Published in final edited form as:

J Gastroenterol Hepatol. 2016 February ; 31(2): 417–426. doi:10.1111/jgh.13072.

Patterns and Prognostic Value of Lymph Node Dissection for Resected Perihilar Cholangiocarcinoma

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Abstract

Background—Lymph node metastasis is a major prognostic factor for perihilar cholangiocarcinoma (PHC). However, prognostic significance of extent of node dissection, lymph node ratio (LNR), number and location of positive nodes remain unclear. We aimed to evaluate whether node status, LNR, number or location of positive nodes are independent factors for staging in PHC, and to determine the minimum requirements for node examination.

Methods—The Surveillance, Epidemiology, and End Results database was used to identify 1,116 resected PHCs from 1998 to 2008. The correlation between nodal status and survival was analyzed retrospectively.

Results—Lymph node metastasis occurred in 43.4% patients and was an independent predictor for overall survival (OS) and cancer-specific survival (CSS). No survival benefit was observed for an increasing number of node retrieval in node-positive patients. However, in node-negative patients, 13 node dissection was of more survival benefit than 3 total lymph node count (TLNC) 12 and TLNC<3 (5-year OS: 52.8% vs. 39.7% vs. 26.3%, $P=0.001$; 5-year CSS: 60.6% vs. 46.3% vs. 30.0%, $P=0.001$). No difference in survival between patients with regional and distant node involvement was found. Survival for patients with >3 positive nodes was significantly worse than that for those with 3 or less (RR: 1.466, $P=0.001$). And patients with LNR>0.27 also had unfavorable prognosis (RR: 1.376; $P=0.001$).

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Disclosures: The authors disclose no conflicts of interest.

Conclusions—To adequately assess nodal status of this life-threatening disease, 13 or more nodes retrieval should be considered. Number of positive nodes and LNR rather than location of metastatic nodes may be defined as parameters for staging of PHC.

Keywords

hilar cholangiocarcinoma; lymph node status; total lymph node count; lymph node ratio

Introduction

Perihilar cholangiocarcinoma (PHC), accounting for approximately 50% of all cholangiocarcinomas, is defined as adenocarcinoma of biliary tract originating from the second degree bile ducts to the insertion of the cystic duct into the common bile duct^{1, 2}. It is a rare tumor, with an incidence of 1–2 per 100,000 in the United States³. Radical resection with negative margins is the only potentially curative treatment for patients with resectable disease. Standard surgical therapy consists of extrahepatic bile duct resection, hepatectomy and en bloc lymphadenectomy. Although recent advances in early detection, perioperative care, and aggressive surgical technique have led to some improvement in patient outcomes, the overall survival (OS) after surgical resection of PHC remains extremely poor, the reported 5-year overall survival rates following radical surgery ranged from 20% to 42% for patients with PHC⁴. Additionally, only less than one half of PHC patients are resectable at initial presentation^{5–7}.

Lymph node (LN) metastasis has been showed as one of the most significantly prognostic factors in PHC^{2, 8–12}. The 5-year survival rate of patients with node-positive disease is less than 25%^{13–15}. Given the dismal prognosis and increasing incidence worldwide¹⁶, consensus about the extent of lymphadenectomy and the number of nodes required to be removed should be formulated, so as to establish an accurate staging. However, the optimal lymphadenectomy during resection for PHC remains a matter of debate in the literature. It has been demonstrated that inadequate LN examination may lead to understaging of several gastrointestinal cancers, namely gastric^{17, 18}, colorectal^{19, 20} and pancreatic cancer^{21, 22}. For PHC, no randomized controlled trials have been performed, given the infrequency with which this disease is encountered. Limited evidence is from a few retrospective cohort studies with inconsistent results. Studies from the Memorial Sloan-Kettering Center suggested that a minimum of 7 LNs retrieval were needed in the surgical specimen to obtain a correct staging^{23, 24}. While Aoba *et al.*²⁵ recommended 5 LNs examination was minimum requirement for adequate staging of PHC, although they mentioned that the minimum number of harvested nodes was increased steeply from 3 to 15 in the seventh edition of UICC TNM classification. Furthermore, the lymph node ratio (LNR, the ratio of positive nodes to the total number of retrieved nodes) has been determined to have strong prognostic value for several gastrointestinal tumors, but its role in PHC remains uncertain²⁶.

