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Trends in the Incidence, Treatment and Outcomes of Patients with Intrahepatic Cholangiocarcinoma in the USA: Facility Type is Associated with Margin Status, Use of Lymphadenectomy and Overall Survival

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Abstract

Introduction Intrahepatic cholangiocarcinoma (ICC) remains an uncommon disease with a rising incidence worldwide. We sought to identify trends in therapeutic approaches and differences in patient outcomes based on facility types.

Methods Between January 1, 2004, and December 31, 2015, a total of 27,120 patients with histologic diagnosis of ICC were identified in the National Cancer Database and were enrolled in this study.

Results The incidence of ICC patients increased from 1194 in 2004 to 3821 in 2015 with an average annual increase of 4.16% ($p < 0.001$). Median survival of the cohort improved over the last 6 years of the study period (2004–2009: 8.05 months vs. 2010–2015: 9.49 months; $p < 0.001$). Among surgical patients ($n = 5943$, 21.9%), the incidence of R0 resection, lymphadenectomy and harvest of ≥6 lymph nodes increased over time ($p < 0.001$). Positive surgical margins (referent R0: R1, HR 1.49, 95% CI 1.24–1.79, $p < 0.001$) and treatment at community cancer centers (referent academic centers; HR 1.24, 95% CI 1.04–1.49, $p = 0.023$) were associated with a worse prognosis. Patients treated at academic centers had higher rates of R0 resection (72.4% vs. 67.7%; $p = 0.006$) and lymphadenectomy (55.6% vs. 49.5%, $p = 0.009$) versus community cancer centers. Overall survival was also better at academic versus community cancer programs (median OS: 11 months versus 6 months, respectively; $p < 0.001$).

Conclusions The incidence of ICC has increased over the last 12 years in the USA with a moderate improvement in survival over time. Treatment at academic cancer centers was associated with higher R0 resection and lymphadenectomy rates, as well as improved OS for patients with ICC.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a relatively rare cancer accounting for approximately 5–20% of all liver malignancies [1, 2]. In the USA, the incidence of ICC has

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increased from 0.44 to 1.18 per 100,000 people during the last three decades with concomitant increases in surgery- and hospital-related charges [3]. While recent reports have suggested a moderate improvement in overall survival (OS) among patients undergoing curative-intent surgery, limited data exist regarding the outcomes of patients with unresectable disease [2, 4]. Increasing evidence has suggested that survival of patients treated for ICC may be influenced by institution volume and the experience of the operating surgeon [5]. In fact, ICC patients treated at high-volume facilities have an improved OS versus patients treated at low-volume institutions [6]. In addition, facility type may also influence outcomes of patients treated for different types of hepatopancreatobiliary (HPB) malignancies, including pancreatic cancer and hepatocellular carcinoma (HCC) [5–7]. To this point, Chu et al. reported a better 5-year OS among patients undergoing pancreatic cancer resection at an academic versus community center [7]. In addition, Hyder and colleagues reported that patients undergoing complex HPB surgery at teaching hospitals had an improved in-hospital mortality versus non-teaching hospitals [8].

A comprehensive assessment of the changes in therapeutic practices for ICC treatment on a nationwide basis is lacking. Previous studies have mostly included data from academic medical centers and, thus, may not reflect population-wide outcomes [2, 9, 10]. Thus, the objective of the present study was to define trends in the incidence, treatment approaches and outcomes of patients with ICC over a 12-year period in the USA. In addition, we sought to identify trends in therapeutic approaches, as well as differences in patient outcomes based on whether individuals were treated in an academic, community or integrated network cancer program.

Methods

Data sources and sample

Patients with a histologic diagnosis of ICC in the National Cancer Database (NCDB) between January 1, 2004, and December 31, 2015, were identified and analyzed. The NCDB, which is sponsored by the Commission on Cancer of the American College of Surgeons and the American Cancer Society, is a clinical database that captures approximately 70% of all newly diagnosed cancers from more than 1500 Commission on Cancer-accredited centers in the USA annually [11]. Patients with ICC were identified from the NCDB Participant User File using the combination of International Classification of Diseases for Oncology (ICD-O-3) topography code C22.1 (intrahepatic bile ducts), histology code 8140 (adenocarcinoma, NOS)/8160 (adenocarcinoma, bile duct) and behavior code 3 (malignant tumor) or topography code C22.0 (liver) in combination with histology code 8160 and behavior code 3. Perihilar (Klatskin) tumors and mixed HCC-ICC tumors were excluded.

Variables and outcomes of interest

During the 12-year period, 27,120 patients diagnosed with histologically proven ICC in the NCDB were considered eligible for analysis. Demographic and clinical data extracted from the NCDB included Charlson/Deyo comorbidity scores, insurance status, educational status, geographic region of the treatment facility and type of facility (academic/research program, integrated network cancer program, comprehensive community cancer program or community cancer program). Insurance status was categorized as private, government plan (Medicare, Medicaid or other government policy) or uninsured/unknown. For patients who underwent curative-intent and palliative surgery, tumor grade, number of satellite lesions, margin status, tumor size, number of nodes harvested and metastatic lymph nodes and pathological tumor stage [according to the American Joint Commission on Cancer/Union for International Cancer Control (AJCC/UICC) staging system, 6th edition before 2009, 7th edition after 2010] was collected [12, 13].

