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The Prognostic Value of SUVmax of ^{18}F-FDG PET/CT in Patients with Metastatic Colorectal Cancer

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Abstract

Objective. The aim of the study was to evaluate the prognostic value of the maximum standardized uptake value (SUVmax) of ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) PET/CT in patients with metastatic colorectal cancer, and to compare it with classical prognostic markers. **Materials and Methods.** The study included 70 patients with metastatic colorectal cancer who had not been treated for the metastatic disease. The patients underwent ^{18}F-FDG PET/CT as part of their routine diagnostic reevaluation. During the analysis, the value of the largest tumor diameter and SUVmax was determined for the lesion with the highest SUVmax observed. The values of CEA and CA 19-9 were recorded 7 days before the PET/CT analysis. **Results.** SUVmax and Carbohydrate antigen (CA)19-9 were found to be independent prognostic markers of disease progression within 12 months. Based on the Receiver Operating Characteristics (ROC) curve analysis, the patients could be divided into two groups: SUVmax≤4.1 vs. SUVmax>4.1. Patients with SUVmax values of 4.1 or less had significantly better progression-free survival within 12 months with an HR (95% CI) of 2.97 (1.4-6.3), relative to patients with SUVmax values above 4.1. **Conclusion.** SUVmax may be used as a novel prognostic marker of disease progression among patients with metastatic colorectal cancer. Values of SUVmax can be used to select patients with a more aggressive type of disease and higher risk for progression within 12 months of PET/CT analysis.

Key Words: PET/CT ▪ SUVmax ▪ Colorectal Cancer ▪ CA 19-9 ▪ Progression Free Survival.

Introduction

Colorectal cancer is the third most commonly occurring cancer in men and the second most commonly occurring cancer in women. In 2018, 1.8 million new cases were reported and over the next 10 years, 50% more, newly diagnosed colorectal cancer cases are expected in the world (1). On the basis of the relevant literature, it may be concluded that PET/CT is present in almost all stages of management of this disease, and is only not indicated as part of the initial diagnosis of patients with colorectal cancer (2). The standardized uptake value (SUV) is the semi-quantitative method most commonly used to determine ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) uptake in attenuation corrected PET images. With this technique, the tumor ^{18}F-FDG concentration is normalized to the amount of injected activity and the total volume of distribution (3). Although there are several studies that have evaluated the role of SUVmax as a predictive marker in such patients, only a few studies have examined the prognostic role of PET/CT parameters in relation to overall survival and progression-free survival in patients with colorectal cancer (4, 5). However, the results of studies investigating the role of PET/CT in the evaluation of treatments have revealed certain potential for

the formation of a prognostic model that would include SUVmax along with classical prognostic markers (6, 7).

Furthermore, pretreatment tumoral ^{18}F-FDG uptake has been shown to represent an independent prognostic factor in patients with liver metastases undergoing any primary treatment modalities for colorectal cancer (8, 9).

The aim of our study was to evaluate the prognostic value of the maximum standardized uptake value (SUVmax) of ^{18}F-FDG PET/CT in patients with metastatic colorectal cancer, and to compare it with classical prognostic markers. Considering that pre-existing prognostic models often include serological tumor markers, in our study we decided to investigate the relationship between SUVmax, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9, and to evaluate the role of SUVmax as an independent prognostic marker of progression-free survival.

Materials and Methods

We performed an exploratory, descriptive-analytical study, with retrospective collection of data.

Study Design

The study included 70 patients with metastatic colorectal cancer at the Clinic of Oncology, University Clinical Center of Sarajevo. The baseline was the date of the PET/CT analysis. After PET/CT analysis, the patients were followed up until the first radiologically verified disease progression. Patients had regular radiological examinations on a 3 month basis (as per guidelines), except for the patients who had earlier check-ups due to clinical indications of disease progression. In March 2019 we established a follow-up cut off when all the patients were examined for disease progression for the last time. The value of tumor markers (CEA and CA19-9) was recorded 7 days before PET/CT analysis. The values of the largest tumor diameter and SUVmax were recorded for the lesion with the highest SUVmax observed during the analysis.

Inclusion Criteria

Patients were included when they met the following criteria: the diagnosis of colorectal cancer had been confirmed by histopathological examination; metastatic disease had been confirmed radiologically or by histopathological examination; patients had not received any systemic treatment for metastatic disease; patients underwent ^{18}F-FDG PET/CT between January 2015 and December 2017 as part of their routine diagnostic reevaluation at the Clinic for Nuclear Medicine of the University Clinical Center of Sarajevo; patients had at least one-year period of adequate follow-up after the entry point; patients had regular evaluation on a 3 month basis, using an appropriate radiological diagnostic modality during the follow-up period.

