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Original Contribution

Validation of the T category for distal cholangiocarcinoma: Measuring the depth of invasion is complex but correlates with survival

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ABSTRACT

According to the current 8th edition of the American Joint Committee of Cancer (AJCC), the T category of distal cholangiocarcinomas is classified based on the depth of invasion (DOI) (T1, < 5 mm; T2, between 5 and 12 mm; T3, > 12 mm). In consideration of the discrepancies between previous studies about the prognostic significance, we aimed to validate the current AJCC T staging system of distal cholangiocarcinomas. DOI was measured using three different methods: DOI1, DOI2, and DOI3. DOI1 was defined and stratified according to the AJCC 8th edition. DOI2 was measured as the distance from an imaginary curved line approximated along the distorted mucosal surface to the deepest invasive tumor cells. DOI3 was defined as the total tumor thickness. DOI2 and DOI3 were also divided into three categories using the same cut-off points as in the AJCC 8th edition. We compared these three DOI methods to the AJCC 7th edition as well. In contrast with the AJCC 7th edition, all three groups showed a correlation with patients' overall survival. Above all, the DOI2 group demonstrated the best significance in multivariate analysis. However, when the C indices were compared between these groups, differential significance proved to be negligible (DOI1 vs DOI2, $p = 0.915$; DOI2 vs DOI3, $p = 0.057$). Therefore, the measurement of DOI does not need to be rigorously and stringently performed. In conclusion, we showed that the current T classification system better correlates with the overall survival of patients with distal cholangiocarcinomas than the previous system.

1. Introduction

Cholangiocarcinoma, an epithelial malignancy arising from the biliary tract, is notorious for late diagnosis and poor prognosis [1]. According to their primary locations, these malignancies can be divided into intrahepatic (inside the liver) and extrahepatic (outside the liver) cholangiocarcinomas. Extrahepatic cholangiocarcinomas are further subclassified into perihilar and distal cholangiocarcinomas. Although perihilar and distal cholangiocarcinomas occupy relatively short segment of the biliary tract, the staging system for these tumors is separately adopted due to their complex histology and different surgical approaches. Perihilar cholangiocarcinomas involve the right, left, or common hepatic duct where liver resection is frequently incorporated into surgical treatment. Distal cholangiocarcinomas involve common bile duct where pancreaticoduodenectomy is needed for curative surgery in many cases. Following surgical resection and pathological assessment, distal cholangiocarcinoma is staged based on the measured depth of invasion (DOI), in contrast with other biliary tract cancers. Accordingly, the distance from the established baseline to the deepest tumor portion should be measured in millimeters under the current staging system for distal cholangiocarcinomas.

The staging system for various cancers has been proposed by the American Joint Committee of Cancer (AJCC) since 1977. Thereafter, the AJCC Cancer Staging Manual has been widely used to evaluate the status of patients and the current 8th edition was published in 2016 [2]. The new system proposed for T stage classification of distal

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Table 1
Comparison of independent studies about the invasion depth of distal cholangiocarcinomas.

Study	No.	M:F ratio	Age (mean years)	AJCC 8th edition						Suggested cut-off points
				T1	T2	T3	Univariate analysis (OS)	Multivariate analysis (OS)	C-index	
Hong et al. [4]	222	2.42	60.2	99	95	28	$p < 0.001$	$p < 0.001$	–	Adj-depth, 5 & 12 mm
Moon et al. [6]	114	1.92	61.9	53	45	13	$p < 0.001$	$p = 0.009$	–	Adj-depth, 5 & 12 mm
Min et al. [7]	179	2.14	65.3	–	–	–	$p = 0.01$	$p = 0.07$	–	Adj-depth, 3 & 10 mm
Kang et al. [8]	293	1.88	65.2	59	155	78	$p < 0.001$	–	0.620 (−0.043 to 0.097[a])	–
Aoyama et al. [9]	404	2.01	70[b]	167	195	42	$p < 0.001$	–	0.624	Tot-depth, 1, 5, & 10 mm
Present study	106	1.41	67.3	66	34	5	$p < 0.001$	$p < 0.001$	0.699 (0.590 to 0.808[c])	Curv-depth, 5 & 12 mm

