

Survival Rate of Colorectal Cancer Patients Receiving Chemotherapy based on Tumor Location and K-Ras Gene Mutation Status: A Systematic Review

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Abstract

Introduction: Colorectal cancer (CRC) is a remarkable global health burden, considering its high morbidity and mortality. For both resectable and unresectable colorectal cancer (CRC), chemotherapy is the first-line option. The survival rate was significantly affected by the location of the tumor and the mutation status of the KRAS gene. This study aimed to systematically synthesize current evidence on how primary tumor location and KRAS mutations influence the survival of colorectal cancer patients receiving chemotherapy. **Methods:** We performed a systematic search of the electronic databases with defined inclusion and exclusion criteria. Independent reviews were performed by two reviewers of the literature that was included. Methodological quality of the studies included was evaluated using the Joanna Briggs Institute (JBI) critical appraisal methods. Information was obtained and qualitatively analyzed. The analysis was performed through a qualitative measure. P-value < 0.05 is considered statistically significant. **Results:** A total of 11 studies were reviewed. All the studies reviewed reported improved quality of methodology. The qualitative synthesis suggested a trend toward worse survival for patients with right-sided tumors, although some studies reported no statistically significant difference between tumor locations. In contrast, the association between KRAS gene mutations and poorer survival outcomes appeared more consistent across studies. Overall, these findings indicate that KRAS mutations and, to a lesser extent, right-sided tumor location may predict unfavorable outcomes in chemotherapy-treated colorectal cancer patients. **Conclusion:** KRAS mutations were linked to poorer survival, while right-sided tumor location showed a less consistent but generally unfavorable trend among chemotherapy-treated colorectal cancer patients.

Keywords: Chemotherapy- colorectal cancer- KRAS- location- survival

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Introduction

Colorectal cancer (CRC) represents a major global health burden due to its high morbidity and mortality rates. It ranks as the third most common cancer and the third leading cause of cancer-related deaths worldwide [1, 2]. Its incidence has also been increasing among younger adults in recent decades [3]. The development of CRC is a multistep process influenced by both genetic and sporadic

alterations. Among these, BRAF and DNA mismatch repair (MMR) pathways are among the most extensively studied genetic aberrations in colorectal carcinogenesis [4-6]. Furthermore, poor histopathological features are often associated with worse clinical outcomes, including metastasis [7].

Chemotherapy remains a key treatment modality

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to control disease progression and alleviate symptoms, particularly for unresectable CRC, and it is also used in adjuvant and neoadjuvant settings [8]. Favorable outcomes have been achieved in both resectable and unresectable cases [9]. As a complementary approach, adherence to healthy dietary habits may enhance chemotherapy efficacy and improve treatment response [10]. However, not all patients benefit equally from chemotherapy, with some showing minimal response or disease progression despite treatment [11].

Angiolymphatic invasion, tumor location, lymph node harvest, and overall clinical condition of the patient are other parameters that influence the efficacy of chemotherapy [12, 13]. KRAS gene mutations have been reported to be responsible for resistance to specific anti-cancer therapies and associated with a more invasive tumor phenotype and worse prognosis [14]. Tumor site has also been linked to clinical outcome; some analyses have proposed that patients with left-sided tumors have improved survival versus right-sided [15]. These two variables KRAS mutation status and sidedness of tumor have come to the forefront as major prognostic and response-to-treatment factors in recent years [16].

Although the prognostic value of tumor location and KRAS mutation in colorectal cancer has been extensively investigated, few studies have specifically consolidated their combined impact among patients receiving chemotherapy. Therefore, this systematic review aims to synthesize and confirm current evidence regarding the influence of primary tumor location and KRAS mutation status on the survival outcomes of colorectal cancer patients treated with chemotherapy.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. A systematic search was performed across several electronic databases, including PubMed, ScienceDirect, EBSCOHost, Cochrane, and ClinicalTrials.gov, using predefined inclusion and exclusion criteria. The search terms were constructed as follows: ("Colorectal" AND ("Cancer" OR "Tumor" OR "Neoplasm" OR "Carcinoma" OR "Malignancy")) AND ("Chemotherapy" OR "Antineoplastic agent") AND ("Survival") AND ("KRAS" OR "Location"). Additional related keywords were applied depending on the specific database. The search strategy primarily employed keyword combinations, although the inclusion of MeSH and Emtree terms may further enhance comprehensiveness in future updates.

