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# Effect of Cetuximab Combined with Chemotherapy in Treating Recurrent and Metastatic Colorectal Cancer: A Real-World Case Series

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**Abstract:** ***Introduction: Recurrent and metastatic colorectal cancer (mCRC) continues to carry a poor prognosis despite recent advances in surgical techniques, chemotherapy, and targeted therapies. Cetuximab, a monoclonal antibody targeting EGFR, is commonly used in mCRC, especially in patients with wild - type RAS and BRAF and proficient mismatch repair. However, its efficacy and optimal timing remain debated due to variability in clinical outcomes and toxicity profiles. This retrospective study evaluates the effectiveness and safety of cetuximab - based regimens in Indian patients with recurrent and metastatic colorectal cancer. Methods: Clinical data from 30 patients with confirmed recurrent or metastatic CRC treated between January 2015 and December 2020 were retrospectively reviewed. All patients had wild - type KRAS and received cetuximab - based chemotherapy. Outcomes assessed included overall survival (OS), progression - free survival (PFS), response rates, and treatment - related adverse events. Results: The median age was 58 years; 83.3% were male. According to AJCC staging, 28 patients (93.3%) had Stage IV disease, and 2 (6.7%) had recurrent disease. ECOG performance status was 1 in 46.7% and 2 in 53.3%. Most had left - sided tumors (73.3%), while 20% had right - sided, and 6.7% had transverse colon involvement. Regarding chemotherapy backbones, 56.7% received cetuximab with 5 - FU - based regimens, 16.6% with capecitabine, and others with methotrexate, paclitaxel - carboplatin, or cetuximab monotherapy. Cetuximab was used in the 1st or 2nd line in 43.3% and in later lines in 56.7%. The median OS was 33 months, with a 2 - year OS rate of 76.7%. Median PFS was 3 months, and the 6 - month PFS rate was 36.7%. Partial responses were observed in 40%, stable disease in 13.3%, and progressive disease in the remainder. ORR at first follow - up was 36.7%, and DCR was 50%. Multivariate analysis indicated better OS and PFS in patients with recurrent disease and those receiving cetuximab earlier in treatment. Conclusion: Cetuximab - based chemotherapy demonstrates favorable outcomes in Indian patients with recurrent and mCRC, particularly when administered early in the treatment course. The therapy is associated with acceptable toxicity and improved survival in select subgroups.***

**Keywords:** Cetuximab, colorectal cancer, recurrent disease, metastasis, targeted therapy, clinical outcomes, toxicity, real - world data

## 1. Introduction

Colorectal cancer (CRC), a prevalent form of cancer globally, will eventually develop into metastatic CRC (mCRC) in around 50% of patients [1]. Currently, mCRC is primarily managed with chemotherapy. Common chemotherapy regimens, including FOLFOX4, FOLFIRI, and XELOX, effectively control tumor growth and improve overall survival (OS) and disease - free survival (DFS) rates in patients. However, these treatments are associated with significant side effects [2, 3]. Recent advancements in targeted therapy have led to major improvements in the treatment of advanced colon cancer. By combining chemotherapy with monoclonal antibodies as targeted medications, the survival period of patients can be extended by more than 24 months [4, 5]. Cetuximab is a molecular targeted medicine that specifically binds to epidermal growth factor receptors (EGFRs) in order to inhibit the growth of tumor cells that have a high expression of EGFRs, therefore impeding the progression of the tumor. Recent research findings indicate that cetuximab has made substantial advancements in the treatment of CRC [6, 7]. Prior studies have indicated that the presence of a mutation in the Kirsten Ras (KRAS) gene is a detrimental indicator for the effectiveness of monoclonal antibodies targeting EGFRs. Recent study indicates that only patients with RAS - wild - type (WT) can experience benefits. However, their response rate is approximately 60% following the initial treatment paired with regular chemotherapy [8 - 10]. Due to the distinct clinical and molecular characteristics of left - sided and right - sided colon cancer, anti - EGFR antibodies are more advantageous in treating RAS - WT left - sided colon cancer, including rectal cancer, compared to right - sided colon cancer [11]. The current study conducted a retrospective analysis to evaluate the effectiveness and safety of combining chemotherapy with cetuximab in treating recurrent and metastatic colorectal cancer (rmCRC) at different stages of treatment. Additionally, the study examined the factors that influence the treatment's effectiveness and prognosis.