OS, overall survival; Adj-depth, tumor invasion depth measured from the adjacent mucosa; Tot-depth, total tumor thickness; Curv-depth, tumor invasion depth measured from the imaginary continuous curved mucosa.
[a] 95% confidence interval of difference with AJCC 7th T stage for C-index.
[b] Median.
[c] 95% confidence interval.

cholangiocarcinomas was one of the biggest changes introduced in that edition. According to the previous AJCC staging system (7th edition), the T stage was determined based on whether the tumor was confined to the bile duct wall. However, this system had been criticized for its ambiguous histological definition, difficulty in application, and above all, the lack of correlation of T stage with patient survival [3-5]. For that reason, the depth-based system was newly suggested to replace the layer-based system for a more accurate prediction of patient survival. Hence, in the 8th edition, the distance is measured from the adjacent normal or dysplastic epithelium to the deepest tumor cells for T stage (T1, < 5 mm; T2, between 5 and 12 mm; T3, > 12 mm).

The new classification of the T category has been proven to be prognostically significant by some studies but not by others [6-10] (Table 1). All studies reported that T stage defined according to the 8th edition were statistically meaningful in univariate survival analysis. A multivariate analysis, however, failed to retain the significance in one study [7]. In addition, some researchers indicated that the prognostic relevance of T stage classification based on the 8th edition was not stronger than that based on the 7th edition [8]. Alternatively, they redefined cut-off points other than 5 and 12 mm and introduced a different method for measuring the depth.

In consideration of the discrepancies between previous studies, we aimed to validate and verify the current AJCC T staging system (8th edition) of distal cholangiocarcinomas. We compared three different methods for measuring DOI and the AJCC 7th edition. For validation, multivariate survival analysis was performed and for verification, the C-index was calculated and values obtained for different systems were compared among the groups.

2. Materials and methods

2.1. Patients

This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (PNUYH) (approval number: 05-2019-061). We searched patients with the pathological diagnosis of “adenocarcinoma” or “cholangiocarcinoma” in the “bile duct” between 1 January 2009 and 31 December 2016 using the retrieval program of the PNUYH Total Medical Information System. Then, specimens from biopsy or palliative surgery were filtered out. After meticulously reviewing the pathology reports and macroscopic images, the perihilar, gallbladder, ampullary, and pancreas head cancers were excluded according to the definition of distal cholangiocarcinomas. A distal cholangiocarcinoma was defined as a cholangiocarcinoma whose center was located between the confluence of the cystic duct and common hepatic duct and the ampulla of Vater [2]. One patient had an unequivocal distal cholangiocarcinoma with an independent lesion of gallbladder carcinoma, so he or she was eliminated from the study. A total of 107 patients were confirmed to have undergone curative surgical treatment (pancreaticoduodenectomy, segmental resection, or Whipple procedure) for distal cholangiocarcinoma.

Clinical information such as age at diagnosis, gender, the operation date, the last follow-up date or the date of death was obtained from patients' electronic medical records. The survival time was calculated in months from the first operation date to either the date of death from any cause or the most recent follow-up. One patient with < 1 month of follow-up period was excluded and a total of 106 patients were included in the study.

2.2. DOI measurement

All hematoxylin-eosin slides of 106 patients were reviewed and histopathological features including tumor grade, tumor size, the previously defined T stage (based on the 7th edition), lymphovascular invasion, perineural invasion, and pancreas or duodenal invasion were analyzed. Numbers of examined and involved lymph nodes were also counted. Concurrently, the representative slide showing the deepest tumor invasion was selected. All selected slides were digitally scanned using the 3DHistech Pannoramic 250 Flash II scanner (3DHistech, Budapest, Hungary), and the depth of tumor invasion was measured using the 3DHistech CaseViewer software tool (version 2.3).

DOI was measured using three different methods, i.e., DOI1, DOI2, and DOI3 (Fig. 1). DOI1 was defined according to the AJCC 8th edition as the distance from the basement membrane of adjacent normal or dysplastic epithelium to the point of deepest tumor invasion [2]. DOI2 was measured as the distance from the imaginary curved line to the deepest invasive front. The imaginary curve was outlined taking the identifiable muscularis mucosa within tumor as the guide line. The curved line was traced from the adjacent normal or dysplastic epithelium and supposed to have a gentle curvature in order to preserve gradual transition between the neighboring tissues. DOI3 was defined as the distance from the top of the tumor surface to the bottom of the tumor (total tumor thickness), same as Moon's DoI2 and Aoyama's ITT (invasive tumor thickness) [6,9]. DOI1 was used to assign the T classification of the AJCC 8th edition: T1 (DOI1 < 5 mm), T2 (5 mm ≤ DOI1 ≤ 12 mm), and T3 (DOI1 > 12 mm). DOI2 and DOI3 were also divided into three groups using the same cut-off points as in the AJCC 8th edition.

