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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports® cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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Pleasanton, CA 94588, USA
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PUBLICATION DATE
March 7, 2018

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Retrospective Study

Prognostic value of lymph nodes count on survival of patients with distal cholangiocarcinomas

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Author contributions: Zhou SJ and Lin HP conducted the analyses and wrote the manuscript; all other authors contributed to the idea of the manuscript and approved the final version.

Supported by the National Natural Science Foundation of China, No. 81301975; and the Chongqing Natural Science Foundation, No. cstc2016jcyjA016.

Institutional review board statement: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent statement: As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

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Received: December 23, 2017

Peer-review started: December 23, 2017

First decision: January 17, 2018

Revised: January 30, 2018

Accepted: February 8, 2018

Article in press: February 8, 2018

Published online: March 7, 2018

Abstract**AIM**

To evaluate the prognostic value of the number of retrieved lymph nodes (LNs) and other prognostic factors for patients with distal cholangiocarcinomas, and to determine the optimal retrieved LNs cut-off number.

METHODS

The Surveillance, Epidemiology and End Results database was used to screen for patients with distal cholangiocarcinoma. Patients with different numbers of retrieved LNs were divided into three groups by the X-tile program. X-tile from Yale University is a useful tool for outcome-based cut-point optimization. The Kaplan-Meier method and Cox regression analysis were utilized for survival analysis.

RESULTS

A total of 449 patients with distal cholangiocarcinoma met the inclusion criteria. The Kaplan-Meier survival analysis for all patients and for N1 patients revealed no significant differences among patients with different retrieved LN counts in terms of overall and cancer-specific survival. In patients with node-negative distal cholangiocarcinoma, patients with four to nine retrieved LNs had a significantly better overall ($P = 0.026$) and cancer-specific survival ($P = 0.039$) than others. In the subsequent multivariate analysis, the number of retrieved LNs was evaluated to be independently associated with survival. Additionally, patients with four to nine retrieved LNs had a significantly lower overall mortality risk [hazard ratio (HR) = 0.39; 95% confidence interval (CI): 0.20-0.74] and cancer cause-specific mortality risk (HR = 0.32; 95%CI: 0.15-0.66) than other patients. Additionally, stratified survival analyses showed persistently better overall and cancer-specific survival when retrieving four to nine LNs in patients with any T stage of tumor, a tumor between 20 and 50 mm in diameter, or a poorly differentiated or undifferentiated tumor, and in patients who were \leq 70-years-old.

CONCLUSION

The number of retrieved LNs was an important independent prognostic factor for patients with node-negative distal cholangiocarcinoma. Additionally, patients with four to nine retrieved LNs had better overall and cancer-specific survival rates than others, but the reason and mechanism were unclear. This conclusion should be validated in future studies.

Key words: Distal cholangiocarcinomas; Lymph node count; Survival analysis; SEER

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Core tip: The prognostic value of retrieved lymph node (LN) counts is still under debate for patients with distal cholangiocarcinomas. The aim of the present study was to evaluate the prognostic value of the number of retrieved lymph nodes and other prognostic factors for patients with distal cholangiocarcinomas and to determine the optimal retrieved LNs cut-off number. A total of 449 patients with distal cholangiocarcinoma were included in this study. The univariate and multivariate analyses revealed that the number of retrieved LNs was independently associated with survival. And, patients with four to nine retrieved LNs had a better overall and cancer-specific survival rate than others.

Lin HP, Li SW, Liu Y, Zhou SJ. Prognostic value of lymph nodes count on survival of patients with distal cholangiocarcinomas. *World J Gastroenterol* 2018; 24(9): 1022-1034 Available from:

URL: <http://www.wjgnet.com/1007-9327/full/v24/i9/1022.htm>
DOI: <http://dx.doi.org/10.3748/wjg.v24.i9.1022>

INTRODUCTION

Cholangiocarcinoma constitutes approximately 15% of hepatobiliary tumors and 3% of gastrointestinal tumors^[1]. According to its anatomic location, cholangiocarcinoma is classified as intrahepatic, perihilar or distal malignancy. Distal cholangiocarcinoma comprise approximately 30% of all cholangiocarcinoma; it is a relatively uncommon disease. The only optimal treatment for distal cholangiocarcinoma is surgical resection, as a result of the insensitivity of cholangiocarcinoma to radiation and chemotherapy^[2]. Additionally, complete tumor resection of distal cholangiocarcinoma always relies on pancreaticoduodenectomy, which is a complicated operation with high morbidity and mortality^[3]. Hence, the postoperative prognosis of patients with distal cholangiocarcinoma has attracted great interest in several studies^[4,5]. Lymph node (LN) status was determined to be a strong predictor for the prognosis of patients with distal cholangiocarcinoma^[6]. Patients without LN metastasis had a better prognosis than those with LN involvement. Thus, an adequate number of retrieved LNs is vital to distinguish N0 patients from N1 ones. The appropriate cut-off of retrieved LNs counts should be determined.

Currently, the number of LNs that should be retrieved is still under debate. Several studies evaluated the prognostic value of retrieved LN counts and tried to determine the benchmark number of examined LNs^[6-9]. Nevertheless, most of them were designed retrospectively with a small sample size, and cases that met their inclusion criteria comprised both perihilar and distal cholangiocarcinomas. The differences in biological and pathological features, as well as surgical strategies and prognoses, between perihilar and distal cholangiocarcinomas lead to a different influence of retrieving LN counts on survival.

The American Joint Committee on Cancer (AJCC) staging system suggested a different appropriate number of retrieved LNs for perihilar and distal cholangiocarcinomas. For distal cholangiocarcinoma, the number that AJCC suggested was 12. However, this suggestion lacks verification because the retrieved LN counts in most previous studies did not reach 12. Additionally, in the study of Kawai *et al.*^[10], patients with more than 12 retrieved LNs only had a moderately better survival rate than patients with a smaller number of retrieved LNs in a univariate analysis, not a multivariate analysis. A subgroup study of Kiriyama *et al.*^[11], using a cohort of N0 patients, found that patients with more than 10 retrieved LNs had a better survival. This subgroup analysis was based on a small sample

size with a univariate analysis, and the cancers of the involved cases were all stages I and II. Therefore, the appropriate cut-off number of retrieved LNs is still unconfirmed.

Our study was performed to evaluate the interactions between the number of retrieved LNs and the prognosis of patients with distal cholangiocarcinoma; additionally, this study determined the appropriate retrieved LN cut-off number. To obtain a larger sample size, the Surveillance, Epidemiology and End Results (SEER) database was used for the selection of patients with at least one retrieved LN.

