Article published online: 2022-09-02

Gastrointestinal Cancer

Treatment of Metastatic Colorectal Cancers in Resource-Constrained Low- and Middle-Income Countries (LMICS) Scenario—Outcomes, Practice Patterns, and Commentary on Treatment Costs

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South Asian J Cancer 2022;11(4):293–298.

Abstract

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Introduction The overall survival (OS) of metastatic colorectal cancers (mCRCs) in clinical practice and resource-constrained low- and middle-income countries (LMICS) like India is not known.

Materials and Methods Data of patients with mCRC treated between January 2013 and August 2017 were accessed from a prospectively maintained database. Demographics, disease characteristics, chemotherapeutic regimens, use of monoclonal antibodies, and survival outcomes in treated patients were collected and analyzed. Costs of treatment options as off 2017 were also interpreted.

Results The data of 403 patients satisfied prespecified inclusion criteria and were included for analysis. The median age of the cohort was 48 years (range: 17–86) with a predominance of rectal cancers (63.3%), liver alone metastases (47.1%), and resected primary (69.7%). Signet ring histology was present in 82 patients (20.3%). The most commonly used first-line regimen (CT1) was modified capecitabine-oxaliplatin (53.3%). Two hundred and nineteen patients (54.3%) received second-line systemic therapy (CT2). Patients received a median of two lines of therapy (range: 1–6). MoAbs were used by 48 patients (13.4%) with CT1 and 34 patients (15.5%) with CT2. Median OS of the entire cohort was 17.61 months (95% confidence interval: 15.48–19.74), which was within the predicted range, as per investigator hypothesis. The presence of signet ring histology ($p < 0.001$), raised carcinoembryonic antigen at baseline ($p = 0.017$), and the absence of a resected primary ($p < 0.001$) predicted inferior median OS.

Conclusions Survival of patients with mCRC in a resource-constrained LMIC scenario like India is approximately 12 to 15 months lower than published trial data. Limited access to targeted therapy and newer expensive treatment options due to financial constraints may contribute to this disparity.

Keywords
- targeted therapy
- India
- low- and middle-income countries
- metastatic colorectal cancer
- overall survival
- resource constrained

DOI https://doi.org/10.1055/s-0041-1736203 ISSN 2278-330X

How to cite this article: Ramaswamy A, Babu V, Kothari R, et al. Treatment of Metastatic Colorectal Cancers in Resource-Constrained Low- and Middle-Income Countries (LMICS) Scenario—Outcomes, Practice Patterns, and Commentary on Treatment Costs. South Asian J Cancer 2022;11(4):293–298.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Metastatic colorectal cancers (mCRC) are a diverse group of cancers with respect to biomarkers, targetable mutations, and treatment patterns. The emergence of RAS/Raf testing as a biomarker for selection of monoclonal antibodies (moAbs; anti-EGFR agents and anti-VEGF agents) and the subsequent use of moAbs has improved upon the survival outcomes seen in mCRCs with systemic chemotherapy alone.[1,2] The median overall survival (mOS) has risen from approximately 14 to 15 months with chemotherapy alone a decade ago to approximately 30 months in certain subgroups, using a combination of chemotherapy and targeted therapy.[3] Additional factors which have improved survival in the last decade include optimization of treatment strategies in the first line (1L), increased use of curative intent treatment strategies in oligometastatic mCRC with liver and lung limited disease, as well as third line (3L) options such as regorafenib and TAS 102.

However, limited feasibility with regard to the use of potentially expensive moAbs in resource-constrained settings may hamper the applicability of survival improvements seen in trials to real-world clinical practice. Such logistic and economic constraints in terms of reduced usage have been recognized with specific regard to bevacizumab, cetuximab and panitumumab in mCRC across centers in predominantly Eastern Europe and to some extent in Western Europe as well. The advent of pembrolizumab and nivolumab in mCRC may further widen such differences between trial data and use in clinical practice. Biosimilars, which are similar versions of licensed biologicals, may offset some of these differences, especially in countries like India where they are routinely available.[4]

With the above reference points in the background, the authors conducted a retrospective analysis of patients with mCRC who were treated in the Tata Memorial Hospital, Mumbai. The aims of the study were to evaluate demographics, treatment patterns and outcomes in patients with mCRC, as well as evaluate receipt of moAbs. Additionally, an attempt was made to throw light on the costs of treatment for mCRC in India and potentially link these variables with how it affects outcomes.