2.3. Statistical analysis

Statistical analysis was conducted using the free version of R

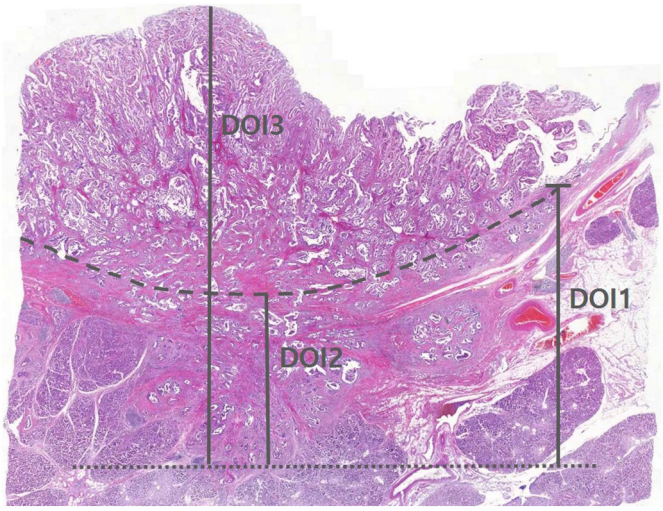

Fig. 1. Three different methods for measuring the depth of invasion: DOI1, DOI2, and DOI3. DOI1 was defined as the distance from the basement membrane of adjacent normal or dysplastic epithelium to the point of deepest tumor invasion. DOI2 was measured as the distance from the imaginary curved line to the deepest invasive front. DOI3 was defined as the distance from the top of the tumor surface to the bottom of the tumor (total tumor thickness).

software 3.6.0 [11]. Survival curves were plotted using the Kaplan-Meier method, and the significances of differences were calculated using the log-rank test and Cox proportional hazards model [12]. Variables that were statistically significant on univariate analysis were included in the multivariate analysis. p-Values of < 0.05 were considered significant. The degree of relevance between measured values was evaluated using Spearman's correlation coefficient. To compare the power of survival stratification between the different methods of measurement (DOI1, DOI2, and DOI3), values of the C-index were calculated and compared using the censored survival data [13].

3. Results

DOI1 and DOI2 could not be measured in one case and DOI3 was used as a substitute for these missing values in the following analysis (Fig. 2A).

3.1. Univariate survival analysis

The age of patients ranged from 27 to 90 years (median, 67 y), and the male to female ratio was 1.4. During a 35-month median follow-up period (range, 3–110 m), 54 of 106 patients (51%) deceased.

3.1.1. Variables other than T category (Table 2)

Male and female patients showed similar survival rate (42.9% and 45.9% respectively). The age at diagnosis did not show a correlation with patients' survival outcome either. Tumor characteristics associated with poor survival were as follows: size $\geq$ 3.5 cm ($p = 0.032$), poor differentiation ($p = 0.041$), lymphovascular invasion ($p = 0.018$), and regional lymph node metastasis ($p < 0.001$). The pancreas or duodenal invasion utilized to determine the T category of the AJCC 7the edition had no prognostic significance. A statistically non-significant

