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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Perioperative Chemotherapy is Associated with Superior Overall Survival in Patients with Synchronous Colorectal Liver Metastases

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ABSTRACT

Background. The sequence of localized and systemic treatment for colorectal liver metastases (CRLM) remains debated. Our objective is to analyze the effect of treatment sequence on overall survival (OS) in patients with CRLM using a large cancer database.

Patients and Methods. The national cancer database (NCDB) was utilized to identify patients with stage IV colorectal cancer (CRC) diagnosed between 2004 and 2016. OS was analyzed using standard univariate and multivariate methods.

Results. We identified 72,376 patients with synchronous CRLM, of whom 43,039 had liver-only metastases. Patients with liver-only CRLM had a median OS of 18.9 months, versus those with CRLM plus extrahepatic sites (11.3 months). In patients with liver-only CRLM, resection of both the primary and metastatic site was associated with median OS 38.9 months versus 30.2 months after resection of the metastatic site alone, and resection of the primary tumor alone (22.3 months, all $p < 0.001$). Receipt of perioperative chemotherapy correlated with a median OS of 44.7 months versus preoperative chemotherapy only (38.4 months) or postoperative chemotherapy only (27.9 months, all $p < 0.001$). Patients who received chemotherapy alone had a median OS of 16.4 months versus those who underwent resection without chemotherapy (9.5 months, $p < 0.001$).

Conclusions. This study reveals a correlation between perioperative chemotherapy and superior OS in patients with liver-only CRLM, and shows that resection of the metastatic site was linked to better OS. Despite obvious cohort heterogeneity, the data can support a resection approach with additional, preferably peri- or preoperative systemic therapy for patients with CRLM.

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy worldwide, and represents the second leading cause of cancer death following lung cancer.[1] Among patients with CRC, approximately 25–30% are expected to develop liver metastases during the course of their disease.[2] These colorectal cancer liver metastases (CRLM) represent a formidable but potentially still curable disease entity, with an associated median survival of 9 months in the absence of other metastatic sites.[3] Surgical resection is the mainstay of curative-intent therapy, and post-resection recurrence risk can be predicted on the basis of established clinical risk factors.[4] Since the availability of more effective combination chemotherapy regimens, the combined use of resection and chemotherapy has become a treatment standard for most patients with higher recurrence risks, while post-chemotherapy resection is still an option even for some initially unresectable CRLM.[5]

However, controversy persists as to the best timing of chemotherapy and resection for technically resectable disease.[6] Despite an early suggestion for improved progression-free survival (PFS), the EORTC randomized trial of perioperative FOLFOX therapy for up to four resectable metastases failed to show a benefit in overall survival (OS),[7] likely due to the benefit from subsequent chemotherapy used in cases of later recurrence. Preoperative chemotherapy allows for a clinical response assessment with its prognostic information,

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but comes at the potential price of chemotherapy-associated liver injury, increased morbidity risks after prolonged chemotherapy, and the challenge around disappearing lesions.[8] Small studies comparing pre- and postoperative chemotherapy have raised the notion whether postoperative treatment leads to better survival outcomes.[9] Therefore, we sought to investigate the pattern of multimodality therapy and the outcomes associated with CRLM resection in conjunction with pre-, peri-, or postoperative chemotherapy using a large cancer database.

PATIENTS AND METHODS

Data Acquisition

A dataset of patients with CRLM was created from the NCDB colorectal cancer dataset through structured queries of histologic subtypes proper for inclusion. Number and histopathologic information including margin status (R category) of CRLMs were captured and recoded as deemed appropriate. Systemic chemotherapy as part of the care episode was captured, including regimen, timing, and duration. Patient demographic, clinical, treatment, and outcome variables were summarized by descriptive statistics.

Patient Selection

All patients with colorectal cancer were identified from the NCDB between 2004 and 2016. Given the distinct natural history and treatment of appendiceal cancer, we excluded these patients from analysis. We excluded in situ disease as well as non-adenocarcinoma histologies. Additionally, patients with extrahepatic metastases, including to the peritoneum, lung, brain, or bone, were identified for OS comparison. Finally, we excluded patients who received intraoperative chemotherapy or those with missing information on resection or systemic treatment.

Statistical Analysis

Patient demographic and clinical characteristics were summarized using the appropriate descriptive statistics, with overall associations assessed using the Kruskal–Wallis or Pearson chi-squared tests. Unadjusted pairwise comparisons were made between groups using the Mann–Whitney or Fisher's exact tests, as appropriate. Short-term outcomes (readmission, 30-day mortality, recurrence) were compared between groups using Fisher's exact tests. Overall survival was summarized using standard Kaplan–Meier methods, with comparisons made using the log-rank test. Multivariable logistic and Cox regression models were used to compare groups while adjusting for relevant patient demographic and clinical characteristics. All model assumptions were verified graphically and odds/hazard ratios with 95% confidence intervals (CI) were obtained from model estimates. Analyses were performed in SAS v9.4 (Cary, NC) with significance accepted at $p < 0.05$.

