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ORIGINAL RESEARCH ARTICLE

Patterns of Treatment Sequences in Chemotherapy and Targeted Biologics for Metastatic Colorectal Cancer: Findings from a Large Community-Based Cohort of Elderly Patients

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Abstract

Background Over the last decade, multiple chemotherapies/targeted biologics have been approved for metastatic colorectal cancer (mCRC). However, evidence is limited with regards to the array of treatments received by mCRC patients.

Objective This study examines treatment sequences (first- to third-line chemotherapy/targeted biologics) and the factors associated with first-line targeted biologics and common treatment sequences for elderly mCRC patients treated in a community setting.

Methods A retrospective cohort study was conducted in mCRC patients diagnosed from January 2004 through December 2009 using the Surveillance, Epidemiology and End Results Medicare-linked database. The treatment sequences administered to elderly mCRC patients were empirically identified.

Results Of 4418 mCRC patients who received treatment, 1370 (31 %) received first, second, and third line; 1164 (26 %) received first and second line; and 1884 (43 %) received only first line. The most common first line of treatment for mCRC patients was 5-fluorouracil/leucovorin + oxaliplatin (FOLFOX) + bevacizumab (23 %) and FOLFOX (23 %). 5-fluorouracil/leucovorin + irinotecan (FOLFIRI)-based regimens were commonly (22 %) administered in second line. The most common treatment sequence was first-line oxaliplatin or irinotecan followed by second-line oxaliplatin or irinotecan + bevacizumab followed by a third-line targeted biologic. Of patients who received first-line therapy, 47 % also received a targeted biologic, and the factors associated were age, comorbidity score, cancer site, geographic location, and year of diagnosis.

Conclusion Elderly mCRC patients receive a multitude of treatments in various sequences. Further exploration of the comparative effectiveness of treatment sequences may yield important information for improving mCRC survival.

Key Points

Elderly metastatic colorectal cancer patients received treatment sequences with multiple drugs administered across various lines of treatment.

Oxaliplatin- or irinotecan-based regimens were the most common chemotherapies, bevacizumab was the most common targeted biologic, and the most common treatment sequence was first-line oxaliplatin or irinotecan followed by second-line oxaliplatin or irinotecan + bevacizumab followed by a third-line targeted biologic.

Future research evaluating the comparative effectiveness and cost effectiveness of treatment lines and sequences for elderly patients with metastatic colorectal cancer should be conducted.

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1 Introduction

Colorectal cancer (CRC) currently ranks third among the most common cancers and cancer deaths in the USA [1–3]. It is estimated there will be about 132,700 new cases of CRC and nearly 49,700 deaths because of CRC in 2015 in the USA [1, 3]. A majority of cases (60 %) and deaths (70 %) occur in those aged ≥65 years. For males between the ages of 40 and 79 years and females aged ≥80 years, CRC is the second leading cause of death [3]. As compared with younger CRC patients, elderly CRC patients have a lower survival rate primarily because of the stage at diagnosis. Moreover, the management of the disease among elderly patients is also poor. Overall, one in four patients has the metastatic form of the disease at diagnosis, and nearly half of CRC patients may develop metastasis during progression of the disease. Metastatic colorectal cancer (mCRC) has a poor prognosis, with an overall survival rate of 5–13 % at 5 years [4, 5], and the cost of treating metastatic disease is twice as high as the cost of cases without metastasis [6].

Until 2004, 5-Fluorouracil, leucovorin (5-FU/LV) had been the standard therapy for mCRC patients, with an estimated median overall survival of 10–14 months. Oxaliplatin and irinotecan in combination with 5-FU/LV, i.e., FOLFOX (5-FU/LV + oxaliplatin) and FOLFIRI (5-FU/LV + irinotecan), respectively, have been commonly prescribed to mCRC patients since 2004 [7]. Targeted biologics such as bevacizumab and cetuximab were approved for treating mCRC patients in 2004, which was followed by the approval of panitumumab in 2006. These clinically proven therapies are current standard treatments that can be administered either as monotherapy or as a combination to form a treatment line. With an array of chemotherapy/targeted therapy options available for mCRC patients, multiple lines of treatment could be administered to a patient as needed during the course of their treatment and thereby form a treatment sequence, where each sequence comprises multiple lines of treatments [7–9]. Currently, there is a lack of standard sequence of chemotherapy and targeted biologics recommended for mCRC patients [8–13]. In the absence of evidence-based guidelines for sequencing therapy, the decision regarding first-line treatment has been generally based on patient factors and preferences while subsequent treatments (after progression) are based on the treatment previously received [14].

Recommendations have been made for healthy elderly patients to be treated with chemotherapy and targeted biologic combinations similar to those administered to younger patients [15]. Specifically, irinotecan (e.g., FOLFIRI)- or oxaliplatin (e.g. FOLFOX)-based regimens with or without bevacizumab for first- and second-line treatment may be the treatment of choice [16–18]. No specific recommendations have been made for the third line of treatment, but targeted biologics have been used in one study and are currently being evaluated in ongoing clinical trials [11, 19, 20]. Although multiple treatment options may be available for mCRC patients, elderly patients have been observed to frequently receive suboptimal treatment, and only a subgroup of elderly patients may receive exhaustive treatment management similar to that received by younger patients [21–25]. Thus, an understanding of the demographic and clinical factors associated with various treatments received by elderly mCRC patients is essential. Moreover, evidence is limited on the current usage of treatment sequences among elderly mCRC patients treated in a non-experimental (community-based) setting, especially with regards to targeted biologics; assessing real-world utilization of treatment sequences may guide in optimizing the adequate sequential use of targeted biologics in routine practice and in-turn judicious use of healthcare resources. Thus, the objective of the study was to describe treatment sequences (first- to third-line chemotherapy and targeted biologics) and the factors associated with the receipt of targeted biologics at first-line and treatment sequences for elderly mCRC patients in community-based settings.