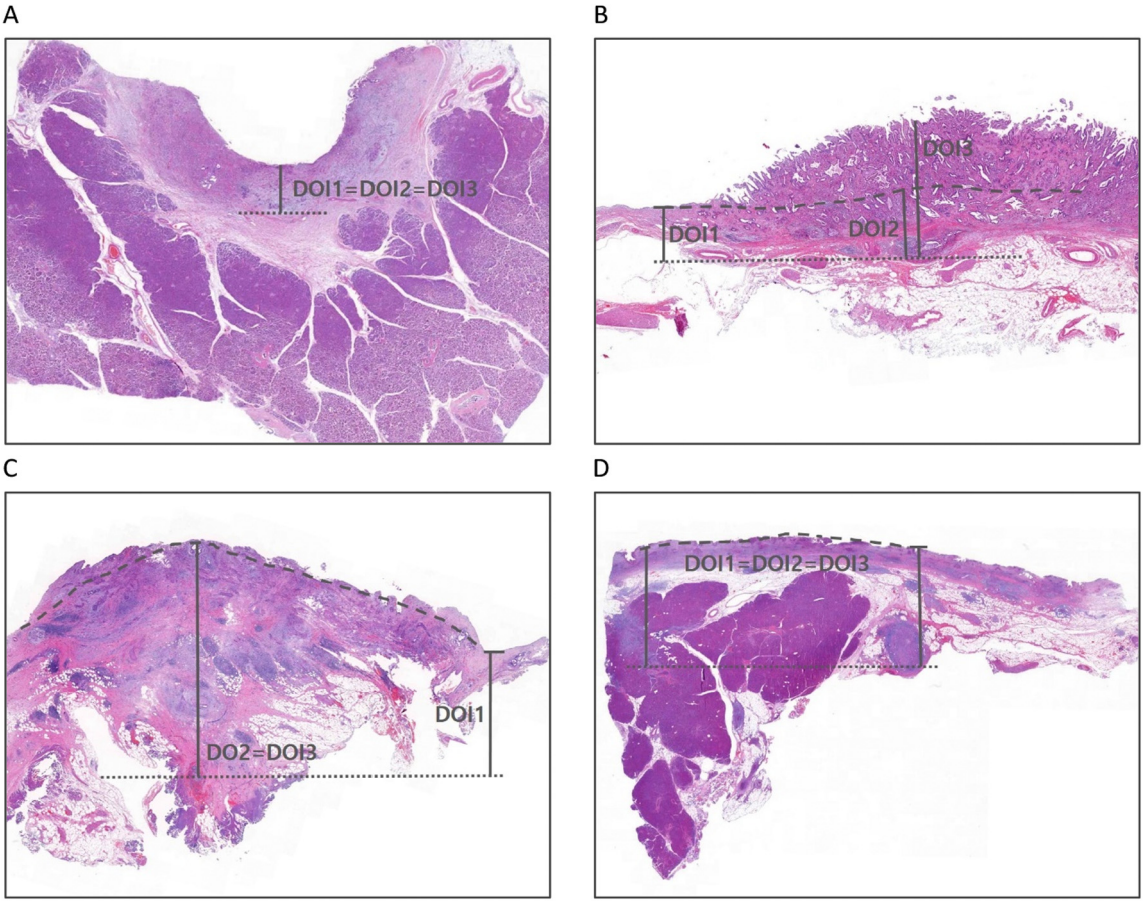

Fig. 2. The various conditions when DOI1, DOI2, and DOI3 were compared. (A) DOI1 and DOI2 could not be measured and DOI3 was used as substitute values. (B) DOI3 was the greatest and DOI2 was slightly greater than DOI1 (DOI3 > DOI2 > DOI1). (C) DOI1 was less than DOI2 and DOI3 that had the same values (DOI2 = DOI3 > DOI1). (D) The three values were all equal (DOI1 = DOI2 = DOI3).

Table 2
Clinicopathological characteristics and univariate survival analysis.

Variables	Characteristics	Number (%)	5-YSR (%) (95% CI)	HR (95% CI)	*p* value
Age[a]		67 (27–90)[b]		1.01 (0.97–1.04)	0.683
Gender	Male	62 (58%)	42.9 (31.0–59.3)	–	
	Female	44 (42%)	45.9 (32.4–64.8)	1.11 (0.64–1.91)	0.7
Tumor size	< 3.5 cm	75 (71%)	48.7 (37.6–63.2)	–	
	≥ 3.5 cm	31 (29%)	31.1 (17.0–57.1)	1.86 (1.06–3.28)	0.032‡
Tumor grade	Well	46 (43%)	47.3 (33.6–66.8)	–	–
	Moderately	45 (42%)	47.4 (33.6–67.0)	1.19 (0.65–2.17)	0.6
	Poorly	15 (14%)	24.0 (9.3–61.9)	2.14 (1.03–4.44)	0.041‡
Pancreas invasion	Absent	54 (51%)	50.5 (37.3–68.3)	–	–
	Present	52 (49%)	37.0 (25.0–54.7)	1.50 (0.88–2.56)	0.14
Duodenal invasion	Absent	101 (95%)	46.4 (36.8–58.5)	–	–
	Present	5 (5%)	–	1.68 (0.60–4.66)	0.3
Lymphovascular invasion	Absent	77 (73%)	49.0 (37.8–63.5)	–	–
	Present	29 (27%)	30.2 (16.6–55.2)	1.95 (1.12–3.39)	0.018‡
Perineural invasion	Absent	17 (16%)	60.0 (36.7–98.5)	–	–
	Present	89 (84%)	40.3 (30.5–53.3)	2.34 (0.93–5.87)	0.071
Resection margin	Negative	99 (93%)	45.3 (35.6–57.8)	–	
	Positive	7 (7%)	–	1.9 (0.68–5.31)	0.2
N category (AJCC 7th)	N0	75 (71%)	51.9 (40.8–66.1)	–	–
	N1	31 (29%)	19.8 (73.1–53.6)	3.03 (1.72–5.35)	< 0.001‡
N category (AJCC 8th)	N0	75 (71%)	51.9 (40.8–66.1)	–	–
	N1	23 (22%)	26.0 (9.9–68.7)	2.45(1.29–4.65)	0.006‡
	N2	8 (8%)	–	6.35 (2.70–15.0)	< 0.001‡