The inclusion criteria consisted of clinical trials involving patients diagnosed with colorectal cancer who received chemotherapy, studies that evaluated KRAS gene mutation and/or tumor location as predictive or prognostic factors, and research reporting survival outcomes such as overall survival (OS) or progression-free survival (PFS). Studies were excluded if no full-text was available or if they were published in languages other than English.

The methodological quality of included studies was

assessed by the Joanna Briggs Institute (JBI) critical appraisal tools [18]. Those studies that satisfied the requirements for quality were entered into further analysis. Literature screening and data extraction were performed by AA and BB independently. Any disagreements were discussed until a consensus was reached. The following information was retrieved: the first author's name, publication year, study design, sample size, male percentage, average or median age of patients at diagnosis, cancer stage (tumor node metastasis), chemotherapy regimens, and survival endpoints. When applicable, information on OS and PFS were extracted.

Current state of knowledge

Recent advances in molecular oncology have enhanced understanding of how tumor biology and genetic alterations influence colorectal cancer (CRC) prognosis and treatment outcomes [4-6, 14]. Tumor location has been recognized as a determinant of clinical presentation, molecular profile, and survival. Right-sided CRCs, originating from the embryologic midgut, frequently exhibit microsatellite instability, mucinous histology, and mutations in KRAS and BRAF, whereas left-sided CRCs, derived from the hindgut, more often display chromosomal instability and overexpression of EGFR and HER2, leading to better responses to anti-EGFR therapy [19-23]. In a single-center cohort of patients undergoing curative resection with adjuvant chemotherapy, tumor sidedness was also associated with overall survival [24].

Consistent with these findings, Ramadan et al. reported that primary tumor location significantly affected overall survival among metastatic CRC patients receiving systemic chemotherapy and biologic therapies [25]. KRAS mutations, observed in approximately 30–50% of CRC cases, drive aberrant MAPK signaling that promotes uncontrolled proliferation, inhibits apoptosis, and confers resistance to anti-EGFR monoclonal antibodies such as cetuximab and panitumumab [26-29]. Patients harboring KRAS mutations consistently demonstrate shorter overall and progression-free survival compared with those with wild-type tumors [30-32].

Furthermore, emerging evidence suggests that tumor sidedness interacts with KRAS status to influence treatment response. Left-sided, KRAS wild-type tumors benefit more from anti-EGFR regimens, whereas right-sided or KRAS-mutant tumors respond better to anti-VEGF therapy such as bevacizumab [33-35]. These findings highlight the importance of integrating molecular profiling and primary tumor location into chemotherapy decision-making, although variability across studies underscores the need for standardized research to validate these prognostic associations [36-38].

Results

Eleven studies were found and included after a thorough search and selection (Figure 1). All studies were deemed to have good methodological quality based on the Joanna Briggs Institute (JBI) appraisal, which confirmed that populations were clearly defined, inclusion

