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Predictors of adjuvant treatment and survival in patients with intrahepatic cholangiocarcinoma who undergo resection

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ABSTRACT

Background: Administration of adjuvant therapy (AT) in patients with intrahepatic cholangiocarcinoma (ICC) remains inconsistent despite recent trial data. This study investigates predictors of receipt of AT and survival.
Methods: Patients with ICC who underwent resection were identified using the NCDB (2004–2014). Logistic regression and Cox analysis were used to determine predictors of AT and survival, respectively. "High-risk" was defined as positive margins/nodes or stage III/IVa disease.
Results: 2813 patients were identified, of whom 42.3% received AT. Patients with positive margins, positive nodes, and higher stage tended to receive AT ($p < 0.001$). Black patients and patients with Medicare/Medicaid were less likely to receive AT. In "high-risk" patients, AT was associated with lower mortality (HR 0.66, 95% CI 0.56–0.78, $p < 0.001$).
Conclusions: AT after ICC resection is associated with improved survival in patients with positive margins, positive nodes, and stage III/IVa disease. There are disparities and regional variations in the receipt of AT.

1. Introduction

Though rare, the incidence of intrahepatic cholangiocarcinoma (ICC) in the United States (US) has been increasing by nearly 9% per year.[1,2] Despite advances in imaging and surgical techniques, ICC continues to have a poor prognosis, with 5-year survival rates of approximately 4%.[3] The only potential for cure is with surgical resection. However, only 50% of ICC tumors are amenable to resection at diagnosis.[4] Of patients who undergo curative-intent hepatectomy, approximately 20% have positive margins on final pathology and approximately 80% recur within 24 months of surgery.[5] Thus, even after resection, 5-year survival rates only improve to 22–30%.[6,7]

In this setting, there has been much debate about the utility of adjuvant therapy (AT) in patients with resected ICC. Prior retrospective data have been inconsistent, with some studies finding no survival benefit associated with receipt of AT,[6] while other reports have demonstrated improved survival with AT.[8,9] Results from the PRODIGE 12-ACCORD 18 (UNICANCER GI) prospective randomized controlled trial (RCT), which accrued 196 patients between 2009 and 2014 who underwent resection of localized biliary tract cancer and randomized them to either surveillance or adjuvant gemcitabine and oxaliplatin, found no statistically significant difference in recurrence-free survival (RFS).[10] The BILCAP RCT, which accrued patients from 2006 to 2014, randomized 447 patients with resected cholangiocarcinoma or gallbladder cancer to observation or capecitabine, and found improved overall survival (OS) in patients who received adjuvant capecitabine.[11] However, both trials included patients with all types of biliary tract cancers, not just ICC, and combined patients with R0 and R1 resections as well as node positive and node negative disease. Given the mixed findings from prospective studies and the rarity of the disease, retrospective analysis of a large national database offers potentially valuable information in evaluating the role of AT.

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The primary objective of this study was to utilize the National Cancer Database (NCDB) to compare the association of adjuvant therapy with OS in patients with resected ICC. Secondary objectives included (1) identifying predictors of receipt of AT and (2) identifying predictors of OS.

2. Methods

2.1. Study design

We conducted a retrospective analysis of patients with clinical stage I-IVa intrahepatic cholangiocarcinoma diagnosed between 2004 and 2014 in the NCDB. The NCDB is a nationwide, facility-based, dataset that captures 70% of all newly diagnosed malignancies in the US. It is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

The diagnosis of ICC was confirmed based on histology codes. Patients with histology codes of combined hepatocellular carcinoma and cholangiocarcinoma were excluded. Only patients who underwent hepatectomy for ICC were included in the analysis. Patients who underwent liver transplantation were excluded. Patients who received neoadjuvant therapy, or who died within 30 days of surgery were also excluded from the analysis. Only patients who received part or all of their treatment at the reporting institution were included in the analysis. This study was exempt from Institutional Review Board review due to the deidentified nature of the database.

2.2. Variable definitions

The NCDB includes basic demographic and clinical characteristics, including Charlson/Deyo Comorbidity Score (CDCC).[12] It also collects socioeconomic data, including income level (median household income for each patient's zip code between 2008 and 2012), education level (percent of adults in the patient's zip code who did not graduate from high school between 2008 and 2012), degree of urbanization (metropolitan, urban, or rural, based on population, as designated by the US Department of Agriculture Economic Research Service), and distance (miles) between the patient's zip code and the reporting facility. The NCDB additionally captures facility-level characteristics, including facility type (category classification by the CoC accreditation program, which includes community cancer programs, comprehensive community cancer programs, academic/research programs, and integrated network cancer programs) and facility region (New England/Mid Atlantic, South Atlantic, North Central, South Central, Mountain, and Pacific).