5-YSR, 5-year survival rate; CI, confidence interval; HR, relative hazards ratio; AJCC, American Joint Committee on Cancer; N, regional lymph nodes.
[a] Continuous variables.
[b] Median years (range).
‡ Statistically significant ($p < 0.05$).

Table 3
Relation among three values of depth of invasion (DOI) acquired from different methods: DOI1 (identical to the AJCC 8th edition), DOI2 (newly devised in this study), and DOI3 (identical to total tumor thickness).

Relationship	Number (%)
DOI3 > DOI1 > DOI2	31 (29%)
DOI3 > DOI2 > DOI1	44 (42%)
DOI3 > DOI1 = DOI2	1 (1%)
DOI3 = DOI1 > DOI2	1 (1%)
DOI3 = DOI2 > DOI1	5 (5%)
DOI3 = DOI1 = DOI2	10 (9%)
DOI1 > DOI3 > DOI2	10 (9%)
DOI1 > DOI2 > DOI3	0 (0%)
DOI1 > DOI2 = DOI3	3 (3%)
DOI1 = DOI2 > DOI3	0 (0%)
DOI2 > DOI3 > DOI1	1 (1%)
DOI2 > DOI3 = DOI1	0 (0%)
DOI2 > DOI1 > DOI3	0 (0%)
Total	106 (100%)

trend of perineural invasion correlating with shorter survival time was noted ($p = 0.071$).

3.1.2. Comparison of DOIs

In more than two-thirds of the cases (82 of 106 cases), DOI3 was the greatest among the three different values (Table 3). Above all, the case of DOI3 > DOI2 > DOI1 was the most predominant (Fig. 2B). DOI3 was the second greatest in 14 cases and was not less than other values. Occasionally, two of the three values were equal to each other (Fig. 2C). Three values were equal (DOI1 = DOI2 = DOI3) in 10 cases (Fig. 2D), including one case in which DOI1 and DOI2 could not be measured and DOI3 was used instead.

The T category of the AJCC 7th edition had no discriminating effect on either of the subgroup (Table 4). The median values of DOI were as follows: 4.1 mm (range, 0.3–26.9 mm) for DOI1, 4.6 mm (range, 0.4–27.4 mm) for DOI2, and 5.8 mm (range, 0.4–27.8 mm) for DOI3. There was a pairwise correlation between DOIs showing the following r_s values: 0.817 for DOI1 vs DOI2 ($p < 0.001$), 0.709 for DOI1 vs DOI3 ($p < 0.001$), and 0.827 for DOI2 vs DOI3 ($p < 0.001$). The prognostic significance decreased slightly in the following order: DOI2 being the

Table 4
Comparison of survival analysis according to the classification of T category and invasion depth.

