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ORIGINAL ARTICLE

Is it safe to administer neoadjuvant chemotherapy to patients undergoing hepatectomy for intrahepatic cholangiocarcinoma? ACS-NSQIP propensity-matched analysis

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Abstract

Background: The use of neoadjuvant chemotherapy (NAC) in patients with intrahepatic cholangiocarcinoma (iCCA) is increasing. The objective of this study was to compare the 30-day post-operative complications and length-of-stay (LOS) between patients undergoing hepatectomy for iCCA with and without NAC.

Methods: A retrospective study was conducted using the ACS-NSQIP database queried from 2014 to 2018. Patients with NAC receipt were propensity-score matched into 1:3 ratio with controls using the greedy-matching algorithm and a caliper of 0.2. Logistic and Poisson regression models were used to estimate the effect sizes.

Results: A total of 1508 patients who underwent hepatectomy for iCCA were included. 706 patients remained after matching and balance were achieved. The NAC group had 110 (60.1%) complications vs. 289 (55.3%) complications in the non-NAC group (p = 0.29). NAC was not associated with worse 30-day postoperative complications [OR 1.24, 95% CI: 0.87–1.76; p = 0.24]. Post-operative LOS in the NAC group was 8.56 days (mean, SD 7.4) vs. non-NAC group 9.27 days (mean, SD 8.41, p = 0.32). NAC was not associated with longer post-operative LOS [RR 0.93, 95% CI:0.80, 1.08; p = 0.32].

Conclusion: NAC may be safely administered without increasing the risk of 30-day complications or post-operative hospital LOS.

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Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common cause of primary liver cancer, and the incidence has been rising globally.[1] Hepatectomy is the only potential cure but only about 20% of patients present with upfront resectable disease.[2–4] Those with locally advanced, unresectable, but non-metastatic iCCA are in some cases offered neoadjuvant chemotherapy (NAC) to downstage the tumor and convert it to resectable disease.[5,6]

Usage of NAC is becoming more common in cholangiocarcinoma treatment as it has several advantages compared to using adjuvant chemotherapy alone.[5] NAC can have a

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"downstaging" effect on unresectable iCCA tumors by shrinking the disease and making them resectable.[7,8] It is also theorized that NAC treats micro-metastatic systemic cancer, potentially resulting in improved overall survival (OS) after iCCA resections.[9–11] However, the immediate post-operative safety of NAC on patients undergoing hepatectomy for iCCA is not well established with conflicting evidence.[9] To our knowledge, there are no population-level studies evaluating the immediate post-operative outcomes of NAC after liver resection. As almost one-fifth of the patients undergoing hepatectomy for iCCA are known to experience major post-operative complications in the absence of NAC, it is crucial to accurately measure the impact of NAC on these outcomes.[12]

The primary objective of this study was to compare the 30-day overall post-operative complications between patients undergoing hepatectomy for iCCA with and without NAC. The secondary aim of this study was to compare the post-operative length of stay in hospital (LOS) between patients undergoing hepatectomy for iCCA with and without NAC. We hypothesized that NAC would have no significant impact on the 30-day post-operative complications and post-operative length of stay for patients undergoing hepatectomy for iCCA.

Methods

This study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies.[13]

Study design and population

A retrospective observational cohort study was conducted using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database.[14] ACS-NSQIP Targeted Hepatectomy Participant Use Files were queried from 2014 to 2018 to identify patients who underwent hepatectomy with a histological diagnosis of iCCA based on final surgical pathology report. The 2014–2018 Targeted Hepatectomy Participant Use Files were merged with the general ACS-NSQIP database based on linkages of unique patient identifiers. All adult patients at the age of 18 or older were included. All patients who received "preoperative systemic chemotherapy" or neoadjuvant chemotherapy, regardless of other concurrent neoadjuvant therapies, were included in the NAC group. Patients who did not receive neoadjuvant chemotherapy were otherwise included in the non-NAC group (Fig. 1).

