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^{18}F-FDG PET/CT Based Quantitative Parameters as Predictive Biomarkers for KRAS Mutations in Metastatic Colorectal Cancer.

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ABSTRACT:

Background: Metastatic colorectal cancer (mCRC) patients with positive KRAS genomic mutations should not receive anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, as stated by the American Society of Clinical Oncology. However, there are some limitations to KRAS mutation testing. Few published studies evaluating the correlation between ^{18}F-FDG PET/CT imaging and KRAS expression in mCRC patients have yielded conflicting results. Aiming to clarify whether ^{18}F-FDG PET/CT scan can be used as a surrogate biomarker for KRAS status in mCRCs in order to optimize treatment strategies, this study explored this relationship.

Patients and Methods: This prospective study included 38 patients (26 males and 12 females) with mCRCs and known KRAS mutational status; all of them underwent pretreatment ^{18}F-FDG PET/CT imaging. Maximum standardized uptake value (SUV_{max}), total lesion glycolysis (TLG) and metabolic tumor volume (MTV) of metastatic lesions with the highest FDG uptake were analyzed. **Results:** SUV_{max} was significantly higher in the mutated KRAS than in the WT-KRAS group (13.1±11.9 vs. 7.01±4.2, respectively; P=0.016). There was an increase in the mean values of MTV and TLG in the KRAS mutant group, albeit without statistical significance (P= 0.450 and 0.908, respectively).

Thus, SUV_{max} was the only PET/CT parameter that could predict KRAS mutations (OR: 1.180, 95% CI: 1.006-1.384; P= 0.041). SUV_{max} cutoff value of >8.8 (AUC of 0.728) yielded the best accuracy (72.8%), with 58.8% sensitivity and 81.0% specificity in predicting KRAS mutations. **Conclusion:** The accumulation of ^{18}F-FDG was significantly higher in metastatic lesions of CRCs with positive KRAS mutations. We propose that ^{18}F-FDG PET/CT based SUV_{max} could be used as a non-invasive surrogate biomarker for KRAS genomic expression in mCRC patients to aid in treatment selection.

Key Words: Metastatic colorectal cancer, KRAS mutations, ^{18}F-FDG PET/CT, Quantitative parameters.

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INTRODUCTION:

Colorectal cancer (CRC) is the third most prevalent malignant tumor in developed countries and the second major cause of cancer-related mortality [(1)]. In developing countries, the number of cases is on the rise [(2)]. Oncogenes are activated when tumor suppressor genes are deactivated by genetic alterations together with environmental risk factors accumulation, resulting in an increase in CRC transformation [(3)].

Eventually, up to 50% of all patients with CRC develop metastases, with 20-25% had metastatic disease at diagnosis [(4)].

The median survival time for mCRC patients has increased significantly in recent years, reaching approximately 30 months due to improved treatment [(5)].

Panitumumab and cetuximab, monoclonal antibodies which are directed against the epidermal growth factor receptor (EGFR), have played a role in this [(6)].

EGFR is a member of the receptor tyrosine kinase family of transmembrane glycoproteins. Upon a ligand binding to the extracellular domain of the receptor, the intracellular kinase domain is activated with subsequent phosphorylation of its tyrosine residues and activation of downstream signaling pathways, involving the phosphatidyl inisitol-3-phosphate kinase (PI3K)/AKT and the Ras-Raf-mitogen-activated protein kinase (MAPK) [(7)].

These signaling pathways regulate cellular proliferation, neovascularization, metastasis dissemination, and resistance to apoptosis [8]. KRAS mutations are identified in about 40% of mCRC patients [9].

The majority of these mutations (90%) involve exon 2 (codons 12 and 13) of the KRAS gene, while the remainder 10% involve codons 61 and 146; roughly 5% for each [10].

According to previous reports, KRAS-mutated tumor cells confer resistance to EGFR inhibitors. On the other hand, this line of therapy has achieved a major clinical benefit for individuals with wild-type (WT) KRAS mCRCs [11] .

