Impact of Neoadjuvant Chemotherapy on the Postoperative Outcomes of Patients Undergoing Liver Resection for Colorectal Liver Metastases: A Population-Based Propensity-Matched Analysis

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BACKGROUND: The role of neoadjuvant chemotherapy in the management of colorectal liver metastases remains controversial. We sought to investigate whether neoadjuvant systemic chemotherapy contributes to clinically significant increases in postoperative morbidity and mortality using a population-based cohort.

STUDY DESIGN: The American College of Surgeons NSQIP Targeted Hepatectomy Participant Use Files were queried from 2014 to 2016 to identify patients with colorectal liver metastases who underwent liver resection. Patients were stratified by receipt of neoadjuvant chemotherapy using propensity score matching. Univariate and multivariable analyses were used to characterize the effect of neoadjuvant chemotherapy on perioperative morbidity and mortality.

RESULTS: After propensity score matching, 1,416 (50%) patients received neoadjuvant chemotherapy before hepatectomy and 1,416 (50%) underwent liver resection without neoadjuvant chemotherapy. There were no differences in age (60 vs 61 years), maximum tumor size (≤5 cm: 79% vs 80%, >5 cm: 21% vs 20%), resection type (partial hepatectomy: 69% vs 70%), simultaneous colectomy (9% vs 9%), or use of preoperative portal vein embolization (5% vs 5%) in those undergoing neoadjuvant chemotherapy compared with those who did not (all, $p > 0.05$). Overall 30-day postoperative morbidity (34% vs 33%), including rates of biliary fistula (6% vs 5%), post-hepatectomy liver failure (5% vs 5%), and mortality rates (0.8% vs 0.7%), were similar among patients who received neoadjuvant chemotherapy vs those who did not (all, $p > 0.05$). On multivariable analysis, receipt of neoadjuvant chemotherapy was not associated with increased morbidity (odds ratio 1.07; 95% CI 0.90 to 1.27; $p = 0.43$) or mortality (odds ratio 1.09; 95% CI 0.44 to 2.72; $p = 0.85$).

CONCLUSIONS: In this propensity-matched population-based cohort study, the use of neoadjuvant systemic chemotherapy was not associated with higher rates of complications, biliary fistula, post-hepatectomy liver failure, or mortality among patients with colorectal liver metastases undergoing liver resection. (J Am Coll Surg 2019;229:69–78. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms

ACS = American College of Surgeons
CLRM = colorectal liver metastases
CRC = colorectal cancer
OR = odds ratio

Colorectal cancer (CRC) is the third leading cause of cancer-related mortality for both men and women in the US, accounting for an expected 50,000 deaths in 2018.[1] Patients with CRC frequently present with metastatic disease, including 25% to 30% who will present with colorectal liver metastases (CRLM).[2] In addition, metachronous liver metastases will develop in many patients with resected CRC. In all, CRLM will develop in approximately 50% of patients with CRC during their lifetime.[3]

Hepatic resection is the standard of care among patients with resectable liver metastases and this strategy is associated with 5-year survival rate >50% when combined with modern systemic chemotherapy.[4,5] Unfortunately, a minority of patients with CLRM are amenable to surgical resection at initial presentation.[6] Therefore, efforts at increasing the resectability rates of patients with CRLM are warranted. To that end, neoadjuvant chemotherapy is commonly used to downstage patients as a means to facilitate margin-negative resection.[7] Neoadjuvant chemotherapy also ensures appropriate patient selection for liver resection,[8] leads to improved progression-free survival compared with surgery-first approaches,[9] and the radiographic and histologic response to chemotherapy provides important prognostic information.[10,11]

Despite the potential benefits of neoadjuvant chemotherapy for CRLM, the hepatotoxic effects of chemotherapy on liver function have long been recognized. In fact, the degree of chemotherapy-associated liver injury has been associated with the type of chemotherapy used.[12] For example, oxaliplatin has been associated with sinusoidal injury[13] and irinotecan has been associated with steatohepatitis.[14] However, whether these histologic changes translate to clinically significant increases in postoperative morbidity or mortality is unclear. Some studies have demonstrated no significant differences in postoperative morbidity or mortality when neoadjuvant chemotherapy was used before liver resection.[15,16] Other studies, however, have concluded that extended durations of preoperative chemotherapy are associated with worse perioperative outcomes after liver resection.[17,18]

Therefore, we set out to investigate whether neoadjuvant chemotherapy is associated with worse postoperative outcomes among patients with CRLM undergoing liver resection using a population-based cohort. We hypothesized that after propensity score matching for factors that typically influence the receipt of neoadjuvant chemotherapy, overall clinical morbidity and mortality would be similar.