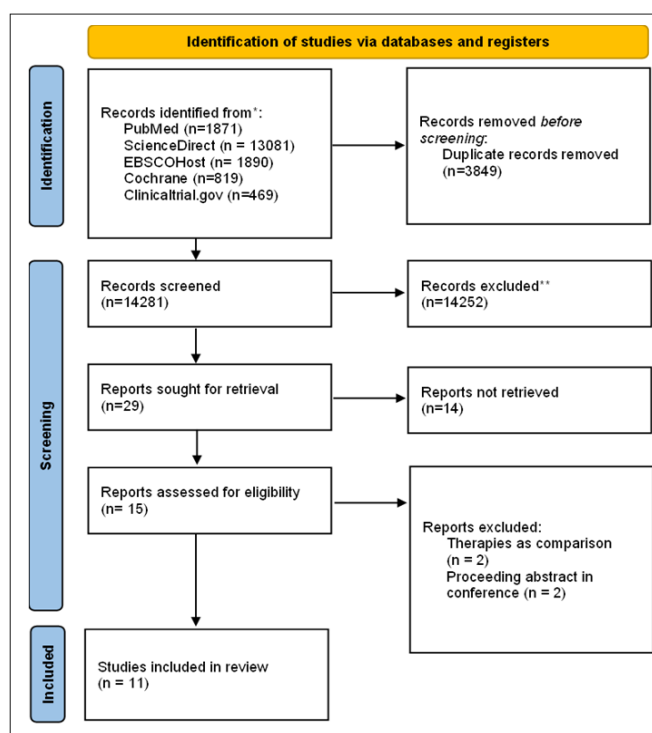


Figure 1. Shows the PRISMA Flow of Study Selection. Out of 18130 records initially identified, 14281 were screened, 14270 were excluded, and 11 studies met the inclusion criteria.

criteria were appropriate, and outcome measures were reliable across studies. (Table 1). The studies were well distributed among Asia, Africa, and Europe. All studies involved patients with colorectal cancer who were admitted for chemotherapy. Most of the included patients had metastatic disease with a mean or median age above 50 years. The majority were male. Where reported, the proportion of left-sided tumors was often higher than right-sided, consistent with global epidemiologic trends (Table 2).

The qualitative synthesis revealed that patients with KRAS gene mutations generally had poorer survival outcomes compared with those with wild-type KRAS

across most included studies. For tumor location, results were more heterogeneous. While several studies indicated worse survival for patients with right-sided tumors, others (e.g., Alkader et al. and Chida et al.) reported no significant difference between right- and left-sided disease. In Signorelli et al., two-year overall survival (OS) was numerically higher in left-sided than right-sided tumors but did not reach statistical significance (82.9% vs 67.5%; $P = 0.32$). In contrast, progression-free survival (PFS) favored left-sided tumors with both a longer median PFS (11 vs 7 months) and a higher 1-year PFS rate (46.8% vs 24.2%; $P = 0.0005$). Therefore, the overall trend suggests that right-sided tumor location may be associated with

Table 1. Summarizes the Methodological Quality of Included Studies, All of which were Rated as “Good” Based on the JBI Cohort Checklist.

Authors	Design	Appraisal Items*											Comments	Reference
		1	2	3	4	5	6	7	8	9	10	11		
Alkader et al	RC	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good	19
Chida et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good	20
De Roock et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good	21
Diez-Alonso et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good	22
Diez-Alonso et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good	23
Jaruhathai et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good	24
Ramadan et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good	25
Rasmy et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good	26
Signorelli et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good	27
Tharin et al	RC	NA	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good	28
Montes et al	RC	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good	29

Abbreviations, RC = Retrospective cohort; Y = Yes; N = No; UC = Unclear; NA = Not applicable. Appraisal Items 1–11 correspond to the Joanna Briggs Institute Checklist for Cohort Studies, assessing (1) similarity of groups, (2) exposure measurement, (3) confounding factors, (4) strategies to deal with confounding, (5) outcome measurement, (6) follow-up completeness, (7) statistical analysis, (8) reliability of outcomes, (9) participant inclusion, (10) study design appropriateness, and (11) overall validity [18].

Table 2. Shows that Most Studies were Retrospective Cohorts Conducted Across Asia, Africa, and Europe, Involving Patients Aged ≥ 51 Years, Predominantly Male, and about Half with KRAS Mutations.

Authors	Design	Location	Population (N)	Age (years)	Male (%)	Right-sided (%)	Metastasis (%)	KRAS mutant (%)	Reference
Alkader et al	RC	Jordania	120	52.6 $\pm$ 12.6	60.8	17.5	100	43.3	19
Chida et al	RC	Japan	696	65 (24-88)	55.3	32.9	100	100	20
De Roock et al	RC	Belgium	113	59.6 $\pm$ 10.7	61.9	-	100	41.6	21
Díez-Alonso et al	RC	Spain	104	63 $\pm$ 10	58.7	19.2	32.7	49	22
Díez-Alonso et al	RC	Spain	149	63 $\pm$ 10	57	43	54.6	50.3	23
Jaruthathai et al	RC	Thailand	153	62.2 $\pm$ 10.9	62.1	-	0	-	24
Ramadan et al	RC	Saudi Arabia	136	64	57.65	16.2	100	-	25
Rasmy et al	RC	Saudi Arabia & Egypt	220	51 (35-76)	65.6	15	100	38.9	26
Signorelli et al	RC	Italy	130	66.5 vs 62.3	63.08	28.4	55.39	46.92	27
Tharin et al	RC	France	702	65.7 $\pm$ 23.6	56.6	35.3	100	47.1	28
Montes et al	RC	Spain	337	65 (32.2-87.4)	62.9	29.1	100	100	29