The Surveillance, Epidemiology, and End Results (SEER) database allows us to examine the survival outcomes of patients across the United States based on specific characteristics, such as age, sex, race, years of diagnosis, TNM stage, surgical status, total lymph node count (TLNC), number of positive nodes and whether radiotherapy was received. Thus, with the

lack of prospective trials and the conflicting results from single-institutional studies, we planned to conduct a population-based research using SEER database to evaluate the relationship between the lymph node status and survival, and to assess the impact of TLNC, absolute number and the location of positive nodes, LNR, and postoperative radiotherapy (PORT) on clinical outcomes.

Materials and Methods

Patients

The SEER program of the National Cancer Institute provides cancer incidence and survival data from population-based cancer registries covering approximately 28 percent of the US population. The SEER 18 registry database (1973–2011) was used as the source of patient information for this study²⁷. To allow sufficient time for follow-up and avoid a long inclusion period, we included cases diagnosed from 1998 through 2008. Patients were limited to those pathologically confirmed PHC, having undergone surgical resection and at least one lymph node examined. PHC were identified using ICD-O-3 histology codes 8000–8152, 8154–8231, 8243–8245, 8250–8576, 8940–8950, and 8980–8981. We excluded carcinoid tumor, neuroendocrine carcinoma, and adenosarcoma. Patients were also excluded if they had a survival time less than one month, presented with distant metastasis, had unknown stage information or no lymph node examined, or if surgery was not performed or surgery type was local excision or unknown. The stepwise extraction process of information from the original SEER database is listed in Supplementary Figure 1.

Data collection and statistical analysis

Demographic and clinicopathologic characteristics comprised region of the SEER registry, age at diagnosis, race, gender, year of diagnosis, staging based on AJCC 6th edition, tumor grade, TLNC, number of positive nodes, location of nodal involvement and receipt of radiotherapy. The LNR was calculated by dividing the number of positive nodes by TLNC in patients who had at least one node involved. Regional LNs included nodes along the cystic duct, common bile duct, hepatic artery, and portal vein. Distant LNs were defined as periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes. The primary endpoints included OS defined as the time from diagnosis until death of any cause or the most recent follow-up, and cancer-specific survival (CSS) calculated from the date of diagnosis to the date of PHC-related death or the most recent follow-up. The X-tile software program (Yale University, New Haven, CT, USA) as described previously²⁸ was used to determine the optimal cutoff values based on the maximal chi-square test. All variables possibly associated with outcomes were analyzed by univariate analysis, including age at diagnosis, gender, race, years of diagnosis, T stage, N stage, histological grade, TLNC, LNR, number and location of positive nodes, as well as PORT. Factors significant in univariate analysis were entered into a multivariate model to assess their prognostic value. Clinical and demographic factors between groups were evaluated using chi-square test. Survival curves were plotted by the Kaplan-Meier method, and differences were analyzed using log-rank test. Multivariate analyses were carried out using the Cox proportional hazard model, and the relative ratios (RR) with 95% confidence interval (95% CI) were calculated appropriately. $P < 0.05$ was considered to be statistically significant. All statistical analyses

were performed using SPSS 16.0 (IBM Corporation). The Sun Yat-Sen Memorial Hospital reviewed this study and declared it exempt because of a lack of protected health information contained in the databases used. And no consent was needed in this study.

Results

Demographic and tumor characteristics

A total of 1,116 patients who met eligibility criteria were included in the analysis (Supplementary Figure 1). The clinical characteristics and baseline characteristics were summarized in Table 1 and Supplementary Table 1. 43.4% of the patients (n=484) were confirmed with lymph node metastasis, among whom 25 (2.3%) patients presented with distant nodal involvement. In the entire cohort, 422 (37.8%) patients received PORT and 663 (59.4%) didn't receive PORT.

Impact of lymph node metastasis on survival

Median overall survival time for all patients was 23 (rang 1–164) months. Univariate analysis revealed that age 70 years, T stage (T3 or T4), N stage (node metastasis), histological grade (poorly or undifferentiated) were associated with worse OS/CSS. These factors were enrolled in multivariate analysis, and the result showed that N stage had the largest significant RR, which confirmed node metastasis as an independent and the most powerful prognostic factor (Table 2). Other independent prognostic factors comprised age, T stage, and histological grade. Figure 1 illustrates the survival curves of resected PHC patients according to the node status (OS: median survival time, 36 vs. 16 months; 49.7% vs. 19.8% at 3 years; vs. 37.8% 13.4% at 5 years; $P=0.001$; CSS: median survival time, 42 vs. 17 months; 53.0% vs. 22.3% at 3 years; 43.7% vs. 16.1% at 5 years; $P=0.001$).

