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Original Article

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Validation of the Eighth American Joint Committee on Cancer Staging System for Distal Bile Duct Carcinoma

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Purpose

T category of the eighth edition of the American Joint Committee on Cancer (AJCC) staging system for distal bile duct carcinoma (DBDC) was changed to include tumor invasion depth measurement, while the N category adopted a 3-tier classification system based on the number of metastatic nodes.

Materials and Methods

To validate cancer staging, a total of 200 surgically resected DBDCs were staged and compared according to the seventh and eighth editions.

Results

T categories included T1 (n=37, 18.5%), T2 (n=114, 57.0%), and T3 (n=49, 24.5%). N categories included N0 (n=133, 66.5%), N1 (n=50, 25.0%), and N2 (n=17, 8.5%). Stage groupings included I (n=33, 16.5%), II (n=150, 75.0%), and III (n=17, 8.5%). The overall 5-year survival rates (5-YSRs) of T1, T2, and T3 were 59.3%, 42.4%, and 12.2%, respectively. T category could discriminate patient survival by both pairwise (T1 and T2, p=0.011; T2 and T3, p < 0.001) and overall (p < 0.001) comparisons. The overall 5-YSRs of N0, N1, and N2 were 47.3%, 17.0%, and 14.7%, respectively. N category could partly discriminate patient survival by both pairwise (N0 and N1, p < 0.001; N1 and N2, p=0.579) and overall (p < 0.001) comparisons. The overall 5-YSRs of stages I, II, and III were 59.0%, 35.4%, and 14.7%, respectively. Stages could distinguish patient survival by both pairwise (I and II, p=0.002; II and III, p=0.015) and overall (p < 0.001) comparisons. On multivariate analyses, T and N categories (p=0.014 and p=0.029) and pancreatic invasion (p=0.006) remained significant prognostic factors.

Conclusion

The T and N categories of the eighth edition AJCC staging system for DBDC accurately predict patient prognosis.

Key words
Bile duct, Extrahepatic, Cholangiocarcinoma, Neoplasm, Staging

Introduction

Bile duct carcinomas, or cholangiocarcinomas, account for 3% of all gastrointestinal cancers worldwide [1], and their incidence is higher in Eastern Asian countries, including Korea, China, and Thailand [2]. Bile duct carcinomas can be further classified as intrahepatic, perihilar, and distal bile duct carcinomas (DBDCs) [3], and DBDCs compromise about 30% of all bile duct carcinomas [3]. In the United States, it is estimated that about 10,910 Americans will be diagnosed with carcinomas of the gallbladder and extrahepatic bile duct in 2015 [4].

Although the American Joint Committee on Cancer (AJCC) has changed the staging system of extrahepatic bile duct (EBD) carcinoma seven times in the last decades [5,6], those staging systems have been criticized for being inaccurate in estimating prognosis [7-9]. First, the previous staging sys-

Table 1. AJCC staging system for distal bile duct carcinoma

AJCC seventh edition		AJCC eighth edition	
Primary tumor (T)			
T1	Tumor confined to the bile duct histologically	T1	Depth of invasion < 5 mm
T2	Tumor invades beyond the wall of 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 the superior mesenteric artery	T3	Depth of invasion > 12 mm
T4	Tumor involves the celiac axis or the superior mesenteric artery	T4	Tumor involves the celiac axis or the superior mesenteric artery
Regional lymph nodes (N)			
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
Distant metastasis (M)			
M0	No distant metastasis	M0	No distant metastasis
M1	Distant metastasis	M1	Distant metastasis
Stage grouping			
IA	T1N0M0	I	T1N0M0
IB	T2N0M0	IIA	T1N1M0 or T2N0M0
IIA	T3N0M0	IIB	T2N1M0 or T3, N0-1, M0
IIB	T1-3, N1M0	IIIA	T1-3, N2M0
III	T4, any N, M0	IIIB	T4, any N, M0
IV	Any T, any N, M1	IV	Any T, any N, M1

AJCC, American Joint Committee on Cancer.

tems did not take into consideration the histologic characteristics of smooth muscle distribution in the EBD. Cancer staging of DBDCs was separated from the staging of proximal or perihilar bile duct carcinoma from the seventh edition of the AJCC staging manual [10]. However, the terminology used in the sixth and seventh editions of the AJCC staging system, which defined T1 and T2 diseases as "confined to the bile duct histologically" and "beyond the wall of the bile duct," was unclear and problematic [10,11], especially when marked stromal response of the invasive carcinoma presents and obscures the lower boundary of the bile duct wall [8]. To overcome the problems of the previous editions of the AJCC cancer staging system for DBDC, an alternative method of T classification was proposed, which measured the depth of tumor invasion from the basal lamina of the adjacent normal epithelium to the most deeply infiltrating tumor cells, and categorized invasion depth as T1, < 5 mm; T2, 5-12 mm; and T3, > 12 mm [12]. This method more powerfully predicted survival in patients with DBDCs than the previously used T classification of seventh edition [9,12,13], and was ultimately incorporated in the T category of the eighth edition [14].

Conversely, the N category of seventh edition AJCC staging system was simple to evaluate the presence or absence of metastatic nodes. Several later studies demonstrated the characteristics of nodal metastasis, including location of the involved lymph nodes, lymphatic spread, and micrometastasis [15-20]. Previous studies by Moon et al. [13] and Schwarz et al. [21] demonstrated that a minimum of 10 lymph nodes were required to assess the accurate N category of DBDC. In addition, several studies emphasized the significance of the 3 tiers of N classification as a prognostic indicator [13,22,23].

In the eighth edition of the AJCC cancer staging for DBDC, the T category was changed according to invasion depth as follows: T1, < 5 mm; T2, 5-12 mm; and T3, > 12 mm. The N category was classified into 3-tiers based on the number of metastatic nodes: N0, no nodal metastasis; N1, 1 to 3 nodal metastases; and N2, 4 or more nodal metastases. A summary of the changes between the seventh and eighth editions of AJCC staging for DBDCs is described in Table 1. Recently, Gonzalez et al. [1] reported a size-based T category for staging DBDCs and revealed its significant relationship with patient survival differences, specifically for intra-pancreatic type DBDCs. They stratified 47 intra-pancreatic DBDC cases based on tumor size as follows: < 2 cm, 2-4 cm, and > 4 cm [1].

To validate the new eighth edition of the AJCC cancer staging system for DBDCs, we compared the clinicopathologic factors including patient survival based on the seventh and

eighth editions of the AJCC cancer staging system for DBDC. In addition, we evaluated the prognostic relevance of size-based criteria for the staging for DBDC.

