival: 35.5%, median relapse-free survival time: 29.2 months.

Table 2. Distribution of the T factor of the 7th edition from the 6th edition

T factor (6th)	*n*	T factor (7th)	*n*
Tis	1	Tis	1
T1a	0		
T1b	11	T1	9
		T2	2
T2	30	T1	15
		T2	13
		T3	2
T3a	57	T1	16
		T2	22
		T3	19
T3b	7	T4	7
T4	1	T4	1

Figure 2B presents the survival curve according to the 7th edition T factor. 5-year survival rates of pTis/T1/T2/T3/T4 were 100%/65.6%/40.1%/13.7%/0%. A significant difference in OS was observed between pT1 and T2 (p = 0.049) and between pT2 and T3 (p = 0.027). In contrast, no significant difference was observed between pTis and T1 (p = 0.39) and between T3 and T4 (p = 0.23).

3.6. Survival curve according to N factor of the 6th and 7th editions

Figure 3 presents the survival curve of the N factor of the 6th and 7th editions. 5-year survival rate was significantly higher in pN0 of the 6th edition than in pN1 of the 6th edition (pN0: 61.8% *vs.* pN1: 18.4%, $p < 0.0001$). In the 7th edition N factor, a significant difference in OS was observed between each group (pN0: 61.8%; pN1: 21.7%; pN2: 0% [pN0 *vs.* pN1: p = 0.0005, pN1 *vs.* pN2: p = 0.0052]).

3.7. Survival curve according to pStage of the 6th and 7th editions

Table 3. Lymph node metastasis rate according to the T factor of the 6th edition and the 7th edition

T factor (6th)	*n*	LNM	T factor (7th)	*n*	LNM
Tis	1	0% (0/1)	Tis	1	0% (0/1)
T1a	0		T1	40	25.0% (10/40)
T1b	11	27.3% (3/11)			
T2	30	20.0% (6/30)	T2	37	40.5% (15/37)
T3a	57	50.9% (29/57)	T3	21	61.9% (13/21)
T3b	7	71.4% (5/7)			
T4	1	0% (0/1)	T4	8	62.5% (5/8)

Figure 4 presents the survival curve according to pStage of the 6th and 7th editions. No significant difference in OS was observed between each pStage group of the 6th edition, whereas a significant difference was found between those of the 7th edition (pStage: 0%, Stage I: 83.0%, Stage IIA: 44.4%, Stage IIB: 19.3%, Stage IIIA: 0%, Stage IIIB: 0%; pStage I *vs.* Stage IIA: p = 0.027, Stage IIA *vs.* Stage IIB: p = 0.0043, Stage IIB *vs.* Stage IIIA: p = 0.01).

4. Discussion

Results of this study indicated that the 7th edition of the JCCB can more accurately predict survival outcomes for resected DCC than the 6th version. T classification of the 6th edition was based on which layer was invaded. Similar layer-based systems have been applied to other gastrointestinal cancers, such as those of the stomach, colon, and rectum, where the distinct and concentric nature of the wall layers provides strong prognostic value (*13,14*). Conversely, the extrahepatic bile duct is characterized by a relatively thin wall and non-uniform concentricity along its course (*15*). It consists of varying proportions of fibrous and loose connective tissues, making it difficult to distinguish