Exclusion Criteria

The exclusion criterion was not fulfilling one of inclusion criteria above.

PET/CT Image Acquisition

The PET/CT was performed using a GE Discovery scanner (GE Healthcare, General Electric, Milwaukee, Wisconsin, USA). Multislice CT and PET emission data were acquired from the skull to the mid-thigh in all patients. Image acquisition started 60 min after intravenous injection of 370 MBq of ^{18}F-FDG. We used the EARL reconstruction protocol with two iterations and 32 subsets.

Statistical Analysis

IBM SPSS Statistics v. 23.0 was used for statistical analysis. The relationship between the largest diameter of the tumor, serological tumor markers (CA 19-9 and CEA), the number of months without disease progression, and SUVmax values was investigated using the Spearman correlation coefficient. The relationship of certain baseline characteristics, i.e. clinical and biochemical variables, and the parameters of PET/CT analysis, with the risk of disease progression within 12 months of PET/

CT analysis, was examined using multivariate Cox hazard analysis. In the survival analysis, progression of the disease within 12 months was the primary outcome measure. The study was performed on the sample of 70 patients since in the first year of follow up there were no deaths or patients lost to follow up. Progression-free survival was calculated from the date of the PET/CT analysis until the date of the disease progression for those patients who had progression of the disease within 12 months. The Kaplan-Meier method with the log-rank test was used to investigate the impact of SUVmax, defined as a dichotomous variable, on disease progression within 12 months.

A follow-up period of a minimum of 12 months was an inclusion criterion in this study. We had 6 patients who were lost to follow-up after 12 months. Those patients were censored at their last eligible and available radiology evaluation. The number of months without disease progression after 1 year of follow-up was used for descriptive statistical analysis only. The Receiver Operating Characteristic (ROC) curve was used to determine the optimal cut-off value for SUVmax. Data are presented as mean with standard deviation or as median with the 1st and 3rd quartiles. P<0.05 was an indicator of significance.

Results

Patients' Characteristics

The study included 70 patients with metastatic colorectal cancer, who underwent ^{18}F-FDG PET/CT at the University Clinical Center of Sarajevo (Table 1).

Correlation between SUVmax and Tumor Diameter

The values of the largest tumor diameter and SUVmax were recorded for the lesion with the highest SUVmax observed during the analysis. A statistically significant positive correlation between the largest tumor diameter and SUVmax was found. Higher tumor diameter values were associated with higher SUVmax values (rho=0.777; P<0.001).

Correlations between SUVmax and Tumor Markers

CEA and CA 19-9 values were recorded 7 days before PET/CT analysis. The median (1st -3rd quartile) CEA was 3.9 (1.6-21.7) ng / mL and CA 19-9 was 13.1 (4.4-46.6) U / mL. A statistically significant positive correlation was found between CEA and SUVmax. Higher CEA values were associated with higher SUVmax values (rho=0.494; P=0.0002). The relationship between CA 19-9 and SUVmax was also examined, however, no statistically significant correlation was found between these variables (rho=0.036; P=0.797).

Correlations between SUVmax and PFS (Progression Free Survival)

The relationship between SUVmax values and PFS was investigated. A statistically significant negative correlation was found between the two variables. Higher SUVmax values were associated with a shorter PFS (rho=-0.384; P=0.001).

Prognosis of Disease Progression within 12 Months

Among the 70 patients in our study, 36 (51.4%) experienced disease progression within 12 months of PET/CT.

Table 1. Summary of Patients' Characteristics

Variable	Age (years)*	Sex, N (%)		Tumor diameter (cm)†		SUVmax†		Disease progression within 12 months, N (%)	
All patients (n=70)	62.2±10.3 years (34-80)	M	29 (41.4)	1.5	(0.0– 3.6)	6.0	(1.5-10.5)	Yes	36 (51.4)
		F	41 (58.6)					No	34 (48.6)

*Mean±standard deviation (minimum -maximum); SUVmax=Maximum standardized uptake value; †Median with 1st and 3rd quartile.

