

Statistical Modeling of Relations Between PET/CT Parameters and CEA in Recurrent and Metastatic Colorectal Cancer

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ABSTRACT

Background: Colorectal cancer (CRC) is a diverse disease with various clinical, pathological and molecular features that affect tumor biological behavior, treatment response and prognosis. **Objective:** The aim of this study was to evaluate the correlation between metabolic 18F-FDG PET/CT parameters (SUVmax, MTV and TLG) and CEA in recurrent and metastatic CRC and to evaluate prognostic value of metabolic 18F-FDG PET/CT parameters in recurrent and metastatic CRC. **Methods:** A descriptive study of 100 patients with previously detected and surgically treated CRC referred to PET/CT with a suspicion of recurrent or metastatic CRC. CEA was measured within three months from the imaging. A low-dose PET/CT was performed per institutional protocol. For each hypermetabolic lesion, metabolic PET/CT parameters (SUVmax, MTV, TLG) were calculated semiautomatically. Pathohistology or clinical data from the follow-up were used as the gold standard. Sensitivity, specificity, PPV and NPV for 18F-FDG PET/CT and CEA in detection of recurrent or metastatic CRC were calculated. Correlation between CEA and SUVmax, MTV and TLG was calculated, separately. To assess the prognostic values of metabolic parameters in CRC, survival analysis with 18-month progression-free survival (PFS) as an endpoint was performed. Microsoft Excel sheets, ROC and Kaplan-Meier curves were used to present the data. Logrank and Tarone-Ware test and Cox model of proportional hazards were used to compare the groups. **Results:** Study included 100 patients, 45 males and 55 females, age range 36-81 years, mean age 61,4 years. Cancer site was colon in 56% and rectum in 44%. Sensitivity, specificity, PPV and NPV of 18F-FDG PET/CT in detection of recurrent or metastatic CRC was 95%, 73%, 70% and 95%, respectively. Sensitivity, specificity, PPV and NPV of CEA in detection of recurrent or metastatic CRC was 58%, 96%, 91% and 78%, respectively. SUVmax, MTV and TLG positively correlated with CEA, but only CEA-TLG correlation was considered significant ($r=0,67$). The regression model analysis revealed: SUVmax (HR=0,63, 95%CI=0,28-1,41, $p=0,214$), MTV (0,59, 95%CI=0,28-1,22, $p=0,111$) and TLG (HR=0,45 95%CI=0,21-0,99, $p=0,028$), and the prognostic role in CRC was proven for TLG only. **Conclusion:** Metabolic 18F-FDG PET/CT parameters may have the prognostic value in CRC, but further multicentric prospective studies are required for validation.

Keywords: Colorectal cancer, 18F-FDG PET/CT, CEA, metabolic parameters, prognostic value.

1. BACKGROUND

Colorectal cancer (CRC) is a diverse disease with various clinical, pathological and molecular features that affect tumor biological behavior, treatment response and prognosis (1-4). CRC is the third most common cancer worldwide, characterized by specific sex, age and geographic distribution. It is considered that over their lifetime, about

4,6% (1 in 22) of men and 4,2% (1 in 24) of women will be diagnosed with CRC (5-7).

Carcinoembryonic antigen (CEA) is a biomarker with the previously established diagnostic and prognostic roles in CRC. A glycoprotein normally present in the fetal tissue has only low levels in the plasma of healthy adults. CEA increases in CRC, but also some

other malignant and benign conditions, e.g. of inflammatory nature (8). Due to its low sensitivity in the early stages of CRC, CEA is not used in screening for CRC, but is recommended in the follow-up, when recurrence or metastatic disease is suspected (9,10). Studies indicate that CEA sensitivity in detection of recurrent or metastatic CRC reaches up to 60%, pending the reference range used and the site of recurrent or metastatic disease (8,11).

When recurrent or metastatic CRC is suspected based on the clinical findings, radiologic imaging or rising CEA, the diagnostic imaging is indicated. Colonoscopy remains the gold standard, while 18F-FDG PET/CT is indicated for (a) restaging in suspected recurrent CRC; (b) preoperative evaluation of potentially resectable recurrence or metastatic disease; and (c) evaluation of treatment response, while further scientific validation is needed (9,10,12,13).

