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Does Hospital Type Affect Lymph Node Evaluation in Intrahepatic Cholangiocarcinoma? Analysis of the National Cancer Database

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ABSTRACT

INTRODUCTION

NCCN guidelines dictate sampling at least 6 lymph nodes for Intrahepatic cholangiocarcinoma (ICC), although prior studies have shown low compliance with this recommendation. This study was performed to compare the extent of lymph node evaluation (LNE), use of neoadjuvant chemotherapy, and survival outcomes of patients undergoing surgical resection of ICC in academic and non-academic institutions.

METHODS

Patients diagnosed with ICC between 2010 and 2017 and who underwent surgical resection were identified through the NCDB. Hospital types were classified as academic or non-academic institutions. The primary outcome measure assessed the difference among academic and non-academic hospitals in obtaining at least 6 lymph nodes.

RESULTS

Overall, 1843 patients were included in the analyses, and 20.46% of patients had >= 6 lymph nodes evaluated. There was no significant difference in the extent of LNE or use of neoadjuvant chemotherapy between institution types. Kaplan-Meier did not demonstrate improved survival with the evaluation of >= 6 nodes. Cox regression analysis did not identify institution type, the extent of LNE, or the use of neoadjuvant chemotherapy as independent predictors of survival.

CONCLUSION

Our study suggests that compliance with NCCN guidelines on LNE in Abstract ICC is low; however, extent of LNE, use of neoadjuvant chemotherapy, and oncologic outcomes were equal in academic and non-academic centers.

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KEYOWRDS

Intrahepatic cholangiocarcinoma; Lymph node; Tumor; Chemotherapy

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a rare form of cancer that carries a poor prognosis, as the disease is often locally advanced at the time of diagnosis [1]. The incidence of ICC has been estimated at 7.7 per 1,000,000 person-years; however, recent studies have found that incidence and mortality are trending upwards in the United States [2,3]. A surgical approach is recommended for most patients with ICC, with complete or partial tumor resections demonstrating the greatest survival benefit [4]. Tumor characteristics, degree of tumor necrosis, liver enzyme values, and lymph node status are significant predictors of outcome [4,5]. Lymph node evaluation is essential for accurate staging and prognostication [6,7]. Nearly a quarter of ICC patients with the early-stage disease were found to have lymph node metastasis upon resection [8].

NCCN guidelines recommend regional lymphadenectomy of at least 6 lymph nodes at the time of surgical resection of the tumor [9]. However, a retrospective analysis published in 2017 found that 52.4% of patients who underwent resection for ICC had at least one lymph node evaluated; only 11.4% of the population studied had a 6 or higher lymph node yield [8]. It is unclear whether rates of adherence to the NCCN guidelines are similar among different types of hospitals (i.e., academic vs. non-academic institutions). Furthermore, it is not well established that higher adherence rates to the NCCN guidelines result in better oncologic outcomes [10].

The focus of this study is to determine whether academic institutions or non-academic institutions are more likely to adhere to the NCCN guidelines regarding lymph node evaluation. In addition, the utilization of neoadjuvant chemotherapy and its influence on lymph node yield will also be analyzed for all healthcare facilities. Lastly, we will investigate whether adherence to the NCCN guidelines and use of neoadjuvant chemotherapy is associated with improved oncologic outcomes and survival.

METHODS

Study Design & Cohort Creation

This multicenter, retrospective cohort study was conducted using data from the National Cancer Database (NCDB). Adult patients diagnosed with ICC from 2000 to 2017 were included in the study cohort. The cohort was generated by first identifying patients with ICC undergoing intrahepatic bile duct resections. Patients with other histological variants of hepatic cancer, multiple primary cancers, metastatic disease at the time of diagnosis, or missing data on lymph node evaluation were excluded. Figure 1 shows the cohort selection.

Step	N
NCDB Inter Bile Dataset	32263
Age >= 18	32254
Year >= 2010, 7th Edition	22015
Required Histology	21527
Have Definitive Surgery	2745
Exclude Stage 4 or M1, Metastasis at dx	2350
Primary Cancer	1884
Exclude if Treatment Information Unknown or not Clear	1874
Lymph Node Harvest not Missing	1843

Figure 1: Patient selection criteria for generation of the study cohort using the National Cancer Database.