2 Methods

2.1 Data Source

The National Cancer Institute governs the Surveillance, Epidemiology and End Results (SEER) program under which participating regions provide cancer registry data that includes information on patient demographics, socioeconomic variables, stage at diagnosis, tumor site, tumor characteristics, and initial treatment after diagnosis. After the expansion of the SEER program in 2000, the 16 participating registries (i.e., San Francisco/Oakland, Detroit, Seattle, Atlanta, Rural Georgia, Los Angeles, San Jose-Monterey area, Greater California, Connecticut, Iowa, New Mexico, Utah, Hawaii, Kentucky, Louisiana, and New Jersey) represent nearly 28 % of the US population, and SEER records 98 % of the cancer-diagnosed cases in these regions [26, 27]. These data have been used for numerous cancer epidemiology and chemotherapy utilization studies; validity and completeness of the database has also been shown in previous studies [28–30]. The SEER-Medicare data linked cancer patients aged ≥65 years from the SEER program to their administrative claims from the Medicare program, which insures individuals aged >65 years in the

USA [26]. Medicare data includes healthcare utilization information for inpatient, outpatient, professional (provider), skilled nursing facility, hospice, and devices and medical equipment.

2.2 Study Population

Patients diagnosed with mCRC at ≥65 years from January 2004 to December 2009 were included. Targeted therapies such as bevacizumab and cetuximab became available for mCRC patients in 2004; hence, analysis was restricted to patients diagnosed after 2004. We used an American Joint Cancer Committee (AJCC) criterion to characterize metastatic disease, and patients with AJCC stage IV were included. Patients who were ascertained as mCRC through autopsy/death certificate were excluded, as patients had already died before receiving any treatment. Also, patients who died within 30 days of diagnosis were excluded as they were unlikely to have received treatment sequences [14, 31, 32]. For the completeness of information on treatment sequences in Medicare claims, patients were required to be enrolled in both Medicare parts A and B without any Health Maintenance Organization (HMO) enrollment from the time of diagnosis to death or end of study. Similar inclusion/exclusion criteria have been used in previous studies [31, 33–36].

2.3 Treatment Identification

We identified systemic chemotherapy and targeted biologics currently approved by the US FDA for treatment of mCRC patients and recommended by the National Comprehensive Cancer Network [7–9], i.e., 5-florouracil, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab. Aflibercept, although approved in 2012, was not included in this study, as Medicare claims were only available until 2010. Chemotherapeutic and targeted biologics agents could be given either as monotherapy or as a combination therapy to form a 'line of treatment'. We identified the first three lines of treatment administered to mCRC patients and used Healthcare Common Procedural Coding System (HCPCS) codes from the Medicare outpatient and physician files to identify chemotherapy or targeted biologics. HCPCS codes used were 5-florouracil—J9190; irinotecan—J9206; leucovorin—J0640, J0641; oxaliplatin—J9263, C9205; bevacizumab—J9035, C9214, S0116; cetuximab—J9055, C9215, and panitumumab—J9303, C9235.

2.4 Line and Sequence Identification

A data-driven 'line of treatment' approach was used to identify the treatment sequences. Start of a line of treatment was determined based on the date of the first claim for the drug. Additionally, for the drug to be considered as a line of treatment, it was required to be re-administered within 35 days (28 + 7 additional days). A combination regimen was defined when an additional drug was administered within 28 days of the first drug claim and was re-administered within 35 days (28 + 7 additional days). End of a line of treatment was defined as (1) a line continues until the end of the study; (2) no drug is administered within 90 days, or (3) a previous line of treatment is interrupted by a new line of treatment [37]. This process was conducted three times to identify three treatment lines. Similar methodology has been used by previous treatment pattern studies [11, 38, 39]. For patients receiving at least two lines of treatments, first- to third-line treatments were combined to define treatment sequences. Finally, we only included patients for whom the gap between treatment lines (first to second line and second to third line) was less than 1 year.

2.5 Patient and Tumor Characteristics

SEER data records demographic information such as age, race, sex, marital status, year of diagnosis, and geographic location at the time of diagnosis. The variable "percent below poverty line at zip code level" obtained from the US Census Data was used as a proxy for patient's socio-economic (poverty) status. The poverty variable was then categorized into quartiles to differentiate individuals living in areas with higher versus lower rates of poverty. Tumor stage, grade and site of cancer (i.e., colon or rectal) were obtained from SEER data. A Charlson Comorbidity Index (CCI) was computed with inpatient, outpatient, and physician claims from 1 year prior to the month of diagnosis using non-cancer comorbid conditions initially identified by Charlson et al. [40–42] to affect overall morbidity and mortality. Metastases type was identified using inpatient, outpatient, and physician claims within 3 months after diagnosis based on the algorithm used by Chawla et al. [43]. *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes were used to identify metastases [Table 1 in the Electronic Supplementary Marerial (ESM)], and patients were considered to have metastases if they had at least one inpatient claim or two outpatient/provider claims on separate days [29, 43, 44].