MATERIALS AND METHODS

Data source

SEER is a public dataset that collects survival and incidence data of various types of cancers and covers more than 25% of the United States' population. SEER data include tumor characteristics such as primary tumor site, TNM staging of tumor, tumor size, type of treatment and cause of death, and demographic characteristics such as race of patients, age of diagnosis, sex, *etc.* Our study used the latest 11 years' data from SEER (from 2004-2014). We downloaded the data from SEER with SEER*Stat Software (version 8.3.4; <https://seer.cancer.gov/seerstat/>).

Patients

Our study was designed to be a retrospective study. The inclusion criteria were (1) patients greater than 20 years in age; (2) patients diagnosed with distal cholangiocarcinoma according to the term "006-BileDuctsDistal" of "CS SCHEMA v0204+"; (3) patients with histology code of 8010, 8020, 8070, 8140, 8144, 8160, 8162, 8163, 8260, 8480, 8490 or 8560; (4) patients with diagnoses that were not confirmed by a death certificate or autopsy; (5) patients with active follow-up; (6) patients from a time span of 2004 to 2014 according to the term "year of diagnosis"; (7) patients with only one tumor who had survived more than 1 mo; (8) patients without distant metastasis (the M0 patients); (9) patients who received intent surgery in terms of the combination of "Surg Prim Site" and "Reason no cancer-directed surgery"; (10) patients who did not receive preoperative radiotherapy according to the terms of "Radiation" and "Surg/Rad Seq"; and (11) patients with at least one retrieved LN according to the terms "Regional Nodes Examined". Demographics of patients such as race, age at diagnosis and marital status, and tumor characteristics such as tumor size, laterality of tumor, grade and stage of tumor were all extracted for subsequent analysis. The terms "SEER cause-specific death classification" and "SEER other cause of death classification" were used to distinguish our two endpoints: all-cause mortality and cancer cause-specific mortality.

Statistical analysis

Statistical analyses were conducted with SPSS (version 23.0; IBM Corp., Armonk, NY, United States). The demographic data of patients were compared by *t* tests (for continuous variables) and chi-square tests (for proportion variables). A *P*-value of < 0.05 was defined to be statistically significant. Patients with different numbers of retrieved LNs were divided into three groups.

The cut-off number of retrieved LNs for grouping was determined by the X-tile program (<http://www.tissuearray.org/rimmlab/>). X-tile from Yale University is a useful tool for outcome-based cut-point optimization. The strategies of the X-tile program for grouping included that it would try each number between the range of the retrieved LN counts as the cut-off; then, the χ^2 score and *P*-value were calculated with this number as the cut-off^[12,13]. Eventually, the number with a maximum χ^2 score and a minimum *P*-value would be suggested to be the final cut-off.

The Kaplan-Meier method (univariate analysis) with log-rank tests and Cox regression analysis (multivariate analysis) were utilized for survival analysis. The overall survival and cancer-specific survival were compared between patients with the different categories of retrieved LNs counts. Then, we performed stratified survival analyses for the number of retrieved LNs, in terms of the confounders that were evaluated to be independently associated with survival in the multivariate analysis.

RESULTS

Patient and demographics details

A total of 449 patients with distal cholangiocarcinoma (2004-2014) met the inclusion criteria for this research. The majority of them were white and male. The distributions of age and the diagnosis year were averaged. Nearly 70% of the patients were married. The size of the tumor was less than 50 mm in most patients. Patient and tumor characteristics are shown in Table 1.

The retrieved LN counts ranged from one to sixty-three. More than half of the patients had > 10 LNs retrieved, and 22.7% of patients had > 20 LNs retrieved. There were 226 N0 patients and 223 N1 patients. Most patients underwent extensive surgery and postoperative chemotherapy; the number of patients who received adjuvant radiotherapy was less.

Impact of the number of retrieved LNs on survival rates

We divided patients with different numbers of retrieved LNs into three groups, by use of the X-tile program. Then, the retrieved LN count was converted from continuous variables into categorical variables to study its impact on survival. As shown in Figure 1, the cut-off numbers for grouping in all patients were 3 and 6, the

Table 1 Characteristics of patients and tumors

Variable	No. of patients, <i>n</i> (%) <i>n</i> = 449
Race	
White	321 (71.5)
Black	35 (7.8)
Other	93 (20.7)
Sex	
Male	286 (63.7)
Female	163 (36.3)
Age at diagnosis, in yr	
≤ 60	128 (28.5)
60-70	171 (38.1)
> 70	150 (33.4)
Marital status	
Married	302 (67.3)
Divorced	33 (7.3)
Separated or single	58 (12.9)
Widowed	40 (8.9)
Unknown	16 (3.6)
Year of diagnosis	
2004-2010	110 (24.5)
2011-2012	160 (35.6)
2013-2014	179 (39.9)
Tumor size, in mm	
≤ 20	203 (45.2)
20-50	191 (42.5)
> 50	15 (3.3)
Unknown	40 (8.9)
Grade	
Well differentiated	54 (12.0)
Moderately differentiated	204 (45.4)
Poorly differentiated	158 (35.2)
Undifferentiated	3 (0.7)
Unknown	30 (6.7)
Stage	
I A	44 (9.8)
I B	60 (13.7)
II A	89 (19.8)
II B	161 (35.9)
III	95 (21.2)
T stage	
T1	49 (10.9)
T2	85 (18.9)
T3	220 (49.0)
T4	95 (21.2)
pN stage	
pN0	226 (50.3)
pN1	223 (49.7)
Surgery type	
Local excision	102 (22.7)
Extensive surgery	347 (77.3)
Adjuvant radiotherapy	
No/Unknown radiotherapy	298 (66.3)
Beam radiation	151 (33.7)
Adjuvant chemotherapy	
No/Unknown chemotherapy	204 (45.4)
Chemotherapy performed	245 (54.6)
No. of LNs retrieved	
1-10	196 (43.7)
11-20	151 (33.6)
> 20	102 (22.7)

LNs: Lymph nodes.

cut-off numbers for N0 patients were 4 and 9, and the cut-off numbers for N1 patients were 4 and 16.

