Burden of Illness in Metastatic Colorectal Cancer

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Background

- Colorectal cancer (CRC) is the third most commonly diagnosed cancer globally with an increasing prevalence and a poor prognosis.[1-3]
- Almost 50% of patients with initially localized CRC will develop metastatic CRC (mCRC),[4] and clinical outcomes for these patients are poor, with a 5-year survival rate of <20%.[5]
- Current standard of care therapies for patients with mCRC have limited efficacy and are associated with substantial toxicity, especially for patients with mCRC refractory to standard therapies.[6]
- Targeted agents may improve survival and safety outcomes compared with traditional chemotherapeutic approaches in patients with mCRC expressing actionable biomarkers.[6,7]
- The objective of this study was to evaluate clinical outcomes and associated healthcare costs by line of therapy among patients with mCRC.

Methods

- This retrospective analysis of Merative™ MarketScan® Commercial and Medicare Supplemental Administrative health claims databases was conducted in adult patients with mCRC initiating systemic therapy between January 1, 2017 and September 30, 2021.
- Demographic and clinical characteristics of patients at baseline were described.
- Key outcomes were treatment patterns, time to discontinuation (TTD), time to next treatment (TTNT), healthcare resource utilization (HCRU), and costs (per-patient-per-month [PPPM] and per visit for inpatient and emergency department [ED] visits only) evaluated for each line of therapy: first-line (1L), second-line (2L), third-line (3L), and fourth-line plus (4L+).
  - Time-to-event analyses were conducted using the Kaplan-Meier method.

Results

Patient characteristics

- In the database, of 63,271 patients with CRC during the study period, 24,253 had evidence of metastatic disease. Of these, 3,455 met all inclusion criteria and received 1L treatment.
- Baseline demographic and clinical characteristics were similar across groups stratified by line of therapy (**Table 1**).

Table 1. Baseline demographics and clinical characteristics for patients with mCRC by line of therapy

Characteristic	1L (n=3,455)	2L (n=1,082)	3L (n=372)	4L+ (n=185)
Age at index[a], years, median (IQR)	56 (50–63)	57 (50–62)	56 (49–61)	55 (50–58)
Male, n (%)	1,884 (54.5)	622 (57.5)	213 (57.3)	111 (60.0)
USA region, n (%)				
North Central	836 (24.2)	244 (22.6)	87 (23.4)	45 (24.3)
Northeast	502 (14.5)	168 (15.5)	60 (16.1)	31 (16.8)
South	1,687 (48.8)	547 (50.6)	179 (48.1)	88 (47.6)
West	429 (12.4)	122 (11.3)	46 (12.4)	21 (11.4)
Insurance type, n (%)				
Commercial	2,948 (85.3)	923 (85.3)	331 (89.0)	178 (96.2)
Medicare	507 (14.7)	159 (14.7)	41 (11.0)	7 (3.8)
Follow-up from 1L[b], months, median (IQR)	14.1 (8.7–24.3)	19.1 (11.8–29.5)	25.5 (17.9–37.0)	32.2 (24.2–47.5)
Primary site, n (%)				
Left	1,292 (37.4)	366 (33.8)	129 (34.7)	61 (33.0)
Right	694 (20.1)	199 (18.4)	64 (17.2)	25 (13.5)
Transverse	151 (4.4)	37 (3.4)	9 (2.4)	3 (1.6)
Indeterminate/other	1,260 (37)	405 (43)	167 (45)	93 (50)
Conflicting	58 (2)	15 (1)	3 (2)	3 (2)
Metastatic site[c], n (%)				
Liver	561 (16.2)	553 (51.1)	216 (58.1)	117 (63.2)
Lung	220 (6.4)	332 (29.8)	145 (39.0)	79 (42.7)
Lymph	1,724 (49.9)	284 (26.2)	96 (25.8)	43 (23.2)
Peritoneum	235 (6.8)	186 (17.2)	56 (15.1)	18 (9.7)
CCI, mean (SD)	0.9 (1.3)	1.2 (1.5)	1.1 (1.5)	1.2 (1.5)
CCI, categorical, n (%)				
0	1,835 (53.1)	449 (41.5)	165 (44.4)	80 (43.2)
1	939 (27.2)	344 (31.8)	110 (29.6)	48 (25.9)
2	367 (10.6)	134 (12.4)	37 (9.9)	21 (11.4)
3+	314 (9.1)	155 (14.3)	60 (16.1)	36 (19.5)