RESULTS

Patient, Tumor, and Treatment Characteristics

A total of 1,089,764 patients with invasive colorectal adenocarcinoma were identified from the NCDB between 2004 and 2016. We identified a total of 72,376 patients with synchronous CRLM; while there is no universal definition for the interval defining synchronous versus metachronous metastases, for the purposes of this study, patients with colorectal liver metastases at the time of diagnosis and registration into the NCDB were considered to have synchronous CRLM. Of these patients, 17,917 had extrahepatic metastases to the peritoneum, lung, brain, or bone in addition to CRLM (M1b and M1c disease), and 54,459 patients had liver-only CRLM. After excluding patients who received only intraoperative chemotherapy, or who had unknown or missing treatment information ($n = 11{,}420$), the number of patients included in our final analysis was 43,039 (Fig. 1).

Of the 43,039 patients included in the final analysis (Table 1), 25,752 patients (59.8%) underwent resection and 38,747 (90.0%) received chemotherapy. The majority of patients ($n = 18{,}352$, or 42.6%) underwent resection followed by postoperative chemotherapy, while 9.8% (4212) received preoperative chemotherapy followed by resection, and 6.1% (2617) received perioperative chemotherapy as well as resection. Only 570 patients (1.3%) underwent resection alone without chemotherapy, while 13,564 patients (31.5%) received chemotherapy alone without resection, and 3724 patients (8.7%) received no treatment at all. Of all the patients included, 7014 (16.4%) were treated with immunotherapy and 3513 (8.1%) received radiation therapy.

The median age of the patients included in the final analysis was 62 years (range 18–90 years). More than half of the patients analyzed were male ($n = 24{,}455$, 56.8%). The majority of patients were listed as white ($n = 34{,}576$, or 81.0%), 6304 (14.8%) were Black, 1248 (2.9%) were Asian, and 575 (1.3%) were of another ethnicity. The median age of the patients who received no treatment was highest at 74 years, while patients who received perioperative chemotherapy had the lowest median age at 56 years ($p < 0.001$). Among patients who did not receive any treatment, 12.2% had a Charlson–Deyo Comorbidity (CC) score of 2 or greater, while in patients who received perioperative chemotherapy and resection, this number was 3% ($p < 0.001$).

