



## Does resection improve overall survival for intrahepatic cholangiocarcinoma with nodal metastases?

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### ABSTRACT

**Background:** The potential benefit of surgical resection of intrahepatic cholangiocarcinoma in patients with locoregionally advanced disease has not been definitively determined.

**Methods:** The National Cancer Database was queried to identify patients with clinical evidence of node-positive intrahepatic cholangiocarcinoma. Resected patients were stratified by margin status and lymph node ratio (nodes positive to nodes harvested). Risk of death was determined using Cox regression models and Kaplan-Meier survival functions.

**Results:** A total of 1,425 patients with T(any)N1M0 intrahepatic cholangiocarcinoma were identified. Two hundred twelve (14.9%) underwent surgical resection. On multivariable Cox regression, R0 resection afforded a survival benefit regardless of lymph node ratio (lymph node ratio > 0.5: hazard ratio 0.466, 95% confidence interval 0.304–0.715; lymph node ratio ≤ 0.5: hazard ratio 0.444, 95% confidence interval 0.322–0.611), whereas a survival benefit was only seen in R1 patients with lymph node ratio ≤ 0.5 (hazard ratio 0.470, 95% confidence interval 0.316–0.701). On Kaplan-Meier, median survival was 11.6 months with chemotherapy, 15.7 months with R0 resection in lymph node ratio > 0.5, and 22.2 months with R0 resection in lymph node ratio ≤ 0.5 (P < .001).

**Discussion:** Margin negative resection is associated with a risk-adjusted survival benefit for patients with clinically N1 intrahepatic cholangiocarcinoma regardless of the degree of regional lymph node involvement.

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### INTRODUCTION

Cancers of the liver and intrahepatic bile ducts are expected to contribute to an estimated 21,600 United States deaths in 2019 [1]. Intrahepatic cholangiocarcinoma (ICC) is currently the second most common primary liver malignancy, and the incidence of ICC appears to be increasing [2]. ICC is, in general, associated with poor survival. Surgical resection is the therapeutic modality that offers the greatest potential to prolong survival and the only therapeutic modality that carries the potential to cure patients presenting with early-stage ICC. ICC is often, however, diagnosed at late stages when patients have distant metastatic disease. Surgical resection in these cases offers no potential to meaningfully impact survival and is used rarely to provide palliation.

Surgical resection in patients with evidence of regional nodal involvement (N1) but no evidence of distant metastatic disease at diagnosis remains somewhat controversial. Consensus guidelines regarding optimal surgical management of patients with clinical evidence of regional lymph node involvement are not definitive. There are no prospective randomized trials comparing resection to systemic therapy alone in patients presenting with clinical evidence of node-positive resectable ICC. Results from various institutional and registry studies have primarily examined predictors of poor outcome including nodal status as a predictive factor. These studies have consistently identified locoregional nodal involvement in ICC to be associated with a significant reduction in overall survival (OS) following resection [3–8]. Such results have led several authors to argue that regional nodal involvement may be a relative contraindication to surgery [9].

Prior institutional studies have included small numbers of patients. Registry studies have not controlled for degree of lymph node involvement. As a result, these studies offer a limited ability to guide surgical decision making relating to resection for patients that present with extensive regional nodal involvement. In the current work, we use the National Cancer Database (NCDB) to examine the impact of surgical resection on OS in patients presenting with pretreatment evidence of

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lymph node involvement. We attempt to control for degree of nodal involvement by stratifying patients by pathologic node ratio in an effort to assess the potential for surgical resection to impact survival in patients that have more extensive nodal involvement at the time of diagnosis. We hypothesized that patients with higher lymph node ratios (LNRs) and positive resection margins would have limited benefit from resection.

## MATERIALS AND METHODS

**Data Source.** The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society containing Health Insurance Portability and Accountability Act-compliant deidentified patient data. The NCDB is a prospectively maintained hospital-based data registry that collects information on >70% of incident malignant diagnoses compiled from 1,500 CoC-accredited institutions nationwide. The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators. Our study obtained the NCDB Participant User Files for diagnosis years 2004–2015. A Data Use Agreement was obtained, and this project met criteria for exemption from the Loyola University Chicago Institutional Review Board (LU# 211870).