2.6 Statistical Analyses

Descriptive statistics (mean, standard deviation, and median time) for each of the treatments (monotherapy or combination) in first, second, and third line, as well as treatment sequences, were calculated. We computed descriptive statistics for patients receiving targeted biologics at first line, and used a logistic regression analysis to assess factors associated with the receipt of targeted biologics in first line. Factors associated with the receipt of commonly administered targeted biologics-based treatment

Table 1 Characteristics of metastatic colorectal cancer patients and patients

Characteristics	All MCRC pts ($n = 9819$)	Pts with mCRC who received either CTX or targeted therapy ($n = 4418$)
Age (years)		
65–69	2098 (21.4)	1333 (30.2)
70–74	2092 (21.3)	1190 (26.9)
75–79	2083 (21.2)	1022 (23.1)
80–84	1851 (18.9)	627 (14.2)
≥85	1695 (17.3)	246 (5.6)
Race/ethnicity		
Caucasians	7924 (80.7)	3693 (83.6)
African Americans	1095 (11.2)	382 (8.7)
Other	800 (8.2)	343 (7.8)
Sex		
Male	4720 (48.1)	2318 (52.5)
Female	5099 (51.9)	2100 (47.5)
Marital status		
Married	4714 (48.0)	2571 (58.2)
Unmarried	4769 (48.6)	1718 (38.9)
Unknown	336 (3.4)	129 (2.9)
Tumor grade		
Well/moderately differentiated	5112 (52.1)	2554 (57.8)
Poorly/undifferentiated	2438 (24.8)	1148 (26.0)
Unknown	2269 (23.1)	716 (16.2)
Comorbidity scores		
0	4712 (48.0)	2357 (53.4)
1	2677 (27.3)	1280 (29.0)
2	1227 (12.5)	430 (9.7)
≥3	1203 (12.3)	351 (7.9)
Metastasis		
Liver	6234 (63.5)	2969 (67.2)
Lung	1692 (17.2)	730 (16.5)
Abdomen	1953 (19.9)	873 (19.8)
Other	1618 (16.5)	696 (15.8)
Unknown	1969 (20.1)	747 (16.9)
Cancer site		
Colon	7559 (77.0)	3276 (74.2)
Rectal	2260 (23.0)	1142 (25.9)
SES (poverty)		
1st (low SES)	2454 (25.0)	989 (22.4)
2nd	2404 (24.5)	1070 (24.2)
3rd	2502 (25.5)	1139 (25.8)
4th (high SES)	2459 (25.0)	1220 (27.6)
Region		
Midwest	1284 (13.1)	566 (12.8)
North east	2212 (22.5)	1000 (22.6)
South	2275 (23.2)	1035 (23.4)
West	4048 (41.2)	1817 (41.1)
Urban/rural		
Less urban/rural	1097 (11.2)	477 (10.8)
Urban	588 (6.0)	268 (6.1)
Metro	8132 (82.8)	3672 (83.1)
Year of diagnosis		
2004	1588 (16.2)	731 (16.6)
2005	1510 (15.4)	696 (15.8)
2006	1811 (18.4)	780 (17.7)
2007	1668 (17.0)	722 (16.3)
2008	1650 (16.8)	752 (17.0)
2009	1592 (16.2)	737 (16.7)

Data are presented as *n* (%)

CTX chemotherapy, *mCRC* metastatic colorectal cancer, *pts* patients, *SES* socio-economic status

sequences were assessed using univariate chi-squared statistic and multinomial logistic regression. In contrast to conventional logistic regression, multinomial logistic regression allowed the use of dependent variables with more than two categories and thereby enabled us to examine any association between multiple treatment sequences and patient/tumor characteristics [45–47]. All analyses were conducted using SAS version 9.3, and statistical significance was determined at $\alpha = 0.05$.

3 Results

Of the 9819 patients diagnosed with mCRC from January 2004 to December 2009 who met other inclusion criteria (Fig. 1 in the ESM); 5192 (53 %) did not receive treatment, 4418 (45 %) received treatment, and 209 (2 %) were excluded, as the gap between first to second line or second to third line was more than 1 year. The baseline characteristics for all mCRC patients and patients who received treatment are shown in Table 1. Overall, the sample comprised 81 % Caucasians, 52 % females, 83 % living in a metropolitan area, 77 % with metastatic colon cancer, and 23 % with metastatic rectal cancer (Table 1). A majority of patients had a liver metastasis (63 %), followed by abdomen (20 %) and lung (17 %). We were not able to identify the type of metastases in 20 % of patients (Table 1) even though they were indicated as metastatic (AJCC stage IV) in SEER. Patients who received treatment were mostly diagnosed before the age of 80 years (80 %) and had a comorbidity score of 0 or 1 (82 %).

3.1 Treatment Lines and Sequences

Of the 4418 patients who received treatment, 1370 (31 %) received first-, second-, and third-line treatment, 1164 (26 %) received first and second-line treatment, and 1884 (43 %) received only first-line treatment. Table 2 shows the top ten

treatment regimens for first-, second-, and third-line treatment, along with duration of therapy. The most common first-line treatments were FOLFOX (oxaliplatin based) + bevacizumab (23 %), FOLFOX [oxaliplatin based (23 %)] alone and 5-FU + leucovorin (12 %) administered for a median duration of 188, 124, and 97 days, respectively (Table 2). In second-line treatment, FOLFOX (oxaliplatin based) + bevacizumab (18 %) was the most common regimen, followed by FOLFIRI (irinotecan based) + bevacizumab (14 %) and FOLFIRI (irinotecan based) alone (8 %). The median duration for FOLFOX (oxaliplatin based) + bevacizumab, FOLFIRI (irinotecan based) + bevacizumab, and FOLFIRI (irinotecan based) alone was observed to be 156, 155, and 111 days, respectively (Table 2). The most common regimens administered in third-line treatment (Table 2) were cetuximab + irinotecan (15 %), FOLFIRI (irinotecan based) + bevacizumab (13 %), and FOLFOX (oxaliplatin based) + bevacizumab (8 %).

