



Clinicopathological Features and Outcomes of Metastatic Colorectal Cancers Treated at a Tertiary Care Hospital: A Bidirectional Observational Study

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ABSTRACT

Background: Metastatic colorectal cancer (mCRC) remains a major contributor to cancer-related mortality worldwide. Real-world data from low- and middle-income countries remain limited.

Materials and methods: This bidirectional observational study included 60 patients with histologically confirmed mCRC treated at a tertiary care center between January 2019 and December 2025. Demographic, clinicopathological, molecular, treatment, and survival data were analyzed. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. Cox proportional hazards regression was used to identify prognostic factors.

Results: The median age was 48.5 years, and 63.3% of patients were male. Extensive metastatic disease was present in 96.7% of patients. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations were detected in 20.7% of patients, whereas microsatellite instability-high (MSI-high) status was identified in one patient. Median PFS and OS were 10.6 and 22.3 months, respectively. On multivariable analysis, peritoneal metastasis independently predicted inferior PFS [hazard ratio (HR) 4.45, 95% confidence interval (CI) 2.16–9.19; $p < 0.001$] and OS (HR 2.83, 95% CI 1.13–7.07; $p = 0.026$). Poorly differentiated histology independently predicted worse OS (HR 3.05, 95% CI 1.03–9.06; $p = 0.045$).

Conclusion: This study highlights the substantial burden of advanced disease in Indian patients with colorectal cancer. Peritoneal metastasis and poor differentiation were associated with adverse outcomes. Improved early detection and wider access to targeted therapies may improve survival outcomes in resource-limited settings.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies worldwide and a major cause of cancer-related mortality, with many patients presenting with or eventually developing metastatic disease.¹ Despite advances in surgery and systemic therapy, metastatic colorectal cancer (mCRC) continues to have poor survival outcomes. While the AJCC TNM staging system remains standard for prognostication, survival differences within the same stage suggest that tumor biology also plays a significant role. Consequently, clinicopathological factors and molecular alterations such as NRAS, KRAS, BRAF mutations, and mismatch repair deficiency have emerged as important prognostic and predictive markers in mCRC.²

Molecular profiling has transformed treatment strategies in metastatic disease, particularly with the use of anti-EGFR therapy and immune checkpoint inhibitors (ICI) in selected patients. However, real-world data regarding clinicopathological profile, molecular characteristics, treatment patterns, and outcomes of mCRC from India and other

low- and middle-income countries (LMICs) remain limited. Therefore, this bidirectional observational study was undertaken to evaluate the demographic profile, clinicopathological features, molecular characteristics, treatment patterns, and survival outcomes of patients with mCRC treated at a tertiary care center, and to identify prognostic factors associated with clinical outcomes in routine practice.

MATERIALS AND METHODS

This bidirectional observational study was conducted at a tertiary care hospital in India after obtaining approval from the institutional ethics committee ESICMC/SNR/IEC-S0400/06–2024 and informed consent. The current trial is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary File S1). Adult patients aged ≥ 18 years with an ECOG performance status of 2 or below who received at least 1 cycle of systemic therapy for histologically confirmed CRC and radiologically and/or pathologically confirmed metastatic disease were included.

Individuals were excluded from the study if they presented with synchronous secondary malignancies, lacked critical data, or were lost to follow-up (LTFU) immediately following diagnosis. The sample size was calculated using the single population proportion formula, assuming a metastatic colorectal cancer prevalence of 22%, 95% confidence interval, and 10% precision, yielding a minimum sample size of 60 patients. All eligible patients during the study period were included in the analysis.

Objectives

The primary objective of this study is to ascertain the overall survival (OS) of patients with mCRC. Secondary objectives include determining progression-free survival (PFS), evaluating clinicopathological characteristics and molecular profile patterns, documenting the treatment protocols employed (including first-line, maintenance, and second-line therapies in accordance with NCCN/ESMO guidelines), and examining the association of clinicopathological and molecular factors with treatment outcomes (PFS and OS) and chemotherapy-related toxicity profiles.