Clinical stage was designated based on American Joint Commission on Cancer (AJCC) 7th edition. Patients with metastatic disease at diagnosis or who were clinical stage IVb were excluded. Tumor size was defined as the largest dimension of the diameter of the primary tumor in centimeters. Margin status (negative or positive (microscopic or macroscopic)) was obtained from final surgical pathologic analysis. Lymph node status (negative, positive, or nodes not examined) was also obtained from surgical pathology. Adjuvant therapy was defined as receipt of chemotherapy or chemoradiation after primary site surgery, as part of the first course of treatment (within 60 days of diagnosis). The primary outcome was OS, defined as months from diagnosis to death. For subset analysis, 'high-risk' patients were defined as those who had positive resection margins, positive lymph nodes, or clinical stage III or IVa disease.

2.3. Statistical analysis

Variables were summarized as median with interquartile range (IQR) or count with percentage. Categorical variables were compared with the Pearson's chi-squared test. Continuous variables were compared with the 2-sample *t*-test, and multivariable logistic regression was used to adjust for potential confounders. Kaplan-Meier curves were used to analyze OS. In the overall cohort and patient subsets where Kaplan-Meier curves comparing patients who did or did not receive AT intersected, proportional hazards could not be assumed, making the log-rank test and Cox proportional hazards model invalid. Therefore, for those cohorts, we used the Gehan-Wilcoxon test, which does not rely on the assumption of proportional hazards, for our survival analyses.[13] For the 'high-risk' patient group, the curves no longer crossed and Cox analysis could be performed. Results of the logistic regression and Cox analysis were reported as odds ratios (OR) and hazard ratios (HR), respectively, with corresponding 95% confidence intervals (CI) and p-values.

All statistical analyses were performed using Stata software, version SE 14.0 (StataCorp, College Station, TX, USA). All tests were 2-sided and statistical significance was accepted at the $p < 0.05$ level.

3. Results

We identified 2813 patients who underwent hepatic resection for stage I-IVa ICC between 2004 and 2014. In our overall cohort, 42.3% of patients received adjuvant therapy (24.1% received adjuvant chemotherapy alone, while 18.2% received adjuvant chemotherapy and radiation) and 57.7% did not. Median (IQR) follow-up time was 2.1 (1.1–3.6) years for all patients in the cohort.

Approximately 46.8% of patients were male, 81.9% were white, 70.1% had a CDCC of 0, and the median (IQR) age was 65 (57–72) years. Additionally, 42.3% of patients were stage I, 24.4% were stage II, 19.1% were stage III, and 14.2% were stage IVa. One-quarter of patients (24.6%) had positive margins (23.3% microscopic residual disease, 1.3% macroscopic residual disease), while 75.4% had negative margins. Of the cohort, 37.4% of patients had negative lymph nodes, 20.8% had positive nodes, and nodes were not examined in 41.8% of patients.

3.1. Patient demographics, disease characteristics, and adjuvant treatment patterns

Univariate analysis demonstrated baseline differences between patients who received AT versus those who did not (Table 1). Patients who received AT were more likely to be < 65 years old ($p < 0.001$) and have CDCC scores of 0 ($p < 0.001$), higher clinical stage ($p < 0.001$), and tumors >5 cm in size ($p = 0.001$). There was no significant difference based on sex, race, or year of diagnosis.

In terms of insurance status, patients with private insurance were more likely to receive AT, while those with Medicare insurance were less likely to receive adjuvant treatment ($p < 0.001$). Patients in the highest income quartile tended to receive AT, while those in the lowest quartile did not ($p < 0.001$). Similarly, patients from regions with the highest education levels were more likely to receive AT, and those in the least educated regions were less likely to receive adjuvant treatment ($p = 0.01$). Whether the region was metropolitan, urban, or rural was not significantly associated with receipt of AT. Patients who lived in the New England/Mid-Atlantic and South Atlantic regions were more likely to receive AT, while

Table 1
Characteristics of patients with resected intrahepatic cholangiocarcinoma, based on receipt of adjuvant therapy.

