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Comparing the effectiveness of panitumumab combined with FOLFOX4 treatment in patients with colon cancer vs. rectal cancer

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Abstract. The greatest cause of cancer-related fatalities globally is colorectal cancer (CRC). Targeted therapies like panitumumab are revolutionizing its treatment. Our study focuses on the impact of KRAS and NRAS genotypes on the efficacy of panitumumab and also on the significance of tumor location (colon vs. rectum) in treatment outcomes. We selected a specific clinical trial (NCT00364013) for further statistical analysis. Our work adds to what has already been learned by showing that KRAS and NRAS genotypes are important for how well panitumumab works to treat CRC. Meanwhile, the P-value of 0.49 demonstrated that, in contrast to what we had previously believed, the tumor site had no significant impact on progression-free survival outcomes. Our research highlights the critical role of genotyping in personalized CRC therapy and raises questions about the established opinion that tumor location impacts therapy outcomes significantly. These findings may help CRC management move toward a more genotype-centric approach, optimizing therapies and reducing expenses. Nevertheless, future studies with more significant cohorts would be needed to confirm these findings, given the larger sample size.

Keywords: colorectal cancer, panitumumab, survival analysis, difference

1. Introduction

Colorectal cancer (CRC) is the most common cancer worldwide. According to the statistics from 2023, CRC will continue to be the second main cause of cancer death in the United States, with 153,020 new cases and 52,550 deaths. The malignancy has become more common among individuals under the age of 50 [1]. Colorectal cancer forms within the gastrointestinal tract and includes the colon sites that are

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present in the longer, tubular region of the intestines, whereas rectal cancer appears in the last few inches of the intestines [2].

The epidermal growth factor receptor, often referred to as EGFR, has been recognized as a potential target in many human cancers, such as colorectal cancer (CRC) [3]. The transmembrane tyrosine kinase receptor EGFR affects various cellular processes [4]. EGFR activity can be increased by a number of factors, including regularly occurring mutations and alterations in the extracellular domain. These mutations in the EGFR increase the activity of downstream pathways for signaling, particularly the RAS pathways, which encourage cancer formation [5].

RAS protein mutations commonly occur in various human cancers, including colorectal cancer (CRC). The significance of KRAS gene mutations has been underlined by findings indicating they are accurate predictors of response to EGFR-targeting treatments [6]. It is essential to understand the development of better methods of treatment to comprehend how the mutation in KRAS may cause resistance against some chemotherapy treatments. Due to mutations in the KRAS gene, additional signaling pathways are still put into effect, resulting in resistance. In metastatic colorectal cancer, Lievre and colleagues have observed an association between KRAS mutations and a reduced response to anti-EGFR therapy. Considering the major treatment ramifications of this discovery, it is essential to consider the KRAS gene mutation condition when choosing targeted therapies [7]. The mutated KRAS gene can still support tumor growth and survival even while EGFR is suppressed. Conversely, when these mutations are not present, the KRAS gene remains in its "wild-type" state. Preliminary studies by Amado and colleagues suggest that patients with this "wild-type KRAS" profile may respond more favorably to therapies like panitumumab [8].

An antibody known as panitumumab specifically targets EGFR, which is found on the surfaces of colorectal cancer cells as well as other cancer cells. By binding to EGFR, panitumumab effectively blocks downstream signaling pathways involved in cell growth and division. Consequently, gaining a deeper understanding of panitumumab's molecular mechanisms could guide the development of personalized treatment plans and improve clinical outcomes [9].

The general principle behind using panitumumab to treat metastatic colorectal cancer (mCRC) encompasses both colon and rectal cancers. These two cancer types, however, may require different treatment approaches. Panitumumab is an option either as a first-line therapy or in subsequent rounds of treatment for colon cancer, whereas it is often administered as pre-operative therapy for rectal cancer. Therefore, understanding the distinct challenges and goals of treating each cancer type is crucial for optimizing the effectiveness of the drug.

