Original Article

Adjuvant chemotherapy for intrahepatic cholangiocarcinoma: approaching clinical practice consensus?

Ariella M. Altman[1], Scott Kizy[1], Schelomo Marmor[1], Jane Y. C. Hui[1], Todd M. Tuttle[1], Eric H. Jensen[1], Jason W. Denbo[2]

[1]Department of Surgery, University of Minnesota, Minneapolis, MN, USA; [2]Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA

Contributions: (I) Conception and design: AM Altman, S Kizy, S Marmor, JY Hui, TM Tuttle, EH Jensen, JW Denbo; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: AM Altman, S Kizy, S Marmor, JY Hui, TM Tuttle, EH Jensen, JW Denbo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jason W. Denbo. Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612-9416, USA. Email: jason.denbo@moffitt.org.

Background: Intrahepatic cholangiocarcinoma (ICC) is rare with limited evidence-based guidelines. This retrospective study evaluates the use of chemotherapy in patients with resected ICC.

Methods: The Surveillance Epidemiology and End Results (SEER) program database was used to identify patients with resected ICC. Patients were stratified by date of diagnosis (2000–2004, 2005–2009, 2010–2014), T, and N stage. Multivariable logistic regression models identified predictors of chemotherapy use. Kaplan-Meier and Cox proportional hazard models were used to identify survival trends.

Results: One thousand and two hundred twenty-three patients met inclusion criteria. Chemotherapy utilization increased over time (33% to 41%, P≤0.05). Chemotherapy use increased in lymph node (LN) positive patients [32% to 60% in 2010–2014; (P≤0.05) and T3/T4 disease (40% to 60% in 2010–2014; P≤0.01], but not in patients with LN negative or T1/T2 disease. LN positivity was associated with utilization of chemotherapy in 2005–2009 and 2010–2014. Overall survival increased from 32 to 41 months (P≤0.05). In LN positive patients, chemotherapy was associated with a decreased hazard ratio of death (P≤0.05) and T3/T4 disease was associated with an increased hazard ratio of death (P≤0.05).

Conclusions: Adjuvant chemotherapy use in ICC has increased. More LN positive or patients with T3/T4 tumors are receiving chemotherapy, which may explain the improvement in overall survival.

Keywords: Cholangiocarcinoma; adjuvant chemotherapy; survival; lymph node (LN); surgical procedures

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is a rare and aggressive primary liver malignancy. In the United States, the incidence of ICC is estimated at 1.2 cases per 100,000 person years (1). Surgical resection for ICC represents the only curative option; however, ICC is frequently diagnosed at advanced stages, precluding resection. Historically survival in ICC has been poor. Even with curative intent surgical resection, median survival is 28 months and 5-year overall survival is 30% (2).

Due to the rarity of the disease, there is minimal level one evidence to guide clinical management of patients with ICC and there is no clinical consensus on the appropriate use of neoadjuvant and adjuvant treatment. There is conflicting data from randomized controlled trials as to the benefit of adjuvant chemotherapy in resected biliary tract cancers (3-6). While it is known that positive lymph nodes (LN), advanced T stage and positive surgical resection margins are poor prognostic factors (2,7-12), a recent

meta-analysis found no additional benefit to adjuvant chemotherapy or radiotherapy in patients undergoing surgical resection (2). However, some subgroup analyses have suggested that patients with advanced T stages or large tumors, positive margins and/or positive LNs, may derive a survival benefit from adjuvant chemotherapy (13-15). In order, to further evaluate the utilization and role of adjuvant chemotherapy for resected ICC in current clinical practice, a large population-based data set was analyzed to characterize chemotherapy utilization in ICC over the last 15 years and to determine whether or not changing practice patterns may have impacted survival. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/hbsn.2019.06.12).

Methods

An augmented version of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program database was used to identify patients diagnosed with ICC from 2000–2014. The SEER database collects patient, tumor and treatment characteristics on patients representing 28% of the United States population (16). The augmented version includes additional chemotherapy data.