		n = 106	5-YSR (%) (95% CI)	HR (95% CI)	*p* value
T category (AJCC 7th)	T1	9	76.2 (52.1–100.0)	–	
	T2	45	45.9 (32.1–65.8)	2.71 (0.64–11.5)	0.2
	T3	52	37.0 (25.0–54.7)	3.55 (0.85–14.9)	0.083
DOI1 - T category (AJCC 8th)	T1	66	51.8 (39.9–67.3)	–	
	T2	34	32.4 (18.9–55.6)	1.84 (1.05–3.23)	0.034*
	T3	5	–	4.53 (1.54–13.4)	0.006*
DOI2	< 5 mm	58	61.8 (49.6–76.9)	–	
	5–12 mm	43	22.1 (11.1–43.9)	2.90 (1.64–5.12)	< 0.001*
	> 12 mm	5	–	6.16 (2.03–18.7)	0.001*
DOI3	< 5 mm	37	60.8 (45.7–80.7)	–	
	5–12 mm	57	39.9 (27.7–57.5)	1.90 (0.99–3.62)	0.053
	> 12 mm	12	12.5 (2.3–68.3)	4.56 (1.98–10.5)	< 0.001*

5-YSR, 5-year survival rate; CI, confidence interval; HR, relative hazards ratio; AJCC, American Joint Committee on Cancer; DOI, depth of invasion.
* Statistically significant ($p < 0.05$).