In the Kaplan-Meier survival analysis, no significant

difference was observed among the three categories of retrieved LN counts for all and N1 patients with distal cholangiocarcinomas. For patients with node-negative distal cholangiocarcinomas, there was a significantly better overall and cancer-specific survival in patients with 4-9 retrieved LNs than in patients with 1-3 or > 9 retrieved LNs. Additionally, we compared overall and cancer-specific survival among each number of retrieved LNs. Because of space limitations, we could only put part of the results into the table (Table 2).

There was a similar trend of survival rate as the retrieved LN count increased in all, N0 and N1 patients; patients with seven retrieved LNs had the best survival rate compared with the others. In N0 patients, patients with seven or nine retrieved LNs had a significantly higher survival rate compared with other patients; this result was confirmed in analysis regarding retrieved LN counts as categorical variables.

Survival analyses in all patients and patients with node-negative distal cholangiocarcinoma

The results of survival analysis for all patients in the present study were similar to previous studies. As shown in Figure 1 and Table 3, retrieved LN counts were not associated with survival in all patients ($P = 0.233$). Factors such as tumor size and T and N stages that were significant in univariate analysis were entered into a multivariate model. N stage was shown to be independently associated with overall survival [hazard ratio (HR) = 1.40; 95% confidence interval (CI): 1.05-1.86]. In terms of cancer-specific survival, T stage [(HR = 1.45; 95%CI: 1.02-2.07)] was shown to be an independent risk factor of survival, along with N stage (HR = 1.42; 95%CI: 1.05-1.92).

For N0 patients, univariate analysis showed that retrieved LN counts, age at diagnosis, and grade of tumor were associated with overall survival. After those factors were entered into multivariate analysis, retrieved LN counts and grade of tumor were determined to be independent risk factors of overall survival. Patients with four to nine retrieved LNs had a significantly lower all-cause mortality risk than other patients (HR = 0.39; 95%CI: 0.20-0.74). In terms of cancer-specific survival, tumor size, grade of tumor, T stage and retrieved LN counts were evaluated to be associated with survival in both univariate and multivariate analyses. There was a significant decrease in terms of cancer cause-specific mortality risk (HR = 0.32; 95%CI: 0.15-0.66) for patients with four to nine retrieved LNs (Table 4).

Stratified analyses for the number of retrieved LNs in patients with node-negative distal cholangiocarcinoma

To further study the interactions between retrieved LN counts and prognoses of patients with node-negative distal cholangiocarcinoma, we performed survival analysis stratified by size, grade, T stage of tumor and age of patients. For patients ≤ 70-years-old, retrieving four to nine LNs resulted in a significantly

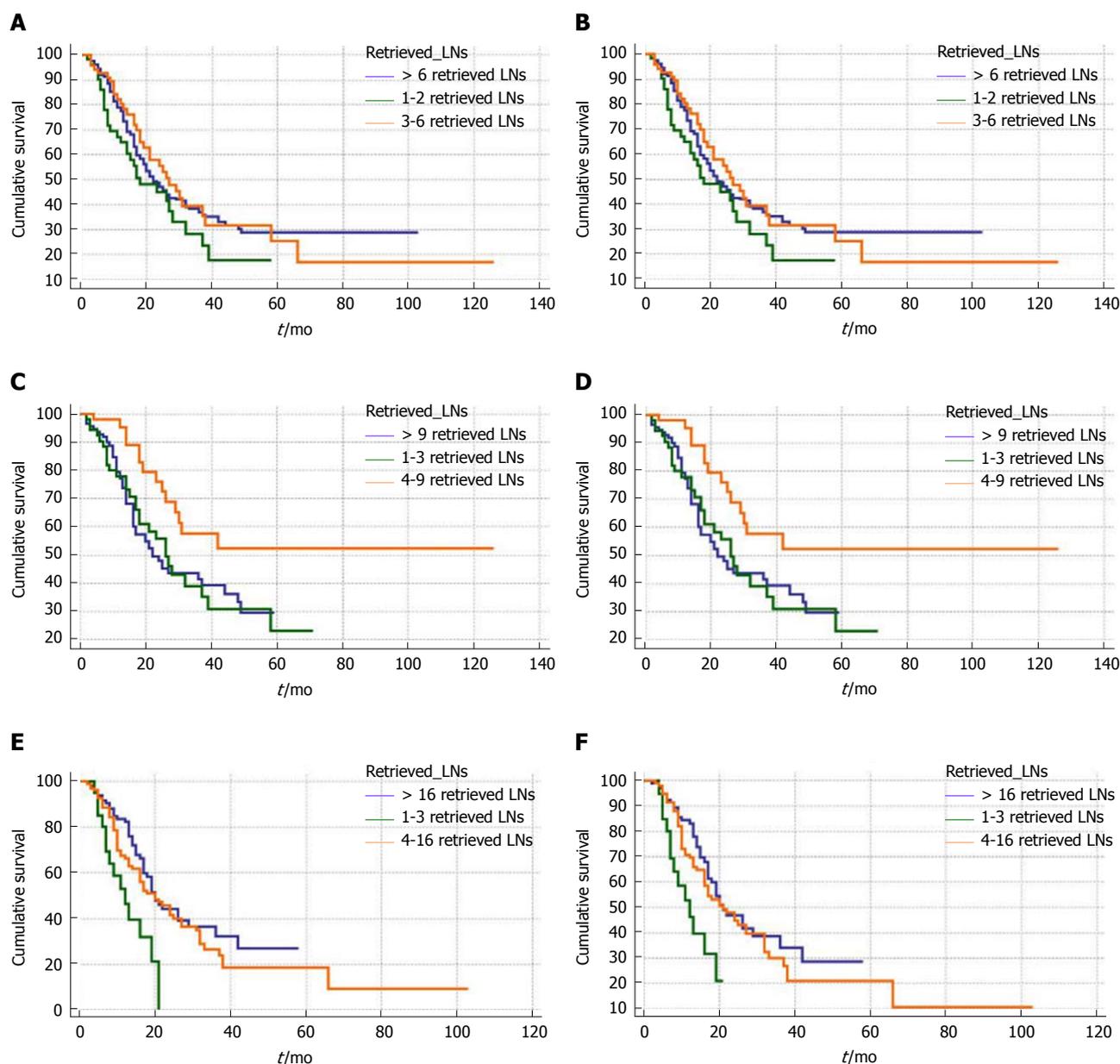


Figure 1 Kaplan-Meier survival curves of all patients in terms of (A) overall survival and (B) cancer-specific survival. There was no significant difference in terms of overall survival ($P = 0.233$) and cancer-specific survival ($P = 0.141$) among the three groups. Kaplan-Meier survival curves of patients with node-negative distal cholangiocarcinoma in terms of (C) overall survival and (D) cancer-specific survival. Patients with four to nine retrieved LNs had a better overall ($P = 0.026$) and cancer-specific ($P = 0.008$) survival than patients with one to three retrieved LNs and patients with more than nine retrieved LNs. Kaplan-Meier survival curves of N1 patients in terms of (E) overall survival and (F) cancer-specific survival. There was no significant difference in terms of overall survival ($P = 0.053$) and cancer-specific survival ($P = 0.0564$) among the three groups. LNs: Lymph nodes.

better survival rate than retrieving one to three LNs in terms of overall survival (Figure 2A) and cancer-specific survival (Figure 3A). Additionally, no significant difference between patients with one to three retrieved LNs and > 9 retrieved LNs in terms of overall and cancer-specific survival was observed.