Definitions

Patients were subcategorized into "Surgery" versus "Non-surgery" groups based on whether a surgical procedure (i.e., wedge resection, segmental resection, hemihepatectomy or extended hepatectomy) occurred. Patients who underwent other procedures (e.g., "tumor destruction, no pathological specimen produced") were included in the non-surgical group. Data on clinical stage were derived from 6th edition of AJCC/UICC staging systems for patients in 2004–2009 and 7th edition for patients diagnosed in 2010–2015 [12, 13]. Cancer programs were defined as community cancer, comprehensive community cancer, integrated network cancer and academic/research programs as characterized by the NCDB based on program structure, provided services and number of cases per year [14]. For the purposes of analyses, community cancer and comprehensive community cancer programs were grouped as "community-based facilities."

Statistical analysis

Continuous variables were reported as medians with interquartile range (IQR). Discrete variables were reported as totals and frequencies. Bivariate analysis was performed using Wilcoxon signed-rank test, Chi-square test or Fisher's exact test as appropriate. To detect increasing/decreasing trends in therapeutic practices over time, linear trend tests were applied to yearly rates for each variable examined. To identify whether trends in therapeutic practices over time differed by facility types, linear regression was utilized. A subset of patients was excluded from the analysis of survival predictors due to insufficient data regarding lymph node dissection, number of lymph nodes harvested and adjuvant/neoadjuvant chemotherapy ($n = 4575$). Overall survival (OS) was defined as the time interval between the date of initial treatment and the date of death; OS was censored at the date of last follow-up for patients who were alive. OS was estimated using the Kaplan–Meier method, and survival among patient groups was compared using log-rank test. Cox proportional hazards regression analysis was used to evaluate any association between patient, tumor and hospital characteristics, and OS, with regression coefficients reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Variables that demonstrated statistically significant associations on the basis of the Lemeshow and Hosmer model were utilized in the multivariable model. In case where two variables were highly correlated and, thus, would introduce issues of multicollinearity, the predictor more strongly associated with the outcome would be kept in the model. Further, proportional hazard assumptions were checked for each variable considered in the multivariable model. In case where the assumptions were not met, variables were re-categorized or removed to ensure no violations to the assumptions. A $p < 0.05$ was considered statistically significant. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Between 2004 and 2015, a total of 27,120 new cases of ICC were identified in the NCDB (Table 1). Median patient age was 67 years (IQR: 58–75). Most patients were male ($n = 13{,}755$, 50.3%), white ($n = 23{,}074$, 84.3%) and had a Charlson/Deyo score of 0 ($n = 18{,}503$, 67.6%). While most patients had Medicare coverage ($n = 14{,}126$, 53.1%), 35.6% ($n = 9464$) had private insurance. At time of presentation, 22% of patients ($n = 6006$) had Stage IV disease, whereas 19.6% ($n = 3584$) presented with Stage I disease; an approximate equal number of patients presented with Stage II and Stage III diseases (stage II: $n = 2759$, 15.1%; stage III: $n = 2798$, 15.3%). The majority of patients with ICC were treated at an academic ($n = 13{,}394$, 49.4%) or community cancer ($n = 10{,}322$, 38.1%) program, whereas a smaller subset was treated at an integrated network cancer program ($n = 2752$, 10.2%; $p < 0.001$).

The vast majority of patients with ICC received medical therapy in the form of chemotherapy, radiotherapy or best supportive therapy ($n = 21{,}177$, 78.1%), whereas 21.9% ($n = 5943$) underwent surgical intervention. Compared with non-surgical patients, individuals who underwent surgical resection were more likely to be female (52.8% vs. 48.9%, $p < 0.001$), white (85.8% vs. 83.9%, $p < 0.001$) and present with Stage I disease (26.5% vs. 13.4%, $p < 0.001$). In addition, academic centers had a higher volume of surgically ($n = 3704$, 62.3%) and medically ($n = 9690$, 45.8%) treated ICC patients. Furthermore, there was an association between insurance status and facility type; specifically, patients with private insurance were more often treated at academic versus community or integrated cancer centers (academic: 36.9% vs. community: 30.6% vs. integrated: 30.5%, $p < 0.001$). In contrast, patients who had Medicare coverage were more often treated at community and integrated cancer programs (academic: 47.1%, community: 59.2%, integrated: 76.5%, $p < 0.001$).

Trends in the incidence and survival of ICC patients

The number of new cases of ICC more than doubled between 2004 ($n = 1194$) and 2015 ($n = 3821$), corresponding to an average annual increase of 4.16% ($p < 0.001$, Fig. 1). Specifically, the number of ICC patients undergoing liver resection (2004: $n = 261$ vs. 2015: $n = 804$) and medical treatment (2004: $n = 933$ vs. 2015: $n = 3017$) more than tripled over the study period ($p < 0.001$, Fig. 1). Of note, the median survival of the entire cohort also improved over the last 6 years of the study period (2004–2009: 8.05 months vs. 2010–2015: 9.49 months; $p < 0.001$).