Characteristic	Received adjuvant therapy (n = 1189)	No adjuvant therapy (n = 1624)	*P*-value
Age >65 years old	450 (37.9%)	894 (55.1%)	<0.001
Male	532 (44.7%)	783 (48.2%)	0.07
Race			0.29
White	958 (82.1%)	1302 (81.7%)	
Black	62 (5.3%)	110 (6.9%)	
Hispanic	79 (6.8%)	98 (6.2%)	
Asian	65 (5.6%)	76 (4.8%)	
Charlson/Deyo score			<0.001
CDCC 0	904 (76.0%)	1069 (65.8%)	
CDCC 1	220 (18.5%)	362 (22.3%)	
CDCC ≥2	65 (5.5%)	193 (11.9%)	
Tumor size			0.001
≤5 cm	505 (47.4%)	823 (54.3%)	
>5 cm	561 (52.6%)	692 (45.7%)	
Clinical stage			<0.001
Stage I	293 (28.0%)	747 (52.8%)	
Stage II	284 (27.2%)	316 (22.3%)	
Stage III	239 (22.9%)	232 (16.4%)	
Stage IVa	229 (21.9%)	121 (8.6%)	
Positive resection margin	410 (37.1%)	239 (15.6%)	<0.001
Lymph node status			<0.001
Negative	418 (35.5%)	629 (38.8%)	
Positive	372 (31.6%)	210 (13.0%)	
Not examined	388 (32.9%)	782 (48.2%)	
Year of diagnosis			0.10
2004–2009	396 (33.3%)	589 (36.3%)	
2010–2014	793 (66.7%)	1035 (63.7%)	
Insurance type			<0.001
Private	615 (52.7%)	574 (36.8%)	
Medicare	460 (39.4%)	857 (54.9%)	
Medicaid	54 (4.6%)	65 (4.2%)	
Other government	19 (1.6%)	26 (1.7%)	
None	19 (1.6%)	38 (2.4%)	
Distance between patient's zip code and hospital (miles)			<0.001
<10 miles	399 (33.6%)	408 (25.1%)	
10–40 miles	457 (38.4%)	514 (31.7%)	
>40 miles	333 (28.0%)	702 (43.2%)	
Facility type			<0.001
Community cancer program	43 (3.8%)	13 (0.8%)	
Comprehensive community cancer program	252 (22.2%)	296 (18.6%)	
Academic/research program	737 (64.9%)	1125 (70.6%)	
Integrated network cancer program	103 (9.1%)	160 (10.0%)	
Median income quartiles (by zip code)			<0.001
>$63,000	477 (40.9%)	535 (33.4%)	
$48,000-$62,999	297 (25.5%)	433 (27.0%)	
$38,000-$47,999	239 (20.5%)	368 (22.9%)	
<$38,000	154 (13.2%)	268 (16.7%)	
Education level (percent of region without high school degree)			0.01
Higher education level (<7%)	358 (30.6%)	427 (26.6%)	
7–12.9%	392 (33.5%)	532 (33.2%)	
13–20.9%	263 (22.5%)	367 (22.9%)	
Lower education level (≥21%)	156 (13.3%)	278 (17.3%)	
Type of region			0.06
Metropolitan	981 (85.6%)	1286 (82.3%)	
Urban	145 (12.7%)	236 (15.1%)	
Rural	20 (1.8%)	40 (2.6%)	
Facility region			<0.001
New England/Mid-Atlantic	348 (30.7%)	361 (22.7%)	
South Atlantic	265 (23.4%)	300 (18.8%)	
North Central	250 (22.0%)	456 (28.6%)	
South Central	113 (10.0%)	254 (15.9%)	
Mountain	38 (3.4%)	56 (3.5%)	
Pacific	121 (10.7%)	167 (10.5%)	

CDCC: Charlson/Deyo Comorbidity Score.

those who lived in the North Central or South Central regions were less likely to receive treatment (p < 0.001). Patients treated at community cancer programs were more likely to be treated with AT than those at academic programs (p < 0.001), and patients who traveled farther to the reporting facility were less likely to receive AT (p < 0.001).

Patients with positive resection margins were more likely to be given AT (37.1% vs 15.6%, p < 0.001). Specifically, patients with microscopic residual disease (35.1% vs 14.8%) or macroscopic residual disease (2.0% vs 0.8%) were more likely than patients with negative margins to receive AT (p < 0.001). Patients with positive lymph nodes were also more likely to receive AT (31.6% vs 13.0%), while those whose nodes were not examined were less likely to receive AT (32.9% vs 48.2%) (p < 0.001).

Table 2
Multivariable analysis of predictors of receipt of adjuvant therapy in patients with resected intrahepatic cholangiocarcinoma.