Materials and Methods

1. Case selection

All cases of surgically resected primary DBDCs between May 2010 and June 2012 from Asan Medical Center were collected. Carcinomas originating in the mucosa of the bile duct and from the junction of the cystic duct-common bile duct to the ampulla of Vater were included in this study. Carcinomas arising in the ampulla of Vater or pancreas were excluded. Finally, 200 cases of DBDCs were included in this study.

Clinical data included patient sex and age, operation date, most recent follow-up date, operation method, postoperative radiation therapy and chemotherapy, and survival status. Pathological data included tumor size and location, growth pattern (papillary, nodular, or diffusely infiltrative pattern), histologic subtype, tumor grade, margin status, perineural and lymphovascular invasion, pancreatic, duodenal, and gallbladder invasion, nodal metastasis, and stage grouping evaluation based on the seventh and eighth editions of the AJCC cancer staging system [10,14]. Tumor size was grossly evaluated and microscopically confirmed. When the discrepancy was present between two measurements, tumor size by microscopic measurement was selected, which was previously described elsewhere [1]. The tumor size was further categorized based on greatest dimension as follows: < 2 cm, 2-4 cm, and > 4 cm [1].

The depth of cancer invasion was measured on slides containing the primary DBDC and was defined as the area of deepest infiltration from the mucosal surface, e.g., from the basal lamina of the adjacent normal epithelium to the most deeply advanced tumor cells. For cases containing high grade dysplasia (or biliary intraepithelial neoplasia [BilIN]-3) at the periphery of the invasive tumors, the basal lamina of the high grade dysplasia (or BilIN-3) was used as the reference, which was previously described [12]. The maximum depth of tumor invasion was categorized into 3 groups: T1, < 5 mm; T2, 5-12 mm; and T3, > 12 mm [7,12].

DBDCs were further classified based on location in the distal bile duct (DBD) as follows: When the tumor was located within the intrapancreatic DBD, the tumor was classified as "intra-pancreatic type"; when the tumor was located in the DBD outside of the pancreas between the junction of cystic duct-common bile duct to just before entering intra-pancreatic DBD, the tumor was classified as "extra-pancreatic type"; when the tumor diffusely involved intra- and extra-pancreatic DBDs, the tumor was classified as "both intra- and extra-pancreatic type" (Fig. 1). Tumor grading was classified as low (well to moderately differentiated tumors) and high grade (poorly differentiated and undifferentiated tumors) [24].

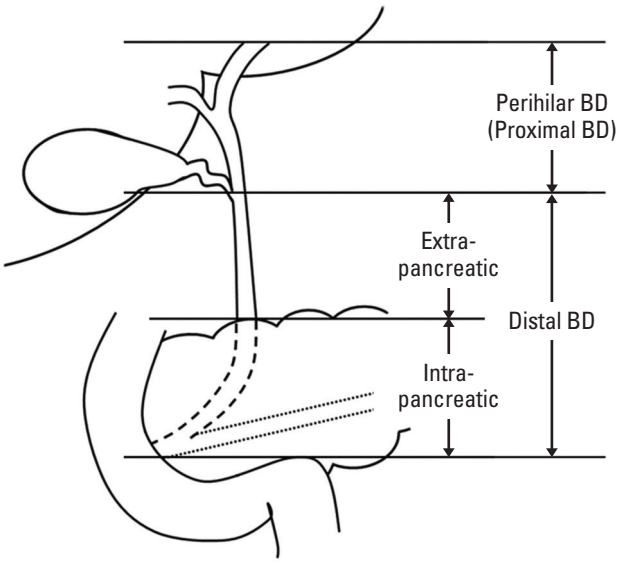

Fig. 1. Schematic drawing of the distal bile duct (BD).

2. Statistical analysis

Statistical analyses were performed with SPSS software ver. 17.0 (SPSS Inc., Chicago, IL). Categorical data were analyzed using Student's t test, the chi-square test, or Fisher's exact test. The survival rate was estimated using the Kaplan-Meier method and the log-rank test was used to calculate its associations with various clinicopathologic factors. The significance of any prognostic factors was investigated with the Cox proportional hazards model. p-values of < 0.05 were considered to denote statistical significance.

3. Ethical statement

The Institutional Review Board of Asan Medical Center approved this study (2013-0527) with a waiver of the informed consent.

Table 2. Characteristics of patients with distal bile duct carcinoma

Variable	No. (%) (n=200)
Operation	
Pancreatoduodenectomy including Whipple	170 (85.0)
Bile duct resection	30 (15.0)
Age, mean±SD (yr)	65.4±9.2
< 60	55 (27.5)
≥ 60	145 (72.5)
Sex	
Male	137 (68.5)
Female	63 (31.5)
Location	
Intra-pancreatic	168 (84.0)
Extra-pancreatic	30 (15.0)
Both intra- and extra-pancreatic	2 (1.0)
Growth pattern	
Papillary	12 (6.0)
Nodular	33 (16.5)
Diffusely infiltrative	155 (77.5)
Histologic subtype	
Tubular adenocarcinoma	198 (99.0)
Mucinous carcinoma	1 (0.5)
Undifferentiated carcinoma	1 (0.5)
Grade	
Low	167 (83.5)
High	33 (16.5)
Size, mean±SD (cm)	2.9±1.2
< 2	39 (19.5)
2-4	132 (66.0)
> 4	29 (14.5)
Pancreatic invasion[a]	
No	53 (31.2)
Yes	117 (68.8)
Duodenal invasion[a]	
No	116 (68.2)
Yes	54 (31.8)
Cystic duct of gallbladder invasion	
No	163 (81.5)
Yes	37 (18.5)
Resection margin status of the bile duct	
No involvement	160 (80.0)
Involved by cancer	40 (20.0)
Lymphovascular invasion	81 (40.5)
Perineural invasion	166 (83.0)
T category, seventh edition	
T1	12 (6.0)
T2	40 (20.0)
T3	148 (74.0)
T4	0
N category, seventh edition	
N0	133 (66.5)
N1	67 (33.5)
AJCC stage grouping, seventh edition	
IA	12 (6.0)
IB	33 (16.5)
IIA	88 (44.0)
IIB	67 (33.5)
III	0
IV	0
Depth of invasion, mean±SD (mm)	9.3±5.0
Total nodes assessed, mean±SD	12.1±7.5
No. of positive nodes, mean±SD	0.9±1.9
T category, eighth edition	
T1	37 (18.5)
T2	114 (57.0)
T3	49 (24.5)
T4	0
N category, eighth edition	
N0	133 (66.5)
N1	50 (25.0)
N2	17 (8.5)
AJCC stage grouping, eighth edition	
I	33 (16.5)
IIA	85 (42.5)
IIB	65 (32.5)
IIIA	17 (8.5)
IIIB	0
IV	0

SD, standard deviation; AJCC, American Joint Committee on Cancer. [a]Calculated using only patients with sufficient available data.