**Study Design.** Patients included for analysis were those that had histologically confirmed invasive ICC as defined by *International Classification of Diseases for Oncology* histology codes 8140, 8160, or 8180 with anatomic primary sites in the liver or intrahepatic bile ducts (*International Classification of Diseases for Oncology* topography codes C22.0 or C22.1) diagnosed from January 1, 2004, to December 31, 2014, and with clinical evidence (definitive axial or endoscopic imaging or percutaneous/endoscopic biopsy positive) for regional nodal involvement at the time of diagnosis but had no evidence of distant metastatic disease. ICC stages thus included cT1–4 N1 M0 and clinical stages IIIC (American Joint Committee on Cancer [AJCC] sixth edition) or IVa (AJCC seventh edition) using the AJCC criteria.

Patients were categorized by treatment type into (1) those that received no treatment, (2) those that received surgical resection, and (3) those that received definitive chemotherapy only. Surgically treated patients were stratified based on whether their pathologic resection margin was microscopically negative (R0) or positive (R1). The NCDB does offer some information on type of resection, allowing for subtype of resection in the following categories: extended lobectomy, lobectomy, and partial hepatectomy. It does not provide information on the extent (number of segments) involved in a partial hepatectomy. Given the small number of patients in our resection cohort and our belief that the margin status was a more important determinate of outcome, we elected to stratify surgical patients by margin and not by type of resection. LNRs were calculated for each surgically treated patient and defined by the number of pathologically positive lymph nodes divided by the total number of regional nodes examined. We elected to further stratify patients around the median LNR into high-LNR (>0.5) and low-LNR ( $\leq 0.5$ ) cohorts based on sensitivity analyses suggesting this break point as potentially the most discriminating.

Patients who underwent liver transplantation or local tumor procedures like radiofrequency ablation were excluded from analysis. We elected to exclude patients who underwent ablation because there were very few ( $n = 11$ ) patients in the NCDB data set that presented with clinical evidence of lymph node involvement but no metastasis and underwent ablation. Given this, meaningful statistical comparisons between this group and the surgical or medical cohort could not be made. Patients that underwent surgical resection but had no pathologic node assessment were excluded from the analysis. Patients diagnosed in 2015 who did not have adequate long-term survival data were excluded from analysis. Patients who had other synchronous malignancies and those treated surgically who were missing margin or regional node

pathologic data were also excluded from the analysis. Because only 13.7% of our surgically managed cohort received neoadjuvant systemic therapy, we were underpowered to assess the utility of this strategy. We elected to leave those patients in the surgical cohort and to adjust the multivariable modeling for receipt of neoadjuvant therapy.

**Statistical Analysis.** Overall survival comparisons were made among node-positive ICC patients based on treatment received. Survival functions were developed using the Kaplan-Meier (KM) method. Equality of survivor functions was assessed with the log-rank test. Unadjusted comparisons of continuous variables were performed using independent Student's  $t$  tests and Wilcoxon rank-sum (Mann-Whitney  $U$ ) tests, as appropriate, and comparisons of proportions between cohorts were performed using Pearson  $\chi^2$ . Factors identified as significant on univariate analysis ( $P < .1$ ) and those considered on the basis of past experience to be clinically relevant were considered for multivariable modeling of OS. Adjusted risk of death was assessed using multivariable Cox proportional hazards (PH) regression models. Our final model adjusted for patient age (per year), sex, race/ethnicity, insurance category, Charlson-Deyo comorbidity score, tumor size greater than or less than 5cm, cancer treatment facility type, and receipt of radiation therapy [2,10,11]. Binary "dummy" variables were generated to serve as dependent variables in each Cox PH model representing risk of surgically managed patients within each margin status or LNR designation referenced to patients managed nonoperatively with chemotherapy. Similar to prior investigations, the nonoperatively managed patients who received systemic chemotherapy were chosen to represent the reference population to investigate the independent effect of surgical resection on survival understanding that this method is subject to selection bias [12].

