



The predictive value of KRAS and NRAS mutations in metastatic colorectal cancer

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Introduction

The most prevalent malignant tumor of the digestive system is colorectal cancer (CRC) and ranks as the third cancer in terms of incidence and mortality after lung and breast malignancies (1). The number of new cases increased from 783 000 (401 000 men and 381 000 women) to 1 361 000 (746 000 men and 614 000 women) in 2012 (2). In Iran, the annual percentage changes in age-standardized incidence rate (ASIR) of CRC increased in both men and women during the last years as 13.7 and 16.4 in women and men, respectively (3).

Approximately 17%-25% of the CRC patients present KRAS mutation. KRAS mutation results in the poorer survival and response to the anti-EGFR therapies (4). However, no evidence detected NRAS mutation to be associated with survival rate in CRC. In this study, it was aimed to assess the prevalence and distribution of NRAS and KRAS mutations in CRC and their correlation with overall survival (OS) and progression-free survival (PFS) of patients.

Methods

Patients and follow-up

The study group included 115 patients with metastatic

colorectal cancer who referred to the oncology clinic of “Emam Khomeini” and “Sina” hospitals during 2016-2017. Diagnosis of metastatic colorectal cancer was made using imaging data and endoscopic biopsy. Also, a prospective analysis was done on patients who referred with PCR results of NRAS and KRAS genes. Patients were followed for 4 years after the diagnosis of metastatic colorectal cancer. Overall and progression free survival during the course of the disease was calculated for patients with wild type and mutant KRAS and/or NRAS genes.

Statistical analysis

PFS and overall survival time were calculated by the Kaplan-Meier method (product limit estimates) and stratified log-rank test using the SPSS program. All p values were 2-sided and statistical significance was set at <0.05.

Results

Patients

The study population included 115 patients (57 males and 58 females), with the mean age of 53.37 ± 10.63 years, ranging from 37 to 87 years. The most common anatomical sites of tumor were sigmoid (28.7%), rectosigmoid

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↑What is “already known” in this topic:

The RAS oncogene family is widely accepted and is the most studied gene among cancer related genes. Approximately, 17%-25% of the CRC patients present KRAS mutation. KRAS mutation results in the poorer survival and response to the anti-EGFR therapies.

→What this article adds:

High frequency of K-ras gene mutations in patients with metastatic colorectal cancer represented a statistically significant association with the overall survival of patients, while NRAS gene did not show any correlation with overall survival in the general population.

(23.5%), descending colon (17.4%), ascending colon (8.7%), cecum (6.1%), transverse colon (5.2%), hepatic curve (5.2%), and splenic curve (3.5%).

The most common sites of metastasis were liver (38.5%), lung (20.3%), lymph nodes (12.5%), bone (8.9%), peritoneum (7.8%), ovary (5.7%), adrenal (3.1%), skull (1%), spleen (1%), and kidney (1%).

Among 115 patients, family history of gastrointestinal cancers was present in 11 patients (9.6%). For KRAS gene, 61 patients were mutant and 54 were wild-type. With respect to NRAS gene, 17 patients were mutant and 98 were wild-type.

Overall survival

The mean overall survival was significantly different between patients with wild type and mutant KRAS, as 37.91 and 28.15 months, respectively, with the Log rank p value of 0.024 (Fig. 1). The same trend was seen in the male population with wild type and mutant KRAS genes as 35.93 and 33.93 months, respectively, with the Log rank p value of 0.055 (Data not shown). The overall survival did not show any difference between KRAS wild type and mutant type in the female population (Log rank, $p=0.071$) or in patients older than 55 years (Log rank

$p=0.497$). However, mutation of KRAS gene was a determining factor in patients younger than 55 years (Log rank $p=0.034$).

NRAS gene did not show any correlation with overall survival in the general population (data not shown).

Progression free survival

The mean progression free survival was significantly different between patients with wild type and mutant KRAS, as 32.57 and 23.98 months, respectively, with the Log rank p value of 0.02. The same trend was seen in the male population with wild type and mutant KRAS genes as 32.48 and 28.73 months, respectively, with the Log rank p value of 0.041 (Data not shown). The progression free survival did not show any difference between KRAS wild type and mutant type in the female population (Log rank $p=0.136$) or in patients older than 55 years (Log rank $p=0.497$).

NRAS gene did not show any correlation with progression free survival in the general population (data not shown). Table 1 shows overall survival (OS) and progression free survival (PFS) of patients with different NRAS/KRAS genes profile.