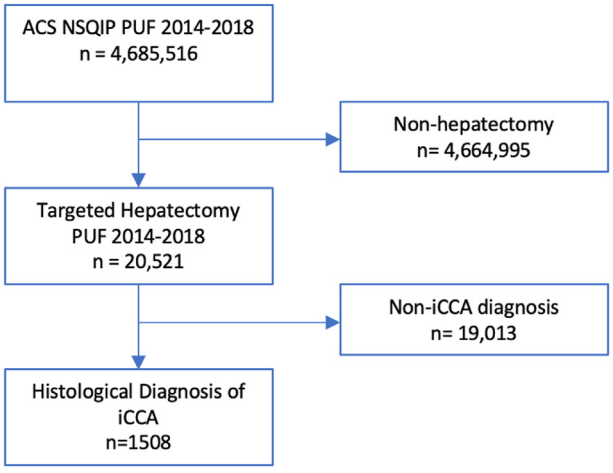

Figure 1 Flow Diagram for cohort selection from American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database with Participant Use Data Files (PUF)

Outcomes

The primary outcome was defined as any 30-day post-operative complications (binary outcome). Post-operative complications consisted of the following collected complications: bile leak, liver failure, wound infection, deep organ space SSI (surgical site infection), respiratory, cardiovascular, renal complications, blood transfusion, PE/DVT (pulmonary embolism/deep vein thrombosis), sepsis, return to OR (operating room), hospitalization >30 days, 30-day readmissions, and 30-day mortality. Major complications were defined as outcome meeting Clavien–Dindo classification III–V.[15] The secondary outcome was defined as the number of days from the date of operation to the date of discharge, or post-operative LOS, measured as a continuous variable.

Exposures

NAC was the main exposure variable defined as the receipt of neoadjuvant systemic chemotherapy regardless of other concurrent neoadjuvant treatment modalities such as locoregional inter-arterial infusion or ablative therapies. Patients who did not receive NAC were categorized into the control group.

Covariates

Covariates were selected based on clinical importance and literature review. Pre-operative through 30-day post-operative data was collected retrospectively. Selected covariates were: age (continuous), sex (binary), Body Mass Index (BMI, kg/m^2, continuous), American Society of Anesthesiologist (ASA) score (I–IV), presence of ascites (binary), congestive heart failure (CHF) (binary), cirrhosis on pathology (binary), chronic obstructive pulmonary disease (COPD, binary), current smoker (binary), type I or II diabetes (binary), dyspnea (binary), hypertension (binary), viral hepatitis (binary), portal vein embolization (PVE, binary), hepatectomy type (partial, left, right, and trisegmentectomy), operative approach (minimally invasive surgery vs. open), pringle maneuver (binary), biliary reconstruction (binary), operation time in minutes (continuous), concurrent intra-operative ablation (binary), intra-operative drain placement (binary), pathological T stage (T0–T2, T3–T4, Tx), pathological N stage (N0, N1–2), and pathological M stage (binary).

Propensity score match (PSM)

To account for confounding by indication in the use of NAC, matched controls were identified. PSM was conducted based on the predicted likelihood of receiving NAC. Multivariable logistic regression was used to calculate propensity scores and estimate the probability of receiving NAC based on age, sex, BMI, ASA score, cirrhosis, COPD, smoking, diabetes, dyspnea, hypertension, viral hepatitis, ascites, CHF, pathological T stage, N stage, M stage, and hepatectomy type. These variables were chosen *a priori* based on the clinical relevance to the decision of offering NAC and relevant literature.[10,16] Pathological T/N/M stagings were used instead as the preoperative or clinical T/N/M stagings were not available in the database. Ascites and CHF were removed from the PSM due to low event counts of less than two. Patients with NAC receipt were matched into a 1:3 ratio with controls using the greedy nearest-neighbor matching algorithm without replacement. The caliper was set at 0.2. Covariate balance between the NAC and non-NAC receiving group was assessed using standardized differences with <10% difference denoting acceptable balance.

