Research Article

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Impact of perioperative chemotherapy on survival outcomes among patients with metastatic colorectal cancer to the liver

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Aim: Compare overall survival (OS) between adjuvant and neoadjuvant chemotherapy and analyze the effect of chemotherapy on OS. **Materials & methods:** National Cancer Database was queried for patients diagnosed with metastatic colorectal adenocarcinoma with isolated liver metastases between 2004 and 2016. We evaluated the OS and chemotherapy effect using Kaplan-Meier estimates and multivariable cox regression analyses. **Results:** Total 6883 patients with metastatic colorectal cancer and liver metastases were included, of which 6042 patients were treated with surgery and chemotherapy and 841 patients were treated with surgery only. Patients who received neoadjuvant chemotherapy had better OS compared with patients who received adjuvant chemotherapy. **Conclusion:** Patients with colorectal cancer with isolated liver metastases who were treated with neoadjuvant chemotherapy had better OS compared with adjuvant chemotherapy.

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Keywords: adjuvant • chemotherapy • colorectal cancer • liver metastases • neoadjuvant • overall survival

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy in the USA and the world and the second leading cause of cancer death in both sexes in 2020 in the USA [1–3]. Due to the majority of the intestinal mesenteric drainage entering the hepatic portal venous system, hepatic metastases develop in approximately half of all colorectal cancer cases with nearly a fifth to a quarter of newly diagnosed metastatic CRC patients present with liver metastases at the time of primary diagnosis [2,4]. Surgical resection alone is the cornerstone of treatment for patients with liver metastases from CRC in whom there is at least a one in six chance of a cure after hepatectomy and apparent clinical cure is achieved in those who survive 10 years [5–7]. In the past 15–20 years, profound improvements in outcomes of metastatic CRC of 5-year survival have more than doubled [4,8,9]. Although new treatment options have doubled overall survival (OS) for advanced disease, survival is still best for those with non-metastatic disease [10]. While the role of surgical resection is established in metastatic disease to the liver, the potential benefit from peri-operative chemotherapy remains unclear [6,11]. While some studies have shown that perioperative chemotherapy with surgery reduced the risk of progression-free survival (PFS) events at 3 years in patients with resectable liver metastases [12], others concluded that preoperative chemotherapy did not prolong survival with colorectal cancer and resectable or marginally resectable liver metastasis [13]. Also, there's a lack of data in assessing the impact of timing of perioperative chemotherapy on survival (pre- vs post-operative), as well as in comparing the effect of single-agent versus multiagent chemotherapy on survival. We studied the survival outcomes of patients with CRC with liver metastases who underwent surgical management alone versus combined surgery and chemotherapy based on a real-world cohort. In addition to that, we assessed the effect of timing of chemotherapy on survival among patients who received chemotherapy and compared the OS between patients who received single-agent and patients who received multiagent chemotherapy as the first line of chemotherapy.

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Patients & methods

Data source

The National Cancer Database (NCDB) is a nationwide database supported by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. About 70% of all cancer cases diagnosed in the USA from more than 1500 cancer centers are included in this database. Details of patients' demographics, malignancy staging and histological characteristics in addition to treatment and outcome information are provided in this database [14]. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the sources of the de-identified 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 of the current study.

After we obtained the approval on our proposed protocol and the letter of support from the cancer committee chair at Cleveland Clinic, the NCDB was queried for patients diagnosed with metastatic colorectal adenocarcinoma between 2004 and 2016. Survival follow-up for the studied cohort is available till December 2016. It's worth mentioning that the metastatic status provided in the database is related to the status at the time of the diagnosis. NCDB doesn't provide the details about the possible non-metastatic cases that subsequently developed metastatic disease.

Patient selection

For our study, we selected the patients who were diagnosed with metastatic colorectal adenocarcinoma with liver metastases at age of 18 or older. We excluded patients with metastases to other sites other than the liver. Patients who didn't have radical surgical resection to the primary tumor and/or did not have surgery to distant metastatic sites were also excluded in addition to patients with unknown chemotherapy status. Also, we excluded patients who lost follow-up which are defined by patients with missing details about their last contact status as alive or dead, and those with missing information about their time from diagnosis to the last contact.

Variables

Using the NCDB, we included the following patient demographic variables: age, gender, race, median income, education level, insurance status, facility type (which includes community cancer program, comprehensive community cancer program, academic/research program and integrated network cancer program) in addition to the geographic area which was classified as metropolitan, urban or rural location. Also, we collected the following disease-related variables: clinical tumor and nodal categories based on American Joint Committee on Cancer staging, microsatellite instability (MSI) status, Charlson-Deyo comorbidity score and chemotherapy status.

Outcome

The primary outcome of this study was OS in months defined as the time from diagnosis to the time of death for any reason.

Statistical analysis

We compared the baseline demographics and characteristics between patients who were treated with surgery and chemotherapy versus patients who were treated with surgery only using the Pearson Chi-square test and t-test.

For OS comparisons, we split the cohort into two separate groups according to the type of treatment the patients received, the first group who was treated with surgery and chemotherapy and the second group who was treated with surgery only. Then, we compared the OS between the two groups. Moreover, we conducted additional OS comparisons (limited to patients who received perioperative chemotherapy) between patients who received adjuvant chemotherapy versus neoadjuvant chemotherapy; and between patients who received single-agent versus multiagent chemotherapy.

OS analyses were evaluated using the Kaplan-Meier survival method. A log-rank test was used to evaluate survival differences between groups. We used Cox regression analysis to conduct multivariable analyses to evaluate the factors associated with improved OS; hazard ratios (HRs) with associated 95% confidence intervals (CI) were accordingly generated, statistical significance was defined as a p-value less than 0.05 for all analyses. The following factors were included in the multivariable model: facility type, age, gender, race, median household income, education level, insurance status, area, Charlson score, clinical T stage, clinical N stage, MSI status and chemotherapy use.