Table 2 Treatment regimens and duration for metastatic colorectal cancer patients by line of therapy

Treatment line and regimens	Patients, *n* (%)	Duration (days)		
		Mean	SD	Median
First line	$N = 4418$			
FOLFOX + bevacizumab	1026 (23.2)	197.5	115.5	188
FOLFOX	1003 (22.7)	139.1	94.4	124
FU/LV	510 (11.5)	130.9	111.1	97
Oxaliplatin	325 (7.4)	126.9	92.3	104
FU/LV + bevacizumab	218 (4.9)	180.2	153.2	132
Oxaliplatin + bevacizumab	216 (4.9)	186.9	114.3	167
FOLFIRI + bevacizumab	194 (4.4)	208.7	158.5	177
FOLFIRI	183 (4.1)	149.2	114.0	136
Bevacizumab	151 (3.4)	186.3	144.0	145
FU	150 (3.4)	84.2	57.3	67
Others	442 (10.0)	135.8	100.0	111
Second line	$N = 2534$			
FOLFOX + bevacizumab	449 (17.7)	183.3	136.5	156
FOLFIRI + bevacizumab	353 (13.9)	198.0	157.2	155
FOLFIRI	202 (8.0)	128.0	83.5	111
Irinotecan	192 (7.6)	126.4	93.0	97
FU/LV + bevacizumab	175 (6.9)	181.1	143.1	139
FOLFOX	157 (6.2)	132.6	74.3	120
Cetuximab + irinotecan	139 (5.5)	155.5	98.8	135
Oxaliplatin + bevacizumab	127 (5.0)	164.3	113.9	128
Bevacizumab	116 (4.6)	194.1	207.3	133
FU/LV	98 (3.9)	144.9	128.8	118
Others	526 (20.8)	138.3	104.7	117
Third line	$N = 1370$			
Cetuximab + irinotecan	207 (15.1)	152.0	124.7	125
FOLFIRI + bevacizumab	184 (13.4)	195.0	158.8	153
FOLFOX + bevacizumab	104 (7.6)	162.1	104.6	138
FOLFIRI	91 (6.6)	119.7	105.3	96
Irinotecan	82 (6.0)	123.0	89.2	89
Cetuximab	78 (5.7)	131.5	137.3	101
FU/LV + bevacizumab	75 (5.5)	199.1	201.3	132
Bevacizumab	71 (5.2)	215.2	180.1	166
Bevacizumab + irinotecan	57 (4.2)	167.2	109.9	134
FOLFOX	51 (3.7)	120.8	71.5	98
Others	370 (30.7)	135.9	112	110

FU 5-fluorouracil, *FOLFOX* 5-FU + LV+ oxaliplatin, *FOLFIRI* 5-FU + LV + irinotecan, *LV* leucovorin, *SD* standard deviation

Table 3 Treatment sequences and duration by line of therapy for metastatic colorectal cancer patients who received at least two lines of treatment

First-line treatment	Second-line treatment	Third-line treatment	*N* (%)[a]	First line (days)		Second line (days)		Third line (days)	
			Total *N* = 2534	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
OX/IR	OX/IR + BV	Targeted biologic	275 (10.9)	114.2 (93.6)	86	195.2 (152.8)	160	188.6 (160.4)	146
OX/IR + BV	OX/IR + BV	Targeted biologic	199 (7.9)	204.7 (119.2)	195	187.4 (153.7)	143	165.0 (121.8)	132
OX/IR	OX/IR + BV	NA	178 (7.0)	110.2 (79.4)	83	169.7 (119.7)	136	NA	NA
OX/IR + BV	OX/IR + BV	NA	169 (6.7)	197.8 (141.7)	168	184.4 (163.0)	145	NA	NA
OX/IR	OX/IR	NA	127 (5.0)	153.3 (86.3)	140	127.2 (77.1)	111	NA	NA
OX/IR	OX/IR	Targeted biologic	99 (3.9)	152.2 (86.4)	145	130.0 (99.2)	97	138.3 (101.1)	115
OX/IR + BV	OX/IR	NA	97 (3.8)	208.0 (127.9)	187	122.8 (73.5)	105	NA	NA
OX/IR + BV	OX/IR	Targeted biologic	89 (3.5)	239.1 (150.9)	209	126.6 (87.1)	112	158.2 (123.7)	120
OX/IR + BV	OX/IR + EGFR	NA	66 (2.6)	199.4 (104.6)	183	141.0 (87.1)	126	NA	NA
OX/IR	OX/IR + BV	OX/IR	66 (2.6)	112.4 (98.6)	84	187.6 (116.4)	167	103.4 (62.8)	93
FU	OX/IR	NA	63 (2.5)	135.5 (102.8)	97	127.1 (69.2)	128	NA	NA
OX/IR + BV	OX/IR + EGFR	Targeted biologic	44 (1.7)	223.7 (118.9)	203	158.0 (98.2)	137	139.1 (96.4)	116
OX/IR + BV	FU + BV	NA	39 (1.5)	202.2 (115.4)	195	205.5 (129.6)	162	NA	NA
OX/IR + BV	FU + BV	Targeted biologic	34 (1.3)	171.3 (51.9)	188	149.9 (123.4)	104	163.1 (141.0)	137
OX/IR + BV	BV	NA	34 (1.3)	211.9 (93.5)	196	277.2 (330.9)	176	NA	NA
FU	OX/IR	Targeted biologic	31 (1.2)	137.9 (170.9)	90	133.0 (104.7)	104	162.4 (142.7)	129
OX/IR + BV	OX/IR + BV	OX/IR	30 (1.2)	183.6 (111.9)	157	184.6 (165.5)	125	92.8 (58.8)	69
OX/IR + BV	BV	Targeted biologic	30 (1.2)	225.1 (118.1)	194	201.2 (142.8)	167	172.4 (165.3)	113
OX/IR + BV	EGFR	NA	30 (1.2)	215.8 (85.0)	212	86.5 (54.9)	70	NA	NA
OX/IR	OX/IR + EGFR	NA	28 (1.1)	158.1 (70.9)	160	160.3 (102.8)	140	NA	NA
FU	OX/IR	OX/IR	27 (1.1)	110.4 (59.3)	89	150.7 (93.5)	118	136.4 (107.5)	103
FU	OX/IR + BV	Targeted biologic	27 (1.1)	105.5 (71.7)	81	200.3 (113.6)	202	117.4 (104.2)	84
FU	FU + BV	Targeted biologic	26 (1.0)	91.8 (63.0)	76	172.7 (143.8)	143	179.1 (127.6)	148
FU	FU + BV	NA	26 (1.0)	108.3 (106.7)	70	184.0 (183.4)	139	NA	NA