Results

1. Patient characteristics

Patient clinicopathologic characteristics are summarized in Table 2. The male to female ratio of the patients was 2.2 with a median age at resection of 67.0 years (range, 35 to 82 years). There were 168 intra-pancreatic (84.0%), 30 extra-pancreatic (15.0%), and 2 both intra- and extra-pancreatic (1.0%) DBDCs. The mean tumor size was 2.9±1.2 cm. About two-thirds of the cases were between 2 and 4 cm (132/200, 66.0%). One hundred seventy cases (85.0%) were pancreatoduodenectomy specimens including Whipple operation or pylorus-preserving pancreaticoduodenectomy, and the

Table 3. Association between T and N categories of the eighth AJCC and clinicopathologic factors in distal bile duct carcinoma patients

Clinicopathologic factor	T category			N category		
	T1	T2	T3	N0	N1	N2
No. of patients	37 (18)	114 (57)	49 (25)	133 (67)	50 (25)	17 (8)
Age, mean±SD (yr)	65.5±8.2	66.0±9.1	64.0±10.1	65.3±9.4	65.9±9.2	64.3±7.8
p-value		0.453			0.815	
Age (yr)						
< 60	9 (24)	27 (24)	19 (39)	36 (27)	15 (30)	4 (23)
≥ 60	28 (76)	87 (76)	30 (61)	97 (73)	35 (70)	13 (77)
p-value		0.126			0.859	
Sex						
Male	25 (68)	76 (67)	36 (74)	92 (69)	34 (68)	11 (65)
Female	12 (32)	38 (33)	13 (26)	41 (31)	16 (32)	6 (35)
p-value		0.686			0.929	
Location						
Intra-pancreatic	7 (19)	20 (17)	3 (6)	18 (13)	11 (22)	1 (6)
Extra-pancreatic	30 (81)	93 (82)	45 (92)	115 (87)	38 (76)	15 (88)
Both intra- and extra-pancreatic	0	1 (1)	1 (2)	0	1 (2)	1 (6)
p-value		0.202			0.052	
Growth pattern						
Papillary	10 (27)	1 (1)	1 (2)	10 (7)	0	2 (12)
Nodular	7 (19)	21 (18)	5 (10)	21 (16)	8 (16)	4 (23)
Diffusely infiltrative	20 (54)	92 (81)	43 (88)	102 (77)	42 (84)	11 (65)
p-value		< 0.001[a)]			0.130	
Size (cm)						
< 2	11 (30)	26 (23)	2 (4)	32 (24)	6 (12)	1 (6)
2-4	22 (59)	70 (61)	40 (82)	83 (62)	37 (74)	12 (71)
≥ 4	4 (11)	18 (16)	7 (14)	18 (14)	7 (14)	4 (23)
p-value		0.022[a)]			0.172	
Histological subtype						
Tubular adenocarcinoma	37 (100)	114 (100)	47 (96)	132 (99)	50 (100)	16 (94)
Mucinous carcinoma	0	0	1 (2)	0	0	1 (6)
Undifferentiated carcinoma	0	0	1 (2)	1 (1)	0	0
p-value		0.184			0.163	
Grade						
Low	33 (89)	96 (84)	38 (78)	113 (85)	42 (84)	12 (71)
High	4 (11)	18 (16)	11 (22)	20 (15)	8 (16)	5 (29)
p-value		0.338			0.321	
Resection margin status of the bile duct						
No involvement	33 (89)	91 (80)	36 (74)	111 (84)	35 (70)	14 (82)
Involved by cancer	4 (11)	23 (20)	13 (26)	22 (16)	15 (30)	3 (18)
p-value		0.196			0.124	
Lymphovascular invasion						
No	29 (78)	71 (62)	19 (39)	90 (68)	24 (48)	5 (29)
Yes	8 (22)	43 (38)	30 (61)	43 (32)	26 (52)	12 (71)
p-value		0.001[a)]			0.002[a)]	
Perineural invasion						
No	15 (40)	13 (11)	6 (12)	28 (21)	5 (10)	1 (6)
Yes	22 (60)	101 (89)	43 (88)	105 (79)	45 (90)	16 (94)
p-value		< 0.001[a)]			0.092	

(Continued to the next page)

Table 3. Continued

Clinicopathologic factor	T category			N category		
	T1	T2	T3	N0	N1	N2
Pancreatic invasion[b)]						
No	20 (67)	27 (29)	6 (13)	43 (37)	8 (20)	2 (12)
Yes	10 (33)	67 (71)	40 (87)	72 (63)	31 (80)	14 (88)
p-value		< 0.001[a)]			0.034[a)]	
Duodenal invasion[b)]						
No	28 (93)	70 (75)	18 (39)	89 (77)	22 (56)	5 (31)
Yes	2 (7)	24 (25)	28 (61)	26 (23)	17 (44)	11 (69)
p-value		< 0.001[a)]			< 0.001[a)]	
N category, eighth edition						
N0	33 (89)	81 (71)	19 (39)	-	-	-
N1 (1-3)	4 (11)	26 (23)	20 (41)	-	-	-
N2 (≥ 4)	0	7 (6)	10 (20)	-	-	-
p-value		< 0.001[a)]			-	

Values are presented as number (%) or mean±standard deviation. AJCC, American Joint Committee on Cancer; SD, standard deviation. [a)]Statistically significant ($p < 0.05$), [b)]Calculated using only patients with sufficient available data.

remaining 30 (15.0%) were specimens of bile duct resection with cholecystectomy. Post-operative radiation therapy and chemotherapy were performed in 37 (18.5%) and 69 (34.5%) patients, respectively. In the pathologic examination of bile duct resection specimens, the status of pancreatic or duodenal involvement by the tumor could not be completely evaluated. Consequently, involvements of the pancreas, duodenum, and/or cystic duct of the gallbladder was observed in 68.8% (117/170 cases), 31.8% (54/170), and 18.5% (37/200), respectively, with either single or multiple organ involvement. Lymphovascular and perineural invasions were frequently observed in 40.5% (n=81) and 83.0% (n=166) of cases, respectively. Involvement of resection margin of the bile duct by cancer was in 20.0% (n=40) of cases. The median follow-up period after surgical resection was 33.8 months (range, 1 to 63 months).