All the above statistical analyses were performed using the SPSS Statistics 27.0

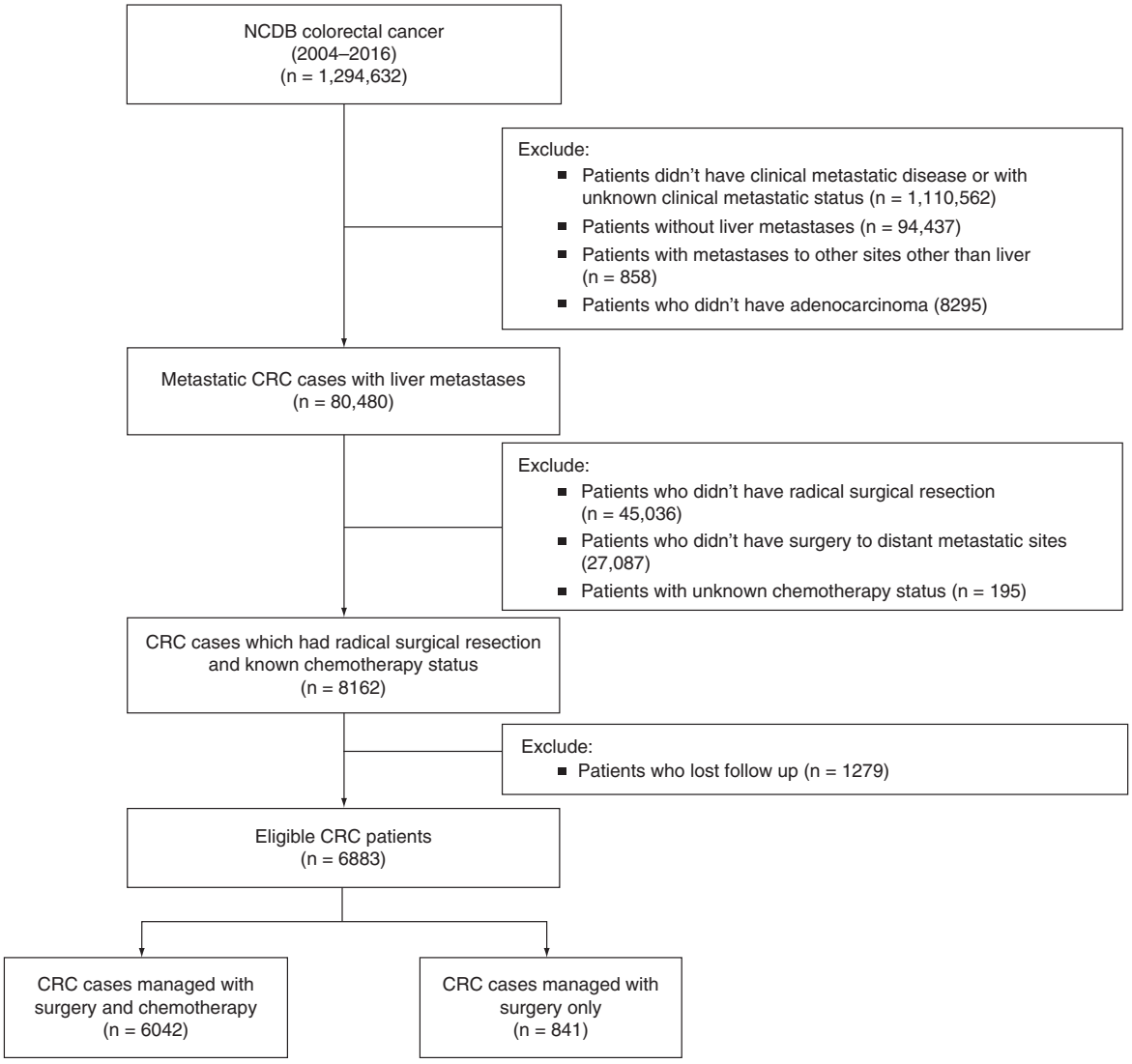

Figure 1. Patient selection flowchart.
CRC: Colorectal cancer; NCDB: National Cancer Database.

To further reduce any potential biases related to the variation in baseline characteristics between the patient group that received chemotherapy and the one that did not receive chemotherapy, we used nearest neighbor, 1:1, propensity score matching using RStudio Version 1.3.1093 (MA, USA).

As a sensitivity analysis, we repeated all the above analyses after excluding patients who died within 90 days of the most definitive primary site surgery (to eliminate the effect of post-surgical complication-related mortality on overall survival).

To further examine the impact of MSI status on the above survival analyses, we repeated the above survival analyses among patients with MSI-H versus those with MSI-L status. In our study, MSI-L includes MSI-stable cases.

Results

Baseline characteristics

Figure 1 provides a flowchart for patient selection within the current study. We ended up with 6883 patients with metastatic CRC and liver metastases; 6042 (87.8%) were treated with surgery and chemotherapy and 841 (12.2%) were treated with surgery only. Compared with the surgery-only group, the perioperative-chemo group was likely

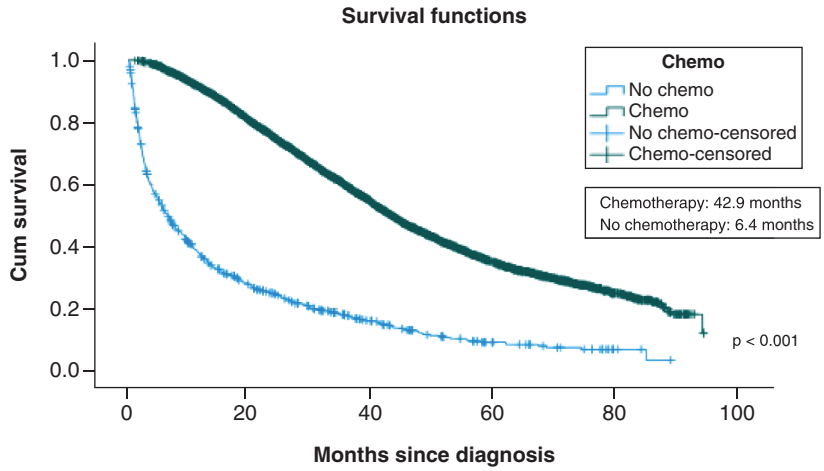

Figure 2. Median overall survival in the whole cohort according to the treatment modality.

to be younger (58 vs 70 years old), males (55.5% vs 47.4%), and had more MSI-L status (27.8 vs 16.6%). The baseline characteristics' comparison between the two groups is summarized in Table 1.

Next, in our sensitivity analysis, we excluded all patients who died within 90 days of most definitive primary site surgery (n = 550), which left us with 6333 patients; 5834 (92.1%) who were treated with surgery and chemotherapy, and 499 (7.9%) who were treated with surgery only. While the percentage of patients who died within the first 90 days of the primary tumor surgery is significant, we are unable to determine the cause of death if it was cancer-related, surgery-related, or due to other reason.

The baseline characteristics' comparison between the two groups is summarized in Table 2.

Survival outcome

The entire cohort

We compared the OS between patients who were treated with surgery and chemotherapy versus patients who were treated with surgery only and found that patients who were treated with surgery and chemotherapy had better OS compared with patients who were treated with surgery only (median OS 42.9 vs 6.4 months; $p < 0.001$) as illustrated in the Kaplan-Meier survival curves (Figure 2). We noted the significant difference in the OS and the very short median OS for patients treated with surgery only. This could be due to multiple factors including the heterogeneity of the patients in this pool.

