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Depth of tumor invasion better predicts prognosis than the current American Joint Committee on Cancer T classification for distal bile duct carcinoma

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Abstract

Background—The American Joint Committee on Cancer (AJCC) T classification system for cholangiocarcinoma does not take into account the unique pathologic features of the bile duct. As such, the current AJCC T classification for distal cholangiocarcinoma may be inaccurate.

Methods—A total of 147 patients with distal cholangiocarcinoma were identified from a single institution database. The prognostic importance of depth of tumor invasion relative to the AJCC T classification system was assessed.

Results—The AJCC T classification was T1 ($n = 11$, 7.5%), T2 ($n = 6$, 4.1%), T3 ($n = 73$, 49.7%), or T4 ($n = 57$, 38.8%). When cases were analyzed according to depth of tumor invasion, most lesions were ≤ 5 mm (<5 mm, 9.5%; range, 5–12, 51.0%; >12 mm, 39.5%). The AJCC T classification was not associated with survival outcome (median survival, T1, 40.1 months; T2, 14.8 months; T3, 16.5 months; T4, 20.2 months; $P = .17$). In contrast, depth of tumor invasion was associated with a worse outcome as tumor depth increased (median survival, <5 mm, not reached; range, 5–12, 28.9 months; >12 mm, 12.9 months; $P = .001$). On multivariate analyses, tumor depth remained the factor most associated with outcome (<5 mm; hazard ratio [HR] = referent vs 5–12 mm; HR = 3.8 vs >12 mm; HR = 6.7 mm; $P = .001$).

Conclusion—The AJCC T classification for distal cholangiocarcinoma does not accurately predict prognosis. Depth of the bile duct carcinoma invasion is a better alternative method to determine prognosis and should be incorporated into the pathologic assessment of resected distal cholangiocarcinoma.

Cholangiocarcinoma is an epithelial cancer originating from bile duct epithelium. The median survival for advanced cholangiocarcinoma is less than 24 months.¹ Although

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cholangiocarcinoma accounts for only 5% of cancer-related deaths in the United States, the incidence of cholangiocarcinoma has been increasing over the last 4 decades.² Surgery remains the only curative option for patients with cholangiocarcinoma, with a 5-year survival rate ranging from 9% to 41% for patients undergoing resection of extrahepatic cholangiocarcinoma.^{3–6} Recent data from our own group have suggested that survival after curative resection of cholangiocarcinoma may have been increasing over the last 3 decades.⁷

Despite these trends, the staging system for cholangiocarcinoma remains inadequate. Specifically, the current T classification of the American Joint Committee on Cancer (AJCC) staging system for cholangiocarcinoma⁸ has been criticized as being prognostically inaccurate.^{9–11} Furthermore, terminology used by the AJCC to define T1 and T2 disease, such as “confined to the bile duct histologically” and “beyond the wall of the bile duct” are vague, and provide no precise anatomic landmarks to define the true extent of disease.¹² Precise definitions of extent of invasion are particularly important with cancers of the bile duct because the bile duct wall, in contrast to other gastrointestinal tract organs, is not uniformly concentric along its length. Rather, the bile duct wall is composed of varying amounts of fibrous tissue or loose connective tissue. A more precise and reproducible definition of the T classification for cholangiocarcinoma is therefore needed.

Previously, our group has proposed using “depth of invasion” as an alternative method to overcome these problems in the current AJCC staging system T classification.¹⁰ Although depth of tumor invasion was shown to predict outcome,^{9,10} there were a number of concerns raised about using it as a prognostic marker. First, the studies on which some of these concerns were based combined hilar and distal cholangiocarcinomas, which in fact may be inappropriate given the distinct biologic behavior¹³ and management of these diseases. Perhaps more importantly, there was concern that the use of depth of tumor invasion might be difficult to reproduce among pathologists. Previous data were also exclusively derived from a single East Asian institution, and so it was not known if these results could be reproduced in other institutions.