BV bevacizumab, *EGFR* epidermal growth factor receptor antibodies, i.e., cetuximab or panitumumab, *FU* 5-fluorouracil based, *NA* not applicable, *OX/IR* oxaliplatin or irinotecan based

[a] Adds up to 72 %, the remaining 28 % are sequence combinations received by less than 1 % of patients

Table 4 Characteristics of metastatic colorectal cancer patients receiving targeted biologic in first line and multivariable regression for factors associated with the receipt of targeted biologics

Characteristics	mCRC patients who received first-line treatment, *N* (column %)	mCRC patients who received first-line with targeted biologic, *N* (row %)	Receipt of first-line targeted biologic, multivariable OR (95 % CI)
Total	$N = 4418$	$N = 2077$	
Age (years)			
65–69	1333 (30.2)	664 (49.8)	Referent
70–74	1190 (26.9)	555 (46.6)	0.88 (0.74–1.04)
75–79	1022 (23.1)	451 (44.1)	0.77 (0.64–0.91)*
80–84	627 (14.2)	280 (44.7)	0.78 (0.64–0.96)*
85+	246 (5.6)	127 (51.6)	0.99 (0.74–1.33)
Race/ethnicity			
Caucasians	3693 (83.6)	1732 (46.9)	Referent
African Americans	382 (8.7)	181 (47.4)	0.94 (0.74–1.20)
Others	343 (7.8)	164 (47.8)	1.05 (0.82–1.34)
Sex			
Male	2318 (52.5)	992 (42.8)	Referent
Female	2100 (47.5)	1085 (51.7)	0.97 (0.85–1.10)
Marital status			
Married	2571 (58.2)	1190 (46.3)	Referent
Unmarried	1718 (38.9)	828 (48.2)	1.09 (0.96–1.25)
Unknown	129 (2.9)	59 (45.7)	1.07 (0.73–1.56)
Tumor grade			
Well/moderately differentiated	2554 (57.8)	1196 (46.8)	Referent
Poorly/undifferentiated	1148 (26.0)	542 (47.2)	1.04 (0.90–1.21)
Unknown	716 (16.2)	339 (47.3)	1.03 (0.86–1.23)
Comorbidity Scores			
0	2357 (53.4)	1122 (47.6)	Referent
1	1280 (29.0)	585 (45.7)	0.85 (0.73–0.98)*
2	430 (9.7)	211 (49.1)	1.00 (0.80–1.25)
≥3	351 (7.9)	159 (45.3)	0.80 (0.63–1.01)
Metastasis			
Liver	2969 (67.2)	1476 (49.7)	1.14 (0.93–1.38)
Lung	730 (16.5)	358 (49.0)	1.06 (0.89–1.26)
Abdomen	873 (19.8)	423 (48.5)	1.00 (0.83–1.20)
Other	696 (15.8)	304 (43.7)	0.77 (0.64–0.92)*
Unknown	747 (16.9)	283 (37.9)	0.68 (0.52–0.88)*
Cancer site			
Colon	3276 (74.2)	1618 (49.4)	Referent
Rectal	1142 (25.9)	459 (40.2)	0.69 (0.59–0.80)*
SES (poverty)			
1st (low SES)	989 (22.4)	457 (46.2)	Referent
2nd	1070 (24.2)	504 (47.1)	1.07 (0.89–1.29)
3rd	1139 (25.8)	549 (48.2)	1.13 (0.93–1.37)
4th (high SES)	1220 (27.6)	567 (46.5)	1.10 (0.89–1.35)
Region			
Midwest	566 (12.8)	247 (43.6)	Referent
North east	1000 (22.6)	443 (44.3)	0.95 (0.76–1.20)
South	1035 (23.4)	533 (51.5)	1.31 (1.05–1.64)*

Table 4 continued

Characteristics	mCRC patients who received first-line treatment, *N* (column %)	mCRC patients who received first-line with targeted biologic, *N* (row %)	Receipt of first-line targeted biologic, multivariable OR (95 % CI)
West	2969 (67.2)	854 (47.0)	1.06 (0.86–1.32)
Urban/rural			
Less urban/rural	477 (10.8)	210 (44.0)	Referent
Urban	268 (6.1)	126 (47.0)	1.24 (0.90–1.71)
Metro	3672 (83.1)	1741 (47.4)	1.29 (1.03–1.61)*
Year of diagnosis			
2004	731 (16.6)	112 (15.3)	Referent
2005	696 (15.8)	368 (52.9)	6.55 (5.09–8.44)*
2006	780 (17.7)	447 (57.3)	7.62 (5.93–9.78)*
2007	722 (16.3)	391 (54.2)	6.70 (5.20–8.62)*
2008	752 (17.0)	376 (50.0)	5.80 (4.51–7.45)*
2009	737 (16.7)	383 (52.0)	6.21 (4.83–7.98)*

CI confidence interval, *mCRC* metastatic colorectal cancer, *OR* odds ratio, *SES* socio-economic status