Abbreviations: RC = Retrospective cohort; KRAS = Kirsten rat sarcoma viral oncogene

Table 3. Indicates that Right-sided Tumors and KRAS Mutations were Generally Associated with Poorer Overall Survival or Progression-free Survival, Although Effect Sizes Varied Across Studies.

Authors	Tumor location	Outcome factors	Reference
		KRAS	
Alkader et al	No significant difference in OS between right- vs left-sided tumor (HR = 1.008; 95% CI = 0.574-1.770, P = 0.978)	Significant difference of OS between KRAS mutant vs wild type (HR = 2.045; 95% CI = 1.291-3.237; P = 0.002)	19
Chida et al	No significant difference in PFS between left- vs right-sided tumor (HR = 0.93; 95% CI = 0.79-1.10, P = 0.417) No significant difference of OS between left- vs right-sided tumor after adjustment (aHR = 0.99; 95% CI = 0.82-1.21, P = 0.976)	Significant difference of PFS between KRAS exon 2 mutation G12c vs non-G12c after adjustment (aHR = 1.43; 95% CI = 1.04 - 1.96, P = 0.03) Significant difference of OS between KRAS exon 2 mutation G12c vs non-G12c after adjustment (aHR = 1.42; 95% CI = 1.01 - 2.00, P = 0.044)	20
De Roock et al	-	Significantly better OS among patients with KRAS wild type vs mutant (43.0 weeks vs 27.3 weeks, P = 0.020)	21
Díez-Alonso et al	-	Significant difference of OS between KRAS mutant vs wild type (HR = 2.484; 95% CI = 1.472-4.192, P = 0.001)	22
Díez-Alonso et al	-	Significant difference of OS between KRAS mutant vs wild type (HR = 2.144; 95% CI = 1.342-3.424, P = 0.001)	23
Jaruthathai et al	Significant difference of OS between right-sided vs left-sided tumor (aHR = 2.875; 95% CI = 1.397-5.920, P = 0.004)	-	24
Ramadan et al	Significantly better OS among patients with left-sided tumors (P = 0.03)	-	25
Rasmy et al	-	Significantly better OS among patients with KRAS wild type vs mutant (25.04 months vs 19.57 months; P = 0.002) Significantly better PFS among patients with KRAS wild type vs mutant (11.45 months vs 9.60 months; P = 0.001)	26
Signorelli et al	Two-year OS is higher in left- vs right-sided tumors but not statistically significant (82.9% vs 67.5%; P = 0.32). Significantly better PFS among patients with left-sided tumors (11 months vs 7 months; P = 0.0005)	-	27
Tharin et al	Folinic acid, 5FU, and oxaliplatin gave satisfactory outcomes when compared to folinic acid, 5FU, and irinotecan among both left-sided tumor and right-sided tumors	-	28
Montes et al	-	Patients with a KRAS mutation among G12S significantly showed poorer outcomes by shortest OS (median 10.3 months; 95% CI = 2.5-18.0)	29

Abbreviations, OS = Overall survival; PFS = Progression-free survival; KRAS = Kirsten rat sarcoma viral oncogene; 5FU = 5-fluorouracil

inferior outcomes, though the evidence is not entirely consistent (Table 3).

Discussion

This systematic review consolidates current evidence on the prognostic significance of tumor location and KRAS mutations in colorectal cancer (CRC) patients receiving chemotherapy. While these factors have long been recognized as important prognostic markers, our synthesis provides a focused understanding of their impact in chemotherapy-treated populations. The findings reaffirm that both molecular and anatomic tumor characteristics remain essential in predicting survival outcomes and guiding individualized therapeutic decisions.