Therefore, the objective of the current study was to empirically evaluate the prognostic validity of the current AJCC cancer staging system for distal cholangiocarcinoma using data from the United States. We additionally investigated which clinicopathologic determinants were most associated with survival after resection of distal cholangiocarcinoma. Specifically, we sought to analyze the prognostic importance of depth of tumor invasion and, in turn, propose a new T classification system with specific relevance to distal cholangiocarcinoma.

PATIENTS AND METHODS

Between January 1, 1984, and December 31, 2004, a total of 210 patients underwent pancreati-coduodenectomy for distal cholangiocarcinoma with curative intent at the Johns Hopkins Hospital, Baltimore, MD. Only patients with documented distal cholangiocarcinoma as defined by disease located below the margin of the duodenum were included. Cases of carcinoma arising in the ampulla of Vater or the pancreas, as well as carcinomas with obvious precancerous epithelial changes in the ampulla of Vater or pancreas, were excluded. Of the 210 cases of distal cholangiocarcinoma, 63 were excluded from the study (32 patients had incomplete follow-up and 31 patients had an insufficient number of slide sections available for re-evaluation and measurement of depth of tumor invasion). Based on these various exclusion criteria, 147 patients with distal cholangiocarcinoma remained for analysis. The Johns Hopkins Institutional Review Board approved this study.

The following data were collected for each patient: demographics; operative details; resection margin status; tumor size and grade; histologic subtype (eg, papillary carcinoma, adenocarcinoma, adenosquamous); presence of lymph node metastasis; presence of perineural and/or vascular invasion; invasion of adjacent pancreas and/or duodenum; and survival status. In addition, data on the maximal depth of tumor invasion were assessed. Specifically, each case was reviewed by 2 independent pathologists (S.M.H. and R.A.A.). Depth of tumor invasion was measured on slides containing the primary tumor and was defined as the area of deepest infiltration from the mucosal surface (eg, from the basal lamina of the adjacent normal epithelium to the most deeply advanced tumor cells). In cases containing carcinoma in situ (CIS) at the periphery of the invasive tumors, the basal lamina of the CIS was used as the reference. Based on our previous work, maximum depth of tumor invasion was categorized into 3 groups: <5 mm; 5–12 mm; and >12 mm.^{9,10}

All statistical analyses were performed using SPSS statistical software (v.17; SPSS, Chicago, IL) and The R Project for Statistical Computing R (<http://www.r-project.org>). Summary statistics were obtained using established methods and presented as percentages, mean, and median values. Chi-square statistics were used to compare frequencies of categorical variables among groups. *P* values less than .05 were considered statistically significant. Variables that were significant on univariate analysis (eg, *P* < .05) were included in the multivariate models. Survival analyses were performed according to the Kaplan-Meier method (log-rank test). Cox proportional-hazards regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI).

RESULTS

Table I shows the clinicopathologic features of the 147 patients in the study. The mean patient age was 61 years (range, 44–92), and the majority of patients were male (61.2%). At the time of the operation, the overwhelming majority (90.5%) of patients underwent an R0 resection, which is defined by the International Union Against Cancer (UICC) and AJCC (UICC/AJCC) staging system as a resection in which there is “no macroscopic or microscopic residual tumor.” On pathologic review, the mean size of the primary neoplasm was 2.0 cm (range, 0.3–8.0) with most neoplasms being either moderately differentiated (*n* = 99; 67.3%) or poorly differentiated (*n* = 43; 29.3%). The majority of patients (*n* = 93; 63.3%) had nodal metastasis associated with the primary neoplasm. Perineural or microscopic vascular invasion was identified in 66.7% (*n* = 98) and 25.9% (*n* = 38) of patients, respectively.

With regard to the extent of local disease, the distal cholangiocarcinoma invaded into the adjacent pancreas or duodenum in 87.1% and 38.8% of cases, respectively. Using the current AJCC T classification, of the 147 distal cholangiocarcinoma lesions, only 11 (7.5%) and 6 (4.1%), respectively, were categorized as T1 and T2. Of the 147 cases, the majority (130 cases) were either T3 (*n* = 73; 49.7%) or T4 (*n* = 57; 38.8%). When cases were analyzed according to depth of tumor invasion, most lesions were 5 mm (<5 mm, *n* = 14, 9.5%; 5–12 mm, *n* = 75, 51.0%; >12 mm, *n* = 58, 39.5%).