METHODS

Data acquisition and cohort selection

A retrospective review of the 2014 to 2016 American College of Surgeons (ACS) NSQIP Targeted Hepatectomy database was performed. The ACS NSQIP is a multi-institutional, prospective database that comprises preoperative, intraoperative, and 30-day postoperative variables from randomly sampled patients undergoing operations at 600 eligible hospitals across the US. The method of data collection implemented by the ACS NSQIP is standardized, resulting in validated data displaying strong reliability. Details of the database, data collection protocols, and variable definitions are available online from the ACS NSQIP website.[19] All patients who underwent liver resection for metastatic CRC were included. Patients were matched between the ACS NSQIP and targeted hepatectomy ACS NSQIP databases based on case ID number.

Study variables and outcomes

Independent variables analyzed included demographics, preoperative health status, relevant comorbidities, preoperative laboratory values, operative variables, and postoperative outcomes. Demographics consisted of age, sex, and race. Variables related to preoperative health included the American Society of Anesthesiologists classification, weight loss (10% of total body weight in 6 months), smoking, and chronic corticosteroid use. Comorbidities included diabetes mellitus, COPD, history of dyspnea, congestive heart failure, hypertension requiring medications, and bleeding disorders. Preoperative laboratory values consisted of total bilirubin, international normalized ratio, and serum albumin levels. Targeted hepatectomy variables included preoperative biliary stent placement, portal vein embolization, and locoregional therapy (ie intra-arterial chemoembolization and/or liver ablation). Operative variables retrieved from the targeted hepatectomy ACS NSQIP data were operative approach (open, minimally invasive), type of resection (trisegmentectomy, total right or left hemihepatectomy, or partial hepatectomy), size of metastatic lesion, number of metastatic lesions (≤3, ±4), operative time, Pringle maneuver performed during resection, concurrent liver ablation, concurrent colectomy (includes proctectomy), biliary reconstruction, and surgical drain placement. Minimally invasive liver resections converted to laparotomy were analyzed on an intention-to-treat basis.

Overall morbidity was defined by incidence of any of the following outcomes occurring within 30 days from operation: superficial, deep, or organ/space surgical site infection, respiratory complications (failure to wean, unplanned re-intubation, pneumonia), thromboembolism (pulmonary embolism, deep vein thrombosis), MI, acute kidney injury, urinary tract infection, postoperative transfusion within 72 hours, bile leak, or post-hepatectomy liver failure. Postoperative invasive interventions, all-cause readmission within 30 days, and reoperation were also included. Perioperative mortality was defined as death within 30 days after operation. Additionally, hospital length of stay and discharge disposition were assessed.

Neoadjuvant chemotherapy was defined as receipt of chemotherapy before the index operation. Major liver resection was defined as right hepatectomy, left hepatectomy, or trisegmentectomy; minor liver resection was defined as partial hepatectomy. Patients who underwent a hepaticojejunostomy anastomosis during the index procedure were classified as having biliary reconstruction. A composite variable was created for a postoperative intervention that consisted of stent placement for biliary obstruction or leak, interventional radiology-guided drain placement or aspiration for abscess, or interventional radiology-guided embolization. Complete definitions for the variables can be found at the ACS NSQIP website.[20]

Statistical analysis

Propensity score matching was used to establish comparable patient cohorts with respect to factors associated with receipt of neoadjuvant chemotherapy.[21] To do this, multivariable logistic regression was used to generate the propensity score, which was estimated as the probability of receiving neoadjuvant chemotherapy conditioned on age, concomitant colectomy, type of liver resection, number of tumors resected, and maximum CRLM tumor size. Matching was performed using a 1:1 optimal matching method protocol without replacement (nearest neighbor approach) with a caliper width equal to 0.25 of the SD of the logit of the propensity score.[22] A caliper of 0.25 meant that for a match to be made, the difference in the logits of the propensity score for pairs of patients from the 2 groups must be $\leq$0.25 times the pooled estimate of the common SD of the logits of the propensity score. We assessed balance between the groups before and after matching using standardized differences; values <10% for a given variable denote a relatively small imbalance.[23]

The study was designed to assess the impact of neoadjuvant therapy on the postoperative outcomes of patients undergoing liver resection for CRLM. Univariate analyses were performed of patient demographics, preoperative characteristics, and perioperative outcomes among patients who did and did not receive neoadjuvant chemotherapy. Categorical variables were assessed using the chi-square test for proportions or Fisher's exact test as appropriate, and continuous variables were analyzed using the Student's *t*-test or Mann-Whitney U test as appropriate. Multivariable logistic regression models were created for analysis of morbidity and mortality measures in matched patients. Specifically, the forward selection method was used to evaluate which demographics, preoperative characteristics, and perioperative factors were associated with postoperative complication and mortality. Variables listed in Table 1 were included in the model selection, with the exception of the listed comorbidities being represented by the American Society of Anesthesiologists classification, given their collinearity, and omission of preoperative laboratory values, as they were commonly missing (range 8.1% to 15.2%). Neoadjuvant therapy and American Society of Anesthesiologists classification were forced into the final models. Similarly, multivariable logistic regression models for morbidity and mortality were created in a subset of patients undergoing extensive liver resection classified as either right hepatectomy or trisegmentectomy.