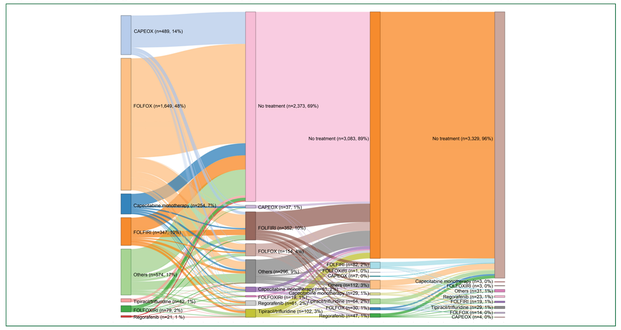
[a]Start of 1L therapy.
[b]Time period from start of 1L therapy to end of follow-up.
[c]Not mutually exclusive (ie, patients can have ≥1 metastatic site).
1L, first-line; 2L, second-line; 3L, third-line; 4L+, fourth-line and beyond; CCI, Charlson Comorbidity Index; IQR, interquartile range; mCRC, metastatic colorectal cancer; SD, standard deviation.

- Median (IQR) follow-up was 14.1 (8.7–24.3), 19.1 (11.9–29.5), 25.5 (17.9–37.0), and 32.2 (24.2–47.5) months for 1L, 2L, 3L, and 4L+, respectively.
- Over one-third of patients had a left-sided primary tumor site, and compared with 1L, a greater proportion of patients in the 2L and 3L settings had hepatic, pulmonary, and peritoneal metastases.
- In later lines of therapy, patients tended to have a higher comorbidity burden (Charlson Comorbidity Index [CCI] score ≥3: 1L, 9.1%; 2L, 14.3%; 3L, 16.1%; 4L+, 19.5%).

Treatment regimens

- A Sankey diagram showing treatment patterns in patients with mCRC is shown in **Figure 1**.

Figure 1. Sankey diagram for chemotherapy-based treatment patterns among patients with mCRC



CAPEOX, capecitabine and oxaliplatin; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, irinotecan.

- FOLFOX- and FOLFIRI-based regimens were both among the 3 most common regimens in the 1L and 2L settings (**Table 2**). FOLFIRI continued to be the most common 3L, and 3rd most common 4L+ regimen.
- 1L patients on FOLFOX and FOLFIRI who proceeded to 2L therapy commonly switched to additional FOLFOX and FOLFIRI regimens.

Table 2. Frequency of chemotherapy-based regimens for the three most commonly used regimens among patients with mCRC by line of therapy

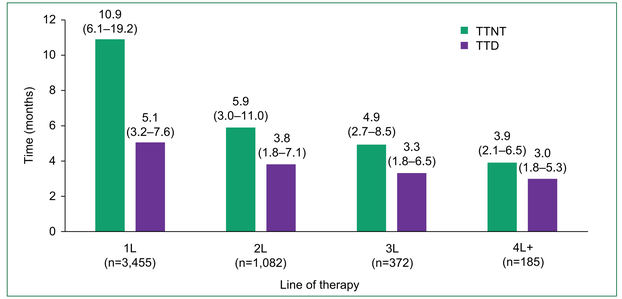
Regimen	Targeted therapy	Anti-VEGF	Anti-EGFR
1L Overall (n=3,455)	1,162 (33.6%)	946 (27.4%)	267 (7.7%)
Most commonly used regimens in 1L			
FOLFOX (n=1,649)	388 (23.5%)	350 (21.2%)	38 (2.3%)
CAPEOX (n=489)	43 (8.8%)	42 (8.6%)	1 (0.2%)
FOLFIRI (n=347)	277 (79.8%)	222 (63.9%)	71 (20.4%)
2L Overall (n=1,082)	686 (63.4%)	482 (44.5%)	228 (21.1%)
Most commonly used regimens in 2L			
FOLFIRI (n=352)	300 (85.2%)	233 (66.2%)	78 (22.1%)
FOLFOX (n=154)	93 (60.4%)	77 (50.0%)	16 (10.4%)
Tipiracil/trifluridine (n=102)	11 (10.8%)	7 (6.9%)	4 (3.9%)
3L Overall (n=372)	194 (52.2%)	110 (29.6%)	87 (23.4%)
Most commonly used regimens in 3L			
FOLFIRI (n=82)	67 (81.7%)	48 (58.5%)	20 (24.4%)
Tipiracil/trifluridine (n=64)	5 (7.8%)	5 (7.8%)	0 (0%)
Regorafenib (n=47)	1 (2.1%)	0 (0%)	1 (2.1%)
4L+ Overall (n=185)	97 (52.4%)	62 (33.5%)	40 (21.6%)
Most commonly used regimens in 4L			
Tipiracil/trifluridine (n=29)	6 (20.7%)	6 (20.7%)	1 (3.4%)
Regorafenib (n=23)	2 (8.7%)	2 (8.7%)	0 (0%)
FOLFIRI (n=19)	16 (84.2%)	11 (57.9%)	5 (26.3%)