Patients age 18 years or older who were diagnosed with ICC from 2000–2014 were identified using the World Health Organizations' International Classification of Disease, 3rd edition (*Table S1*). Patients were included if they underwent a therapeutic intent surgical resection for ICC (*Table S2*). Patients with metastatic disease or those whom received radiation therapy as a component of first-line therapy were excluded. The study was exempt from review by the Institutional Review Board of the University of Minnesota as only de-identified patient data was used.

Patients were stratified into three cohorts based on date of diagnosis, 2000–2004, 2005–2009, and 2010–2014. Patient, tumor, and treatment characteristics as well as survival was analyzed for all three groups. A 2-sided chi-square test and Cochran-Armitage test for trend were used to compare patient characteristics and chemotherapy utilization rates during the 15-year period. Multivariable analysis of factors associated with the receipt of chemotherapy was performed on patients in each time period. Kaplan-Meier survival curves and Cox proportional hazard ratio (HR) models were performed to evaluate overall survival. Statistical significance was considered as $P \leq 0.05$. All statistical analysis was performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 1,223 patients underwent surgical resection for ICC from 2000–2014 and met study inclusion criteria. All patients were divided into three cohorts based on time of diagnosis; 194 patients were diagnosed in 2000–2004, 379 patients were diagnosed in 2005–2009 and 650 patients were diagnosed in 2010–2014. Patient, tumor and treatment characteristics for the three cohorts are listed in *Table 1*.

Utilization of chemotherapy

There was a significant trend for increased chemotherapy utilization over the three time periods (33%, 37% and 41% in 2000–2004, 2005–2009 and 2010–2014 respectively, P=0.027). There was an increase in the utilization of chemotherapy in patients with node positive disease from 32% to 57% to 62% (*Figure 1A*, P=0.014), but not in node negative patients (41% to 36% to 43%, P=0.381, data not shown). The T stage classification was missing in 80% of patients in the 2000–2004 cohort. For this reason, T stage was not included in the analysis for the first time period. From 2005–2009 to 2010–2014 there was a significant increase in chemotherapy use in patients with T3/T4 tumors from 46% to 60% (*Figure 1B*, P=0.004); however, chemotherapy utilization did not change in those with T1 (33% in 2005–2009 and 34% in 2010–2014, P=0.421) and T2 disease (43% in 2005–2009 and 40% in 2010–2014, P=0.785, data not shown).

Multivariable regression analysis was performed to evaluate factors associated with chemotherapy utilization in each time period (*Table 2*). All regression models included patient age, gender, race, grade, LN status and T stage. T stage was excluded from the analysis for the first time period [2000–2004] due to missing data, as described above. From 2000–2004, only missing grade compared to grade I was a predictor of decreased odds of chemotherapy. From 2005–2009, LN positive status was independently associated with an increased odds of receipt of chemotherapy. Factors associated with a decreased odds of chemotherapy use were increasing age and male gender. From 2010–2014 both LN positive status and T stage 3/4 were independently associated with an increased odds of chemotherapy receipt. The factors associated with a decreased odds of chemotherapy use were age and male gender.

Table 1 Patient, tumor and treatment characteristics for patients with surgically resected ICC. N=1,223

Characteristics	2000–2004		2005–2009		2010–2014		P value
	n	%	n	%	n	%	
Age							<0.0001
18–54	59	30	99	36	110	17	
55–69	64	33	167	44	320	49	
70+	71	37	113	30	220	34	
Sex							0.694
Female	95	49	199	52	328	51	
Male	99	51	180	48	322	49	
Race							0.330
White	150	77	288	76	527	81	
Black	12	6	30	8	37	6	
Other	32	17	61	16	86	13	
T stage							<0.0001
I	22	11	158	42	319	49	
II	3	1	87	23	170	26	
III	8	4	86	23	92	14	
IV	5	3	30	8	52	8	
Missing/ unknown	156	80	18	5	17	3	
Size							<0.0001
<2 cm	14	7	23	6	51	8	
2–5 cm	45	23	132	35	251	39	
>5 cm	79	41	176	46	303	47	
Missing	56	29	48	13	45	7	
Grade							0.003
I	24	12	43	11	67	10	
II	65	33	162	43	286	44	
III	38	20	97	26	158	24	
Unknown/ missing	67	35	77	20	139	22	
LAD							0.269
None	97	50	177	47	312	48	
1–5	66	34	146	39	247	38	
≥6	31	16	56	15	91	14	
Node status							0.549
Node positive	31	16	56	15	91	14	
Node negative	59	30	139	37	240	37	
Unknown	104	54	184	49	319	49	
Chemotherapy							0.027†
No/unknown	130	67	240	63	383	59	
Yes	64	33	139	37	267	41	
Chemoradiation							0.0002
No/unknown	159	82	330	77	585	90	
Yes	35	18	49	13	65	10	