Results of regression were reported as adjusted odds ratio (OR) and 95% CI. All analyses were performed with 2-sided p values ($\alpha = 0.05$). Statistical analyses including the propensity score were performed using SAS/STAT 14.2 of SAS, version 9.4 (SAS Institute).

RESULTS

Study sample

Of the 11,243 liver resections included in the ACS NSQIP Targeted Hepatectomy Participant Use Files from 2014 to 2016, 3,779 were performed for CRLM: 2,255 (60%) received neoadjuvant therapy and 1,524 (40%) did not. The demographic, clinical, and operative characteristics of the unmatched cohorts are reported in eTable 1. After propensity score matching, 2,832 patients were included in the current study: 1,416 (50%) received neoadjuvant therapy and 1,416 (50%) did not.

Table 1 displays the demographic, clinical, and operative characteristics of matched patients who did and did not receive neoadjuvant therapy before hepatectomy. There were no differences in age (60 vs 61 years), maximum tumor size ($\leq$5 cm: 79% vs 80%, >5 cm: 21% vs 20%) resection type (partial: 69% vs 70%; left hepatectomy: 8% vs 7%; right hepatectomy: 17% vs 18%; trisegmentectomy: 6% vs 6%), or use of simultaneous colectomy (9% vs 9%) (all, $p > 0.05$), confirming successful propensity score matching. The median number of metastatic tumors treated overall was 1 (interquartile range 1 to 3), with a

Table 1. Patient Demographics, Preoperative, and Perioperative Characteristics after Propensity Score Matching

Variable	Neoadjuvant	No neoadjuvant	Standardized difference, %	p Value
Cases, n (%)	1,416 (50)	1,416 (50)	—	—
Age, y, mean (SE)	60.2 (0.29)	60.8 (0.32)	−5	0.16
Sex, n (%)			7	0.21
Male	836 (59)	803 (57)		
Female	580 (41)	613 (43)		
Race, n (%)			13	0.02
White	1,008 (72)	952 (67)		
Black	92 (7)	93 (7)		
Asian	45 (3)	36 (3)		
Other/unknown	271 (19)	335 (24)		
American Society of Anesthesiologists class, n (%)			11	0.11
1	3 (0)	3 (0)		
2	301 (21)	283 (20)		
3	1,022 (72)	999 (71)		
4	89 (6)	124 (9)		
Weight loss, n (%)	59 (4)	34 (2)	9	0.01
Recent smoker, n (%)	191 (13)	175 (12)	3	0.40
Steroid use, n (%)	48 (3)	28 (2)	8	0.03
Diabetes, n (%)	182 (13)	219 (15)	−7	0.05
COPD, n (%)	41 (3)	38 (3)	−1	0.82
Dyspnea, n (%)	55 (4)	62 (4)	−2	0.57
Congestive heart failure, n (%)	4 (0)	4 (0)	0	1.00
Hypertension, n (%)	622 (44)	637 (45)	−2	0.57
Bleeding disorder, n (%)	59 (4)	52 (4)	2	0.56
Laboratory test result				
Bilirubin, mg/dL, mean (SE)	0.56 (0.01)	0.59 (0.01)	−9	0.01
INR >1.5, n (%)	10 (1)	20 (2)	2	0.10
Albumin, g/dL, mean (SE)	3.93 (0.01)	4.05 (0.01)	−25	<0.01
Biliary stent, n (%)	18 (1)	10 (1)	5	0.13
Portal vein embolization, n (%)	67 (5)	65 (5)	0	0.93
Locoregional therapy, n (%)	21 (1)	14 (1)	4	0.31
Surgical approach, n (%)			4	0.06
Open	1,123 (79)	1,077 (76)		
MIS	292 (21)	334 (24)		
Resection type, n (%)			0	0.79
Partial hepatectomy	982 (69)	988 (70)		
Left hepatectomy	112 (8)	101 (7)		
Right hepatectomy	237 (17)	248 (18)		
Trisegmentectomy	85 (6)	79 (6)		
Metastatic tumor size, n (%)			0	0.52
≤5 cm	1,114 (79)	1,128 (80)		
>5 cm	302 (21)	288 (20)		
Metastatic tumor treated, n (%)			0	0.07
1−3	1,201 (85)	1,234 (87)		
≥4	215 (15)	182 (13)		
Operative time, min, mean (SE)	254 (2.98)	241 (2.94)	11	<0.01
Pringle maneuver, n (%)	438 (31)	375 (26)	9	0.01