At a median follow-up of 16.8 months (range, 1.1–134.2), 3- and 5-year overall survival rates were 33% and 18%, respectively, with a median survival of 20.3 months. On univariate analysis, a number of clinicopathologic factors were associated with survival. Specifically, significant predictors of poor survival included lymph node metastasis, the presence of perineural or microscopic vascular invasion, invasion into the adjacent pancreas, as well as depth of tumor invasion (Table II). Patients with lymph node metastasis had a median survival of 15.0 months compared with 40.8 months for those without nodal metastasis (*P* = .003). The presence of perineural and microscopic vascular invasion were also associated

with a poor prognosis. Whereas patients with no perineural invasion had a median survival of 31.4 months, those with peri-neural invasion had a median survival of 14.7 months ($P < .001$). Similarly, the presence of microscopic vascular invasion was associated with a significantly worse long-term outcome. Patients with microscopic vascular invasion had a median survival of 12.1 months compared to 24.5 months for patients without microscopic vascular invasion ($P < .0001$).

Univariate analysis revealed no significant difference in survival based on age, sex, tumor histology, or histologic grade. Perhaps, most interestingly, statistical analyses also showed that the AJCC T classification was not associated with survival outcome in patients undergoing resection of distal cholangiocarcinoma. The median survival of patients with T1, T2, T3, and T4 lesions were 40.1, 14.8, 16.5, and 20.2 months, respectively ($P = .17$) (Fig 1). In fact, there was no difference in overall survival in comparisons of T1–T2 lesions ($P = .51$), T2–T3 lesions ($P = .36$), or T3–T4 lesions ($P = .99$).

Unlike the AJCC T classification, depth of tumor invasion was a strong predictor of long-term outcome ($P < .0001$) (Fig 2). Patients with a distal cholangiocarcinoma lesions measuring >12 mm had a median survival of only 12.9 months (95% CI, 10.5–15.5 months) compared with 28.9 months (95% CI, 11.3–39.5 months) for patients with distal cholangiocarcinoma lesions measuring 5 to 12 mm ($P = .001$). The median survival of patients with distal cholangiocarcinoma measuring <5 mm had not been reached ($P = .005$). These data corresponded to 5-year survival rates of 69.3%, 21.5%, and 4.1% for patients with distal cholangiocarcinoma lesions measuring <5 mm, 5–12 mm, and >12 mm, respectively ($P < .001$).

Increasing tumor depth was associated with an increased likelihood of having other adverse pathologic tumor characteristics. Specifically, those patients with a depth of tumor invasion >12 mm were significantly more likely to have lymph node metastasis, perineural invasion, and invasion into the adjacent pancreas (Table III). To assess whether depth of tumor invasion would remain a predictor of disease-specific death after adjusting for these factors, multivariate analyses were performed. As noted in Table IV, after adjusting for adverse pathologic factors such as lymph node metastasis, perineural and microscopic vascular invasion, as well as invasion into the adjacent pancreas, depth of tumor invasion remained the most potent predictor of survival.

Depth of tumor invasion was associated with an incrementally higher risk of disease-specific death as tumor depth increased (Table IV). Patients with a distal cholangiocarcinoma measuring 5 to 12 mm or >12 mm had more than a 3-fold or 6-fold increased risk of death, respectively, compared with patients who had a lesion measuring <5 mm (<5 mm, referent; 5–12 mm, HR = 3.8; >12 mm, HR = 6.7; both $P < .05$).