Data are presented as means  $\pm$  standard deviation, median with interquartile range (IQR), or counts with percentages, as appropriate. Adjusted hazard ratios (HRs) are represented with the 95% confidence interval (CI). Statistical tests were 2-sided. All statistical analyses were performed using Stata software (Version 14.2; StataCorp LLC, College Station, TX).

## RESULTS

**Demographic, Facility, and Treatment Characteristics.** In total, 1,425 patients with clinically node-positive, nonmetastatic ICC treated during the study period met our inclusion criteria. Of those, 212 (14.9%) underwent a surgical resection with curative intent, and 1,213 (85.1%) were managed nonoperatively. Patient and treatment facility characteristics for these 2 cohorts are summarized in Table 1. Patients who underwent surgery tended to be younger, were more likely to be privately insured, were more likely to be treated at an academic facility, were more likely to have a tumor size less than or equal to 5 cm, and were more likely to receive radiation therapy during their treatment course than those that did not undergo surgical resection ( $P \leq .018$ ).

Operative, tumor, and treatment characteristics for those who underwent surgical resection are summarized in Table 2. These results are broken down by pathologic status of the resection margin. Our sample included 75 (35.4%) patients who had a positive microscopic margin (R1) after resection. Median lymph node sampling (R0: 4, IQR 2–8; R1: 4, IQR 2–8;  $P = .521$ ) and median number of pathologically positive nodes (R0: 2, IQR 1–3; R1: 2, IQR 1–3;  $P = .513$ ) for patients undergoing R0 resection were identical to those for patients undergoing R1 resection. There were, likewise, no differences between margin status cohorts regarding resection type, LNR, tumor size, grade, neoadjuvant or adjuvant use of chemotherapy, or radiation therapy ( $P > .161$ ).

**Univariate Survival Analysis by Margin Status and Node Ratio.** Figure 1 depicts the KM survival functions for patients with node-positive ICC based on treatment received. For these analyses, patients with missing survival data were excluded. The final number of patients for both the

**Table 1**  
Patient and treating facility characteristics for patients undergoing treatment of node positive ICC

	No surgery		Surgery		P
	n = 1,213		n = 212		
Age (y), mean (SD)	64.2	12.4	59.5	12.4	<.001*
Male, n (%)	621	51.2%	96	45.3%	.112
Race, n (%)					.354
White	1023	84.3%	173	81.6%	
Black	106	8.7%	17	8.0%	
Asian/PI	56	4.6%	14	6.6%	
Other	28	2.3%	8	3.8%	
Insurance, n (%)					.001*
Uninsured	50	4.1%	3	1.4%	
Private	482	39.7%	115	54.2%	
Medicaid	83	6.8%	15	7.1%	
Medicare	569	46.9%	73	34.4%	
Other	29	2.4%	6	2.8%	
Charlson-Deyo, n (%)					.309
0	831	68.5%	156	73.6%	
1	261	21.5%	42	19.8%	
2	66	5.4%	6	2.8%	
3+	55	4.5%	8	3.8%	
Facility type, n (%)					<.001*
Community	55	4.5%	4	1.9%	
Comp community	340	28.0%	25	11.8%	
Academic	686	56.6%	142	67.0%	
Integrated network	97	8.0%	27	12.7%	
Unknown	35	2.9%	14	6.6%	
Facility location, n (%)					<.001*
Northeast	264	21.8%	55	25.9%	
Southeast	245	20.2%	56	26.4%	
North Central	325	26.8%	55	25.9%	
South Central	149	12.3%	15	7.1%	
West	195	16.1%	17	8.0%	
Unknown	35	2.9%	14	6.6%	
Tumor size, n (%)					.018*
≤5 cm	382	31.5%	87	41.0%	
>5 cm	827	68.2%	125	59.0%	
Unknown	4	0.3%	0		
Grade					<.001*
Well differentiated	35	2.9%	15	7.1%	
Mod differentiated	195	16.1%	97	45.8%	
Poorly differentiated	266	21.9%	65	30.7%	
Undifferentiated	8	0.7%	5	2.4%	
Unknown	709	58.5%	30	14.2%	
Chemotherapy, n (%)	742	61.2%	118	55.7%	.065
Radiation therapy, n (%)	216	17.8%	61	28.8%	<.001*

MIS, minimally invasive surgery, Comp, comprehensive, PI, Pacific Islander.