Surgical resection cohort: trends in pathological characteristics, treatment details and survival

Among the 5943 patients who underwent surgery and had pathological tumor characteristics available, median tumor size was 5.2 cm (IQR: 3.3–8.0 cm) (Table 2). Median tumor size at presentation (median: 5.2 cm, IQR: 3.3–8.0 cm) remained largely stable over the time periods examined ($p = 0.07$). Most patients presented with a moderately differentiated tumor ($n = 2801$, 47.1%); 26.4% ($n = 1571$) and 9.9% ($n = 589$) presented with a poorly or well-differentiated tumor, respectively. Roughly two-thirds of patients had pT1 ($n = 1809$, 34.6%) or pT2 ($n = 1544$, 29.5%) tumors. The majority of patients ($n = 4267$, 71.8%) had negative surgical margins; however, a minority had

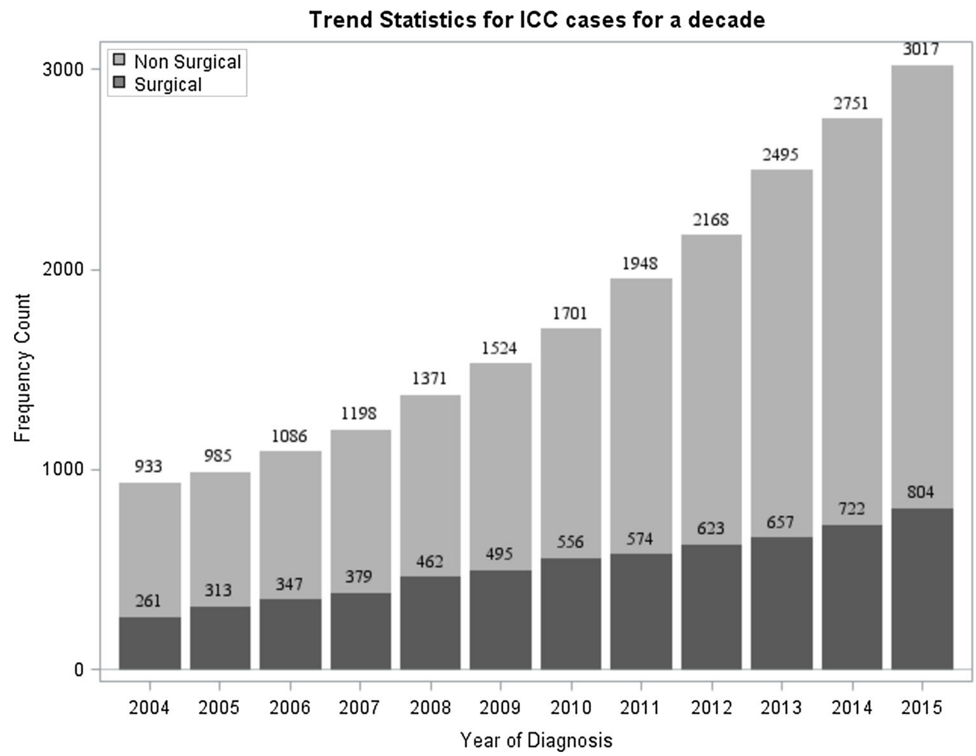
Table 1 Comparison of patient characteristics in surgical versus non-surgical ICCs

Variables	Total (*n* = 27,120)	Non-surgical (*n* = 21,177)	Surgical (*n* = 5943)	*p* value
Age, median (IQR)	67 (58–75)	68 (58–83)	64 (56–72)	<0.001
Gender				<0.001
Male	13,755 (50.3%)	10,831 (51.1%)	2924 (47.2%)	
Female	13,615 (49.7%)	10,346 (48.9%)	3269 (52.8%)	
Race				<0.001
White	23,074 (84.3%)	17,762 (83.9%)	5312 (85.8%)	
Black	2296 (8.4%)	1869 (8.8%)	427 (6.9%)	
Other	2000 (7.3%)	1546 (7.3%)	454 (7.3%)	
Primary payer				<0.001
Medicare	14,126 (53.1%)	11,310 (55%)	2816 (46.8%)	
Private	9464 (35.6%)	6812 (33.1%)	2652 (44.1%)	
Medicaid	2115 (8.0%)	1699 (8.3%)	416 (6.9%)	
Not insured	884 (3.3%)	749 (3.6%)	135 (2.2%)	
Urban/rural areas				0.7
Metro	22,216 (84.3%)	17,206 (84.4%)	5010 (84%)	
Urban	3648 (13.8%)	2806 (13.8%)	842 (14.1%)	
Rural	476 (1.8%)	364 (1.8%)	112 (1.9%)	
Charlson/Deyo score				<0.001
0	18,503 (67.6%)	14,238 (67.2%)	4265 (68.9%)	
1	5842 (21.3%)	4513 (21.3%)	1329 (21.5%)	
2	1670 (6.1%)	1321 (6.2%)	349 (5.6%)	
$\geq$3	1355 (5%)	1105 (5.2%)	250 (4%)	
Median income				<0.001
<38,000	4500 (16.7%)	3568 (17.1%)	932 (15.3%)	
38,000–47,999	6296 (23.4%)	4942 (23.7%)	1354 (22.2%)	
48,000–62,999	7223 (26.8%)	5611 (26.9%)	1612 (26.4%)	
$\geq$63,000	8936 (33.2%)	6729 (32.3%)	2207 (36.2%)	
Percent no high school degree				<0.001
$\geq$29% or more	4503 (17.1%)	3586 (17.6%)	917 (15.4%)	
20%–28.9%	5968 (22.6%)	4706 (23.1%)	1262 (21.2%)	
14%–19.9%	6276 (23.8%)	4884 (23.9%)	1392 (23.4%)	
<14%	9610 (36.5%)	7233 (35.4%)	2377 (40%)	
Overall tumor stage (AJCC)				<0.001
Stage I	3584 (19.6%)	1982 (13.4%)	1575 (26.5%)	
Stage II	2759 (15.1%)	1930 (13.1%)	816 (13.7%)	
Stage III	2798 (15.3%)	2239 (15.2%)	531 (8.9%)	
Stage IV	6006 (22.2%)	5578 (26.3%)	428 (7.2%)	
Unknown	12,041 (44.4%)	9448 (44.6%)	2593 (43.6%)	
Facility type				<0.001
Academic cancer program	13,394 (49.4%)	9690 (45.8%)	3704 (62.3%)	
Community cancer program	10,322 (38.1%)	8945 (42.2%)	1377 (23.2%)	
Integrated network cancer program	2752 (10.2%)	2088 (9.9%)	664 (11.2%)	
Unknown	652 (2.4%)	454 (2.1%)	198 (3.3%)	