This is primarily due to that mutated KRAS activates the RAS/MAPK pathway independently of the ligand binding-induced EGFR stimulation. Thus, all patients with mCRC must have their KRAS mutation profiled before starting such therapy [12]. Based on the American Society of Clinical Oncology recommendations, patients with mCRC harboring mutated KRAS in codons 12 and 13 should not be treated with anti-EGFR monoclonal antibodies [10].

However, there is a possibility that KRAS may be misinterpreted as WT due to intra-tumoral genetic heterogeneity within a primary CRC and subsequent sampling errors [13].

In addition, primary CRCs and their metastases may have inconsistencies in KRAS mutational status [14]. Moreover, obtaining a sample of metastatic lesions for KRAS mutational analysis is often difficult and requires invasive procedures [15].

A non-invasive imaging technique capable of predicting KRAS status could therefore compensate for the above mentioned limitations of KRAS testing. ^{18}F-fluorodeoxyglucose positron emission tomography / computed tomography (^{18}F-FDG PET/CT) is a non-invasive tool that had been widely used for initial staging, surveillance, monitoring the treatment response, as well as prognostication of CRC through imaging of glucose metabolism and measuring of ^{18}F-FDG uptake in tumor cells [15]. Several articles used ^{18}F-FDG PET/CT to precisely assess the relationship between KRAS mutations and the metabolic activity of primary CRCs [16-21].

However, only a few published studies with conflicting results had investigated the association between KRAS expression and metabolic activity of metastatic lesions in CRCs [15,22] .The aim of this study was to explore the relationship between ^{18}F-FDG PET/CT based metabolic parameters of metastatic lesions and KRAS expression in patients with mCRC for optimization of treatment strategies.

PATIENTS AND METHODS:

Study population: This prospective study was approved by the Institutional Medical Ethics Committee, and each patient signed a written informed consent form. A total of 43 patients with mCRCs who were referred for PET/CT scan between September 2019 and January 2021 were initially enrolled in our study. Patients with unavailable molecular pathology reports (n=5) were excluded, leaving a valid cohort of 38 patients (26 males and 12 females) with a mean age of 47.7±14.1 years (range: 20-80 years), all of them underwent PET/CT imaging before starting treatment. CT or magnetic resonance imaging, or a combination of the two modalities was used to confirm metastases. No biopsies were taken from metastatic lesions.

Patient preparation and PET/CT acquisition: Prior to ^{18}F-FDG PET/CT imaging, all patients were fasted for at least 4-6 hours. We took a blood glucose reading (which didn't exceed 200 mg/dl) just before IV injection of approximately 3.7 MBq (0.1 mCi/kg) of ^{18}F-FDG. All patients received adequate oral hydration of approximately 1000 ml of water after tracer administration, and they were asked to empty their bladders immediately before imaging. After the ^{18}F-FDG injection, image acquisition began 45-60 minutes later. Patients were instructed to avoid motion during the acquisition time without specific precautions for breathing. The PET/CT images were obtained from the vertex to the midthighs with the arms kept above the head (Biograph mCT, ultra HD lutetium oxyorthosilicate (LSO) PET/CT, Siemens Healthcare, Erlangen, Germany).

The CT scan for PET/CT was performed in a craniocaudal direction without IV contrast using a 16 slice multi-detector scanner with the following parameters: slice thickness of 5 mm, a pitch of 0.8, rotation time of 0.6 seconds, tube voltage of 130 kV, and tube current of 125 mAs. CT data were used for image fusion and attenuation correction. Immediately following the CT scan, a three-dimensional PET emission scan was acquired with a 2-minute acquisition time per bed position. The total acquisition time was approximately 25 minutes. PET images were reconstructed using a time of flight (TOF)+ true X algorithm with 4 iterations, 10 subsets, and a 5-mm Gaussian filter.

Analysis of PET/CT images: During the analysis of PET/CT images which was carried out by two experienced nuclear medicine physicians unaware of the tumor mutational status, only the metastatic lesions were considered. A metastatic lesion was considered to be present if the ^{18}F-FDG uptake was located outside the anatomic sites of physiologic uptake or had a greater intensity than the normal liver parenchyma or adjacent normal tissues. Transaxial, sagittal, and coronal CT as well as the corresponding fused PET/CT images were analyzed on the manufacturer's workstation (Syngo. via, Siemens Healthcare).