Variable	Odds Ratio (95% CI)	*P*-value
Positive resection margin	2.85 (2.24–3.63)	<0.001
Lymph node status		
Negative	Reference	
Positive	2.02 (1.48–2.74)	<0.001
Not examined	0.75 (0.60–0.95)	0.02
Age >65 years old	0.49 (0.37–0.66)	<0.001
Male	0.79 (0.65–0.97)	0.03
Race		
White	Reference	
Black	0.54 (0.34–0.84)	0.01
Hispanic	0.76 (0.49–1.17)	0.22
Asian	1.12 (0.71–1.75)	0.64
Charlson/Deyo score		
CDCC 0	Reference	
CDCC 1	0.84 (0.66–1.09)	0.19
CDCC ≥2	0.46 (0.32–0.67)	<0.001
Tumor size >5 cm	1.31 (1.07–1.61)	0.01
Clinical stage		
Stage I	Reference	
Stage II	2.10 (1.63–2.70)	<0.001
Stage III	1.77 (1.29–2.41)	<0.001
Stage IVa	2.11 (1.46–3.04)	<0.001
Year of diagnosis		
2004–2009	Reference	
2010–2014	1.40 (1.10–1.78)	0.01
Insurance type		
Private	Reference	
Medicare	0.74 (0.56–0.98)	0.03
Medicaid	0.58 (0.34–0.97)	0.04
Other government	0.71 (0.34–1.52)	0.38
None	0.58 (0.28–1.21)	0.15
Distance between patient's zip code and hospital (miles)		
<10 miles	Reference	
10–40 miles	0.78 (0.60–1.01)	0.06
>40 miles	0.41 (0.31–0.54)	<0.001
Facility type		
Community cancer program	Reference	
Comprehensive community cancer program	0.29 (0.13–0.68)	0.004
Academic/research program	0.28 (0.12–0.65)	0.003
Integrated network cancer program	0.28 (0.11–0.67)	0.004
Median income quartiles (by zip code)		
>$63,000	Reference	
$48,000-$62,999	0.84 (0.62–1.14)	0.26
$38,000-$47,999	0.94 (0.67–1.32)	0.72
<$38,000	1.14 (0.73–1.76)	0.56
Education level (percent of region without high school degree)		
Higher education level (<7%)	Reference	
7–12.9%	1.17 (0.88–1.56)	0.27
13–20.9%	1.01 (0.71–1.45)	0.95
Lower education level (≥21%)	0.83 (0.53–1.28)	0.40
Facility region		
New England/Mid-Atlantic	Reference	
South Atlantic	1.07 (0.78–1.46)	0.68
North Central	0.54 (0.40–0.72)	<0.001
South Central	0.50 (0.34–0.73)	<0.001
Mountain	0.74 (0.40–1.36)	0.34
Pacific	0.71 (0.49–1.03)	0.07

CI: confidence interval; CDCC: Charlson/Deyo Comorbidity Score.

3.2. Independent predictors of receiving adjuvant therapy

On multivariable analysis, positive margins (OR 2.9, 95% CI 2.2–3.6, p < 0.001) and positive lymph nodes (OR 2.0, 95% CI 1.5–2.7, p < 0.001) were significantly associated with receipt of AT, while patients whose nodes were not examined were less likely to receive AT (OR 0.8, 95% CI 0.6–0.95, p = 0.02) (Table 2). Other independent predictors of receiving AT included age <65 years old (p < 0.001), female sex (p = 0.03), higher clinical stage (p < 0.001), tumor >5 cm in size (p = 0.01), and being diagnosed in the second half of the study period (p = 0.01). Predictors of not being treated with AT included black race (p = 0.01), CDCC ≥2 (p < 0.001), Medicare (p = 0.03) or Medicaid (p = 0.04) insurance, traveling >40 miles to the reporting hospital (p < 0.001), and being treated in the North Central (p < 0.001) and South Central (p < 0.001) regions of the US. Compared to patients at community cancer programs, patients at comprehensive community cancer programs (p = 0.004), academic programs (p = 0.003), and integrated network cancer programs (p = 0.004) were less likely to receive AT. There were no associations between regional income or regional education level and receipt of AT.

A sensitivity analysis categorizing margin status as negative, microscopic residual disease, or macroscopic residual disease (instead of negative vs positive margins) found similar results. Microscopic residual disease (OR 2.9, 95% CI 2.2–3.7, p < 0.001) and macroscopic residual disease (OR 2.7, 95% CI 1.1–7.0, p = 0.03) remained independent predictors of receipt of AT.

3.3. Analysis of overall survival

On unadjusted analysis, Kaplan-Meier curves of the overall cohort demonstrated no association between long-term OS and receipt of AT (p = 0.10) (Fig. 1). Of note, the curves crossed at

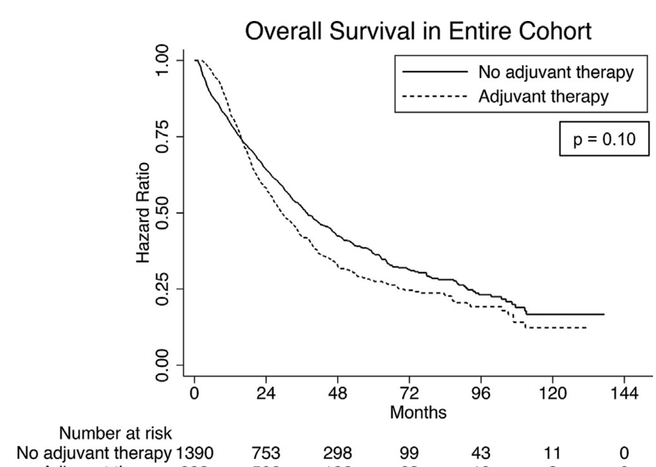

Fig. 1. Kaplan-Meier curves depicting overall survival in the overall cohort of patients with resected intrahepatic cholangiocarcinoma, by receipt of adjuvant therapy.

approximately 20 months after diagnosis, suggesting that AT may initially be associated with improved OS. However, the relationship did not persist after 20 months.