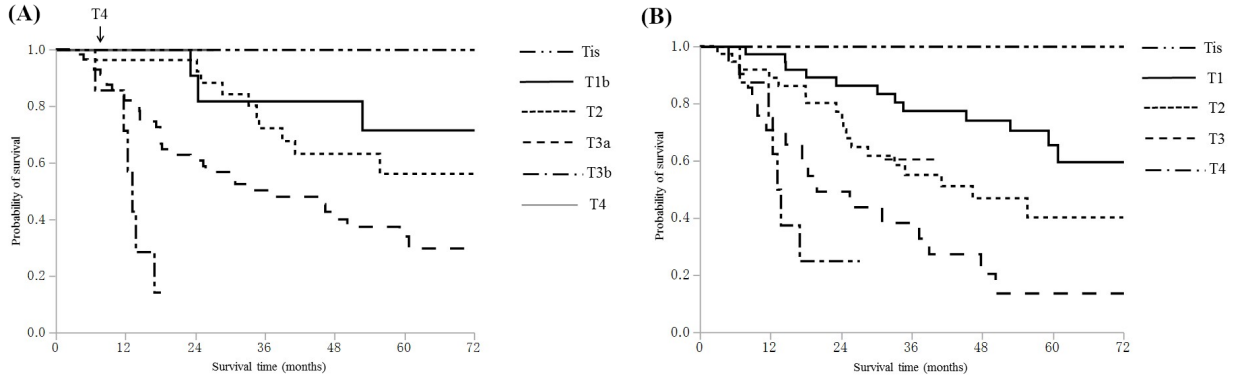

Figure 2. Survival curves according to the T factor. (A) 6th edition (pTis *vs.* T1b; $p = 0.57$, pT1b *vs.* T2; $p = 0.39$, pT2 *vs.* T3a; $p = 0.68$, pT3a *vs.* T3b; $p = 0.02$, pT3b *vs.* T4; $p = 0.21$); **(B)** 7th edition (pTis *vs.* T1; $p = 0.39$, pT1 *vs.* T2; $p = 0.049$, pT2 *vs.* T3; $p = 0.027$, pT3 *vs.* T4; $p = 0.23$).

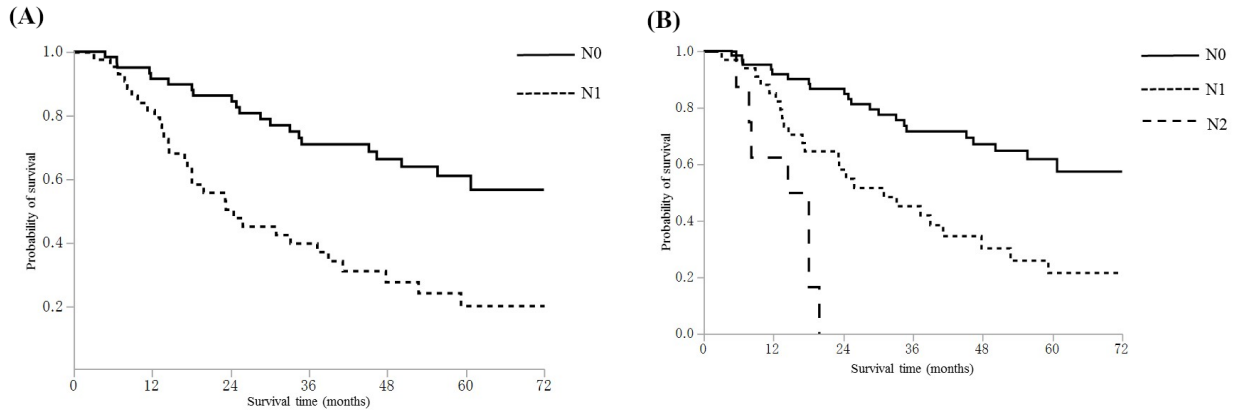

Figure 3. Survival curve according to the N factor. (A) 6th edition (pN0 *vs.* N1; $p < 0.0001$); **(B)** 7th edition (pN0 *vs.* N1; $p = 0.0005$, pN1 *vs.* N2; $p = 0.0052$).

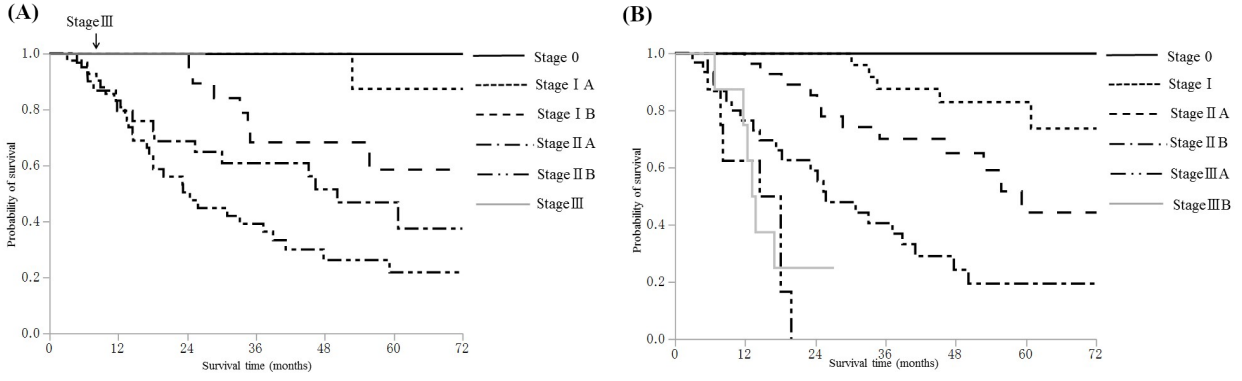

Figure 4. Survival curve according to stage. (A) 6th edition (pStage 0 *vs.* StageIA; $p = 0.09$, p StageIA *vs.* StageIB; $p = 0.09$ pStageIB *vs.* StageIIA; $p = 0.22$, pStageIIA *vs.* StageIIB; $p = 0.10$, pStageIIB *vs.* StageIII; $p = 0.37$); **(B)** 7th edition (pStage 0 *vs.* StageI; $p = 0.43$, pStageI *vs.* StageIIA; $p = 0.027$, pStageIIA *vs.* StageIIB; $p = 0.0043$, pStageIIB *vs.* StageIIIA; $p = 0.01$, pStageIIIA *vs.* IIIB; $p = 0.86$).