†, a two-tailed Cochrane-Armitage test for trend was used. LAD, lymphadenectomy; ICC, intrahepatic cholangiocarcinoma.

Overall survival

Median overall survival was 32 months during both the early time periods (2000–2004 and 2005–2009) and improved to 41 months in 2010–2014 (P=0.033, *Figure 2A*). For patients with low-risk tumor characteristics (LN negative disease and T1/T2 tumors), the median survival was 55 months in 2000–2004, 40 months in 2005–2009, and 52 months in 2010–2014 (P=0.045, *Figure 2B*). For patients with high-risk tumor characteristics (LN positive disease or T3/T4 tumors), median survival was 23.5, 34.5 and 44 months for 2000–2004, 2005–2009, 2010–2014 respectively, (P=0.03, *Figure 2C*). Among patients with LN positive disease, median overall survival was 19 months when patients received no chemotherapy and 23 months when patients received chemotherapy (*Figure 3A*, P≤0.02). For patients with LN negative disease, there was no significant improvement in median overall survival associated with receipt of chemotherapy—median overall survival was 46 months without chemotherapy and 59 months with chemotherapy (*Figure 3B*, P=0.08).

Using cox proportional hazard models for the entire cohort, male sex, advanced grade (grade III compared to grade I), advanced T stage (stage 2 compared to stage 1, stage 3/4 compared to stage 1) and LN positive disease were all associated with an increase in the hazard ratio of death (*Table 3*). Receipt of chemotherapy was not found to

