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ORIGINAL ARTICLE

Trends in the Multimodality Treatment of Resectable Colorectal Liver Metastases: an Underutilized Strategy

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Abstract

Objective Advances in multimodality therapy have led to increased survival for patients with metastatic colorectal cancer, but the impact on patients undergoing resection for colorectal liver metastases is unclear. The purpose of this study was to evaluate patterns of treatment for resectable colorectal liver metastases in the USA over the last two decades.

Methods Using the Surveillance, Epidemiology, and End Results-Medicare database, 1,926 patients who underwent hepatic resection for colorectal liver metastasis between 1991 and 2007 were included and divided into two cohorts: period 1 (1991–2000) and period 2 (2001–2007). Demographic data, treatment patterns, and outcomes of the two periods were compared by univariate methods. Multivariable regression models were constructed to predict the use of perioperative chemotherapy, postoperative complications, and 90-day mortality following liver resection.

Results The overall use of perioperative chemotherapy was 33 % and did not differ between periods, but shifted from postoperative to preoperative over time. By multivariable analysis, older age, black race, stage III primary cancer, and metachronous disease were predictive of lesser likelihood of chemotherapy use. The use of preoperative chemotherapy was not associated with any increase in perioperative morbidity or mortality.

Conclusions Despite increased survival and widespread recommendations for the use of multimodality therapy, the overall resection rate and use of perioperative chemotherapy for resectable colorectal liver metastases remain underutilized and have not increased over time. Efforts to investigate barriers to the widespread use of multimodality therapy for these patients are warranted.

Keywords Chemotherapy · Hepatic resection · Colorectal cancer

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide and in the USA.[1] Many patients present with or develop metastatic (stage IV) disease during their lifetime, although it is potentially curable if diagnosed early. The liver is the most common site of spread, with approximately 15–25 % of patients presenting with synchronous colorectal liver metastasis (CRLM) and an additional 15–40 % developing metachronous disease.[2,3] In these patients, resection of all disease remains the best chance for long-term survival with 5-year survival rates of 35–60 %.[3–5] Unfortunately, only a minority of patients (10–20 %) with CRLM are candidates for resection. Furthermore, even after successful hepatic resection, up to 50–70 % of patients eventually recur, suggesting that many patients may have occult metastatic disease at the time of resection.[5–7] Historically, few options remained for

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these patients with the exception of palliative systemic chemotherapy (CTX).

Within the last decade, several new systemic and biologic agents have been approved for the treatment of metastatic colorectal cancer (mCRC) and have led to an unprecedented increase in median survival to as high as 30 months in several studies.[8–12] As a result of these advances, the use of neoadjuvant (preoperative) or adjuvant (postoperative) systemic CTX for potentially resectable CRLM has become an attractive option. The use of perioperative CTX (both pre- and postoperative) has been associated with an improvement in progression-free survival (PFS) in a large randomized study and has been recommended by the National Comprehensive Cancer Network (NCCN) for the treatment of resectable CRLM.[13,14] The utilization and acceptance of this multimodality strategy in the USA in the modern era of CTX, however, has not been adequately studied. Most studies are either small or from single-institution databases and may not be generalizable to the overall USA patient population.

The purpose of this study was to evaluate the patterns of care and outcomes for resectable CRLM in the USA using the population-based Surveillance, Epidemiology, and End Results (SEER)-Medicare database. In particular, we aimed to identify temporal changes over the last two decades in the use of multimodality therapy, its potential barriers to use, as well as its impact on perioperative morbidity and mortality.