AJCC American Joint Commission on Cancer

either microscopic (*n* = 724, 12.2%) or grossly positive (*n* = 81, 1.4%) margins. Among 3290 (55.4%) patients who had a lymphadenectomy, the majority had less than 6 lymph nodes examined (*n* = 2426, 73.8%). N0 disease was noted among 41.8% (*n* = 2490) of patients, whereas metastatic lymph nodes (N1) were present in 40.1%

Fig. 1 Trends in treatment of choice for patients with ICC



($n = 2385$). There was an increase in the proportion of patients who had an R0 resection, lymphadenectomy and 6 or more lymph nodes examined over time ($p < 0.001$, Fig. 2a–c). The proportion of patients who underwent major hepatectomy (≥3 segments) decreased from 75.9% in 2004 to 69.9% in 2015 ($p < 0.001$). In contrast, the use of minimally invasive surgery for ICC increased from 16.3% in 2010 to 24.9% in 2015 ($p = 0.002$). Of note, the proportion of patients who received neoadjuvant chemotherapy also increased over time ($p < 0.001$, Fig. 2d). Specifically, from 2004 to 2009, 23.2% ($n = 501$) of patients received neoadjuvant therapy compared with 29.4% ($n = 1184$) from 2010 to 2015 ($p < 0.001$). Similarly, the use of adjuvant therapy increased over time (2004–2009: 8.09% vs. 2010–2015: 11.6%; $p < 0.001$).

Median survival of ICC patients after resection improved during the last 6 years of the study period (2004–2009: 30.55 months vs. 2010–2015: 36.14 months; $p < 0.001$). On multivariable analysis, certain clinical and pathological variables were associated with OS (Table 3, Supplemental Table 1). For example, patients with moderately, poorly or undifferentiated tumors had a 78% increased risk of death versus patients with well-differentiated ICC (HR 1.78, 95% CI 1.30–2.44; $p < 0.001$). Perhaps not surprising, increasing pathological tumor category (referent pT1: pT3, HR 1.52, 95% CI 1.23–1.88; $p < 0.001$; pT4, HR 1.65, 95% CI 1.25–2.18; $p < 0.001$), metastatic lymph node status (referent pN0: pN1, 1.81, 95% CI 1.53–2.15; $p < 0.001$) and positive margins (referent R0: R1, HR 1.49, 95% CI 1.24–1.79; $p < 0.001$; R2, HR 1.32, 95% CI 1.06–1.64; $p = 0.013$) were each associated with a worse prognosis. Interestingly, compared with patients who did not undergo lymphadenectomy, patients who had ≥6 lymph nodes examined had a better prognosis (HR 0.76, 95% CI 0.58–0.99; $p = 0.045$). Of note, receipt of neoadjuvant therapy was not associated with prognosis (HR 0.96, 95% CI 0.80–1.16; $p = 0.674$). Patients treated at community cancer centers did, however, have a worse prognosis (HR 1.24, 95% CI 1.04–1.49; $p = 0.023$) versus patients treated at an academic cancer programs.

Non-surgical cohort: trends in chemotherapy, radiotherapy and survival

In total, 21,177 (78.1%) ICC patients underwent non-surgical management. Chemotherapy ($n = 10{,}707$, 50.6%) was the primary treatment modality with an increase in utilization over time ($p < 0.001$, Supplemental Figure 1). Multiagent chemotherapy was preferred over single-agent chemotherapy, as utilization of multiagent chemotherapy was five times higher than single-agent chemotherapy by 2015 ($p < 0.001$). Utilization of radiotherapy also increased among patients over time ($p < 0.001$, Supplemental Figure 1). Of note, median survival of non-surgical patients improved during the last 6 years (2004–2009: 5.49 months vs. 2010–2015: 6.74 months; $p < 0.001$).

Table 2 Clinical and pathological features of patients in resection group ($n = 5943$, 21.9%)

Variables	*n* (%)
Largest tumor size (mm) (median, IQR)	52 (33–80)
Tumor grade	
Well	589 (9.9%)
Moderate	2801 (47.1%)
Poor	1571 (26.4%)
Undifferentiated	64 (1.1%)
Unknown	918 (15.5%)
Surgical margin	
R0	4267 (71.8%)
R1	724 (12.2%)
R2	81 (1.4%)
Unknown	871 (14.7%)
Overall tumor stage (AJCC)	
Stage I	1575 (26.5%)
Stage II	816 (13.7%)
Stage III	531 (8.9%)
Stage IV	428 (7.2%)
Unknown	2593 (43.6%)
Lymph node surgery	
No	2566 (43.2%)
Yes	3290 (55.4%)
Unknown	87 (1.5%)
No. of lymph nodes examined	
1–5	2426 (73.8%)
6 or more	783 (23.8%)
Unknown	81 (2.46%)
Chemotherapy	
Adjuvant chemotherapy	597 (10.1%)
Neoadjuvant chemotherapy	1619 (27.2%)
Tumor category	
pT1	1809 (34.6%)
pT2	1544 (29.5%)
pT3	898 (17.2%)
pT4	329 (6.3%)
Unknown	652 (12.5%)
Node status	
N0	2490 (41.8%)
N1	2385 (40.1%)
Unknown	1068 (18.7%)