Based on these data, we proposed a revised stage grouping (Table V). Survival of patients based on the current, 6th edition of the *AJCC Cancer Staging Manual*⁸ T and N stage groupings was compared to the newly proposed staging system. As noted in Figure 3, the AJCC stage grouping had a poor ability to discriminate survival outcome among patients undergoing resection of distal cholangiocarcinoma. Specifically, the median survival of patients with stage IA, IB, IIA, IIB, and III disease was 40.8, 14.8, 39.6, 14.4, and 20.2 months, respectively ($P = .15$) (Fig 3). In fact, there was no difference in overall survival comparing a stage IA lesion to a stage IB lesion ($P = .24$), stage IB to IIA lesions ($P = .88$), stage IIA to IIB lesions ($P = .11$), or stage IIB to III lesions ($P = .47$).

In contrast, the newly proposed stage grouping was a strong predictor of long-term outcome ($P < .0001$) (Fig 4). Using the newly proposed staging system that incorporated depth of tumor invasion, patients with stage III lesions had a median survival of only 14.7 months

(95% CI, 11.1–18.3 months) compared with 36.5 months (95% CI, 19.5–53.5 months) for patients with stage II disease ($P = .01$). The median survival of patients with stage I distal cholangiocarcinoma had not been reached (proposed stage I vs II, $P = .02$; proposed stage I vs III, $P < .0001$). These data corresponded to 5-year survival rates of 69.3%, 28.7%, and 8.5% for patients with distal cholangiocarcinoma lesions with stage I, II, and III disease, respectively ($P < .0001$).

DISCUSSION

Cholangiocarcinoma has an annual incidence of about 1 in 100,000 in the United States,¹⁴ and its incidence is increasing at a rate faster than hepatocellular carcinoma. Resection remains the cornerstone of curative therapy for cholangiocarcinoma. The most optimal utilization of the pathologic specimen for staging, however, remains ill defined. In fact, current AJCC staging for cholangiocarcinoma fails to reflect the distinct biology of the disease. The AJCC staging system combines both proximal and distal extrahepatic cholangiocarcinoma into a single T classification scoring scheme.⁸ The combination of proximal and distal cholangiocarcinoma lesions into a single staging system may be inappropriate.¹³ Furthermore, the use of vague terms to define the extent of disease may be misleading,¹² as noted previously.

The current study is important because it critically assessed the performance of the current AJCC T classification system in a cohort of patients exclusively with distal cholangiocarcinoma. In addition, to our knowledge, this study is the first to investigate the prognostic importance of depth of tumor invasion in a Western series of patients with distal cholangiocarcinoma. Our data have important implications, because we found the current AJCC T staging systems to poorly stratify patients after resection of distal cholangiocarcinoma. Rather, depth of the bile duct carcinoma invasion was found to be a much better alternative method to determine prognosis than the current AJCC T classification scheme.

Currently, the AJCC T staging system uses tumor location within the extrahepatic bile duct to help categorize patients into prognostic groups (eg, T2 vs T3). For example, 2 neoplasms with the same depth of invasion in different portions of the bile duct may have different T classifications under the current staging system because of the different surrounding structures, such as the liver or pancreas, according to the portion of the bile duct. However, the fact that a smaller neoplasm invades the pancreas (T3) compared with a larger lesion that has no evidence of pancreas invasion (T2) due to its location may be more a reflection of anatomy than biology. Our data support this theory, as patients with T2 versus T3 lesions had comparable median survival (T2, 14.8 months vs T3, 16.5 months; $P = .36$). In fact, the failure of the current AJCC T staging system was particularly striking (Fig 3). The AJCC T classification scheme failed to demonstrate statistically significant differences in survival between any of the T subgroups.