2. Comparison between T and N categories of the eighth AJCC and clinicopathologic factors

The associations between T and N categories of the eighth AJCC cancer staging scheme and clinicopathologic factors of patients with DBDCs are shown in Table 3. The patients with higher T category tended to have diffusely infiltrative pattern ($p < 0.001$), larger tumor (p=0.022), and presence of perineural ($p < 0.001$), lymphovascular (p=0.001), pancreatic ($p < 0.001$), and duodenal ($p < 0.001$) invasions. In addition, strong association was observed between T and N categories ($p < 0.001$).

Similarly, the patients with higher N category tended to have more frequent lymphovascular (p=0.002), pancreatic (p=0.034), and duodenal ($p < 0.001$) invasions.

3. Patient survival based on T category

The median depth of invasion of DBDC was 8.0 mm (range, 1 to 28 mm). According to the eighth AJCC staging system, 37 cases were categorized as T1 (18.5%), 114 as T2 (57.0%), and 49 as T3 (24.5%) tumors. The median survival time in patients with T2 and T3 tumors was 36.3 months and 19.9 months, respectively, while the median survival time in those with T1 was not reached. The 1-year, 3-year, and 5-year survival rates (YSRs) of patients with T1 tumors were 97.2%, 80.3%, and 59.3%, respectively; conversely, those of patients with T2 tumors were significantly decreased at 86.0%, 50.4%, and 42.4%, respectively. The 1-, 3-, and 5-YSRs of patients with T3 tumors were also significantly decreased at 65.3%, 28.6%, and 12.2%, respectively. Patients with DBDCs showed an overall significant survival difference based on the T category of the eighth edition scheme ($p < 0.001$) (Fig. 2A). When pairwise comparisons were performed, all pairs of T category showed significant differences in patient survival from each other (T1 and T2, p=0.011; T2 and T3, $p < 0.001$).

Conversely, based on the seventh AJCC staging system, 12 were categorized as T1 (6.0%), 40 as T2 (20.0%), and 148 as T3 (74.0%) tumors. The median survival times in patients with T2 and T3 tumors were 41.2 months and 27.5 months, respectively, while the median survival time in those with T1 was not reached. The 1-, 3-, and 5-YSRs were all 91.7% in patients with T1 tumors, 92.5%, 69.7%, and 40.8% in patients

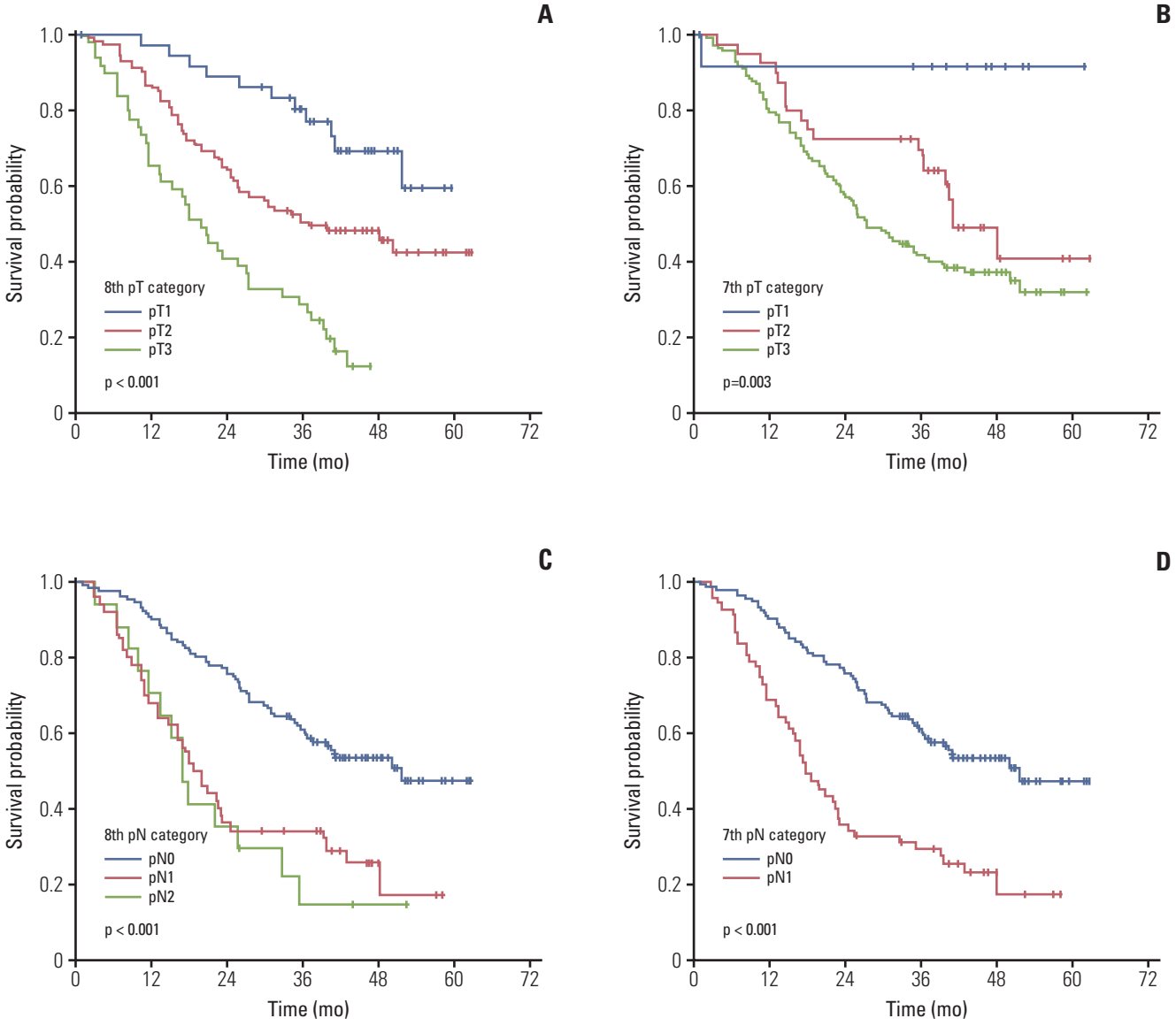

Fig. 2. Overall survival stratified by T and N categories of distal bile duct carcinomas according to the American Joint Committee on Cancer. T categories of the eighth edition (A) and the seventh edition (B) and N categories of the eighth edition (C) and the seventh edition (D).

with T2 tumors, and 79.6%, 41.7%, and 32.0% in patients with T3 tumors, respectively. Patients with DBDCs showed an overall significant survival difference based on the T category of the seventh edition AJCC staging scheme (p=0.003) (Fig. 2B). The pairwise comparisons showed a significant difference between patients with T1 and T2 tumors (p=0.023); however, there was no significant survival difference between patients with T2 and T3 tumors (p=0.066).