Statistical analysis

Continuous data were summarized using mean and standard deviation (SD). Independent-sample t-test were used to compare the differences between NAC and non-NAC groups for normally distributed data. Wilcoxon–Mann Whitney test was used for non-normally distributed data. Count data were summarized as a proportion and analyzed using chi-square or Fisher's exact test. After PSM, a univariable logistic regression model was used for the primary outcome, 30-day post-operative complications. A generalized estimating equation (GEE) was used for the logistic regression model to account for clustering from the PSM. Effect estimates were reported as OR (odds ratio) with 95% CI (confidence intervals). For the secondary outcome, the number of days from operation to discharge or post-operative hospital LOS, a Poisson regression model was constructed using GEE. Effect estimates were reported as relative risk (RR) with 95% CI. A multivariable model was not constructed as the PSM was used to adjust for balancing the measured confounders. A non-parametric Cochran–Armitage test was used to report any significance in the trend of NAC use over the study period. Statistical significance was defined as a probability of 0.05 α, and two-sided tests were conducted throughout. For age (continuous), those coded "90+" were re-classified as missing (n = 2, 0.1%) as they could not be measured in continuous scale. Only one variable, viral hepatitis had a missing value percentage greater than 5%. The 8.2% missing value of viral hepatitis was missing at random based on the distribution plots and thus, multiple imputations were not performed. All analyses were performed using the SAS University Edition v9.4 software (SAS Institute, North Carolina, USA) and R version 4.0.5.[17] SAS PSMATCH procedure was used for PSM.

Results

Study sample

Patient characteristics are summarized in Table 1. A total of 1508 patients with a histological diagnosis of iCCA were included (Fig. 1). Before matching, 196 patients (13.0%) were in the NAC group and 1312 patients (87.0%) were in the non-NAC group. Of the 196 patients who received NAC, 187 (95.4%) received NAC only without concurrent neoadjuvant therapies. Eight (4.1%) patients received NAC with locoregional inter-arterial infusion, and one (0.5%) patient received NAC with locoregional inter-arterial infusion and locoregional liver ablation. Patients in the NAC group were significantly more likely to be younger, male, undergoing trisegmentectomy and PVE. Patients in the non-NAC group were significantly more likely to be having cirrhosis, diabetes, severe COPD, hypertension, and viral hepatitis. After 1:3 PSM, a total of 706 patients were remaining with 523 patients in the non-NAC group and 183 in the NAC group. The covariates included in the PSM (age, sex, BMI, ASA score, cirrhosis, COPD, smoking status, diabetes, dyspnea, hypertension, hepatitis, pathological T stage, N stage, M stage, and hepatectomy type) were well-balanced between the two treatment groups with all SD under 10%.

Primary outcome post PSM – 30-day post-operative complications

A total of 399 complications occurred within 30 days of surgery (Table 2). The NAC group had 110 complications (60.1%) vs. 289 (55.3%) in the non-NAC group (p = 0.29). The 30-day mortality rate was not statistically significantly different between NAC vs. non-NAC group (4.9 vs. 7.5%, p = 0.32). In the univariable logistic regression model, NAC was not associated with a higher odds of 30-day postoperative complications (OR 1.24 [95% CI, 0.87–1.76]; p = 0.24). For supplementary results, the peri-operative outcomes prior to the PSM are presented in Table S1. Assessing of major complications only (Clavien–Dindo classification III–V) showed no difference in the overall results (Table S2). In the univariable logistic regression model after PSM, NAC was not associated with a higher odds of 30-day major postoperative complications (OR 0.72 [95% CI, 0.49–1.06)]; p = 0.10). When the PSM analysis was repeated only including patients who have undergone right hepatectomy or trisegmentectomy, the results did not change (Tables S3 and S4). In the univariable logistic regression model after PSM including only with patients who have undergone right hepatectomy or trisegmentectomy, NAC was not associated with a higher odds of 30-day postoperative complications (OR 1.14 [95% CI, 0.68–1.89]; p = 0.62).