Total lymph node count and survival

Of the 1,116 patients with at least one LN examined, the average TLNC was 8.27 ± 7.34 , and the median TLNC was 6 (range 1–53). It is well-known that inadequate examination of LN will lead to the understating of cancers^{17–22}. Therefore, to assess the minimum requirement for histological examination of LN in PHC, several cutoff values were created for survival comparisons. We found no survival benefit for an increasing number of lymph node retrieval in node-positive patients (Table 3). However, in node-negative patients, TLNC was significantly associated with extended survival time when modeled both as a continuous variable and using cut-points for removal of 2, 3, 5, 10, 15, 18 and 20 lymph nodes (Table 3). Indeed, 20 or more node retrieval is beyond clinical reality. Thus, to determine the optimal cut-point, X-tile software was used to divide the patients into three groups according to their TLNC (TLNC ≥ 13 , 3 $\leq$ TLNC ≤ 12 and TLNC < 3). Patients with TLNC ≥ 13 showed significant better prognosis than the other two groups (OS: median survival time, 64 vs. 37 vs. 28 months; 65.2% vs. 50.5% vs. 39.4% at 3 years; 52.8% vs. 39.7% vs. 26.3% at 5 years; $P=0.001$; CSS: median survival time, 111 vs. 48 vs. 30 months; 69.7% vs. 54.1% vs. 41.6% at 3 years; 60.6% vs. 46.3% vs. 30.0% at 5 years; $P=0.001$; Figure 2A, Table 4). And survival of patients with 3 $\leq$ TLNC ≤ 12 was also much more favorable than that of patients with TLNC < 3 (Figure 2A, Table 4). Moreover, multivariate analysis confirmed TLNC ≥ 13

was one of the independent favorable predictors for OS (RR=0.498, 95% CI 0.369–0.671; $P=0.001$) and CSS (RR=0.419, 95% CI 0.300–0.585; $P=0.001$; Table 4).

Survival analysis in patients with lymph node metastasis

In patients with node-positive disease, total number of positive nodes was correlated with survival ($n \leq 3$ vs. $n > 3$; OS: median survival time 17 vs. 13 months, 16.3% vs. 4.1% at 5 years, $P=0.001$; CSS: median survival time 18 vs. 15 months, 18.9% vs. 5.6% at 5 years, $P=0.001$; Figure 2B; Table 5). The largest difference in the outcomes was also identified when choosing 0.27 as a cutoff value for LNR (LNR ≤ 0.27 vs. LNR > 0.27 ; OS: median survival time 18 vs. 14 months, 18.9% vs. 8.6% at 5 years, $P=0.001$; CSS: median survival time 20 vs. 15 months, 21.4% vs. 11.2% at 5 years, $P=0.001$; Figure 2C; Table 5). Next, we assessed the significance of the location of positive nodes. There were no difference in survival between patients with or without distant node metastasis (Regional node metastasis vs. distant node metastasis; OS: median survival time 16 vs. 16 months, 13.5% vs. 12.0% at 5 years, $P=0.982$; CSS: median survival time 17 vs. 17 months, 16.1% vs. 16.8% at 5 years, $P=0.957$; Figure 2D; Table 5). After adjusting for confounders, positive LNs > 3 and LNR > 0.27 remained significantly associated with poor OS and CSS (Table 5).

Adjuvant radiotherapy and survival

We evaluated the clinical significance of PORT as well. 422 patients (37.8%) received PORT and those with nodal involvement were more likely to receive PORT than those without node metastasis (N+ 43.2%, N0 33.7%, $P=0.002$). There were no significant differences in OS or CSS between patients who received PORT and those who did not (Table 2), even when stratified by lymph node status (Supplementary Figure 2, Table 4 and 5). Interestingly, a trend of short-term survival benefit of PORT in node-positive patients was observed, although it failed to achieve a statistically significant level (OS: median survival time, 14 vs. 17 months; 17.4% vs. 22.3% at 3 years; $P=0.083$; CSS: median survival time, 16 vs. 18 months; 20.0% vs. 24.8% at 3 years; $P=0.058$; Supplementary Figure 2C).