1L, first-line; 2L, second-line; 3L, third-line; 4L+, fourth line and beyond; CAPEOX, capecitabine and oxaliplatin; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor.

Median TTD and TTNT

- Median TTNT and TTD were longest in patients receiving 1L treatment and decreased across lines of therapy (**Figure 2**).

Figure 2. Median TTNT and TTD (IQR) for patients with mCRC by line of therapy



1L, first-line; 2L, second-line; 3L, third-line; 4L+, fourth-line and beyond; ED, emergency department; mCRC, metastatic colorectal cancer; TTD, time to discontinuation; TTNT, time to next treatment.

HCRU and costs

- The proportion of patients who experienced ≥1 inpatient and ≥1 ED visit during 2L treatment was 17.0% (n=184) and 24.5% (n=265), respectively (**Table 3**).
- During 2L treatment, patients had a mean (SD) of 3.7 (7.3) mCRC treatment–related outpatient visits per month; mean (SD) number of other outpatient visits and mCRC-related pharmacy visits were 7.6 (7.4) and 1.7 (6.2), respectively.
- For patients receiving 2L therapy, mean (SD) PPPM inpatient and ED visit costs were $1,509 ($6,070) and $1,299 ($28,429), respectively; overall, the mean (SD) total costs for patients on 2L treatment were $63,779 ($145,664).
- Higher PPPM costs for mCRC-related pharmacy and total costs were observed in later lines of therapy.

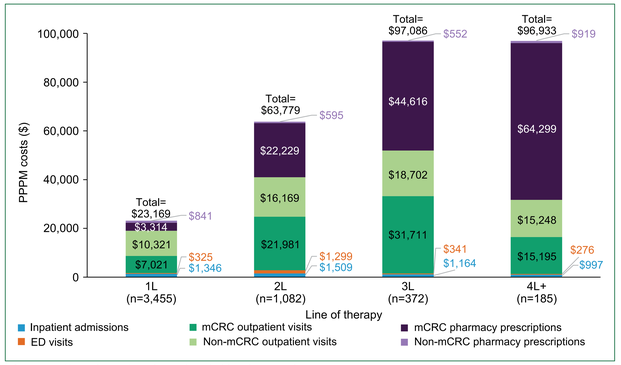
Table 3. HCRU and costs[a] by line of therapy