Materials and Methods

The study is a retrospective analysis of mCRC patients who were evaluated during the period of January 2013 to August 2017 in the Department of GI Medical Oncology at Tata Memorial Hospital. Data was obtained from a prospectively maintained metastatic CRC database. Decisions regarding metastatic nature of disease was made by a dedicated gastrointestinal (GI) multidisciplinary joint clinic (MDJC).

Patients satisfying all the following criteria were included in the analysis:

1. Histologically proven colorectal adenocarcinoma, either by cytology or biopsy.
2. Definitive evidence of metastatic disease, as per scans and physical examination.
3. Administered at least one cycle of chemotherapy at our hospital or at least one follow-up after starting treatment.

After MDJC, patients were evaluated for fitness for chemotherapy by the Department of Medical Oncology and were then offered chemotherapy with targeted therapy based on feasibility. All RAS and BRAF testing were only offered to patients who were financially and logistically feasible for receipt of moAbs, based on discussion with the treating medical oncologist. Baseline demographic details, including comorbidities, prior treatment history, and therapeutic options used, were recorded. As per standard institution criteria, baseline disease evaluation included, at minimum, a carcinoembryonic antigen (CEA) test, biopsy (primary or metastatic site), contrast-enhanced CT scan of the thorax, abdomen and pelvis or, rarely, a fluorodeoxyglucose (FDG) positron emission tomography (PET) CT scan.

The investigators (AR and VO) drew up an imaginary treatment-outcomes and cost scenario for a patient with full access to the complete sequence of treatment (patient A) for mCRC as opposed to a patient with financial constraints to treatment (patient B) (►Fig. 1). This construct was made, based on available survival data from randomized trials and an estimate of treatment alone costs (without consideration of logistic costs, costs of treatment-related investigations and treatment-related adverse events as per 2017 figures) prior to data analysis of the study cohort. The investigators hypothesized that median OS of

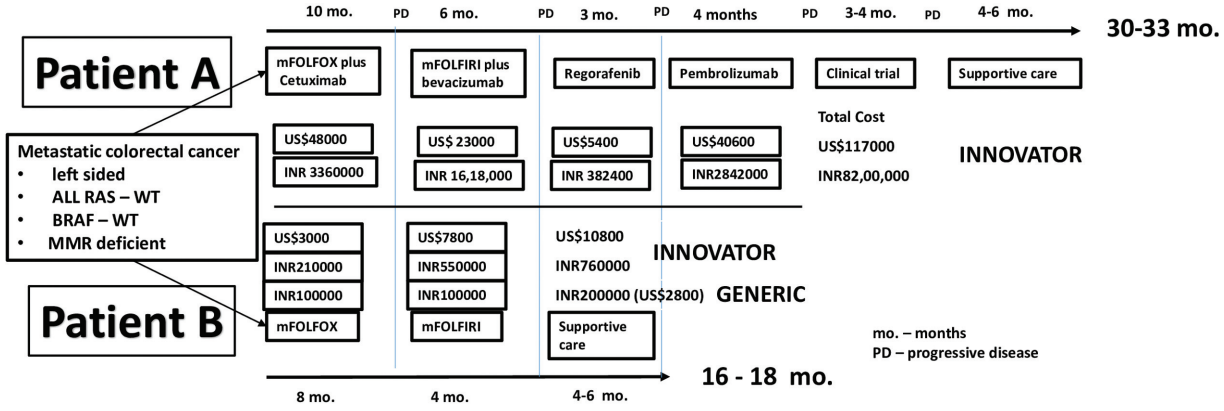

Fig. 1 Imaginary comparative treatment scenario—individualized treatment in an Indian patient with complete access to treatment options (**A**) versus nontrial Indian patient with limited access to therapy (**B**).

the entire study cohort would range between 16 to 18 months, that is, similar to imaginary patient B.

Outcome Variables

Toxicity assessment was done at every patient visit and recorded as per National Cancer Institute (NCI) – Common Terminology Criteria for Adverse (CTCAE) version 4.0. Response to treatment was evaluated clinically on every visit with contrast-enhanced CT (CECT) scan after three to four cycles of chemotherapy or earlier as per physician decision. Prognostic factors evaluated included age (< 40 years vs. ≥ 40 years), site of primary (right-sided vs. left-sided cancers), signet ring histology (presence versus absence), mucinous histology (presence vs. absence), CEA levels at baseline (raised vs. within normal limits), and resection of primary.

Progression-free survival (PFS) was calculated from date of diagnosis to date of progression, cessation of chemotherapy due to adverse events, loss to follow-up, and withdrawal from therapy or death (in case of no documented progression). PFS1 was calculated for first-line chemotherapy and PFS2 for second line chemotherapy. OS was calculated from date of diagnosis to date of death or loss to follow-up.