Data Sources and Study Variables

The NCDB is a dataset maintained by the American College of Surgeons and the American Cancer Society and includes patient data from over 1,500 centers across the United States. Our patient population was obtained from the Hepatic Participant Use Data File (PUF). PUFs are de-identified data files available to selected investigators at the Commission on Cancer (CoC) approved institutions to advance patient care.

Our study compared academic institutions (i.e., Academic/Research Programs) to non-academic institutions (i.e., Community Cancer Programs, Comprehensive Community Cancer Programs, and Integrated Network Cancer Programs). Patient-level variables obtained from the NCDB included age, sex, race (White, black, other), insurance status (not insured, private insurance, Medicaid, Medicare, other government), income level, education level, urban/rural status, and Charlson-Deyo co-morbidity score. Disease and treatment variables obtained from the NCDB included clinical-stage, receipt of neoadjuvant chemotherapy, surgical margin status, and tumor grade.

Statistical Analysis

Mean, standard deviation with t-test across groups were reported for continuous variables. Frequency, percentage, Chi-square tests were reported for categorical variables. Multivariable regression with adjusting all variables listed above was conducted for complete cases only. Poisson regression with robust variance and clustering on the hospital was used for our primary outcome-lymph node evaluation ≥6. We tested hospital type as binary academic hospital and 4 categories separately. A fractional polynomial test was used to check continuous variable linearity assumption. Due to violation of the assumption, age was re-categorized into quartiles. Subgroup analysis was conducted using the same approach for patients with and without neoadjuvant therapy. The significance level is set to $p \leq 0.05$. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Demographics

A total of 1,843 patients were included in the final study cohort. The average age of patients was 63.09 years (Median: 64 years), and 45.5% were male. Most patients were white (83.7%), were insured by Medicare (47.1%), and resided in metro settings (79.4%). Lastly, most patients (87.6%) did not receive neoadjuvant chemotherapy prior to resection.

Impact of Institution Type on Lymph Node Evaluation

Within the cohort, 1,147 patients (62.2%) underwent surgical resection at academic institutions, while 633 (34.3%) were resected at non-academic institutions. The remaining 63 (3.4%) patients had missing data regarding hospital type. There was no difference in lymph node evaluation between the academic and non-academic centers (64.7% *vs.* 31%; p=0.16). No institution was found to be more likely to evaluate ≥6 lymph nodes. Table 1 highlights patient characteristics based on lymph node evaluation. Figure 2A highlights the percentage of ≥6 lymph node evaluations at each hospital type.

In the total cohort, patients treated at academic institutions (RR 0.91, 95% CI [0.687-1.204]) were not more likely to have ≥6 lymph node evaluations than those at non-academic institutions. Multivariable analysis based on all the hospital types also demonstrated that there was no difference in lymph node evaluation between academic/research programs and community cancer programs (RR: 0.797 [95%CI: 0.275-2.31]), comprehensive community cancer programs (RR: 1.002 [95%CI: 0.708-1.417]), or integrated network cancer programs (RR: 1.317 [95%CI: 0.918-1.89]). Table 2 highlights the results of the multivariable analysis.

Impact of Neoadjuvant Therapy on Lymph Node Evaluation

Patients who received neoadjuvant chemotherapy had similar node yields (13.8% *vs.* 11.9%; p = 0.33). Figure 2B highlights neoadjuvant chemotherapy's effect on the total lymph nodes evaluated at each hospital type. The multivariable analysis also revealed that in the total cohort, patients who received neoadjuvant chemotherapy (9.37 [0.638-1.375]) were not more likely to have ≥6 lymph

nodes evaluated. Table 2 and Table 3 highlight the results of the multivariable analysis.