Subset analysis demonstrated stark differences in OS between patients with and without 'high-risk' characteristics. While the Kaplan-Meier curves of patients with negative margins who did or did not receive AT continued to intersect ($p = 0.18$), the curves of patients with positive margins did not cross and instead demonstrated a significant association with improved OS in patients who received AT ($p < 0.001$) (Fig. 2a and b). This association was also seen on further subset analyses of patients with microscopic ($p < 0.001$) and macroscopic residual disease ($p < 0.001$). Similarly, the curves of patients with negative nodes overlapped ($p = 0.34$), while the curves of patients with positive nodes did not and also demonstrated a significant association with improved survival with AT ($p < 0.001$) (Fig. 2c and d). When stratifying patients by clinical stage, patients with stage I or II disease again had overlapping Kaplan-Meier curves, and, in fact, demonstrated association with

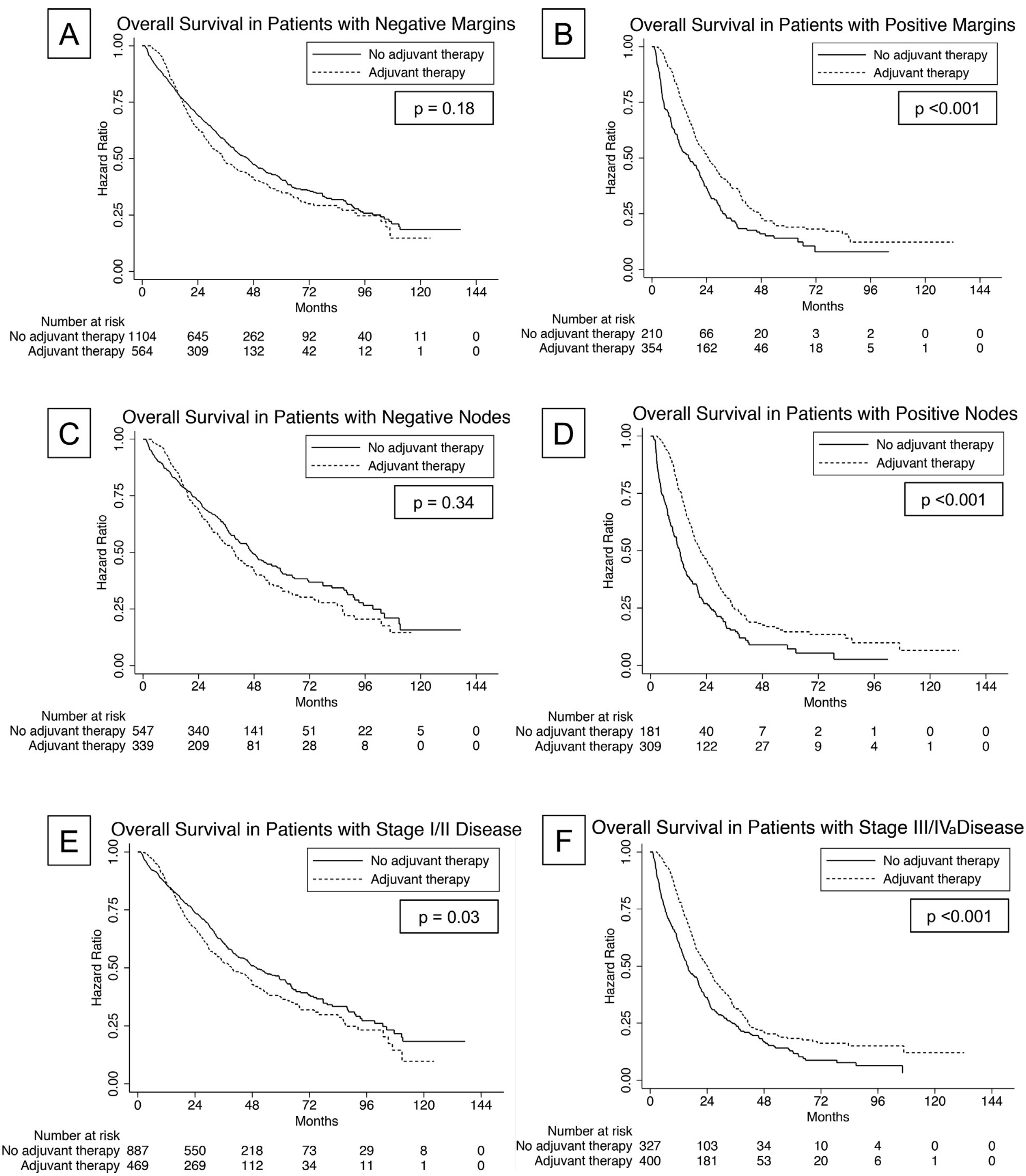

Fig. 2. Kaplan-Meier curves depicting overall survival in subsets of patients with resected intrahepatic cholangiocarcinoma, by receipt of adjuvant therapy. Patient subsets are (a) negative margins, (b) positive margins, (c) negative nodes, (d) positive nodes, (e) stage I or II disease, and (f) stage III or IVa disease.

worse OS with receipt of AT ($p = 0.03$) (Fig. 2e). On the other hand, the curves of patients with stage III or IVa disease did not overlap, and, once again, demonstrated an improved association with OS with receipt of AT ($p < 0.001$) (Fig. 2f).

3.4. Overall survival analysis of 'high-risk' patient subset

A total of 1306 patients had 'high-risk' characteristics (positive margins, positive nodes, or stage III or IVa disease). In this group, rates of 1-year and 5-year OS were 60.8% and 14.4% in patients who did not receive AT, and 78.8% and 19.5% in those who received AT ($p < 0.05$ for 1-year OS; $p > 0.05$ for 5-year OS). Upon stratifying patients by type of AT, rates of 1-year and 5-year OS were 78.5% and 21.5% in those who received adjuvant chemotherapy, and 79.0% and 17.8% in those who received adjuvant chemoradiation ($p > 0.05$ for both 1-year and 5-year OS).