Discussion

PHC, the most common type of cholangiocarcinoma, is an aggressive and hard-treated disease with dismal long-term prognosis¹. Several studies identified lymph node status as one of the most important prognostic factors^{2, 11, 12}. Radical surgery remains the only potentially curative treatment for PHC so far. Over the past two decades, studies showed that insufficient nodes retrieval during surgery or pathological examination would lead to underestimation of tumor stage in several gastrointestinal cancers^{17–22}. According to these data, recommendations for the minimum number of nodes examined in gastric^{17, 18}, colorectal^{19, 20}, and pancreatic cancer^{21, 22, 29} resection specimens were established. However, guidelines addressing the minimum requirement of lymph nodes examination for PHC are all ambiguous^{3, 30, 31} and no consensus statement has been formulated. Limited evidence with inconsistent results was obtained mainly from single-institutional retrospective studies. An analysis of 20 068 patients with gallbladder cancer, ampullary cancer, and extrahepatic bile duct cancer from SEER database suggested that a minimum of 10 LNs retrieval was required for adequate staging³². However, the biggest weakness of the

study is that it combined all tumor types of extrahepatic bile duct together in the analysis. It is not an optimal analysis method because of significant distinctions in the inherent tumor biology and outcomes. Another cohort study of 144 resected PHCs from Memorial Sloan-Kettering Cancer Center estimated the optimal TLNC was 7²³. Nevertheless, the median TLNC, the most fundamental index in this study, was only 3 (range: 0–16). Due to lack of convincing evidence, Aoba *et al.*²⁵ criticized the seventh edition of UICC TNM classification in which TNLC was increased from 3 to 15. And they suggested that the realistic number would be 5. But Hakeem *et al.*³³ found that patients with 20 or more nodes removed had worse 5-year OS than those with < 20 nodes. With the rarity of PHC, most researches had a very long inclusion period (ranged from 16 to 30 years)^{23, 32–34}. Given this, there might be selection bias resulted from the changes in perioperative management techniques over the course of a study.

The current population-based study comprised 1,116 resected PHC patients diagnosed between 1998 and 2008. The median TLNC was 6 (range 1–53), and the average was 8.27 ± 7.34 in this study. Since a low TLNC considerably decreases the quality of a study, our study is reliable in this context. We found 43.4% patients were node positive, which is consistent with previous reports^{10, 11, 35}, and we identified node metastasis as an independent and the most powerful prognostic factor among other classical factors (T stage, histological grade). Indeed, based on our results, added TLNC would bring marked survival benefit for node-negative patients but not for node-positive ones. And multivariate analysis evaluated that TLNC ≥ 13 was an independent favorable predictor for OS and CSS. The prolongation of survival may be owing to accurate staging and removal of tissues at risk for recurrence, which are resulted from elaborative and sufficient lymph nodes examination. We advocate that retrieving at least 13 lymph nodes during the radical resection of PHC to adequately assess nodal status. In addition, no survival benefit was observed for an increasing number of lymph node retrieval in node-positive patients. Therefore, once regional positive nodes are found, further removal does not change survival, which could intraoperatively modify operations to more palliative intent, sparing risk, time and morbidity.

Prognostic significance of the location of lymph node metastasis is another topic of debate. In the 7th edition of the AJCC staging system, N2 was introduced as a new N-stage for metastasis to lymph nodes beyond the hepatoduodenal ligament³. However, several large cohort studies determined that N2 patients had similar survivals with N1 patients^{8, 25}. We also observed no statistical differences in OS and CSS between patients with regional and distant node metastasis. These results suggested that the prognosis of PHC patients with node metastasis seemed to be related to the presence of metastatic nodes rather than their location. However, the number of patients with distant node metastasis was likely too small. We should be cautious about these results because of the limited generalization, but these data accord with findings of others^{8, 25}. LNR, which may improve distinction between prognostic groupings by taking into account the number of positive nodes, as well as the adequacy of lymphadenectomy and its pathologic analysis (total number of nodes examined and identified in the surgical specimen), has been realized to be a powerful predictor in gastrointestinal malignancies²⁶. Likewise, we found that survival for patients with LNR of

0.27 or less was significantly better than that for patients with LNR greater than 0.27, which is similar to the results of previous studies (cut-points ranged from 0.2 to 0.37)^{25, 33, 34}. We then assessed the predictive value of number of positive nodes. Significant worse survival was observed in patients with more than 3 positive nodes. Overall, we determined that number of positive nodes and LNR rather than location of metastatic nodes could provide notable prognostic value in resected PHC, which may be important for improving TNM staging (e.g. a N1 staged disease with LNR 0.27 or less obviously differs from N1 staged disease with LNR greater than 0.27).