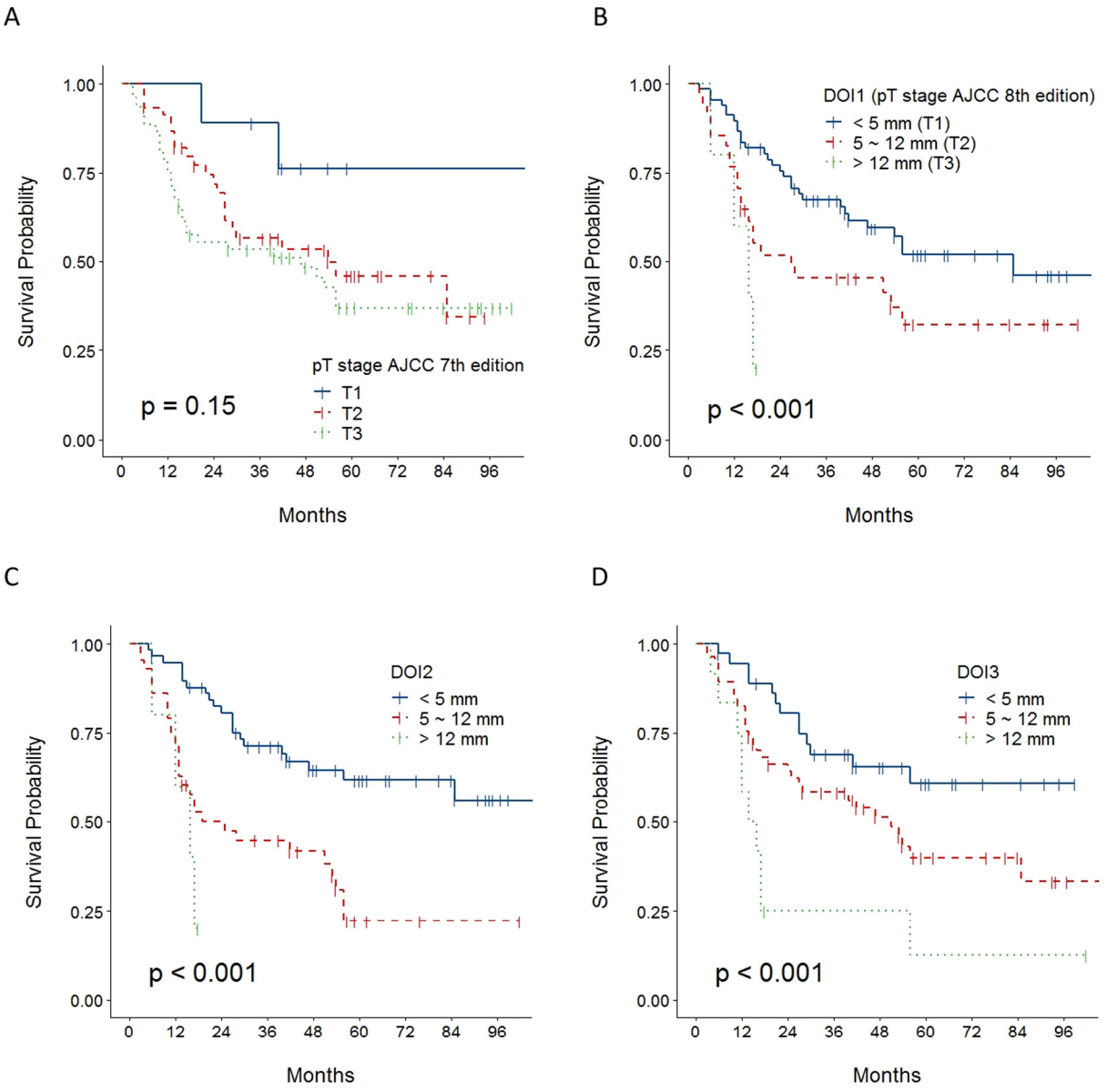

Fig. 3. Kaplan-Meier survival analysis according to (A) the classification of the T category based on the 7th AJCC system, (B) DOI1, (C) DOI2, and (D) DOI3. The patient groups DOI1, DOI2 and DOI3 were all prognostically well classified with cut-off values of 5 and 12 mm.

highest, followed by DOI3 and DOI1 (Fig. 3).

3.2. Multivariate survival analysis (Table 5)

The DOI1 (T category of the AJCC 8th edition), DOI2, and DOI3 groups were analyzed for survival by incorporating the following parameters: tumor size, grade, lymphovascular invasion, and lymph node metastasis. Unexpectedly, the DOI2 group showed the best correlation with patient survival and demonstrated a similar significance for such correlation with lymph node metastasis. In contrast, the influence of the DOI1 and DOI3 groups was behind the effect of lymph node metastasis.

3.3. C-index

The C-indices were 0.658 for the 7th T category ($p = 0.008$), 0.699 for the 8th T category ($p < 0.001$), 0.761 for DOI2 group ($p < 0.001$) and 0.703 for DOI3 group ($p < 0.001$). The extent of significance was the highest in the DOI2 group. Differential significance between the C-indices proved to be negligible (DOI1 vs DOI2, $p = 0.915$; DOI2 vs DOI3, $p = 0.057$).

4. Discussion

In this study, the patient groups DOI1, DOI2 and DOI3 were all prognostically well classified with cut-off values of 5 and 12 mm. In particular, results from the DOI2 group revealed that this method was the best measuring approach. While DOI1 is used as a proven method for the current AJCC T staging, it is sometimes difficult to obtain accurate quantifications using this method.

To take a measurement of the distance, two points are needed. One of these points is the deepest invasive front of the tumor, which can be effortlessly located. For DOI1, the other point is the basement membrane of the adjacent normal or dysplastic epithelium. However, that is a line and not a point. Furthermore, it is an irregularly curved line that is often difficult to identify. The investigators who proposed the depth-based system noted that the layer-based system has limited applicability due to the desmoplastic stromal reaction, which is a

Table 5
Comparison of multivariate survival analysis according to the invasion depth.

	DOI1 - T category (AJCC 8th)		DOI2		DOI3	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
DOI1						
< 5 mm	–					
5–12 mm	1.39 (0.77–2.51)	0.277				
> 12 mm	3.41 (1.04–11.19)	0.043*				
DOI2						
< 5 mm			–			
5–12 mm			2.10 (1.12–3.96)	0.021*		
> 12 mm			5.01 (1.42–17.73)	0.012*		
DOI3						
< 5 mm					–	
5–12 mm					1.60 (0.82–3.10)	0.166
> 12 mm					3.15 (1.17–8.45)	0.023*
Size (≥ 3.5 cm)	1.18 (0.90–1.53)	0.235	1.19 (0.91–1.56)	0.200	1.15 (0.87–1.51)	0.325
Grade						
Well						
Moderately	1.13 (0.61–2.11)	0.692	1.06 (0.57–1.98)	0.849	1.11 (0.59–2.08)	0.742
Poorly	1.31 (0.58–2.94)	0.513	1.27 (0.58–2.77)	0.544	1.07 (0.44–2.65)	0.877
Lymphovascular invasion	1.09 (0.54–2.17)	0.813	1.25 (0.62–2.52)	0.527	1.13 (0.56–2.29)	0.726
LN metastasis	4.95 (1.75–13.97)	0.003*	3.98 (1.40–11.31)	0.010*	4.68 (1.66–13.18)	0.004*

AJCC, American Joint Committee on Cancer; DOI, depth of invasion; HR, relative hazards ratio; CI, confidence interval; LN, lymph node.
* Statistically significant ($p < 0.05$).

characteristic feature of extrahepatic cholangiocarcinoma. Although the depth-based system was developed to resolve the problem caused by the desmoplastic reaction, the measurement of invasion depth was also difficult because of the desmoplastic reaction.

