

Research Article

The Relationship Between Metabolic Parameters, 18F-Fluorodeoxyglucose/Positron Emission Tomography, and RAS Mutation in Patients with Metastatic Colorectal Cancer: A Descriptive Cross-Sectional Study

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Abstract

Objectives: This study aimed to predict the RAS mutation by using imaging techniques and routine clinical or laboratory findings without tissue samples.

Methods: The study was conducted in a retrospective cross-sectional plan in a tertiary-care health center between January 2010 and December 2016. Data collection was done from the patient files using the hospital's electronic patient registry. The primary outcome variable was the presence of RAS mutations as evaluated from the primary surgical specimens. Besides, data was collected on blood count parameters, serum CEA, and CA 19-9 levels. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated. Forty-five patients who underwent 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) with pathologically confirmed metastatic colorectal adenocarcinoma were included in the study.

Results: In our study the presence of RAS mutation was 40%(n=18). When the findings were compared according to the presence of RAS mutation, a statistically significant difference was found only in age at diagnosis (p=0.038). TLG (Total Lesion Glycolysis) significantly correlated with all other variables and age at diagnosis (p<0.05). A logistic regression model with age at diagnosis and TLG as explanatory variables had a sensitivity of 70.6% and a specificity of 81.5% in detecting RAS mutation.

Conclusion: Although data on TLG and RAS mutations are valuable, they should be supported by studies with a larger cohort.

Keywords: Colorectal cancer, k-ras genes, PET/CT

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Colorectal cancer (CRC) is the third most common cause of malignant conditions.^[1]

Around 140 000 new patients are expected yearly in the United States, a country with approximately 350 000 population. Turkey has comparatively higher prevalence rates of above 46.5/100 000 people.^[2] CRC usually develops from adenomatous polyps and results from a series of genetic

alterations, leading to the inactivation of tumor suppressor genes and DNA repair genes together with the activation of oncogenes.^[3] Patients without KRAS and NRAS mutations are referred to have “wild-type” tumors, while those mutations are called mutant cases.^[4] Mutations of these genes are expected in 10–40% of the cases, and it is considered as important in treatment selection as well as prognosis.^[5]

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Today, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) is widely used for staging, restaging and treatment response evaluation of several malignancies.^[6-10] PET imaging has been shown to be remarkable predictor of progression in many tumors,^[11-14] and can also be used to determine functional response to therapy and to measure metabolic activity when changing therapy.^[15] Initially, the use of FDG PET to characterize lesions was thought to have an important role. Recent literature suggests that baseline TLG may be in agreement with the results.^[16] FDG has been shown to be a prognostic marker for intra-tumor heterogeneity and disease aggression.^[17-21]

The relationship between FDG PET imaging findings and the presence of mutations has raised the interest of several researchers. However, on one side, the present studies demonstrate conflicting results,^[22,23] and on the other hand, the number of research on colorectal cancer patients is limited.^[22-25] Furthermore, there is no research done in a relatively homogeneous specific population of patients with metastatic colorectal adenocarcinoma. Thus, it is still a necessity to conduct studies investigating the relationship between PET findings and RAS mutations.

On the other hand, investigations are supporting the relationship of colorectal cancer and neutrophil/lymphocyte ratio, thrombocyte/lymphocyte ratio, and total lesion glycolysis (TLG), besides the well-known tumor markers carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9).^[26,28] Therefore, we hypothesized that a thorough survey on the relationship of RAS mutation status, and metabolic markers such as neutrophil/lymphocyte ratio, thrombocyte/lymphocyte ratio, and 18F-FDG PET imaging parameters could shed further light into the diagnosis and management of metastatic CRC.

Objectives

The aim of this study was to investigate the relationship between neutrophil/lymphocyte ratio, thrombocyte/lymphocyte ratio, serum carcinoembryonic antigen (CEA), CA-19.9 levels, 18F-FDG PET/CT parameters, and RAS mutational status in metastatic colorectal adenocarcinoma patients.

Methods

Study Design

The study was conducted in a retrospective cross-sectional plan. Study reporting was done following the STROBE guidelines.^[29] The study protocol was approved by the Local Ethics Committee at Ankara University Medical Faculty (IRB number: 3/1; Date: 15 August 2016).

Setting

The study was conducted at Ankara University Hospital, Department of Medical Oncology, between January 2010 and December 2016. The study hospital is a tertiary-care health center in the capital of Turkey. Established in 1988, the Department of Medical Oncology serves oncology patients with a capacity of 47 inpatient beds and 14 doctors.