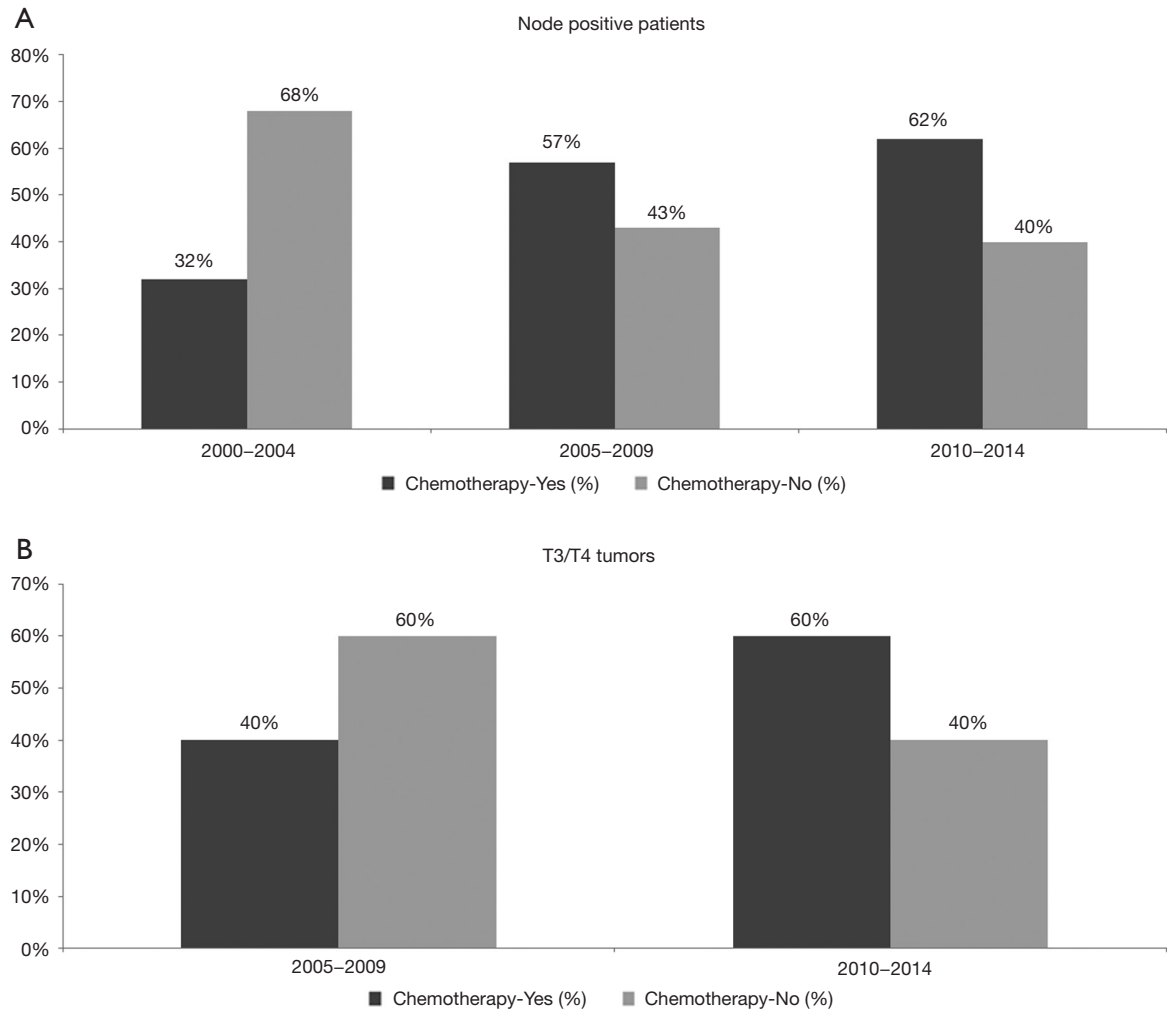

Figure 1 Chemotherapy utilization in node positive patients and patients with advanced T stage tumors. (A) Chemotherapy use in node positive patients across the three time periods, P=0.014; (B) chemotherapy use in T3/T4 patients in 2005–2009 and 2010–2014, P=0.004. The initial time period is excluded due to significant missing data.

be protective (HR 0.94, P=0.486). A separate analysis was performed on the subgroup of patients with LN positive disease (*Table 4*). In this patient cohort, only receipt of chemotherapy was found to significantly decrease the hazard ratio of death, while advanced T stage (T3/T4) was found to significantly increase the hazard ratio of death.

Discussion

This study used a national dataset to evaluate the utilization of adjuvant chemotherapy in surgically resected ICC patients over a 15-year period, and found that the use of adjuvant chemotherapy has evolved. The administration of chemotherapy has increased over time, largely due to increased use in patients with LN positive disease and/or T3/T4 tumors. On the other hand, the use of chemotherapy has remained stable in patients with LN negative disease and/or T1/T2 tumors. Furthermore, multivariate analysis of the most recent time period [2010–2014] revealed that LN positive status and T stage 3/4 were independently associated with an increased odds of chemotherapy receipt. Over the 15-year time period, overall survival improved for all patients, from 32 months [2000–2004] to 41 months [2010–2014], and was most dramatic for patients with LN positive disease or T3/T4 tumors. This improvement in survival may, in part, be explained by increased use of

Table 2 Predictors of chemotherapy utilization use over time

Characteristics	2000–2004			2005–2009			2010–2014		
	OR	95% confidence interval		OR	95% confidence interval		OR	95% confidence interval	
Age									
18–49	Ref			Ref			Ref		
50–59	1.17	0.45	3.05	0.46*	0.23*	0.93*	0.69	0.36	1.31
60–69	0.54	0.20	1.44	0.67	0.33	1.35	0.61	0.34	1.11
70+	0.43	0.17	1.08	0.28*	0.13*	0.57*	0.27*	0.15*	0.50*
Gender									
Female	Ref			Ref			Ref		
Male	0.86	0.45	1.64	0.57*	0.36*	0.90*	0.63*	0.45*	0.88*
Race									
Non-Hispanic White	Ref			Ref			Ref		
Black	1.44	0.39	5.37	0.46	0.18	1.16	0.63	0.30	1.31
Other	1.72	0.72	4.09	0.86	0.46	1.61	0.82	0.50	1.36
Grade									
I	Ref			Ref			Ref		
II	0.73	0.27	1.96	0.64	0.31	1.32	1.37	0.77	2.47
III	0.32	0.10	1.08	0.91	0.41	2.01	1.26	0.67	2.37
Missing	0.30*	0.10*	0.86*	1.01	0.44	2.29	1.10	0.58	2.11
Lymph node status									
LN–	1.06	0.49	2.27	1.18	0.71	1.96	1.20	0.83	1.74
LN+	1.19	0.46	3.11	2.80*	1.44*	5.45*	2.39*	1.43*	3.97*
None/unknown	Ref			Ref			Ref		
T stage									
1 & 2	–	–	–	Ref			Ref		
3 & 4	–	–	–	0.99	0.61	1.64	2.28	1.52	3.41
Missing	–	–	–	0.35	0.11	1.18	0.83	0.27	2.56