(Continued)

Table 1. Continued

Variable	Neoadjuvant	No neoadjuvant	Standardized difference, %	p Value
Concurrent ablation, n (%)	298 (21)	218 (15)	14	<0.01
Concurrent colectomy, n (%)	133 (9)	132 (9)	0	1.00
Biliary reconstruction, n (%)	15 (1)	21 (2)	−3	0.32
Surgical drain, n (%)	516 (37)	537 (38)	−2	0.43

ASA, American Society of Anesthesiologists; INR, international normalized ratio; MIS, minimally invasive surgery.

median of 2 (interquartile range 1 to 3) in the neoadjuvant group and a median of 1 (interquartile range 1 to 2) in the no neoadjuvant group. There were no differences in the use of preoperative portal vein embolization (5% vs 5%), use of minimally invasive approaches (21% vs 24%), or placement of a surgical drain (37% vs 38%) (all, $p > 0.05$).

Short-term outcomes

Table 2 reports the postoperative outcomes of matched patients who did and did not receive neoadjuvant chemotherapy. Overall 30-day morbidity (34% vs 33%; $p = 0.43$) and mortality (0.8% vs 0.7%; $p = 1.0$) were similar between the 2 groups. Importantly, there were no differences in bile leak (6% vs 5%; $p = 0.57$), post-hepatectomy liver failure (5% vs 5%; $p = 1.0$), or need for post-hepatectomy intervention (8% vs 8%; $p = 0.78$). Although patients who underwent neoadjuvant chemotherapy experienced longer length of stay (mean 6.5 vs 6.1 days; $p = 0.04$), there were no differences in discharge disposition (96% vs 95% discharge to home; $p = 0.42$) or readmission rates (10% vs 8%; $p = 0.06$).

Multivariable analysis

Tables 3 and 4 report the results of multivariable logistic regression for overall morbidity and mortality in the matched cohort, respectively. Earlier portal vein embolization, open surgical approach, operative time longer than 4 hours, major hepatectomy, simultaneous colectomy, tumor resection size >5 cm, and placement of surgical drain were associated with increased risk of a postoperative complication (all, $p < 0.05$) and neoadjuvant chemotherapy (OR 1.07; 95% CI 0.90 to 1.27; $p = 0.43$) was

Table 2. Postoperative Outcomes for Patients Undergoing Liver Resection for Colorectal Liver Metastases by Receipt of Neoadjuvant Chemotherapy

Variable	Total	Neoadjuvant	No neoadjuvant	p Value
Postoperative length of stay, d, mean (SE)	6.3 (0.10)	6.5 (0.13)	6.1 (0.13)	0.04
Discharged home, n (%)	2,702 (95)	1,356 (96)	1,346 (95)	0.42
Any postoperative complication, n (%)	948 (33)	484 (34)	464 (33)	0.43
Surgical site infection	278 (10)	134 (9)	144 (10)	0.53
Fail to wean from ventilator	40 (1)	22 (2)	18 (1)	0.63
Reintubation	45 (2)	17 (1)	28 (2)	0.13
Pneumonia	94 (3)	47 (3)	47 (3)	1.00
Pulmonary embolism	36 (1)	19 (1)	17 (1)	0.87
Deep vein thrombosis	43 (2)	26 (2)	17 (1)	0.22
MI	24 (1)	16 (1)	8 (1)	0.15
Acute kidney injury	16 (1)	9 (1)	7 (0)	0.80
Urinary tract infection	61 (2)	33 (2)	28 (2)	0.60
Blood transfusion within 72 h	450 (16)	224 (16)	226 (16)	0.92
Bile leak, any, n (%)	162 (6)	85 (6)	77 (5)	0.57
Prolonged drain placement >3 d	81 (51)	46 (55)	35 (46)	0.44
Requiring drain placement	62 (39)	31 (37)	31 (41)	—
Requiring reoperation	17 (11)	7 (8)	10 (13)	—
Postoperative liver failure, n (%)	130 (5)	65 (5)	65 (5)	1.00
Readmission (all cause), n (%)	257 (9)	143 (10)	114 (8)	0.06
Reoperation, n (%)	70 (3)	36 (3)	34 (2)	0.90
Postoperative intervention, n (%)	220 (8)	108 (8)	112 (8)	0.78
Perioperative mortality, n (%)	21 (0.7)	11 (0.8)	10 (0.7)	1.00

