Impact of Clinicopathological Features on Prognosis in KRAS Mutant Metastatic Colorectal Cancer

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ABSTRACT

Despite the poor prognosis of KRAS mutant metastatic colorectal cancer (mCRC), some KRAS mutant mCRC patients have a better prognosis and survival rate than other RAS mutant mCRC patients. We aimed to determine the impact of the clinicopathological features and the type of mutational status on the survival rate of patients diagnosed with KRAS mutant mCRC. The Kaplan–Meier method and the log-rank test were used to analyse overall survival (OS). Cox regression analyses were used to determine the association between OS and other explanatory variables. We demonstrated that left-sided mCRC had better OS rates compared with right-sided mCRC (p= 0.007). De novo metastatic disease had better OS rates compared with the absence of de novo metastatic disease (p=0.001). Additionally, absence of de novo metastatic disease and right sided tumors were shown to be poor prognostic markers for OS in multivariate analysis (p< 0.001 and p= 0.001, respectively). Right-sided colon tumors and the absence of de novo metastatic disease are poor prognostic markers for OS.

Keywords: KRAS mutant, Metastatic, Colon cancer

INTRODUCTION

Colorectal cancer is the second most common cancer diagnosed in females and the third most common cancer diagnosed in males worldwide.[1] Approximately 25% of all colorectal cancer patients are initially diagnosed with metastatic disease.[2] The Kirsten rat sarcoma virus (KRAS) mutation is associated with poor prognosis for survival and predicts resistance to epidermal growth factor receptor (EGFR) targeted agents.[3,4] In literature impact of KRAS mutation on prognosis were studied. It was found that the KRAS mutation stimulated tumor invasion.[5] And there are some microenvironmental differences according to KRAS mutation status.[6] These reasons may be responsible for poor prognostic effect of KRAS mutation.

The prevalence of the KRAS mutation is almost 40% of all colorectal cancer patients.[7] Other rat sarcoma virus (RAS) mutations are rare with a prevalence of 4% for NRAS mutations and < 1% for HRAS mutations. Ninety five percent of KRAS mutations occur in KRAS G12, G13, or Q61 codons.[8,9]

Current colorectal treatment guidelines recommend chemotherapy and antivascular endothelial growth factor (VEGF) agent (bevacizumab at first line) combinations as treatments for mismatch repair stable RAS mutant mCRC.[8] Despite the poor prognosis of KRAS mutant mCRC, some KRAS mutant mCRC patients have a better prognosis and survival rate than other KRAS mutant mCRC patients.

Table 1. General Characteristics and overall survival

Characteristics			n= 101 (%)	OS	p
Age (years median min-max)			63 (30-85)		
Age < 65			53 (53)	28 (20.971-35.029)	0.455
Age ≥ 65			48 (47)	28 (16.416-39.584)	
Gender	Female		44 (44)	28 (16.108-39.892)	0.886
	Male		57 (56)	28 (18.853-37.147)	
De novo metastatic	Yes		85 (84)	30 (21.192-38.808)	**0.001**
	No		16 (16)	18 (11.705-24.295)	
Neo/Adjuvant	Yes		17 (16)	22 (16.250-27.750)	0.097
chemotherapy	No		84 (84)	28 (22.462-33.538)	
Tumors sideness	Right colon		26 (26)	20 (14.493-25.507)	**0.007**
	Left colon		75 (74)	32 (23.317-40.683)	
Metastatic site	Liver	No	25 (25)	30 (25.516-34.484)	0.688
		Yes	76 (75)	28 (22.125-33.875)	
	Lung	No	64 (63)	24 (11.804-36.196)	0.300
		Yes	37 (37)	29 (24.014-33.986)	
	Peritoneum	No	82 (81)	28 (22.411-33.589)	0.528
		Yes	19 (19)	35 (8.138-61.862)	
	Bone	No	95 (93)	28 (21.320-24.680)	0.759
		Yes	6 (7)	28 (7.488-48.512)	
Non regional		No	87 (86)	28 (22.148-33.852)	0.340
lymph nodes		Yes	14 (14)	38 (20.926-55.074)	
Number of metastatic	1 region		65 (64)	28 (20.914-35.086)	0.177
sites	≥ 2 region		36 (36)	29 (20.115-37.885)	
Mutation Status	Codon 12		83 (82)	28 (20.472-35.528)	0.800
	Codon 13		18 (18)	28 (19.701-36.299)	
Primer site	Cecum		11 (11)		
	Ascenden colon		9 (9)		
	Transvers Colon		8 (8)		
	Descenden Colon		6 (6)		
	Sigmoid Colon	39 (38)			
	Rectum	28 (28)			

We aimed to determine the impact of the clinicopathological features and the type of mutational status on the survival rate of patients diagnosed with KRAS mutant mCRC.