We were unable to perform multivariable Cox proportional hazard analysis of the overall cohort because the Kaplan-Meier curves intersected (Fig. 1), rendering the assumption of proportional hazards invalid. However, when examining the 'high-risk' patient population alone, the Kaplan-Meier curves of those who did or did not receive AT did not intersect, and demonstrated a significant association between improved OS and receipt of AT ($p < 0.001$) (Fig. 3).

In this 'high-risk' subset, multivariable Cox analysis was performed to identify independent predictors of survival. After adjusting for multiple confounders, AT was associated with significant improvement in OS compared to no AT in high-risk patients (HR 0.66, 95% CI 0.56–0.78, $p < 0.001$) (Table 3). Independent predictors of worse OS were age >65 years old ($p = 0.03$), CDCC ≥ 2 ($p = 0.01$), and tumor size >5 cm ($p = 0.01$). Sex, race, and insurance type were not associated with survival. Patients in the lowest income quartile had worse survival than patients in the highest income quartile ($p = 0.01$). Patients who were treated at academic programs had improved OS compared to those at community cancer programs ($p = 0.01$). US region and distance between the patient's zipcode and the reporting hospital did not correlate with survival in patients with high-risk tumors.

4. Discussion

Given the rarity of intrahepatic cholangiocarcinoma, the role of adjuvant therapy has been difficult to elucidate and prospective trials have historically had trouble accruing patients. Therefore,

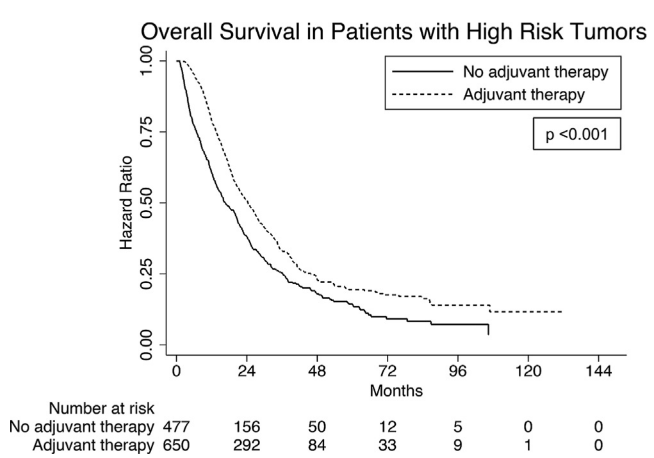

Fig. 3. Kaplan-Meier curves depicting overall survival in patients with resected intrahepatic cholangiocarcinoma with 'high-risk' features (positive margins, positive nodes, or stage III or IVa disease), by receipt of adjuvant therapy.

retrospective analyses of large databases have become increasingly important in examining trends in management. This study of the NCDB demonstrates a significant survival advantage associated with adjuvant therapy in patients with resected intrahepatic cholangiocarcinoma who have positive margins, positive lymph nodes, or advanced clinical stage III or IVa disease. Even after adjusting for multiple patient and tumor characteristics, the association between improved OS and receipt of AT holds true in 'high-risk' patients.