Clinical Data Collection and Statistics

For the purposes of this study, demographic data and baseline clinical data were collected retrospectively from GI Medical Oncology Information System and electronic medical record system. All data was entered in SPSS software version 21 and used for analysis. Descriptive statistics, including median, frequency and percentage for categorical variables, was used to describe age, gender distribution, treatment, and response to treatment. Median PFS1, PFS2, and OS were calculated using Kaplan–Meier estimates, while log rank test was used for univariate comparisons. Multivariate analysis by Cox regression method for prognostic factors was done irrespective of results of univariate analysis.

Results

Baseline Characteristics

A total of 403 patient's data satisfied the inclusion criteria, and they were available for analysis. The median age of the cohort was 48 years (range: 17–86 years). Majority of the cancers were rectal primaries (63.3%), with signet ring histology seen in 82 patients (20.3%). Other characteristics are detailed in ►Table 1.

Characteristics of Chemotherapy (►Table 2)

The most common first-line regimen (CT1) used was modified capecitabine-oxaliplatin (CAPOX) in 215 patients (53.3%), while 85 patients (21.1%) received modified 5-fluorouracil/leucovorin-irinotecan (mFOLFIRI). Of the 403 patients in total, 219 (54.3%) patients received second-line therapy (CT2). The most common second-line regimens (CT2) used were irinotecan-based, mFOLFIRI in 84 patients (38.3%) and CAPIRI (capecitabine-irinotecan) in 33 patients (15.1%), followed by oxaliplatin-based regimens in 47 patients (21.5%). Third-line treatment (CT3) was given in 84 patients of the entire cohort

Table 1 Baseline demographic and clinical characteristics ($n = 403$)

Characteristic	Number (percentage where applicable)
Median age (years)	48 (range:17–86)
• Age < 40 years	129 (32)
• Age ≥ 40 years	274 (68)
Gender	
• Female	155 (38.5)
• Male	248 (61.5)
Site of disease	
• Left sided (nonrectal)	67 (16.6)
• Rectal	255 (63.3)
• Right-sided	63 (15.6)
• Transverse	17 (4.2)
• Epicenter not identified	01 (0.2)
Histopathology	
• Poorly differentiated	113 (28)
• Well-differentiated/ moderately differentiated	219 (54.3)
• Adenocarcinoma, not specified	71 (17.6)
Mucinous histology	
• Yes	72 (17.9)
• No	331 (82.1)
Signet ring histology	
• Yes	82 (20.3)
• No	321 (79.7)
Baseline CEA status	
• CEA > ULN	246 (61)
• CEA ≤ ULN	67 (16.6)
• CEA not available	90 (22.3)
Disease status at baseline	
• Baseline metastatic	183 (45.4)
• Recurrent metastatic	220 (54.6)
Prior adjuvant/neoadjuvant chemotherapy	
• Yes	200 (49.7)
• No	203 (50.3)
Sites of metastases	
• Liver	190 (47.1)
• Lung	127 (31.5)
• Peritoneal	133 (33)
• Nonregional nodes	145 (36)
• Osseous	32 (7.9)
• Krukenberg's	21 (5.2)
> 1 site of metastases	249 (61.8)

Abbreviations: CEA, carcinoembryonic antigen; ULN, upper limit of normal.

Table 2 Characteristics of systemic chemotherapy

Characteristics	Number (percentage where applicable)
CT1	403 (100)
• mCAPOX	215 (53.3)
• FOLFIRINOX	17 (4.2)
• mFOLFIRI	85 (21.1)
• mFOLFOX-7	48 (11.9)
• Capecitabine monotherapy	13 (3.2)
• 5 FU/LV monotherapy	17 (4.2)
• Others	12 (2.9)
CT2	219 (54.3)
• mFOLFIRI	84 (38.4)
• CAPIRI	33 (15.1)
• mCAPOX/mFOLFOX-7	47 (21.5)
• mFOLFIRINOX	02 (0.9)
• Single agent irinotecan	10 (4.6)
• Capecitabine monotherapy	20 (9.1)
• 5 FU/LV monotherapy	03 (1.4)
• Metronomic chemotherapy	16 (7.3)
• Single agent cetuximab	01 (0.4)
• Regorafenib	01 (0.4)
CT3	84 (20.3)
• mCAPOX/mFOLFOX-7	18 (21.4)
• mFOLFIRI/CAPIRI	29 (34.5)
• Single agent irinotecan	03 (3.6)
• Metronomic chemotherapy	17 (20.2)
• Single agent monoclonal	01 (1.1)
• Capecitabine monotherapy	06 (7.1)
• Regorafenib	06 (7.1)
• Tegafur/Uracil	04 (4.8)
Patients receiving fourth-line therapy	31 (7.7)

Abbreviations: CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy.