Subsequently, the above results were confirmed in multivariate survival analyses after adjusting for all confounders (Table 5). As shown in Figures 2 and 3 and Table 5, similar results were found for patients with any T stage of tumor, tumor size between 20 and 50 mm, and tumors that were poorly defined or undifferentiated. The prognostic effect of retrieved LN

counts was not present when analyses were limited to well or moderately differentiated tumors, tumors ≤ 20 mm, and patients greater than 70 years in age.

DISCUSSION

Nodal status is a well-studied indicator for the prognosis of patients with distal cholangiocarcinoma. In addition to the stage of LNs, the prognostic value of positive node counts and lymph node ratios has been evaluated in several studies^[6,10,11]. While the prognostic value of the number of retrieved LNs is still under debate, the optimal cut-off number of retrieved LNs

Table 2 Impact of the number of retrieved lymph nodes on survival rates

Retrieved LNs counts	No.	3-yr OS	95%CI	3-yr CSS	95%CI
For all patients					
1	26	29.51%	10.90-51.07	29.51%	10.90-51.07
3	23	35.33%	13.50-58.23	43.64%	18.10-66.88
5	18	46.55%	16.40-72.36	51.20%	17.95-77.03
7	22	63.31%	35.24-81.81	63.31%	35.24-81.84
9	16	57.29%	27.94-78.40	66.20%	32.37-86.00
11	16	37.09%	11.27-63.72	40.46%	12.19-67.77
13	11	28.41%	4.52-59.96	28.41%	4.52-59.96
15	13	16.46%	0.90-50.11	16.46%	0.90-50.11
17	15	15.80%	0.82-49.22	17.01%	0.84-51.90
19	9	34.29%	4.81-68.55	34.29%	4.81-68.55
21	12	47.62%	19.35-71.52	47.62%	19.35-71.52
23	5	33.86%	5.73-66.35	33.86%	5.73-66.35
25	15	37.50%	9.37-66.61	37.50%	9.37-66.61
For N0 patients					
1	17	40.38%	14.15-65.68	40.38%	14.15-65.68
3	18	43.65%	17.20-67.68	47.01%	18.51-71.34
5	11	30.00%	1.23-71.92	37.50%	1.10-80.80
7	16	76.15%	42.67-91.65	76.15%	42.67-91.65
9	5	66.67%	5.41-94.52	66.67%	5.41-94.52
11	9	50.79%	15.67-78.07	59.26%	18.59-84.95
13	4	37.50%	1.10-80.80	37.50%	1.10-80.80
15	6	26.67%	0.97-68.61	26.67%	0.97-68.61
17	4	-	-	-	-
19	2	-	-	-	-
21	6	55.56%	7.34-87.61	55.56%	7.34-87.61
23	1	-	-	-	-
25	7	42.00%	7.01-75.34	52.50%	8.42-84.55
For N1 patients					
1	9	14.29%	0.71-46.49	14.29%	0.71-46.49
3	5	33.33%	0.90-77.41	33.33%	0.90-77.41
5	7	53.57%	13.20-82.50	53.57%	13.20-82.50
7	6	55.56%	7.34-87.61	55.56%	7.34-87.61
9	11	45.00%	13.88-72.41	58.33%	18.02-84.41
11	7	25.00%	1.23-64.59	25.00%	1.23-64.59
13	7	41.67%	5.60-76.65	41.67%	5.60-76.65
15	7	35.71%	1.41-77.98	35.71%	1.41-77.98
17	11	17.05%	0.84-51.92	18.94%	0.87-55.82
19	7	26.67%	0.97-68.61	26.67%	0.97-68.61
21	6	43.64%	11.29-72.96	43.64%	11.29-72.96
23	4	-	-	-	-
25	8	28.57%	4.11-61.15	28.57%	4.11-61.15

CI: Confidence interval; CSS: Cancer-specific survival; LNs: Lymph nodes; OS: Overall survival.

is also unconfirmed. Several studies of other diseases revealed the difference in retrieved LNs' influence on survival between N0 and N1 patients^[8,14,15]. Nevertheless, for N0 patients, more LNs retrieved significantly improved survival. Therefore, studies of distal cholangiocarcinoma on retrieved LN counts should be performed in a cohort of N0 patients for whom the prognostic value of retrieved LN counts has never been systematically studied.

Our study screened 449 patients with distal cholangiocarcinoma in a population-based database; a total of 226 patients with node-negative distal cholangiocarcinoma were among them. Retrieved LN counts did not show its prognostic value in the whole cohort and N1 patients. However, in patients with node-negative distal cholangiocarcinoma, patients with four to nine retrieved LNs were determined to have a significantly better prognosis than patients with ≤ 3

retrieved LNs in terms of overall and cancer-specific survivals. Additionally, tumor size, grade and T stage of tumor were evaluated to be independent risk factors of cancer-specific survival. Therefore, retrieving at least four LNs would be optimal for patients with node-negative distal cholangiocarcinoma.