\* P < .05.

KM analysis and Cox PH analysis (section below) was 1,118 patients. Median OS for patients who underwent R0 resection with or without systemic therapy was 20.1 months. That for patients undergoing an R1 resection was 16.9 months. Patients who were treated nonoperatively with systemic chemotherapy with or without radiation therapy had a median OS of 11.6 months, whereas patients who did not receive surgery, chemotherapy, or radiation therapy had a median OS of 2.8 months.

Figure 2 represents the KM survival functions generated for patients who underwent surgical resection stratified by LNR. The LNRs had a non-normal distribution with a median LNR of 0.5. Patients with low LNRs demonstrated the best OS. For these patients, the median OS was similar regardless of surgical margin status. Median OS for low-LNR patients undergoing an R0 resection was 22.0 months. That for low-LNR patients undergoing an R1 resection was 21.5 months. The margin status seemed to have a greater impact on outcome for patients who had high LNR. When more than half of lymph nodes sampled were positive (high LNR), patients had a median OS of 15.7 months when they underwent R0 resections. When patients with a high LNR underwent an R1 resection, there was OS pattern similar to that for patients undergoing treatment with chemotherapy alone: median OS of 11.8 months.

**Table 2**  
Treatment characteristics for patients who underwent surgery stratified by margin status

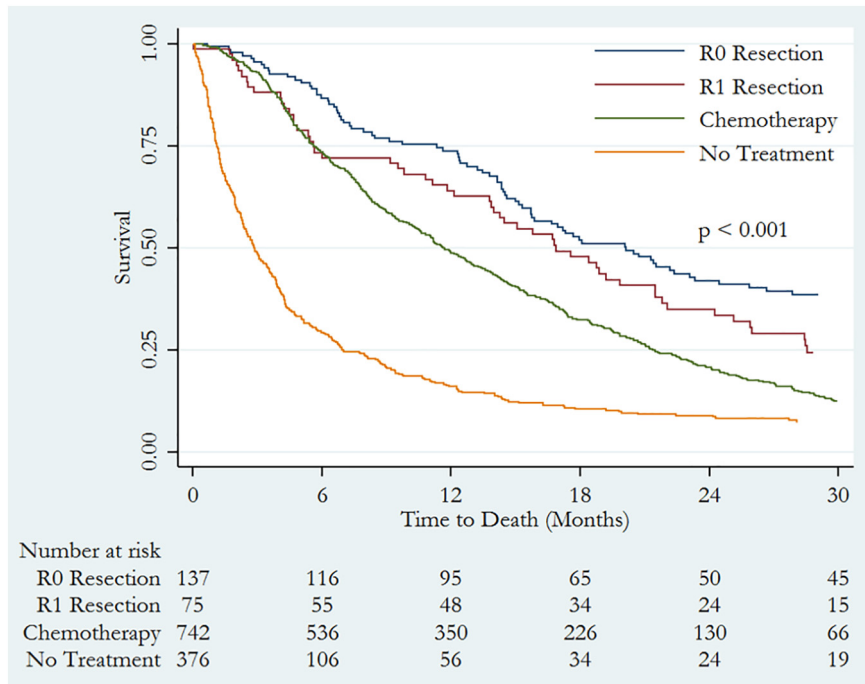
	R0 margin		R1 margin		P
	n = 137		n = 75		
Resection type					.390
Wedge/segmental	36	26.3%	15	20.0%	
Lobectomy	36	26.3%	27	36.0%	
Extended lobectomy	27	19.7%	17	22.7%	
Partial hepatectomy	36	26.3%	16	21.3%	
NOS	2	1.5%	0		
Nodes sampled (median, IQR)	4	2–8	4	2–8	.521
Nodes positive (median, IQR)	2	1–3	2	1–3	.513
LNR > 0.5	50	36.5%	33	44.0%	.284
Tumor size, n (%)					.721
≤5 cm	55	40.1%	32	42.7%	
>5 cm	82	59.9%	43	57.3%	
Grade					.857
Well differentiated	9	6.6%	6	8.0%	
Mod differentiated	65	47.4%	32	42.7%	
Poorly differentiated	43	31.4%	22	29.3%	
Undifferentiated	3	2.2%	2	2.7%	
Unknown	17	12.4%	13	17.3%	
Chemotherapy, n (%)					.545
Adjuvant	54	39.4%	30	40.0%	
Neoadjuvant	13	9.5%	9	12.0%	
Sandwich	3	2.2%	4	5.3%	
None/unknown	59	43.1%	28	37.3%	
Radiation therapy, n (%)	35	25.5%	26	34.7%	.161