Propensity score matching yielded 1682 patients for analysis: 841 patients in the no chemotherapy group and 841 patients in the chemotherapy group. Comparison of baseline characteristics between the groups after propensity score matching is shown in Supplementary Table A.

We compared the OS between patients who received chemotherapy versus patients who didn't receive chemotherapy using Kaplan-Meier analysis on the propensity score-matched groups and found that patients who received chemotherapy had better OS than those who didn't receive chemotherapy as illustrated in the Kaplan-Meier survival curves ($p < 0.001$) (Supplementary Figure A).

Excluding patients who died within 90 days of most definitive primary site surgery

After excluding patients who died within 90 days of the most definitive primary site surgery, we compared the OS between patients who were treated with surgery and chemotherapy versus patients who were treated with surgery only. We found that patients who were treated with surgery and chemotherapy had better OS compared with patients who were treated with surgery only (median OS was 43.6 months vs 16.6 months; $p < 0.001$) as illustrated in the Kaplan-Meier survival curves (Figure 3).

Propensity score matching yielded 998 patients for analysis: 499 patients in the no chemotherapy group and 499 patients in the chemotherapy group. Baseline characteristics comparison between the groups after propensity score matching is shown in Supplementary Table B.

Table 1. Baseline characteristics of metastatic colorectal cancer patients with liver metastases according to the treatment modality as found in the National Cancer Database between 2010 and 2016.

Characteristics	All cases (n = 6883)	Surgery only (n = 841) (12.2%)	Surgery and chemotherapy (n = 6042) (87.8%)	p-value and test
Mean age in years	59.54 ± 13.05	70.28 ± 12.92	58.04 ± 12.35	<0.001 t-test
Sex				<0.001; Chi-square
Female	3130 (45.5%)	442 (52.6%)	2688 (44.5%)	
Male	3753 (54.5%)	399 (47.4%)	3354 (55.5%)	
Race				0.062; Chi-square
White	5682 (82.6%)	672 (79.9%)	5010 (82.9%)	
African American	826 (12.0%)	124 (14.7%)	702 (11.6%)	
Others	329 (4.8%)	38 (4.5%)	291 (4.8%)	
Unknown	46 (0.7%)	7 (0.8%)	39 (0.6%)	
Facility type				<0.001; Chi-square
Community cancer program	443 (6.4%)	87 (10.3%)	356 (5.9%)	
Comprehensive Community Cancer Program	2015 (29.3%)	361 (42.9%)	1654 (27.4%)	
Academic/Research Program	3158 (45.9%)	244 (29.0%)	2914 (48.2%)	
Integrated Network Cancer Program	835 (12.1%)	134 (15.9%)	701 (11.6%)	
Unknown	432 (6.3%)	15 (1.8%)	417 (6.9%)	
Median household income 2012–2016				<0.001; Chi-square
Less than US$40,227	1188 (17.3%)	186 (22.1%)	1002 (16.6%)	
US$40,227–$50,353	1501 (21.8%)	199 (23.7%)	1302 (21.5%)	
US$50,354- $63,332	1567 (22.8%)	193 (22.9%)	1374 (22.7%)	
US$63,333+	2539 (36.9%)	254 (30.2%)	2285 (37.8%)	
Unknown	88 (1.3%)	9 (1.1%)	79 (1.3%)	
Education level 2012–2016 (percentage of not graduated from high school)				<0.001; Chi-square
17.6% or more	1237 (18.0%)	217 (25.8%)	1020 (16.9%)	
10.9–17.5%	1803 (26.2%)	246 (29.3%)	1557 (25.8%)	
6.3%-10.8%	2017 (29.3%)	202 (24.0%)	1815 (30.0%)	
Less than 6.3%	1753 (25.5%)	171 (20.3%)	1582 (26.2%)	
Unknown	73 (1.1%)	5 (0.6%)	68 (1.1%)	
Insurance status				0.384; Chi-square
No	225 (3.3%)	34 (4.0%)	191 (3.2%)	
Yes	6567 (95.4%)	795 (94.5%)	5772 (95.5%)	
Unknown	91 (1.3%)	12 (1.4%)	79 (1.3%)	
Area				0.237; Chi-square
Metro counties	5545(80.6%)	697 (82.9%)	4848 (80.2%)	
Rural counties	137 (2.0%)	17 (2.0%)	120 (2.0%)	
Urban counties	1031 (15.0%)	112 (13.3%)	919 (15.2%)	
Unknown	170 (2.5%)	15 (1.8%)	155 (2.6%)	
Clinical T stage				<0.001; Chi-square
T0	18 (0.3%)	1 (0.1%)	17 (0.3%)	
T1	316 (4.6%)	36 (4.3%)	280 (4.6%)	
T2	208 (3.0%)	17 (2.0%)	191 (3.2%)	
T3	1617 (23.5%)	135 (16.1%)	1482 (24.5%)	
T4	621 (9.0%)	115 (13.7%)	506 (8.4%)	
Tis	15 (0.2%)	0 (0.0%)	15 (0.2%)	
Unknown	4,088 (59.4%)	537 (63.9%)	3551 (58.8%)	

MSI: Microsatellite instability.

Table 1. Baseline characteristics of metastatic colorectal cancer patients with liver metastases according to the treatment modality as found in the National Cancer Database between 2010 and 2016 (cont.).

Characteristics	All cases (n = 6883)	Surgery only (n = 841) (12.2%)	Surgery and chemotherapy (n = 6042) (87.8%)	p-value and test
Clinical N stage				<0.001; Chi-square
N0	2732 (39.7%)	329 (39.1%)	2403 (39.8%)	
N1	1694 (24.6%)	166 (19.7%)	1528 (25.3%)	
N2	684 (9.9%)	98 (11.7%)	586 (9.7%)	
Unknown	1773 (25.8%)	248 (29.5%)	1525 (25.2%)	
MSI status				<0.001; Chi-square
MSI-H	208 (3.0%)	30 (3.6%)	178 (2.9%)	
MSI-L	1818 (26.4%)	140 (16.6%)	1678 (27.8%)	
Unknown	4857 (70.6%)	671 (79.8%)	4186 (69.3%)	
Charlson-Deyo score				<0.001; Chi-square
0	5325 (77.4%)	523 (62.2%)	4802 (79.5%)	
1	1207 (17.5%)	220 (26.2%)	987 (16.3%)	
2	258 (3.7%)	71 (8.4%)	187 (3.1%)	
3	93 (1.4%)	27 (3.2%)	66 (1.1%)	

MSI: Microsatellite instability.