	1L (n=3,455)	2L (n=1,082)	3L (n=372)	4L+ (n=185)
HCRU				
≥1 inpatient admission during treatment, n (%)	630 (18.2)	184 (17.0)	53 (14.2)	16 (8.6)
≥1 ED visit during treatment[b], n (%)	940 (27.2)	265 (24.5)	91 (24.5)	35 (18.9)
mCRC-related outpatient visits[c], mean (SD)	2.4 (4.0)	3.7 (7.3)	3.8 (7.9)	2.6 (5.7)
Non-mCRC outpatient visits, mean (SD)	6.7 (4.9)	7.6 (7.4)	7.7 (8.3)	6.6 (7.2)
mCRC-related pharmacy prescriptions[d], mean (SD)	0.7 (3.2)	1.7 (6.2)	3.2 (8.6)	4.1 (9.5)
Non-mCRC prescriptions, mean (SD)	2.2 (2.4)	3.1 (4.9)	3.3 (5.7)	3.0 (4.7)
PPPM costs				
Inpatient, mean (SD)	$1,346 ($9,404)	$1,509 ($6,070)	$1,164 ($4,154)	$997 ($4,491)
ED visit, mean (SD)	$325 ($1,914)	$1,299 ($28,429)	$341 ($1,103)	$276 ($936)
Outpatient mCRC treatment–related costs, mean (SD)	$7,021 ($24,988)	$21,981 ($74,451)	$31,711 ($132,744)	$15,195 ($29,831)
Non-mCRC outpatient visit costs, mean (SD)	$10,321 ($19,773)	$16,169 ($60,859)	$18,702 ($72,008)	$15,248 ($54,903)
mCRC-related pharmacy costs, mean (SD)	$3,314 ($26,891)	$22,229 ($93,640)	$44,616 ($145,597)	$64,299 ($161,855)
Non-mCRC pharmacy costs, mean (SD)	$841 ($15,336)	$593 ($1,819)	$552 ($1,782)	$919 ($2,874)
Total costs (inpatient, outpatient, and pharmacy), mean (SD)	$23,169 ($47,428)	$63,779 ($145,664)	$97,086 ($203,891)	$96,933 ($165,677)
Costs per visit[e]				
Inpatient, mean (SD)	$28,435 ($30,031)	$25,655 ($22,395)	$24,606 ($22,256)	$24,910 ($15,047)
ED visit, mean (SD)	$2,554 ($3,673)	$2,411 ($2,992)	$2,447 ($3,233)	$2,628 ($2,176)

[a]All results are shown in mean (SD); costs were adjusted for inflation to 2021 US dollars using the Consumer Price Index.
[b]Inpatient, ED, outpatient treatments, non-mCRC outpatient visits, mCRC-related pharmacy visits, and non-mCRC pharmacy visits are mutually exclusive among all patient utilization.
[c]mCRC-related outpatient visits were identified using procedure codes.
[d]mCRC-related pharmacy visits were identified using NDC codes.
[e]Calculated among patients with ≥1 inpatient or ED visit. Each hospitalization could include multiple inpatient services; the cost per hospitalization was calculated.
1L, first-line; 2L, second-line; 3L, third-line; 4L+, fourth-line and beyond; ED, emergency department; HCRU, healthcare resource utilization; NDC, national drug code; mCRC, metastatic colorectal cancer; PPPM, per-patient-per-month; SD, standard deviation.

- Per-visit inpatient and ED costs were comparable across lines of therapy (**Figure 3**).
- Outpatients visit costs (mCRC and non-mCRC–related costs) were higher in later lines of therapy; mCRC and non-mCRC–related costs comprised 56% and 44%, respectively, of total outpatient visits across all lines of therapy.
- Pharmacy costs also increased by line of therapy; mCRC-related costs comprised almost all pharmacy costs (98%), with only 2% being non-mCRC–related costs.

Figure 3. Key components of total PPPM costs[a] for patients with mCRC by line of therapy



[a]For each line of therapy, the sum of all costs may not equal the total costs shown due to rounding.
1L, first-line; 2L, second-line; 3L, third-line; 4L+, fourth-line and beyond; mCRC, metastatic colorectal cancer; PPPM, per-patient-per-month.

Limitations

- Some baseline characteristics may not be captured, including comorbidity burden and other primary cancers present in patients prior to mCRC, due to the limited baseline period (6 months).
- Sample sizes in later lines of therapy were small, resulting in considerable variance in HCRU and associated costs.

Conclusions

- There is an unmet need for effective therapies in 2L+ mCRC, where clinical outcomes are poor.
  - Treatment patterns demonstrate limited options for patients.
- There was substantial treatment drop-off among 1L-treated patients with mCRC with ~69% of patients on 1L treatment who did not receive 2L therapy, indicating potentially burdensome 1L treatments or progression of disease; HCRU costs also markedly increased from 1L to 2L and from 2L to 3L.
- The economic burden of mCRC is substantial, particularly in later lines of therapy, and patients continue to have a poor prognosis; further studies are needed to explore targeted therapeutic strategies that may provide improved outcomes for patients in this setting.

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