More retrieved LNs could promote the accuracy of LNs staging to avoid the under-staging effect, thus to improve survival of patients with distal cholangiocarcinoma. Studies on cholangiocarcinoma demonstrated there were micrometastases in approximately 5% of LNs which were diagnosed as negative nodes^[16]. The more LNs that were resected and retrieved meant less micrometastases were left, therefore the survival of patients with more retrieved LNs counts could be improved. Additionally, more retrieved LNs represented adequate surgical, pathological and institutional care^[17]. What's more, anatomic studies determined that more

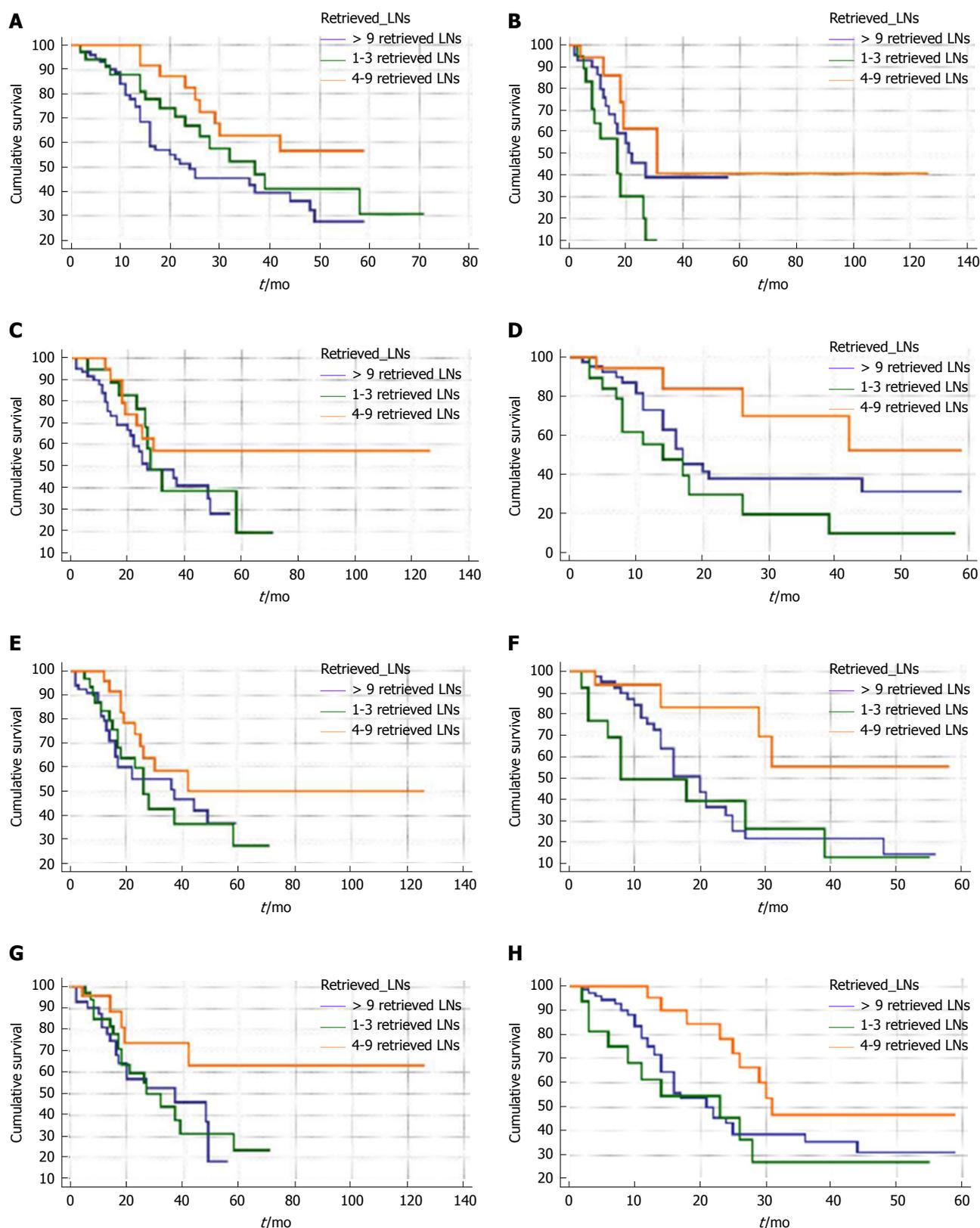


Figure 2 Kaplan-Meier survival curves of stratified analyses in (A) patients ≤ 70 -years-old, (B) > 70 -years-old, (C) with tumors of ≤ 20 mm, (D) with tumors of 20 to 50 mm, (E) with tumors defined as well or moderately differentiated, (F) with tumors defined as poorly or undifferentiated, (G) with tumors of T1/T2 stage, and (H) with tumors of T3/T4 stage in terms of overall survival. Patients with four to nine retrieved LNs had a significantly better overall survival than patients with one to three retrieved LNs and patients with more than nine retrieved LNs in the group of patients ≤ 70 -years-old ($P = 0.029$), with tumors of 20 to 50 mm ($P = 0.018$), with tumors defined as poorly or undifferentiated ($P = 0.030$), and with tumors of T3/T4 stage ($P = 0.041$). LNs: Lymph nodes.