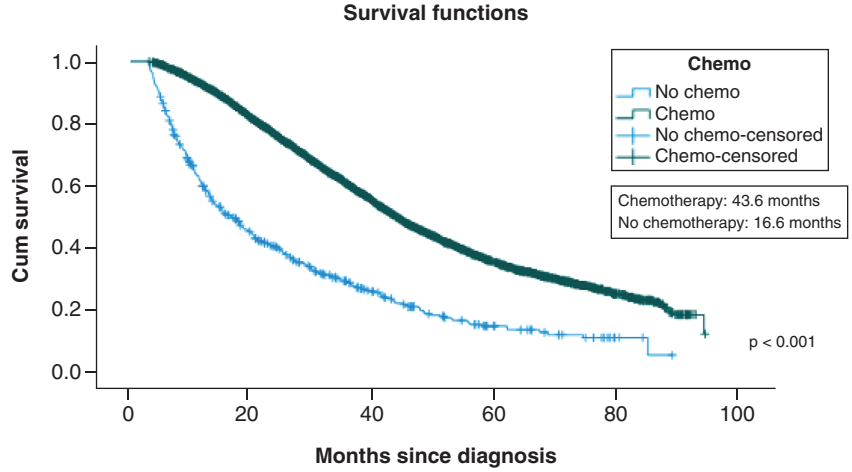

Figure 3. Median overall survival according to the treatment modality after excluding patients with 90-day mortality of most definitive primary site surgery.

We compared the OS between patients who received chemotherapy versus patients who didn't receive chemotherapy using Kaplan-Meier analysis on the propensity score-matched groups and found that patients who received chemotherapy had better OS than those who didn't receive chemotherapy as illustrated in the Kaplan-Meier survival curves ($p < 0.001$) (Supplementary Figure B).

Subgroup analysis among patients who received chemotherapy

Single versus multiagent chemotherapy

After including only patients who received chemotherapy and excluding patients with the unknown number of chemotherapy agents they received, we compared the OS between patients who received single-agent chemotherapy and patients who received multiagent chemotherapy. We found patients who received multiagent chemotherapy had statistically significant better OS compared with patients who received single-agent chemotherapy (median OS was 43.7 months vs 36.1 months; $p < 0.001$) as illustrated in the Kaplan-Meier survival curves (Figure 4).

Table 2. Baseline characteristics of metastatic colorectal cancer patients with liver metastases according to the treatment modality after excluding patients with 90-day mortality of most definitive primary site surgery as found in the National Cancer Database between 2010 and 2016.

Characteristics	All cases (n = 6333)	Surgery only (n = 499) (7.9%)	Surgery and chemotherapy (n = 5834) (92.1%)	p-value and test
Mean age in years	58.90 ± 12.83	69.47 ± 13.34	57.99 ± 12.38	<0.001 t-test
Sex				<0.001; Chi-square
Female	2882 (45.5%)	274 (54.9%)	2608 (44.7%)	
Male	3451 (54.5%)	225 (45.1%)	3226 (55.3%)	
Race				0.256; Chi-square
White	5242 (82.8%)	401 (80.4%)	4841 (83.0%)	
African American	743 (11.7%)	68 (13.6%)	675 (11.6%)	
Others	304 (4.8%)	24 (4.8%)	280 (4.8%)	
Unknown	44 (0.7%)	6 (1.2%)	38 (0.7%)	
Facility type				<0.001; Chi-square
Community cancer program	387 (6.1%)	42 (8.4%)	345 (5.9%)	
Comprehensive Community Cancer Program	1798 (28.4%)	200 (40.1%)	1598 (27.4%)	
Academic/Research Program	2987 (47.2%)	171 (34.3%)	2816 (48.3%)	
Integrated Network Cancer Program	742 (11.7%)	73 (14.6%)	669 (11.5%)	
Unknown	419 (6.6%)	13 (2.6%)	406 (7.0%)	
Median household income 2012–2016				0.002; Chi-square
Less than US$40,227	1073 (16.9%)	105 (21.0%)	968 (16.6%)	
US$40,227–$50,353	1377 (21.7%)	122 (24.4%)	1255 (21.5%)	
US$50,354–$63,332	1439 (22.7%)	119 (23.8%)	1320 (22.6%)	
US$63,333+	2362 (37.3%)	147 (29.5%)	2215 (38.0%)	
Unknown	82 (1.3%)	6 (1.2%)	76 (1.3%)	
Education level 2012–2016 (percentage of not graduated from high school)				<0.001; Chi-square
17.6% or more	1116 (17.6%)	128 (25.7%)	988 (16.9%)	
10.9–17.5%	1646 (26.0%)	145 (29.1%)	1501 (25.7%)	
6.3–10.8%	1866 (29.5%)	117 (23.4%)	1749 (30.0%)	
Less than 6.3%	1637 (25.8%)	106 (21.2%)	1531 (26.2%)	
Unknown	68 (1.1%)	3 (0.6%)	65 (1.1%)	
Insurance status				0.581; Chi-square
No	200 (3.2%)	19 (3.8%)	181 (3.1%)	
Yes	6049 (95.5%)	472 (94.6%)	5577 (95.6%)	
Unknown	84 (1.3%)	8 (1.6%)	76 (1.3%)	
Area				0.470; Chi-square
Metro counties	5095(80.5%)	411 (82.4%)	4684 (80.3%)	
Rural counties	129 (2.0%)	12 (2.4%)	117 (2.0%)	
Urban counties	952 (15.0%)	67 (13.4%)	885 (15.2%)	
Unknown	157 (2.5%)	9 (1.8%)	148 (2.5%)	
Clinical T stage				0.002; Chi-square
T0	14 (0.2%)	0 (0.0%)	14 (0.2%)	
T1	298 (4.7%)	25 (5.0%)	273 (4.7%)	
T2	199 (3.1%)	14 (2.8%)	185 (3.2%)	
T3	1516 (23.9%)	86 (17.2%)	1430 (24.5%)	
T4	540 (8.5%)	59 (11.8%)	481 (8.2%)	
Tis	13 (0.2%)	0 (0.0%)	13 (0.2%)	
Unknown	3753 (59.3%)	315 (63.1%)	3438 (58.9%)	

MSI: Microsatellite instability.

Table 2. Baseline characteristics of metastatic colorectal cancer patients with liver metastases according to the treatment modality after excluding patients with 90-day mortality of most definitive primary site surgery as found in the National Cancer Database between 2010 and 2016 (cont.).