* Significant at $\alpha = 0.05$

Treatment sequences administered to patients, along with durations, are shown in Table 3. The most common treatment sequence was first-line oxaliplatin or irinotecan followed by second-line oxaliplatin or irinotecan + bevacizumab followed by a third-line targeted biologic (OI-OIB-TB). This sequence was given to nearly 11 % of patients, with a median of 86 days first-line, 160 days second-line, and 146 days third-line treatment (Table 3). The second most common sequence (8 %) was first-line oxaliplatin or irinotecan + bevacizumab (median 195 days) followed by second-line oxaliplatin or irinotecan + bevacizumab (median 143 days) followed by a third-line targeted biologic (median 132 days; OIB-OIB-TB). Other common sequences (Table 3) received by patients were first-line oxaliplatin or irinotecan followed by second-line oxaliplatin or irinotecan + bevacizumab (OI-OIB) and first-line oxaliplatin or irinotecan + bevacizumab followed by second-line oxaliplatin or irinotecan + bevacizumab (OIB-OIB). For sequences OI-OIB and OIB-OIB, no third-line treatment was observed. Sequences with bevacizumab in first line were observed to be administered for a relatively longer duration of time than sequences without bevacizumab in first line (Table 3).

3.2 Factors Associated with Receipt of Targeted Biologic and Treatment Sequences

Characteristics of patients receiving targeted biologics at first-line therapy, along with logistic regression results, are shown in Table 4. Of patients who received first-line therapy, 47 % also received a targeted biologic (Table 4). As compared with patients aged 65–69 years, patients aged 75–79 or 80–84 years were less likely to receive targeted biologics (Table 4). Patients with a comorbidity score of 1 and with metastatic rectal cancer were also less likely to receive a targeted biologic at first line. Patients residing in the South as well as in metropolitan areas were relatively more likely to receive targeted biologics and, as expected, utilization of targeted biologics was higher among patients diagnosed in the years 2005–2009 than among those diagnosed in 2004 (Table 4).

Table 5 shows the univariate comparison of characteristics of patients who received the commonly administered targeted biologic-based treatment sequences using the chi-squared statistic. In the univariate analysis between treatment sequences, statistically significant differences were only observed with regards to comorbidity score, other metastasis, and year of diagnosis (Table 5). Factors associated with commonly administered treatment sequences, assessed using multinomial logistic regression with treatment sequence (four categories) as the dependent variable and OI-OIB as the reference category, are presented in Table 6. Patients aged 75–79 years were significantly less likely to receive three-line treatment sequences, i.e., OIB-OIB-TB and OI-OIB-TB, than an OI-OIB treatment sequence (Table 6). Female mCRC patients were observed to be 0.37 times less likely to receive an OIB-OIB-TB treatment sequence, and patients with a comorbidity score of 1 (vs. 0) were less likely to receive OIB-OIB-TB, OI-OIB-TB, and OIB-OIB treatment sequences (Table 6).

Table 5 Characteristics of metastatic colorectal cancer patients by commonly administered treatment sequences

Characteristics	Treatment sequences				
	OI-OIB-TB ($N = 275$)	OIB-OIB-TB ($N = 199$)	OI-OIB ($N = 178$)	OIB-OIB ($N = 169$)	P value
Age (years)					0.0600
65–69	108 (39.3)	81 (40.7)	56 (31.5)	56 (33.1)	
70–74	84 (30.6)	72 (36.2)	57 (32.0)	49 (29.0)	
75–79	56 (20.4)	32 (16.1)	47 (26.4)	38 (22.5)	
≥80	27 (9.8)	14 (7.0)	18 (10.1)	26 (15.4)	
Race/ethnicity					0.4093
Caucasian	235 (85.5)	173 (86.9)	144 (80.9)	142 (84.0)	
Other	40 (14.6)	26 (13.1)	34 (19.1)	27 (16.0)	
Sex					0.1751
Male	161 (58.6)	113 (56.8)	86 (48.3)	91 (53.9)	
Female	114 (41.5)	86 (43.2)	92 (51.7)	78 (46.2)	
Marital status					0.2983
Married	189 (68.7)	125 (62.8)	114 (64.0)	102 (60.4)	
Unmarried/unknown	86 (31.3)	74 (37.2)	64 (36.0)	67 (39.6)	
Tumor grade					0.7064
Well/moderately differentiated	176 (64.0)	121 (60.8)	105 (59.0)	107 (63.3)	
Poorly/undifferentiated/unknown	99 (36.0)	78 (39.2)	73 (41.0)	62 (36.7)	
Comorbidity scores					0.0129*
0	173 (62.9)	123 (61.8)	84 (47.2)	97 (57.4)	
1	71 (25.8)	49 (24.6)	69 (38.8)	44 (26.0)	
≥2	31 (11.3)	27 (13.6)	25 (14.0)	28 (16.6)	
Metastasis					
Liver	206 (74.9)	143 (71.9)	126 (70.8)	128 (75.7)	0.6458
Lung	41 (14.9)	31 (15.6)	22 (12.4)	26 (15.4)	0.8079
Abdomen	57 (20.7)	37 (18.6)	31 (17.4)	25 (14.8)	0.4608
Other	43 (15.6)	19 (9.6)	34 (19.1)	18 (10.7)	0.0248*
Unknown	37 (13.5)	29 (14.6)	31 (17.4)	24 (14.2)	0.7010
Cancer site					0.0829
Colon	194 (70.6)	155 (77.9)	128 (71.9)	135 (79.9)	
Rectal	81 (29.5)	44 (22.1)	50 (28.1)	34 (20.1)	
SES (poverty)					0.2732
1st (low SES)	62 (22.6)	41 (20.6)	34 (19.1)	41 (24.3)	
2nd	56 (20.4)	53 (26.6)	48 (27.0)	37 (21.9)	
3rd	69 (25.1)	53 (26.6)	43 (24.2)	54 (32.0)	
4th (high SES)	88 (32.0)	52 (26.1)	53 (29.8)	37 (21.9)	
Region					0.0915
Midwest	31 (11.3)	18 (9.1)	20 (11.2)	15 (8.9)	
North east	55 (20.0)	41 (20.6)	38 (21.4)	36 (21.3)	
South	45 (16.4)	45 (22.6)	49 (27.5)	48 (28.4)	
West	144 (52.4)	95 (47.7)	71 (39.9)	70 (41.4)	
Urban/rural					0.1894
Less urban/rural	22 (8.0)	18 (9.1)	19 (10.7)	24 (14.2)	
Metro/urban	253 (92.0)	181 (91.0)	159 (89.3)	145 (85.8)	
Year of diagnosis					<0.0001*
2004–2005	109 (39.6)	52 (26.1)	56 (31.5)	40 (23.7)	
2006–2007	90 (32.7)	95 (47.7)	48 (27.0)	56 (33.1)	
2008–2009	76 (27.6)	52 (26.1)	74 (41.6)	73 (43.2)	