4. Patient survival based on N category

The total number of examined nodes assessed ranged from 1 to 36 (mean, 12.1±7.5; median, 11.0). Among them, the number of metastatic nodes ranged from 0 to 11 (mean, 0.9±1.9; median, 0). The majority of the tumors were N0 (133 cases, 66.5%). According to the eighth AJCC staging system, nodal metastasis was seen in 67 cases, including 50 N1 (25.0%) and 17 N2 (8.5%). Survival curves based on the N category are depicted in Fig. 2C and D. The 1-, 3-, and 5-YSRs

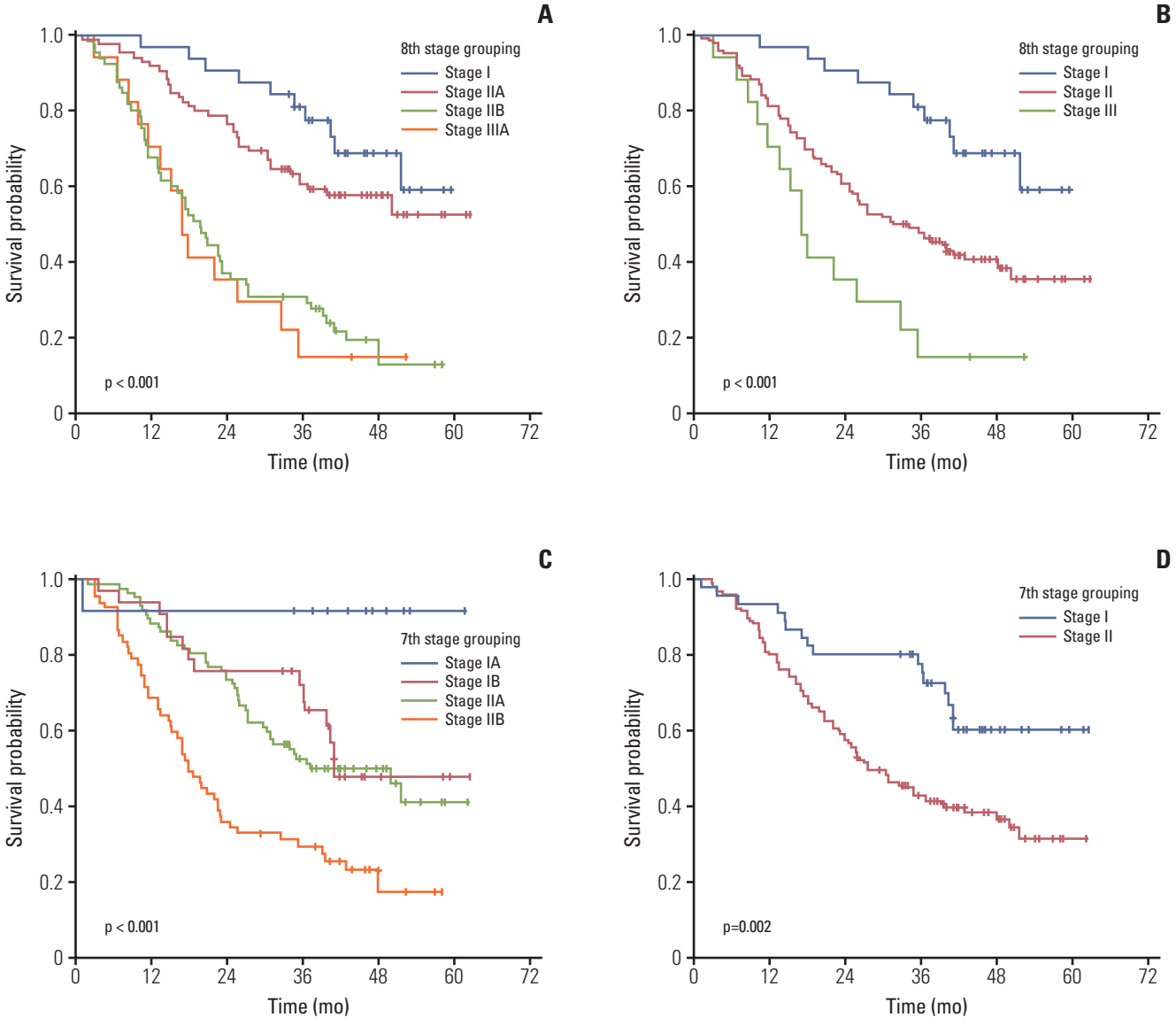

Fig. 3. Overall survival stratified by stage group of distal bile duct carcinomas according to the American Joint Committee on Cancer eighth edition (A and B) and seventh edition stage grouping (C and D).

in patients with N0 tumors were 90.2%, 61.1%, and 47.3%, respectively. Those in patients with N1 and N2 tumors were decreased, corresponding to 68.0%, 34.0%, and 17.0% in N1 patients and 70.6%, 14.7%, and 14.7% in N2 patients, respectively. Overall patient survival was significantly decreased among patients with metastatic nodes ($p < 0.001$) (Fig. 2C). The median survival times of patients with N1 and N2 tumors (18.8 and 17.0 months, respectively) were significantly shorter than that of patients with N0 (51.8 months; $p < 0.001$, each). However, the survival times of the patients with N1 and N2 tumors were not significantly different ($p=0.579$). The median survival time of the patients with metastatic nodes (18.0 months) was significantly shorter than that of those without metastatic nodes (51.8 months; $p < 0.001$). Therefore, patient survival was significantly decreased when the patients had metastatic nodes as defined by the seventh edition scheme (Fig. 2D).