Characteristics	All cases (n = 6333)	Surgery only (n = 499) (7.9%)	Surgery and chemotherapy (n = 5834) (92.1%)	p-value and test
Clinical N stage				0.008; Chi-square
N0	2535 (40.0%)	219 (43.9%)	2316 (39.7%)	
N1	1577 (24.9%)	100 (20.0%)	1477 (25.3%)	
N2	607 (9.6%)	37 (7.4%)	570 (9.8%)	
Unknown	1614 (25.5%)	143 (28.7%)	1471 (25.2%)	
MSI status				<0.001; Chi-square
MSI-H	192 (3.0%)	20 (4.0%)	172 (2.9%)	
MSI-L	1718 (27.1%)	92 (18.4%)	1626 (27.9%)	
Unknown	4423 (69.8%)	387 (77.6%)	4036 (69.2%)	
Charlson-Deyo score				<0.001; Chi-square
0	5325 (77.4%)	523 (62.2%)	4802 (79.5%)	
1	1207 (17.5%)	220 (26.2%)	987 (16.3%)	
2	258 (3.7%)	71 (8.4%)	187 (3.1%)	
3	93 (1.4%)	27 (3.2%)	66 (1.1%)	

MSI: Microsatellite instability.

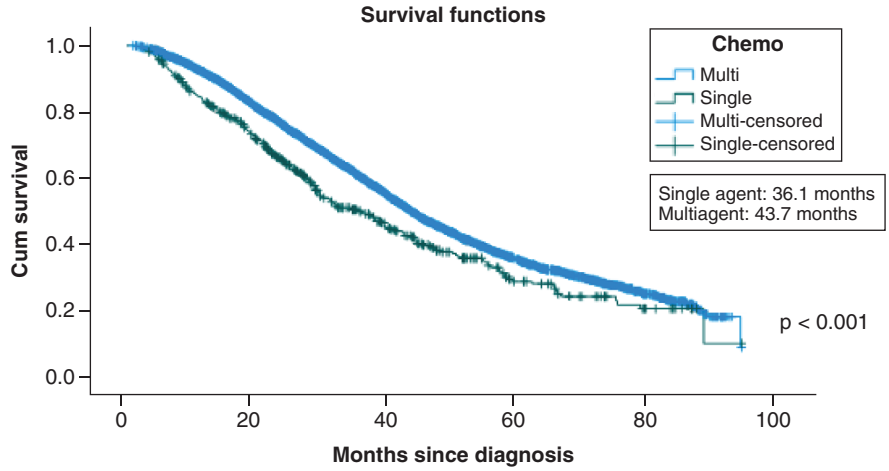

Figure 4. Median overall survival comparison between single agent and multiagent chemotherapy.

Propensity score matching yielded 958 patients for analysis: 479 patients received single-agent chemotherapy and 479 patients received multiagent chemotherapy. We compared the OS between patients who received single-agent chemotherapy and patients who received multiagent chemotherapy using Kaplan-Meier analysis on the propensity score-matched groups and found that patients who received multiagent chemotherapy had statistically significant better OS compared with patients who received single-agent chemotherapy as illustrated in the Kaplan-Meier survival curves ($p < 0.001$) (Supplementary Figure C).

In multivariable analysis, we found multiagent chemotherapy was associated with better OS compared with single chemotherapy (HR 0.728; 95% CI 0.549–0.966; $p = 0.028$).

Adjuvant versus neoadjuvant chemotherapy

After excluding patients who did not received chemotherapy and with unknown time duration between diagnosis and surgery and time duration between diagnosis and chemotherapy, we compared the OS between patients who received neoadjuvant chemotherapy versus patients who received adjuvant chemotherapy. We found patients were

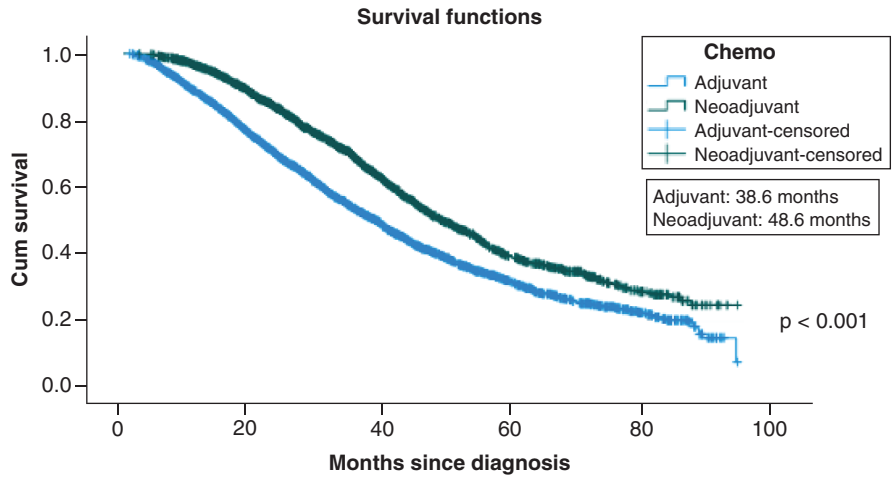

Figure 5. Median overall survival comparison between adjuvant and neoadjuvant chemotherapy.

treated with neoadjuvant chemotherapy had statistically significant better OS compared with patients were treated with adjuvant chemotherapy (median OS was 48.6 months vs 38.6 months; $p < 0.001$) as illustrated in the Kaplan-Meier survival curves (Figure 5).

Propensity score matching yielded 4428 patients for analysis: 2214 patients received chemotherapy before surgery and 2214 patients received chemotherapy after surgery. We compared the OS between patients who received chemotherapy before surgery and patients who received chemotherapy after surgery using Kaplan-Meier analysis on the propensity score-matched groups and we found that patients who received chemotherapy before surgery had statistically significant better OS compared with patients who received chemotherapy after surgery as illustrated in the Kaplan-Meier survival curves ($p < 0.001$) (Supplementary Figure D).

In multivariable analysis, we found no significant difference in OS between adjuvant versus neoadjuvant chemotherapy (HR 1.123; 95% CI 0.959–1.315; $p = 0.150$).

Subgroup analysis according to MSI status

Chemotherapy & surgery versus surgery only

After excluding patients with unknown MSI status, we ended up with 2026 metastatic CRC patients with liver metastases and known MSI status. We split the patients into two groups according to the MSI status: MIS-H group and MSI-L group, then we compared the OS between patients who were treated with surgery and chemotherapy versus patients who were treated with surgery only in each MSI group. We found that patients who were treated with surgery and chemotherapy had better OS compared with patients who were treated with surgery only in both MSI-H and MSI-L groups as illustrated in the Kaplan-Meier survival curves (Supplementary Figure E).