Participants

Patients who underwent 18F-FDG PET/CT for staging of pathologically confirmed metastatic colorectal adenocarcinoma during the study period were included in the study. Patients without a PET scan (n=221) and those with incomplete information in the medical records (n=4) were excluded. The final sample consisted of 45 patients (Fig. 1).

Variables

Data collection was done from the patient files using the hospital's electronic patient registry. The primary outcome variable was the presence of RAS mutations as evaluated from the histopathological examination of primary surgical specimens. Besides, data was collected on blood count parameters, serum CEA, and Ca-19-9 levels. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated.

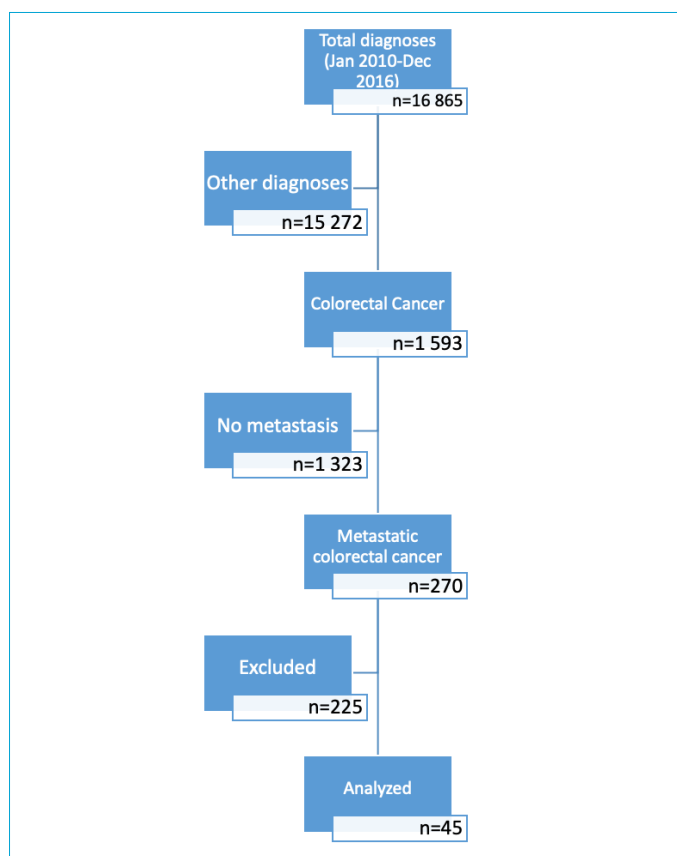


Figure 1. Study flow diagram.

Whole-body PET/CT images were acquired with a GE Discovery ST PET/CT series scanner (General Electric Medical Systems, Milwaukee, USA) 45-60 minutes after injection of 296-370 MBq 18F-FDG. Images from the vertex to the proximal femur were obtained while the patients were in the supine position. PET images were acquired for 4 min per bed position. Emission PET images were reconstructed with non-contrast low-dose CT images that were obtained with the use of a standardized protocol of 140 kV, 70 mA, tube rotation time of 0.5 s per rotation, a pitch of 6, and a slice thickness of 5 mm. Patients were allowed to breathe normally during the procedure. Attenuation-corrected PET/CT fusion images were reviewed in three planes (transaxial, coronal, and sagittal) using Advance Workstation Volume share 5 (General Electric Medical Systems, Milwaukee, USA).

RAS mutation detection in tissue samples was made according to the standard-of-care procedures validated by the pathology laboratory.

Serum CA 19.9 and CEA measurements were made by the chemiluminescent immunometric method using Immulite (Euro/DPC Ltd., Llanberis, UK).

Bias

All eligible patients were included without sampling. Data extraction from the medical records was made by the same researcher (EK), then double-checked and confirmed by another colleague.

Statistical Methods

PET/CT images were evaluated and confirmed visually and semi-quantitatively with maximum standardized uptake value (SUVmax) by the consensus of two experienced nuclear medicine specialists. During the evaluation of 18F-FDG PET/CT images, metabolic tumor volumes (MTV) were calculated by drawing automatically the isocontour region of interests (ROI) from all visually FDG uptake lesions. Total lesion glycolysis was calculated by multiplying the selected PET volume by the average SUV within that volume: $TLG = (MTV) \times (SUV_{mean})$.