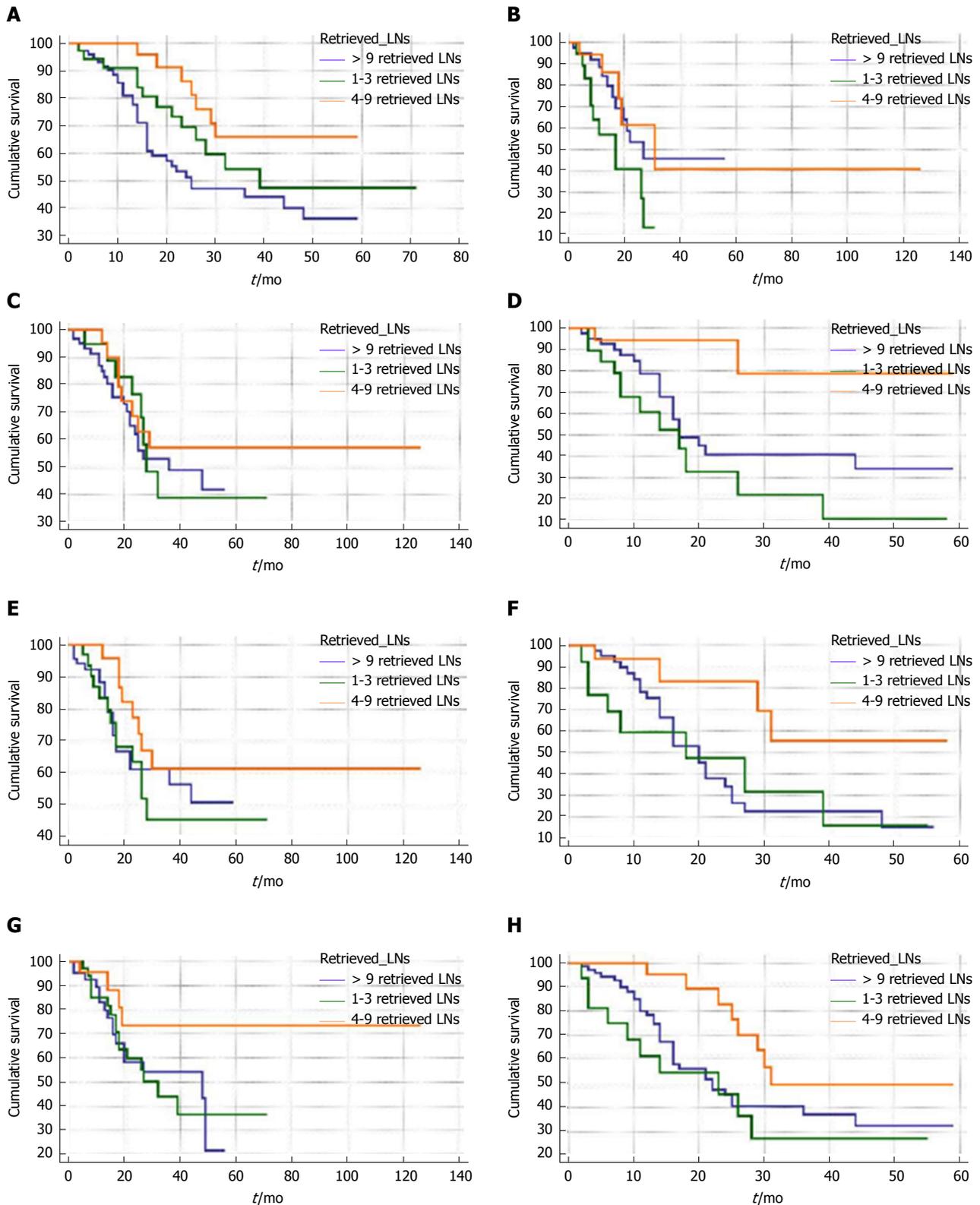


Figure 3 Kaplan-Meier survival curves of stratified analyses in (A) patients ≤ 70 -years-old, (B) > 70 -years-old, (C) with tumors of ≤ 20 mm, (D) with tumors of 20 to 50 mm, (E) with tumors defined as well or moderately differentiated, (F) with tumors defined as poorly or undifferentiated, (G) with tumors of T1/T2 stage, and (H) with tumors of T3/T4 stage in terms of cancer-specific survival. Patients with four to nine retrieved LN had a significantly better cancer-specific survival than patients with one to three retrieved LN and patients with more than nine retrieved LN in the group of patients ≤ 70 -years-old ($P = 0.025$), with tumors of 20 to 50 mm ($P = 0.006$), with tumors defined as poorly or undifferentiated ($P = 0.049$), and with tumors of T3/T4 stage ($P = 0.041$). LN: Lymph nodes.

Table 3 Univariate and multivariate survival analyses of factors associated with overall and cancer-specific survival of all patients with distal cholangiocarcinoma

Variables	Overall survival					Cancer-specific survival				
	Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
	3-yr OS	χ^2	P value	HR (95%CI)	P value	3-yr OS	χ^2	P value	HR (95%CI)	P value
Race		2.22	0.329				1.95	0.377		
White	33.3%					36.1%				
Black	34.8%					36.9%				
Other	38.9%					42.1%				
Sex		0.44	0.507				0.54	0.463		
Male	35.3%					38.3%				
Female	37.7%					40.9%				
Age at diagnosis, in yr		1.89	0.387				0.48	0.783		
≤ 60	31.2%					35.8%				
60-70	39.1%					41.4%				
> 70	30.7%					36.8%				
Marital status		5.02	0.285				5.98	0.201		
Married	37.3%					39.6%				
Divorced	-					-				
Separated or single	31.4%					35.3%				
Widowed	34.1%					-				
Unknown	-					-				
Year of diagnosis		1.82	0.402				3.25	0.197		
2004-2010	37.3%					41.4%				
2011-2012	30.9%					33.2%				
2013-2014	-					-				
Tumor size, in mm		8.04	0.045		0.230		8.76	0.032		0.249
≤ 20	40.8%			Reference		44.0%			Reference	
20-50	29.9%			1.25 (0.94-1.67)		33.2%			1.23 (0.91-1.68)	
> 50	0.0%			1.67 (0.86-3.23)		0.0%			1.76 (0.91-3.43)	
Unknown	37.7%			0.95 (0.57-1.58)		46.3%			0.96 (0.56-1.65)	
Grade		6.77	0.079				6.92	0.074		
Well differentiated	48.6%					52.4%				
Moderately differentiated	32.6%					38.9%				
Poorly or undifferentiated	30.3%					32.6%				
Unknown	43.2%					43.2%				
T stage		5.57	0.018		0.270		11.16	< 0.001		0.037
T1/T2	44.3%			Reference		51.6%			Reference	
T3/T4	29.6%			1.19 (0.87-1.64)		32.6%			1.45 (1.02-2.07)	
N stage		10.64	0.001		0.020		12.27	< 0.001		0.022
N0	44.5%			Reference		47.4%			Reference	
N1	26.9%			1.40 (1.05-1.86)		30.3%			1.42 (1.05-1.92)	
Surgery type		1.20	0.272				0.73	0.393		
Local excision	44.0%					45.3%				
Extensive surgery	34.4%					37.9%				
Adjuvant radiotherapy		0.16	0.683				0.79	0.372		
No/Unknown radiotherapy	39.9%					44.3%				
Beam radiation	29.5%					30.5%				
Adjuvant chemotherapy		1.10	0.293				2.92	0.087		
No/Unknown chemotherapy	41.2%					47.5%				
Chemotherapy performed	32.2%					33.3%				
No. of LNs retrieved		2.91	0.233				3.90	0.141		
1-2	23.6%					29.9%				
3-6	35.6%					39.4%				
> 6	36.0%					39.0%				

CI: Confidence interval; HR: Hazard ratio; LNs: Lymph nodes; OS: Overall survival.

resected LNs could improve the underlying tumor-host interactions and reset the immunological balance to improve survival^[18].