Secondary outcome post PSM – post-operative length of stay in hospital

The post-operative LOS in hospital or days from operation to discharge were similar between the groups (NAC mean 8.56 days

Table 1 Patient characteristics categorized by neoadjuvant chemotherapy (NAC) status

Variables	Before PSM (n = 1508)				After PSM (n = 706)			
	Non-NAC	NAC	p value	Standardized Difference	Non-NAC	NAC	p value	Standardized Difference
Patients, n	1312	196			523	183		
Age, years, mean (SD)	65.0 (10.8)	60.8 (11.3)	<0.001	0.39	61.7 (11.6)	60.5 (11.5)	0.21	0.11
Male, n (%)	622 (47.4)	82 (41.8)	0.17	0.11	226 (43.2)	76 (41.5)	0.76	0.03
BMI, kg/m^2, mean (SD)	29.7 (6.3)	29.2 (6.5)	0.33	0.08	29.4 (6.4)	29.1 (6.6)	0.59	0.05
ASA score III–IV, n (%)	1029 (78.5)	156 (79.6)	0.80	0.03	410 (78.4)	145 (79.2)	0.89	0.02
Ascites, n (%)	8 (0.6)	1 (0.5)	1.00	0.01	4 (0.8)	1 (0.5)	1.00	0.03
CHF, n (%)	6 (0.5)	1 (0.5)	1.00	0.01	1 (0.2)	1 (0.5)	1.00	0.06
Cirrhosis, n (%)	163 (12.4)	13 (6.6)	0.03	0.20	39 (7.5)	12 (6.6)	0.81	0.04
COPD, severe, n (%)	79 (6.0)	5 (2.6)	0.07	0.17	16 (3.1)	5 (2.7)	1.00	0.02
Current Smoker, n (%)	215 (16.4)	31 (15.8)	0.92	0.02	77 (14.7)	29 (15.8)	0.81	0.03
Diabetes, n (%)	320 (24.4)	35 (17.9)	0.06	0.16	102 (19.5)	33 (18.0)	0.74	0.04
Dyspnea, n (%)	95 (7.2)	11 (5.6)	0.50	0.07	30 (5.7)	10 (5.5)	1.00	0.01
Hypertension, n (%)	764 (58.2)	92 (46.9)	0.00	0.23	262 (50.1)	88 (48.1)	0.70	0.04
Hepatitis, viral, n (%)	151 (12.6)	9 (4.9)	0.00	0.28	24 (4.6)	9 (4.9)	1.00	0.02
PVE, n (%)	47 (3.6)	31 (15.8)	<0.001	0.42	32 (6.1)	28 (15.3)	<0.001	0.30
Hepatectomy type, n (%)			<0.001	0.42	32 (6.1)	28 (15.3)	0.44	0.03
Partial hepatectomy	562 (42.8)	61 (31.1)			155 (29.6)	58 (31.7)		
Left hepatectomy	259 (19.7)	28 (14.3)			94 (18.0)	26 (14.2)		
Right hepatectomy	250 (19.1)	36 (18.4)			106 (20.3)	32 (17.5)		
Trisegmentectomy	241 (18.4)	71 (36.2)			168 (32.1)	67 (36.6)		
T stage (pathological), n (%)			0.14	0.15	49 (9.4)	17 (9.3)	0.86	0.02
T0–T2	993 (75.7)	137 (69.9)			131 (25.0)	62 (33.9)		
T3–T4	224 (17.1)	38 (19.4)			164 (31.5)	46 (25.3)		
Tx	95 (7.2)	21 (10.7)			28 (5.4)	11 (6.0)		
N1–2 stage (pathological), n (%)	242 (18.4)	34 (17.3)	0.79	0.03	353 (67.6)	130 (71.0)	1.00	0.01
M1 stage, (pathological), n (%)	24 (1.8)	5 (2.6)	0.68	0.05	32 (6.1)	28 (15.3)	1.00	0.003

ASA = american society of anesthesiologist, BMI = body mass index, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, NAC = neoadjuvant chemotherapy, PSM = propensity score match, SD = standard deviation, Standardized difference = difference in means or proportions divided by standard error; imbalance defined as absolute value greater than 0.10 (small effect size).

[SD 7.4] vs. non-NAC 9.27 days [SD 8.41]; p = 0.32) (Table 2). In the univariable Poisson regression model, NAC was not associated with longer post-operative LOS [RR 0.93 (95% CI, 0.80, 1.08), p = 0.32].