Single versus multiagent chemotherapy

After excluding patients with unknown MSI status, we ended up with 1789 metastatic CRC patients with liver metastases and known MSI status who received chemotherapy with a known number of chemotherapy agents they received. We split the patients into two groups according to the MSI status: MIS-H group and MSI-L group, then we compared the OS between patients who received single-agent chemotherapy and patients who received multiagent chemotherapy in each MSI group. In the MSI-L group, we found patients who received multiagent chemotherapy had statistically significant better OS compared with patients who received single-agent chemotherapy. Whereas in the MSI-H group, there was no difference in OS between the two treatment groups. This finding in the MSI-H group, could be related to the idea that our chemotherapy data is limited to the first line treatment only (Supplementary Figure F).

Adjuvant versus neoadjuvant chemotherapy

After excluding patients with unknown MSI status, we ended up with 1755 metastatic CRC patients with liver metastases and known MSI status who received chemotherapy with known time from diagnosis to surgery and time

from diagnosis to chemotherapy. We split the patients into two groups according to the MSI status: MSI-H group and MSI-L group, then we compared the OS between patients who received chemotherapy before surgery and patients who received chemotherapy after surgery in each MSI group. In the MSI-L group, we found patients who received chemotherapy before surgery had statistically significant better OS compared with patients who received chemotherapy after surgery. Whereas in the MSI-H group, there was no difference in OS between the two treatment groups (Supplementary Figure G).

Multivariable analysis

Multivariable analysis was done to assess factors affecting OS. In the entire cohort, factors associated with worse OS were older age (HR 1.021; 95% CI 1.018–1.025; $p < 0.001$), African American race compared with Caucasian race (HR 1.171; 95% CI 1.058–1.296; $p = 0.002$), not having insurance (HR 1.217; 95% CI 1.027 -1.442; $p = 0.024$), clinical N1 and N2 stage compared with N0 stage (HR 1.224; 95% CI 1.122–1.335; $p < 0.001$ and HR 1.907; 95% CI 1.699 -2.141; $p < 0.001$, respectively), community cancer program (HR for Academic/Research Program and Integrated Network Cancer Program compared with community cancer program was 0.625; 95% CI 0.549–0.712; $p < 0.001$ and HR 0.842; 95% CI 0.726–0.978; $p = 0.024$, respectively), higher Charlson-Deyo scores (HR for Charlson-Deyo scores 0 compared with the Charlson-Deyo score of 3 was 0.768; 95% CI 0.602–0.980; $p = 0.034$), MSI-high (HR for MSI-stable compared with MSI-high was 0.818; 95% CI 0.677–0.988; $p = 0.037$) and not receiving chemotherapy (HR for receiving chemotherapy compared with not receiving chemotherapy was 0.300; 95% CI 0.275–0.328; $p < 0.001$) (Table 3).

In the sensitivity cohort (after excluding patients who died within 90 days of the most definitive primary site surgery), factors associated with worse OS were age (HR 1.021; 95% CI 1.018–1.025; $p < 0.001$), African American race compared with white race (HR 1.179; 95% CI 1.057–1.315; $p = 0.003$), community cancer program (HR for Academic/Research Program and Integrated Network Cancer Program compared with community cancer program was 0.664; 95% CI 0.576–0.766; $p < 0.001$ and HR 0.830; 95% CI 0.704–0.978; $p = 0.026$, respectively), clinical N1 and N2 stage compared with N0 stage (HR 1.206; 95% CI 1.100–1.322; $p < 0.001$ and HR 1.809; 95% CI 1.597 -2.050; $p < 0.001$, respectively), and not receiving chemotherapy (HR for receiving chemotherapy compared with not receiving chemotherapy was 0.472; 95% CI 0.422–0.529; $p < 0.001$) (Table 4).

Discussion

To our knowledge, this is the largest real-world study that looked at the chemotherapy effect in metastatic CRC with only liver metastases who were treated with metastasectomy and compared the OS between patients who received perioperative chemotherapy versus patients treated with surgery only in addition to comparing the OS between adjuvant chemotherapy and neoadjuvant chemotherapy and comparing the OS between single-agent and multiagent chemotherapy.

Our study showed that patients with metastatic CRC with liver metastases who were treated with chemotherapy in addition to surgery had statistically significant better OS compared with patients who didn't receive chemotherapy. Also, in the multivariable analysis, we found that chemotherapy was independently associated with better OS.

There is limited data about the role of perioperative chemotherapy in patients with liver metastases from CRC. Most of the studies had a small number of patients and were designed to evaluate the effect of chemotherapy on recurrence- and PFS rather than overall survival. And the majority of the studies that evaluated the effect of chemotherapy on OS didn't report a significant difference in the OS between patients who received perioperative chemotherapy and patients who did not.

Nordlinger *et al.,* in a European Organization for Research and Treatment of Cancer trial based on 364 patients with metastatic CRC and up to four liver metastases, who were recruited from 78 hospitals from different European countries, compared the outcomes of 182 patients who received perioperative FOLFOX-4 chemotherapy to those of 182 patients who had surgery only. Initial results showed chemotherapy was associated with better 3-year PFS compared with surgical resection alone. After a median follow-up of 8·5 years, it was found that patients who received perioperative chemotherapy had a better median OS and 5-year OS, but it wasn't statistically significant. There are multiple factors in that study that could contribute to the lack of difference in the OS between the two groups. In addition to the small number of included patients, the study was designed with PFS being the primary end point whereas OS was a secondary end point. Also, the perioperative group had a higher number of non-cancer deaths compared with the surgery-only group [12,15]. Similarly, Portier *et al.,* in the FFCD trial compared the outcomes between patients who had surgery only versus patients who had adjuvant chemotherapy

Table 3. Multivariate analysis for metastatic colorectal cancer patients with liver metastases.