Table 2. Univariate Cox Regression Hazard Analysis of Prognostic Markers of Disease Progression within 12 Months

Variable	All patients (N=70)			
	B	P	HR	95% CI for HR
Age	-0.008	0.626	0.922	0.958-1.026
Sex	0.051	0.881	1.052	0.542-2.041
Tumor diameter	0.145	0.02	1.156	1.023-1.306
SUVmax	0.030	0.001	1.031	1.012-1.050
CEA	0.007	0.066	1.007	1.00-1.014
CA19-9	0.004	0.013	1.004	1.001-1.008

B=Unstandardized regression coefficient; P=p-value; HR=Hazard risk; 95% CI for HR=95% confidence interval for hazard risk; SUVmax=Maximum standardized uptake value; CEA=Carcinoembryonic antigen; CA19-9=Carbohydrate antigen 19-9.

Table 3. Multivariate Cox Regression Hazard Analysis of Prognostic Markers of Disease Progression within 12 Months

Variable	All patients (n=70)			
	B	p	HR	95% CI for HR
SUVmax	0.074	0.005	1.077	1.023-1.134
CA 19-9	0.005	0.01	1.005	1.001-1.009

B=Unstandardized regression coefficient; P=p-value; HR=Hazard risk; 95% CI for HR=95% confidence interval for hazard risk; SUVmax=Maximum standardized uptake value; CA19-9=Carbohydrate antigen 19-9.

Table 2 depicts the results of the univariate Cox hazard model of prognostic factors for disease progression within 12 months of PET/CT analysis. Tumor diameter, SUVmax value, and CA 19-9 value were found to be positively related with progression within 12 months (Table 2). Variables that were significant univariates were included in the multivariate Cox regression hazard analysis.

Table 3 shows the results of multivariate analysis. SUVmax and Ca19-9 were found to be independent prognostic markers of disease progression within 12 months (Table 3).

Measurement of SUVmax Cut-Off Value

ROC analysis identified a cut-off value of 4.1 as significant for SUVmax (area under the curve 0.65; P=0.031; 95% CI 0.52–0.78; Figure 1). The sensitivity and specificity at this value were 75% and 54.9%, respectively. On the basis of the ROC curve analysis, the patients could be divided into two groups: SUVmax≤4.1 vs. SUVmax>4.1.

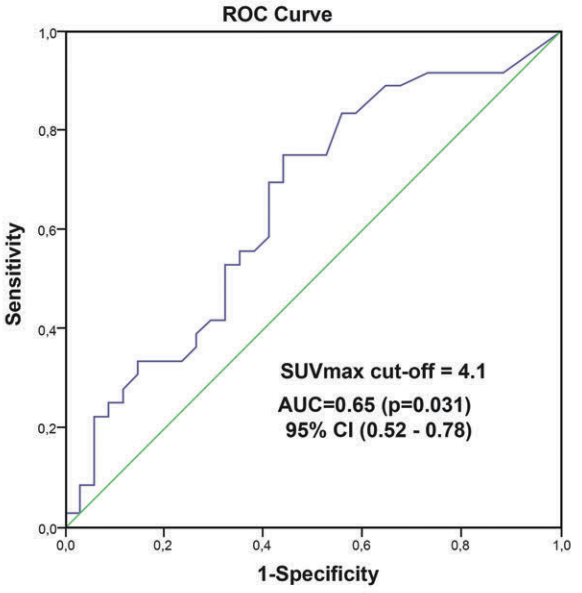

Figure 1. ROC curve SUVmax in prognosis of disease progression within 12 months.
ROC Curve=Receiver Operating Characteristics; AUC=Area Under the Curve; CI=confidence interval.

Survival Analysis

Survival without disease progression within 12 months was examined in relation to the cut-off value of SUVmax determined by the ROC analysis (SUVmax=4.1) and the hazard risk was calculated (Figure 2).