Local recurrence after surgical resection is one of the main challenges for cure of PHC, which provides an important justification for the use of adjuvant therapy. Nevertheless, the role of PORT in PHC patients is poorly defined. A pooled analysis of 20 studies found that adjuvant chemotherapy or chemoradiation was associated with improved survival in patients with biliary tract cancers, especially in patients with node-positive disease³⁶. In our study, PORT failed to provide statistical survival benefit for resected PHC patients, regardless of the node status. Further randomized controlled trials are needed to shed light on this question.

The SEER database allows us to compare the outcomes of a relative rare cancer in cohorts with large sample size, but certain limitations should be acknowledged. No information is provided on margin status, which is a well-known important prognostic factor for PHC. And other data, namely performance status, use of chemotherapy, radiation dose, preoperative biliary drainage, Bismuth tumor type, protocols of lymphadenectomy and pathological examination, as well as comorbidities of patients, are also unavailable in SEER.

Conclusions

The present study of 1,116 resected PHC patients from SEER database evaluated lymph node metastasis as a critical independent and powerful poor prognostic factor. Patients with PHC undergoing radical resection should ideally have at least 13 lymph nodes examined to avoid understaging. Once regional positive nodes are found during resection, further removal will not change survival. For node-positive patients, number of positive nodes and LNR rather than location of metastatic nodes showed significant prognostic value, which might be used as elements for a new staging system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grant from the Doctoral Fund of Ministry of Education of China (No. 20120171110076); grant [2013]163 from Key Laboratory of Malignant Tumor Molecular Mechanism and Translational Medicine of Guangzhou Bureau of Science and Information Technology; grant KLB09001 from the Key Laboratory of Malignant Tumor Gene Regulation and Target Therapy of Guangdong Higher Education Institutes.

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Figure 1.

Kaplan-Meier curves of all resected perihilar cholangiocarcinoma patients according to the node status. Both overall survival (A) and cancer-specific survival (B) were significantly worse in node-positive patients ($P=0.001$).

Figure 2.

Kaplan-Meier curves of 632 N0 patients and 484 N+ patients. (A) Node-negative patients were categorized into 3 groups according to total lymph node count (TLNC, TLNC ≥ 13 , 3 $\leq$ TLNC < 12 , and 1 $\leq$ TLNC < 2). Patients with TLNC ≥ 13 had a better prognosis than the other two groups. (B) Positive nodes ≤ 3 indicated a longer overall survival time (median overall survival time, 17 vs. 13 months; 5-year OS 16.3% vs. 4.1%; $P=0.001$). (C) The outcome of patients with lymph node ratio (LNR) ≤ 0.27 was significantly better than that of LNR > 0.27 (median overall survival time, 18 vs. 14 months; 5-year OS 18.9% vs. 8.6%; $P=0.001$). (D) There were no survival difference between patients with regional nodes metastasis and those with distant nodes metastasis ($P=0.982$).

Table 1

Summary of 1,116 Patients' Characteristics

Characteristics	Number (%)
Age	
<70	684(61.3)
70	432(38.7)
Gender	
Male	686(61.5)
Female	430(38.5)
Race	
White	865(77.5)
Black	81(7.3)
Other [†]	170(15.2)
Year of diagnosis	
1998–2002	386(34.6)
2003–2008	730(65.4)
T stage [#]	
T1	206(18.5)
T2	255(22.9)
T3	525(47.0)
T4	130(11.6)
N stage [#]	
N0	632(56.6)
N1	484(43.4)
Regional	459(41.1)
Distant	25(2.3)
Grade	
I	163(14.6)
II	522(46.8)
III	324(29.0)
IV	9(0.8)
Unknown	98(8.8)
PORT [‡]	
No	663(59.4)
Yes	422(37.8)
Unknown	31(2.8)
Extent of surgery	
Local excision	495(44.4)
Radical surgery	597(53.5)
Unknown	24(2.1)
Total	1,116

[†] Other, American Indian/AK Native, Asian/Pacific Islander;

[‡] PORT, Postoperative radiotherapy;

[#] T stage, N stage, American Joint Committee on Cancer (AJCC) 6th edition.