Variables	HR	95%CI	p-value
Facility type			
Community cancer program	Reference		
Comprehensive Community Cancer Program	0.973	0.853–1.108	0.676
Academic/Research Program	0.625	0.549–0.712	<0.001
Integrated Network Cancer Program	0.842	0.726–0.978	0.024
Unknown	1.140	0.931–1.395	0.204
Age	1.021	1.018–1.025	<0.001
Gender			
Female	0.950	0.890–1.013	0.118
Male	Reference		
Race			
African American	1.171	1.058–1.296	0.002
Others	0.868	0.734–1.026	0.098
Unknown	0.571	0.363–0.898	0.015
White	Reference		
Median household income 2012–2016			
Less than US$40,227	Reference		
US$40,227–$50,353	1.020	0.917–1.136	0.710
US$50,354–$63,332	0.972	0.867–1.089	0.620
US$63,333+	0.892	0.787–1.011	0.074
Unknown	0.604	0.298–1.226	0.163
Education level 2012–2016 (percentage of not graduated from high school)			
17.6% or more	Reference		
10.9–17.5%	0.965	0.873–1.067	0.483
6.3–10.8%	0.929	0.832–1.038	0.192
Less than 6.3%	0.965	0.850–1.095	0.579
Unknown	1.384	0.634–3.022	0.415
Insurance status			
No	1.217	1.027–1.442	0.024
Unknown	0.982	0.740–1.303	0.900
Yes	Reference		
Area			
Metro counties	Reference		
Rural counties	1.020	0.814–1.276	0.866
Urban counties	1.027	0.934–1.131	0.580
Unknown	1.089	0.886–1.338	0.417
Charlson score			
0	0.768	0.602–0.980	0.034
1	0.830	0.646–1.067	0.145
2	1.109	0.837–1.468	0.471
3	Reference		
Clinical T stage			
T0	Reference		
T1	0.591	0.311–1.122	0.108
T2	0.473	0.246–0.911	0.025
T3	0.475	0.253–0.889	0.020
T4	0.739	0.393–1.390	0.348
Tis	0.667	0.262–1.696	0.395
Unknown	0.626	0.335–1.170	0.142

HR: Hazard ratio; MSI: Microsatellite instability.

Table 3. Multivariate analysis for metastatic colorectal cancer patients with liver metastases (cont.).

Variables	HR	95%CI	p-value
Clinical N stage			
N0	Reference		
N1	1.224	1.122–1.335	<0.001
N2	1.907	1.699–2.141	<0.001
Unknown	1.325	1.219–1.440	<0.001
MSI status			
MSI-H	Reference		
MSI-L	0.818	0.677–0.988	0.037
Unknown	0.833	0.695–0.999	0.49
Chemotherapy			
NO	Reference		
Yes	0.300	0.275–0.328	<0.001

HR: Hazard ratio; MSI: Microsatellite instability.

with fluorouracil and folinic acid in 173 patients with liver metastases from CRC. They found that patients who received adjuvant chemotherapy had better 5-year OS, but it wasn't statistically significant. Several factors could be behind this result, the study wasn't designed with overall survival as an end point, also recurrences in both groups were treated by second-line chemotherapy, or by repeat liver resections, which influenced the natural history of the disease [16]. Hasegawa *et al.,* in a randomized controlled trial, assigned 180 patients with CRC liver metastasis into two groups; patients who received adjuvant chemotherapy with uracil-tegafur and leucovorin and patients who had had surgery only. They found that patients who received adjuvant chemotherapy had significantly reduced recurrence compared with the patients who had surgery only, but there was no difference in the OS (66.1% vs 66.8%; p = 0.409). Multiple limitations also may have contributed to this result; the short period of follow-up (median follow-up was less than 5 years), a small number of included patients, and the way the study was designed with recurrence-free survival as the primary end point whereas the OS was a secondary end point [17]. Kemeny *et al.,* did a randomized trial of 75 patients with one to three hepatic metastases of CRC where patients were randomized to hepatic resection alone or resection followed by hepatic arterial infusion of floxuridine and systemic 5-FU. The results showed that patients who received chemotherapy had a better 4-year OS and median OS, but the difference wasn't statistically significant (p = 0.6) [18].

While the previously mentioned studies failed to show a significant effect of chemotherapy on OS, another study reported a positive effect of chemotherapy on OS. A pooled analysis of two trials done by Mitry *et al.,* that included 278 patients with metastatic CRC (171 patients with liver metastases from the FFCD trial and 107 patients with liver or lung metastases from the ENG trial) and found that compared with patients who had surgery alone, patients who had adjuvant chemotherapy had better median PFS and median OS, but the differences were not statistically significant. Whereas, in multivariable analysis, they found that adjuvant chemotherapy was associated with better PFS and OS [19] which aligns with our findings.

On the other hand, Kanemitsu *et al.,* in a randomized trial of 300 patients with metastatic CRC with an unlimited number of liver metastases, found that patients who had adjuvant modified FOLFOX6 regimen had better disease-free survival, but a numerically worse 3-year OS and worse 5-year OS compared with patients who had hepatectomy alone, but the differences were not statistically significant [20].

Among patients who received chemotherapy, we found that patients were treated with neoadjuvant chemotherapy had better OS compared with patients were treated with adjuvant chemotherapy. Also, we found patients who received multiagent chemotherapy had better OS compared with patients who received single-agent chemotherapy.

The vast majority of trials, that were done on metastatic CRC, assessed the effect of perioperative chemotherapy compared with surgical resection only, and while the comparison between adjuvant and neoadjuvant chemotherapy in non-metastatic CRC has been investigated, there are very few prospective studies done in metastatic cases. While some studies suggest neoadjuvant chemotherapy is beneficial in unresectable disease and helps in improving the complete resection success rate [21], other studies showed that neoadjuvant chemotherapy was associated with increased liver toxicity and suggest adjuvant chemotherapy was more beneficial in managing micro-metastases with less liver toxicity-related complications [22–25].

Table 4. Multivariate analysis for metastatic colorectal cancer patients with liver metastases after excluding patients with 90-day mortality of most definitive primary site surgery.

Variables	HR	95%CI	p-value
Facility type			
Community cancer program	Reference		
Comprehensive Community Cancer Program	1.012	0.877–1.169	0.867
Academic/Research Program	0.664	0.576–0.766	<0.001
Integrated Network Cancer Program	0.830	0.704–0.978	0.026
Unknown	1.184	0.956–1.466	0.121
Age	1.021	1.018–1.025	<0.001
Gender			
Female	0.974	0.910–1.044	0.459
Male	Reference		
Race			
African American	1.179	1.057–1.315	0.003
Others	0.890	0.746–1.061	0.194
Unknown	0.572	0.354–0.923	0.022
White	Reference		
Median household income 2012–2016			
Less than US$40,227	Reference		
US$40,227–$50,353	1.017	0.907–1.139	0.778
US$50,354–$63,332	0.961	0.851–1.085	0.521
US$63,333+	0.883	0.773–1.009	0.068
Unknown	0.659	0.310–1.403	0.280
Education level 2012–2016 (percentage of not graduated from high school)			
17.6% or more	Reference		
10.9%–17.5%	0.967	0.868–1.077	0.540
6.3%–10.8%	0.927	0.824–1.043	0.207
Less than 6.3%	0.949	0.829–1.087	0.453
Unknown	1.225	0.533–2.813	0.632
Insurance status			
No	1.179	0.981–1.418	0.079
Unknown	1.007	0.747–1.357	0.965
Yes	Reference		
Area			
Metro counties	Reference		
Rural counties	1.037	0.821–1.311	0.758
Urban counties	1.028	0.929–1.138	0.596
Unknown	1.133	0.913–1.407	0.257
Charlson score			
0	0.870	0.656–1.155	0.335
1	0.928	0.694–1.240	0.613
2	1.299	0.940–1.796	0.113
3	Reference		
Clinical T stage			
T0	Reference		
T1	0.820	0.383–1.754	0.609
T2	0.652	0.301–1.413	0.279
T3	0.643	0.304–1.359	0.247
T4	0.981	0.462–2.083	0.960
Tis	0.844	0.295–2.416	0.752
Unknown	0.836	0.397–1.762	0.638

HR: Hazard ratio.