Material and Methods

Data Source and Study Population

This study consisted of a secondary analysis of prospectively collected data from the linked SEER-Medicare database of patients aged 65 years or older who underwent resection for CRLM between 1991 and 2007. The date of initial liver resection was considered "zero time" for the purpose of the analysis. The study cohort included only patients who were continuously enrolled in both Medicare Parts A and B for at least 6 months before and 3 months after resection and who were not enrolled in a managed care plan during the study period. Patients who underwent other liver-directed therapy such as radiofrequency ablation (RFA), chemoembolization, radiation, or hepatic artery infusion without resection were excluded from this study. For patients who had undergone multiple liver resections for CRLM, only the first resection was included in this study. Patients with colorectal adenocarcinoma were identified by the International Classification of Diseases for Oncology (ICD-O-3) topography, behavior, and histology codes and other histology codes were excluded. Identification of patients with primary colorectal cancer with hepatic metastasis was accomplished using an established algorithm that employed the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes and Current Procedural Terminology (CPT) codes for malignant neoplasm of liver and secondary malignant neoplasm of liver and hepatic resection.[15] Patients diagnosed with an additional primary liver cancer were excluded. Vanderbilt University Medical Center Institutional Review Board approved this study.

Identification of Chemotherapy

Chemotherapy administration was identified with CPT codes 96400–96549; ICD-9 diagnostic codes V58.1, V66.2, and V67.2; and ICD-9 procedure code 99.25. Preoperative and postoperative CTX was defined as the administration of CTX within 6 months before liver resection and within 3 months after liver resection, respectively.

Outcome and Predictor Variables

Independent variables such as perioperative procedures, treatments, and complications were selected a priori based on clinical relevance and then identified from the SEER-Medicare database using ICD-9-CM diagnosis and procedure codes as well as CPT codes. Previous studies have demonstrated the validity of Medicare billing codes to assess a wide range of outcomes.[16–18] The Charlson comorbidity index was used to identify and adjust for comorbid conditions.[19,20] Perioperative complications were defined as those that occurred during the hospital stay following hepatic resection, identified by ICD-9CM codes, and included surgical reexploration, percutaneous drain placement, postoperative hemorrhage, anemia or gastrointestinal hemorrhage, wound dehiscence, liver and abdominal abscesses, peritonitis, biliary and intestinal fistula, any post-op infection, and any GI complication.

Statistical Analyses

Univariate comparisons were assessed using the two-sample student t test and the chi-square test. For purposes of analyses, the distribution of the total number of comorbid conditions per patient was divided into tertiles: 0, 1, and ≥2 comorbidities. To assess temporal trends, the data were separated into two distinct time periods based on the approval of systemic and biologic agents for mCRC: Period 1 (PD1) included patients diagnosed or resected between 1991 and 1999 prior to the approval of these agents and period 2 (PD2) included patients diagnosed or resected between 2000 and 2007 after the approval of these agents. These groups were initially compared using standard univariate tests. In order to fully account for preoperative therapy 6 months prior to resection, the first date of entry into this study was July 1, 1991. A minimum follow-up of 3 months to account for 90-day mortality as well as the use of postoperative therapy was required.

Using multivariable logistic regression methods, odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated for associations with the receipt of perioperative CTX, in-hospital complications, and 90-day mortality after liver resection. Interaction of these factors with the year of treatment was also performed. For purposes of comparison, three representative years (1992, 2000, and 2007) were selected for multivariable analysis. All reported p values are two-tailed and $p<0.05$ was considered statistically significant. Analyses were performed using SAS statistical software, version 9.2 (SAS Inc., Cary, NC).

Results

Patient and Primary Tumor Characteristics

Utilizing the SEER-Medicare linked database, 349,667 patients with CRC between July 1, 1991 and December 31, 2007 were initially identified. After applying inclusion and exclusion criteria, a total of 1,926 patients (5.9 %) were included in this study (Table 1).

Although the number of patients with CRC (103,295 vs. 69,117) and CRLM (18,798 vs. 13,880) as well as the total number of liver resections for CRLM (1,293 vs. 633) in the SEER-Medicare database was higher in PD2 (2000–2007), this was most likely due in large part to the expansion of SEER in 2000. The percentage of patients undergoing liver resection for CRLM when compared to the number of patients diagnosed with CRLM, however, was significantly higher (6.9 vs. 4.6 %, $p=0.01$) during PD2 compared to PD1.