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Table 2
Univariate and Multivariate Analyses for Overall Survival and Cancer Specific Survival in 1,116 Study Patients

Overall Survival(OS)							Cancer Specific Survival(CSS)					
Variable	M*	Survival Rate(%)		Multivariate		Univariate P	RR(95% CI)	P	Survival Rate(%)		Multivariate	
		3 years	5 years	RR(95% CI)	P				M	3 years	5 years	RR(95%CI)
Age(years)						0.021	1.179(1.028–1.352)	0.018				
<70	24	38.3	28.5						26	40.8	31.7	
70	22	34.2	25.2						25	38.8	32.5	
Gender						0.144						0.080
Male	24	38.8	28.7						26	42.3	33.7	
Female	23	33.4	24.9						25	36.4	29.3	
Race						0.437						0.162
White	23	37.0	27.6						26	40.9	33.2	
Black	22	32.1	21.7						22	33.5	23.7	
Other [‡]	24	37.3	28.5						25	39.1	30.5	
Years of diagnosis												0.199
1998–2002	23	35.2	25.9			0.248			24	38.2	29.8	
2003–2008	24	37.5	28.1						26	41.0	33.4	
T stage [#]						0.001	1.212(1.049–1.400)	0.009				0.001
T1, T2	32	46.8	35.4						40	52.0	42.9	
T3, T4	20	29.6	21.5						21	31.7	24.5	
N stage [#]						0.001	2.076(1.803–2.389)	0.001				0.001
N0	36	49.7	37.8						42	53.0	43.7	
N1	16	19.8	13.4						17	22.3	16.1	
Grade [§]						0.001						0.001
I, II	26	41.5	29.8				1.000(reference)		29	45.0	35.1	1.000(reference)
III, IV	18	26.8	21.2				1.280(1.116–1.468)	0.001	20	30.0	25.2	1.299(1.123–1.503)
Unknown	22	36.7	30.3						25	38.8	33.5	
PORT [‡]						0.968						0.670
No	24	37.4	27.9						26	41.0	32.9	

Variable	Overall Survival(OS)					Cancer Specific Survival(CSS)				
	Survival Rate(%)			Univariate		Survival Rate(%)			Univariate	
	M*	3 years	5 years	P	RR(95% CI)	M	3 years	5 years	P	RR(95%CI)
Yes	23	35.7	26.2			25	38.3	30.1		
Unknown	20	35.5	27.9			23	43.8	39.4		
Extent of surgery				0.953					0.792	
Local excision	23	37.2	28.3			25	39.9	32.2		
Radical surgery	24	36.7	26.4			26	40.6	31.9		
Unknown	19	26.1	26.1			19	27.6	27.6		

* M, Median survival time (month);

[†] Other, American Indian/AK Native, Asian/Pacific Islander;

[‡] PORT, Postoperative radiotherapy;

[#] T stage, N stage, American Joint Committee on Cancer (AJCC) 6th edition;

[§] Grade, I, Well differentiated, II, Moderately differentiated, III, Poorly differentiated, IV, Undifferentiated; $P < 0.05$ was considered to be statistically significant.

Table 3

Impact of Total Lymph Node Counts (TLNCs) on Survivals

TLNCs [‡]	No.	M [†]	Overall Survival(OS)			Cancer Specific Survival(CSS)			
			Survival Rate (%)		P	Survival Rate (%)		P	
			3 years	5 years		3 years	5 years		
N0 patients									
<2	110	29	36.4	22.7	0.001	30	38.7	27.2	0.001
2	522	40	52.5	41.1		55	56.1	47.3	
<3	193	28	39.4	26.3	0.001	30	41.6	30.0	0.001
3	439	43	54.2	43.0		60	58.1	49.9	
<5	309	32	45.3	33.1	0.004	34	47.6	36.8	0.001
5	323	43	53.9	42.4		63	58.4	50.7	
<10	469	33	46.7	35.1	0.006	36	49.6	40.2	0.002
10	163	56	58.4	46.0		71	63.0	53.9	
<15	552	33	47.1	35.6	0.003	37	50.4	41.1	0.001
15	80	71	68.0	53.8		111	71.2	62.6	
<18	579	33	47.7	35.9	0.002	38	50.9	41.5	0.001
18	53	80	71.5	59.9		110	76.5	69.2	
<20	599	34	48.4	36.5	0.011	39	51.5	42.2	0.003
20	33	111	72.7	61.8		111	81.5	72.4	
N1 patients									
<2	35	14	17.1	14.3	0.502	14	18.1	15.1	0.288
2	449	16	20.0	13.4		17	22.7	16.2	
<3	77	15	14.3	11.7	0.223	16	16.5	13.5	0.153
3	407	16	20.8	13.8		17	23.4	17.4	
<5	142	15	16.9	12.3	0.560	16	19.2	14.0	0.330
5	342	16	20.9	13.8		17	23.6	16.9	
<10	269	16	19.3	13.8	0.952	16	21.8	16.5	0.885
10	215	17	20.3	12.9		18	23.0	15.5	
<15	366	16	20.2	13.5	0.698	17	22.9	15.9	0.653
15	118	17	18.3	13.7		17	20.4	17.5	