Table 3. Multivariable Analysis for Any Postoperative Complication in Patients Undergoing Liver Resection for Colorectal Liver Metastases

Variable	Odds ratio	95% CI	p Value
Neoadjuvant chemotherapy	1.07	0.90−1.27	0.43
Portal vein embolization	1.65	1.11−2.44	0.01
Tumor size >5 vs ≤5 cm	1.32	1.07−1.62	<0.01
Open vs laparoscopic approach	1.53	1.23−1.90	<0.01
Operative time			
4−6 vs <4 h	1.74	1.44−2.11	<0.01
>6 vs <4 h	2.93	2.27−3.78	
Major vs minor liver resection	1.34	1.10−1.62	<0.01
Concurrent colectomy	1.46	1.11−1.92	<0.01
Surgical drain	1.48	1.24−1.76	<0.01

The area under the receiver operator curve of the model was 0.690.

not (Table 3). On multivariable logistic regression, mortality was associated with operative time longer than 6 hours, use of Pringle maneuver, and biliary reconstruction (all, $p < 0.05$), and neoadjuvant chemotherapy (OR 1.09; 95% CI 0.44 to 2.72; $p = 0.85$) was not (Table 4).

In the subset of patients who underwent either a right hepatectomy or trisegmentectomy ($n = 649$), neoadjuvant chemotherapy was not found to be associated with morbidity (OR 0.95; 95% CI 0.68 to 1.33; $p = 0.75$) or mortality (OR 0.94; 95% CI 0.22 to 4.12; $p = 0.84$) on multivariable logistic regression analysis. These data are shown in eTables 2 and 3, respectively.

DISCUSSION

The role of neoadjuvant systemic chemotherapy in the management of patients with resectable CRLM continues to be debated. One ongoing controversy is the safety of neoadjuvant chemotherapy on post-hepatectomy outcomes, given the hepatotoxic effects of commonly used chemotherapy regimens for CRC.[17,18] Earlier studies on this topic have been limited by their retrospective design, small sample sizes, and selection biases, as patients who received neoadjuvant chemotherapy typically had worse clinicopathologic features or more extensive tumor burden. In an effort to mitigate these biases, a propensity-matched population-based cohort study was used to investigate the influence of neoadjuvant chemotherapy on postoperative morbidity and mortality; there were no detrimental associations of neoadjuvant chemotherapy including post-hepatectomy specific outcomes, such as biliary fistula and post-hepatectomy liver failure. These findings suggest that neoadjuvant chemotherapy is a safe and appropriate treatment strategy for select patients with resectable CRLM.

Table 4. Multivariable Analysis for Perioperative Mortality in Patients Undergoing Liver Resection for Colorectal Liver Metastases

Variable	Odds ratio	95% CI	p Value
Neoadjuvant chemotherapy	1.09	0.44−2.72	0.85
Operative time			0.02
4−6 vs <4 h	2.02	0.62−6.60	
>6 vs <4 h	5.45	1.63−18.2	
Pringle maneuver	2.95	1.19−7.33	0.02
Biliary reconstruction	9.44	1.76−50.8	<0.01

The area under the receiver operator curve of the model was 0.861.

An important finding in the current study is that approximately 60% of patients in the ACS NSQIP-targeted hepatectomy database, which reflects national trends in care delivery, received neoadjuvant chemotherapy. There are multiple reasons why providers might choose to administer neoadjuvant chemotherapy for patients with CRLM, so it might not be surprising that such a high proportion of patients receive neoadjuvant chemotherapy. Neoadjuvant therapy can treat occult metastases and has been shown to improve progression-free survival in randomized controlled trials.[9] Administration of neoadjuvant chemotherapy might also allow testing for tumor response to chemotherapy providing key prognostic information.[24] Indeed, some clinicians have recommended preoperative chemotherapy in all patients with a diagnosis of CRLM.[25] Finally, because only about 25% of patients with CLRM are amenable to surgical resection at initial presentation,[6] neoadjuvant chemotherapy can be used to downstage patients with advanced disease to facilitate subsequent margin-negative resection.[7] On the other hand, the hepatotoxic effects of systemic chemotherapy are well known. Oxaliplatin and irinotecan, both commonly used agents for CRC, are associated with sinusoidal injury and steatohepatitis, respectively, the latter having been associated with increased 90-day mortality.[14] In addition to chemotherapy-associated liver injury, other disadvantages to neoadjuvant chemotherapy include the risks of bevacizumab on wound healing, as well as patient deconditioning, which can occur during administration of systemic therapies.[26] Nevertheless, it has remained unclear whether these risks translate to increased complications after liver resection in the general population.