## 2. Materials and Methods

### Study Design

This study is a single - center, retrospective audit in which the data were collected in a retrospective fashion, encompassing patient, disease, and treatment characteristics.

### Patients

This study is a retrospective audit conducted at a single center. The data was collected retrospectively and includes information on patient demographics, disease features, and treatment details. The trial comprised a cohort of 30 patients, who were diagnosed with mCRC and were admitted to our hospital between January 2015 and December 2020. The inclusion criteria encompassed individuals who were at least 18 years old, had inoperable recurrent or metastatic colorectal cancer (mCRC), tested positive for WT - KRAS by genetic

testing, had an ECOG performance status of 0 - 2, and had no contraindications to chemotherapy. The exclusion criteria encompassed patients who exhibited intolerance to chemotherapy due to severe cardiac, pulmonary, hepatic, or renal conditions, those with metastases in the central nervous system, and individuals with additional malignancies.

**Objectives**

The primary objective of the study was to evaluate effectiveness of cetuximab based chemotherapy through overall survival (OS), progression - free survival (PFS), overall response rate (ORR), disease control rate (DCR) and safety through incidences of hematological and nonhematological toxicities in patients with recurrent and metastatic colorectal carcinomas.

**Study Methods**

Staging was performed for all the patients with confirmed histopathological diagnosis based on TNM classification of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) 8$^{th}$ edition. All patients were administered cetuximab based chemotherapy by the investigator in the given period of time. Cetuximab was first infused at 400 mg/m2 for 120 min and biweekly dose of 500 mg/m2. Combined chemotherapy was conducted as follows: mFOLFOX6 regimen with oxaliplatin intravenously dripped at 85 mg/m2, calcium folinate intravenously dripped at 400 mg/m2 and fluorouracil intravenously injected at 400 mg/m2 on d 1 and then fluorouracil persistently pumped at 2, 400 mg/m2 for 46 h (two weeks were taken as a course of treatment), XELOX regimen with oxaliplatin intravenously dripped at 130 mg/m2 on d 1 and capecitabine tablets orally administered at 850 mg/m2 twice daily during d 1 - 14 (a course of treatment lasted for three weeks), or FOLFIRI regimen with irinotecan intravenously dripped at 180 mg/m2, calcium folinate intravenously dripped at 400 mg/m2 and fluorouracil intravenously injected at 400 mg/m2 on d 1 and then fluorouracil continuously pump - infused at 1, 200 mg/ m2 for 22 h on d 1 - 2 (two weeks were set as a cycle of treatment). Informed consent was waived off in view of retrospective nature of the study.

**Study Endpoints**

In addition to the typical demographic information, the effectiveness of treatment using cetuximab was evaluated. The patients were evaluated using OS, PFS, ORR, and DCR. PFS was defined as the time interval between the initiation of cetuximab and either the occurrence of disease progression or death from any cause, or the most recent follow - up date, whichever came first. The OS was determined by calculating the time from the date of diagnosis to the date of death due to any cause. ORR was determined by patients who achieved complete response (CR) or partial response (PR) during the initial assessment. DCR was defined as the absence of disease progression and comprised patients with CR, PR, and stable disease (SD). The patient's survival was assessed retrospectively during the entire length of the trial.

**Statistical Analysis**

Data was descriptively analyzed using mean and standard deviation or median and interquartile range depending upon the normality of the data. Normality of the data was checked using the Shapiro–Wilk test while categorical variables were reported using frequency and percentage. ORR (CR + PR) and DCR (CR + PR + SD) were reported using frequency and percentage and their 95% Clopper–Pearson confidence interval (CI). Predictors of PFS, and OS were compared using Mantel–Haenszel log rank test and survival curves were generated using Kaplan–Meier method. The corresponding 6 - month and 2 - year survival rates were reported. Median follow - up was calculated using the reverse Kaplan–Meier method. Multivariate analysis was conducted using the cox proportional hazard regression. Proportional hazard assumption was tested using Schoenfeld's residual and did not violate in this data set. Data was analyzed using IBM SPSS version 25.0 (IBM Corp., Armonk, New York, United States) and R Studio version 1.2.1335.