TLNCs [‡]	Overall Survival(OS)				Cancer Specific Survival(CSS)				
	No.	M [†]	Survival Rate (%)		P	M	Survival Rate (%)		
			3 years	5 years			3 years	5 years	
<18	401	16	20.0	13.5	0.891	17	22.5	15.8	0.958
18	83	17	18.8	13.0		17	21.6	18.0	
<20	426	16	20.0	13.4	0.887	17	22.4	16.0	0.944
20	58	17	17.7	13.3		18	21.7	16.3	

[†]M, Median survival time (month);

[‡]TLNCs, Total lymph node counts; *P*<0.05 was considered to be statistically significant.

Table 4
Univariate and Multivariate Analyses for Overall Survival and Cancer Specific Survival in 632 N0 Patients

Variable(No.)	Overall Survival(OS)					Cancer Specific Survival(CSS)				
	M [#]	Survival Rate(%)			P	Survival Rate(%)	P	Multivariate		
		3 years	5 years	Univariate				RR(95% CI)	RR(95% CI)	P
Age				0.013	1.306(1.075–1.588)	0.007	0.617			
<70(386)	39	51.9	40.4			42	53.9	43.4		
70(246)	31	46.2	33.5			43	51.6	44.4		
Gender				0.322						0.321
Male(398)	39	51.2	39.8			48	54.2	45.4		
Female(234)	33	47.0	34.3			37	50.9	40.5		
Race				0.279						0.036
White(478)	38	50.9	39.0			48	54.9	46.4	1.000(reference)	
Black(49)	31	19.8	13.3			33	46.4	32.3	0.693(0.531–0.905)	0.007
Other [†] (105)	32	44.9	29.6			32	47.6	37.5	0.932(0.620–1.402)	0.737
Years of diagnosis				0.414						0.529
1998–2002(217)	35	49.8	35.9			41	52.8	41.3		
2003–2008(415)	36	49.6	39.2			43	53.1	45.3		
T stage [#]				0.001	1.463(1.209–1.771)	0.001			1.679(1.361–2.071)	0.001
T1, T2(328)	48	56.2	43.6			64	61.1	51.6		
T3, T4(304)	28	42.6	31.5			30	44.4	35.3		
T1NC ^{&}				0.001						0.001
1–2(193)	28	39.4	26.3		1.000(reference)	30	41.6	30.0	1.000(reference)	
3–12(325)	37	50.5	39.7		0.694(0.563–0.854)	48	54.1	46.3	0.666(0.533–0.833)	0.001
13(114)	64	65.2	52.8		0.498(0.369–0.671)	111	69.7	60.6	0.419(0.300–0.585)	0.001
Grade [§]				0.010						0.002
I, II(405)	43	54.3	39.8			53	57.8	46.4		
III, IV(168)	26	38.7	32.4			29	41.5	36.4		
Unknown(59)	33	49.2	40.6			50	52.4	45.8		
PORT [‡]				0.787						0.624

Variable(No.)	Overall Survival(OS)						Cancer Specific Survival(CSS)					
	Survival Rate(%)			Univariate			Survival Rate(%)			Univariate		
	M*	3 years	5 years	P	RR(95% CI)	P	M	3 years	5 years	P	RR(95%CI)	P
No(404)	37	50.3	37.4				43	54.0	44.1			
Yes(213)	34	48.7	38.5				39	50.7	42.1			
Unknown(15)	31	46.7	37.3				66	60.0	60.0			
Extent of surgery				0.658						0.637		
Local excision	34	48.3	37.9				39	51.4	43.0			
Radical surgery	38	51.0	37.3				48	54.7	44.0			
Unknown	22	50.0	50.0				22	50.0	50.0			

* M, Median survival time (month);

† Other, American Indian/AK Native, Asian/Pacific Islander.