For quantitative analysis: A volume of interest (VOI) was drawn on all of the metastatic lesions to calculate SUV. Then, the metabolic parameters: maximum standardized uptake value (SUVmax), total lesion glycolysis (TLG), and metabolic tumor volume (MTV) were determined and analyzed for the metastases with the highest FDG uptake. These parameters were automatically software calculated.

Mutation analysis of KRAS: A molecular pathology report was used to determine the KRAS mutational status of each individual case. Qiagen QIAamp DNA FFPE Tissue Kits were used to extract DNA from the formalin-fixed, paraffin-embedded tumor samples. DNA amplification was performed by polymerase chain reaction using mutation-specific K-Ras primers.

Statistics: The Data were analyzed using SPSS software version 21 (IBM Inc., Armonk, New York, NY, USA). All values were expressed as distribution frequencies, percentages, ranges and mean ± standard deviation as appropriate. For data with normal distribution, parametric tests (independent samples t-test) were used, while non-parametric tests (Mann-Whitney U-test) were used for data with non-normal distribution. To compare the distribution of categorical variables between the two groups, the Pearson chi-square test was used. The determinants were examined using logistic regression analysis. To determine the optimal cut-off value for KRAS mutation prediction, we used receiver operating characteristic (ROC) curve analysis. Statistical significance was defined as a P value of less than 0.05.

RESULTS:

Clinico-pathological characteristics:

Thirty-eight patients (26 males and 12 females, mean age of 47.7±14.1 years, (range: 20-80 years) with mCRCs and available KRAS mutation analysis were prospectively enrolled in this study, all of them underwent PET/CT imaging before starting treatment. Twenty-two (57.9%) patients had metastases at the time of diagnosis, while the remaining 16 (42.1%) presented with metastatic disease after treatment of the early primary. A left-sided caner colon was found in 55.3% of cases, followed by a rectal/anorectal primary tumor (36.8%), while only 7.9% of patients had right sided cancer colon. The majority of patients had non-mucinous adenocarcinoma (92.1%), G2 primary lesion (73.7%), and normal carcino-embryonic antigen (CEA) (63.2%). Seventeen (44.7%) patients had KRAS mutations, while 21 (55.3%) had WT-KRAS ***(Table 1)***. The presence of peritoneal, regional nodal, distant nodal and distant organ metastasis was found in 15, 12, 9, and 16 patients respectively ***(Table 2)***.

Association between patient and tumor characteristics, and KRAS mutation status: As shown in ***Table (3)***, no significant difference was observed between both groups in terms of age (P=0.254), sex (P=0.796), site of the primary tumor (P=0.278), histologic type (P=0.104), grading (P=0.321), CEA level (P=0.393) or metastatic pattern (P=0.224-0.984).

Association between PET/CT parameters and status of KRS mutation: As shown in ***Table (4)***, we found that the mean tumor SUV_{max} was significantly higher in patients with KRAS-mutant than in those with KRAS-WT (13.1±11.9 vs 7.01±4.2, respectively; P=0.016). On the other hand, the mean values of both MTV and TLG were higher for the mutated KRAS group, yet without statistical significance (P= 0.450 and 0.908, respectively).

Predictive value of SUV_{max} for KRAS mutation: On binary logistic regression analysis, the SUV_{max} was a fair predictor for KRAS mutation; it increased the predictive percentage from 55.3% to 68.4% (odds ratio of 1.18, 95% CI: 1.006-1.384, P= 0.041) ***(Table 5)*.** Then, SUV_{max} parameter has been subjected to further ROC curve analysis; which showed that SUVmax cut-off value of >8.8 [AUC: 0.728 (95% CI: 0.564–0.892, P = 0.007)] displayed a sensitivity of 58.8 %, a specificity of 81%, and an accuracy of 72.8% in predicting KRAS mutation ***(Figure 1)*.**

Table (1): Clinical and demographic characteristics of the study population (n=38).