Previous studies investigating the impact of neoadjuvant chemotherapy on postoperative outcomes of liver resection have been contradictory. For example, Zhu and colleagues[16] retrospectively analyzed 466 patients with resectable CRLM between 2000 and 2010. These patients were divided by receipt of chemotherapy administration before hepatic resection. Results from this study demonstrated no differences between the 2 groups in terms of postoperative morbidity (neoadjuvant: 33.9% vs no neoadjuvant: 25.8%; $p > 0.05$). In a separate study, Scoggins and colleagues[15] performed a retrospective analysis of 186 patients with CRLM who underwent hepatectomy from 1996 to 2006. These authors reported that among the 112 (60%) patients who underwent neoadjuvant chemotherapy, there was no increase in postoperative morbidity (49% vs 47%; $p = 0.81$). In contrast, Adam and colleagues[27] reviewed a multicentric cohort study of 1,471 patients who underwent resection of CRLM in the LiverMetSurvey International Registry, reporting that the rate of postoperative complications was higher among patients who received neoadjuvant chemotherapy (37.2% vs 24.0%; $p < 0.01$). Similarly, Nordlinger and colleagues[9] reported that patients randomized to perioperative chemotherapy experienced an increase in postoperative "reversible" complications (eg intra-abdominal infections, biliary fistulas, and hepatic failure) (25% vs 16%; $p = 0.04$), but not mortality (1% vs 1%).[28] Whether the findings from the current study differ because of the definition of complication used, the relative early timing of operation after chemotherapy in the Nordlinger trial (recommended 2 to 5 weeks), or other reasons, remains unknown.

The use of a multi-institutional, prospectively collected database allows a permissive design in patient selection. With more than 100 hospitals across the US sampled, our results do not strictly apply to academic institutions. This is a major distinguishing factor compared with earlier studies. Most previous reports have focused on large academic institutions in which multidisciplinary expertise, well-defined clinical protocols and high patient volume ensure optimal postoperative outcomes. In contrast, the current study is the first to address this question in a population-based approach. That our findings are relatively consistent with earlier studies is meaningful in that it suggests the safety of neoadjuvant therapy before liver resection is relatively generalizable to non-academic centers. However, it is also important to recognize that the majority of patients in the current study underwent minor resections, with few patients having >3 tumors, tumors >5 cm, or requiring extended resections. Therefore, caution should be given to generalizing these findings to all patients, especially those with advanced tumors requiring extended liver resections.

A major limitation of the current study is the lack of information on chemotherapy regimen, duration of neoadjuvant therapy, and overall tumor response. This is important because earlier investigations have demonstrated that extended durations of preoperative chemotherapy are associated with worse perioperative outcomes after liver resection.[17,18] In these studies, durations of ≤6 cycles were not associated with increased postoperative morbidity. Lastly, isolating effects of specific chemotherapy agents in this data set is not possible. Therefore, these findings should not be generalized equally for all chemotherapy regimens, and caution should be used with agents previously associated with adverse outcomes, such as bevacizumab. Based on previous large institutional series,[17,18] as well as the EORTC 40983 trial,[9] the authors' preference is for all patients with potentially resectable CRLM to be considered for perioperative chemotherapy. We recommend 6 cycles of folinic acid, fluorouracil, and oxaliplatin (ie FOLFOX) ± bevacizumab (which is typically held on the last cycle). Patients are restaged and surgical resection is considered 4 to 6 weeks after chemotherapy for those with stable or responding disease.

Other limitations of the study pertain to the ACS NSQIP database. First, the preoperative intent of neoadjuvant chemotherapy in this population (eg downstaging, patient selection) is unknown, which could potentially lead to selection biases in the 2 groups. Second, data on hospital and surgeon volume, both important determinants of outcomes after hepatobiliary surgery,[29] were not available. Third, despite the additional detail in the targeted hepatectomy database, operative information is still confined to CPT codes, so additional details about "partial hepatectomy" are not available. Fourth, we acknowledge that pathologic tumor size serves as a surrogate for clinical tumor size, as the latter is not available in the ACS NSQIP database and might have been influenced by the receipt of neoadjuvant chemotherapy. Fifth, despite the use of propensity scores, other measured and unmeasured differences might have existed between the treatment groups in this retrospective cohort study. Finally, perioperative outcomes in the ACS NSQIP database are limited to 30 days after operation, which might be insufficient to capture all postoperative complications.[30,31] Despite these limitations, a major strength of the current study is the use of a population-based cohort, which permits a larger sample size and evaluation of "real-world" practices among a diverse set of institutions. In addition, the use of propensity score matching leads to more balanced groups, minimizing the selection biases present in previous retrospective studies.