The relationship between KRAS mutations, tumor sidedness, and survival outcomes in CRC is complex. While KRAS mutations are consistently associated with poorer overall and progression-free survival, the prognostic effect of tumor location appears more heterogeneous across studies [19-29]. Anatomically, the left and right sides of the colon differ in embryologic origin; right-sided tumors derive from the midgut, whereas left-sided tumors originate from the hindgut, resulting in distinct gene expression and molecular profiles [30-32]. Left-sided CRCs are more likely to activate the WNT and MYC pathways, with increased β -catenin, HER2, and EGFR expression, whereas right-sided CRCs more frequently exhibit RAS and BRAF mutations as well as JAK-STAT pathway activation, correlating with microsatellite instability and mucinous histology [33, 34]. These molecular distinctions contribute to differing therapeutic responses and survival outcomes.

Previous studies have demonstrated that right-sided CRCs tend to have larger tumor size, poorer differentiation, and higher rates of signet-ring and mucinous histology, which are associated with unfavorable prognosis [35, 36]. Multiple analyses have confirmed that patients with right-sided tumors generally exhibit worse overall survival compared with those with left-sided tumors [33-35]. However, this trend is not universal, as some studies (e.g., Alkader et al. and Chida et al.) found no statistically significant difference between tumor locations [19, 20]. These findings illustrate that PFS benefits by tumor sidedness may be more pronounced than OS differences in some cohorts, as seen in Signorelli et al., where the two-year OS difference was not statistically significant despite a significantly better PFS for left-sided tumors. Variations in chemotherapy regimens, patient characteristics, and statistical adjustments for confounders may explain these discrepancies [25, 28].

From a treatment perspective, the efficacy of first-line chemotherapy combinations such as FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) and FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) has shown comparable outcomes for left- and right-sided tumors [28]. Nonetheless, the use of monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) has demonstrated differential benefits depending on tumor location and KRAS status. Patients with left-sided, KRAS

wild-type tumors experience longer overall survival with anti-EGFR therapy compared to those with right-sided tumors, who respond better to anti-VEGF therapy such as bevacizumab [36, 37]. This pattern emphasizes the clinical relevance of molecular and anatomic factors in therapeutic selection for metastatic CRC.

Mechanistically, KRAS mutations have been shown to promote tumor progression via sustained activation of the MAPK pathway, leading to uncontrolled cellular proliferation and resistance to apoptosis [38]. Studies by Drosten and Barbacid, as well as Fang and Richardson, demonstrated that KRAS mutations enhance MAPK activity and reduce GTPase function, thereby accelerating carcinogenesis [38, 39]. The prevalence of KRAS mutations in CRC ranges from 30% to 52%, consistent with our findings [40]. Moreover, emerging data highlight the heterogeneity among KRAS mutation subtypes; for example, G12C mutations are associated with particularly poor outcomes in terms of both OS and PFS compared to other exon 2 mutations [20, 29]. These findings suggest that not all KRAS mutations exert equivalent biological effects, and that further research is warranted to refine prognostic models based on mutation subtypes.

Taken together, the evidence from this systematic review confirms that both right-sided tumor origin and KRAS mutation predict unfavorable survival outcomes in chemotherapy-treated CRC patients. These findings align with prior meta-analyses emphasizing the importance of tumor biology and sidedness in personalized therapy [33-37]. Integrating KRAS testing and primary tumor location into routine clinical decision-making may therefore improve treatment stratification and optimize outcomes. However, heterogeneity in study design, treatment regimens, and reporting underscores the need for larger, prospective, and standardized studies to confirm these associations across diverse patient populations.

In conclusion, this systematic review confirms the consistent adverse prognostic impact of KRAS mutations and a variable but overall unfavorable trend for right-sided tumors in chemotherapy-treated colorectal cancer. These findings underscore the importance of integrating tumor biology and location into therapeutic decision-making and support the continued refinement of personalized treatment strategies.

Ethical considerations

Ethical approval and consent were not required.

Conflict of interest

The authors declare no conflict of interest.

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Author Contributions

Study Design

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Final Approval

All authors have read and approved the final manuscript

Registration

This systematic review is registered in the PROSPERO international prospective register of systematic reviews (registration number CRD2024628344). The complete protocol is available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42024628344.

Patient and Public Involvement

No patient or public involvement was applicable to this study, as it is a systematic review and does not involve the collection of primary data from individuals.

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