R0, microscopically negative surgical margin; R1, microscopically positive surgical margin; NOS, not otherwise specified.

**Cox PH Model by Margin Status and Node Ratio.** We used Cox PH regression modeling to compare patients who underwent surgical resection to those who underwent systemic chemotherapy adjusting for patient age, sex, race, insurance, Charlson-Deyo score, tumor size, and treatment facility type (Table 3). In general, patients undergoing surgical resection demonstrated a significantly lower adjusted risk of death than those undergoing chemotherapy alone. This was true for patients who had high (HR 0.608; 95% CI 0.437–0.846) and low (HR 0.456; 95% CI 0.352–0.591) LNRs. When surgical patients were further stratified by resection margin status, however, patients that had a high LNR and underwent an R1 resection did not appear to benefit from the surgical resection. All patients who had an R0 resection demonstrated lower risk of death than those who were treated with chemotherapy alone. This was true for patients undergoing R0 resection with high (HR 0.466; 95% CI 0.304–0.715) LNRs and those undergoing R0 resection with low (HR 0.444; 95% CI 0.322–0.611) LNRs. Among patients undergoing an R1 resection, only those with a low LNR also demonstrated a lower risk of death than patients undergoing treatment with chemotherapy alone (HR 0.470; 95% CI 0.316–0.701). By contrast, patients undergoing R1 resection and having a high pathologic LNR demonstrated a risk of death identical to that for patients undergoing chemotherapy alone (HR 0.019; 95% CI 0.616–1.687).

**DISCUSSION**

This study aimed to determine if surgical resection is associated with improved OS for patients with ICC and extensive regional nodal involvement. This study used patients treated with systemic chemotherapy alone as a comparison cohort. After adjusting for patient, pathologic stage, and facility factors, margin negative (R0) surgical resection demonstrated a reduced risk of death. This benefit appeared to be independent of degree of nodal involvement, as patients with high and low LNRs who underwent R0 resection demonstrated a significant survival advantage over those undergoing chemotherapy alone. Among patients who underwent an R1 resection, only those that had a low LNR appeared to benefit from resection. No difference in adjusted risk of