5. Patient survival based on AJCC stage grouping

By the eighth edition definitions, the tumors were classified into stages I (33 cases, 16.5%), IIA (85, 42.5%), IIB (65,

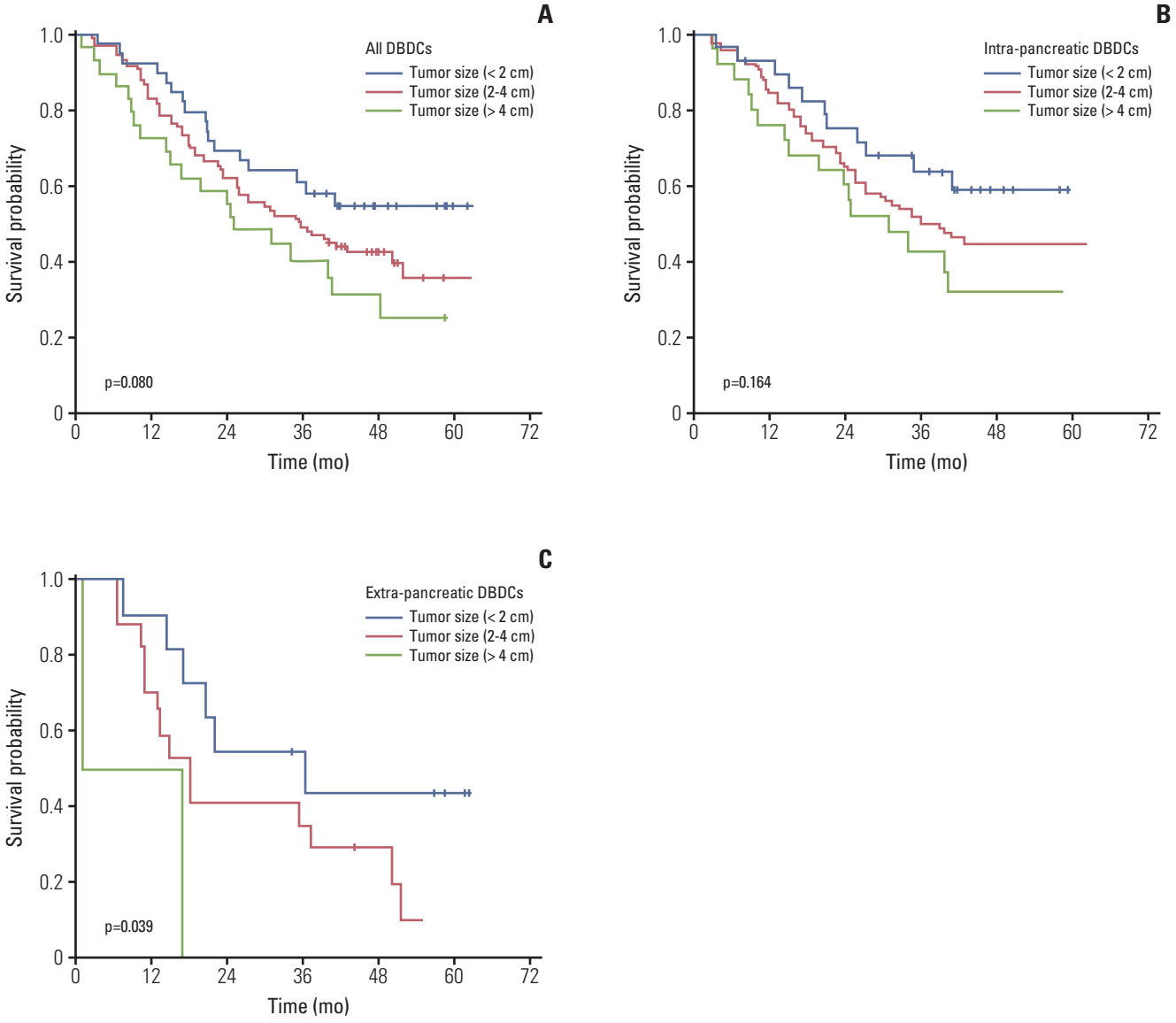

Fig. 4. Overall survival stratified by size-based criteria of distal bile duct carcinomas (DBDCs). All DBDCs (A), including intra-pancreatic, extra-pancreatic, and both intra- and extra-pancreatic types. Intra-pancreatic (B) and extra-pancreatic (C) DBDCs.

32.5%), and IIIA (17, 8.5%). Neither stages IIIB nor IV were seen among our cases. The stage grouping of the new eighth edition was a strong predictor of long-term outcome ($p < 0.001$) (Fig. 3A). By pairwise comparisons, the 5-YSR of stage IIA patients was significantly better than that of stage IIB patients ($p < 0.001$). However, other pairs of stage groupings showed no significant differences in patient survival (stages I and IIA, p=0.148; IIB and IIIA, p=0.691), corresponding to the 5-YSRs of 59.0%, 52.4%, 12.9%, and 14.7% for patients with stage I, IIA, IIB, and IIIA tumors, respectively. After simplifying the stage grouping, patients with stages II and III tumors had a median survival of 31.6 and 17.0 months, respectively. The median survival of patients with stage I tumors had not been reached, because more than 50% of the patient were still alive. Consequently, patients with higher stage tumors tended to have significantly shorter survival ($p < 0.001$) (Fig. 3B). When pairwise comparisons were performed, all pairs of stages were significantly correlated to patient survival (stages I and II, p=0.002; II and III, p=0.015). This corresponded to a 5-YSR of 35.4% and 14.7% for patients

Table 4. Univariate and multivariate analysis of distal bile duct carcinoma patients

Variable	Univariate analysis				Multivariate analysis		
	5-YSR (%)	HR	95% CI	p-value	HR	95% CI	p-value
Location				0.098			
Extra-pancreatic	23.2	-	-	-			
Intra-pancreatic	44.7	0.6	0.4-1.0	0.041[a)]			
Both intra- and extra-pancreatic	0	1.4	0.3-5.9	0.662			
Growth pattern				0.001[a)]			0.070
Papillary	55.6	-	-	-	-	-	-
Nodular	64.8	1.2	0.4-3.6	0.808	1.5	0.3-7.5	0.626
Diffusely infiltrative	30.6	2.9	1.1-7.8	0.041[a)]	2.8	0.7-12.4	0.168
Size (cm)				0.082			
< 2	54.6	-	-	-			
2-4	35.4	1.5	0.9-2.5	0.146			
> 4	25.0	2.1	1.1-4.0	0.026[a)]			
Involvement of bile duct margin by cancer	18.2	2.1	1.4-3.1	0.001[a)]	1.3	0.7-2.4	0.340
Lymphovascular invasion	33.9	1.5	1.1-2.2	0.022[a)]	1.5	1.0-2.3	0.085
Pancreatic invasion	33.9	3.4	2.0-5.9	< 0.001[a)]	2.3	1.3-4.0	0.006[a)]
Duodenal invasion	32.2	1.9	1.3-2.9	0.003[a)]	0.9	0.6-1.6	0.804
T category (eighth AJCC)				< 0.001[a)]			0.014[a)]
T1 (< 5 mm)	59.3	-	-	-	-	-	-
T2 (5-12 mm)	42.4	2.3	1.2-4.3	0.013[a)]	1.6	0.7-4.0	0.281
T3 (> 12 mm)	12.2	5.2	2.6-10.1	< 0.001[a)]	3.0	1.2-7.7	0.023[a)]
N category (eighth AJCC)				< 0.001[a)]			0.029[a)]
N0	47.3	-	-	-	-	-	-
N1 (1-3)	17.0	2.5	1.7-3.8	< 0.001[a)]	1.7	1.1-2.8	0.030[a)]
N2 (≥ 4)	14.7	3.1	1.7-5.6	< 0.001[a)]	2.2	1.1-4.3	0.024[a)]