(20.3%; $n = 403$). Metronomic chemotherapy (oral low dose capecitabine and cyclophosphamide) was used in 38 patients (9.4%).

Characteristics of Targeted Therapy (►Table 3)

A total of 48 patients (13.4%) received moAbs with chemotherapy as part of CT1. Bevacizumab was used in 25 patients, while cetuximab was administered in 23 patients. As many as 34 patients (15.5%; $n = 219$) received moAbs along with CT2, with bevacizumab being commonly used.

Survival Outcomes and Prognostic Factors (►Table 4)

The median follow-up for the entire cohort was 39.49 months (range: 7.36–73.95). Median PFS on CT1 (PFS1) was 10.91 months (95% confidence interval [CI]: 9.29–12.52), while median PFS on CT2 (PFS2) was 7.39 months (95% CI: 6.65–8.14). A total of 303 patients had died as of cut-off date for analysis, with median OS for the entire cohort being 17.61 months (95% CI: 15.48–19.74) (►Fig. 2).

Of the prognostic factors evaluated, the presence of signet ring histology (11.17 months Vs. 19.65 months; $p < 0.001$) and raised CEA at baseline (15.28 months. versus 25 months.; $p = 0.017$) predicted inferior OS, while patients with a resected primary had a superior OS (23.95 months vs. 9.70 months.; $p < 0.001$) on multivariate analysis. Younger age, while significant on univariate analysis, did not predict inferior OS on multivariate analysis ($p = 0.07$).

Table 3 Characteristics of targeted therapy

Characteristics	Number (percentage where applicable)
Use of moAbs with CT1 ($n = 403$)	48 (13.4)
• Bevacizumab	25
• Cetuximab	23
Use of moAbs with CT2 ($n = 219$)	34 (15.5)
• Bevacizumab alone	14
• Aflibercept	06
• Cetuximab	13
• Panitumumab	01
Use of moAbs with CT3 ($n = 84$)	14 (16.7)
• Bevacizumab	06
• Cetuximab	06
• Panitumumab	02

Abbreviation: moAbs, monoclonal antibodies.

Discussion

The management of mCRC has grown remarkably over the last decade, be it with respect to validated biomarkers, treatment options, or improved survival of patients. Current median OS rates that are oft quoted are in the range of 24 to 36 months, especially in trials which have examined chemotherapy-moAB combinations. However, differences in patient selection between trials and real-world scenarios as well the added lack of access to potentially newer treatment options hamper survival outcomes in low- and middle-income countries (LMICS) with respect to moAbs.[5,6]

Our retrospective analysis of 403 patients with advanced CRC is the first such dataset from India and is a reflection of treatment patterns and outcomes in a resource-constrained scenario. A significant proportion of young patients (< 40 years—32%) and rectal cancers (63.3%) and higher percentage of signet ring cancers (20.3%) were seen in the current cohort and such trends have been shown previously from our institute.[7,8] The presence of an increasing proportion of younger patients having rectal cancer is of significant importance, as there is growing evidence that they likely

Table 4 Factors affecting OS

Characteristic	OS (months)	*p*-Value (univariate analysis)	*p*-Value (multivariate analysis)	Hazard ratio (95% confidence interval)
Age • < 40 years • ≥ 40 years	12.58 19.48	0.001	0.07	0.80 (0.623–1.019)
Site of primary • Left-sided • Right-sided	17.74 17.64	0.541	–	–
Mucinous histology • Present • Absent	20.38 16.30	0.449	–	–
Signet ring histology • Present • Absent	11.17 19.65	< 0.001	< 0.001	1.69 (1.282–2.229)
CEA levels at baseline • Raised • WNL	15.28 25.00	0.007	0.017	0.66 (0.472–0.929)
Resection of primary • Yes • No	23.95 9.70	< 0.001	< 0.001	3.075 (2.400–3.939)

Abbreviations: CEA, carcinoembryonic antigen; OS, Overall survival; WNL, Within normal limits.