IQR interquartile range, *AJCC* American Joint Commission on Cancer

Trends in practices and survival among academic, community and integrated network cancer programs

Trends in practices among academic, community and integrated network cancer programs were investigated. Interestingly, trends over time in the incidence of R0 resection ($p < 0.001$) and lymphadenectomy ($p = 0.0012$) were different based on facility type (Fig. 3a–d). For example, an R0 resection was more common among academic (72.4%) versus community (67.7%) programs ($p = 0.006$). Similarly, lymph node dissection was more commonly performed at academic (55.6%) versus community (49.5%) cancer hospitals ($p = 0.009$). In contrast, the proportion of patients who had ≥ 6 lymph nodes examined was similar among different facility types (academic: 23.1% vs. community: 20.7% vs. integrated: 20.2%; $p > 0.05$). Similarly, rates of major hepatectomy were comparable among academic (71.9%), community (67.5%) and integrated programs (74.6%) ($p = 0.65$). Utilization of preoperative chemotherapy was, however, more common at community (30.4%) versus academic (24.7%) programs ($p < 0.001$), while its use was similar among academic and integrated programs (academic: 24.7% vs. integrated: 23.9%; $p = 0.61$). Finally, the use of adjuvant chemotherapy was higher at academic (9.9%) and integrated (12.5%) programs compared with community centers (7.55%, $p < 0.001$, Supplemental Table 2).

Among non-surgical patients, academic cancer programs were more likely to utilize chemotherapy (51.7%) versus community (44.7%) and integrated (46.2%) cancer centers ($p < 0.001$, Supplemental Figure 2a, b). Similarly, radiotherapy was more frequently employed in academic cancer programs (15.0%) versus community cancer programs (11.2%) ($p < 0.001$). In addition, median survival of patients treated at academic cancer programs was better compared with individuals treated at an integrated network or a community cancer program (median OS: 11 months vs. 8 months vs. 6 months, respectively; $p < 0.001$, Fig. 4).

Discussion

ICC is a rare tumor of the liver accounting for 3% of all gastrointestinal malignancies [15]. Advances in the understanding of the biologic behavior and available multimodality treatments for this aggressive tumor have progressed over the last decade [2]. Nevertheless, ICC still carries a dismal prognosis with a 5-year OS of less than 20% [15]. The possibility of "cure," defined as the chance of mortality returning to the same level as that expected in the general population, unfortunately remains approximately at 10% among patients undergoing resection for ICC [16]. While several studies have been published using multiinstitutional data, these reports were largely derived from highly specialized hepatobiliary centers and, thus, may not be reflective of population-based practices and outcomes [17]. In addition, data on patient outcomes