Characteristics	No. (%)
Age, years Mean±SD (range)	47.7±14.1 (20-80)
Sex • Male • Female	 26 (68.4) 12 (31.6)
Primary tumor location • Left colon • Rectal/anorectal • Right colon	 21 (55.3) 14 (36.8) 3 (7.9)
Time for metastasis diagnosis • At the time of initial diagnosis • Relapse after management of the early primary	 22 (57.9) 16 (42.1)
Histologic type • Non-mucinous adenocarcinoma • Mucinous adenocarcinoma	 35 (92.1) 3 (7.9)
Histologic grading • Well differentiated (G 1) • Moderately differentiated (G 2) • Poorly differentiated (G 3)	 6 (15.8) 28 (73.7) 4 (10.5)
Tumor marker; CEA (ng/ml) • Normal • High	 24 (63.2) 14 (36.8)
KRAS mutational status • Mutant • Wild	 17 (44.7) 21 (55.3)

Table (2): Distribution of metastatic lesions on PET/CT.

Metastatic sites	Frequency in the study population
Peritoneum	15
Regional lymph nodes	12
Distant lymph nodes	9
Liver	10
Lung	7
Bone	2
Urinary bladder	1
Ureter	1
Adnexa	1

Table (3): Patient and tumor characteristics according to KRAS mutation status.

Characteristics	n =38	Wild KRAS		Mutated KRAS		*P*
		No.	%	No.	%	
Age (years)						
< 50	23	11	47.8	12	52.2	
≥ 50	15	10	66.7	5	33.3	0.254*
Sex						
Male	26	14	52.8	12	46.2	
Female	12	7	58.3	5	41.2	0.796*
Primary tumor location						
Left colon	21	14	66.7	7	33.3	
Rectal/anorectal	14	6	42.9	8	57.1	
Right colon	3	1	33.3	2	66.7	0.278*
Histologic type						
Non-mucinous adenocarcinoma	35	18	51.4	17	48.6	
Mucinous adenocarcinoma	3	3	100	0	0	0.104*
Histologic grading						
Well differentiated (G 1)	6	5	83.3	1	16.7	
Moderately differentiated (G 2)	28	14	50	14	50	
Poorly differentiated (G 3)	4	2	50	2	50	0.321*
Tumor marker; CEA (ng/ml)						
Normal	24	12	50	12	50	
High	14	9	64.3	5	44.4	0.393*
Regional nodal metastasis						
Yes	12	6	50	6	50	
No	26	15	57.7	11	42.3	0.658*
Distant nodal metastasis						
Yes	9	5	55.6	4	44.4	
No	29	16	55.2	13	44.8	0.984*
Peritoneal metastasis						
Yes	15	10	66.7	5	33.3	
No	23	11	47.8	12	52.2	0.254*
Distant organ metastasis						
Yes	16	7	43.8	9	56.2	
No	22	14	63.6	8	36.4	0.224*
Liver metastasis						
Yes	10	5	50	5	50	
No	28	16	57.1	12	42.9	0.697*
Pulmonary metastasis						
Yes	7	4	57.1	3	42.9	
No	31	17	54.6	14	45.4	0.912*

***Chi-square test**

Table (4): Association between PET/CT quantitative parameters and KRAS mutation.

Parameter	Wild KRAS		Mutated KRAS		*P*
	Mean	SD	Mean	SD	
SUV_{max}	7.01	4.2	13.1	11.9	0.016
MTV	23.0	43.5	35.6	116.1	0.450
TLG	96.0	116.1	190.6	54.6	0.908

Table (5): Logistic regression analysis and odds ratio estimation for predicting KRAS mutation.

Parameter	Odds ratio	95% confidence interval	*P*
SUV_{max}	1.180	1.006-1.384	0.041
TLG	1.002	0.991-1.012	0.783
MTV	0.996	0.947-1.047	0.865

