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.
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

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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. Afiblercept, 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 Material (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

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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

| Table 1 | Characteristics of metastatic colorectal cancer patients and patients |
|---------|------------------------------------------------------------------|

**Table 1 continued**

| Characteristics | All MCRC pts ($n = 9819$) | Pts with mCRC who received either CTX or targeted therapy ($n = 4418$) |
|----------------|----------------------------|------------------------------------------------------------------|
| 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

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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                 |                |      |    |        |
| 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                |                |      |    |        |
| 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 |
| FOLFIRI                    | 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                 |                |      |    |        |
| 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 |
| FOLFIRI                    | 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

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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 (%)                 | Mean (SD)            | Median |
| Total                |                       |                      |
| BV                   | 105 (2.8)             | 86                   | 146    |
| OX/IR                | 187.4 (15.7)          | 150                  | 122.8  |
|                    | 204.7 (17.0)          | 151                  | 116.4  |
| Oxaliplatin, EGFR    | 204.7 (17.0)          | 151                  | 116.4  |
| FU                   | 253 (10.9)            | 114.2 (93.6)         | 146    |
| FU + BV              | 187.4 (15.7)          | 150                  | 122.8  |
| FU + BV              | 204.7 (17.0)          | 151                  | 116.4  |
| BV                   | 105 (2.8)             | 86                   | 146    |
| OX/IR                | 187.4 (15.7)          | 150                  | 122.8  |
|                    | 204.7 (17.0)          | 151                  | 116.4  |
| Oxaliplatin, EGFR    | 204.7 (17.0)          | 151                  | 116.4  |
| FU                   | 253 (10.9)            | 114.2 (93.6)         | 146    |
| FU + BV              | 187.4 (15.7)          | 150                  | 122.8  |
| FU + BV              | 204.7 (17.0)          | 151                  | 116.4  |

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)*                                                |

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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 (OIB-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 (OIB-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)                  |                                               |                      |                      |                  |                  |         |
| 65–69                        |                                               | 108 (39.3)           | 81 (40.7)            | 56 (31.5)        | 56 (33.1)        | 0.0600  |
| 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               |                                               |                      |                      |                  |                  |         |
| Caucasian                    |                                               | 235 (85.5)           | 173 (86.9)           | 144 (80.9)       | 142 (84.0)       | 0.4093  |
| Other                        |                                               | 40 (14.6)            | 26 (13.1)            | 34 (19.1)        | 27 (16.0)        |         |
| Sex                          |                                               |                      |                      |                  |                  |         |
| Male                         |                                               | 161 (58.6)           | 113 (56.8)           | 86 (48.3)        | 91 (53.9)        | 0.1751  |
| Female                       |                                               | 114 (41.5)           | 86 (43.2)            | 92 (51.7)        | 78 (46.2)        |         |
| Marital status               |                                               |                      |                      |                  |                  |         |
| Married                      |                                               | 189 (68.7)           | 125 (62.8)           | 114 (64.0)       | 102 (60.4)       | 0.2983  |
| Unmarried/unknown            |                                               | 86 (31.3)            | 74 (37.2)            | 64 (36.0)        | 67 (39.6)        |         |
| Tumor grade                  |                                               |                      |                      |                  |                  |         |
| Well/moderately differentiated|                                               | 176 (64.0)           | 121 (60.8)           | 105 (59.0)       | 107 (63.3)       | 0.7064  |
| Poorly/undifferentiated/unknown|                                | 99 (36.0)            | 78 (39.2)            | 73 (41.0)        | 62 (36.7)        |         |
| Comorbidity scores           |                                               |                      |                      |                  |                  |         |
| 0                            |                                               | 173 (62.9)           | 123 (61.8)           | 84 (47.2)        | 97 (57.4)        | 0.0129* |
| 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                  |                                               |                      |                      |                  |                  |         |
| Colon                        |                                               | 194 (70.6)           | 155 (77.9)           | 128 (71.9)       | 135 (79.9)       | 0.0829  |
| Rectal                       |                                               | 81 (29.5)            | 44 (22.1)            | 50 (28.1)        | 34 (20.1)        |         |
| SES (poverty)                |                                               |                      |                      |                  |                  |         |
| 1st (low SES)                |                                               | 62 (22.6)            | 41 (20.6)            | 34 (19.1)        | 41 (24.3)        | 0.2732  |
| 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                       |                                               |                      |                      |                  |                  |         |
| Midwest                      |                                               | 31 (11.3)            | 18 (9.1)             | 20 (11.2)        | 15 (8.9)         | 0.0915  |
| 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            |                                               |                      |                      |                  |                  |         |
| 2004–2005                    |                                               | 109 (39.6)           | 52 (26.1)            | 56 (31.5)        | 40 (23.7)        | <0.0001*|
| 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 $p = 0.05$
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)                          | Referent  | Referent   | Referent|
| 65–69                                |           |            |         |
| 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                       | Referent  | Referent   | Referent|
| Caucasian                            |           |            |         |
| Other                                | 0.54 (0.29–1.00) | 0.63 (0.37–1.10) | 0.74 (0.41–1.36) |
| Sex                                  | Referent  | Referent   | Referent|
| Male                                 |           |            |         |
| Female                               | 0.63 (0.41–0.99)* | 0.67 (0.44 – 1.00) | 0.76 (0.48–1.19) |
| Marital status                       | Referent  | Referent   | Referent|
| Married                              |           |            |         |
| Unmarried/unknown                    | 1.29 (0.81–2.05) | 0.94 (0.61–1.45) | 1.29 (0.81–2.06) |
| Tumor grade                          | Referent  | Referent   | Referent|
| Well/moderately differentiated       |           |            |         |
| Poorly/undifferentiated/unknown      | 0.94 (0.6–1.46) | 0.83 (0.55–1.26) | 0.91 (0.57–1.44) |
| Comorbidity scores                   | Referent  | Referent   | Referent|
| 0                                    |           |            |         |
| 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                          | Referent  | Referent   | Referent|
| Colon                                |           |            |         |
| Rectal                               | 0.62 (0.38–1.03) | 1.01 (0.65–1.59) | 0.59 (0.35–1.00)* |
| SES (poverty)                        | Referent  | Referent   | Referent|
| 1st (low SES)                        |           |            |         |
| 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                               | Referent  | Referent   | Referent|
| Midwest                              |           |            |         |
| 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                          | Referent  | Referent   | Referent|
| Less urban/rural                     |           |            |         |
| Metro/urban                          | 1.25 (0.57–2.74) | 1.25 (0.59–2.61) | 0.76 (0.36–1.62) |
| Year of diagnosis                    | Referent  | Referent   | Referent|
| 2004–2005                            |           |            |         |
| 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)

OI-OIB-TB 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 α = 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

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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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