The AJCC system suggested the optimal number of retrieved LNs of patients with distal cholangiocarcinoma should be 12. Whereas study of Sasaki *et al*^[6] demonstrated there was no difference between patients with ≥ 12 retrieved LNs and < 12 retrieved

LNs in terms of overall survival. A subgroup analysis in the study of Kiriya *et al*^[11] revealed that patients with stage I or II tumors who had more than 10 LNs retrieved had a better survival rate than others. While 83.2% of patients in their study retrieved more than 12 LNs, the number of patients with < 10 retrieved LNs was very small (*n* = 22), and their results were based on a univariate analysis. Therefore, selection

Table 4 Univariate and multivariate survival analyses of factors associated with overall and cancer-specific survival of patients with node-negative distal cholangiocarcinoma

Variable	Overall survival					Cancer-specific survival				
	Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
	3-yr OS	χ^2	P value	HR (95%CI)	P value	3-yr OS	χ^2	P value	HR (95%CI)	P value
Race		0.82	0.663				0.13	0.939		
White	44.3%					46.8%				
Black	49.4%					49.4%				
Other	40.4%					44.0%				
Sex		1.32	0.250				0.77	0.377		
Male	39.5%					46.0%				
Female	47.0%					49.8%				
Age at diagnosis, in yr		3.85	0.049		0.056		2.73	0.097		
≤ 70	49.8%			Reference		51.8%				
> 70	31.4%			1.51 (0.98-2.33)		35.7%				
Marital status		6.30	0.177				6.52	0.163		
Married	42.9%					48.5%				
Divorced	-					-				
Separated or single	31.8%					39.6%				
Widowed	46.9%					46.9%				
Unknown	-					-				
Year of diagnosis		3.41	0.181				4.05	0.131		
2004-2010	50.0%					52.1%				
2011-2012	36.5%					41.4%				
2013-2014	48.8%					54.0%				
Tumor size, in mm		7.47	0.058				9.11	0.027		0.036
≤ 20	47.3%					49.6%			Reference	
20-50	36.9%					40.0%			1.57 (0.98-2.53)	
> 50	0.0%					0.0%			3.08 (1.16-8.21)	
Unknown	46.8%					60.8%			0.72 (0.30-1.71)	
Grade		9.65	0.021		0.014		12.56	0.005		0.003
Well differentiated	56.8%			Reference		63.3%			Reference	
Moderately differentiated	43.5%			1.59 (0.84-2.99)		51.8%			1.44 (0.70-2.97)	
Poorly or undifferentiated	26.0%			2.35 (1.24-4.46)		30.5%			2.90 (1.43-5.88)	
Unknown	57.0%			0.76 (0.27-2.16)		57.0%			1.14 (0.37-3.50)	
T stage		1.35	0.244				4.63	0.031		0.030
T1/T2	48.7%					58.4%			Reference	
T3/T4	37.1%					38.7%			1.69 (1.05-2.71)	
Surgery type		0.10	0.748				0.23	0.631		
Local excision	45.7%					48.2%				
Extensive surgery	44.1%					47.0%				
Adjuvant radiotherapy		1.64	0.199				1.53	0.215		
No/Unknown radiotherapy	48.2%					53.2%				
Beam radiation	35.5%					37.2%				
Adjuvant chemotherapy		1.31	0.251				1.48	0.222		
No/Unknown chemotherapy	46.3%					53.8%				
Chemotherapy performed	38.5%					42.1%				
No. of LNs retrieved		7.24	0.026		0.013		6.47	0.039		0.008
1-3	35.1%			Reference		40.9%			Reference	
4-9	52.3%			0.39 (0.20-0.74)		60.0%			0.32 (0.15-0.66)	
> 9	39.3%			0.85 (0.53-1.36)		44.9%			0.62 (0.36-1.07)	

CI: Confidence interval; CSS: Cancer-specific survival; HR: Hazard ratio; LNs: Lymph nodes; OS: Overall survival.

bias should be kept in mind when interpreting their results. The fact that retrieving more than 10 or 12 LNs is an indicator of better prognosis is still disputable.

The present study denoted that retrieving more than nine LNs did not indicate a better prognosis in patients with node-negative distal cholangiocarcinoma, but an increase in terms of all-cause mortality risk and cancer cause-specific mortality risk was observed compared with retrieving four to nine LNs. For patients with distal cholangiocarcinoma, retrieving too many LNs did not obtain better outcomes. This result was contrary to the prevailing dogma that a better prognosis was always

associated with higher retrieved LN counts.

There were several hypotheses for the reason why more retrieved LNs represented a worse prognosis. Necrosis represented an aggressive biology of tumor and a decreased survival rate; it had a close association with LN hyperplasia. LN hyperplasia always resulted in increases in the size and number of detectable LNs; therefore, more retrieved LNs (detectable LNs) were related to a worse prognosis^[19-21]. The other hypothesis was that there might be a difference at the molecular level between tumors with more and less detectable LNs. Tumors with more detectable LNs, *i.e.*

Table 5 Stratified analyses of overall and cancer-specific survival according to the number of retrieved LNs for N0 patients

Variable	4-9 retrieved LNs (1-3 retrieved LNs as the reference)				> 9 retrieved LNs (1-3 retrieved LNs as the reference)			
	Overall survival		Cancer-specific survival		Overall survival		Cancer-specific survival	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age, in yr								
≤ 70	0.33 (0.13-0.86)	0.023	0.34 (0.13-0.89)	0.030	1.02 (0.49-2.14)	0.940	0.93 (0.46-1.88)	0.848
> 70	0.32 (0.11-0.98)	0.047	0.33 (0.11-1.04)	0.059	0.63 (0.26-1.49)	0.294	0.40 (1.55-1.04)	0.059
Tumor size, in mm								
≤ 20	0.55 (0.21-1.46)	0.232	0.61 (0.22-1.68)	0.340	1.34 (0.60-2.97)	0.472	0.96 (0.41-2.23)	0.921
20-50	0.22 (0.07-0.69)	0.010	0.12 (0.03-0.55)	0.007	0.54 (0.24-1.21)	0.134	0.48 (0.21-1.12)	0.090
> 50	-	-	-	-	-	-	-	-
Grade								
Well or moderately differentiated	0.56 (0.24-1.30)	0.180	0.47 (0.18-1.20)	0.114	0.99 (0.49-2.01)	0.994	0.74 (0.34-1.62)	0.454
Poorly or undifferentiated	0.23 (0.07-0.79)	0.020	0.26 (0.07-0.89)	0.032	0.69 (0.31-1.58)	0.389	0.75 (0.32-1.78)	0.514
T stage								
T1/T2	0.30 (0.11-0.85)	0.024	0.30 (0.09-0.94)	0.039	0.79 (0.39-1.59)	0.501	0.76 (0.36-1.59)	0.467
T3/T4	0.34 (0.13-0.85)	0.022	0.31 (0.12-0.79)	0.016	0.66 (0.31-1.41)	0.285	0.65 (0.30-1.39)	0.267

CI: Confidence interval; HR: Hazard ratio; LNs: Lymph nodes.

more retrieved LNs, might belong to another subset of distal cholangiocarcinoma that acts biologically more aggressively^[19]. Additionally, routine histologic techniques for retrieving LNs may ignore the micrometastases, leading to the under-staging of LNs. Hence, without the application of immunohistochemical techniques that was determined to increase the detection rate of micrometastases, more retrieved LNs could not promote the accuracy of LN staging or improve patient survival. And, we wanted to know if more retrieved LNs reflected extended lymphadenectomy that may result in increasing postoperative complications. However, because of the limitation of the SEER database, we could not compare the background data in the > 9 retrieved LNs group with that in four to nine retrieved LN groups.