5-YSR, 5-year survival rate; HR, relative hazards ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.
[a)]Statistically significant ($p < 0.05$).

with stage II and III tumors, respectively, and 59.0% for those with stage I tumors.

On the contrary, survival of the seventh AJCC stage grouping is presented in Fig. 3C and D. As noted in Fig. 3C, the seventh AJCC stage grouping also had a good ability to discriminate survival outcome in overall comparison. ($p < 0.001$). In brief, the 5-YSR of patients with stage IA tumors (91.7%) was significantly better than that of patients with stage IB (47.8%, p=0.032), and patients with stage IIA tumors (41.0%) had significantly better 5-YSR than those with stage IIB (17.4%, $p < 0.001$). However, no significant difference in patient survival was observed between patients with stages IB and IIA (p=0.487). After simplifying the stage grouping, only stages I and II were identified. Finally, patients with stage I tumors had a tendency for longer survival than those with stage II tumors (p=0.002) (Fig. 3D), corresponding to a 5-YSR of 59.9% and 31.1% for patients with stage I and II tumors, respectively.

6. Patient survival based on tumor size

Among patients with DBDCs (n=200), about two-thirds of the tumors (132 cases, 66.0%) were between 2 and 4 cm in size. Thirty-nine cases (19.5%) had tumors < 2 cm in size and 29 (14.5%) were > 4 cm. The patients with a tumor size < 2 cm had better 5-YSRs (54.6%) than those with tumors between 2 and 4 cm (35.4%), which displayed no significant difference in survival outcomes according to size-criteria (p=0.080) (Fig. 4A).

Among intra-pancreatic type tumors (n=168), similar to the above, 115 (68.4%) were between 2 and 4 cm in size. Twenty-eight (16.7%) cases had tumors < 2 cm in size and 25 (14.9%) were > 4 cm. Although we analyzed survival in patients with intra-pancreatic type DBDCs only, we could not identify a statistical significance in terms of size-based classification (p=0.164) (Fig. 4B).

Conversely, among patients with extra-pancreatic type tumors (n=30), larger tumor size (> 4 cm) was related to

worse patient survival (p=0.039) (Fig. 4C). There were 11 (36.7%) tumors < 2 cm in size, 17 (56.7%) tumors between 2 and 4 cm, and 2 (6.6%) tumors that were > 4 cm. Both patients with tumor size > 4 cm died before 1.4 years after surgery. The 5-YSRs of patients with tumor size < 2 cm and 2 to 4 cm were 43.6% and 9.8%, respectively. By pairwise comparison, a significant difference was seen between patients with tumors between 2 and 4 cm in size and those with > 4 cm (p=0.011); however, there was no significant difference in the survival of patients with tumors < 2 cm in size and those between 2 and 4 cm (p=0.126).

7. Univariate and multivariate analyses

By univariate analysis, there were no significant differences in survival based on the following: age, sex, postoperative radiation therapy and/or chemotherapy, specified location and size of the tumor, histologic subtype, differentiation, perineural invasion, and gallbladder involvement. However, the following clinicopathologic factors were associated with worse survival of DBDC patients (Table 4): diffusely infiltrative growth pattern (p=0.001), involvement of bile duct resection margin (p=0.001), the presence of lymphovascular (p=0.022), pancreatic (p < 0.001), and duodenal invasions (p=0.003), and T and N categories (p < 0.001, each). By multivariate analysis, lower T (p=0.014) and N (p=0.029) categories and the absence of pancreatic invasion (p=0.006) were good independent prognostic predictors of overall survival in DBDC patients.

Discussion

Our present study validates the new eighth edition of the AJCC staging system in patients with DBDC and reveals that it was superior to the seventh edition in terms of predicting patient prognosis.

For any given malignancy, TNM staging is one of the most powerful prognostic indicators of disease-specific survival. In general, the pathologic T category is defined by anatomic and histologic findings. The hollow viscus organs in the gastrointestinal tract have a well-defined anatomic layering, so it is easier to clarify T classification by anatomic layering, for example, the lamina propria, muscularis mucosa, submucosa, muscularis propria, subserosa, and serosa. However, for the biliary tree, it is difficult to define the bile duct boundary with obvious anatomic descriptions owing to a thin wall, sparse and incomplete smooth muscle, and abundant vascular and neural networks of periductal adipose tissue [8]. Moreover, particularly in cancer status, the bile duct boundary is commonly obscured by desmoplastic reactions and inflammation, which makes the distinction between T2 and T3 of the seventh edition AJCC more difficult in DBDC [7]. In addition to a problematic and unclear anatomic definition, the T category of the seventh edition AJCC staging system failed to reveal a significant relationship with patient outcome [7,13]. Conversely, the progressive new T category of the eighth AJCC for DBDC can be applied objectively and has shown reliable results in the prediction of patient outcome [9,12,13]. The predictive role of the T category of the eighth edition AJCC staging system for DBDC in terms of patient prognosis has been described in a few studies conducted in Western [9] and Eastern [13] countries. Previously, our group proposed a new T category measuring the depth of invasion in DBDCs and demonstrated its strong correlation with patient survival [9]. A validation study by Moon et al. [13] also reported that the T category of the eighth AJCC for DBDC was significantly associated with patient survival (p < 0.001) [13]. However, they did not observe a difference in survival among patients with T2 and T3 tumors (p=0.16), albeit differences were observed between T1 and T2 tumors (p=0.004). On the contrary, we revealed that the T category of the eighth AJCC staging system for DBDC discriminated patient survival in both pairwise (T1 and T2, p=0.011; T2 and T3, p < 0.001) and overall (p < 0.001) comparisons. This discrepancy may be related to the small number of T3 cases (13/117, 11.7%) analyzed in the previous study [13].