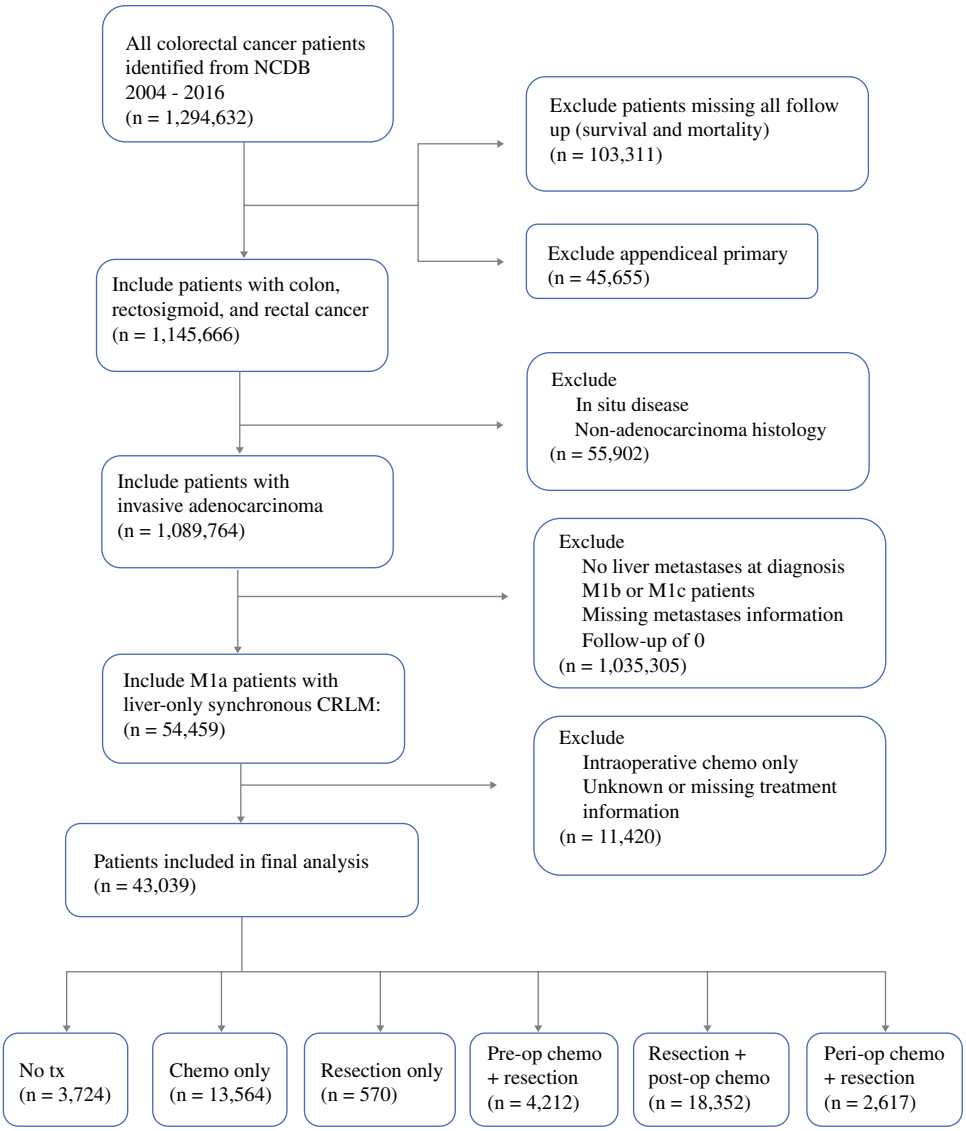

FIG. 1 Flow chart illustrating determination of patient treatment cohorts

Survival

Effect of Metastatic Pattern on Survival

Patients with liver-only metastases had a 5-year OS of 14% and median OS of 18.9 months (CI 18.7–19.2 months), while patients with liver metastases as well as extrahepatic metastases had a 5-year OS of 4% and median OS of 11.3 months (CI 11.0–11.6 months, $p < 0.001$, Fig. 2).

Prognostic Impact of Tumor and Resection Characteristics

Multivariable analysis demonstrated that higher primary tumor grade, one or more positive nodes at the primary site, and margin positivity had a negative impact on survival ($p < 0.001$, Table 2). There were significant OS differences in the T subcategory cohorts. Resection of the primary site was associated with a 14% lower hazard of death (HR 0.86; 95% CI 0.79–0.93, $p < 0.001$). Examination of 1–14 lymph nodes in resection of the primary site was associated with a 20% reduction in the hazard of death (HR 0.80; 95% CI 0.66–0.96, $p < 0.001$), while examination of ≥ 15 lymph nodes was associated with a 38% reduction in the hazard of death (HR 0.62; 95% CI 0.52–0.74, $p < 0.001$). No data on number of metastases were available in the NCDB database.

Local Excision Versus Colectomy in Patients with Synchronous Metastatic Disease

Among patients with metastatic disease who underwent local excision only, 64.2% had colon cancer and 35.8% had rectal cancer; local excision in the setting of colon cancer mostly consisted of endoscopic polypectomy. Among patients who underwent colorectal enteric resection (i.e., colectomy or proctectomy), 88.8% had colon cancer and 11.2% had rectal cancer. Patients with metastatic disease who underwent local excision of the primary tumor had no

TABLE 1 Patient demographic and clinical characteristics by cohort

		No treatment	Chemotherapy alone	Resection alone	Preoperative chemotherapy + resection	Resection + postoperative chemotherapy	Perioperative chemotherapy + resection	All patients	*P* value
Overall	*N*	3725 (8.7)	13,565 (31.5)	570 (1.3)	4212 (9.8)	18,353 (42.6)	2617 (6.1)	43,042 (100.0)	
Age	Mean/std/*N*	72.2/13.8/3725	62.0/13.1/13565	70.7/13.3/570	57.8/11.8/4212	61.3/12.7/18353	55.4/11.8/2617	61.9/13.4/43042	<.001
	Median/min/max	74.0/19.0/90.0	62.0/18.0/90.0	73.0/26.0/90.0	58.0/18.0/90.0	61.0/18.0/90.0	56.0/20.0/88.0	62.0/18.0/90.0	
Age*	< 40	71 (1.9%)	595 (4.4%)	12 (2.1%)	276 (6.6%)	822 (4.5%)	240 (9.2%)	2016 (4.7%)	<.001
	40-50	172 (4.6%)	1736 (12.8%)	29 (5.1%)	722 (17.1%)	2473 (13.5%)	560 (21.4%)	5692 (13.2%)	
	50-60	456 (12.2%)	3517 (25.9%)	68 (11.9%)	1340 (31.8%)	4920 (26.8%)	826 (31.6%)	11,127 (25.9%)	
	60-70	769 (20.6%)	3723 (27.4%)	135 (23.7%)	1163 (27.6%)	5077 (27.7%)	678 (25.9%)	11,545 (26.8%)	
	≥ 70	2257 (60.6%)	3994 (29.4%)	326 (57.2%)	711 (16.9%)	5061 (27.6%)	313 (12.0%)	12,662 (29.4%)	
Sex	Male	1994 (53.5%)	8023 (59.1%)	265 (46.5%)	2612 (62.0%)	10,017 (54.6%)	1544 (59.0%)	24,455 (56.8%)	<.001
	Female	1731 (46.5%)	5542 (40.9%)	305 (53.5%)	1600 (38.0%)	8336 (45.4%)	1073 (41.0%)	18,587 (43.2%)	
Race	White	2896 (78.4%)	10,719 (79.8%)	457 (81.0%)	3525 (84.4%)	14,704 (80.6%)	2275 (87.2%)	34,576 (81.0%)	<.001
	Black	648 (17.6%)	2131 (15.9%)	82 (14.5%)	445 (10.6%)	2792 (15.3%)	206 (7.9%)	6304 (14.8%)	
	Asian	107 (2.9%)	381 (2.8%)	21 (3.7%)	134 (3.2%)	510 (2.8%)	95 (3.6%)	1248 (2.9%)	
	Other	41 (1.1%)	193 (1.4%)	4 (0.7%)	75 (1.8%)	230 (1.3%)	32 (1.2%)	575 (1.3%)	
Charlson Deyo combined comorbidity	0	2494 (67.0%)	10,586 (78.0%)	358 (62.8%)	3423 (81.3%)	13,911 (75.8%)	2138 (81.7%)	32,910 (76.5%)	<.001
	1	775 (20.8%)	2162 (15.9%)	148 (26.0%)	618 (14.7%)	3436 (18.7%)	402 (15.4%)	7541 (17.5%)	
	2	270 (7.2%)	535 (3.9%)	45 (7.9%)	122 (2.9%)	743 (4.0%)	57 (2.2%)	1772 (4.1%)	
	≥ 3	186 (5.0%)	282 (2.1%)	19 (3.3%)	49 (1.2%)	263 (1.4%)	20 (0.8%)	819 (1.9%)	
30-Day mortality		n/a	n/a	120 (21.5%)	118 (3.0%)	31 (0.2%)	5 (0.2%)	274 (1.1%)	<.001
90-Day mortality		n/a	n/a	199 (35.9%)	255 (6.6%)	466 (2.6%)	23 (0.9%)	943 (3.8%)	<.001