The demographic and clinical characteristics of the 1,926 patients with surgically resected CRLM in the two time periods are outlined in Table 2. In both eras, the majority of patients were men, white, and resided in an urban setting. The mean age was 73. The primary lesion was most commonly located in the colon in both periods (74.6 vs. 77.6 %, $p=0.14$), and the majority of patients presented with late-stage disease in both cohorts. The percentage of patients with synchronous lesions (as defined by liver resection within 12 months of the diagnosis of primary CRC), however, was significantly higher in PD1 (58.8 vs. 46.5 %, $p<0.01$). While the majority of patients had no comorbidities, patients who undergone resection in PD2 appeared to have a significantly higher number of comorbidities ($p<0.01$).

Table 1 Definition of analytical cohort (includes patients from July 1, 1991 to December 31, 2007)

Total number of patients diagnosed with colorectal cancer	349,667
Patients with continuous Medicare A and B coverage[a] and no managed care plan	217,162
Patients with colorectal adenocarcinoma histology only	202,564
Age ≥65 years	172,412
Patients with liver metastases	32,764
Patients without an additional primary liver cancer	32,678
Patients who underwent liver resection	1,926

[a] For at least 6 months prior to resection and 3 months after resection

Table 2 Demographics of resected patients in PD1 and PD2

	1991–1999[a]	2000–2007[b]	p value
Mean age at resection±SD	73.1±5.8	73.1±5.9	0.77
Male	329 (52.0)	745 (57.6)	0.02
White	566 (89.4)	1,135 (87.8)	0.29
Black	35 (5.5)	84 (6.5)	0.41
Urban	582 (91.9)	1,175 (91.0)	0.44
Primary site, colon	472 (74.6)	1,003 (77.6)	0.14
Primary stage			0.64
Stage I	25 (4.2)	67 (5.4)	
Stage II	90 (15.1)	202 (16.2)	
Stage III	170 (28.5)	367 (29.4)	
Stage IV	310 (51.9)	606 (48.6)	
Synchronous disease[c]	372 (58.8)	601 (46.5)	<0.01
Charlson comorbidities			<0.01
0	480 (75.8)	911 (70.5)	
1	124 (19.6)	307 (23.7)	
2	16 (2.5)	53 (4.1)	
≥3	13 (2.1)	22 (1.7)	

Data shown as n (percent) unless otherwise noted

[a] Includes patients undergoing liver resection for CRLM from July 1, 1991 to December 31, 1999

[b] Includes patients undergoing liver resection for CRLM from January 1, 2000 to December 31, 2007

[c] Defined as liver resection within 12 months of primary CRC diagnosis

Comparison of Treatment Patterns Between Time Periods

Perioperative CTX was utilized in only a minority of patients during both time periods, with approximately two-thirds of patients receiving no CTX in the 6 months prior or 3 months after resection (Table 3). Although the overall use of CTX did not change, the pattern of use was significantly different during the two time periods ($p<0.01$). The use of preoperative CTX increased from 8.2 to 14.5 % from PD1 to PD2, while the use of postoperative CTX decreased from 24.5 to 17.9 %. Both preoperative *and* postoperative CTX was utilized in <1.5 % of patients during both periods (data not shown).

Segmental resection was more common than a formal lobectomy in both periods. The overall mean length of hospital stay decreased from 9.4 to 8.2 days ($p<0.01$) from PD1 to PD2, while the overall 30-, 60-, and 90-day mortality did not

Table 3 Treatment patterns of resected patients in PD1 and PD2

	1991–1999[a]	2000–2007[b]	*p* value
Chemotherapy use			<0.01
Preoperative[c]	52 (8.2)	185 (14.5)	
Postoperative[d]	155 (24.5)	229 (17.9)	
Neither	424 (67.2)	863 (67.6)	
Type of liver resection			0.88
Lobectomy	211 (33.3)	423 (32.7)	
Segmental resection	422 (66.7)	870 (67.3)	
Mean LOS±SD	9.4±6.8	8.2±5.6	<0.01
Mortality			
30-day	35 (5.5)	50 (3.9)	0.10
60-day	47 (7.4)	75 (5.8)	0.17
90-day	52 (8.2)	109 (8.4)	0.87
Complications[e]			<0.01
0	440 (69.5)	1,023 (79.1)	
1	154 (24.3)	230 (17.8)	
≥2	39 (6.2)	40 (3.1)	