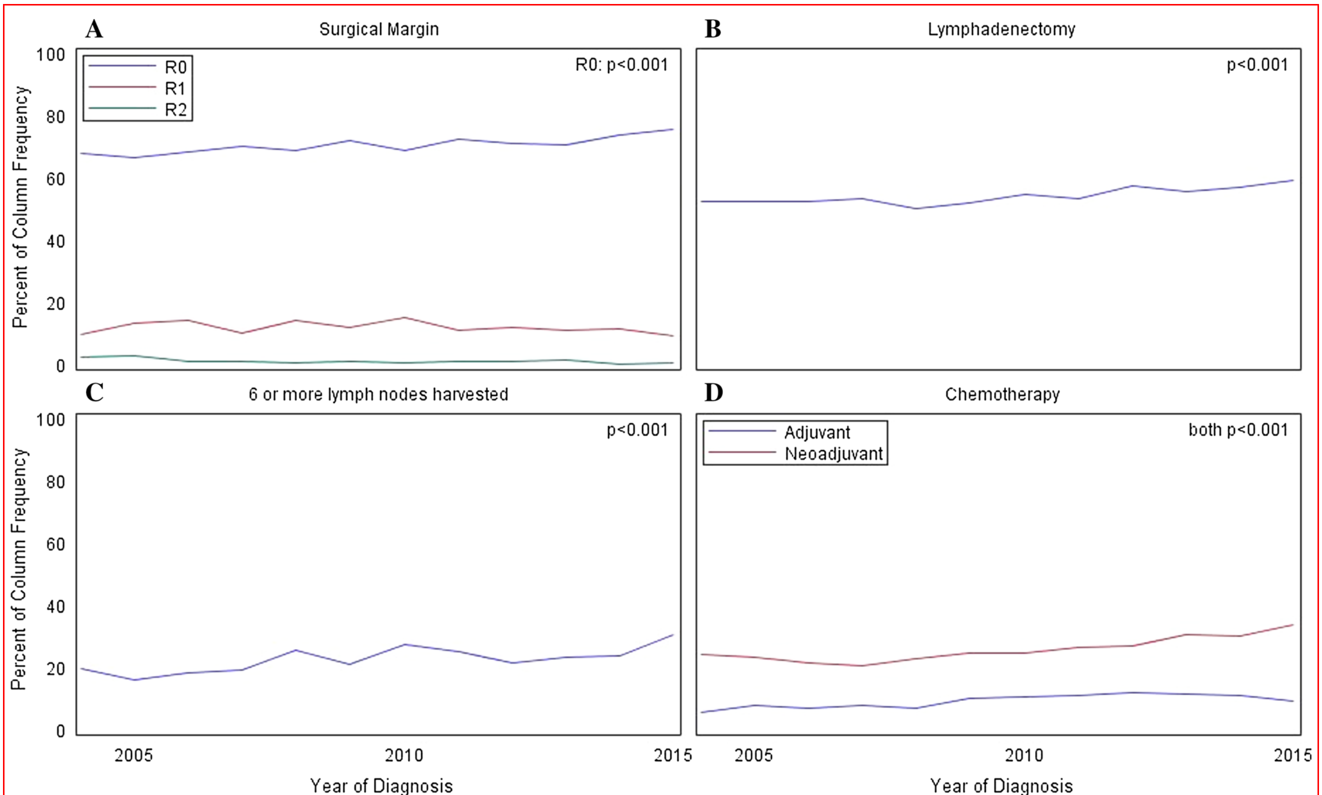


Fig. 2 Trends in surgical margins (**a**), lymphadenectomy (**b**), ≥6 lymph nodes harvested (**c**) and the use of chemotherapy (**d**) among patients undergoing resection for ICC

stratified by type of cancer center over time have not been investigated. The current study was important because it specifically defined therapeutic trends, as well as long-term outcomes among patients with ICC using a large, national representative dataset. Of note, while the number of new cases of ICC more than doubled between 2004 and 2015, patients with ICC had a modest improvement in survival over the time periods examined. Perhaps of most interest, there were differences in treatment and outcomes based on the treatment center. In particular, academic cancer programs were more likely to perform lymphadenectomy and achieve an R0 resection compared with community cancer centers. In addition, patients with ICC who were treated at an academic cancer program had a longer median OS versus a community cancer program.

While surgery remains the cornerstone of curative-intent therapy for ICC, many patients present with advanced disease that is not amenable to resection. To this point, among patients in the NCDB who had a diagnosis of ICC, the vast majority of patients were treated with chemotherapy as the primary treatment modality, with a much smaller subset treated with radiotherapy. Over time, multiagent chemotherapy was used much more often than single-agent chemotherapy ($p < 0.001$). These data suggest widespread adoption of data from the randomized controlled Advance Biliary Cancer (ABC)-02 trial, which compared gemcitabine monotherapy versus gemcitabine/cisplatin doublet therapy [18]. In this study, among patients with locally advanced or metastatic cholangiocarcinoma, doublet therapy was associated with an improvement in both time-to-progression and progression-free survival. While trials comparing this regimen to other doublet regimens have not been performed, gemcitabine/oxaliplatin, gemcitabine/nabpaclitaxel, gemcitabine-S1 or fluorouracil/leucovorin is alternative multiagent options for patients with unresectable cholangiocarcinoma. Of note, concurrent with a greater use of multiagent chemotherapy, median survival of non-surgical patients also improved over time.

In the current study, only roughly 1 in 5 patients who had a diagnosis of ICC underwent surgical resection. This is consistent with a Surveillance, Epidemiology and End Results (SEER) analysis previously published by our group [2]. Several components of surgery for ICC have been highlighted as critical to achieving optimal outcomes. In particular, the performance of lymphadenectomy has now been included as an important element in the staging of ICC patients according to the AJCC staging manual [12].

Table 3 Bivariable and multivariable Cox proportional hazard model for predictors of overall survival after resection

Variables	Bivariable model		Multivariable model	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender				
Female	Ref		Ref	
Male	1.20 (1.04–1.32)	<0.001	1.32 (1.14–1.54)	<0.001
Race				
Black/other	Ref		Ref	
White	1.21 (0.96–1.51)	0.11	0.80 (0.63 –1.03)	0.080
Facility type				
Academic cancer program	Ref		Ref	
Community cancer program	1.20 (1.01–1.43)	0.039	1.24 (1.04–1.49)	0.023
Integrated network cancer program	0.99 (0.79–1.24)	0.988	1.05 (0.83–1.33)	0.695
Charlson comorbidity score				
0	Ref		Ref	
≥1	1.07 (0.91–1.26)	0.44	1.07 (0.90–1.28)	0.44
Age (years)	1.01 (1.00–1.01)	0.015	1.01 (1.002–1.018)	0.014
Tumor grade				
Well	Ref		Ref	
Moderately/poorly/undifferentiated	1.69 (1.25–2.27)	<0.001	1.78 (1.30–2.44)	<0.001
Unknown	1.30 (0.92–1.83)	0.14	1.38 (0.95–2.00)	0.087
Surgical margin				
R0	Ref		Ref	
R1	1.56 (1.32–1.85)	<0.001	1.49 (1.24–1.79)	<0.001
R2	1.52 (1.25–1.85)	<0.001	1.32 (1.06–1.64)	0.013
Pathological T category				
pT1	Ref		Ref	
pT2	1.37 (1.14–1.66)	0.001	1.13 (0.93–1.38)	0.232
pT3	1.81 (1.48–2.20)	<0.001	1.52 (1.23–1.88)	<0.001
pT4	2.08 (1.61–2.71)	<0.001	1.65 (1.25–2.18)	<0.001
Pathological N status*				
pN0	Ref		Ref	
pN1	1.91 (1.65–2.2)	<0.001	1.81 (1.53–2.15)	<0.001
Lymphadenectomy				
No	Ref		Ref	
Completed with <6 LNs	1.10 (0.90–1.35)	0.35	0.86 (0.69–1.07)	0.243
Completed with ≥6 LNs	1.14 (0.89–1.45)	0.28	0.76 (0.58–0.99)	0.045
Neoadjuvant therapy				
No	Ref		Ref	
Yes	1.26 (1.07–1.49)	0.006	0.96 (0.80–1.16)	0.674