statistically significant difference in 5-year survival compared with those who underwent colectomy (19 vs. 18% respectively); any resection had a significantly greater 5-year survival compared with no procedure (4%) ($p < 0.001$, Fig. 3A). Median OS was highest in patients who underwent colectomy (22.1 months, CI 22.0–22.3 months), compared with those who underwent local excision (18.8 months, CI 17.6–20.2 months) or no procedure (9.1 months, CI 9.0–9.3 months).

Operative Treatment of the Primary and Metastatic Sites in Isolated Liver Metastases

In patients with liver-only metastases, resection of both the primary and metastatic site was associated with the best 5-year survival (31%) and median OS (38.9 months, CI 37.6–39.9 months) (Fig. 3B). Patients who underwent metastasectomy alone had a 5-year survival of 24% and median OS of 30.2 months (CI 27.4–33.5 months), while those who underwent colectomy alone had a 5-year survival of 15% and median OS of 22.3 months (21.9–22.7 months). Patients who did not undergo resection had a 5-year survival of 5% and median OS of 10.7 months (10.4–11.0 months, $p < 0.001$ for all).

Effect of Treatment Sequence on Survival

In patients with liver-only metastases, receipt of chemotherapy regardless of timing relative to resection was associated with a median OS of 25.1 months (CI 24.8–25.4 months), compared with 3.4 months (CI 3.1–3.6) for patients who did not receive chemotherapy (Fig. 4). In patients who only underwent resection of the primary tumor (Fig. 5A), treatment with perioperative chemotherapy and resection correlated with the best 5-year survival (28%) and median OS (36.8 months, CI 34.7–39.4 months). Patients who received preoperative chemotherapy followed by resection of the primary tumor had a 5-year survival of 26% and median OS of 34.6 months (CI 33.1–36.0 months), and those who underwent resection of the primary tumor followed by postoperative chemotherapy had a 5-year survival of 16% and median OS of 25.9 months (CI 25.4–26.4 months). Patients who underwent metastasectomy with or without resection of the primary tumor and received perioperative chemotherapy had the best 5-year survival (45%) and

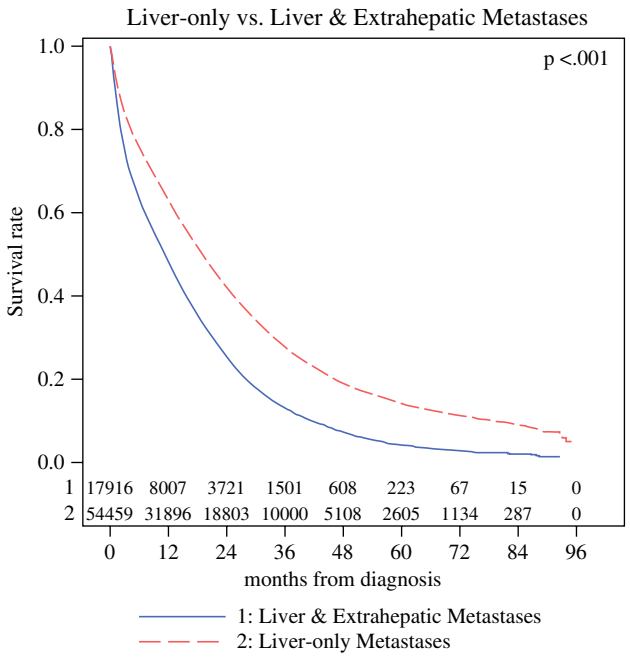

FIG. 2 Kaplan–Meier analysis comparing overall survival between patients with liver-only CRLM (red) and patients with both CRLM and extrahepatic metastases (blue)