Part of the problem resides in the fact that distal cholangiocarcinoma grows in the narrow and complex luminal structure. So, in some cases, the surgical specimens were cut perpendicularly along the long axis of the bile duct, making it impossible to measure DOI1. For example, in Aoyama's study, DOI1 (for T category of the AJCC 8th edition) could not be measured in more than half of the cases (222 of 404 cases) [9]. Instead, DOI3 (a total tumor thickness) was used as an alternative parameter to determine and analyze the T category of the AJCC 8th edition. Despite the alternative approach, their results showed a significant survival discrimination between T1 vs T2 ($p < 0.001$) and T2 vs T3 ($p = 0.001$). Thus, we inferred that the flexible approach to the measurement could be acceptable.

Although the relationship among DOI1, DOI2, and DOI3 was mostly dependent on the tumor growth pattern, DOI3 was the greatest in more than two-thirds of the cases. This is a natural consequence since DOI3 is defined as the total depth of the tumor. In tumors accompanied by surface erosion, DOI3 was the second greatest. DOI1 was usually greater than DOI2 and DOI3 in ulcerative tumors. Meanwhile, DOI2 tended to decrease in tumors with exaggerated desmoplastic reaction, which pulled down the level of the mucosa. All three different measurements were equal (DOI1 = DOI2 = DOI3) in 10 cases, which were flat (9 cases), or unmeasurable (1 case) tumors.

DOI3 or total tumor thickness is relatively easy to measure and shows a correlation with patient survival still significantly. Although the cut-off values were applied differently, both Moon's and Aoyama's study verified that the deeper DOI3 was, the shorter the patients lived. Our data showed the same results.

In case of DOI2, despite the unexpectedly strong relevance with the survival time, it is the most subjective way of measuring. This approach is modified from the method used for measurement of the invasion depth of submucosal invasive colorectal carcinoma [14]. This method is quite complicated and interobserver discordance was presented [15]. However, the main idea used in that approach is that the choice of the baseline for the measurement was not fixed but adjusted to the shape of the tumor and neighboring mucosa. Thus, we drew a line along the silhouette of the muscularis mucosa of distal cholangiocarcinoma and measured DOI2 using this line as a reference. Although DOI2 gave superior results with regards to the survival analysis than DOI1 and DOI3, the difference was not significant when the C-index was compared.

The current AJCC 8th edition accomodates Hong's suggestion that the use of DOI would better predict prognosis as opposed to the previous 7th edition [2,5]. Hong's method for measuring and stratifying DOI has also been adopted without modification in the AJCC 8th edition. This method, however, requires careful gross sectioning of the bile duct so that the deepest tumor invasion (from the basal lamina of the adjacent normal or dysplastic epithelium) can be measured. According to the AJCC 8th edition, a best estimate should be given when the depth of invasion is difficult to measure. However, Aoyama et al. strictly applied Hong's definition and categorized 222 of 404 cases (55%) as unmeasurable because the basal lamina of the bile duct was not observable in those cases [9]. On the contrary, Kang et al. took Hong's definition more arbitrarily [8]. Although their method was explicitly described based on guidelines of the AJCC 8th edition (i.e., Hong's definition), they actually measured a total tumor thickness depicted in their figures rather than measuring from the basal lamina of the adjacent normal or dysplastic epithelium. Nevertheless, according to Kang's findings, the T category of the AJCC 8th edition gave better survival correlation (T1 vs. T2, $p = 0.001$; T2 vs. T3, $p = 0.014$) than those of the 7th edition. We, therefore, deduced that there was no need to rigorously and stringently measure DOI of distal cholangiocarcinomas. Rather, a relatively subjective measurement can be an acceptable approach in clinical practice.

Pathologists measure macroscopically and microscopically lengths, depths, areas or volumes of variable organs, tumors, lesions and cells on a relative or absolute scale every day. Sometimes, it is a challenging task to measure those values accurately. However, as Hong mentioned, the values given by pathologists are still the best estimate.

In conclusion, we showed that the current T classification system better correlates with the overall survival of patients with distal cholangiocarcinomas than the previous system. Nonetheless, the modified cut-off values may be accommodated through further explorations.

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