In contrast, depth of tumor invasion of the distal cholangiocarcinoma was decidedly a predictor of survival when analyzed either as a continuous or categorical variable (Table III, Fig 4). Whereas the median survival had not been reached for patients with neoplasms measuring <5 mm, the median survival of patients with lesions measuring >12 mm was only 12.9 months. Previous data have also noted the prognostic importance of depth of tumor invasion for cholangiocarcinoma.^{9,10} Furthermore, other investigators have noted that a lack of tumor invasion, such as extra-hepatic bile duct carcinomas with extensive intra-epithelial ductal spread, carry a much better prognosis.^{15–18}

The current study serves to both independently confirm depth of tumor invasion as an important prognostic factor in a Western cohort of patients with distal cholangiocarcinoma, as well as demonstrate that depth of tumor invasion remains discriminatory in its ability to stratify patients with regard to overall survival even after adjusting for competing risk factors (eg, lymph node metastasis, perineural and microscopic vascular invasion, as well as invasion into the adjacent pancreas) (Table IV). Other important pathologic risk factors associated with survival included lymph node metastasis and the presence of perineural or microscopic vascular invasion. Similar to most other solid gastrointestinal malignancies, the presence of metastatic disease in the regional lymph nodes was associated with a significantly worse outcome in this study. In fact, patients without lymph node metastasis had a median survival that was more than twice as great as patients with nodal metastasis (Table II). Peri-neural invasion and vascular invasion also portended a worse long-term outcome, as others have noted similarly.^{19–21}

Unlike other studies, however, we were able to show that these adverse pathologic factors were significantly more likely to be present in patients with cholangiocarcinoma with a greater depth of tumor invasion (eg, >12 mm) (Table III). These data suggest that a greater depth of tumor invasion portends poor tumor biology and, as expected, a worse overall survival. Interestingly, after controlling for these other poor prognostic factors, depth of tumor invasion remained an independent predictor of outcome. As such, these data imply that, even in the presence of other competing risk factors, depth of tumor invasion may be the single best factor to predict outcome.

The current study had a number of limitations. Depth of tumor invasion was assessed only in a cohort of patients with distal cholangiocarcinoma. Whether depth of tumor invasion is an accurate predictor of outcome in patients with mid-duct or hilar cholangiocarcinoma will need to be examined in future studies. Furthermore, whereas depth of tumor invasion was strongly associated with outcome, measurement of tumor depth is not performed routinely for bile duct neoplasms; pathologists will need to learn how to take these measurements reproducibly. There is, however, precedent in other types of neoplasms (eg, melanoma) for using depth of tumor invasion as a standard prognostic factor. Although there was good concordance between the 2 pathologists (S.M.H. and R.A.A.) in the current study, additional studies are needed to determine the concordance rates of depth of cholangiocarcinoma tumor invasion measurements among pathologists across institutions.

In conclusion, the current AJCC T classification for distal cholangiocarcinoma does not accurately stratify patients with regard to prognosis. Depth of the bile duct carcinoma invasion is a better method for determining prognosis and should be incorporated routinely into the pathologic assessment of resected distal cholangiocarcinoma.

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Fig 1.

Kaplan-Meier survival analysis stratified according to the current 6th edition of the *AJCC Cancer Staging Manual* T classification staging scheme. There was no significant survival difference among the groups ($P = .17$).

Fig 2.

Kaplan-Meier survival analysis stratified according to depth of tumor invasion. Unlike the American Joint Committee on Cancer (AJCC) T classification, depth of tumor invasion was a strong predictor of long-term outcome. The 5-year survival rates of patients with distal cholangiocarcinoma lesions measuring <5 mm, 5–12 mm, and >12 mm were 69.3%, 21.5%, and 4.1%, respectively ($P < .0001$).

Fig 3.

Kaplan-Meier survival analysis stratified according to the current 6th edition of the *AJCC Cancer Staging Manual* stage grouping scheme. There was no significant survival difference among the stage groups ($P = .15$).

Fig 4.

Kaplan-Meier survival analysis based on our proposed stage grouping that incorporates depth of tumor invasion. Unlike the American Joint Committee on Cancer (AJCC) stage grouping, the proposed new stage grouping was a strong predictor of long-term outcome. The 5-year survival rates of patients with distal cholangiocarcinoma of proposed stages I, II, and III were 69.3%, 28.7%, and 8.5%, respectively ($P < .0001$).