## 3. Results

A total of 30 patients (median age of 58 years at the time of analysis) were evaluated. AJCC staging system revealed 28 (93.3%) patients to be in Stage IV and 2 (6.7%) in recurrent. The ECOG PS was 1 in 14 (46.7%) and 2 in 16 (53.3%). Majority of patients were males (83.3%) with 5 patients (16.7%) having multiple comorbidities and the rest having single or none.22 patients had left sided CRC while, 6 patients had right sided disease while 2 patients had disease in the transverse colon (TC).56.7 % patients had received cetuximab in a background of 5FU based chemotherapy, 16.6 % received with capecitabine based chemotherapy, 1 patient with methotrexate, 2 patients with paclitaxel and carboplatin while 10 % had received cetuximab as a single agent.13 patients (43.3%) had received cetuximab based chemotherapy in 1$^{st}$ and 2$^{nd}$ line, while the rest received the same in 3$^{rd}$ and above lines. Median OS (mOS) was 33 months and 2 - year OS rate in the study was 76.7% while median PFS (mPFS) was 3 months and 6 - month PFS rate was 36.7 %.12 patients (40%) had partial response; 4 patients (13.3%) had stable disease response while the rest had disease progression on initial assessment. ORR was 36.7 % at first follow - up while DCR was 50 %. Patient characteristics are depicted in Table 1. Kaplan Meier Survival Curves for OS and PFS are depicted in Fig 1 and Fig 2 respectively.

**Table 1:** Patient Characteristics

| | |
|---|---|
| **Gender** | |
| Male | 25 |
| Female | 5 |
| **Age (Median)** | 58 years |
| **PS (ECOG)** | |
| I | 14 |
| II | 16 |
| **Stage –** | |
| Recurrent | 2 |
| Metastatic | 28 |
| **Comorb** | |
| Multiple | 5 |
| Single/None | 25 |
| **Sidedness** | |
| Left | 22 |
| Right | 6 |
| TC | 2 |
| **Line of therapy** | |
| **1$^{st}$/2$^{nd}$** | 13 |
| **3$^{rd}$/4$^{th}$** | 17 |