The utility of AT in patients with resected ICC has not been well-established in the current literature. A multi-institutional retrospective review of 1154 patients with resected ICC found no association with improved survival in patients who received AT in the overall cohort, but demonstrated improved OS in patients with T2/T3/T4 or N1 disease.[9] A systematic review and meta-analysis of biliary tract cancers, including ICC, found no significant association between OS and receipt of AT, although the authors did note a survival benefit in patients with node-positive disease or R1 disease who received AT.[14] On the other hand, another systematic review and meta-analysis only including patients with ICC found no correlation between AT and OS.[6]

Two RCTs have recently been conducted, but interestingly, they provide conflicting results.[10,11] The PRODIGE 12-ACCORD 18 (UNICANCER GI) trial accrued 196 patients at 33 French centers between 2009 and 2014, and randomized patients to either gemcitabine and oxaliplatin or surveillance.[10] R0 resection rates were similar between groups (86.2% vs 87.9%) as were lymph node invasion rates (37.2% vs 36.4%). With a median follow-up time of 44.3 months, the authors found no significant difference in RFS rates (30.4 vs 22.0 months, $p = 0.31$). Unfortunately, the study was likely underpowered, as the sample size was chosen based on a larger expected difference in RFS.

Several months after preliminary data from the UNICANCER GI trial were published, the results from the BILCAP RCT were presented at the American Society of Clinical Oncology 2017 Annual Meeting.[11] This highly-anticipated trial accrued 447 patients with resected biliary tract cancers at 44 sites in the United Kingdom between 2006 and 2014, 19% of whom had intrahepatic cholangiocarcinoma. Patients were randomized to adjuvant capecitabine or observation. Of randomized patients, 62% had R0 resections and 46% were node-negative. Follow-up time was at least 36 months in >80% of surviving patients. Based on intention to treat analysis, there was no significant difference in OS. However, in per-protocol analysis, adjuvant capecitabine was associated with significantly improved OS compared to observation (53 vs 36 months, HR 0.75, 95% CI 0.58–0.97, $p = 0.028$). There was no difference in RFS between the two groups.

A third RCT that is currently underway, the European ACTICCA-1 trial, was recently amended in light of the BILCAP data and compares adjuvant gemcitabine and cisplatin with adjuvant capecitabine after resection of biliary tract cancers.[15]

These RCTs combined all types of biliary tract cancers in order to maximize sample sizes. Unfortunately, however, prior studies have demonstrated that ICC may be biologically distinct from other biliary tract cancers.[16,17] Due to the rarity of the disease, these trials were unable to perform additional subset analyses due to already limited power. Therefore, in resorting to large databases, such as NCDB, our study demonstrates that specific subsets of patients appear to potentially benefit from AT. We found that patients with positive margins, metastatic nodal disease, and advanced stage who received AT had significantly increased OS associated with treatment, which is also consistent with prior retrospective analyses.[6,8,9,18] Our findings thus provide additional reinforcement based on a large retrospective analysis that a potential benefit to adjuvant therapy exists in patients with high-risk features. Of note,

Table 3
Cox proportional multivariable analysis of predictors of mortality in high-risk patients with resected intrahepatic cholangiocarcinoma.

Characteristic	Hazard Ratio (95% CI)	*P*-value
Received adjuvant therapy	0.66 (0.56–0.78)	<0.001
Age >65 years old	1.29 (1.03–1.63)	0.03
Male	1.16 (0.99–1.36)	0.06
Race		
White	Reference	
Black	0.97 (0.68–1.38)	0.86
Hispanic	0.95 (0.67–1.34)	0.77
Asian	1.05 (0.72–1.53)	0.81
Charlson/Deyo score		
CDCC 0	Reference	
CDCC 1	1.03 (0.84–1.27)	0.79
CDCC ≥2	1.47 (1.12–1.93)	0.01
Tumor size >5 cm	1.25 (1.07–1.46)	0.01
Year of diagnosis		
2004–2009	Reference	
2010–2014	1.04 (0.89–1.22)	0.64
Insurance type		
Private	Reference	
Medicare	0.90 (0.71–1.14)	0.38
Medicaid	1.27 (0.83–1.96)	0.27
Other government	0.54 (0.22–1.31)	0.17
None	1.12 (0.64–1.98)	0.69
Distance between patient's zip code and hospital (miles)		
<10 miles	Reference	
10–40 miles	0.93 (0.76–1.13)	0.46
>40 miles	0.88 (0.70–1.10)	0.26
Facility type		
Community cancer program	Reference	
Comprehensive community cancer program	0.56 (0.33–0.94)	0.03
Academic/research program	0.53 (0.32–0.86)	0.01
Integrated network cancer program	0.61 (0.35–1.07)	0.09
Median income quartiles (by zip code)		
>$63,000	Reference	
$48,000-$62,999	1.20 (0.95–1.51)	0.12
$38,000-$47,999	1.23 (0.95–1.60)	0.11
<$38,000	1.57 (1.12–2.22)	0.01
Education level (percent of region without high school degree)		
Higher education level (<7%)	Reference	
7–12.9%	0.99 (0.80–1.23)	0.95
13–20.9%	0.89 (0.68–1.16)	0.39
Lower education level (≥21%)	0.67 (0.47–0.94)	0.02
Facility region		
New England/Mid-Atlantic	Reference	
South Atlantic	1.15 (0.90–1.46)	0.26
North Central	1.09 (0.87–1.36)	0.47
South Central	1.05 (0.78–1.41)	0.74
Mountain	1.18 (0.77–1.80)	0.46
Pacific	1.08 (0.80–1.47)	0.61