Table 4. Multivariate analysis for metastatic colorectal cancer patients with liver metastases after excluding patients with 90-day mortality of most definitive primary site surgery (cont.).

Variables	HR	95%CI	p-value
Clinical N stage			
N0	Reference		
N1	1.206	1.100–1.322	<0.001
N2	1.809	1.597–2.050	<0.001
Unknown	1.305	1.195–1.427	<0.001
MSI status			
MSI-H	Reference		
MSI-L	0.820	0.670–1.002	0.053
Unknown	0.835	0.688–1.014	0.068
Chemotherapy			
NO	Reference		
Yes	0.472	0.422–0.529	<0.001

HR: Hazard ratio.

Despite its use it is not very common, using neoadjuvant chemotherapy in the sitting of unresectable colorectal liver metastases, which is referred to as conversion chemotherapy, seems to have a survival benefit in these cases. This area of interest is still under extensive study and evaluation. The ideal chemotherapy regimen has not been established yet and different matters regarding to the chemotherapy timing, dosage and live toxicity should be taken into consideration [26,27]. Adam *et al.,* evaluated the impact of conversion chemotherapy on the outcome of 1104 patients with unresectable colorectal liver metastases. They found that conversion chemotherapy allowed 12.5% of patients with unresectable colorectal liver metastases to be rescued by liver surgery [28].

In the setting of not having a head-to-head comparison between adjuvant and neoadjuvant chemotherapy in metastatic disease [29,30], the National Comprehensive Cancer Network guidelines still recommends using peri-operative chemotherapy for a total of 6 months without a preference for adjuvant or neoadjuvant chemotherapy [31].

When it comes to the comparison between the single-agent and multiagent chemotherapy, few studies looked at that in the setting of metastatic disease. Seymour *et al.,* evaluated 2135 patients with inoperable metastatic or locoregional CRC and compared the OS in three different chemotherapy strategies; the first group received single-agent as a first line and single-agent as a second line, the second group received single-agent as a first line and combination chemotherapy as a second line, the third group received combination chemotherapy as a first line. The study showed that the group treated with combination chemotherapy as a first line had better OS compared with the group that received single-agent chemotherapy in both first and second line. Interestingly, there was no statistically significant difference in the OS between the group that received single-agent chemotherapy as a first and second line and the group that received single-agent chemotherapy as a first line and combination chemotherapy as a second line. These results are similar to our result in one way that patients who received multiagent chemotherapy as a first line had better OS than patients who received single-agent as a first line. Unfortunately, the NCDB doesn't provide details about the second line chemotherapy to be able to compare patients according to second line chemotherapy like the mentioned study [32]. The biggest limiting factor in this study is that recruited patients were selected as a poor-prognosis group who were definitely incurable and patients with operable metastases were excluded.

Koopman *et al.,* in phase III randomized controlled trial (CAIRO study), reported no statistically significant difference in the OS between patients with advanced CRC who received combination chemotherapy as a first line and patients who received the same chemotherapy agents but were given sequentially [33]. Similar to what we mentioned before, the chemotherapy details in NCDB are limited to first line chemotherapy.

It is worth mentioning that the two mentioned studies [32,33] enrolled metastatic CRC cases are not amenable for curative surgery, while patients in our study received surgery for the primary tumor and the metastatic liver metastases.

Our study has some limiting factors that need to be discussed; first, the type of chemotherapy that patients received was not available. This could have impacted the outcomes of some patients receiving adjuvant chemotherapy. Second, the differentiation between single-agent and multiagent chemotherapy is limited to the first line of

chemotherapy not total chemotherapy the patient may have received. Third, the distribution and completeness of surgical resection of liver metastases were not specified in the database. Fourth, data about liver metastases like number, dimension, site or resectability and molecular profile (RAS/BRAF) are not available in NCDB. This is an important element that could have affected patients' outcomes if there is an imbalanced between both groups. Fifth, NCDB also doesn't have details about other oncologic end points like disease-free survival and cancer-specific survival (both represent important end points to evaluate the effect of chemotherapy). Sixth, the retrospective nature of data collection within the NCDB might have affected the veracity of the analyses as well.

It is worth mentioning as well that in our study, patients who had surgery only were older compared with patients who received perioperative chemotherapy (mean age in years 70 vs 58) which could be a significant factor that affects the difference in the OS between the two groups as older patients tend to have more comorbidities and as a result more likely not to receive chemotherapy. To account for this potential bias, we did a propensity score matching for age and Charlson comorbidity score as well as multivariable Cox regression analysis incorporating other relevant baseline factors.

Conclusion & future perspective

In conclusion, our study shows that the addition of chemotherapy to surgery improves the OS in metastatic CRC with liver metastases treated with metastasectomy. Also, neoadjuvant and multiagent chemotherapy seem to improve the OS compared with adjuvant and single-agent chemotherapy, respectively. Further large-scale studies are needed to evaluate the effect of chemotherapy role and timing not only on recurrence and PFS but also on OS.

Summary points

- Colorectal cancer (CRC) is the third most diagnosed malignancy and the second leading cause of cancer-related death in the USA.
- About 50% of CRC cases develop liver metastases.
- The survival benefit of perioperative chemotherapy in patients with metastatic CRC with liver metastases is still unclear.
- We compare overall survival (OS) between adjuvant and neoadjuvant chemotherapy and analyze the effect of chemotherapy on OS.
- We found that perioperative chemotherapy improves the OS in metastatic CRC with liver metastases.
- In metastatic CRC with liver metastases neoadjuvant and multiagent chemotherapy improves the OS compared with adjuvant and single-agent chemotherapy, respectively.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2021-0239

Author contributions

F Baidoun: data analysis, data interpretation, manuscript writing. Z Merjaneh: manuscript writing. R Nanah: manuscript writing. AM Saad: manuscript editing, critical revision. O Abdel-Rahman: study concept, manuscript editing, critical revision.

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