	<6 nodes		>= 6 nodes		
	N	**%**	**N**	**%**	**p-value**
Academic Hospital					0.16
No	516	35.2	117	31	
Yes	903	61.6	244	64.7	
Facility Type					0.37
Community Cancer Program	28	1.9	9	2.4	
Comprehensive Community Cancer Program	296	20.2	69	18.3	
Academic/Research Program	903	61.6	244	64.7	
Integrated Network Cancer Program	192	13.1	39	10.3	
Neoadjuvant Chemotherapy					0.33
No	1290	88	325	86.2	
Yes	175	11.9	52	13.8	
AJCC Clinical T					0.007
0	7	0.5	1	0.3	
1	541	36.9	121	32.1	
2	395	26.9	94	24.9	
3	110	7.5	49	13	
4	42	2.9	14	3.7	
AJCC Clinical N					<0.0001
0	1200	81.9	255	67.6	
1	132	9	83	22	
Sex					0.46
Male	673	45.9	165	43.8	
Female	793	54.1	212	56.2	
Race					0.36
White	1221	83.3	322	85.4	
Black	97	6.6	25	6.6	
Other	131	8.9	25	6.6	
Hispanic Origin					0.16
No	1333	90.9	348	92.3	
Yes	104	7.1	19	5	
Surgical Margin					0.33
Negative Margin	1042	71.1	279	74	
Positive Margin	241	16.4	55	14.6	
Primary Payor					0.001
Private Insurance	581	39.6	185	49.1	
Medicaid	77	5.3	12	3.2	
Medicare	703	48	166	44	
Other	105	7.2	14	3.7	
No High School Degree Quartiles 2012-2016					0.11
>=17.6%	271	18.5	63	16.7	
10.9%-17.5%	298	20.3	56	14.9	
6.3%-10.8%	395	26.9	98	26	
<6.3%	353	24.1	103	27.3	
Median Income Quartiles 2012-2016					0.18
Missing	152	10.4	58	15.4	
<$40,227	206	14.1	39	10.3	
$40,227-$50,353	257	17.5	63	16.7	
$50,354-$63,332	306	20.9	66	17.5	
>=$63,333	545	37.2	151	40.1	
Urban/Rural					0.009
Metro	1195	81.5	269	71.4	
Urban	175	11.9	64	17	
Rural	24	1.6	5	1.3	
Charlson-Deyo Score					0.005
0	990	67.5	283	75.1	
>= 1	476	32.5	94	24.9	
Behavior					0.99
Carcinoma in Situ	1	0.1	0	0	
Invasive	1465	99.9	377	100	
Grade					0.26
Well differentiated, differentiated, NOS	135	9.2	34	9	
Moderately Differentiated, Moderately Well Differentiated, Intermediate Differentiation	737	50.3	207	54.9	
Poorly Differentiated	395	26.9	100	26.5	
Undifferentiated, Anaplastic	16	1.1	2	0.5	
Cell Type not Determined, not Stated not Applicable, Unknown Primaries, High Grade Dysplasia	183	12.5	34	9	

Table 1: Demographics lymph node harvest.

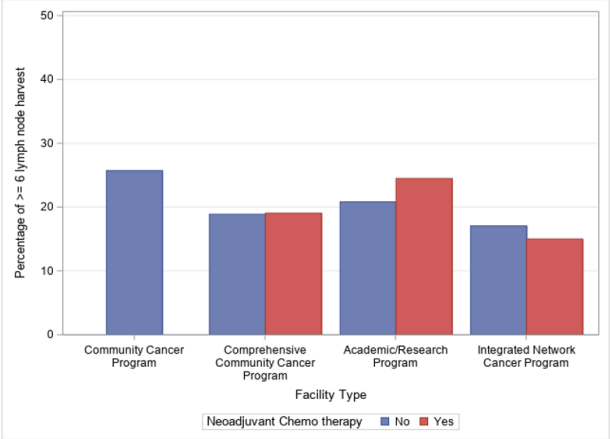

Figure 2A: Effect of institution type and neoadjuvant chemotherapy on LN harvest. Patient population broken down as those who received neoadjuvant chemotherapy (red) and those who did not (blue). Percentage of >=6 LN harvested at 4 hospital types.

	RR	**95% CI**		**p-value**
Facility Type				
Community Cancer Program	0.797	0.275	2.31	0.6763
Comprehensive Community Cancer Program	1.002	0.708	1.417	0.9931
Academic/Research Program	Ref			
Integrated Network Cancer Program	1.317	0.918	1.89	0.1344
Neoadjuvant Chemotherapy				
No	Ref			
Yes	0.953	0.651	1.396	0.8048
Age				
<=55	Ref			
56-64	0.854	0.588	1.241	0.4087
65-71	1.034	0.683	1.564	0.876
>= 72	1.04	0.66	1.638	0.8655
AJCC Clinical T				
1	Ref			
2	0.989	0.721	1.356	0.9438
3	1.681	1.153	2.449	0.0069
4	1.329	0.682	2.59	0.4025
AJCC Clinical N				
0	Ref			
1	2.247	1.67	3.022	<.0001
Sex				
Male	Ref			
Female	1.086	0.825	1.429	0.5559
Race				
White	Ref			
Black	0.976	0.595	1.599	0.9221
Other	0.572	0.283	1.157	0.1199
Surgical Margin				
Negative Margin	Ref			
Positive Margin	0.614	0.402	0.937	0.0238
Insurance				
Private Insurance	1.466	1.041	2.065	0.0285
Medicaid	0.816	0.311	2.141	0.6797
Medicare	Ref			
Other	0.507	0.195	1.315	0.1626
Income				
<$40,227	Ref			
$40,227-$50,353	1.234	0.724	2.106	0.4395
$50,354-$63,332	1.155	0.69	1.933	0.583
>=$63,333	1.365	0.84	2.22	0.2096
Charlson-Deyo Score				
0	Ref			
>= 1	0.833	0.616	1.126	0.2345
Grade				
Well differentiated, differentiated, NOS	Ref			
Moderately Differentiated, Moderately Well Differentiated, Intermediate Differentiation	1.038	0.659	1.635	0.871
Poorly Differentiated	1.116	0.692	1.801	0.6523