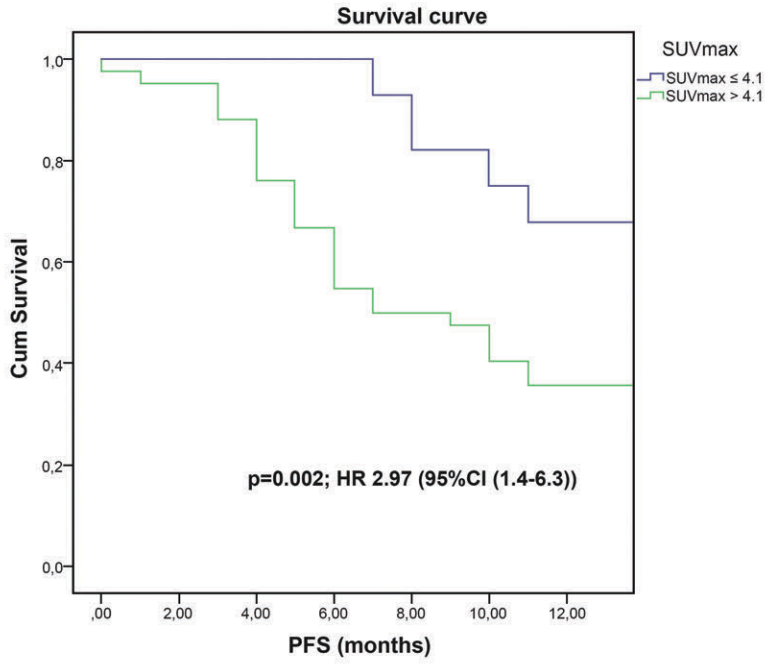

Figure 2. Kaplan-Meier curve of progression-free survival within 12 months for patients stratified based on a cut-off value of SUVmax of 4.1.
PFS=Progression-Free Survival.

Average (± standard deviation) progression-free survival in patients with SUVmax above 4.1 was 11.3±9.37 months, and in patients with SUVmax below 4.1 was 19.6±12.05 months (P=0.001).

Discussion

The aim of our study was to evaluate the role of SUVmax in the prognosis of disease progression in patients with metastatic colorectal cancer. The relationship of SUVmax with serological tumor markers (CEA and CA19-9) was also evaluated. The aim of this testing is to try to find indicators that are routinely used in the evaluation of patients with colorectal cancer that might suggest that we could benefit from PET/CT analysis, which is an expensive diagnostic modality. Certain studies have shown a clear relationship between SUVmax and survival predictions in gastrointestinal cancers such as gastric cancer and esophageal cancer (10, 11).

However, only a few studies have been reported on the role of SUVmax in the prediction and prognosis of outcomes in colorectal cancer. Such studies typically address the role of PET/CT parameters in evaluating the effectiveness of a particular therapeutic modality, rather than the possible impact on prognosis of overall survival or event-free survival (12, 13).

Due to the signs we had identified in the relevant literature that SUVmax could be a novel prognostic marker, we decided to investigate the clinical value of SUVmax as a prognostic marker through univariate and multivariate Cox regression analysis, and to compare it with classical colorectal cancer prognostic markers.

A significant relationship with disease progression within 12 months was calculated for the largest tumor diameter, SUVmax value and CA 19-9. SUVmax and CA19-9 were the only independent markers of progression within 12 months. Statistical analysis showed that SUVmax was the best prognostic marker of progression of the included variables within 12 months. Although CA19-9 showed no significant correlation with SUVmax, multivariate analysis revealed a significant positive effect on disease progression.

Since SUVmax was the best prognostic marker of progression within 12 months, a ROC analysis was performed to determine the clinical value of this prognostic marker. The AUC score of our ROC analysis suggests that SUVmax is sufficiently reliable as a prognostic marker. It may be assumed that the AUC value would be even higher on a larger sample of patients. In order to prove the clinical value of the results we obtained, a Kaplan-Meier survival curve was performed. Patients with an SUVmax value of 4.1 or less (cut-off values obtained by ROC analysis) had significantly better progression-free survival within 12 months, with an HR of 2.97, relative to patients with SUVmax values above 4.1.

We compared our results with a study conducted by Shi et al. (5). In this study the authors included 107 newly diagnosed patients with various stages of colorectal cancer. In the multivariate Cox regression hazard analysis, it was demonstrated that TNM stage and SUVmax were the only independent prognostic markers of survival within 60 months in these patients. The SUVmax cut-off that was optimal for the prognosis of survival was 11.85, and it had a sensitivity of 73.3% and specificity of 75.3%. Patients with SUVmax below 11.85 had significantly longer survival (5). The SUVmax cut-off value in this study was higher than that observed in our analysis. A possible explanation may be that the patients in this study were newly diagnosed and had not been treated with any therapeutic modality so far.