Data shown as *n* (percent) unless otherwise noted

[a] Includes patients undergoing liver resection for CRLM from July 1, 1991 to December 31, 1999

[b] Includes patients undergoing liver resection for CRLM from July 1, 2000 to December 31, 2007

[c] Defined as having received chemotherapy within 6 months before resection

[d] Defined as having received chemotherapy within 3 months after resection

[e] In-hospital complications following resection

significantly change. Overall in-hospital morbidity following resection, however, significantly decreased (Table 3).

Factors Associated with the Receipt of Perioperative CTX

When comparing patients with synchronous disease (defined as liver resection within 1 year of diagnosis of CRC) to patients with metachronous disease (defined as liver resection greater than 1 year after diagnosis of CRC) across both time periods, a significantly higher percentage of patients received perioperative chemotherapy in the synchronous group (47 vs. 19 %, $p<0.001$). Multivariable associations of multiple factors and the receipt of perioperative CTX either in the preoperative and/or postoperative setting during three representative years are shown in Table 4. In comparison to white patients, black patients were significantly less likely to receive perioperative CTX. Older patients were also significantly less likely to receive perioperative CTX throughout the study period (OR 0.29–0.51 for age 75, 0.09–0.26 for age 85), and although the impact of age appeared to lessen over time, this change was not significant (age–year interaction $p=0.12$). Patients with

Table 4 Factors affecting the use of perioperative chemotherapy in representative years

	Year	OR	95 % CI
Race (ref=white)			
Black	1992	0.83	0.26–2.61
	2000	0.59	0.36–0.98
	2007	0.44	0.21–0.95
All others	1992	1.0	0.33–3.05
	2000	0.9	0.55–1.48
	2007	0.83	0.39–1.78
Gender (ref=female)			
Male	1992	1.24	0.74–2.08
	2000	1.06	0.84–1.32
	2007	0.92	0.64–1.31
Age (ref=65)			
75	1992	0.29	0.18–0.47
	2000	0.39	0.32–0.48
	2007	0.51	0.37–0.70
85	1992	0.09	0.03–0.22
	2000	0.15	0.10–0.23
	2007	0.26	0.13–0.49
Stage of primary cancer (ref=IV)			
I	1992	1.1	0.25–4.87
	2000	1.06	0.57–1.97
	2007	1.03	0.43–2.49
II	1992	0.45	0.20–1.05
	2000	0.69	0.69–1.00
	2007	1.00	0.58–1.74
III	1992	0.40	0.19–0.84
	2000	0.59	0.43–0.81
	2007	0.83	0.51–1.34
Comorbidity (ref=2)			
0	1992	1.93	0.50–7.55
	2000	1.27	0.71–2.25
	2007	0.87	0.41–1.85
1	1992	2.16	0.51–9.14
	2000	1.32	0.72–2.43
	2007	0.86	0.38–1.92
Complications (ref=yes)			
No	1992	0.91	0.52–1.60
	2000	1.08	0.84–1.39
	2007	1.25	0.81–1.92
Type of resection (ref=lobectomy)			
Segmental resection	1992	0.67	0.38–1.20
	2000	0.79	0.62–1.02
	2007	0.91	0.62–1.34
Location of primary cancer (ref=colon)			
Rectal	1992	0.74	0.40–1.37
	2000	1.0	0.76–1.30
	2007	1.29	0.85–1.98

Table 4 (continued)

	Year	OR	95 % CI
Timing of metastases (ref=synchronous[a])			
Metachronous	1992	0.13	0.06–0.26
	2000	0.21	0.15–0.28
	2007	0.31	0.20–0.48

[a] Defined as liver resection within 12 months of primary CRC diagnosis

stage III disease were also less likely to receive perioperative CTX in 1992 and 2000 compared to those with stage IV disease (OR 0.40, 95 % CI 0.19–0.84; OR 0.59, 95 % CI 0.43–0.81, respectively), but by 2007, this difference was no longer significant. Finally, patients with metachronous disease (liver resection ≥12 months after diagnosis of primary CRC) were also significantly less likely to receive perioperative CTX as compared to those with synchronous disease throughout all time periods (OR 0.13, 95 % CI 0.06–0.26 in 1992; OR 0.21, 95 % CI 0.15–0.28 in 2000; OR 0.31, 95 % CI 0.20–0.48 in 2007). Gender, stage I and II disease, presence of comorbidities, complications, type of liver resection, and location of primary cancer were not significantly associated with the likelihood of receiving perioperative CTX (Table 4).