Table 2: Multivariable analysis based on facility type.

	RR	95% CI		p-value
Academic Hospital				
No	Ref			
Yes	0.909	0.687	1.204	0.5068
Neoadjuvant Chemotherapy				
No	Ref			
Yes	0.937	0.638	1.375	0.7378
Age				
<=55	Ref			
56-64	0.857	0.589	1.247	0.4193
65-71	1.03	0.681	1.556	0.8895
>= 72	1.043	0.664	1.64	0.8547
AJCC Clinical T				
1	Ref			
2	0.987	0.719	1.356	0.9371
3	1.698	1.165	2.476	0.0059
4	1.327	0.681	2.585	0.4055
AJCC Clinical N				
0	Ref			
1	2.205	1.635	2.973	<.0001
Sex				
Male	Ref			
Female	1.081	0.821	1.424	0.5777
Race				
White	Ref			
Black	0.976	0.596	1.6	0.9238
Other	0.55	0.274	1.104	0.0925
Surgical Margin				
Negative Margin	Ref			
Positive Margin	0.606	0.397	0.925	0.0202
Primary Payor				
Private Insurance	1.461	1.04	2.05	0.0286
Medicaid	0.839	0.32	2.198	0.7212
Medicare	Ref			
Other	0.51	0.197	1.324	0.1669
Median Income Quartiles				
< $40,227	Ref			
$40,227-$50,353	1.247	0.733	2.122	0.416
$50,354-$63,332	1.169	0.699	1.953	0.5522
>=$63,333	1.363	0.843	2.202	0.2065
Charlson-Deyo Score				
0	Ref			
>=1	0.825	0.61	1.117	0.2143
Grade				
Well Differentiated, Differentiated, NOS	Ref			
Moderately Differentiated, Moderately Well Differentiated, Intermediate Differentiation	1.027	0.655	1.612	0.9063
Poorly Differentiated	1.102	0.685	1.773	0.6889

Table 3: Multivariable analysis based on LN harvest ≥6.

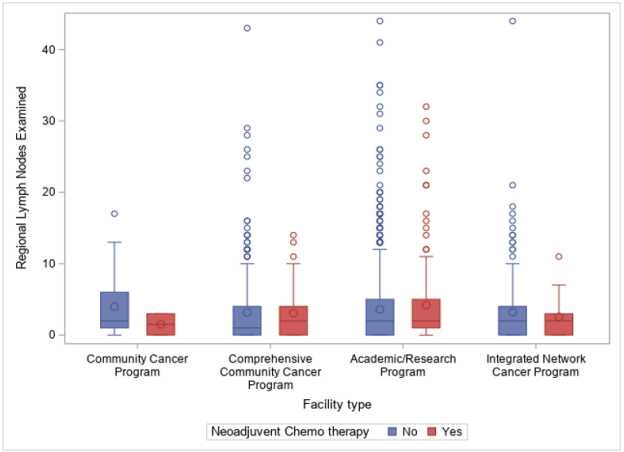

Figure 2B: Effect of institution type and neoadjuvant chemotherapy on LN harvest. Patient population broken down as those who received neoadjuvant chemotherapy (red) and those who did not (blue). Mean number of LN harvested at 4 hospital types.