median OS (54.8 months, CI 51.9–57.9 months) (Fig. 5B). Patients who received preoperative chemotherapy followed by metastasectomy had the next best survival, with a 5-year OS of 35% and median OS of 45.4 months (43.2–47.9 months). Those who underwent metastasectomy followed by postoperative chemotherapy had a 5-year survival of 31% and median OS of 37.7 months (36.1–39.3 months). In the entire cohort of patients with liver-only metastases, receipt of perioperative chemotherapy and resection (either of the primary, liver metastases, or both) was associated with a median OS of 44.7 months (CI 43.2–46.2 months). While patients who received chemotherapy without resection had a higher median OS (16.4 months, CI 16.1–16.7) than those who underwent metastasectomy without receiving systemic therapy (median OS 9.5 months, CI 7.3–11.5 months), the 5-year survival associated with metastasectomy alone was 14% compared with only 6% for chemotherapy alone. The median OS of patients who received no treatment at all was 1.9 months (CI 1.8–2.1 months), with a 5-year survival of 4% ($p < 0.001$ for all). Multivariate analysis also demonstrated that compared with chemotherapy alone, perioperative chemotherapy with metastasectomy was associated with the highest reduction in hazard of death (HR 0.33, CI 0.28–0.40, $p < 0.001$) versus preoperative (HR 0.43, CI 0.36–0.51, $p < 0.001$) and postoperative (HR 0.48, CI 0.41–0.57, $p < 0.001$) chemotherapy (Table 2). In patients who underwent metastasectomy, radiation treatment was not associated with a statistically significant reduction in hazard of death, but receipt of immunotherapy was associated with an 11% reduction in hazard of death (HR 0.89, CI 0.85–0.93, $p < 0.001$). Resection of the primary tumor in patients who underwent metastasectomy was associated with a 16% reduction in hazard of death (HR 0.84, CI 0.72–0.98, $p = 0.023$).

DISCUSSION

In patients with resectable CRLM, surgical resection is the only potentially curative treatment option. Despite this, the recurrence rate following resection of CRLM has been reported as high as 48–80%.[5,10] Therefore, systemic therapy is an important adjunct to resection. The national comprehensive cancer network (NCCN) guidelines outline two potential strategies for combining systemic therapy with resection in patients with resectable CRLM: either preoperative chemotherapy followed by resection and then postoperative chemotherapy, or upfront resection followed by postoperative chemotherapy.[11] The theoretical benefits of a preoperative chemotherapy approach include early control of microscopic metastatic disease, increased likelihood that chemotherapy will be completed successfully, ability to assess tumor response to the selected agent, and the ability to identify patients with rapid progression of disease, sparing them the morbidity of a futile operation.[10,12] On the contrary, other studies have shown that preoperative chemotherapy is associated with steatohepatitis and increased 90-day mortality,[13] especially when the systemic therapy extents six cycles.[14] In addition, postoperative morbidity is a lesser challenge after CRLM resection than after other complex visceral cancer resections, as most patients are able to undergo chemotherapy after hepatectomy.

Several studies have examined the effect of chemotherapy on survival in patients with resectable CRLM. Two randomized controlled trials (RCTs) compared the addition of postoperative fluorouracil (5-FU) and folinic acid (or leucovorin, LV) against resection alone, and while both trials showed a significant improvement in disease-free survival (DFS) with the addition of 5-FU/LV, neither trial demonstrated a benefit on OS.[15,16] The 2008 EORTC 40983 trial compared the effect of perioperative FOLFOX against resection alone, and while the as-treated (AT) analysis showed a significantly longer PFS in the perioperative chemotherapy group,[17] the 2013 follow-up to the trial showed that OS did not differ between the groups in either the intention-to-treat (ITT) analysis nor the AT analysis after a 5-year follow-up.[7] Similarly, the New EPOC trial, which evaluated the addition of cetuximab to perioperative chemotherapy for patients with K-RAS wild-type CRC, showed no significant improvement in progression-free survival (PFS) with the inclusion of cetuximab; in fact, the addition of cetuximab was associated with a lower OS.[18,19] More recently, the EXPERT RCT,

TABLE 2 Multivariate survival model—metastasectomy

Variable		Hazard ratio	*P* value
Treatment received	No treatment versus chemotherapy alone	2.79 (2.67, 2.90)	< .001
	Metastasectomy alone versus chemotherapy alone	1.10 (0.91, 1.33)	
	Preoperative chemotherapy + metastasectomy versus chemotherapy alone	0.43 (0.36, 0.51)	
	Metastasectomy + postoperative chemotherapy versus chemotherapy alone	0.48 (0.41, 0.57)	
	Perioperative chemotherapy + metastasectomy versus chemotherapy alone	0.33 (0.28, 0.40)	
Age	40–50 versus < 40	1.01 (0.93, 1.10)	< .001
	50–60 versus < 40	1.04 (0.96, 1.13)	
	60–70 versus < 40	1.23 (1.14, 1.33)	
	≥ 70 versus < 40	1.65 (1.53, 1.79)	
Sex	Female versus male	1.06 (1.03, 1.09)	< .001
Race	Black versus white	1.07 (1.03, 1.12)	< .001
	Asian versus white	0.88 (0.81, 0.97)	
	Other versus white	0.77 (0.67, 0.89)	
Charlson Deyo combined comorbidity	1 versus 0	1.17 (1.12, 1.21)	< .001
	2 versus 0	1.38 (1.28, 1.47)	
	≥ 3 versus 0	1.54 (1.41, 1.69)	
Grade	Moderately differentiated versus well differentiated	1.04 (0.97, 1.12)	< .001
	Poorly differentiated versus well differentiated	1.63 (1.50, 1.76)	
	Undifferentiated versus well differentiated	1.56 (1.35, 1.80)	
Nodes positive	0 versus none examined	0.99 (0.80, 1.22)	< .001
	1 versus none examined	1.20 (0.95, 1.52)	
	2–3 versus none examined	1.25 (0.99, 1.57)	
	4–6 versus none examined	1.50 (1.19, 1.88)	
	7+ versus none examined	2.07 (1.65, 2.60)	
Nodes examined	1–14 versus 0	0.80 (0.62, 1.02)	< .001
	15+ versus 0	0.59 (0.46, 0.76)	
T category	T0 versus T1	1.21 (0.96, 1.54)	< .001
	T2 versus T1	0.85 (0.75, 0.95)	
	T3 versus T1	0.93 (0.88, 0.99)	
	T4 versus T1	1.16 (1.09, 1.24)	
	Tis versus T1	0.94 (0.63, 1.40)	
Margins	Positive versus negative	1.58 (1.45, 1.71)	< .001
Radiation	Yes versus no	0.97 (0.89, 1.06)	0.519
Immunotherapy	Yes versus no	0.89 (0.85, 0.93)	< .001
Resection of primary tumor	Yes versus no	0.84 (0.72, 0.98)	0.023