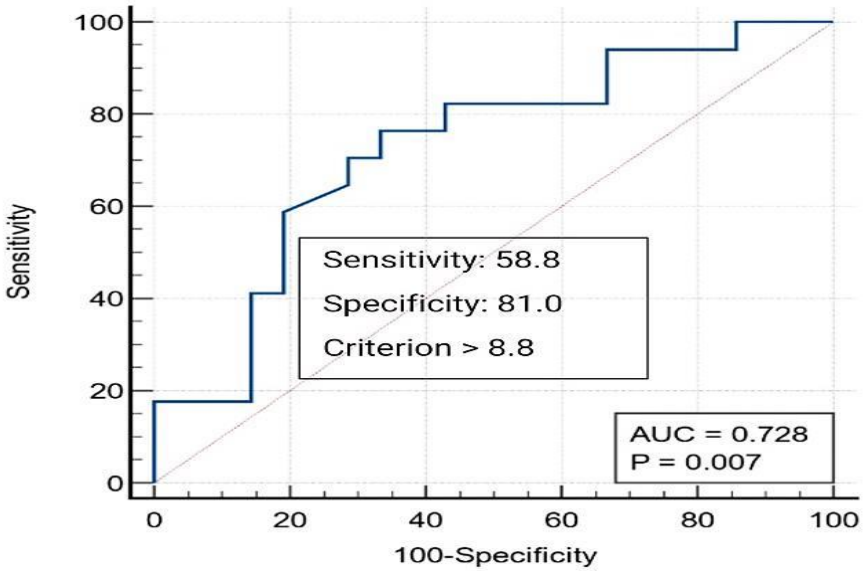

Figure (1): ROC curve and AUC value for predicting KRAS mutation based on SUV_{max}.

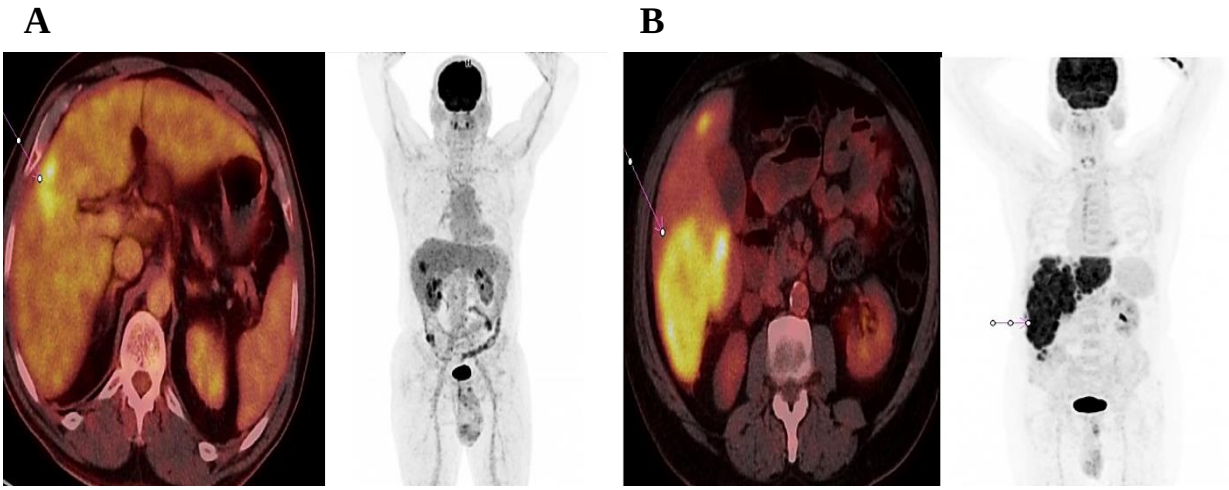

Figure (2): **(A)** A 62-year-old male patient with pathologically proven moderately differentiated colorectal adenocarcinoma of WT-KRAS presented with metastasis three years after treating the early primary lesion. Fused ^{18}F-FDG PET/CT images (left) and MIP (right) sowed liver metastatic focal lesion with SUV_{max} of 5. **(B)** A 64-year-old male with pathologically proven moderately differentiated colorectal adenocarcinoma of mutant-type KRAS presented with liver metastasis at the time of initial diagnosis. Fused ^{18}F-FDG PET/CT images (left) and MIP (right) showed extensive hepatic metastases with SUV_{max} of 8.5.

DISCUSSION:

The determination of the mutational status of KRAS is essential in the management of mCRC as the presence of such mutations prohibits therapy with EGFR inhibitors [(23)]. However, despite the establishment of monoclonal antibodies to EGFR in mCRC patients with WT-KRAS, up to 50% of them don't respond to this line of therapy [(24)]. This may be attributed to intra-tumoral KRAS heterogeneity within a primary CRC tumor [(13)]. Thus, dissected biopsies for KRAS analysis may not reflect the correct gene status of the whole tumor [(16)].