Factors Associated with Complications After Liver Resection

Multivariable associations of factors with in-hospital complications after liver resection during three representative years are shown in Table 5. Patients with stage I or II primary cancer appeared to have significantly fewer complications in 1992 as did patients with stage I primary cancer in 1997. All other variables including race, age, stage of primary cancer, comorbidities, type of liver resection, location of primary cancer, presence of synchronous disease, and receipt of preoperative CTX were not significantly associated with in-hospital complications following liver resection in any of the representative time periods.

Factors Associated with Mortality After Liver Resection

Table 6 illustrates the multivariable analysis of various factors associated with an increase in 90-day mortality. Older patients were at a much higher risk of 90-day mortality after resection when compared to those aged 65 (OR 2.39, 95 % CI 1.83–3.13 for age 75 and OR 5.72, 95 % CI 3.34–9.81 for age 85). Other factors including race, gender, stage and primary tumor location, comorbidities, synchronous disease, type of liver resection, complications, and receipt of preoperative CTX were not associated with any significant increase in mortality. Since the overall mortality was low, specific changes and interaction over time were not analyzed.

Table 5 Factors associated with complications following liver resection in representative years

	Year	OR	95 % CI
Race (ref=white)			
Black	1992	1.04	0.37–2.90
	2000	0.90	0.56–1.45
	2007	0.79	0.35–1.81
All others	1992	0.60	0.19–1.88
	2000	0.63	0.37–1.07
	2007	0.65	0.25–1.66
Gender (ref=female)			
Male	1992	1.01	0.62–1.65
	2000	1.09	0.87–1.36
	2007	1.15	0.78–1.71
Age (ref=65)			
75	1992	1.05	0.69–1.58
	2000	1.19	0.98–1.43
	2007	1.33	0.96–1.84
85	1992	1.09	0.48–2.50
	2000	1.41	0.97–2.06
	2007	1.77	0.92–3.37
Stage of primary cancer (ref=4)			
I	1992	0.15	0.02–0.95
	2000	0.42	0.20–0.89
	2007	1.06	0.38–2.96
II	1992	0.73	0.34–0.95
	2000	0.87	0.61–1.23
	2007	1.01	0.56–1.83
III	1992	0.83	0.42–1.65
	2000	0.76	0.56–1.04
	2007	0.71	0.41–1.22
Comorbidity (ref=2)			
0	1992	1.01	0.33–3.14
	2000	0.94	0.57–1.54
	2007	0.87	0.39–1.93
1	1992	0.84	0.25–2.87
	2000	0.69	0.40–1.18
	2007	0.58	0.24–1.39
Chemotherapy (ref=preoperative/both)			
Postoperative or none	1992	0.57	0.24–1.31
	2000	1.0	0.70–1.43
	2007	1.64	0.94–2.88
Type of resection (ref=lobectomy)			
Segmental resection	1992	0.67	0.39–1.14
	2000	0.82	0.65–1.05
	2007	0.99	0.65–1.51
Location of primary cancer (ref=colon)			
Rectal	1992	1.25	0.70–2.21
	2000	1.29	0.99–1.68
	2007	1.33	0.84–2.10

Table 5 (continued)

	Year	OR	95 % CI
Timing of metastases (ref=synchronous[a])			
Metachronous	1992	1.19	0.63–1.13
	2000	0.84	0.63–1.13
	2007	0.63	0.39–1.02