*, statistical significance. OR, odds ratio.

chemotherapy in these high-risk patients. In patients with LN positive disease, adjuvant chemotherapy was the only factor that decreased the hazard ratio of death.

ICC has a high rate of recurrence and poor overall survival when treated with surgical resection alone, highlighting the importance of adjuvant therapies. The ABC-02 trial evaluated chemotherapy in advanced biliary tract cancer and found a survival benefit of 3 months for combination gemcitabine and cisplatin over gemcitabine alone (17). The study included patients with advanced biliary tract cancers, less than 60% of whom had cholangiocarcinoma and only 20% of patients were initially treated with curative intent surgery (17). Two recent randomized controlled trials looked at the role of adjuvant chemotherapy specifically. The BILCAP study was intended to more clearly define the role of adjuvant chemotherapy in biliary tract tumors by randomizing patients after upfront curative intent resection to receive either capecitabine or observation alone (6). After a median follow-up of 60 months, there was no significant difference in overall

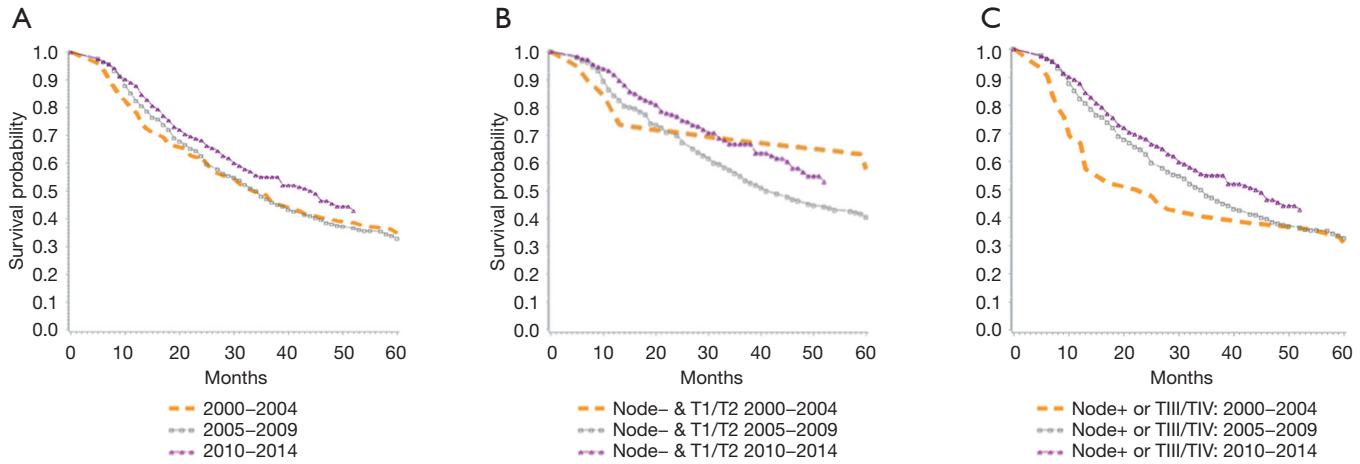

Figure 2 Kaplan Meier survival curves for patients with surgically resected intrahepatic cholangiocarcinoma from 2000–2014. (A) Survival curve of all surgically resected intrahepatic cholangiocarcinoma patients from 2000–2014. Median survival 32, 32 and 41 months in 2000–2004, 2005–2009 and 2010–2014 respectively (P=0.033); (B) median survival for patients with lymph node negative and T1/T2 tumors across the three time periods. Median survival 55, 40 and 52 months for 2000–2004, 2005–2009, 2010–2014 respectively, P=0.045; (C) median survival for patients with lymph node positive or T3/T4 tumors across the three time periods. Median survival 23.5, 34.5 and 44 months for 2000–2004, 2005–2009, 2010–2014 respectively, (P=0.03).