	HR	95% CI		p-value
Academic Hospital				
No	Ref			
Yes	0.958	0.776	1.184	0.6937
Lymph Node Harvest				
>= 6	0.987	0.757	1.287	0.9233
< 6	Ref			
Neoadjuvant Chemotherapy				
No	Ref			
Yes	0.761	0.543	1.065	0.1109
Age				
<=55	Ref			
56-64	1.186	0.874	1.609	0.2733
65-71	1.7	1.183	2.443	0.0042
>= 72	2.275	1.561	3.316	<.0001
AJCC Clinical T				
1	Ref			
2	1.769	1.415	2.212	<.0001
3	1.936	1.381	2.713	0.0001
4	1.474	0.889	2.442	0.1324
AJCC Clinical N				
0	Ref			
1	1.124	0.83	1.522	0.4514
Sex				
Male	Ref			
Female	1.061	0.868	1.295	0.5645
Race				
White	Ref			
Black	1.1	0.712	1.699	0.6686
Other	0.88	0.587	1.318	0.5341
Surgical Margin				
Negative Margin	Ref			
Positive Margin	1.651	1.277	2.135	0.0001
Insurance				
Private Insurance	1.252	0.934	1.677	0.1324
Medicaid	1.668	0.944	2.949	0.0781
Medicare	Ref			
Other	1.461	0.904	2.362	0.1215
Income				
<$40,227	Ref			
$40,227-$50,353	1.085	0.768	1.531	0.6444
$50,354-$63,332	1.03	0.731	1.453	0.8653
>=$63,333	0.868	0.635	1.186	0.3733
Charlson-Deyo Score				
0	Ref			
>= 1	1.166	0.944	1.439	0.1537
Grade				
Well Differentiated, Differentiated, NOS	Ref			
Moderately Differentiated, Moderately Well Differentiated, Intermediate Differentiation	1.134	0.799	1.609	0.4812
Poorly Differentiated	1.701	1.183	2.444	0.0041

Table 4: Cox regression.

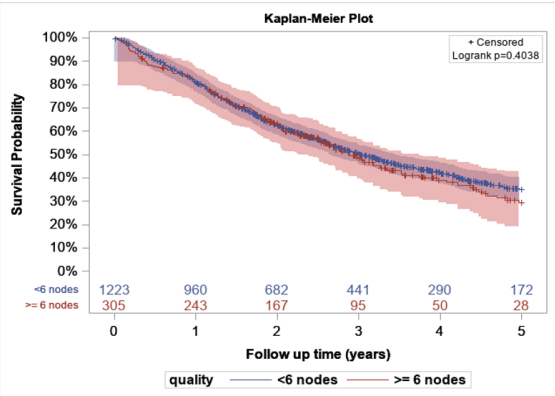

Figure 3A: Kaplan-Meier Plot of 5-years survival probability for patients undergoing resection for ICC. Kaplan-Meier plot of 5-years survival for patients with <6 and >=6 LN harvested.

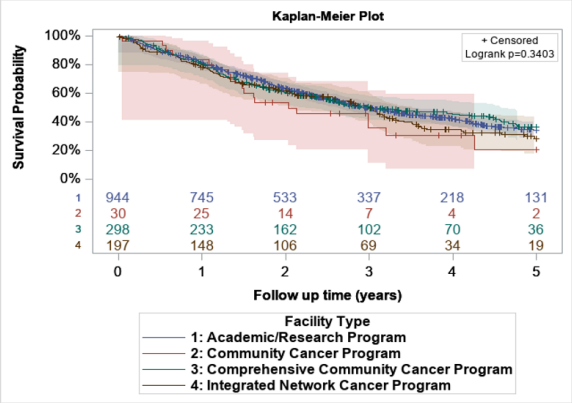

Figure 3B: Kaplan-Meier Plot of 5-years survival probability for patients undergoing resection for ICC. Survival curves for patients stratified by treating hospital type: Academic/research (blue), community cancer program (red), comprehensive community cancer program (green), and integrated network cancer program (brown).

Influences on 5-Years Survival

Evaluation of ≥6 lymph nodes was not associated with improved 5-years survival compared to the evaluation of <6 (HR: 0.987 [95%CI: 0.757-1.287]). Five-years survival was similar at academic and non-academic hospitals (HR: 0.958 [95%CI: 0.776-1.184]). Neoadjuvant chemotherapy also did not influence survival (HR: 0.761 [95%CI: 0.543-1.065]). Predictors of decreased 5-years survival include age ≥72 (HR: 2.275 [95%CI: 1.561-3.316]) and positive surgical margins after resection (HR: 1.651 [95%CI: 1.277-2.135]). Table 4 highlights the results of the Cox regression. Figure 3A and Figure 3B are Kaplan-Meier plots highlighting the effect of LN evaluation and hospital type on patients' 5-years survival.