Statistical Analysis

Data were collected on patient demographic variables, including age, sex, socioeconomic status, ECOG status, primary tumor site (right colon from cecum to right 2/3rd of transverse colon, the left colon from splenic flexure,

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descending colon and sigmoid colon and rectum including rectosigmoid junction and rectum), comorbidities, histological subtype, tumor grade, molecular markers (KRAS, NRAS, MSI by IHC) and characteristics of metastatic disease (such as the number and location of metastatic sites, oligometastatic versus extensive metastatic patterns, and radiological tumor burden). Additionally, treatment details were documented, including first-line (CAPOX, FOLFOX, FOLFIRI), targeted therapies (bevacizumab, cetuximab, panitumumab), maintenance therapy, subsequent lines of treatment, and chemotherapy toxicity using CTCAE version 5.0.

Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), based on distribution assessed using the Shapiro–Wilk test. Categorical variables were summarized as frequencies and percentages. OS was defined as the time from the diagnosis to death from any cause or last follow-up. PFS was defined as the time from the diagnosis to documented radiological progression or death, whichever occurred first. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test.

Univariable analysis was performed to evaluate the association between clinicopathological variables and survival outcomes. Variables with a p -value < 0.10 on univariable analysis were included in multivariable analysis using Cox proportional hazards regression to identify independent prognostic factors. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. A significance level of 5% ($p < 0.05$) was considered statistically significant. The statistical analysis was conducted using Jamovi.

RESULTS

In this bidirectional observational study, a total of 60 patients with mCRC were included. Three patients with ECOG PS > 2 and one patient with second synchronous malignancy were excluded (Fig. 1A).

The baseline characteristics of the included patients are given in Table 1. Synchronous metastases were more frequent than metachronous metastases across all primary tumor sites.

In this study, two patients with oligometastatic CRC and ECOG PS 2 underwent curative-intent surgery postinduction chemotherapy. One received 8 CAPOX cycles with bevacizumab, followed by right hemicolectomy and complete hepatic metastatectomy, with no residual disease, and is under follow-up. The second, after 6 CAPOX cycles with bevacizumab, had subtotal colectomy plus wide hepatic metastatectomy but experienced disease progression after 19.8 months and started on CAPIRI with bevacizumab.

Among 58 patients receiving first-line chemotherapy, 7 were LTFU, and 42 had disease progression. 7 died before progression, 4 from organ failure and 3 from unknown causes. At analysis, 2 remained on treatment without progression.

In the first-line setting, the commonly administered regimens are given in Figure 1B.

Out of 42 patients with disease progression, 38 received second-line therapy. The most common regimen was CAPIRI plus bevacizumab (47.4%; $n = 18$), followed by FOLFIRI plus bevacizumab (18.4%; $n = 7$) and FOLFIRI plus cetuximab (10.5%; $n = 4$). Other regimens were CAPOX plus bevacizumab (7.9%; $n = 3$), CAPIRI alone (2.6%; $n = 1$), FOLFOX plus bevacizumab (2.6%; $n = 1$), and CAPIRI plus

cetuximab (2.6%; $n = 1$). Nivolumab was given to one patient (2.6%). Tegafur monotherapy was administered to 2 patients (5.3%) with poor ECOG PS, unfit for combination chemotherapy.

Disease progression following second-line therapy was observed in 7 patients who proceeded to receive third-line treatment. Among these, 2 patients died due to progressive disease, and 2 patients were LTFU. The remaining three patients continued on treatment at the time of analysis with regorafenib.