There were several limitations in our study. First, although a population-based database was utilized to screen patients, the total number of patients involved in our study was still not large enough compared with congener studies for other diseases. Second, information for adjuvant chemotherapy and radiotherapy in survival analysis did not contain the details of the protocols, and the SEER database did not provide data. Third, disease-free survival could not be calculated because of the lack of information about local recurrence in the SEER. Fourth, patients who received preoperative radiation were excluded. There might be patients who received radiation in some other centers that were not recorded in the SEER, so the down-staging effect of radiation could not be entirely ruled out. Fifth, the number of lymph nodes retrieved may depend upon the type of surgical procedures. And, the lymph nodes distant from the lesion (for example, nodes from Whipple's procedure) may not have the same predicting value as these from local or limited resection specimen. However, the detailed operation methods were unknown because of the limitation of the SEER, *i.e.* we could not know how many patients underwent pancreatoduodenectomy or segmental bile duct resection. Sixth, the number

of lymph nodes retrieved may rely on lymph node dissection skill in each individual institution (grossing by resident vs practicing pathologists or pathologist assistant). But, the SEER database only provided the information of the region where the patients were from, and the classes of hospital were unknown. Therefore, such institution bias should be taken into consideration when interpreting our results. Seventh, we could only compare survival among the groups of patients with four to nine lymph nodes and others based upon pathological stage and not clinical stage due to the limitation of SEER (the SEER database only provided the information of pathological stage for patients with resectable distal cholangiocarcinomas). Eighth, the AJCC staging system utilized in the present study was the 6th edition, which was not the most commonly used one nowadays (due to limitations of SEER). Finally, we could not get the data referring to the surgical margin status in SEER; surgical margin status was an important prognostic factor in patients with resected distal cholangiocarcinoma.

In conclusion, the number of retrieved LNs did not show its prognostic value in the whole group of patients (a mixture of N0 and N1 patients) and N1 patients. However, the number of retrieved LNs was an independent prognostic factor of overall and cancer-specific survival for patients with node-negative distal cholangiocarcinoma. Patients with four to nine retrieved LNs had better overall and cancer-specific survival rates than others, but the reason and mechanism were unclear. The future studies should consider more operation- and adjuvant therapy-related parameters into their analysis to evaluate our results.

ARTICLE HIGHLIGHTS

Research background

Lymph node (LN) status was determined to be a strong predictor for the prognosis of patients with distal cholangiocarcinoma. However, the prognostic

value of the retrieved LNs counts in distal cholangiocarcinoma is still under debate.

Research motivation

The benchmark number of retrieved LNs has been determined in many gastrointestinal carcinomas, in addition to the distal cholangiocarcinomas. Previous studies regarding the retrieved LNs counts in distal cholangiocarcinomas were limited by their small sample size, and the patients in those studies comprised both perihilar and distal cholangiocarcinomas. The present study tried to determine the interactions between the retrieved LNs counts and the prognosis in patients with only distal cholangiocarcinomas, and a population-based database was used for patients' selection that provided a sufficient sample size.

Research objectives

We aimed to evaluate the prognostic value of the number of retrieved LNs for patients with distal cholangiocarcinomas and to determine the optimal retrieved LNs cut-off number.

Research methods

The Surveillance, Epidemiology and End Results (SEER) database was used to screen for patients with distal cholangiocarcinoma. The retrieved LNs counts were transformed from continuous variables to categorical variables, and the cut-off was defined by the X-tile program. The overall and cancer-specific survival was compared between the different categories of retrieved LNs counts by the means of the Kaplan-Meier method and Cox regression analysis. Then, we performed stratified analyses by the clinical factors that were evaluated to be independently associated with survival in the Cox regression analysis, among patients within the different LNs groups.

Research results

A total of 449 patients with distal cholangiocarcinoma were included in the present study. The Kaplan-Meier survival analysis for all patients and for N1 patients revealed no significant differences among patients with different retrieved LN counts in terms of overall and cancer-specific survivals. In patients with node-negative distal cholangiocarcinoma, patients with four to nine retrieved LNs had a significantly better overall ($P = 0.026$) and cancer-specific ($P = 0.039$) survival than others. In the subsequent multivariate analysis, the number of retrieved LNs was evaluated to be independently associated with survival. Additionally, patients with four to nine retrieved LNs had a significantly lower overall mortality risk (hazard ratio (HR): 0.39; 95% confidence interval (CI): 0.20-0.74) and cancer cause-specific mortality risk (HR: 0.32; 95%CI: 0.15-0.66) than other patients. Additionally, stratified survival analyses showed persistent better overall and cancer-specific survival when retrieving four to nine LNs in patients with any T stage of tumor, a tumor between 20 and 50 mm in diameter, or a poorly differentiated or undifferentiated tumor and in patients who were ≤ 70 -years-old.

Research conclusions

The number of retrieved LNs was an important independent prognostic factor for patients with node-negative distal cholangiocarcinoma. Additionally, patients with four to nine retrieved LNs had a better overall and cancer-specific survival rate than patients with less than four or more than nine retrieved LNs.

Research perspectives

Although our study revealed retrieving four to nine LNs in patients with node-negative distal cholangiocarcinoma had better overall and cancer-specific survival rates than others, the reason and mechanism for that were unclear. The future studies should consider more operation- and adjuvant therapy-related parameters into their analysis to evaluate our results.

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P- Reviewer: Antonini F, Nah YW, Xu RL **S- Editor:** Wang XJ
L- Editor: Filipodia **E- Editor:** Huang Y





Published by **Baishideng Publishing Group Inc**
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ISSN 1007-9327