Peri-operative outcome post-PSM

The NAC group had a higher bleeding rate requiring transfusions (43.2% vs. 29.4%, p < 0.001), pringle maneuver use (33.9 vs. 25.0%, p = 0.03) and longer operative time (345.4 vs. 314.8 min, p = 0.02).

Temporal trends in NAC use for iCCA hepatectomy

No statistically significant trend in the NAC utilization was observed from 2014 to 2018 using the Cochran–Armitage test for trend (p = 0.34, Fig. 2). The lowest NAC use (9.6%) was observed in 2014 and the highest use (17.1%) in 2015. The slope of the linear trend line was positive (y = 0.0262x + 0.1734).

Discussion

In this national multicenter propensity-score matched study, the receipt of NAC before iCCA resection was not significantly associated with increased 30-day post-operative complications or longer hospital LOS. A total of 196 patients (13.0%) of patients received NAC over the years of 2014–2018, which lies within the published NAC usage rate of 5.6–39.8%.[10–12,16,18] There was no statistically significant trend in NAC use for iCCA hepatectomy over the period from 2014 to 2018 (p = 0.34). The findings from our study contribute new evidence in the impact of NAC on short-term postoperative outcomes and hospital LOS.

Table 2 Peri-operative Outcome variables compared by neoadjuvant chemotherapy status

Variables	After PSM (n = 706)			
	Non-NAC (n = 523)	NAC (n = 183)	p	Standardized difference
Any 30-day postoperative complication, n (%)	289 (55.3)	110 (60.1)	0.29	0.10
Superficial SSI, n (%)	26 (5.0)	14 (7.7)	0.25	0.11
Deep organ space SSI, n (%)	94 (18.0)	30 (16.4)	0.71	0.04
Wound disruption, n (%)	5 (1.0)	1 (0.5)	0.96	0.05
Bile leak, n (%)	111 (21.3)	31 (16.9)	0.25	0.11
Post-hepatectomy liver failure, n (%)	68 (13.0)	22 (12.0)	0.83	0.03
Bleeding requiring transfusion, n (%)	154 (29.4)	79 (43.2)	0.001	0.29
Sepsis, n (%)	47 (9.0)	10 (5.5)	0.18	0.14
Septic shock, n (%)	28 (5.4)	13 (7.1)	0.49	0.07
Stroke/CVA, n (%)	3 (0.6)	1 (0.5)	1.00	0.004
Pneumonia, n (%)	25 (4.8)	6 (3.3)	0.52	0.08
Pulmonary embolism, n (%)	11 (2.1)	4 (2.2)	1.00	0.01
Ventilator > 48 h, n (%)	30 (5.7)	11 (6.0)	1.00	0.01
Acute renal failure, n (%)	20 (3.8)	6 (3.3)	0.91	0.03
Myocardial infarction, n (%)	6 (1.1)	0 (0.0)	0.32	0.15
Cardiac arrest requiring CPR, n (%)	13 (2.5)	1 (0.5)	0.19	0.16
Return to OR, n (%)	31 (5.9)	8 (4.4)	0.55	0.07
Hospitalization >30 days, n (%)	17 (3.3)	6 (3.3)	1.00	0.002
30-day readmission, n (%)	84 (16.1)	38 (20.8)	0.18	0.12
30-day mortality, n (%)	39 (7.5)	9 (4.9)	0.32	0.11
Days from operation to discharge, mean (SD)	9.3 (8.4)	8.6 (7.4)	0.32	0.09
MIS operative approach, n (%)	49 (9.4)	17 (9.3)	1.00	0.003
Pringle maneuver, n (%)	131 (25.0)	62 (33.9)	0.03	0.20
Biliary reconstruction, n (%)	164 (31.5)	46 (25.3)	0.14	0.14
Concurrent intra-operative ablation, n (%)	28 (5.4)	11 (6.0)	0.87	0.03
Intra-operative drain placement, n (%)	353 (67.6)	130 (71.0)	0.45	0.07
Operation time, minutes, mean (SD)	314.8 (155.3)	345.37 (138.2)	0.02	0.21

CPR = cardiopulmonary resuscitation, CVA = cerebrovascular accident, MIS = minimally invasive surgery, NAC = neoadjuvant chemotherapy, OR = operating room, PSM = propensity score match, SD = standard deviation, SSI = surgical site infection Standardized difference (SMD) = difference in means or proportions divided by standard error; imbalance defined as absolute value greater than 0.10 (small effect size).