The Shapiro-Wilk test was performed to see if the numerical variables were normally distributed. The difference between mean SUVmax and TLG of metastatic lesions of RAS mutant groups was analyzed by the Mann-Whitney U test. Relationships between NLR, TLR, serum CEA, Ca19-9 levels, and PET variables were analyzed by Spearman correlation analysis. Logistic regression analysis was used to search for variables predicting RAS mutation. SPSS for Windows 25 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. P-values less than 0.05 were considered significant.

Results

Participants

Data for 45 participants were analyzed. Of the participants, 30 (66.7%) were males, and 15 (33.3%) were females. The mean age at disease recurrence was 61.51 ± 9.64 years.

Descriptive Data

RAS mutation was present in 40% (n=18), while the wild type was seen in 60% (n=27) of the patients. The mean NLR was slightly increased but still in the normal range. The same applied to the mean PLR values. On the other hand, both the mean CEA and CA19-9 levels were above the reference ranges. Furthermore, the mean SUVmax and TLG values were high, too (Table 1).

Outcome data

When the findings were compared according to the presence of RAS mutation, a statistically significant difference was found only in age at diagnosis (Table 2).

When the relationships between the numerical variables were evaluated, it was found that TLG was significantly correlated with all other measurements and age at the time of diagnosis (Table 3).

A logistic regression model was built to assess the independent factors affecting RAS mutation status. Age at diagnosis was included in the model as it was significant in univariate analysis. Additionally, TLG was included in the model due to its strong correlation with age at diagnosis. Using the Enter method, the model had a sensitivity of 70.6% and a specificity of 81.5% in detecting RAS mutation (Table 4).

Discussion

Key Results

The mean age of those with RAS mutation at the time of colorectal cancer diagnosis was higher than those without the mutation. In colorectal cancer cases, TLG was associated

Table 1. Descriptive findings of the study variables

	Mean	SD	Min.	Max.
Age at diagnosis	60.13	10.19	38	78
Neutrophil/lymphocyte ratio	2.91	1.77	0.72	8.50
Thrombocyte/lymphocyte ratio	152.73	83.26	41.30	404.00
Carcinoembryonic antigen	115.37	227.06	1	1 000
CA19-9	203.93	495.88	0.80	1986.00
SUVmax	12.70	7.61	2	44
Total lesion glycolysis	401.97	614.09	0	2723.83

SD: Standard deviation.

Table 2. Comparison of findings according to the presence of the RAS mutation

	Presence of RAS mutation	n	Mean	SD	Z	p
Age at diagnosis	No	27	57.59	10.36	2.075	0.038
	Yes	18	63.94	8.87		
Neutrophil/lymphocyte ratio	No	27	2.87	1.80	0.348	0.728
	Yes	18	2.97	1.79		
Thrombocyte/lymphocyte ratio	No	27	158.60	97.61	0.382	0.702
	Yes	18	143.94	56.86		
Carcinoembryonic antigen	No	25	135.48	224.44	0.518	0.604
	Yes	18	87.44	234.19		
CA19-9	No	25	213.07	525.33	1.145	0.252
	Yes	18	191.23	466.50		
SUVmax	No	27	11.99	6.23	0.487	0.627
	Yes	18	13.76	9.42		
Total lesion glycolysis	No	27	455.96	737.67	0.533	0.594
	Yes	18	320.98	363.62		

Z: Mann Whitney U test value; SD: Standard deviation.

Table 3. Relationship between age and outcome of patients

	NLR	TLR	CEA	CA 19-9	SUV max	TLG
Age at diagnosis						
r	0.047	0.131	0.261	0.21	0.305	0.306
p	0.76	0.392	0.09	0.176	0.041	0.041
Neutrophil/lymphocyte ratio						
r		0.673	0.253	0.117	0.302	0.495
p		<0.001	0.101	0.454	0.044	0.001
Thrombocyte/lymphocyte ratio						
r			0.132	-0.034	0.255	0.338
p			0.399	0.826	0.09	0.023
Carcinoembryonic antigen						
r				0.647	0.079	0.443
p				<0.001	0.614	0.003
CA19-9						
r					0.12	0.394
p					0.443	0.009
SUVmax						
r						0.434
p						0.003

NLR: Neutrophil/lymphocyte ratio, TLR: Thrombocyte/lymphocyte ratio, CEA: Carcinoembryonic antigen, TLG: Total lesion glycolysis.