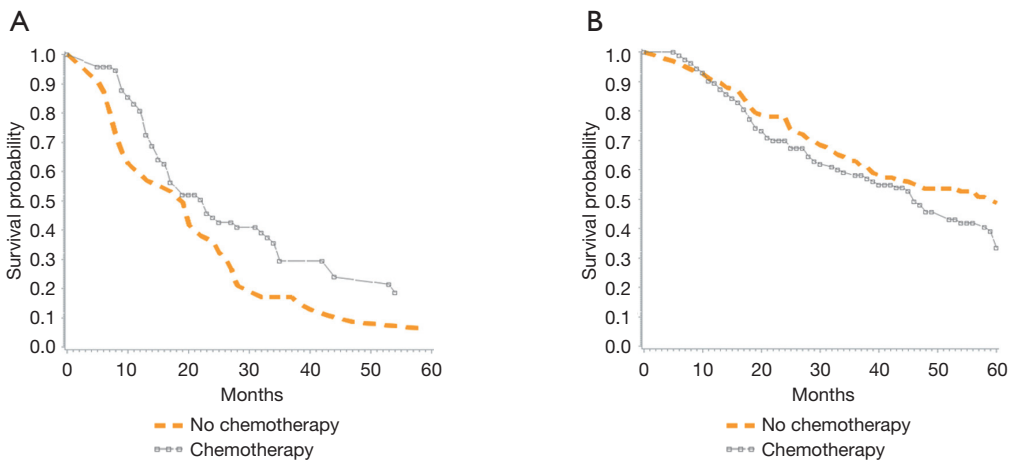

Figure 3 Kaplan Meier survival curves of patients with surgically resected intrahepatic cholangiocarcinoma from 2000–2014 with lymph node positive and lymph node negative disease stratified by receipt of adjuvant chemotherapy. (A) Patients with lymph node positive disease stratified by chemotherapy receipt. Median survival 19 months without chemotherapy and 23 months with receipt of chemotherapy (P≤0.02); (B) patients with lymph node negative disease stratified by chemotherapy receipt. Median survival 46 months without chemotherapy and 59 months with chemotherapy (P=0.08).

survival when analyzed under an intention-to-treat analysis—though interpretation of the results of the study have sparked much controversy (6,18).The Prodige 12 trial evaluated adjuvant gemcitabine and oxaliplatin and found no significant difference in recurrence free survival between the two arms, with a median follow-up of 46.5 months (5).

Previous studies have attempted to clarify the efficacy and role of chemotherapy in the adjuvant setting by retrospectively analyzing large data sets. Most studies have found that adjuvant chemotherapy was not associated with

Table 3 Cox proportional hazards ratio of death for all patients with surgically resected ICC from 2000–2014

Characteristics	Hazard ratio	95% confidence interval		P value
Age				
18–49	Ref			
50–59	1.13	0.84	1.52	0.432
60–69	1.17	0.87	1.56	0.297
70+	1.32	0.99	1.77	0.058
Gender				
Female	Ref			
Male	1.21*	1.01*	1.44*	0.034*
Race				
Non-Hispanic White	Ref			
Black	0.87	0.60	1.26	0.456
Other	0.98	0.77	1.26	0.875
Year of diagnosis				
2000–2004	Ref			
2005–2009	0.91	0.64	1.29	0.580
2010–2014	0.78	0.54	1.13	0.189
Grade				
I	Ref			
II	1.17	0.85	1.62	0.329
III	1.43*	1.02*	2.02*	0.040*
Missing	1.54*	1.10*	2.17*	0.013*
T stage				
1	REF			
2	1.44*	1.11*	1.85*	0.005*
3 & 4	2.21*	1.74*	2.80*	<0.0001*
Missing	1.26	0.87	1.83	0.217
Lymph node status				
None/unknown	Ref			
LN–	0.96	0.57	1.62	0.884
LN+	2.63*	1.47*	4.71*	0.001*
Chemotherapy				
No/unknown	Ref			
Yes	0.94	0.78	1.13	0.486

*, statistical significance. ICC, intrahepatic cholangiocarcinoma.