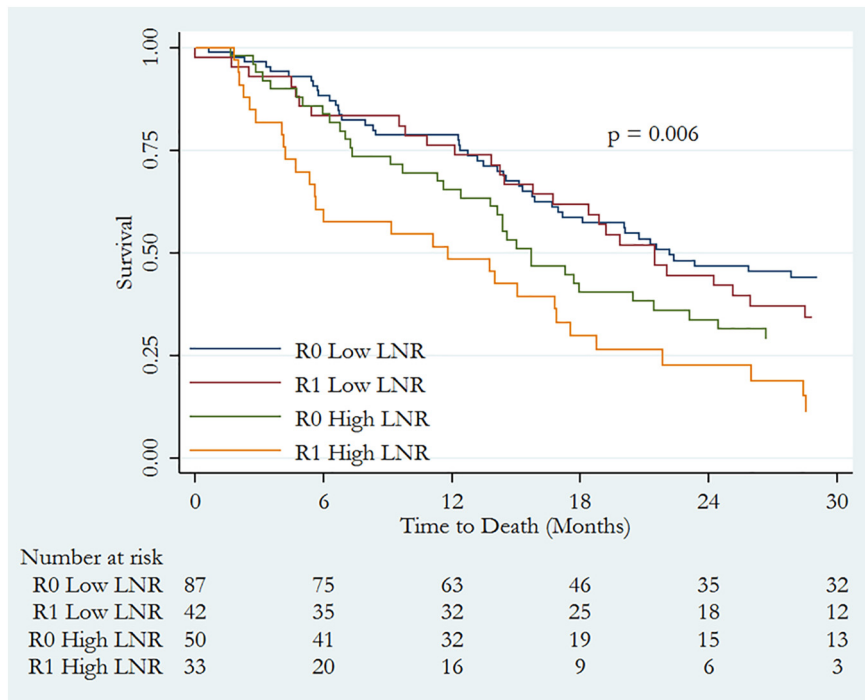


**Fig 1.** Kaplan-Meier survival analysis for node-positive ICC, by treatment type. *R0*, microscopically negative surgical margin; *R1*, microscopically positive surgical margin. Chemotherapy: nonoperative management including systemic chemotherapy; no treatment: nonoperative management without systemic chemotherapy or radiation therapy.

death was detected among those having an *R1* resection and high LNR compared to patients undergoing chemotherapy alone. The low observed rate of attempted curative-intent resection in this population almost certainly reflects surgeon hesitancy to offer resection, with this hesitancy driven primarily by prior clinical experience. Results from historical series have been uniformly typified by low rates of disease-specific survival after resection in patients with locally advanced and

node-positive ICC and have led to an ingrained nihilism. Our study offers data that suggest appropriately selected patients with advanced ICC may have meaningful benefit from surgical resection.

Existing literature evaluating appropriate treatment of patients with clinical evidence of extensive nodal metastases at the time of diagnosis is limited. Prior studies have generally involved single-center retrospective reviews that include almost exclusively patients with node-



**Fig 2.** Kaplan-Meier survival analysis for node-positive ICC for patients who underwent resection, by margin status and LNR. *R0*, microscopically negative surgical margin; *R1*, microscopically positive surgical margin. LNR = number of pathologically positive nodes divided by total nodes examined. Low LNR was defined by ratio  $\leq 0.5$ ; high LNR was defined by ratio  $> 0.5$ .

**Table 3**  
Multivariable Cox PH regression model for risk of death

	HR	95% CI	
Any surgery			
Low LNR	0.456*	0.352	0.591
High LNR	0.608*	0.437	0.846
R0 resection			
Low LNR	0.444*	0.322	0.611
High LNR	0.466*	0.304	0.715
R1 resection			
Low LNR	0.470*	0.316	0.701
High LNR	1.019	0.616	1.687

Multivariate regression model adjusting for age, sex, Charlson-Deyo comorbidity score, tumor size, race, insurance, cancer facility type, and treatment with radiation. Reference is patients who underwent nonoperative management with systemic chemotherapy.

LNR = number of pathologically positive nodes divided by total nodes examined. Low LNR was defined by ratio  $\leq 0.5$ ; high LNR was defined by ratio  $> 0.5$ .

R0, microscopically negative surgical margin; R1, microscopically positive surgical margin.