Based on the current evidence, it is unclear whether the use of NAC for iCCA hepatectomy impacts the short-term post-operative outcomes or not. Immediate post-operative complications after hepatectomy may hinder the provision of adjuvant chemotherapy and worsen the long-term OS.[19,20] Our results corroborate the findings from a single-center French study, showing no difference in the 90-day morbidity, mortality, and hospital LOS when comparing upfront iCCA resection vs resection after downstaging locally advanced iCCA using NAC.[16] However, this study is limited by its small sample size (n = 76) and the use of non-adjusted statistical analysis in reporting these outcomes. Our study instead uses a national multicenter database to conduct the largest PSM to adjust for all the measured confounders and balance the baseline characteristics between the NAC vs. non-NAC groups to minimize confounding bias. It is to note that T/N/M staging and the extent of hepatectomy was incorporated into the matching process, as patients with locally advanced iCCA are known to have a higher likelihood of receiving NAC.[21,22]

One multi-institutional study from Buettner *et al.*, comparing NAC + resection vs. upfront resection for iCCA, reported that while the NAC use was associated with a higher incidence of post-operative complications, it was not associated with increased hospital LOS or major morbidities.[18] However, this study does not specify which complications were measured and whether they were short- or long-term outcomes. Using the ACS-NSQIP

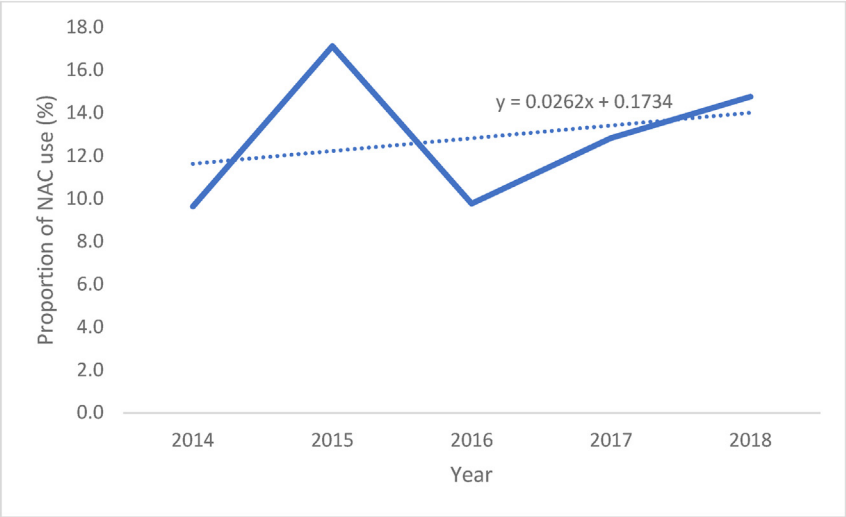

Figure 2 Trend in the NAC use for patients who underwent hepatectomy for intrahepatic cholangiocarcinoma

database, we were able to evaluate the 30-day complications more granularly. The safety of NAC has been previously explored using the ACS-NSQIP database and validated in the settings of colon cancer, colorectal liver metastases, and pancreatic ductal adenocarcinoma.[23–25] Our findings are in line with the study results from other cancer fields which have demonstrated that NAC is not associated with worse 30-day post-operative outcomes. However, our results did show that NAC use was significantly associated with increased risk of perioperative blood transfusion usage. This was despite a higher Pringle maneuver use observed in the NAC group and appropriately balancing the baseline characteristics of cirrhosis, tumor stage, and the extent of hepatectomy, amongst other comorbidities. This might be explained by the concurrent observations of a longer operative time and higher PVE rate in the NAC group, implying that the NAC group may have undergone more anatomically and technically challenging surgeries, which may represent a source of residual confounding despite the propensity-score matching.[26] Bone marrow suppression and a lower starting hemoglobin post-chemotherapy may have also contributed to the increased transfusion rates in the NAC group.[27]