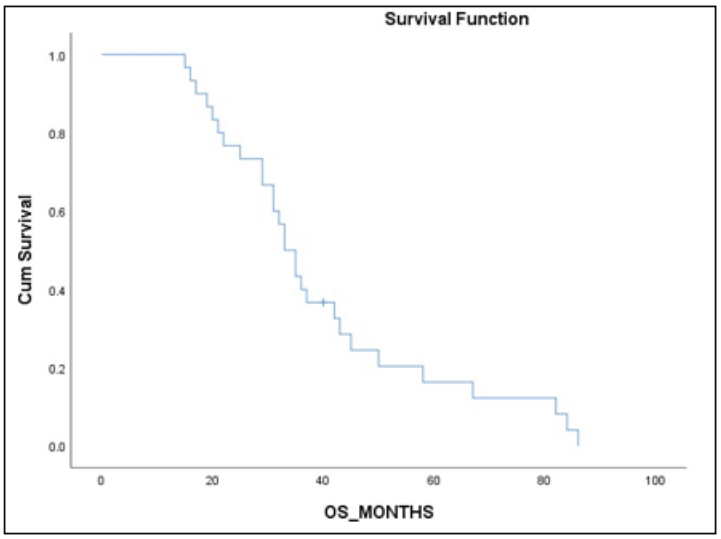


**Figure 1:** KM curve showing OS in months. mOS – 33 months

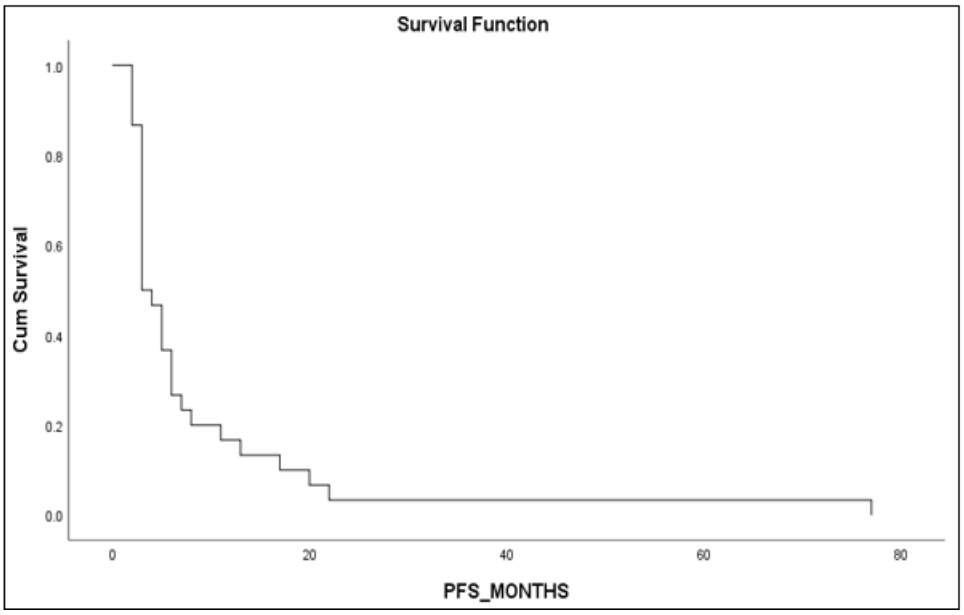


**Figure 2:** KM curve showing PS in months. mPFS – 3 months

**Toxicity Profile**

No patients died of severe adverse reactions during treatment. All patients had different degrees of adverse reactions, mainly including bone marrow suppression, rash, gastrointestinal reactions, hepatic and renal function damage, neurotoxicity and hand - foot syndrome, and most of them were grade I - II and improved after symptomatic treatment. The following adverse reactions were of grade III and above: rash (22%), diarrhea (15%), mucositis (10%) and fatigue (16.7%).

**Prognostic Factors**

The effects of the gender, PS, stage, line of treatment and comorbidities was evaluated as far as clinical outcomes are concerned. Median OS was 36 months (20.97 - 51) in females, compared to 33 months (29.32 - 36.7) in males (p=0.13). Median OS was 32 months (24.6 - 39.3) in patients with PS 1, compared to 33 months (25.1 - 40.8) in PS 2 (p=0.86). Median OS was 37 months in patients with recurrent disease, compared to 33 months (28.9 - 37.1) in metastatic stage (p=0.30). Median OS was 35 months (26.8 - 43.2) in patients with who have received cetuximab based chemotherapy in 1$^{st}$ or 2$^{nd}$ line, compared to 33 months (27.6 - 38.4) in patients receiving the same treatment in 3$^{rd}$ and above lines (p=0.88). Median OS was 33 months (28.1 - 37.9) in patients with none or single comorbidity, compared to 35 months (0.7 - 69.35) in patients with multiple comorbidities (p=0.465). Median PFS was 6 months (0 - 12.4) in females, compared to 3 months (2 - 4) in males (p=0.09). Median PFS was 5 months (2.3 - 7.6) in patients with PS 1, compared to 3 months (2.4 - 3.4) in PS 2 (p=0.94). Median PFS was 7 months in patients with recurrent disease, compared to 3 months (2.1 - 3.9) in metastatic stage (p=0.32). Median PFS was 5 months (3.6 - 6.4) in patients with who have received cetuximab based chemotherapy in 1$^{st}$ or 2$^{nd}$ line, compared to 3 months (2.6 - 3.4) in patients receiving the same treatment in 3$^{rd}$ and above lines (p=0.79). Median PFS was 3 months (2.1 - 3.9) in patients with none or single comorbidity, compared to 5 months (3.2 - 6.7) in patients with multiple comorbidities (p=0.51).

## 4. Discussion

Studies have shown that EGFR is significantly expressed in 72 - 82% of patients with advanced mCRC and is strongly