between invasion confined within the bile duct wall and invasion beyond it (*16*). Moreover, the presence of desmoplastic reactions, edematous stroma, congestion, necrosis, and inflammatory cell infiltration around invasive adenocarcinoma often obscures the histological architecture, making layer discrimination challenging even for experienced pathologists (*17*). The study found no significant difference in OS between each T factor, except between T3a and T3b, in the 6th edition. Previous studies also reported that the layer-based T classification failed to stratify postoperative survival in patients with DCC (*18,19*).

In contrast, the 7th (Japanese) edition classifies the T category based on either DOI or ITT, depending on measurability.

DOI has been widely used in other cancer types with shallow depth, such as cutaneous melanoma, where it serves as a strong prognostic indicator (*20*). Several studies have suggested that measuring depth of bile duct carcinoma invasion provides better prognostic discrimination than layer-based classifications (*15,21*). In this study, DOI was measured from the basal lamina of the adjacent normal bile duct epithelium to the deepest point of tumor invasion. However, in more advanced or circumferential tumors, the basal lamina is often indistinct or unidentifiable, making DOI measurement infeasible. In such cases, ITT was used as a substitute in the current T classification system. Aoyama *et al.* reported that the ITT classification exhibited a more favorable prognostic discrimination than the T classification of the 7th and 8th editions of the American Joint Committee on Cancer (AJCC) Staging (*22*). This study demonstrated that the updated T classification in the 7th edition provides a significant prognostic stratification among each T category, in contrast to the 6th edition, which failed to show such distinctions. Hence, it was deduced that T classification according to the use of ITT and DOI (when ITT could not be measured), rather than extent of tumor invasion, was more likely to reflect prognosis. However, a major limitation of the DOI and ITT classifications was that they did not permit reliable preoperative radiologic assessment by clinicians. Further validation in larger, multicenter studies is warranted to confirm prognostic utility and clinical applicability of this revised classification.

As for the N factor, the previous classification based solely on presence or absence of LNM had been revised in the 7th edition to a system based on number of LNM (0, 1–3, ≥ 4 or more nodes). In other gastrointestinal cancers — such as esophageal, gastric, and colorectal cancers — both the UICC classification and Japanese General Rules also adopt N classifications based on the number of LNMs, and these systems had been shown to accurately predict patient prognosis (*23-25*). Regarding DCC, Suzuki *et al.* reported that both number of positive lymph nodes and lymphatic invasion were significant prognostic factors following pancreaticoduodenectomy for DCC (*26*). In addition, several studies have demonstrated that the N categories defined in the 8th edition of the AJCC classification effectively predict patient outcomes (*19,21*). Others have found that absolute number of metastatic lymph nodes is a stronger predictor of survival compared to lymph node ratio (LNR) in DCC (*27*). Consistent with these findings, the present study also showed significant differences in OS between N0 and N1, and between N1 and N2, according to the latest classification. Recent reports have emphasized prognostic importance of both number of retrieved lymph nodes and lymph node ratio (*i.e.*, ratio of metastatic to total retrieved lymph nodes). Furthermore, some researchers have proposed that evaluation of at least 11 or 12 lymph nodes is necessary for accurate N staging in DCC (*19,28*). Schwart *et al.* reported that survival prediction in extrahepatic biliary duct cancer is strongly influenced by both total number of retrieved LNs and number of negative LNs (*29*). In contrast, Hong *et al.* found no significant association between survival and number of retrieved LNs (*30*). These discrepancies underscore need for further investigation into optimal number of examined lymph nodes and their prognostic value.

Our study demonstrates that the stage classification system in the 7th edition more accurately stratifies 5-year OS rates across stages than the 6th edition. This improvement appears to be attributable to the revised T and N classifications, which, as shown above, are significantly associated with patient prognosis.

Major limitations of the present study were the small sample size, its retrospective design, and the unstandardized adjuvant chemotherapy indications and regimens. Multicenter prospective studies with larger sample sizes are warranted to elucidate the validity of the latest edition of the JCCB.

In conclusion, as a result of the revisions of the T and N factor classifications, the 7th edition of the JCCB may more accurately predict survival outcomes for resected DCC than the 6th edition.

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