Table ICharacteristics of distal cholangiocarcinoma cases ($n = 147$ patients)

Factor	Characteristics	No. (%)
Sex	Male	90 (61.2)
	Female	57 (38.8)
Differentiation	Well	5 (3.4)
	Moderately	99 (67.3)
	Poorly	43 (29.3)
Histologic type	Adenocarcinoma	143 (97.3)
	Papillary carcinoma	3 (2.0)
	Adenosquamous	1 (0.7)
T classification	T1	11 (7.5)
	T2	6 (4.1)
	T3	73 (49.7)
	T4	57 (38.8)
Nodal metastasis	Absent	54 (36.7)
	Present	93 (63.3)
Resection margin	Absent	133 (90.5)
	Present	14 (9.5)
Perineural invasion	Absent	49 (33.3)
	Present	98 (66.7)
Vascular invasion	Absent	109 (74.1)
	Present	38 (25.9)
Pancreas invasion	Absent	19 (12.9)
	Present	128 (87.1)
Duodenal invasion	Absent	90 (61.2)
	Present	57 (38.8)
Depth of invasion	<5 mm	14 (9.5)
	5–12 mm	75 (51.0)
	>12 mm	58 (39.5)

Table II
Univariate analysis of pathologic features affecting patient survival with distal extrahepatic bile duct carcinoma

Variable	Characteristics	Median survival (month)	95% confidence interval		P value
			Lower	Upper	
Sex	Male	20.2	12.2	28.2	.79
	Female	16.6	7.8	25.4	
Differentiation	Well	12.7	10.2	15.2	.09
	Moderate	26.0	16.2	35.8	
T classification	Poor	11.3	7.0	15.5	
	T1	40.1	30.2	51.4	.17
	T2	14.8	0	52.5	
	T3	16.5	11.3	21.7	
	T4	20.2	9.7	30.7	
Nodal metastasis	Absent	40.8	25.6	55.9	.003
	Present	15.0	11.9	18.1	
Resection margin	Negative	18.9	11.1	26.7	.23
	Positive	19.0	7.3	30.7	
Perineural invasion	Absent	31.4	15.3	47.6	.001
	Present	14.7	10.9	18.5	
Vascular invasion	Absent	24.5	12.0	37.0	<.0001
	Present	12.1	8.0	16.2	
Pancreas invasion	Absent	40.8	32.9	48.7	.02
	Present	18.7	12.5	24.9	
Duodenal invasion	Absent	18.7	8.1	29.4	.50
	Present	20.2	9.7	30.7	
Depth of invasion	<5 mm	*	–	–	<.0001
	5–12 mm	28.9	18.3	39.5	
	>12 mm	12.9	10.5	15.5	

* Cannot be calculated because 78.6% of patients were alive.

Table III

Associations between classification of invasion depth and clinicopathologic variables

Factor	No. (%)			<i>P</i> value
	<5 mm	5–12 mm	>12 mm	
Nodal metastasis	3 (3.2)	41 (44.1)	49 (52.7)	<.0001
Perineural invasion	5 (5.1)	50 (51.0)	43 (43.9)	.02
Vascular invasion	1 (2.6)	17 (44.7)	20 (52.6)	.07
Pancreas invasion	4 (3.1)	69 (53.9)	55 (42.7)	<.0001

Table IV

Multivariate analysis for distal neoplasms

Variable	Relative risk	<u>95% confidence interval</u>		<i>P</i> value
		Lower	Upper	
Nodal metastasis	1.15	0.73	1.80	.55
Perineural invasion	1.70	1.11	2.61	.015
Vascular invasion	1.73	1.12	2.65	.013
Pancreas invasion	0.98	0.46	2.08	.95
Depth of invasion				.001
<5 mm	1			—
5–12 mm	3.81	1.13	12.85	.031
>12 mm	6.69	1.94	23.08	.003

Table V

Proposed new stage grouping for distal cholangiocarcinoma that incorporates depth of tumor invasion

T classification	N classification	Stage
T1 (depth of invasion, <5 mm)	N0	I
T2 (depth of invasion, 5–12 mm)	N0	II
T3 (depth of invasion, >12 mm)	N0	III
Any T (T1, T2, or T3)	N1	III