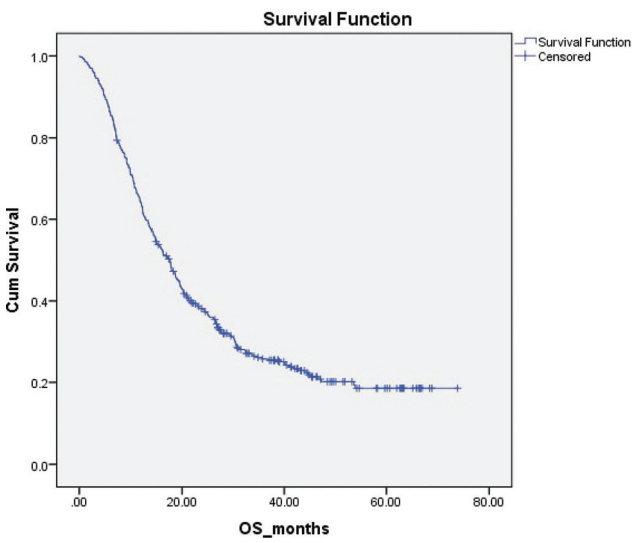

Fig. 2 Kaplan–Meier curve for overall survival (OS) of entire cohort.

constitute a biologically and clinically distinct cohort, who do not maximally benefit from current treatment paradigm.[9] We have used a cut-off of 40 years in view of the lower median age of the entire cohort.

The majority of patients were started on modified capecitabine-oxaliplatin (mCAPOX) (capecitabine 2000 mg/m^2 instead of 2500mg/m^2) (53.3%; $n = 403$) as first-line chemotherapy (CT1) as opposed to mFOLFOX, as this avoids the use of a central line without loss of efficacy. Only 54.3% of patients proceeded to CT2 post CT1, and this is at variance from patients who are able to receive CT2 in clinical trials as well as real-world data (62–74%). A high-baseline disease burden (> 1 site of metastases—61.8%) and possibly poor Eastern Cooperative Oncology Group performance status (ECOG PS) with increased disease burden postprogression on CT1 may contribute to lesser patients receiving CT2.

Two other treatment-related factors are significant in the current cohort—an increased prevalence of a resected primary (69.7%; $n = 403$) and limited use of targeted therapy with CT1 (13.4%) as well as CT2 (15.5%). The increased percentage of a resected primary is because of the study cohort including a high proportion (54.6%) with recurrent metastatic disease (►**Supplementary Table S1**, available online only). Available retrospective evidence and metanalysis have suggested that carefully selected patients with mCRC may have survival benefit with resection of the primary (and possible resection of metastatic sites).[10] Despite the findings in retrospective studies, including the current one, resection of the primary should only be considered in clearly defined situations and not as routine/standard in mCRC.

The limited administration of targeted therapy in the entire cohort is not unexpected. In a LMICS country with a per capita of approximately US$ 1700 (2017 data) like India, a majority of patients will only be able to afford CT1 and CT2 without targeted therapy, and this would cost approximately INR 200,000 (US$ 2,800), assuming generic chemotherapeutic agents are used (►**Fig. 1**—patient B). The proportion of patients feasible for the entire gamut of treatment options (similar to patient A) in terms of financial feasibility would be very few, as per our institution data. A complete cost-effectiveness analysis using Markov models would be required to evaluate the actual cost-benefit ratio of treatment sequencing in mCRC in the Indian scenario, and this is beyond the scope of the current study.

The imaginary construct (►**Fig. 1**) also was accurate in its prediction of median OS (predicted range: 16–18 months.)

for the study cohort. With a median follow-up of 39.49 months, the median OS was 17.61 months (95% CI: 15.48–19.74) and is reflective of patients receiving predominantly two lines of chemotherapy (without moAbs) followed by supportive care.

An important subtext that emerges from this study is the importance of being able to offer available treatment options to patients with mCRC. Just as the use of HER2 directed therapy has dramatically changed the outcomes in metastatic breast cancer, so too has the use of anti-EGFR and anti-VEGF therapy improved outcomes in mCRC. The use of targeted therapy and beyond extends OS to approximately 12 to 15 months over chemotherapy alone. Such therapy-related factors should also be considered when governmental funding of treatment is being planned and accounted.

Our study, while being retrospective in design and a single institution datum, has the strength of being representative of how patients with mCRC are treated in the LMICS scenario, where patient selection and availability of treatment options are markedly different when compared with trial patients. However, multiple caveats in the current study need to be acknowledged. In the current era, testing for all RAS and BRAF in mCRC patients is almost mandatory, and we have not provided any information on the same. This is primarily because of our policy of offering this test to patients who are financially feasible for targeted therapy and not otherwise. We have attempted to highlight financial constraints faced by patients in the Indian scenario in terms of crude comparative absolute costs for treatment without using appropriate health economic modelling approaches. Such an approach implies the need for a more systematic evaluation of the cost-effectiveness of all aspects of systemic therapy for mCRC in the Indian context.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
None.

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