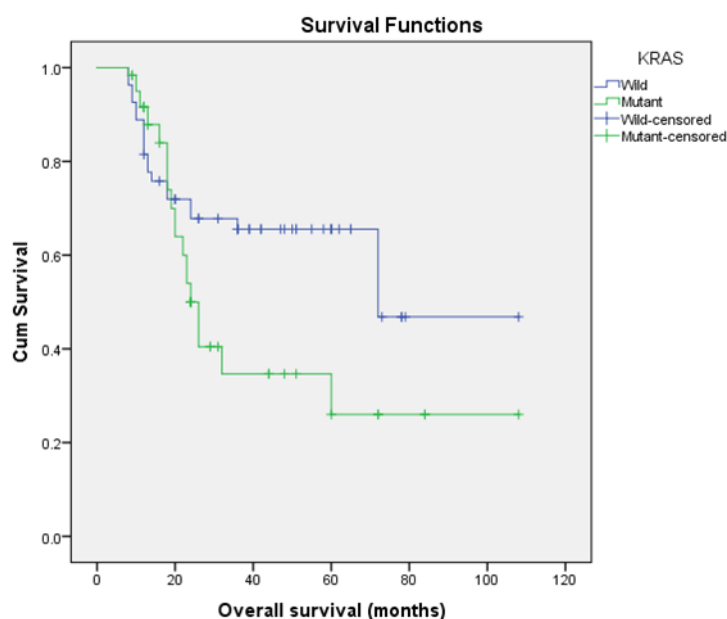


Fig. 1. Overall survival between wild and mutant Kras genes

Table 1. Overall survival (OS) and progression free survival (PFS) of patients with different NRAS/KRAS genes profile

	KRAS population		NRAS population	
	KRAS wild-type (n=54)	KRAS mutant (n=61)	NRAS wild-type (n=98)	NRAS mutant (n=17)
Overall survival				
No. of events	20	34	46	8
Mean, months	37.91	28.15	33.47	28.47
95% CI	31.29 to 44.52	22.70 to 33.60	28.75 to 38.19	17.76 to 39.18
P (log rank test)	0.024		0.589	
Progression-free survival				
No. of events	20	34	46	8
Mean, months	32.57	23.98	28.54	25
95% CI	26.31 to 38.84	19.38 to 28.59	24.30 to 32.78	15.16 to 34.84
P (log rank test)	0.020		0.653	

Discussion

One of the most exciting developments in cancer research has been the identification of specific point mutations in human tumor cells. As for other types of cancer, genomic instability plays a critical role in CRC and where 3 different groups have been identified as the pathogenic mechanisms, including mainly microsatellite instability (MSI), chromosomal instability (CIN), and CpG island methylator phenotype (CIMP), which all together represents up to 80%–85% of the causes of all CRC cases (5). Since 2013, RAS oncogenes have been known as the most important predictive genetic marker of overall survival and resistance to anti-EGFR therapy in clinical practice (6); therefore, RAS testing in the workup of colorectal cancer is of a great interest (7). The purpose of this study was to determine the incidence of mutation in KRAS and NRAS gene and to describe whether the mutation status of KRAS and NRAS modify overall survival or progression free survival of patients.

Prevalence of KRAS mutation was reported as 40% in the study by Dinu D and approx%-65% in other studies (8). In this study, a prevalence of 53.04% (61 out of 115 patients) was reported for KRAS mutation in metastatic colorectal cancer patients.

Moreover, it was observed that the status of KRAS mutation was correlated with overall survival and progression free survival of patients. Previous reports have confirmed that KRAS gene status presents prognostic significance in colorectal cancer. The mutation found on codon 13 determines a statistically less significance in patients with stage I and II of the disease. Pyrosequencing was introduced as a reliable and reproducible method in determining KRAS gene status (9).

In addition, the results of the data analysis suggested that NRAS mutations are rare (17 out of 115 patients) in colorectal cancer and provide no notable relationship with survival rates. This finding was in line with previous findings by Irahara et al who detected NRAS mutation in 2.2% of patients with colorectal cancer (10). Little is known on the impact of NRAS mutation in colorectal cancer. Some studies have shown that NRAS mutations seem to arise at a later stage in the development of malignancy, unlike KRAS mutations which arise early.

Overall survival and progression free survival of metastatic colorectal cancer patients are related to a variety of variables, including genetic alterations, site and burden of metastasis, and primary site of the tumor. One of the limitations of this study was that it was not possible to assess the impact of primary site of the tumor and the site of metastasis in the survival of colorectal cancer patients.

Conclusion

In summary, in this study, it was found that the frequency of NRAS mutation is relatively low in colorectal cancer and patients characterized by wild type state of KRAS present larger survival rates. Additional studies should be conducted to describe underlying mechanisms by which RAS oncogenes impact survival rates of colorectal cancer patients.

Conflict of Interests

The authors declare that they have no competing interests.

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