In this study, we examined the prognostic significance of panitumumab in patients with wild-type KRAS through a phase III randomized trial. Participants in this study had primary malignancies originating either from the colon or the rectum. The main goal of this study was to find out if patients with primary rectal cancer responded differently to panitumumab monotherapy in terms of progression-free survival (PFS) and overall survival (OS) than those with primary colon cancer, especially when the tumors had wild-type (WT) KRAS.

2. Method

2.1. Data Source

The data for the current study were derived from randomized clinical trials (NCT00364013) published on Project Data Sphere (PDS). The trial, which ran from August 2006 to March 2013, included 935 patients with colorectal cancer and had both control and intervention arms. Patients in the intervention group received both panitumumab and FOLFOX, while those in the comparative group received FOLFOX alone. All procedures complied with institutional and national research committees' ethical guidelines. All study participants gave informed consent.

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2.2. KRAS and NRAS Genotypes:

According to Amado et al. (2008), panitumumab's effectiveness in treating colorectal cancer patients depends on the presence of wild-type KRAS and NRAS genes[10]. Each patient sample's KRAS and NRAS exon expression (exons 2, 3, and 4) was described in the dataset. Out of the 935 colorectal cancer samples, 401 with wild-type KRAS and NRAS were selected for research and analysis. Samples with wild-type expression across all examined exons were included.

2.3. Data Collection

From the dataset, we collected information on treatment type (panitumumab plus FOLFOX or FOLFOX alone), age at diagnosis, gender, race, body weight, body height, diagnosis type (colon or rectal), and mutations in KRAS and NRAS exons, along with overall survival (OS) and progression-free survival (PFS). Our study primarily focuses on the efficacy difference between colon and rectal cancer groups; therefore, our Cox regression model is based solely on the intervention group. Patients in this group were identified by actual treatment data from the dataset.

Table 1. The distribution of sample features

Characteristic	FOLFOX alone, N=194[1]	Panitumumab + FOLFOX, N=207[2]	p-value
LIVERMET			0.4
N	28 (14%)	24 (12%)	
Y	166 (86%)	183 (88%)	
SEX			0.7
Female	70 (36%)	71 (34%)	
Male	124 (64%)	136 (66%)	
RACE			0.4
Asian	1 (0.5%)	3 (1.4%)	
Black or African American	4 (2.1%)	2 (1.0%)	
Hispanic or Latino	4 (2.1%)	10 (4.8%)	
Other	3 (1.5%)	2 (1.0%)	
White or Caucasian	182 (94%)	190 (92%)	
B_METANM			0.010
1	37 (19%)	47(23%)	
2	73 (38%)	70(34%)	
3	51(26%)	49 (24%)	
4	22 (11%)	39(19%)	
5	8 (4.1%)	0 (0%)	
6	3 (1.5%)	2 (1.0%)	
DIAGTYPE			0.4
Colon	119 (61%)	135 (65%)	
Rectal	75 (39%)	72 (35%)	

Note: [1]n (%); [2]Pearson's Chi-squared test; Fisher's exact test

Table 1 shows a visualization of the results of the KM analysis of tumor types in the group using panitumumab. The P value is 0.49. Under the condition that the proportions of the two tumor types are similar, the P value indicated that the tumor type was significantly unrelated to survival rate in the patient population using panitumumab.

Based on their primary tumor diagnosis, patients with wild-type KRAS and NRAS were divided into colon and rectal cancer groups. The primary outcome measure for this study was PFS among patients receiving panitumumab plus FOLFOX treatment. PFS was outlined in the NCT00364013/protocol as

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the period of time from the date of randomization to the date of disease progression. As a secondary outcome measure, OS was calculated from the time of randomization to the date of death. Age at diagnosis, gender, body weight, and body height were included as covariates in the Cox regression model. Most patients in the dataset were white, constituting about 94% of the patient population. Asians, African Americans, Hispanics, and other races made up the remaining 6%. Therefore, we opted to exclude race as a factor in our final model.