PATIENTS AND METHODS

The patients diagnosed with KRAS mutant metastatic colorectal in Kayseri City Hospital and Erciyes University Medical Oncology were retrospectively reviewed. Patients under the age of 18, those with nonmetastatic diseases, and individuals with RAS wild-type metastatic colorectal cancer were excluded from this study. Patients with only KRAS mutations were included in the study.

Data collected from the hospital's patient records included patient characteristics, chemotherapy regimens given to patients, metastatic sites, number of metastatic sites, mutation type, location of the primary tumor in colon. General characteristics were presented in Table 1. Kaplan Meier analysis were used to compare overall survival of the patients with metastatic KRAS mutant colon cancer according to general characteristics. Results of the Kaplan Meier analysis were presented in Table 1.

The patients with metastatic KRAS mutant colon cancer analysed with univariate and multivariate analysis to determine impact of factors on overall survival.

Table 2. Univariate and multivariate analysis for OS

Variables		Univariate HR, 95% CI	p	Multivariate HR, 95% CI	p
Age		0.997 (0.968-1.026)	0.814		
Age	< 65 vs ≥ 65	0.804 (0.450-1.436)	0.461		
Gender	Male or Female	1.042 (0.592-1.833)	0.887		
Mutation status	Codon 12 vs 13	0.914 (0.452-1.849)	0.803		
De novo metastatic	No vs Yes	0.329 (0.163-0.663)	**0.002**	0.250 (0.120-0.521)	**< 0.001**
Tumor site	Right vs left	0.444 (0.241-0.819)	**0.009**	0.349 (0.184-0.661)	**0.001**
Number of metastasis	1 or ≥ 2	0.674 (0.376-1.208)	0.185		
Liver metastasis	Yes vs No	1.152 (0.574-2.313)	0.691		
Bone metastasis	Yes vs No	0.853 (0.306-2.379)	0.762		
Lung metastasis	Yes vs No	1.352 (0.758-2.410)	0.303		
Peritoneal metastasis	Ye vs No	0.785 (0.367-1.681)	0.533		
Nonregional lymph node metastasis	Yes vs No	0.662 (0.280-1.568)	0.348		

The present study was approved by the Kayseri City hospital Ethic Committee (30.7.2024 No: 2024/156).

Statistical Analysis

The descriptive statistics used for the data were the frequency and percentage for categorical variables and the median (min-max) for continuous variables. The Kaplan–Meier method and log-rank test were used to analyse OS. Cox regression analysis were used to determine the association between the OS and other explanatory variables. OS was defined from the diagnosis of metastatic disease to the date of death or last known contact. A p value <0.05 was regarded statistically significant. Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) software was used in all statistical analyses.

RESULTS

Patients and Characteristics

A total of 101 patients diagnosed KRAS mutant metastatic colorectal cancer were included in the study. The median age was 63 (30-85) years old. 44 (44%) of them were female and 57 (56 %) of them were male. KRAS 12 mutation was present in 83 (82%) of the patients and KRAS13 mutation was present in 18 (18%) of the patients. All patient characteristics were summarized in Table 1.

Kaplan Meier analysis revealed that the OS was longer in patients had de novo metastatic disease than the patients had absence of de novo metastatic disease in metastatic KRAS mutant colorectal cancer. Also the patients had left colon tumors had longer OS than the patients had right colon tumors in metastatic KRAS mutant colorectal cancer (Table 1).

Univariate analysis revealed that absence of de novo metastatic disease and right sided tumors are correlated with poor OS rates in metastatic KRAS mutant colorectal cancer with hazard ratio 0.329 (0.163-0.663), p= 0.002 and 0.444 (0.241-0.819), p= 0.009, respectively. Multivariate analysis revealed that absence of de novo metastatic disease and right sided tumors are correlated with poor OS rates in metastatic KRAS mutant colorectal cancer with hazard ratio 0.250 (0.120-0.521), p< 0.001 and 0.349 (0.184-0.661), p= 0.001, respectively. (Table 2).