Table 4 Cox proportional hazards ratio of death for patients with lymph node positive, surgically resected ICC from 2000–2014

Characteristics	Hazard ratio	95% confidence interval		P value
Age				
18–49	Ref			
50–59	0.82	0.46	1.48	0.515
60–69	0.91	0.50	1.66	0.767
70+	0.73	039	1.35	0.309
Gender				
Female	Ref			
Male	0.96	0.63	1.45	0.847
Race				
Non-Hispanic White	Ref			
Black	0.54	0.16	1.76	0.303
Other	0.93	0.50	1.72	0.806
Year of diagnosis				
2000–2004	Ref			
2005–2009	0.44	0.19	1.00	0.050
2010–2014	0.61	0.27	1.38	0.233
Grade				
I	Ref			
II	1.20	0.54	2.64	0.652
III	137	0.60	3.11	0.455
Missing	1.89	0.70	4.55	0.154
T stage				
1 & 2	Ref			
3 & 4	2.15	1.34	3.46	0.002
Missing	0.68	0.30	1.53	0.349
Chemotherapy				
No/unknown	Ref			
Yes	0.46*	0.30*	0.72*	0.001*

*, statistical significance. ICC, intrahepatic cholangiocarcinoma.

improved survival when the entire cohort of surgically resected ICC patients was analyzed (2,13). Multiple studies have determined that positive LN status, advanced T stage and positive surgical resection margins are all poor

prognostic factors (2,7-12). Additional studies have shown an association between the use of adjuvant chemotherapy and improved survival when administered to the subgroup of patients with poor prognostic factors (13-15,19,20). For example, Miura *et al.* analyzed 2,751 patients in the National Cancer Database and found that the addition of chemotherapy was associated with a survival benefit only in patients with positive LNs, advanced T stages and positive resection margins (14). This was replicated in a large review of the SEER database (13). Further, a systematic review encompassing over 6,000 patients with biliary tract cancer found no significant improvement in overall survival with adjuvant treatment, except for in patients with high-risk features (positive margins and positive LNs) (21). The current study, redemonstrated that patients with LN positive or T3/T4 disease have worse overall survival, and suggests that the increased utilization of chemotherapy over time in these subgroups of patients may help explain the improvements noted in overall survival.

Despite LN positivity being an important factor to help determine which patients may benefit from chemotherapy as demonstrated in this and prior studies (11,13,14,21,22), the rate of any lymphadenectomy in the SEER database was only 52.1% during the period of study, and did not change over the 15-year time period. Previous studies have reported low rates of pathologic LN evaluation in ICC, with only 10% of patients undergoing an adequate [defined as 6 or more LN evaluated (23)] lymphadenectomy (13,24). Selective, inadequate and omitting lymphadenectomy in patients with ICC may result in nodal under-staging and possibly under treatment with adjuvant therapy.

Due to the sparsity of strong level one evidence, current National Comprehensive Cancer Network guidelines are not specific with respect to adjuvant treatment (25). For patients without evidence of residual disease, either observation, clinical trials or chemotherapy are acceptable options. In patients with microscopic residual disease or positive LNs, recommendations include enrollment in a clinical trial or chemotherapy with or without chemoradiation. Hopefully, the ongoing ACTICCA-1 trial, which initially randomized patients to observation or adjuvant gemcitabine-cisplatin after curative intent resection will help clarify the role of adjuvant chemotherapy (26). However, due to the rarity of biliary tract tumors, randomized trials uniformly include patients with ICC, extrahepatic cholangiocarcinoma, and gallbladders cancer. For instance, the Prodige 12 trial included only 86 patients with ICC while the BILCAP trial included only 84 patients (5,6). Although this improves the study's statistical power, this practice may not be clinically appropriate, particularly in light of emerging data that genetic mutations differ across these distinct biliary tract cancers (27).