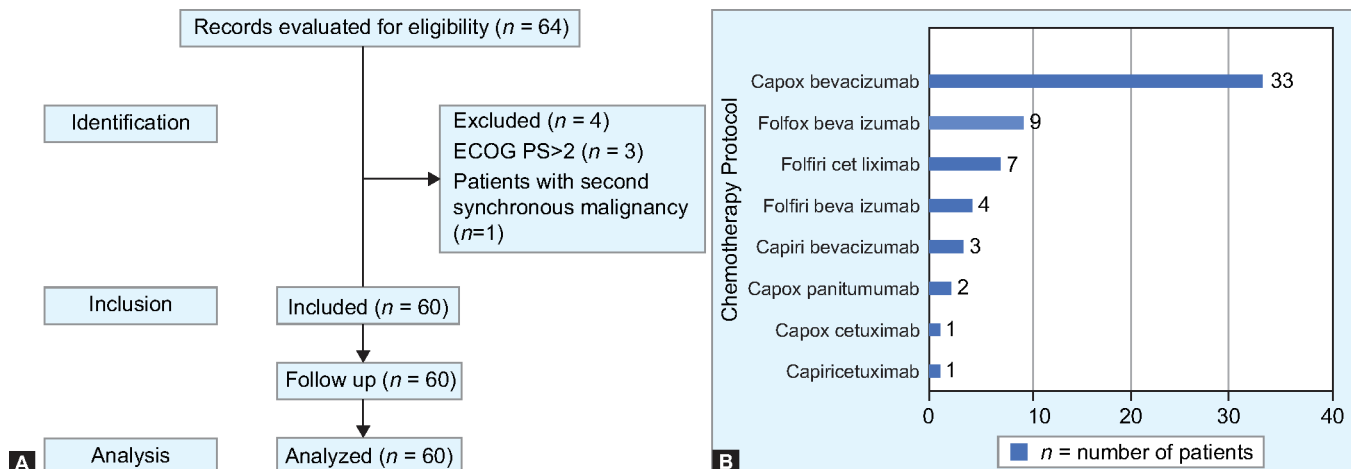
Microsatellite instability-high status through IHC was seen in one patient, who received first-line treatment with FOLFIRI combined with cetuximab for 6 cycles. Upon progression, nivolumab was given as a single agent in the second line for 2 cycles. Unfortunately, the patient died due to a nondisease-related cause (accident).

SURVIVAL OUTCOMES

Overall Survival

The estimated mOS for the entire cohort was 22.3 months (95% CI: 19.4–NE) (Fig. 2A) with a median follow-up duration of 22.2 months, and the factors affecting OS were NRLN, peritoneal metastasis, and grade (Fig. 2B and Table 2).

NRLN involvement was significantly associated with worse OS. On univariable analysis, NRLN metastases were associated with increased risk of death (HR 9.30, 95% CI 1.19–72.51; $p = 0.033$), although this was not retained on multivariable analysis (HR 6.68, 95% CI 0.72–61.95; $p = 0.095$). mOS was 21.7 months (95% CI 18.4–NE) in patients with NRLN metastases, while median OS was not reached in those without involvement. Peritoneal metastasis was significantly associated with inferior OS,



Figs 1A and B: (A) Study conduction flowchart according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines; (B) chemotherapy protocol 1 regimen

Table 1: Characteristics of the included variables

Variables	Value
Age (years), median (range)	48.5 (22–78)
Sex, <i>n</i> (%)	
Female	22 (36.7)
Male	38 (63.3)
Marital status, <i>n</i> (%)	
Married	60 (100)
Comorbidities, <i>n</i> (%)	
Present	22 (36.7)
Absent	38 (63.3)
ECOG performance status, <i>n</i> (%)	
0	9 (15.0)
1	10 (6.7)
2	41 (68.3)
Smoker/alcoholic, <i>n</i> (%)	
Smoker	5 (8.3)
Alcoholic	10 (16.7)
Both	12 (20.0)
Site, <i>n</i> (%)	
Left	22 (36.7)
Right	22 (36.7)
Rectum	16 (26.6)
Metastatic sites, <i>n</i> (%)	
Nonregional lymph node	54 (90.0)
Peritoneal	33 (55.0)
Liver	52 (86.7)
Lung	20 (33.3)
Bone	2 (3.3)
Brain	2 (3.3)
Ovary	3 (5.0)
Metastatic patterns, <i>n</i> (%)	
Oligometastatic	2 (3.3)
Extensive	58 (96.7)
Metastatic types, <i>n</i> (%)	
Synchronous	37 (61.7)
Metachronous	23 (38.3)
Grade, <i>n</i> (%)	
Well-differentiated	18 (30.0)
Moderately differentiated	28 (46.7)
Poorly differentiated	14 (23.3)
Histology, <i>n</i> (%)	
Adenocarcinoma NOS	58 (96.7)
Mucinous adenocarcinoma	2 (3.3)
MSI, <i>n</i> (%)	
High	1 (1.7)
Stable	59 (98.3)
KRAS, <i>n</i> (%)	
Mutated	12 (20.7)
Wild	46 (79.3)
NRAS, <i>n</i> (%)	
Mutated	1 (1.7)
Wild	57 (98.3)
BRAF, <i>n</i> (%)	
Wild	58 (100)

with mOS of 19.4 months compared to not reached in those without peritoneal involvement. It remained significant on both univariable and multivariable analysis. Poorly differentiated tumors showed a trend toward worse OS, whereas well-differentiated tumors were associated with significantly lower mortality risk. On multivariable analysis, poorly differentiated tumors remained an independent adverse prognostic factor, while well-differentiated histology retained significant survival benefit.