Table 4. Variables in the equation of the logistic regression model

	B	Wald	p	Exp (B)	95% CI for EXP (B)	
					Lower	Upper
Age at diagnosis	0.112	6.503	0.011	1.119	1.026	1.22
Total lesion glycolysis	0	2.934	0.087	1	1	1
Constant	-6.917	6.609	0.01	0.001		

CI: Confidence interval.

with all other study variables, including age at diagnosis. In a logistic regression model with age at diagnosis and TLG as explanatory variables, the presence of RAS mutation could be predicted with 70.6% sensitivity and 81.5% specificity.

Limitations

Further information about potentially relevant factors such as a family history of cancer or inflammatory bowel disease could help build a better predictive model. The relatively low number of cases can be mentioned as another limitation of the study.

Interpretation

The prevalence of CRC increases with age. Besides, socio-economically developed societies are under higher risk due to the changing eating habits.^[30] CRC is also the third most common type of cancer in Turkey.^[31] When the stage of established CRC cases in Turkey was evaluated, it was found that 24.1% have distant metastasis.^[31] Determining the early diagnosis and prognosis of these cancers is critical to reducing mortality and morbidity.^[32]

Fluorodeoxyglucose (FDG) is maintained at a high concentration in tumors compared to normal tissues and is easily detected as foci with high numbers on FDG-PET images. Therefore, FDG-PET is a clinically used method for the detection of primary metastases of various tumors such as lymphoma, malignant melanoma, lung and colon cancer, and follow-up of the treatments applied.^[33] It is frequently used to detect cancer recurrence or metastasis after surgery in colon pathologies.

KRAS gene mutations are detected in 30-40%^[34] of colorectal cancers, 25-40% in lung adenocarcinomas^[35] and 90% in pancreatic cancer.^[36] Additionally, NRAS gene mutations are seen in 3-4% of patients with colon cancer.^[37]

The presence of mutations in KRAS or NRAS is an indication that the patient will not respond well to anti-epidermal growth factor receptor (EGFR) treatments such as tyrosine kinase inhibitor and monoclonal antibody therapy.^[38] Therefore, KRAS and NRAS mutation analysis play a decisive role in the treatment of various cancers, especially colon and rectal cancer; that is, it is a biomarker for cancer.

Invasive procedures, such as surgery, are required to obtain the material on which RAS mutation analysis can be performed. Therefore, the idea of developing a method that can predict RAS mutation with data that can be obtained with simpler clinical applications has emerged. It was thought that the logistic regression analysis created could serve this idea, and it was seen that the results obtained could reach acceptable levels to predict RAS mutation. Although the data on TLG and RAS mutation are valuable,

these parameters cannot be used as a substitute for molecular analysis.

Another striking finding of this study is the correlation of TLG with all other variables. This finding suggested that this method, which has been shown to be very effective in diffuse large B cell lymphoma^[39] and is still used in patients with colorectal cancer, will find more areas of application in the future.

The prevalence of RAS mutation is higher in western populations (55%) than in Asian societies (41-49%).^[40] In a retrospective study of 75 patients in Turkey, KRAS gene mutation was detected in 50.7% of CRC cases.^[41] The rate in our study was lower. However, another study found that the KRAS gene was mutant in 32.1% of the participants.^[42] As studies on RAS gene mutation become widespread, we will be able to have an idea about its true rate. However, according to the available data, the frequency of RAS mutations in Turkey can be said to be similar to those detected in Asian populations.

At the time of diagnosis, it was reported that most patients with sporadic cancer were over 50 years old, while 75% of rectal cancer patients and 80% of colon cancer patients were 60 years or older.^[43] In a study conducted in Turkey, the average age at the time of diagnosis of RAS mutants was higher than the age of patients with wild type cancers.^[41] Similarly, in our study, the mean age of those with RAS mutation at the time of diagnosis was higher. Besides, it has been reported that those with positive RAS have a worse prognosis.^[44] It was wondered whether the high mean age at the time of diagnosis contributed to the poor prognosis. It is thought that other studies are needed to elucidate this issue.

Conclusion

The presence of RAS mutation is significantly associated with age at diagnosis. Furthermore, although TLG is not associated with RAS mutation, it is highly correlated with age at diagnosis, CEA, CA-19.9, TLR, and NLR. Although a model using TLG and age at diagnosis can be predicted to predict the presence of RAS mutation, which is an important indicator in the selection of appropriate treatment methods, these parameters cannot be used alone instead of molecular analysis.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee at Ankara University Medical Faculty (IRB number: 3/1; Date: 15 August 2016).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.K.; Design – E.K.; Supervision – C.S.; Materials – E.K.; Data collection &/or processing – E.K.; Analysis and/or interpretation – C.S.; Literature search – E.K.; Writing – E.K.; Critical review – E.K.

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