CONCLUSIONS

In this propensity-matched population-based analysis, the use of neoadjuvant systemic chemotherapy was not associated with worse postoperative outcomes after liver resection for CRLM. Although additional prospective studies are needed to determine the optimal regimen, duration, and specific survival impact of systemic chemotherapy, neoadjuvant approaches should be considered safe and included as part of the multidisciplinary management of select patients with resectable CRLM.

Author Contributions

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Discussion

DR MARGO SHOUP (Warrenville, IL): The authors used the NSQIP database for hepatectomy patients from 2014 to 2016 to identify patients with colorectal liver metastasis who underwent resection. They appropriately used propensity score matching to evaluate more than 2,800 patients, half who had received chemotherapy preoperatively and half who did not. Although their conclusion is that neoadjuvant systemic chemotherapy was not associated with higher rates of complications, the devil is in the details, and this is what leads to my questions.

In your analysis, only 6% of the patients underwent trisegmentectomy, as you called it. It is good to see that these operations are not being performed very frequently anymore because there is very little reason to do so with all the other methods we have of local treatment and systemic therapy. I actually would have hoped that the number would be a little bit smaller, to tell you the truth. But we are all pushing the envelope these days for liver resections with formal right hepatectomies combined with partial left plus ablation or other such resections, and it is those patients that we are most concerned about regarding liver failure or other postoperative complications. I did not see a separate group for bilobar resection with ablation. How do you categorize these patients in your data?

Next, the data are a mix of apples and oranges, really, when you look at complications, because most of us are not really that concerned about a serious complication occurring on a patient who underwent 4 cycles of FOLFOX followed by a segment 2 liver resection. However, a patient who has 12 cycles of chemotherapy with Avastin (bevacizumab) and then undergoes bilobar resection raises a lot of concern. I know the database cannot determine the type of chemotherapy. I suppose it probably cannot determine the length of chemotherapy, or the number of cycles, or if there is targeted therapy involved, but these are really the important issues at hand that we can actually use to affect our practice or prognosis. Hopefully you can comment on that. I am concerned that this study will open the door for the go-ahead for liver resection in all patients undergoing chemotherapy before surgery, while we know that there are real dangers, and the extent of resection and future liver remnant needs to be seriously considered before undertaking surgery.

You demonstrated that there is an increased risk of complications in patients having a longer operation, portal vein embolization, concurrent colectomy, and major hepatectomy. These are usually patients who have extensive disease and perhaps have a longer course of therapy with a larger resection, and these are precisely the patients we need to focus on with the preoperative chemotherapy. It would be really helpful if you could reevaluate your data to look specifically at the type and number of cycles of chemotherapy with or without Avastin and other targeted therapies. Your conclusion, while carefully written to address this study only, cannot and should not be applied to the practice of multidisciplinary teams of surgical and medical oncologists who deal with much more complicated issues than what can be extracted from these data.

DR YUN SHIN CHUN (Houston, TX): Unless a formal left or right hepatectomy was performed, patients undergoing bilateral resection with ablation were categorized as undergoing a minor hepatectomy. In the NSQIP database, almost a quarter of patients underwent ablation. Our institutional practice is to perform resection over ablation because of the increased risk of local tumor progression. A major limitation is absence of data on the duration and regimen of chemotherapy. The aim of the study was to examine a broad patient population from hundreds of hospitals in the US. Most of these patients were not referred to tertiary centers for an extended resection. The important finding of this study is that despite the absence of randomized data showing an improvement in overall survival, nearly two-thirds of patients are receiving neoadjuvant chemotherapy without an increase in complications. The caveat is that most of the patients in the study did not undergo an extended hepatectomy.

DR VICTOR ZAYDFUDIM (Charlottesville, VA): I believe NSQIP uses ICD-9 codes during the time period of this study. If so, how did you use ICD-9 codes to distinguish between different types of metastases to deliver? How do you know these are colorectal metastases, not neuroendocrine metastases or some other metastases?

DR YUN SHIN CHUN (Houston, TX): Are you referring to the morphology vs histology classification?

DR VICTOR ZAYDFUDIM (Charlottesville, VA): I am referring to the diagnosis codes. I believe NSQIP uses ICD-9 codes for coding these patients, and those are typically not specific for what kind of metastasis the patient has to the liver.

DR JORDAN M CLOYD (Columbus, OH): In the targeted hepatectomy database, that information is available as the specific histology indication for resection. We used that as opposed to the diagnosis available in the general NSQIP database.