LN lymph node, *CI* confidence interval, *HR* hazard ratio, *ref* reference

*pNx was deemed to violate the proportional hazards assumptions and, thus, was removed from the multivariable model

Appropriate staging is important in making therapeutic decisions, as well as in stratifying patient prognosis [2, 19, 20]. Recently, the 8th edition of the AJCC staging manual recommended ≥6 lymph nodes be evaluated to stage ICC patients adequately [21]. Of note, among patients in the NCDB, only about one-half (55.4%) of patients even had at least one lymph node examined. Furthermore, the proportion of patients who had ≥6 lymph nodes evaluated was low across all facility types (academic: 23.1% vs. community: 20.7% vs. integrated: 20.2%), yet did increase somewhat over the years (Fig. 3). This is consistent with previous SEER and

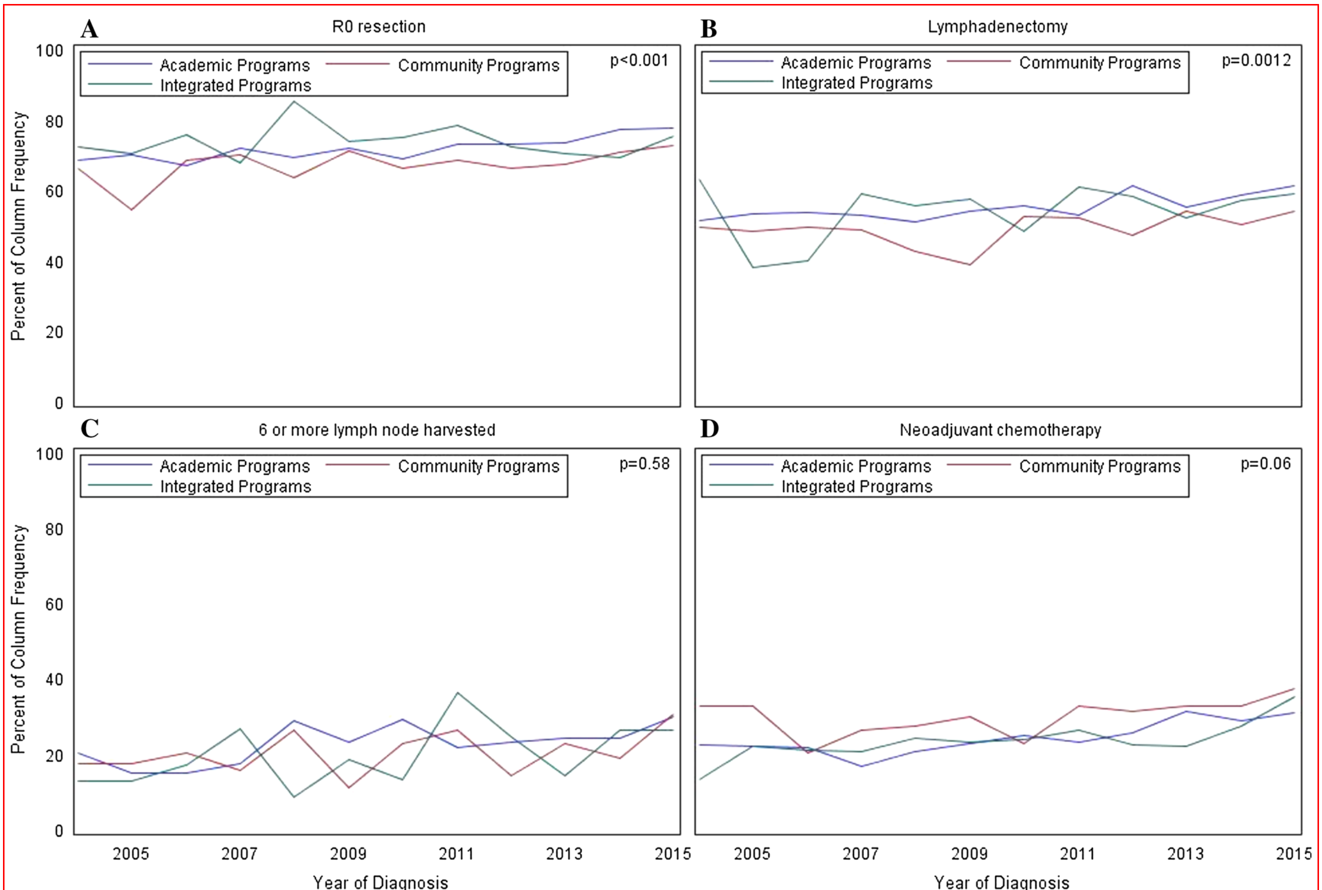


Fig. 3 Trends in surgical margins (**a**), lymphadenectomy (**b**), ≥6 lymph nodes harvested (**c**) and the use of neoadjuvant chemotherapy (**d**) among patients undergoing resection for ICC stratified by facility type