Data are presented as n (%) unless otherwise indicated

OI-OIB first-line oxaliplatin or irinotecan followed by second-line oxaliplatin or irinotecan + bevacizumab, *OIB-OIB* first-line oxaliplatin or irinotecan + bevacizumab followed by second-line oxaliplatin or irinotecan + bevacizumab, *OI-OIB-TB* OI-OIB followed by a third-line targeted biologic, *OIB-OIB-TB* OIB-OIB followed by a third-line targeted biologic, *SES* socio-economic status

* Significant at $\alpha = 0.05$

Table 6 Multinomial logistic regression for factors associated with receipt of commonly administered treatment sequences

Factors	OI-OIB-TB	OIB-OIB-TB	OIB-OIB
Age (years)			
65–69	Referent	Referent	Referent
70–74	0.87 (0.52–1.45)	0.77 (0.47–1.25)	0.89 (0.52–1.54)
75–79	0.43 (0.24–0.77)*	0.59 (0.35–1.00)*	0.78 (0.43–1.41)
80+	0.45 (0.20–1.01)	0.73 (0.36–1.50)	1.36 (0.65–2.85)
Race/ethnicity			
Caucasian	Referent	Referent	Referent
Other	0.54 (0.29–1.00)	0.63 (0.37–1.10)	0.74 (0.41–1.36)
Sex			
Male	Referent	Referent	Referent
Female	0.63 (0.41–0.99)*	0.67 (0.44 – 1.00)	0.76 (0.48–1.19)
Marital status			
Married	Referent	Referent	Referent
Unmarried/unknown	1.29 (0.81–2.05)	0.94 (0.61–1.45)	1.29 (0.81–2.06)
Tumor grade			
Well/moderately differentiated	Referent	Referent	Referent
Poorly/undifferentiated/unknown	0.94 (0.6–1.46)	0.83 (0.55–1.26)	0.91 (0.57–1.44)
Comorbidity scores			
0	Referent	Referent	Referent
1	0.45 (0.28–0.72)*	0.52 (0.34–0.81)*	0.51 (0.31–0.84)*
≥2	0.61 (0.32–1.18)	0.57 (0.31–1.06)	0.92 (0.48–1.74)
Metastasis (yes vs. no)			
Liver	0.77 (0.36–1.66)	1.16 (0.58–2.36)	1.00 (0.45–2.25)
Lung	1.36 (0.72–2.57)	1.21 (0.67–2.18)	1.38 (0.72–2.65)
Abdomen	1.03 (0.53–1.98)	1.28 (0.71–2.30)	0.84 (0.43–1.67)
Other	0.39 (0.20–0.75)*	0.83 (0.47–1.44)	0.50 (0.26–0.98)*
Unknown	0.56 (0.21–1.47)	0.87 (0.36–2.15)	0.65 (0.23–1.80)
Cancer site			
Colon	Referent	Referent	Referent
Rectal	0.62 (0.38–1.03)	1.01 (0.65–1.59)	0.59 (0.35–1.00)*
SES (poverty)			
1st (low SES)	Referent	Referent	Referent
2nd	0.92 (0.48–1.77)	0.55 (0.30–1.02)	0.70 (0.36–1.37)
3rd	0.88 (0.44–1.76)	0.65 (0.35–1.23)	1.09 (0.55–2.16)
4th (high SES)	0.69 (0.34–1.41)	0.69 (0.36–1.31)	0.58 (0.28–1.21)
Region			
Midwest	Referent	Referent	Referent
North east	1.38 (0.60–3.19)	0.87 (0.41–1.84)	1.59 (0.66–3.79)
South	0.88 (0.39–2.02)	0.51 (0.24–1.07)	1.22 (0.53–2.84)
West	1.43 (0.66–3.10)	1.17 (0.59–2.32)	1.37 (0.61–3.09)
Urban/rural			
Less urban/rural	Referent	Referent	Referent
Metro/urban	1.25 (0.57–2.74)	1.25 (0.59–2.61)	0.76 (0.36–1.62)
Year of diagnosis			
2004–2005	Referent	Referent	Referent
2006–2007	2.55 (1.48–4.40)	1.17 (0.71–1.93)	1.75 (0.97–3.14)
2008–2009	0.84 (0.49–1.45)	0.59 (0.36–0.94)*	1.50 (0.87–2.57)

Data are presented as odds ratio (95 % confidence interval)

OIB-OIB first-line oxaliplatin or irinotecan + bevacizumab followed by second-line oxaliplatin or irinotecan + bevacizumab, *OI-OIB-TB* OI-OIB followed by a third-line targeted biologic, *OIB-OIB-TB* OIB-OIB followed by a third-line targeted biologic, *SES* socio-economic status

* Significant at $\alpha = 0.05$

Metastatic rectal cancer patients were also less likely to receive an OIB-OIB treatment sequence.