[a] Defined as liver resection within 12 months of primary CRC diagnosis

Discussion

The purpose of the current study was to investigate trends in the management of resectable metastatic colorectal cancer to the liver in patients ≥65 years old over the past two decades utilizing a large population-based dataset. Although the percentage of patients with CRLM undergoing resection has increased over time, only a small minority of patients appear to undergo resection. The majority of patients undergoing liver resection did not receive any form of CTX in the perioperative setting. Although there appeared to be an increase in the use of preoperative CTX over time, this was associated with a proportional decrease in the use of postoperative therapy following resection, resulting in no significant change in the overall use of multimodality therapy. Additionally, we found that older patients, black patients, patients with stage III primary cancer as well as patients with metachronous disease were less likely to receive perioperative CTX. Finally, in those who received CTX prior to resection, there was no increase in perioperative morbidity or mortality.

Table 6 Factors associated with 90-day mortality after resection

	OR	95 % CI
Race (ref=white)		
Black	1.34	0.72–2.52
All others	0.93	0.89–2.21
Gender (ref=female)		
Male	1.31	0.93–1.85
Age (ref=65)		
75	2.39	1.83–3.13
85	5.72	3.34–9.81
Stage of primary cancer (ref=4)		
I	0.71	0.27–1.92
II	0.75	0.43–1.32
III	1.03	0.65–1.62
Comorbidity (ref=2+)		
0	0.62	0.32–1.23
1	0.90	0.44–1.84
Chemotherapy (ref=preoperative/both)		
Postoperative or none	1.10	0.64–1.87
Type of resection (ref=lobectomy)		
Segmental resection	0.74	0.52–1.07
Location of primary cancer (Ref=colon)		
Rectal	0.77	0.50–1.20
Timing of metastases (ref=synchronous[a])		
Metachronous	0.71	0.45–1.10
Complications (ref=yes)		
No	0.65	0.46–0.94

[a] Defined as liver resection within 12 months of primary CRC diagnosis

In total, we identified 1,926 patients (5.9 %) as having undergone liver resection of CRLM in the SEER-Medicare database cohort. Although the percentage of patients undergoing resection increased over time, the overall utilization of liver resection is low compared to single-institution and referral center studies. Several large single-institution reports have suggested that up to 20 % of patients with CRLM are initially resectable and that another 10–15 % may become resectable with the use of preoperative CTX.[21–24] Other large population-based studies, however, have also reported a low utilization of surgical management for patients with CRLM (5–7 %).[25,26] The reason for the low incidence of liver resection for CRLM is likely multifactorial. Given that our study population was limited to patients 65 years or older, this may be related in part to a lower utilization of liver operations among the elderly population. Although several studies have suggested that advanced chronological age should not be regarded as a medical contraindication for hepatic resection of CRLM,[27,28] this study demonstrated that 90-day mortality is significantly higher among older patients despite comparable in-hospital complication rates. To some extent, the low incidence of resection may also be the result of underreporting. However, as others have noted, SEER-Medicare data generally have a high level of agreement for identifying CRC patients who have undergone an operation especially when excluding patients with any managed healthcare plans or those with lapses in continuous coverage.[25]

In comparing the period from 1991–1999 to 2000–2007, we noticed several other interesting trends. Although the demographic patterns of the patients undergoing resection appeared similar, those undergoing resection in the modern era had a significantly higher number of comorbidities. Despite this, overall mortality remained low, and the overall in-hospital complication rate as well as length of hospital stay appeared to decrease over time. This suggests that even in the elderly population, advances in the perioperative management of patients undergoing liver resection have improved over time and have kept both morbidity and mortality rates relatively low.