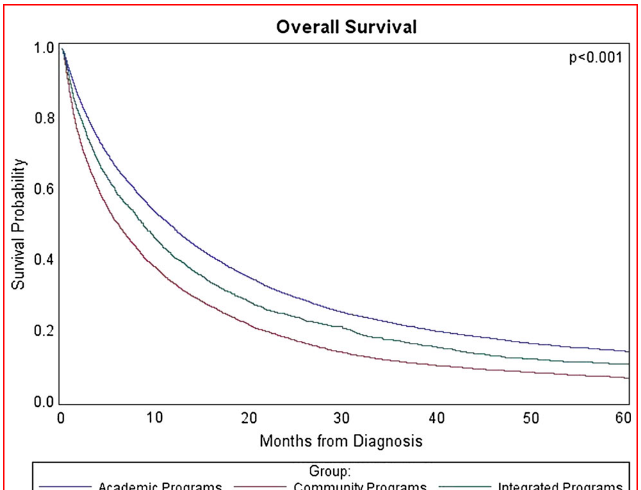


Fig. 4 Kaplan–Meier curve showing differences in survival of ICC patients treated at different hospital settings

multiinstitutional data published from our research group [9, 22]. Of note, the excision of ≥6 lymph nodes was associated with better outcomes. Another factor that can be controlled at the time of surgery is the resection margin. In the current study, the overall incidence of a R0 resection was 71.8% (academic: 72.4% vs. community: 67.7% vs. integrated: 74.4%). Of note, the proportion of patients who underwent major hepatectomy decreased over time. This change in extent of resection may have been related to the higher use of neoadjuvant therapy in the context of treating patients with ICC in a multimodality setting. In addition, neoadjuvant chemotherapy was more frequently used in community rather than academic or integrated cancer centers. While the reason for the difference in utilization of neoadjuvant therapy was undoubtedly multifactorial, it may have been related to the lack of surgical expertise for a rare, complex tumor such as ICC resulting in earlier initiation of chemotherapy in community programs. Interestingly, concurrent with the widespread adoption of minimally invasive techniques, the use of minimally invasive surgery for ICC increased from 16.3% in 2010 to 24.9% in 2015 ($p = 0.002$). In turn, laparoscopic resection has been demonstrated to have acceptable short-term outcomes without compromising oncologic outcomes such as R0 margins, as well as overall- and recurrence-free survival among patients with ICC [23].

Following surgical resection, OS was generally poor, yet OS did improve somewhat over the study period (2004–2009: 30.55 months vs. 2010–2015: 36.14 months; $p < 0.001$). While the reason for this is undoubtedly multifactorial, the improvement may be due in part to higher rates of R0 resections and lymph node dissection over time. Of interest, survival following resection was noted to be better at academic centers, which also had a higher proportion of lymphadenectomy and R0 resection compared with community cancer programs. Although data on treatment protocols after recurrence were not provided in the NCDB, the improved OS noted among patients treated at academic centers may have been attributed to the higher rates of chemotherapy and radiotherapy for unresectable patients compared with community programs. Indeed, aggressive multimodal treatment after recurrence has been shown to prolong survival for ICC patients [24, 25].

Treatment variations of HPB malignancies among different facility types may influence patient outcomes [6, 8]. In fact, our group had previously reported that teaching hospitals were associated with better outcomes for patients undergoing complex HPB surgery in the USA [8]. In a separate study, Chu et al. reported a better 5-year OS among patients who underwent pancreatic cancer resection at an academic program compared with community hospitals, despite patients at academic centers having more adverse pathological factors [7]. Favorable outcomes have also been reported for patients with HCC treated at high- versus low-volume institutions [6]. By developing expertise and experience in treating rare diseases such as ICC, specialty centers are more able to individualize and improve care delivered to patients with ICC. In the current study, patients who underwent treatment for ICC at an academic center had a better long-term survival versus an integrated or community program (11 months vs. 8 months vs. 6 months, respectively; $p < 0.001$). Collectively, the superior outcomes of patients treated at academic centers, as well as the relative rarity of ICC, emphasize the need for regionalization of ICC treatment to academic cancer programs. Nevertheless, as noted in the current study, insurance status also influenced the facility type in which treatment of ICC took place.

Several limitations should be considered when interpreting the results of the current study. While the NCDB included data from approximately 70% of all patients with cancer diagnoses in the USA, information pertaining to some specific treatment details was limited. Details on management of recurrent disease among patients who underwent surgery, as well as the role of loco-regional therapies in the non-surgical patients, were not available. Furthermore, population-based registry data can be subject to errors during abstraction and coding processes, but given the large population size, the influence of any coding bias was likely random and unlikely to impact the results.

In conclusion, the incidence of ICC has increased over the last 12 years in the USA. Although overall survival of ICC patients remains poor, moderate improvement has been noted over time. Treatment of unresectable ICC has shifted from monotherapy to multiagent systemic chemotherapy. Among patients undergoing resection, the incidence of lymphadenectomy, as well as R0 resection, has also increased over time. The largest adoption of these changes was noted at academic cancer centers, which in turn had the best long-term survival outcomes for patients being treated for ICC. As such, the regionalization of care for patients with ICC to experienced centers should be strongly considered.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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