the first to compare perioperative chemotherapy directly against postoperative chemotherapy, found no difference in PFS or OS between the two groups.[20] In addition to these RCTs, multiple retrospective studies examining the effect of treatment sequence on survival in patients with resectable CRLM have shown no benefit of perioperative or preoperative chemotherapy over postoperative therapy.[9,12,21–24]

Nevertheless, studies that have stratified patients by risk of recurrence suggest that there still may be a benefit to perioperative chemotherapy, specifically in high-risk patients. For example, in 2015, Ayez et al. examined the effect of preoperative chemotherapy on overall survival in patients with resectable CRLM.[25] The authors stratified patients using the clinical risk score (CRS) described by Fong et al.[4] and found that patients with a high CRS did have a significantly better OS with preoperative chemotherapy, while patients with a low CRS did not.[25] More recently, Ninomiya et al. stratified patients with resectable CRLM into risk of recurrence on the basis of number and size of hepatic metastases, presence of resectable extrahepatic metastases, and nodal status of the primary tumor; they found that high-risk patients with synchronous metastases who received preoperative chemotherapy had a significantly better OS and surgical failure-free survival than those who underwent upfront surgery, whereas there was no difference in survival between treatments for low-risk patients.[26] In the EORTC 40983 trial, the majority

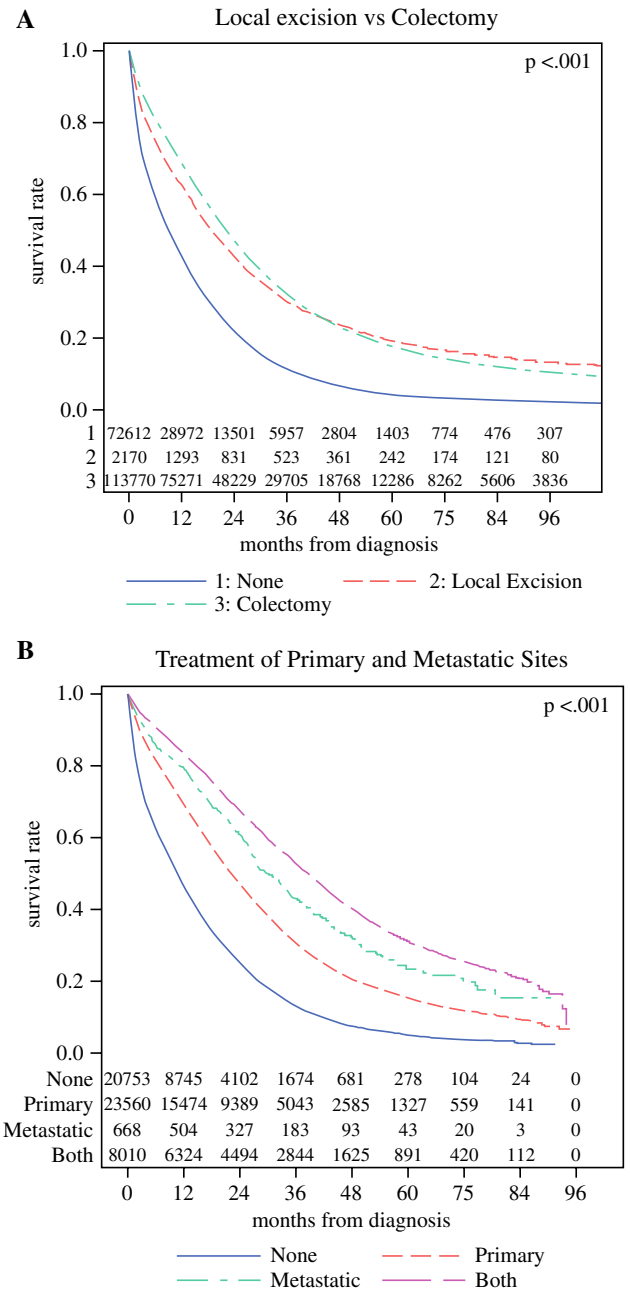

FIG. 3 Kaplan–Meier analysis comparing overall survival for various resection types; **A** OS comparison between patients who did not undergo resection of the primary colorectal site (blue), patients who underwent local excision only (red), and patients who underwent colectomy (green); **B** OS comparison between patients who did not undergo resection of either the primary tumor or metastatic site (blue), patients who only underwent resection of the primary tumor (red), patients who only underwent metastasectomy (green), and patients who underwent resection of both the primary tumor and metastatic site (purple)

(64.8%) of patients had metachronous metastases,[7,17] and therefore this trial represented a lower-risk cohort than the patients in our study.