2.4. Statistical Analysis

The dataset provides information on progression-free survival (PFS) and overall survival (OS) for patient samples. We employed Cox regression models (the proportional hazards model) and Kaplan-Meier survival estimates (the KM method) to evaluate the associations between tumor type and survival rate in colorectal cancer patients. Due to the limited number of samples, progression-free survival (PFS) was used to construct hazard functions.

First, we selected all potential influencing factors on survival rate as covariates to construct a Cox regression model. This included eight covariates: actual treatment, sex, age, baseline weight, tumor diagnosis, etc. A proportional hazards (PH) hypothesis test was carried out for these eight covariates. The p-values for all covariates were well above 0.1, indicating that all covariates met the PH hypothesis; thus, time dependence did not need to be considered in the regression model. The Akaike Information Criterion (AIC) method was used to optimize the model. Five variables were kept and used to fit the Cox regression model: tumor type, age, sex, number of baseline metastatic sites, and actual treatment. The hazard ratios (HR) and 95% confidence intervals (95% CI) were determined for each factor.

Second, we subdivided the study population based on each sample's actual treatment. According to the data, there were 207 samples with wild-type KRAS and NRAS that had been treated with panitumumab. The KM method was employed to evaluate the associations between tumor type and treatment outcomes in patients who used panitumumab. This study used a significance level of 0.05 for statistical inferences other than interactions. All p-values reported in this study are two-sided. All analyses were performed using R (version 4.2.3).

3. Result

3.1. KRAS and NRAS Genotype Selection

In alignment with Amado et al.'s (2008) seminal work, our study necessitated the selection of colorectal cancer samples exhibiting wild-type KRAS and NRAS for assessing panitumumab's efficacy. We screened a dataset containing 935 patient samples and isolated 401 samples where all exons (2, 3, and 4) for both KRAS and NRAS genes were expressed as wild-type. This meticulous screening strategy involved evaluating the expression profiles of six exons across the two genes to confirm wild-type status.

3.2. Survival Metrics

Our dataset provided data points for both progression-free survival (PFS) and overall survival (OS). Due to the limited sample size, we employed PFS as the primary outcome metric to construct hazard functions.

3.3. Cox regression models

Initially, eight covariates were chosen for the Cox proportional hazards model, encompassing factors like actual treatment, sex, age, baseline weight, and tumor diagnosis. Preliminary tests for the proportional hazards (PH) assumption yielded p-values greater than 0.1 for all covariates, indicating that none violated the time-dependency assumption. Subsequent optimization using the Akaike Information Criterion (AIC) method led to the retention of five key factors: actual treatment, age, sex, number of baseline metastatic sites (B_METANM), and tumor type. Hazard ratios (HR) and their corresponding 95% confidence intervals (95% CI) were computed for each retained covariate.

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3.4. Kaplan-Meier Analysis

After segregating the study population by actual treatment, 207 samples with wild-type KRAS and NRAS were identified as having received panitumumab. A Kaplan-Meier survival analysis was conducted specifically on this subset to assess the influence of tumor type on survival outcomes.

3.5. Statistical software and significance level

All statistical calculations were carried out using R software (Version 4.2.3). All statistical tests were run with a significance level of 0.05, with the exception of interaction terms. P-values are always reported on both sides.

3.6. Finding

Through Cox regression modeling, we found that the actual treatment (HR: 0.73, 95% CI: 0.59–0.91) and the number of baseline metastatic sites (HR: 1.14, 95% CI: 1.04–1.26) were significant predictors of survival. Contrarily, our results do not support a significant impact of tumor origin on survival, as evidenced by a P-value of 0.80 in the Cox model and 0.49 in the Kaplan-Meier analysis. Our findings have major implications for current colorectal cancer treatment paradigms, offering compelling evidence for a genotype-centric rather than anatomical origin-centric approach. Further research is needed to fully substantiate these promising results.