The short-term morbidity of NAC usage in iCCA hepatectomies may have been overlooked because most published studies use the long-term OS as the primary endpoint in the interest of "gold standard" oncological outcomes.[5,9,28] For instance, one recent study from the United States (U.S.) reported an improved OS of patients who underwent resection after downstaging with NAC compared to those who underwent upfront resection for localized disease followed by adjuvant chemotherapy.[10] This finding was supported by another National Cancer Database study from the U.S. showing improved OS of stage II–III iCCA patients undergoing resection after NAC over upfront surgery.[11] With the growing evidence of potential long-term survival benefits of NAC use for locally advanced or unresectable iCCA, it is conceivable that there has been an increase in the use of NAC over time.[8,22] Over the limited time period of 2014–2018, our study showed no increase in the temporal trend of NAC use for patients undergoing hepatectomy for iCCA in North America ($p = 0.34$). However, our trend of NAC use is limited to those who successfully underwent hepatectomy, not capturing the patients who received NAC but never made it to the operation.

ACS-NSQIP database does not report which type of NAC was used. Gemcitabine and cisplatin (GemCis) would have been the most likely choice during our study period (2014–2018) based on the ABC-02 trial published in 2010 supporting this combined GemCis regimen vs. gemcitabine alone.[7,29] However, with discoveries of actionable mutations in iCCA (i.e. IDH1/2 mutations and FGFR2 fusions) and ongoing phase II randomized clinical trials using GemCis + abraxane or gemcitabine + oxaliplatin + lenvatinib and toripalimab, the findings from our study will have to be validated with these potential NAC regimens.[8,28,30,31] Furthermore, incorporation of trans-arterial radioembolization in the neoadjuvant setting may further improve the outcomes as it has potential survival benefits for patients with unresectable, chemotherapy-refractory iCCA.[32]

Our study has several limitations. This is a retrospective study that may not have accounted for all unmeasured and residual confounders. ACS-NSQIP database does not provide beyond the 30-day post-operative outcomes. Selection bias may exist as the patients who received NAC but did not get hepatectomy due to disease progression or complications would not be captured in this database. This missing denominator of the number of patients who started with a plan for NAC before iCCA resection limits the feasibility assessment of NAC use in this setting. However, such "selection" of patients with aggressive tumor biology is often perceived to be the strength of offering NAC

before offering a major abdominal surgery.[10] To best mitigate such selection bias, PSM was used to adjust all measured confounders before conducting any analysis. However, the PSM reduced the sample size resulting in a potential increased risk of type II error and decrease in power to adequately detect outcome differences. Furthermore, pathological tumor characteristics such as tumor multifocality and vascular invasion status were not available in this database and may therefore represent sources of unmeasured confounding. As clinical T/N/M stagings were not available in the database, pathological T/N/M stagings were used instead in the PSM. This may introduce differential measurement bias as the pathological T/N/M stagings may be potentially impacted by NAC. Finally, the neoadjuvant chemotherapy drug regimen details, indication, duration, interval between discontinuation and surgery, response and any chemotherapy-related complications are not captured in the dataset (as a group, we usually stop chemotherapy in these cases ~4 weeks before the surgery). Nonetheless, ACS-NSQIP has a major strength of being a national multicenter database that allows collecting sufficient data on rare diseases like iCCA.

Conclusion

In conclusion, NAC may be safely administered pre-operatively without increasing the risk of 30-day complications or post-operative hospital LOS. The results from this study could guide physicians' counseling on patients when offering NAC before iCCA resection. Well-designed randomized controlled studies will be needed to validate these results further.

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Authorship page

WJC: conception, statistical analysis, manuscript write-up.
TI: manuscript write-up.
MC: manuscript write-up.
SG: manuscript write-up.
BE: statistical analysis, manuscript write-up.
GS: conception, manuscript write-up.

Disclaimer

The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in this program are the sources of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Declaration of interests

None of the authors have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.03.010.