DISCUSSION

In our study, we demonstrated that the OS was longer in patients that had de novo metastatic disease than in the patients that had an absence of de novo metastatic disease in metastatic KRAS mutant colorectal cancer. Additionally, the patients that had left colon tumors had a longer OS than the patients that had right colon tumors in metastatic

KRAS mutant colorectal cancer. We demonstrated that the absence of de novo metastatic disease and right-sided tumors were correlated with poor OS rates in metastatic KRAS mutant colorectal cancer patients.

The KRAS mutation is one of the poor prognostic marker of mCRC (3). This finding was explained in detailed in a report that also stated that KRAS mutant tumors were less likely to have microsatellite instability than KRAS wild colorectal cancer (CRC) (10). Some studies showed that the types of KRAS mutations in mCRC have different effects on OS. Li et al. reported that codon 12 mutations have a poor prognostic effect on OS in colon cancer that especially exhibit 12D and 12V mutations. However, this poor OS rate was not observed in colon cancers that exhibited codon 13 mutations. This study included all stages of colon cancer and not only metastatic disease.[11] In our study, there were no statistical differences for OS between patients that exhibited codon 12 and 13 mutations. Additionally, only metastatic colorectal cancer patients were included in the study. In another report, it was demonstrated that in stage II-III colorectal cancer, the KRAS mutation was not a poor prognostic factor.[12] Furthermore, the mutation type was not a poor prognostic marker for disease-free survival.

We demonstrated that the patients that had de novo metastatic disease had longer OS than the patients with an absence of de novo metastasis in KRAS mutant colorectal cancer. The prognosis of synchronous or metachronous metastasis of colorectal cancer is controversial.[13] Synchronous and metachronous disease have different gen expression pathways so their prognoses are different.[14] Garajova et al. reported on a study that investigated the impact of primary tumor location on patterns of recurrence and OS after hepatic resection in synchronous and metachronous recurrence. They demonstrated that synchronous liver metastasis is a poor prognostic factor for OS.[13] In their results, 39% of the patients had the KRAS mutation. Unlike this study, only KRAS mutant patients were included in the present study. Chida et al. reported on a study that researched the prognostic impact of the KRAS codon 12C mutation in mCRC. They demonstrated that the KRAS G12C mutation was significantly correlated with shorter OS. In this study, 78% of the patients had synchronous metastasis in KRAS 12C mutant colon cancer and 64% of the patients had metachronous metastasis. However, there were no statistically significant differences between these two groups. They demonstrated that the synchronous or metachronous disease had a statistically significant correlation with OS in the results of the univariate analysis but not in the multivariate analysis.[15] Similar to this study, in the present study, the absence of de novo metastatic disease was correlated with poor OS in the results of the univariate analysis. However, we demonstrated a statistically significant correlation in the results of the multivarite analysis. In some reports, the chemosensitivity of the tumor is more important than whether the tumor is synchronous or metachronous.[13] Synchronous tumors seem to be more chemosensitive than metachronous tumors. This hypothesis was explained with a partial chemoresistance in patients with metachronous disease because of prior adjuvant treatment.[16] In the present study, 16% of the patients had metachronous disease and all of them had received adjuvant or neoadjuvant treatment.

Additionally, right-sided tumors had a poor prognosis for OS. This finding is consistent with the results found in literature.[17] Right-sided tumors are different from left-sided tumors as they have higher rates of BRAF mutations, TP53, KRAS mutations, and MSI-high disease.[18,19] However, this survival difference between the right- and left-sided tumors were not explained by disease stage or known mutational status (20). Unlike the present study, another study reported that for the patients had a KRAS mutation, there were no survival differences between the right and left colon.[21]

Our study had some limitations. Firstly, the study was of a retrospective nature. Secondly, only a small sample of the patient population was analysed. Lastly, there were no details about other mutational status, for example, BRAF and MSI status, in our study.

Conclusion

In conclusion, we demonstrated that right sided colon tumors and the absence of de novo metastatic

disease are poor prognostic markers for OS. It must be evaluated carefully while treated metastatic KRAS mutant colorectal cancer patients that located right colon and in situation metachronous disease. Maybe more intensive regimens (e.g triplet regimens with anti VEGF combinations) should be considered in these patients.

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