Progression-Free Survival

The estimated mPFS for the entire cohort was 10.6 months (95% CI: 8.47–14.3) (Fig. 2C), and the factors affecting PFS were NRLN, peritoneal metastasis, grade, and KRAS (Fig. 2D and Table 3).

NRLN involvement was significantly associated with worse PFS, with a higher risk of progression on both univariable and multivariable analysis. Patients without NRLN had longer mPFS (19.55 months, 95% CI 14.97–NR) compared to those with involvement (9.97 months, 95% CI 8.13–13.2). Peritoneal metastasis was associated with increased risk of progression on both univariable and multivariable analysis. Patients with peritoneal metastasis had markedly shorter mPFS compared to those without (7.97 months, 95% CI 7.03–10.6 vs. 14.87 months, 95% CI 11.37–19.5). Univariable analysis showed well-differentiated tumors had lower progression risk; poorly differentiated had a non-significant increased risk. Multivariable analysis found neither tumor type had independent prognostic significance for PFS, though well-differentiated showed a trend toward improved outcomes. KRAS wild-type showed a non-significant trend toward improved PFS on univariable analysis, which was not retained on multivariable analysis. mPFS was 8.47 months in KRAS-mutated versus 11.37 months in wild-type.

Toxicity Patterns

Forty-five patients received oxaliplatin-based regimens, and 15 received irinotecan-based regimens. Diarrhea was the most common toxicity, followed by neutropenia, HFS, thrombocytopenia, and neuropathy (Table 4).

DISCUSSION

This bidirectional observational study provides important real-world insights into the clinicopathological profile, molecular characteristics, treatment patterns, and outcomes of mCRC in a tertiary care setting in India. The median age at diagnosis in our cohort (48.5 years) was notably lower than that

reported in Western populations, supporting emerging evidence of an increasing burden of EOCRC in LMICs.^{2,3} Male predominance was observed, consistent with global epidemiological trends.¹ The low prevalence of family history suggests predominance of sporadic disease, although hereditary syndromes may be underrecognized because of limited genetic testing availability.⁴

Most patients have extensive metastatic disease, while only a small proportion have oligometastatic disease, reflecting delayed diagnosis and limited screening uptake. Synchronous metastases were common, further emphasizing advanced presentation at diagnosis. The liver was the most frequent metastatic site, consistent with established dissemination patterns in CRC.^{5,6} However, the prevalence of peritoneal metastasis (55%) was considerably higher than that

reported in Western literature, where rates are generally around 20–30%.⁵ This may reflect advanced disease burden, referral bias associated with a tertiary care center, or differences in staging practices. Similarly, the high frequency of NRLN metastasis may be related to extensive PET-based detection and radiological interpretation criteria. Bone and brain metastases relatively uncommon, in line with previously reported dissemination patterns. Only two patients were eligible for curative-intent surgery, highlighting the limited opportunity for potentially curative interventions in routine practice.