associated with malignant characteristics such as tumor cell invasion, metastasis, and tumor angiogenesis [11]. Research conducted in China and other locations has shown that a high level of EGFR expression is associated with a negative prognosis [12]. The EGFR subfamily is a part of the tyrosine kinase receptor family. Abnormal activation of EGFRs is strongly linked to the growth, migration, and angiogenesis of cancerous tumors [13]. Cetuximab, a monoclonal antibody that targets EGFRs, can inhibit the binding of epidermal growth factor to the EGFR site and suppress the activation of intracellular tyrosine kinases. This effectively blocks the signaling pathway involved in cell growth. Consequently, it has gained significant attention in recent years as a potential treatment for EGFR KRAS - WT (wild type) colon cancer [14]. A study demonstrated that patients with KRAS - WT mCRC can significantly benefit from the combination of cetuximab and chemotherapy, resulting in a notable extension of their overall survival by over 30 months [15]. A meta - analysis of 2, 188 patients with metastatic colorectal cancer (mCRC) revealed that the prevalence of KRAS gene mutation is 38% (829 out of 2, 188). In addition, the response rate to cetuximab therapy was assessed by grouping patients based on their KRAS status. The results showed a significant difference in the response rate between the group with KRAS mutations and the group without mutations [14% (119/829) vs.39% (529/1, 359) ] ($p<0.01$). Furthermore, the group with KRAS mutations had significantly shorter mPFS and mOS compared to the group without mutations ($p<0.05$). These findings indicate that KRAS - mutant patients do not experience any tumor response or benefits in terms of PFS and OS after receiving chemotherapy plus cetuximab [16]. In the phase III CRYSTAL trial conducted by Van Cutsem et al, patients were randomly allocated to either the C225 + FOLFIRI group or the FOLFIRI group. The former group exhibited significantly greater rates of ORR, mPFS, and mOS compared to the later group (57.3% vs.39.7%, 9.9 months vs.8.4 months, and 23.5 months vs.20 months, respectively). These differences were found to be statistically significant ($p<0.0001$, $p=0.0012$, and $p=0.0094$) [17]. The results of the OPUS research demonstrated that the objective response rate (ORR), mPFS, and mOS were significantly greater in the C225 + FOLFOX group compared to the FOLFOX group (57.3% vs.34%, $p=0.0027$, 8.3 months vs.7.2 months, $p=0.0064$, and 22.8 months vs.18.5 months, $p=0.39$) [18]. In the CALGB 80405 trials, the effectiveness of various targeted drugs combined with chemotherapy regimens was compared. The subgroup analysis revealed statistically significant differences between C225 + FOLFOX and C225 + FOLFIRI in terms of ORR, mPFS, and mOS. Specifically, C225 + FOLFOX had an ORR of 67% compared to 62% for C225 + FOLFIRI, mPFS of 11.3 months compared to 12.7 months, and mOS of 32.5 months. The duration of the study was 32 months compared to 19 months [19]. The aforementioned trials indicate that the combination of cetuximab with chemotherapy can significantly improve the outcomes of patients with advanced CRC, increasing their ORR and prolonging their PFS and OS. However, these benefits are not statistically associated with a specific chemotherapy regimen. In this study, there were no significant differences found between various parameters when analyzed together. However, both the median OS and PFS showed a more favorable trend in patients with recurrent disease compared to those with metastatic disease. Additionally, patients who received cetuximab - based chemotherapy in the first and second lines had better outcomes compared to those who received it in the third line and beyond. The initial follow - up of cetuximab - based chemotherapy yielded an ORR of 36.7%, with DCR of 50%, which was similar to the percentage seen in the existing literature. In the trial, the mOS was 33 months, with a 2 - year OS rate of 76.7%. The mPFS was 3 months, with a 6 - month PFS rate of 36.7%. The decreased mPFS can be attributable to several factors, including the predominant use of cetuximab in the third line of treatment and beyond, the lower PS of the patients, the smaller sample size, and the non - uniformity of the combination chemotherapy regimens. Regarding safety, the majority of adverse events seen were of grade I - II, and they showed improvement following symptomatic therapy. Indian patients had higher incidence rates of rash and diarrhea compared to their Western counterparts. The outcomes of this study indicated that the recurrent tumors compared to metastatic tumors, as well as initiating cetuximab - based treatment in the first or second line rather than in subsequent lines, was an autonomous risk factor that influenced the mPFS and mOS of patients. The discrepancy in this outcome compared to the one documented in the literature is likely attributed to the limited sample size and the variation in methodology. [20, 21]. This retrospective study was constrained by its restricted sample size and less complete follow - up content. Hence, the findings of this investigation should be validated through future multicenter, large - sample prospective clinical studies, incorporating immunohistochemistry and testing of tumor markers and genes.

## 5. Conclusions

Cetuximab plus chemotherapy is efficacious while in treating recurrent and mCRC, resulting in a higher long - term survival rate and a lower disease progression rate, more so in recurrent setting and when used as 1$^{st}$ and 2$^{nd}$ line therapy. The effect is associated with tolerable adverse reactions as far as Indian set of patients is concerned.

**Conflict of Interest:** The authors declare no conflict of interests.

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