\*  $P < .05$ .

negative disease or a relatively small number of patients treated surgically with N1 disease [2,13–15]. A single-center (Memorial Sloan Kettering Cancer Center) evaluation of 82 ICC resections found that resection offered their patients the best opportunity for long-term survival; however, only 7 patients with N1 disease underwent resection with curative intent [2]. Many larger reports derive from an international consortium of major hepatobiliary centers. These generally support surgical resection of locoregionally advanced disease in select cases; however, these analyses have not directly compared surgery versus chemotherapy for ICC identified pretreatment as having extensive locoregional node involvement [7,16,17]. This international group has examined predictors of survival following ICC resection and developed a prognostic nomogram with important clinical utility following resection; however, the lymphadenectomy rate was relatively low, with only 49% of patients undergoing a lymphadenectomy of any extent. In addition, node harvest and LNR trends were not examined as predictors in their Cox regression [7]. One previous NCDB analysis identified predictors of survival in 160 patients with N1 ICC treated with major hepatectomy; however, outcomes were not compared to patients undergoing systemic chemotherapy, and missing data required imputation of lymph node harvest counts [5]. Another NCDB study examined 1,009 patients with T(any) N1 M0 ICC to evaluate the effect of surgery and adjuvant therapy on survival and found improved survival with surgically resected patients, especially when a negative margin is achieved. This study did not evaluate lymph node yield and thus the effect of LNR on outcomes [18]. A study using Surveillance, Epidemiology, and End Results data identified 169 patients treated with node-positive ICC and was not able to demonstrate a survival advantage for surgical resection when compared to chemotherapy alone; however, this study was limited by sample size (21 patients represented in the control group) and lacked details regarding lymph node harvest, number of lymph nodes positive, and pathologic margin status [12].

Lymph node involvement (N1 disease) in ICC has been clearly associated with worse OS, and therefore, the prognostic value of evaluating the regional lymph nodes in ICC has been well established. Currently, National Comprehensive Cancer Network (NCCN) guidelines, along with many reported prior investigations, support hepatic resection of ICC lesions to a goal of negative margins, with regional lymphadenectomy to be performed in select cases [9]. Released in 2016, the AJCC eighth edition recommends recovery of at least 6 lymph nodes from appropriate nodal stations for complete pathologic staging following resection. In spite of these findings/recommendations, there is no definitive evidence that lymph node harvest impacts OS, and performance of a concurrent lymphadenectomy during ICC resection is highly variable even in experienced centers [8]. A 2014 systematic review found that only 78.5% of ICC resections include a lymphadenectomy at the time of resection but also found that half of those performed yield

pathologically positive nodes (N1) [3]. One retrospective analysis found that a lymphadenectomy including at least 6 nodes was only performed in 44.6% of cases from a sample of more than a thousand ICC resections at major hepatobiliary centers [8]. A recent NCDB study evaluating 120 patients with clinical N1 ICC treated with surgery found no specific threshold for the number of lymph nodes harvested associated with a survival advantage in R0 or R1 resected ICC. The investigators cautioned surgeons to consider the limited survival benefit in relationship to the prognostic utility of lymphadenectomy [19]. Others have advocated for consideration of routine lymphadenectomy [5,6]. The current study findings identify LNR as an important prognostic indicator and would support the practice of performing a more formal regional lymphadenectomy in patients with ICC.

Evidence for the prognostic utility of the LNR has been reported in other gastrointestinal cancers including pancreatic, gallbladder, and colon cancer [20–22]. This ratio may potentially have a more limited utility in resections for ICC due to lesser lymph node harvests achieved and the fact that lymphadenectomy is highly variable in the care of these patients. This analysis was unable to evaluate nodal ratios for patients who underwent resection but had zero nodes examined (26 patients) because these patients are unable to provide a degree of pathologic nodal involvement. In spite of this potential limitation, our findings would suggest that LNR can be used in this disease. To our knowledge, use of nodal ratio for developing prognostic models in node-positive ICC resection has not been previously reported. In the present study, we report that high LNRs are associated with reduced OS following resection of clinically node-positive ICC.