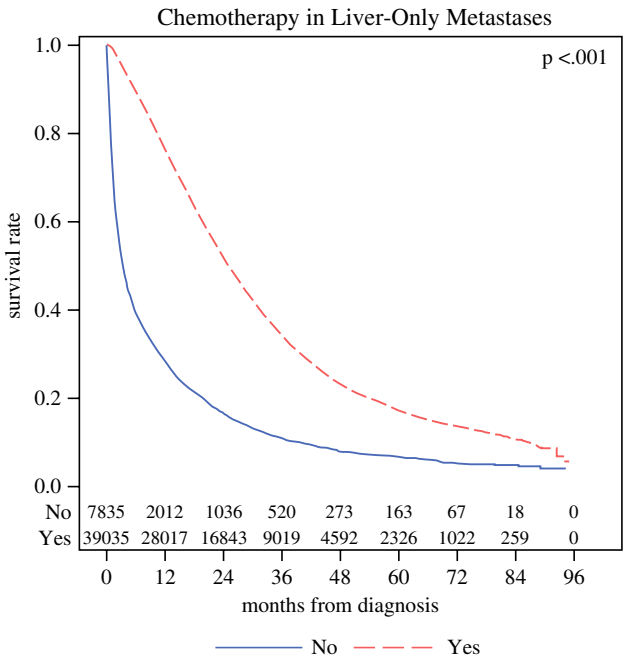

FIG. 4 Kaplan–Meier analysis comparing overall survival between patients with liver-only metastases who received chemotherapy (red) and patients who did not receive chemotherapy (blue)

In patients with resectable CRLM, the other considerations include the relative timing of resection of the primary tumor, metastasectomy, and radiation treatment (when applicable) in addition to timing of systemic therapy. Traditional approaches included either colectomy followed by liver resection, or simultaneous colectomy and liver resection, with perioperative chemotherapy.[27] In more recent years, an alternative liver-first approach has been proposed, in which chemotherapy is administered upfront, followed by liver resection and subsequent resection of the primary.[28] In addition to the theoretical benefits of preoperative chemotherapy discussed above, Mentha et al. discussed that the liver-first approach allowed time for preoperative radiation in rectal cancer, prior to proctectomy. The METASYNC trial published in 2021 compared simultaneous resection versus the traditional staged approach and found no difference in the 60-day complication rate between the two approaches.[29] The decision regarding staged versus simultaneous approaches and timing of resection of the primary tumor depends on multiple factors, including the burden of disease in the liver, anticipated extent of colorectal/liver resections, and symptoms and condition of the patient, and should if at all possible be made after multidisciplinary discussion.

This study demonstrated multiple limitations of the NCDB. In addition to the effect of timing of systemic therapy in relation to resection on OS, another important question in the treatment of CRLM is whether staged versus simultaneous resection is associated with better outcomes.