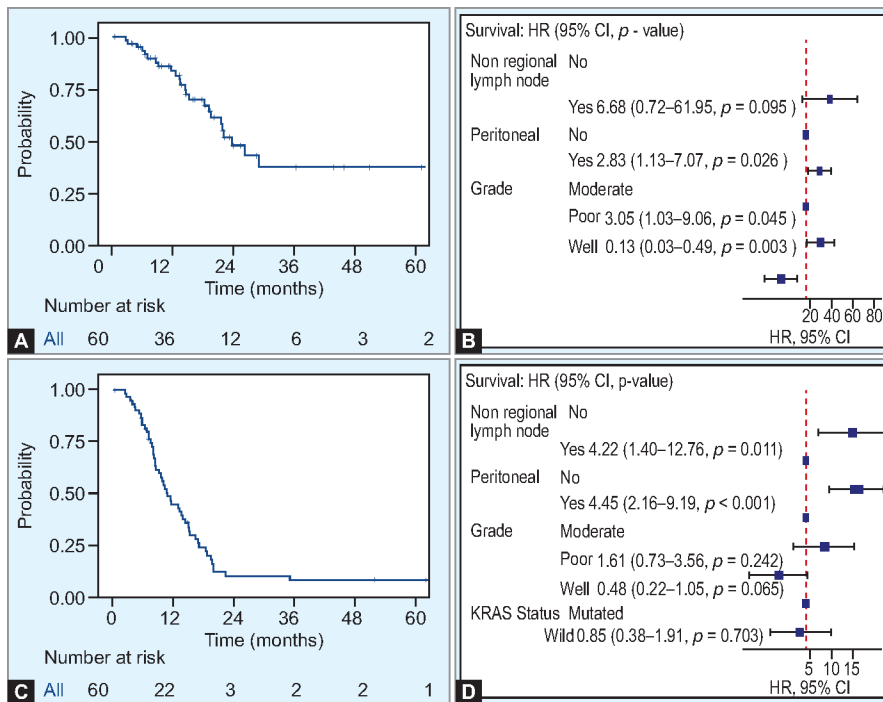
Moderately differentiated adenocarcinoma constituted the majority, comparable to previous studies.⁷ The prevalence of KRAS mutations was lower than globally reported frequencies, while NRAS mutations were infrequent and no BRAF

mutations were identified.⁸ MSI-high tumors were also uncommon compared with Western datasets.⁹ These differences may reflect population-specific molecular heterogeneity and limited sample size.

CAPOX plus bevacizumab was the most commonly used first-line regimen, consistent with NCCN and ESMO recommendations.^{10,11} Second-line treatment commonly involved irinotecan-based regimens following oxaliplatin exposure.¹² However, considerable heterogeneity existed in chemotherapy backbones. Limited access to anti-EGFR therapy and immunotherapy was largely influenced by institutional procurement systems and drug availability, reflecting real-world treatment challenges in resource-constrained settings.

The mPFS (10.6 months) and mOS (22.3 months) observed in our study were broadly comparable to other Indian real-world studies, although somewhat lower than outcomes reported in clinical trials where OS often exceeds 30 months.^{13–15} This discrepancy likely reflects advanced disease burden at presentation, restricted access to targeted therapies, treatment interruptions, and substantial LTFU. Peritoneal metastasis emerged as an independent adverse prognostic factor for both PFS and OS, consistent with prior studies demonstrating poorer outcomes in patients with peritoneal dissemination.^{16,17} NRLN metastasis was also associated with inferior PFS, although these findings should be interpreted cautiously given the unusually high prevalence of nodal disease in our cohort.¹⁸ Poorly differentiated tumors were associated with inferior OS, consistent with previous reports linking poor differentiation to aggressive tumor biology.¹⁹

Although KRAS wild-type showed a trend toward improved PFS, statistical significance was not maintained on multivariable analysis, possibly due to limited sample size, treatment heterogeneity, and restricted anti-EGFR use.^{20,21}



Figs 2A to D: (A) Overall survival (OS) of the entire cohort; (B) factors affecting OS; (C) progression-free survival (PFS) of the entire cohort; (D) factors affecting PFS

Table 2: Multivariable analysis of different prognostic factors for OS

Variable	n (%)	HR (univariable)	HR (multivariable)
NRLN			
No	6 (10.0)	–	–
Yes	54 (90.0)	9.30 (1.19–72.51, $p = 0.033$)	6.68 (0.72–61.95, $p = 0.095$)
Peritoneal			
No	27 (45.0)	–	–
Yes	33 (55.0)	2.99 (1.29–6.94, $p = 0.011$)	2.83 (1.13–7.07, $p = 0.026$)
Grade			
Moderate	28 (46.7)	–	–
Poor	14 (23.3)	2.68 (0.96–7.45, $p = 0.059$)	3.05 (1.03–9.06, $p = 0.045$)
Well	18 (30.0)	0.13 (0.04–0.42, $p = 0.001$)	0.13 (0.03–0.49, $p = 0.003$)