‡ PORT, postoperative radiotherapy;

T stage, American Joint Committee on Cancer (AJCC) 6th edition;

& TLNC, Total lymph node counts;

§ Grade, I, Well differentiated, II, Moderately differentiated, III, Poorly differentiated, IV, Undifferentiated; $P < 0.05$ was considered to be statistically significant.

Table 5

Univariate and Multivariate Analyses for Overall Survival and Cancer Specific Survival in 484 Node-Positive Patients

Variable(No.)	Overall Survival(OS)					Cancer Specific Survival(CSS)						
	M*	Survival Rate(%)		Multivariate		M	Survival Rate(%)		Multivariate			
		3 years	5 years	Univariate P	RR(95% CI)		P	3 years	5 years	Univariate P	RR(95%CI)	P
Age					0.430					0.388		
<70(298)	17	20.7	13.0			17	22.9	15.8				
70(186)	14	18.3	14.2			16	21.3	16.6				
Gender					0.613					0.346		
Male(288)	17	21.5	13.3			18	24.9	16.4				
Female(196)	15	17.1	13.6			16	18.7	15.6				
Race					0.147					0.099		
White(387)	16	19.8	13.3			17	22.7	16.1				
Black(32)	11	12.5	9.4			11	13.1	9.8				
Other ^{†‡} (65)	17	23.1	15.7			17	24.9	18.7				
Years of diagnosis					0.238					0.123		
1998–2002(169)	15	16.6	13.0			16	18.5	14.5				
2003–2008(315)	17	21.5	13.5			18	24.4	16.8				
T stage [#]					0.689					0.351		
T1, T2(133)	15	23.6	15.1			18	28.0	19.8				
T3, T4(351)	16	18.3	12.8			17	20.4	14.8				
TLR ^{&}					0.001	1.376(1.128–1.678)	0.002			0.001	1.374(1.116–1.693)	0.003
0.27(228)	18	27.1	18.9			20	29.1	21.4				
>0.27(256)	14	13.3	8.6			15	16.1	11.2				
Positive LNs					0.001	1.466(1.166–1.844)	0.001			0.001	1.387(1.0861.771)	0.009
3(373)	17	22.7	16.3			18	25.1	18.9				
>3(111)	13	9.9	4.1			15	12.2	5.6				
LN ^s Extent [*]					0.982					0.957		
Regional(459)	16	20.0	13.5			17	22.7	16.1				
Distant(25)	16	16.0	12.0			17	16.8	16.8				

Variable(No.)	Overall Survival(OS)					Cancer Specific Survival(CSS)				
	Survival Rate(%)			Univariate		Survival Rate(%)			Univariate	
	M*	3 years	5 years	P	RR(95% CI)	M	3 years	5 years	P	RR(95%CI)
Grade [§]				0.001					0.006	
I, II(280)	17	23.0	15.6		1.000(reference)	18	25.7	18.2		1.000(reference)
III, IV(165)	13	14.7	9.7		1.338(1.090–1.642)	15	17.4	12.8		1.301(1.047–1.617)
Unknown(39)	15	17.9	15.0		1.170(0.821–1.669)	16	18.7	15.6		1.259(0.877–1.807)
PORT [‡]				0.083					0.058	
No(259)	14	17.4	13.1			16	20.0	15.0		
Yes(209)	17	22.3	13.6			18	24.8	17.2		
Unknown(16)	16	25.0	18.8			18	27.3	20.5		
Extent of surgery				0.509					0.282	
Local excision	16	18.5	12.2			17	20.3	14.0		
Radical surgery	16	21.3	14.7			17	24.6	18.1		
Unknown	16	0.0	0.0			17	0.0	0.0		

* M. Median survival time (month);

[‡] Other, American Indian/AK Native, Asian/Pacific Islander.

[‡] PORT, Postoperative radiotherapy;

[#] T stage, American Joint Committee on Cancer (AJCC) 6th edition;

[&] TLR, Lymph node ratio;

[§] Grade, I, Well differentiated, II, Moderately differentiated, III, Poorly differentiated, IV, Undifferentiated; $P < 0.05$ was considered to be statistically significant.

* LNs Extent, Lymph nodes extent.

Regional: Cystic duct (node of the neck of the gallbladder)

Pericholedochal (node around common bile duct)

Node of the foramen of Winslow

Hilar (in the hepatoduodenal ligament)

Hepatic, periportal, periduodenal, peripancreatic (near head of pancreas only)

Distant: Celiac artery, Superior mesenteric artery, Superior mesenteric vein, Para-aortic, Pericaval.