Despite the lack of level one evidence or strong clinical guidelines, clinical practice has evolved towards the use of adjuvant chemotherapy predominantly in patients with poor prognostic features. In 2000–2004 chemotherapy was administered to 33% of patients with resected ICC and increased to 41% in 2010–2014. However, this increase is due to increased utilization in patients with LN positive disease and/or T3/T4 tumors, whereas there is not a corollary increase in patients with node negative or low T stage disease. From 2000–2004, no clinically significant predictors of chemotherapy utilization were identified. In the most recent time period [2010–2014], patients with LN positive disease or T3/T4 tumors had an increased odds of chemotherapy receipt, while older patients and males had a decreased odds of receiving chemotherapy. Median overall survival for all surgically resected patients improved from 32 months in 2000–2004 to 41 months in 2010–2014. In patients with LN positive disease or T3/T4 tumors, median overall survival improved from 23.5 to 44 months while median survival was relatively stagnant among patients with LN negative and T1/T2 disease. The evolution of chemotherapy utilization may be partially responsible for the improvements seen in overall survival.

Although this is a robust, population-based study on chemotherapy in surgically resected ICC, it is important to acknowledge some of the study's limitations. As a review of a large population dataset, it is subject to retrospective and reporting biases. Furthermore, as a retrospective study it is subject to selection bias as there is no randomization of treatments cohorts. Also, using the SEER database there were a significant number of missing values, particularly for T stage in the early cohorts. The SEER database also does not specify the date of chemotherapy, the specific agents/drugs given, or any details about the duration of therapy. Lastly, SEER does not report resection status or contain information on recurrence status. Resection margin status is an important prognostic indicator in resected ICC and likely factors into adjuvant treatment decisions. Nonetheless, given the rarity of ICC, this is a large study evaluating adjuvant chemotherapy for ICC over-time in the United States.

Despite these limitations, this study suggests that clinicians are administering chemotherapy with increased frequency to patients with poor prognostic features

following surgical resection of ICC. Specifically, clinicians are increasing chemotherapy utilization in patients with LN positive disease or T3/T4 tumors, while the utilization of chemotherapy among patients with LN negative disease or T1/T2 tumors has remained stable. Furthermore, the increased utilization of chemotherapy in patients with poor prognostic features may partially explain the improvement in overall survival over the last 15 years. It is likely that the previous retrospective studies have influenced clinical management contributing to this shift, as robust definitive level one evidence is still lacking. The data from this study suggests that the oncologic community is moving towards a clinical practice consensus on the use of adjuvant chemotherapy for ICC, but is undoubtedly awaiting further clarity that can only be provided by well-designed, robust randomized clinical trials.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/hbsn.2019.06.12). The authors have no conflicts of interest to declare.

Ethical Statement: The study was exempt from review by the Institutional Review Board of the University of Minnesota as only de-identified patient data was used. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 International Classification of Disease, 3rd edition codes defining the cohort of patients with intrahepatic cholangiocarcinoma

Topography	Histology
C220	8160/3, 8161/3
C221	8000/3, 8001/3, 8010/2, 8010/3, 8011/3, 8012/3, 8020/3, 8030/3, 8031/3, 8032/3, 8140/2, 8140/3, 8160/3, 8161/3, 8255/3

Table S2 Surveillance and Epidemiology End Results Program 2003 liver and intrahepatic bile duct site specific surgery codes to define the surgical cohort of resected intrahepatic cholangiocarcinoma patients

Code	Description
20	Wedge or segmental resection, NOS
21	Wedge resection
22	Segmental resection, NOS
23	Segmental resection, one
24	Segmental resection, two
25	Segmental resection, three
26	Segmental resection and local tumor destruction
30	Lobectomy [simple or] NOS
36	Right lobectomy
37	Left lobectomy
38	Lobectomy and local tumor destruction
50	Extended lobectomy, NOS
51	Right lobectomy
52	Left lobectomy
59	Extended lobectomy and local tumor destruction
65	Excision of a bile duct
66	Excision of a bile duct plus partial hepatectomy

NOS, not otherwise specified.