Adjuvant systemic therapy after resection has also been repeatedly demonstrated to be associated with improved oncologic outcomes in ICC but had variable patterns of implementation nationally [16,17,23]. A recent meta-analysis found that adjuvant chemotherapy (particularly gemcitabine-based regimens) improved oncologic outcomes for resectable ICC [24]. NCCN supports treatment with chemotherapy for advanced inoperable disease [17]. In contrast, a recent NCDB analysis found that less than half of patients with ICC were treated in adherence with this NCCN guideline and received systemic therapy [17]. The present study results corroborate this prior evidence of the utility of systemic therapy in node-positive ICC demonstrating that, among patients with advanced ICC who are not taken to surgery, those that receive systemic therapy as an alternative do have improved OS relative to those that have advanced ICC and do not receive systemic therapy. Although treatment patterns nationally can be variable, the investigators felt that the improved outcomes noted in patients treated with chemotherapy made this group an appropriate choice for a comparative control group in our adjusted analysis. Systemic chemotherapy offers the next best alternative treatment to surgery for patients with node-positive cholangiocarcinoma.

The low incidence of clinically node-positive ICC significantly impacts the ability of registry and single-institutional studies to provide reliable guidance to practitioners. Multi-institutional efforts potentially using collaborative randomized trials may better examine the benefit of surgical resection over systemic chemotherapy, chemoradiation, or locoregional catheter-based therapies for patients with clinically node-positive ICC. Future studies may develop nomograms to aid in presurgical clinical decision making for these complex patients, similar to the one developed to predict lymph node metastasis before resection in ICC [14]. In addition, future prospective efforts may allow us to identify the appropriate use of lymphadenectomy in ICC and the optimal technique and harvest amounts to improve meaningful oncologic outcomes [8].

This study has several limitations which are important to recognize. NCDB prospectively collects data on participants, but our study is by nature a retrospective observational study that is subject to selection and omitted variable bias. Selection bias almost certainly resulted in disproportionately advanced cancers being represented in the cohort that received chemotherapy without surgery. This would be expected to inappropriately increase our observed benefit of surgical resection. Our

analysis allowed for risk adjustment in multivariable regression models for many relevant patient-, tumor-, and facility-level factors. We were not, however, able to adjust for several factors that would be expected to have an effect on OS because these are not included in the NCDB: anatomic location of the tumor, multifocal morphology, presence of microscopic vascular invasion, and amount and type of chemotherapy given [2,7,14]. Similarly, we are unable to evaluate several specific features of operative technique because the NCDB Intrahepatic Bile Duct Surgery Codes do not allow us to do it. For example, with the data from the NCDB, we are able to distinguish hepatic lobectomy from partial hepatectomy but cannot subtype partial hepatectomy by number of hepatic segments resected. Such technical features of the surgeries performed undoubtedly impact clinical outcome, and our inability to adjust for them may affect our findings and conclusions. Another significant limitation relates to the average number of lymph nodes sampled. The median number of nodes sampled was 4. Low lymph node samplings make working with LNRs mathematically challenging. We did feel, however, that attempting to evaluate the effect of the degree of nodal involvement was of significant clinical relevance and worth attempting. Our data would suggest that the LNR may act as a surrogate for degree of nodal involvement and that patients with lower degrees of nodal involvement are more likely to benefit from resection.

In spite of apparent limitations, this study supports the role for curative hepatic resection of select patients with nonmetastatic ICC and extensive regional nodal involvement. These findings offer justification for surgical resection of these advanced tumors, especially when preoperative imaging studies demonstrate a potential for R0 resection. The findings of this study suggest that even patients with high degrees of nodal involvement demonstrate a survival benefit from R0 surgical resection in comparison to patients with clinical node-positive, nonmetastatic ICC patients treated with systemic therapy alone.

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#### Conflict of Interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

#### Author Contribution

**Patrick J. Sweigert:** conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing (original draft and review), visualization, project administration; **Emanuel Eguia:** methodology, software, validation, formal analysis, data curation, writing (review); **Haroon Janjua:** methodology, validation, resources, data curation, writing (review); **Sean P Nassooy:** validation, formal analysis, writing (review); **Lawrence M. Knab:** methodology, validation, investigation, writing (review); **Gerard Abood:** methodology, validation, investigation, writing (review); **Paul C. Kuo:** methodology, validation, investigation, writing (review); **Marshall S. Baker:** conceptualization, methodology, software, validation, formal analysis, investigation, resources, writing (original and review), visualization supervision, project administration.

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