Additionally to the discordant KRAS expression between primary CRCs and their matched metastases [(25)]. Actually, it stills uncertain whether KRAS testing of primary CRCs is enough for characterizing its related metastatic lesions, some studies found a high level of KRAS concordance between primary CRCs and their metastatic lesions (90- >95%) [(26-28)]. While a lower value (~70%) has been recorded by others [(13,14)]. Furthermore, the poor quality of the DNA in diagnostic tumor tissue samples resulting in a failure to identify KRAS status [(15)].

Therefore, it has become imperative to find a substitute biomarker for KRAS genomic expression such as ^{18}F-FDG PET/CT imaging to overcome the above mentioned obstacles to KRAS testing and to provide genomic data without the necessity for surgery or biopsy, which is particularly difficult for metastatic lesions where tumor tissue sampling is usually inaccessible.

^{18}F-FDG PET/CT is used for the in vivo evaluation of the glucose metabolism by measuring ^{18}F-FDG uptake, a glucose analogue. ^{18}F-FDG is transported into cancer cells by glucose transporter-1(GLUT1), and then it is trapped intracellularly via phosphorylation to FDG-6-phosphate mediated by hexokinase II enzyme [29]. Previous studies suggested that, under normoxic conditions, upregulation of GLUT1 expression and thus increased glucose uptake in CRC cells is fundamentally dependent on KRAS mutations [16,30]. In line with previous reports [17,18,21], we didn't encounter significant association between age, sex, CEA levels or histological grade and KRAS mutation.

In contrast, ***Oner et al.*** noticed significant relation between high CEA levels [yet not very strong (P=0.03; AUC: 0.676)] and KRAS expression [12].

Also, we didn't observe significant difference in the pattern of metastasis between mutated KRAS and WT groups. ***Arslan et al.*** showed similar results; the locoregional, distant nodal, and distant organ metastasis didn't differ significantly between the two groups [20].

On the other hand, ***Cho et al.*** reported that patients with mutant KRAS had significantly more frequent pulmonary metastasis, while hepatic metastasis was significantly more associated with KRAS-WT (P=0.006 for each) [18] and ***Lv et al.*** showed a significant association between KRAS mutation and distant metastasis (P=0.029) [21]. Additionally, we didn't find significant difference in the primary tumor locations or its histologic types between patients in the mutated group and those in the WT group, which comes in agreement with ***He et al.*** [31]. Multiple earlier studies have assessed the role of ^{18}F-FDG PET/CT in the prediction of KRAS mutations in primary CRCs, and their conclusions have demonstrated a positive link between high ^{18}F-FDG uptake and KRAS mutations [16-21].

In a pilot study, ***Kawada et al.*** observed that SUV_{max} and tumor: liver ratio (TLR) of the primary lesions with positive KRAS/BRAF mutations were significantly high compared to WT (P=0.006 and 0.001, respectively). They also reported that an SUV_{max} cutoff value of 13 yielded 74% sensitivity, 75% specificity and 75% accuracy in predicting KRAS/BRAF mutations **(16)**.

In a large study, ***Chen et al.*** concluded that the SUV_{max} could predict KRAS mutations in CRC patients (P=0.007), while MTV and TLG couldn't (P=0.12 and 0.09, respectively), and when they used an SUV_{max} cutoff value of 11; the sensitivity, specificity, and accuracy were of 52.4%, 71.7%, and 70% respectively in predicting KRAS mutations **(19)**.

In a recent study conducted by ***Arslan et al.*** pointing out the prognostic value of KRAS mutation and ^{18}F-FDG PET/CT imaging in patients with CRC, they observed a significantly increased mean SUVmax of primary lesions in patients with positive mutation (P=0.001), and believed that an increased FDG uptake in the presence of KRAS mutation could have an adverse effect on prognosis **(20)**.