CI: confidence interval; CDCC: Charlson/Deyo Comorbidity Score.

our data also suggest that AT may be associated with worse OS in patients with stage I or II disease. Unfortunately, we cannot surmise why this may be, as it is impossible to identify in the database if patients experienced drug-related toxicity or if they had other, unrecorded high-risk features that prompted them to receive AT and that we were unable to control for.

Based on the BILCAP trial preliminary results, many medical oncologists have begun to offer adjuvant therapy to more patients with resected biliary tract cancers. The National Comprehensive Cancer Guidelines for intrahepatic cholangiocarcinoma also recommend adjuvant chemotherapy in patients with positive margins.[19] In our attempt to define the role of AT in patients with resected ICC, we found marked under-utilization of adjuvant therapy, with only 63.2% of patients with positive margins and 63.9% of patients with positive nodes receiving AT. Importantly, we noted that there were stark disparities based on race and socioeconomic factors. For example, black patients were significantly less likely than white patients to receive AT, and patients with Medicare or Medicaid insurance were less likely to receive AT than patients with private insurance. These distressing findings increase the importance of examining barriers in access to care because, even among patients who underwent treatment at accredited CoC hospitals, there were still marked disparities in receipt of multimodal care.

Additional interesting disparities uncovered included the findings that patients treated at academic programs were less likely to receive AT than those treated at community programs, and that patients who lived further away from the reporting facility were also less likely to receive AT. These results may be explained by patients traveling farther for surgery but then returned to their local facilities for adjuvant therapy, though we attempted to control for this by only including patients who received all or part of their treatment at the reporting institution. We also noted regional variations in administration of AT, with patients in the New England/Mid-Atlantic area significantly more likely to receive AT than those in the Central regions, highlighting national variations in receipt of AT based on geographic location within the United States.

In terms of overall survival, the rates of 1-year and 5-year OS in our overall cohort (80.8% and 32.9%, respectively) are similar to previously published rates in other cohorts of resected patients.[5,7,20] On multivariable Cox analysis of high-risk patients, we found that receipt of AT was associated with significantly improved OS. Independent predictors of worse OS included advanced age, more comorbidities, and tumor size >5 cm. Of note, there were again notable disparities uncovered. For example, patients in the lowest quartile of regional income had significantly worse OS than patients in the highest income quartile, a troubling finding that has also been shown previously in a study of patients with ICC in the Texas Cancer Registry.[21]

Limitations of this study include its retrospective nature, leading to the potential for selection bias. Despite adjusting for many characteristics, other confounding factors may have contributed to why patients received AT or not, such as a complicated postoperative course and treatment at non-CoC institutions. Furthermore, the database does not specify what types of chemotherapy regimens patients received, or if patients received locoregional therapies, such as transarterial chemoembolization. By combining patients who likely received different types of chemotherapy regimens, the association between AT and OS may not be accurately representative of the efficacy of currently-used regimens. Despite these limitations, our study identifies important confirmatory findings associated with the use of AT, particularly in high-risk patients, as well as uncovers some interesting discrepancies in the administration of multimodal therapy in a disease as aggressive as ICC.

5. Conclusions

This study of a large nationwide cohort of patients with resected ICC demonstrates that adjuvant therapy is associated with significant improvements in OS in patients with 'high-risk' tumors (positive margins, positive lymph nodes, and clinical stage III or IVa). In addition, only 63.2% of patients with positive margins and 63.9% of patients with positive nodes received adjuvant therapy. Furthermore, under-utilization of AT was likely due to racial and socioeconomic barriers to care, as independent predictors of receipt of AT included white race and private insurance. Additional delineation of the disparities associated with AT receipt warrant further study.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.02.036.

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