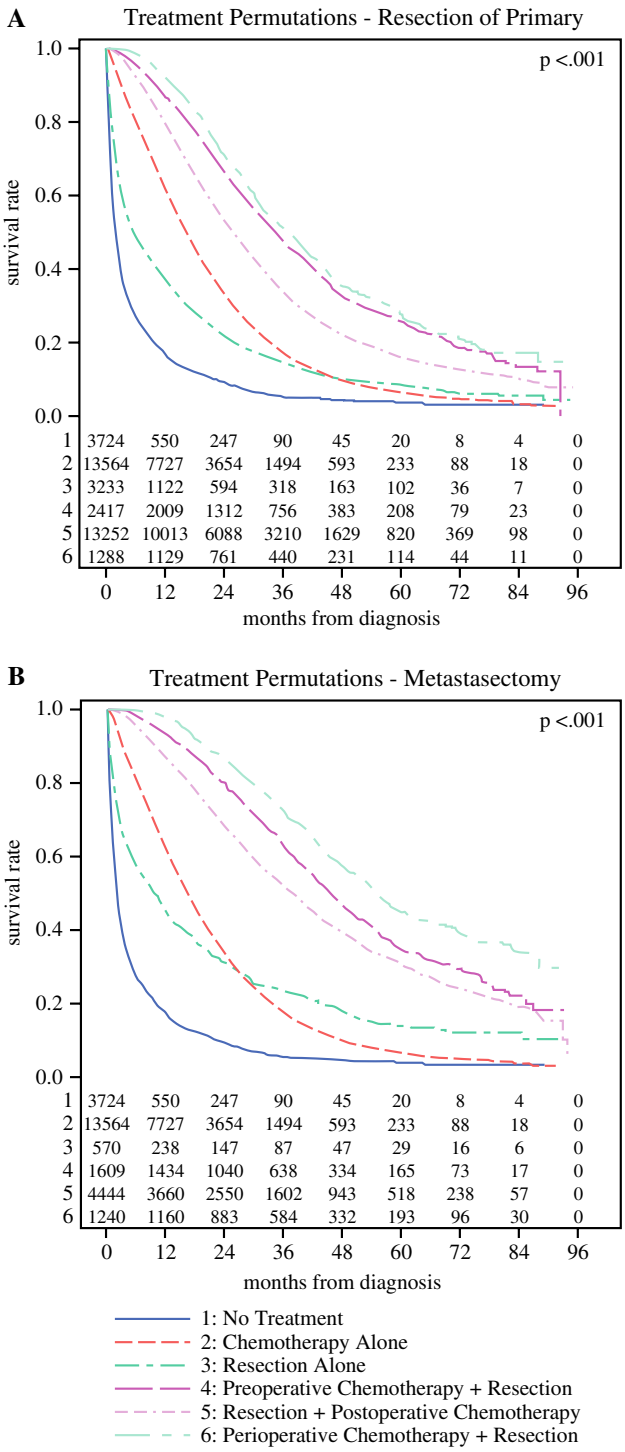

FIG. 5 Kaplan–Meier analysis comparing the effect of various treatment sequences on overall survival, separated by operative categories; **A** treatment group comparisons with resection of primary tumor, patients with liver-only metastases who underwent neither resection nor chemotherapy (blue), patients who underwent chemotherapy alone (red), patients who underwent resection of the primary tumor alone (green), patients who underwent preoperative chemotherapy followed by resection of the primary alone (brown), patients who underwent resection of the primary alone followed by chemotherapy (purple), and patients who underwent perioperative chemotherapy and resection of the primary alone (light green); **B** treatment group comparisons to resection of colorectal liver metastasis: neither resection nor chemotherapy (blue), patients who underwent chemotherapy alone (red), patients who underwent hepatectomy alone (green), patients who underwent preoperative chemotherapy followed by hepatectomy (brown), patients who underwent hepatectomy followed by chemotherapy (purple), and patients who underwent perioperative chemotherapy and hepatectomy (light green) ▶

However, we were unable to answer that question using the NCDB due to lack of information on timing and sequence of colectomy and hepatectomy in patients who underwent both resections. For this reason, the study had to be limited to patients with synchronous CRLM. Similarly, NCDB does not collect longitudinal data such as occurrence of metachronous metastases or disease recurrence, which have significant impact on the disease course. In addition, we were unable to stratify patients by risk of recurrence, as we did not have detailed information on metastatic disease burden, such as number or size of hepatic metastases in the resected CRLM in each group. With regard to systemic treatment, the database lacks information about type of chemotherapy or number of cycles administered, and we could not identify patients who were initially deemed unresectable and later rendered resectable by systemic treatment.

Despite the limitations of the database, the data encouragingly reveal that the majority of patients with CRLM are undergoing multimodality treatment. Our analysis showed that treatment with perioperative chemotherapy in conjunction with metastasectomy was associated with a statistically significantly higher median OS of 54.8 months, compared with either preoperative chemotherapy alone or upfront resection followed by postoperative chemotherapy. Additionally, patients who underwent resection of both the primary and metastatic site(s) had the best median OS (38.9 months), as one would expect, but even in patients who only underwent resection of one site or the other, metastasectomy alone was associated with a better OS than resection of the primary site alone. Finally, the data show the effect of chemotherapy on OS: receipt of chemotherapy was associated with a > 20-month OS benefit compared with no chemotherapy, and the survival curve of patients who underwent resection without chemotherapy plummets more acutely than all patients who received chemotherapy. Although our compared cohorts had differences in demographics and performance status, the distinctions in OS between treatment groups were still present on multivariable analysis. For example, the cohort who underwent resection alone (either resection of the primary, liver metastases, or both) had a 30-day mortality of 21.5%, versus ≤ 3.0% for patients who underwent a combination of resection and systemic therapy, which likely includes patients who underwent emergency resection associated with early complications that made them unfit for systemic therapy. Multivariable analysis

demonstrated that metastasectomy alone was not associated with any obvious survival benefit over chemotherapy alone (HR 1.10, CI 0.91–1.33).

We acknowledge that the inclusion of patients over a 12-year period is associated with heterogeneity in outcomes, given that treatment options have increased and overall management of these patients has improved in the last several years. A benefit of the large sample size obtained from the NCDB for this study was the adequate power to identify a correlation between perioperative chemotherapy and superior overall survival. However, as with retrospective studies in general, association between OS benefit and a specific therapy may represent selection bias due to patients who received these treatments differing from the overall cohort. In the larger cohort of patients with invasive colorectal adenocarcinoma of any stage that included 1,089,764 patients, the overall percentage of patients who received immunotherapy was 1.5% compared with 16.4% in our final cohort; we speculate that this discrepancy reflects the fact that our final cohort represents a highly selected patient group in whom a larger subset may have been receiving immunotherapy on clinical trials.

Despite the stated limitations associated with any retrospective analysis, this is one of few studies to identify a correlation between perioperative chemotherapy and superior overall survival in patients with synchronous liver-only CRLM. Although further investigation is needed to conclusively identify the optimal treatment sequence, our findings demonstrate a general benefit to hepatectomy, but an inferior survival of patients who undergo hepatectomy alone without chemotherapy. Accordingly, all patients presenting with non-emergent, resectable CRLM deserve a formal multimodality evaluation prior to finalizing the treatment plan.

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