Table 2. The relationship between survival rate and various factors

Characteristic	HR[1]	95% Cl[1]	p-value	q-value[2]
ATRT				
FOLFOX alone	-	-		
Panitumumab + FOLFOX	0.73	0.59,0.91	0.004	0.019
AGE	1.01	1.00,1.02	0.089	0.11
SEX				
Female	-	-		
Male	0.80	0.63,1.01	0.062	0.10
B_METANM	1.14	1.04,1.26	0.008	0.019
DIAGTYPE				
Colon	-	-		
Rectal	0.98	0.78,1.23	0.8	0.8

Note: [1]HR = Hazard Ratio, Cl = Confidence Interval; [2]False discovery rate correction for multiple testing

Table 2 shows the association between 5 factors retained by the AIC method and colorectal cancer survival rate. Survival rate was observed to be significantly associated with 2 factors: Actual Treatment (ATRT) (HR: 0.73, 95% CI: 0.59 – 0.91), Number of BL Metas Site (B_METANM) (HR: 1.14, 95% CI: 1.04 – 1.26). The P value of tumor type is 0.80 >> 0.05. Tumor type was statistically significantly unrelated to survival rate.)

Expanding on the research results, it's worth noting that the sample population was carefully curated to match the broader study's demographic distribution, but with the specific characteristic of having wild-type KRAS and NRAS genotypes. This allowed for a more nuanced evaluation of panitumumab's efficacy across a homogenized genetic background.

The Akaike Information Criterion (AIC) method, employed for model optimization, led to the retention of five potentially influential factors. However, only actual treatment (ATRT) and the number of baseline metastatic sites emerged as significant determinants for survival rates.

With a 95% confidence interval [CI] of 0.59 to 0.91, the hazard ratio (HR) for actual treatment was 0.73, indicating that the type of treatment received significantly impacted survival. The HR for the number of baseline metastatic sites was 1.14 (95% CI: 1.04–1.26), signifying that the more metastatic sites a patient had at baseline, the worse their survival rate tended to be.

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In contrast to these important findings, a P-value of 0.80 demonstrated that the origin of the tumor, either the colon or the rectum, was statistically insignificant for predicting survival results. The Kaplan-Meier (KM) survival analysis in Figure 1 further supports this idea. The P-value in one group of panitumumab-treated patients is 0.49, which is significantly higher than the 0.05 threshold for statistical significance. These findings indicate that panitumumab treatment outcomes were unaffected by the location of the tumor, which has significant implications for the medical treatment of colorectal cancer.