Our results are compatible with the results of a study that examined the prognostic value of routine PET/CT in 70 patients with colorectal cancer, but who were found to have hepatic metastases. This analysis showed that patients with SUVmax below the cut-off value of 4.48 showed significantly longer progression-free survival (14). In our study, CEA showed a statistically significant positive correlation with SUVmax. Serological marker analysis is a cheaper diagnostic procedure than PET/CT analysis. The relationship between CEA and SUVmax demonstrated in this study may indicate the complementarity of the two methods. Increased CEA values may be an indicator for referring patients to PET/CT analysis. Lu et al. (15) conducted a meta-analysis of eleven studies, with a total of 510 patients, in order to investigate the diagnostic performance of ^{18}F-FDG-PET or PET/CT in the detection of recurrent colorectal cancer occurring in patients with elevated CEA. The pooled estimates of sensitivity and specificity of ^{18}F-FDG-PET/CT in the detection of tumor recurrence in CRC patients with elevated CEA were 94.1% and 77.2%, respectively. The results of this meta-analysis may contribute to the idea of using elevated CEA values as a sign for referring patients to PET/CT analysis. Certainly, future research with more patients may analyze this relationship more precisely and clarify it even further.

Although authors in some studies did not identify a significant relationship between CEA and SUV max, our results are certainly supported by the results of a study on 212 patients, where the authors identified a significant positive correlation between CEA and CA19-9 with SUVmax and other PET/CT parameters (16, 17). The authors of this study concluded that, although CEA is far from the ideal marker, its wide use and the fact that CEA reflects tumor metabolic features more than morphological ones, may certainly be of great benefit to clinicians (18). In the study conducted by Jones et al. (19), CEA was found to be an independent predictor of SUV-max values.

Our data could have an impact on the management of patients with metastatic colorectal cancer. Patients with a more aggressive disease (in our study patients with SUVmax values above 4.1) have worse prognosis and decisions on their further treatment should be made by a multidisciplinary team. Our recommendation for practicing surgeons is to postpone surgical treatment in this group of patients due to the possibility that surgery could shorten their survival. However, SUVmax with specific cut-off values has a limited role since the SUVmax variation is multifactorial and its use should be validated through further studies.

Limitations of the Study

Our study has several limitations. It is limited by its retrospective design and selection bias. We collected our data retrospectively while selecting patients who underwent PET/CT after confirmation of metastatic disease. A major problem with designing a randomized, prospective study with a control group on this topic is the ethical dilemma since it is well-known that PET/CT is superior to other radiological modalities when it comes to evaluation of malignant disease (20). The study was conducted at a single institution, with a relatively small sample of patients. The patient sample was heterogeneous since we did not divide patients up on the basis of the site of metastasis and type of therapy they had received. In this exploratory study we wanted to show proof of the concept

that SUVmax could be used as a prognostic tool in patients with metastatic colorectal cancer. The different sites of metastatic disease among our patients should not affect values of SUVmax, since Hofman et al. (21) concluded that the intensity of uptake of ^{18}F-FDG is parallels between primary tumors and metastatic tumors. Further, larger studies are needed to evaluate the relationship between SUVmax values, different types of therapy, different sites of metastatic disease and the joint effect of these variables on prognosis in patients with metastatic colorectal disease.

Conclusion

SUVmax may be used as a novel prognostic marker of progression among patients with metastatic colorectal cancer. Values of SUVmax can be used to select patients with more aggressive types of disease and a higher risk for progression within 12 months of PET/CT analysis. The relationship between CEA and SUVmax demonstrated in this study may indicate the complementarity of the biochemical and radiological examination methods. Increased CEA values may be an indicator for referring patients to PET/CT analysis.

What Is Already Known on this Topic:
PET/CT is indicated in all stages of management and evaluation of colorectal cancer, except in the initial diagnosis. The parameters of the PET/CT analysis, such as SUVmax, have already been investigated as possible predictive markers in patients diagnosed with colorectal cancer. Previous studies have typically focused on the role of SUVmax as a marker of the effectiveness of a certain therapeutic modality.

What this Study Adds:
Focusing on the role of SUVmax as a prognostic marker, this study could further clarify the possibility of identification patients with more aggressive types of colorectal cancer. Selection of these patients at an early stage of the disease would affect the treatment strategy. The complementarity of SUVmax and classical prognostic markers of colorectal cancer presented in this study could influence daily clinical practice.

Authors' Contributions: Conception and design: ES and TC; Acquisition, analysis and interpretation of data: ES, TC, AP, ISP and ŠC; Drafting the article: ES, TC, ŠC, SB and AP; Revising it critically for important intellectual content: SB, SVZ, AP, ISP and NB; Approved final version of the manuscript: ES, TC, AP and SB.

Conflict of Interest: The authors declare that they have no conflict of interest.

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