In keeping with the results of the aforementioned studies, we confirmed a considerably higher FDG uptake in the mutated than in the WT group ***(Figure 2)*** in terms of a significantly higher mean tumor SUV_{max} (13.1±11.9 vs. 7.01±4.2, respectively; P=0.016). We also found that the tumor SUV_{max} is the only quantitative parameter that could predict KEAS mutation (OR:1.180, 95% CI:1.006-1.384; P= 0.041) and SUV_{max} cutoff value of >8.8 (AUC of 0.728) yielded the best accuracy (72.8%), with a sensitivity of 58.8% and a specificity of 81.0% in forecasting KRAS mutation.

In contrast, ***Oner et al.*** reported no significant association between the ^{18}F- FDG PET/CT related parameters, that were; SUV_{max}, MTV, and TLG and KRAS expression (P=0.93, 0.26, and 0.37, respectively) **(12)**.

To the best of our knowledge, this is the third study to investigate the relationship between KRAS gene mutations and ^{18}F-FDG accumulation in CRC metastatic lesions; only two studies with contradictory results had been conducted for this purpose **(15,22)**. ***Kawada et al.*** retrospectively studied 35 patients with mCRC; for metastatic lesions larger than 1 cm, they stated that high SUV_{max} values were significantly associated with mutated KRAS (8.3±4.1 vs. 5.7±2.4, respectively; P=0.03).

In addition, they reported that the optimal SUV_{max} cut-off of 6.0 with an AUC of 0.70 conferred the highest sensitivity (68%), specificity (74%), and accuracy (71.4%) in predicting KRAS status.

On the other hand; when all metastatic lesions; regardless of their size were analyzed, no statistically significant difference in SUV_{max} was found between the two groups (P=0.84) [15].

While, **Krikelis et al**. retrospectively examined a total of 44 patients with mCRC and in contrast to ours, they found no statistically significant association between the ^{18}F-FDG accumulation and KRAS genomic expression (P=0.47). Although in the mutated group, SUV_{max} values tended to be higher [22].

The complexity of the factors undrlying ^{18}F-FDG uptake into tumor cells may be attributed to this discrepancy, including tumor-related factors (hypoxia and tumor size) and non-tumor related factors (inflammation, recent chemotherapy, and diabetes mellitus) [32,33]. In hypoxic cells, hypoxia-inducible factor-1alpha (HIF-1 $\propto$) mediates glucose uptake and metabolism [34]. ***Iwamoto et al.*** suggested that, under hypoxic conditions, the KRAS mutation partially induces FDG uptake through the upregulation of HIF-1$\propto$. [35].

Some studies ruled out patients with uncontrolled diabetes, suspected inflammation in terms of high C-reactive protein ($\geq$ 5mg/L) and patients who received chemotherapy within six months prior to their studies. Furthermore, they analyzed mCRC lesions according to their size [15] in an attempt to reduce the partial volume effect's bias that could result in SUV_{max} underestimation particularly for small-sized tumors as previously documented [36].

This might explain the contradictory results of the discussed studies in the current work.

Limitations of the study: Only KRAS mutations were studied; while PIK3CA, BRAF, and NRAS mutations weren't. Although the prevalence is less than that of KRAS mutations (about 15, 10% & 3%, respectively)[37-39] ,their presence may cause resistance to EGFR inhibitors in WT-KRAS CRC patients [13].

In addition, because tissue samples from metastatic lesions are typically inaccessible, the dissected specimens used for molecular testing were only extracted from the primary lesions, yet a recent large meta-analysis demonstrated the presence of remarkably high concordance across a number of individual biomarkers (including KRAS), suggesting that molecular testing of either the primary or metastasis is adequate for determining biomarker status to personalize treatment [(40)].

On the other hand, the study's strong points were the prospective design and the review of PET/CT images by two experienced nuclear medicine specialists, along with the division and analysis of CRCs according to their histopathologic type and grading.

CONCLUSIONS:

In summary, we found that the accumulation of ^{18}F-FDG was significantly higher in the metastatic lesions of CRCs carrying KRAS mutations than in those with WT-KRAS. ^{18}F-FDG PET/CT based SUV_{max} could be used as a non-invasive surrogate biomarker for KRAS genomic expression to improve treatment strategies of mCRC patients. However, further prospective studies of a larger sample size are necessary to validate our results.

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