Table 3: Multivariable analysis of different prognostic factors for PFS

Variable	n (%)	HR (univariable)	HR (multivariable)
NRLN			
No	6 (10.3)	–	–
Yes	52 (89.7)	4.11 (1.44–11.77, $p = 0.008$)	4.22 (1.40–12.76, $p = 0.011$)
Peritoneal			
No	25 (43.1)	–	–
Yes	33 (56.9)	3.72 (1.96–7.05, $p < 0.001$)	4.45 (2.16–9.19, $p < 0.001$)
Grade			
Moderate	28 (48.3)	–	–
Poor	14 (24.1)	1.57 (0.75–3.28, $p = 0.230$)	1.61 (0.73–3.56, $p = 0.242$)
Well	16 (27.6)	0.40 (0.20–0.80, $p = 0.009$)	0.48 (0.22–1.05, $p = 0.065$)
KRAS status			
Mutated	12 (20.7)	–	–
Wild	46 (79.3)	0.52 (0.24–1.12, $p = 0.095$)	0.85 (0.38–1.91, $p = 0.703$)

Table 4: First-line chemotherapy toxicity

Toxicity	Oxaliplatin-based (n = 45), n (%)	Irinotecan-based (n = 15), n (%)	Total (n = 60), n (%)
Diarrhea (grade 1–2)	12 (26.7)	6 (40.0)	18 (30.0)
Diarrhea (grade ≥ 3)	4 (8.9)	2 (13.3)	6 (10.0)
Neutropenia (grade 1–2)	11 (24.4)	5 (33.3)	16 (26.6)
Neutropenia (grade ≥ 3)	3 (6.6)	1 (6.7)	4 (6.6)
Thrombocytopenia (any grade)	9 (20.0)	2 (13.3)	11 (18.3)
Peripheral neuropathy (grade 1–2)	8 (17.7)	2 (13.3)	10 (16.6)
Peripheral neuropathy (grade ≥ 3)	2 (4.4)	0 (0.0)	2 (3.3)
Hand–foot syndrome (grade 1–2)	14 (31.1)	2 (13.3)	16 (26.6)
Hand–foot syndrome (grade ≥ 3)	3 (6.7)	0 (0.0)	3 (31.7)

A major practical challenge in this study was substantial LTFU, particularly in later treatment lines, reflecting real-world issues such as financial constraints, travel burden, and inadequate structured follow-up systems. Toxicity patterns were generally consistent with established evidence, with irinotecan-based regimens associated with greater gastrointestinal and hematological toxicity and oxaliplatin associated with neuropathy; however, most toxicities were manageable, supporting the feasibility of combination chemotherapy in this setting.

Overall, this study highlights the high burden of advanced disease at presentation, the need for improved screening and early detection strategies, and the impact of limited access to precision oncology therapies in real-world Indian practice. Strengthening molecular diagnostic infrastructure, improving access to targeted therapies, and developing robust patient follow-up systems may help improve outcomes in mCRC.

This study provides valuable real-world evidence from a routine tertiary care setting, reflecting the practical challenges encountered in everyday oncology practice, including variability in patient characteristics, treatment access, and follow-up. A major strength of the study was the comprehensive

evaluation of both clinicopathological and molecular factors, including primary tumor site, metastatic pattern, RAS/BRAF mutation status, MSI status, and treatment details, which enabled a broader understanding of disease behavior and outcomes in mCRC. Furthermore, the use of multivariable analysis strengthened the reliability and clinical relevance of the findings by adjusting for potential confounders and identifying independent prognostic factors influencing PFS and OS. However, several limitations should be considered while interpreting the results. As a single-center retrospective study conducted at a tertiary care institution, the findings may not be fully generalizable to broader populations because of variations in referral patterns, patient demographics, and institutional practices. In addition, heterogeneity in treatment regimens, targeted therapy use, and sequencing strategies could have influenced outcomes, while a significant proportion of patients LTFU may have affected survival analysis and long-term outcome assessment.

CONCLUSION

In conclusion, this study provides real-world evidence on mCRC from a tertiary care setting

in India, demonstrating that outcomes are influenced by metastatic burden, tumor biology, and access to therapy. While survival outcomes are broadly consistent with other LMIC data, differences from clinical trial results highlight the impact of real-world constraints. Strengthening early detection and expanding availability of targeted therapies are critical steps toward improving outcomes in this population.

SUPPLEMENTARY MATERIAL

Supplementary file (STROBE Checklist) is available online at the journal website.

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