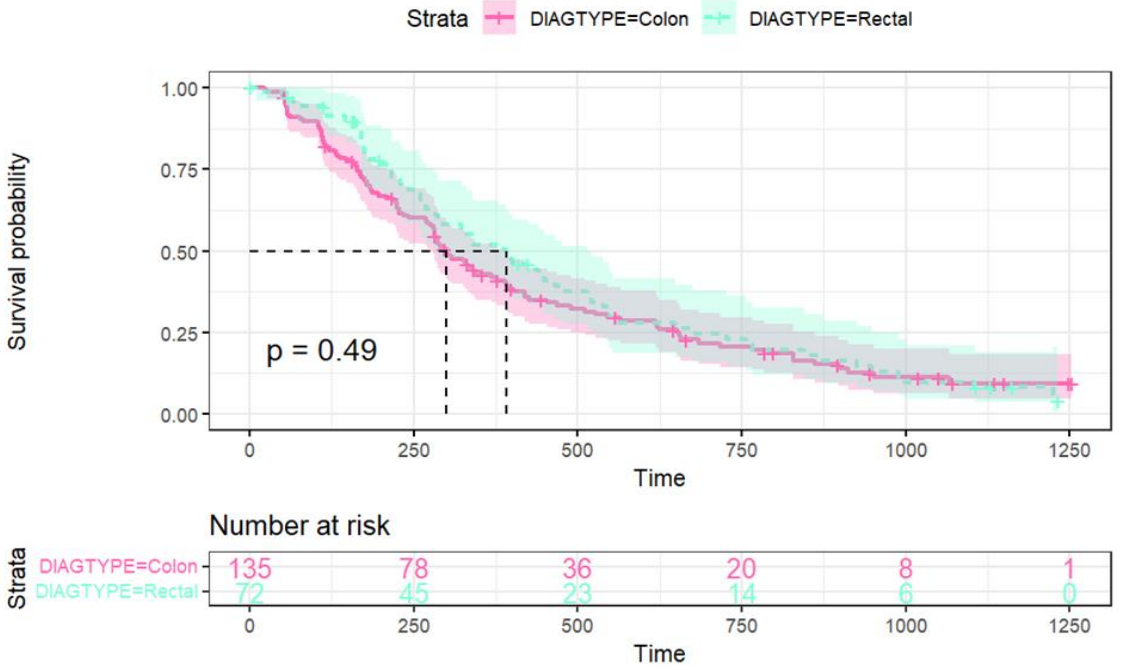

Figure 1. KM curve and risk table of tumor type.

Figure 1 shows a visualization of the results of the KM analysis of tumor types in the group using panitumumab. The P value is 0.49. Under the condition that the proportions of the two tumor types are similar, the P value indicated that the tumor type was significantly unrelated to survival rate in the patient population using panitumumab.

In combination, these findings give evidence that genotype-specific treatment approaches are better than anatomical location-specific ones in the treatment of colorectal cancer. This might prompt us to take another look at the current colorectal cancer treatment paradigms, which could result in genotype treatment being more efficient.

4. Discussion

One of the most common cancer-related deaths is colorectal cancer (CRC), and its treatment has significantly changed as molecular biology has been better understood in recent years. The development of targeted therapies like panitumumab has made cancer treatment more customized. In addition to analyzing the differences in treatment outcomes based on the origin of the tumor, which could originate from either the colon or rectum, our study looked into finding out the role of gene genotypes in the effects of panitumumab among colorectal cancer patients. With a research result from Amado, our results demonstrated the previous result with more evidence that patients with wild-type genotypes are more likely to respond to panitumumab and treatment.

The question of whether the location of the tumor's origin within the colorectal system had no impact on treatment outcomes It was a surprising finding that the location of the tumor, either the colon or rectum, with a p-value of 0.49, had no impact on treatment. The study raises a new question about the specific treatment plan and provides more options for understanding CRC management. The

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insignificance of tumor origin in panitumumab efficacy may require a revision of the current study. The result could lead to standardized genotype-driven treatments and may improve the need to categorize treatments that, considering the location of the tumor's origin, could be more simplified and increase the efficiency of other therapy options. Even though our results confirm the importance of the KRAS and NRAS genotypes found in earlier studies, they don't agree on how the primary site of the tumor works. This discovery could become important in refocusing clinical procedures as well as improving genotype-specific rather than site-specific therapies.

The small number of participants in this research is a disadvantage that needs further study. Furthermore, because of the complexity of the colorectal system, multiple pathways and resistance mechanisms could apply to further research. Our findings may be ideal for additional research that is warranted, considering the tumor's origin site might lack significance.

5. Conclusion

The goal of this research is to find significant predictors of survival in colorectal cancer patients based on clinical data and compare the effectiveness of Panitumumab combined with FOLFOX4 treatment in patients with colon cancer vs. rectal cancer. We draw the following conclusions:

Among all potential influencing factors, actual treatment (ATRT) and the number of baseline metastatic sites proved to be significant determinants of survival rates. Panitumumab combined with FOLFOX4 treatment is effective in improving patient survival rate. An increase in the number of baseline metastatic sites decreases the survival rate of patients.

Tumor origin was not statistically significant in predicting survival outcome. There is no significant difference in the effectiveness of Panitumumab combined with FOLFOX4 treatment in patients with different tumor origins.

This paper provides a reasonable explanation for not distinguishing the tumor origin among colorectal cancer patients in the clinical treatment of colorectal cancer with Panitumumab combined with FOLFOX4 treatment. However, whether it is necessary to distinguish patients' tumor origin in clinical treatment remains a complex issue. There are still many drugs and treatment that need to be further confirmed in subsequent studies.