We also evaluated survival difference by Gonzalez's size-based criteria for staging in our DBDC cases, but could not find any survival differences. Based on our observations, the sized-based proposal by Gonzalez et al. [1] did not segregate patient survival of DBDCs. This result suggested that a T category based on invasion depth has more important survival implications than a T category based on cancer size in DBDCs, similar to T categories of other hollow viscus organs, such as stomach and colorectal cancers.

Several groups demonstrated a minimum of 10 lymph nodes should be examined for the precise evaluation of nodal status of DBDCs [13,21]. Schwartz and Smith analyzed the Surveillance, Epidemiology, and End Results (SEER) data and demonstrated that patient survival was strongly influenced by the total examined lymph node count [21]. Moon et al. [13] evaluated various cut-off values according to the number of total lymph nodes examined using 111 cases and revealed the cut-off value was 10 (1 to 9 vs. ≥ 10 of total number of nodes assessed) for differentiating patient survival time [13]. On the contrary, our group previously concluded that increasing retrieval of nodes does not affect patient survival in EBD carcinomas, but this study contained both perihilar cholangiocarcinomas and DBDCs and did not discriminate patient survival [22]. Therefore, we investigated the difference in patient survival time between groups with 1 to

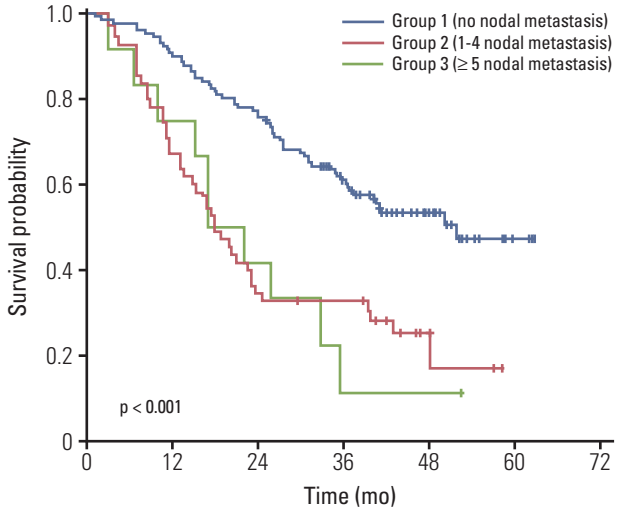

Fig. 5. Overall survival stratified by number of metastatic lymph nodes.

9 and 10 or more lymph nodes examined, using our present cases; however, no statistically significant differences were observed between the two groups (p=0.670, data not shown).

Including our present study, several previous studies demonstrated the prognostic significance of the 3 tiered N category [13,22,23,25]. In present study, we observed significant survival differences among DBDC patients based on N category of the eighth AJCC staging system in overall comparison and in pairwise comparison between N0 and N1 patients, similar to the previous studies [13,22,23,25]. However, there are discrepant results of patients' survival between N1 and N2 groups. We did not find significant survival difference between N1 and N2 patients, which was concordant with that of Kang et al.'s study [25]. However, different with the present study, previous results of Moon et al. [13] and Kiriyama et al. [23] demonstrated significant differences in survival between patients with N1 and N2 tumors [13,23]. Due to this discrepancy in patients' survival analysis between N1 and N2 groups, further multi-center studies with large number of cases are required for validating N category of the eighth AJCC staging system.

Our group previously proposed a different cutoff for nodal classification, comprising group 1 (no nodal metastasis), group 2 (1-4 nodal metastases), and group 3 (≥ 5 nodal metastases) [22]. However, our previous study included both perihilar cholangiocarcinomas and DBDCs [22]. We divided our present cases into group 1 (133 cases, 66.5%), group 2 (55, 27.5%), and group 3 (12, 6.0%) according to our previously proposed criteria for the N category, and demonstrated a statistically significant difference between three groups, similar to results of the N category of the eighth edition ($p < 0.001$) (Fig. 5). The median survival times of the patients in groups 2 and 3 (18.0 and 17.0 months, respectively) were shorter than that of patients in group 1 (51.8 months; $p < 0.001$, each). Meanwhile, there was no significant difference in survival time between the patients in groups 2 and 3 (p=0.765), similar to the results of the N category of the eighth edition. Consequently, further studies are needed to enhance the predictive role of the N category of DBDCs in terms of patient prognosis.

A few previous studies validated T category of the eighth AJCC staging scheme of DBDCs [13,25]. Moon et al. [13] demonstrated the superiority of the eighth edition to the seventh edition for predicting patient prognosis, similar to our study. Kang et al. [25] also reported significant survival differences of both pair-wise (T1 vs. T2, T2 vs. T3) and overall comparisons of the eighth edition of the AJCC staging scheme, while no survival difference was observed between T1 and T2 comparison of the seventh edition scheme. In concordance with the previous reports, the results of the present study strongly support that the T category of the eighth edition scheme can discriminate DBDC patients' survival better than the previous scheme.

On applying the depth of invasion in DBDCs, there are important things which pathologists and clinicians should be considered. For the pathologists, invasion to adjacent organs, such as direct spread into the pancreas, duodenum, gallbladder, colon, stomach, or omentum, are recommended to be reported in addition to T category, which was descried in the eighth edition AJCC cancer staging manual [14]. For the clinicians, currently preoperative radiologic evaluation for T category of DBDCs is not available due to lack of pathologic-radiologic correlation of depth of invasion of DBDCs. Therefore, further studies of pathologic-radiologic correlation of depth of invasion of DBDCs are required.

Our study has a few limitations. First, the present study was a single institutional study and included 200 cases. Although 200 cases were not small case number for statistical analysis, further multi-institutional or multi-national studies with larger number of cases and longer follow-up period are required for more solid conclusion. Second, no T4 cases were seen in the present study, because all included cases were only surgically resected cases. Therefore, the further study including both surgically resected and unresectable cases is required for survival comparisons between T3 and T4 groups.

In summary, the current eighth edition of the AJCC cancer staging system for DBDCs changed the T and N categories, which enhanced its ability to discriminate patient survival beyond that of the previous scheme of the seventh edition. Further changes are needed for better survival estimation in patients with DBDCs.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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