Significant advances in CTX use for patients with mCRC and CRLM have been made over the last several decades. Whereas traditional response rates to CTX were about 20 %,[29] since 1999, the approval of multiple systemic CTX agents as well as targeted agents has increased response rates to as high as 60 %.[30–32] In addition, these agents have been shown to significantly prolong overall survival in patients with metastatic disease.[33–36] These improvements have led to multiple studies suggesting the effectiveness of multiagent regimens in patients with either resectable or potentially resectable CRLM,[32,37–39] and the recent prospective randomized EORTC 40983 trial showed a significant improvement in PFS in eligible patients undergoing liver resection for CRLM who received perioperative FOLFOX when compared to those who underwent resection alone.[13] In agreement with these studies, NCCN guidelines over the past decade have recommended multimodality therapy either in the preoperative and/or postoperative setting for most patients.[14] Despite this, we noted that only about one-third of patients received some type of perioperative systemic CTX, although patients with synchronous disease were significantly more likely to receive perioperative chemotherapy than those with metachronous disease. Although this percentage seems lower than what would be expected, it is consistent with a recent study using SEER-Medicare in which 47 % of patients undergoing *any* liver-directed procedure (including resection, ablation, or combinations) received perioperative chemotherapy.[15] In order to investigate the sensitivity of detecting chemotherapy use with our algorithm, we queried patients with a stage III metachronous primary colon cancer and found that 71 % received adjuvant chemotherapy within 2 months of resection. This is consistent with other large population databases studying adjuvant therapy for colon cancer, particularly in the elderly, both in the USA and in Europe.[40–44]

In an attempt to investigate potential reasons for underutilization of CTX use, a multivariable model was constructed. In agreement with studies in both resected primary colorectal cancer and other malignancies, black patients were significantly less likely to receive CTX for resectable CRLM, and this disparity did not change over time. Although the presence of comorbidities did not affect the use of perioperative CTX, multimodality therapy was also underutilized in older patients.

The *pattern* of perioperative CTX use appeared to change over time, however. The use of preoperative therapy appeared to significantly increase during the modern era when compared to before 2000, while the use of postoperative therapy proportionally decreased. Approximately 1 % of patients received both preoperative and postoperative CTX during the entire study period. One of the potential barriers for the use of preoperative CTX for CRLM is potential hepatic toxicity and a corresponding increase in complication rates following resection.[13,45–47] In looking at factors associated with morbidity and mortality after resection, however, there was no increase in patients receiving preoperative therapy when compared to postoperative or surgical resection alone in either multivariable model.

The current study has several limitations. As discussed above, randomized data, albeit from Europe, supporting the use of perioperative chemotherapy for resectable CRLM was published in 2008.[13] At the time of our study initiation, SEER-Medicare data for colorectal cancer were available only through 2007, and therefore, our study does not reflect any changes in practice following this trial. Additional studies utilizing more contemporary data as it becomes available will be necessary to investigate additional changes in the use of perioperative chemotherapy. In addition, administrative datasets may not accurately record all the CTX given and can therefore suffer from underreporting. Validation studies, however, have suggested that for many agents, including those used in the treatment of colorectal cancer, there is good sensitivity and specificity of SEER-Medicare data compared to reviews of patient medical records.[17] Furthermore, the results of this study are similar to those of other studies of treatment patterns among the elderly using different large population databases. While SEER captures relatively specific data on primary tumor characteristics, detailed data on metastasis including size, number of lesions, grade, and margin status are not available so that we could not stratify our findings based on metastatic disease burden. In addition, because we utilized a dataset linked to Medicare, only patients aged ≥65 years were included. Whether results from the current study can be extrapolated to younger patient populations will require further study. Nevertheless, with an aging population, these results may be particularly applicable to our patients in the upcoming years. Finally, as in all nonrandomized studies, it is possible that other variables not captured by SEER or Medicare significantly affected the use and effectiveness of multimodality and surgical therapy for CRLM.

Conclusion

In conclusion, we found that although the overall utilization of liver resection for CRLM has increased over time, it remains relatively low among Medicare beneficiaries. Mortality following liver resection remains low, and in-hospital complications appear to have decreased despite an increase in the comorbidities of patients undergoing resection. Despite the approval and success of numerous CTX and targeted agents for CRLM, their use in the treatment of resectable CRLM remains limited, with only about 30 % of patients having received perioperative CTX. Future studies should seek to better understand the factors that impact the differences and trends in the relative utilization of perioperative and operative interventions as well as to identify barriers preventing more widespread use of multiagent CTX regimens in the treatment of resectable CRLM.

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