Contribution Statements

Abstract: Siyao Chen + Xiya Zhao + Haoyang Xu
Introduction: Siyao Chen
Method: Xiyao Zhao
Result: Haoyang Xu + Siyao Chen
Statistical Models, Graph, Table: Haoyang Xu
Discussion: Siyao Chen
Conclusion: Haoyang Xu

Acknowledgement

"+" indicates joint contribution.

References

[1] Siegel, R. L., Wagle, N. S., Cercek, A., Smith, R. A., & Jemal, A. (2023). Colorectal cancer statistics, 2023. CA: A Cancer Journal for Clinicians, 73(3), 233-254. https://doi.org/10.3322/caac.21772

[2] Paschke, S., Jafarov, S., Staib, L., Kreuser, E.-D., Maulbecker-Armstrong, C., Roitman, M., Holm, T., Harris, C. C., Link, K.-H., & Kornmann, M. (2018). Are Colon and Rectal Cancer Two Different Tumor Entities? A Proposal to Abandon the Term Colorectal Cancer. International Journal of Molecular Sciences, 19(9), 2577. https://doi.org/10.3390/ ijms19092577

[3] Amado, R. G., Wolf, M., Peeters, M., Van Cutsem, E., Siena, S., Freeman, D. J., Juan, T., Sikorski, R., Suggs, S., Radinsky, R., Patterson, S. D., & Chang, D. D. (2008). Wild-type KRAS is

required for panitumumab efficacy in patients with metastatic colorectal cancer. Journal of Clinical Oncology, 26(10), 1626-1634. https://doi.org/10.1200/JCO.2007.14.7116

[4] Burke, P., Schooler, K., & Wiley, H. S. (2001). Regulation of Epidermal Growth Factor Receptor Signaling by Endocytosis and Intracellular Trafficking. Molecular Biology of the Cell, 12(6), 1897–1910. https://doi.org/10.1091/mbc.12.6.1897

[5] Wee, P., & Wang, Z. (2017). Epidermal Growth Factor Receptor Cell Proliferation Signaling Pathways. Cancers (Basel), 9(5), 52. https://doi.org/10.3390/cancers9050052

[6] Janakiraman, M., Vakiani, E., Zeng, Z., Pratilas, C. A., Taylor, B. S., Chitale, D., Halilovic, E., Wilson, M., Huberman, K., Ricarte Filho, J. C., Persaud, Y., Levine, D. A., Fagin, J. A., Jhanwar, S. C., Mariadason, J. M., Lash, A., Ladanyi, M., Saltz, L. B., Heguy, A., Paty, P. B., & Solit, D. B. (2010). Genomic and biological characterization of exon 4 KRAS mutations in human cancer. Cancer Research, 70(14), 5901-5911. https://doi.org/ 10.1158/0008-5472.CAN-10-0192

[7] Dinu, D., Dobre, M., Panaitescu, E., Bîrlă, R., Iosif, C., Hoara, P., Caragui, A., Boeriu, M., Constantinoiu, S., & Ardeleanu, C. (2014). Prognostic significance of KRAS gene mutations in colorectal cancer - preliminary study. J Med Life, 7(4), 581-587. PMC4316144.

[8] Amado, R. G., Wolf, M., Peeters, M., Van Cutsem, E., Siena, S., Freeman, D. J., Juan, T., Sikorski, R., Suggs, S., Radinsky, R., Patterson, S. D., & Chang, D. D. (2016). Wild-Type KRAS Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer. Journal of Clinical Oncology, 26(10). https://doi.org/10.1200/JCO.2007.14.7116

[9] Dubois, E. A., & Cohen, A. F. (2009). Panitumumab. British Journal of Clinical Pharmacology, 68(4), 482–483. https://doi.org/10.1111/j.1365-2125.2009.03492.x

[10] Amado, R. G., Wolf, M., Peeters, M., Van Cutsem, E., Siena, S., Freeman, D. J., ... & Chang, D. D. (2008). Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. Journal of clinical oncology, 26(10), 1626-1634.