DR STEVEN A CURLEY (Tyler, TX): I just want to echo something that Dr Shoup said, and point out a massive limitation of using the NSQIP database. You do not know the denominator of

eTable 1. Patient Demographic, Preoperative, and Perioperative Characteristics Before Propensity Score Matching

Variable	Neoadjuvant	No neoadjuvant	Standardized difference, %	p Value
Patients, n (%)	2,255 (60)	1,524 (40)	—	—
Age, y, mean (SE)	58 (0.24)	61 (0.31)	−24	<0.01
Sex, n (%)			−2	0.41
Male	1,315 (58)	868 (57)		
Female	940 (42)	656 (43)		
Race, n (%)			7	0.14
White	1,571 (70)	1,032 (68)		
Black	154 (7)	99 (7)		
Asian	75 (3)	41 (3)		
Other/unknown	455 (20)	352 (23)		
American Society of Anesthesiologists class, n (%)			11	0.02
1	5 (1)	3 (0)		
2	490 (22)	304 (20)		
3	1,616 (72)	1,074 (71)		
4	139 (6)	134 (9)		
5	0 (0)	1 (0)		
Weight loss, n (%)	100 (4)	35 (2)	11	<0.01
Recent smoker, n (%)	293 (13)	191 (13)	1	0.68
Steroid use, n (%)	78 (3)	30 (2)	9	<0.01
Diabetes, n (%)	289 (15)	236 (16)	−7	0.02
COPD, n (%)	52 (2)	43 (3)	−3	0.34
Dyspnea, n (%)	81 (4)	66 (4)	−3	0.26
Congestive heart failure, n (%)	8 (0)	6 (0)	0	1.00
Hypertension, n (%)	907 (40)	688 (45)	−9	<0.01
Bleeding disorder, n (%)	87 (4)	56 (4)	0	0.80
Laboratory test result				
Bilirubin, mg/dL, mean (SE)	0.56 (0.01)	0.59 (0.01)	−10	<0.01
International normalized ratio >1.5, n (%)	21 (1)	22 (2)	5	0.16
Albumin, g/dL, mean (SE)	3.95 (0.01)	4.05 (0.01)	−22	<0.01
Biliary stent, n (%)	20 (1)	11 (1)	1	0.71
Portal vein embolization, n (%)	144 (6)	71 (5)	7	0.03
Locoregional therapy, n (%)	45 (2)	19 (1)	5	0.09
Surgical approach, n (%)			10	<0.01
Open	1,835 (81)	1,171 (77)		
Minimally invasive	419 (19)	348 (23)		
Resection type, n (%)			17	<0.01
Partial hepatectomy	1,373 (61)	1,059 (70)		
Left hepatectomy	171 (8)	110 (7)		
Right hepatectomy	476 (21)	265 (17)		
Trisegmentectomy	235 (10)	90 (6)		
Metastatic tumor size, n (%)			4	0.16
≤5 cm	1,758 (81)	1,158 (79)		
>5 cm	403 (19)	300 (21)		
Metastatic tumor treated, n (%)			−27	<0.01
1−3	1,656 (77)	1,259 (87)		
4 or more	498 (23)	184 (13)		
Operative time, min, mean (SE)	266 (2.37)	240 (2.85)	22	<0.01
Pringle maneuver, n (%)	695 (31)	405 (27)	9	<0.01

(Continued)

eTable 1. Continued

Variable	Neoadjuvant	No neoadjuvant	Standardized difference, %	p Value
Concurrent ablation, n (%)	513 (23)	244 (16)	17	<0.01
Concurrent colectomy, n (%)	272 (12)	138 (9)	9	<0.01
Biliary reconstruction, n (%)	28 (1)	25 (2)	−3	0.33
Surgical drain, n (%)	854 (38)	584 (38)	0	0.79

eTable 2. Multivariable Analysis for any Postoperative Complication in Patients Undergoing Right Hepatectomy and Trisegmentectomy Resection for Colorectal Liver Metastases

Variable	Odds ratio	95% CI	p Value
Neoadjuvant chemotherapy	0.946	0.68−1.33	0.75
Operative time			<0.01
4−6 vs <4 h	1.42	0.96−2.1	
>6 vs <4 hours	2.51	1.54−4.10	
Surgical drain	2.05	1.50−2.87	<0.01

The area under the receiver operator curve of the model was 0.687.

eTable 3. Multivariable Analysis for Perioperative Mortality in Patients Undergoing Right Hepatectomy and Trisegmentectomy Resection for Colorectal Liver Metastases

Variable	Odds ratio	95% CI	p Value
Neoadjuvant chemotherapy	0.94	0.22−4.12	0.84
Presence of >3 treated colorectal liver metastases	6.21	1.41−27.5	0.02

The area under the receiver operator curve of the model was 0.850.