DISCUSSION

We found no difference in lymph node evaluation between the academic and non-academic centers in ICC patients. In all facilities studied, less than 30% of patients received adequate LN sampling per NCCN guidelines. There was no statistical difference in the utilization of neoadjuvant chemotherapy among the hospital types, and the use of neoadjuvant chemotherapy did not significantly influence lymph node evaluation. The NCCN guidelines recommend evaluating a minimum of 6 lymph nodes at the time of surgical resection [9]. However, lymphadenectomy remains inconsistent in the surgical management of ICC patients. Zhang et al. demonstrated that only 11.4% of patients received an adequate evaluation of 6 lymph nodes [8].

5-years survival outcomes were similar at academic and non-academic institutions. Neither adequate lymph node evaluation (≥6) nor neoadjuvant chemotherapy was associated with improved 5-years survival. Factors that negatively affected 5-years survival were age (≥72 years old) and positive surgical margins after resection.

Similar studies regarding surgical resection of other cancers have found that academic institutions achieve adequate LN evaluation as per NCCN guidelines more often than non-academic institutions [11-15]. The findings of this study do not support an institutional difference in the treatment of ICC. There appears to be an overarching hesitancy to perform adequate lymph node evaluation on ICC patients undergoing surgical resection, regardless of institution, possibly due to concern for postoperative complications [16,17]. These concerns are not unfounded, as one meta-analysis found that lymphadenectomy was associated with increased postoperative morbidity, with similar survival outcomes [10]. However, this study has been criticized, with opponents suggesting that the patients who underwent lymphadenectomy had more advanced disease at the time of resection and thus required more extensive intervention [10,17]. While minimizing the risk

of complications is desirable; there is no conclusive evidence that performing thorough lymphadenectomy on non-cirrhotic ICC patients increases morbidity and mortality.

Lymph node evaluation remains one of the most important prognostic factors for staging ICC, influencing treatment plans and care goals [6,7]. However, it remains unclear if greater LN evaluation improves oncologic outcomes and survival. Our study and several others suggest that evaluation of ≥6 lymph nodes do not affect overall survival.10,16 In contrast, other studies did demonstrate improved oncologic outcomes [18,19]. More comprehensive research is required to clarify the association between LN evaluation and survival outcomes. Until such a time, the issue remains contested.

The role of neoadjuvant chemotherapy for ICC patients has not been adequately established [10-12]. The results of our study do not support the widespread use of neoadjuvant chemotherapy. Neoadjuvant chemotherapy did not influence lymph node evaluation. Furthermore, our findings align with previous work showing that the use of neoadjuvant chemotherapy does not affect the long-term survival of ICC patients. The lack of adequate evidence supporting the efficacy of neoadjuvant chemotherapy for the management of ICC may explain why academic and non-academic institutions utilized neoadjuvant chemotherapy at similarly low rates.

Arguably the most notable finding of our study is that ICC patients have similar outcomes regardless of institution. Those who underwent surgical resection at academic and non-academic institutions were equally likely to receive adequate lymphadenectomy and had comparable 5-years survival metrics. There is data suggesting that hospital designation is associated with lower surgical mortality rates for many cancer procedures [20]. While our study did not investigate complication or mortality rates, it is encouraging that non-academic institutions (which generally do not benefit from the funding and resources of academic institutions) deliver comparable outcomes to patients. This can be reassuring to patients who cannot receive care from academic institutions due to geographic or financial barriers.

There are several limitations to the study. First, as we used retrospective data, the relationships identified represent correlation rather than causation. Second, a minority of patients in the final cohort received neoadjuvant chemotherapy, limiting the strength of the analysis. Third, confounding factors may have influenced recorded lymph node evaluation, including pathologic studies on surgical specimens. Fourth, we did not assess the role of surgeon experience or hospital volume in lymph node evaluation. Finally, this study does not explore the impact of comorbid conditions such as cirrhosis or postoperative complications.

CONCLUSION

Lymph node evaluations for intrahepatic cholangiocarcinoma are similar at academic and non-academic institutions. Use of neoadjuvant chemotherapy and adequate lymph node evaluation was similar across all institutions, and neither factor was found to improve 5-years survival. In addition, compliance with the NCCN recommended evaluation of ≥6 lymph nodes were low regardless of hospital type.

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CONFLICT OF INTEREST

All authors report no conflict of interest.

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