4 Discussion

Important advances in treatments for mCRC patients over the last decade have provided clinicians with a multitude of treatment options. The addition of oxaliplatin or irinotecan to 5-FU/LV increased the median survival up to 19.5 months as compared with 14.8 months with 5-FU/LV alone [48, 49]. Moreover, the availability of targeted biologics such as bevacizumab has been found to increase the overall survival to as high as 25.5 months [50]. Thus, irinotecan- or oxaliplatin-based chemotherapy regimens have been recommended, and the addition of bevacizumab has been considered a reasonable option [16, 17]. Sequencing of these chemotherapies and targeted biologics is equally important, as treatments received during the first few months of the diagnosis are critical [7, 51, 52], but correct sequencing of treatments could be challenging, and evidence of current utilization patterns may be informative [16, 17]. We used community-based SEER-Medicare linked data to identify the treatment patterns, sequences, and associated factors for mCRC patients diagnosed from 2004 to 2009.

FOLFOX- or oxaliplatin-based regimens were most frequently administered to mCRC patients as their first-line treatment, which is consistent with previous findings among relatively younger patients [6, 11, 38]. Bikov et al. [53] found 5-FU-based treatment to be the most common therapy and oxaliplatin-based therapy as the second most common treatment; however, their analyses only included elderly metastatic colon cancer patients diagnosed until 2007 [53], and prescribing patterns may have changed in the subsequent years. The observation that FOLFOX- or oxaliplatin-based regimens are preferred as first-line treatment is consistent with their relatively better toxicity profile as compared with FOLFIRI- or irinotecan-based regimens [50, 54, 55]. However, a recent systematic review concluded that first-line oxaliplatin- or irinotecan-based regimens are equally efficacious for mCRC patients [16], and the efficacy and safety of these treatments for elderly patients has been found to be comparable to that in younger patients [15]. Nearly half of the patients had a targeted biologic as a part of their first-line treatment, with a significant increase in patients receiving a targeted biologic in the last decade as shown by the results of our study and that by Abrams et al. [38]. As the evidence supporting the survival benefit of targeted biologics for elderly patients becomes more widespread, elderly mCRC patients may often receive targeted biologics during first-line treatment. Alternatively, we also found that patients in older age groups, 75–79 and 80–84 years, and patients with higher comorbidity scores had a lower likelihood of receiving a targeted biologic in first line, which reflects concerns with regards to prevalence of more comorbidities, cardiovascular, and cerebrovascular toxicities, and less access to specialist care in these older patients [14, 56, 57].

Consistent with previous findings, FOLFIRI- or irinotecan-based regimens were relatively more common in second-line treatment, and cetuximab + irinotecan was the most common regimen at the third line [11, 53]. Treatment sequencing showed mCRC patients receiving treatments (first to third line) in various sequences. The two most common sequences consisted of patients receiving three lines of treatment, with the difference being the receipt of bevacizumab in the first line. Bevacizumab was commonly observed to be administered as second-line treatment in combination with chemotherapy among patients who had previously been treated with bevacizumab in the first line. Previous studies by Abrams et al. [38] and Hess et al. [11] found similar results, but treatment with bevacizumab in second line following progression with bevacizumab in first line was not recommended during the time of the study. However, based on some recent studies, it has now been included in the National Comprehensive Cancer Network guidelines [58–60]. Our results show that mCRC patients receive treatments in sequences that may not necessarily be recommended or clinically shown to have survival benefit. While clinical trials [19, 20] are underway to definitively examine the comparative efficacy of different treatment sequences, comparative-effectiveness studies using community-level data may provide evidence to better inform clinicians. Additionally, as patients may receive a treatment continuum to prolong their survival, the overall cost to treat mCRC patients would increase considerably and thereby necessitate economic evaluation of treatment sequences.

Study results should be interpreted in light of the following limitations. First, identification of lines of treatment administered was limited to the first three lines. Since, 80–90 % of mCRC patients receive a maximum of three lines of treatment [11, 61], this limitation should not substantially reduce the applicability of our findings. Second, only drugs that require administration by a healthcare provider were considered for our analysis, and orally administered drugs (e.g., capecitabine) were not included because Medicare part D data were not available. A previous study by Hess et al. [11] found that capecitabine was administered to 8.9 % at first line, 4.9 % at second line, and 6.9 % at third line. Third, we only included patients with a gap between treatment lines of less than 1 year. However, additional analyses including these patients showed results similar to our primary analyses (Tables 2 and 3 in the ESM). Fourth, the factors assessed were

limited to patient and tumor characteristics available from the SEER-Medicare dataset and did not include patient or physician preferences, which are known to influence treatment receipt. Finally, findings of the study are only generalizable to mCRC patients aged ≥65 years who are not enrolled in Medicare Part C plans.

5 Conclusion

Based on the study results, we observed that elderly mCRC patients receive a treatment continuum with multiple drugs administered across various lines of treatment. As recommended and similar to studies in younger populations, oxaliplatin- or irinotecan-based regimens were the most common chemotherapies, with bevacizumab the most common targeted biologic administered. Treatment sequencing studies using real-world data among overall and elderly mCRC populations are limited, and future studies should evaluate the utilization of treatment sequences using other national data sources. Additionally, studies assessing the comparative and cost effectiveness of the most common treatment sequences identified should be conducted to provide evidence-based recommendations for clinicians and policy makers.

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Compliance with Ethical Standards

Ethical approval The study was determined as exempt by the Committee for the Protection of Human Subjects at the University of Texas Health Science Centre at Houston.

Conflicts of interest Rohan C. Parikh, Xianglin L. Du, Robert O. Morgan and David R. Lairson have no conflicts of interest that are directly relevant to the content of this study

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