As a hybrid imaging modality, 18F-FDG-PET/CT integrates anatomic and metabolic information in a single study. Metabolic information describes tissue metabolism from the perspective of glucose utilization. Quantitatively describing glucose metabolism has become a standard of reporting by including SUVmax (maximum standardized uptake value) in a PET/CT report, with an arbitrary SUVmax threshold of 2.5 to discern benign from malignant lesions. Some other metabolic parameters include MTV (metabolic tumor volume) corresponding to tumor burden and TLG (total lesion glycolysis) corresponding to tumor aggressiveness. They are also volumetric parameters, and their role in increasing specificity of 18F-FDG PET/CT study is still to be validated (14-17). Volumetric parameters may have a prominent role in the treatment response evaluation.

2. OBJECTIVE

Given the long established role of CEA in the follow-up of CRC and the emerging role of PET/CT, the study is aimed at evaluating the correlation between most commonly used 18F-FDG PET/CT metabolic parameters (SUVmax, MTV and TLG) and CEA in recurrent and metastatic CRC, and also the prognostic roles that 18F-FDG PET/CT metabolic parameters may have in recurrent and metastatic CRC.

3. MATERIAL AND METHODS

A descriptive, retrospective-prospective study was performed on 100 patients with previously detected and surgically treated CRC, who were referred to 18F-FDG PET/CT imaging to the Clinic of Nuclear Medicine, Clinical Center of Sarajevo University with a suspicion of recurrent or metastatic CRC between January, 2016 and January, 2020. The suspicion was raised by rising CEA, equivocal radiologic findings or clinical findings. Inclusion criteria were previous curative resection, diagnosis of colorectal adenocarcinoma and chemoradiotherapy, if administered more than six months ago. CEA was measured within 3 months from PET/CT study, and the levels above 5 ng/ml were considered abnormal. A low-dose whole-body PET/CT was performed per institutional protocol upon the administration of 370,0 MBq of 18F-fluodeoxyglucose I.V. and oral contrast agent, on an integrated PET/CT scanner (GE, 610 Discovery, GE Healthcare), For visual and semiquantitative analysis, vendor software (Advantage Workstation, Release 4.6. Software, GE) was used. SUVmax,

MTV, TLG were calculated semiautomatically for each focus of increased glucose metabolism. SUVmax (g/ml) was calculated as maximum 18F-FDG value in the voxels within the region of interest (ROI) divided by injected dose and corrected for radioactive decay and body weight. SUVmax cut-off value of $SUV > 2,5$ was used. MTV (cm³) was calculated by calculating in all voxels within a ROI with SUVs higher or equal to the predetermined threshold of $SUV > 2,5$. TLG was a product of SUVmean and MTV.

True positives were FDG-positive consistent with recurrence, as proven by the gold standard. True negatives had no FDG-positive pathological, or structural lesions. False positives were FDG-positive in normal anatomic structures, benign or inflammatory lesions. False negatives were FDG-negative with normal CT, but proved positive on the gold standard. Sensitivity, specificity, PPV and NPV for 18F-FDG PET/CT and CEA in detection of recurrent CRC were calculated. Metabolic PET/CT parameters were correlated with CEA. To evaluate the prognostic values of metabolic parameters in CRC, prognostic models were created, and survival analysis was performed with the 18-month progression-free survival (PFS) as an endpoint. For statistical analysis, Minitab 20.4, IBM SPSS Statistics 27.0, Medcalc 20.023 and XLSTAT 2018.1 were used. Microsoft Excel sheets, ROC and Kaplan-Meier curves were used to present the data. For each analysis, $p < 0.05$ was considered statistically significant.

INCIDENTAL FINDINGS OF COVID-19 PULMONARY LESIONS ON PET/CT FOR BREAST CANCER - CASE STUDY

A fifty-year-old patient with breast cancer was referred to a follow-up PET/CT exam in order to evaluate for the treatment response.

The patient was diagnosed with HER-2 positive invasive ductal breast cancer after the radical right mastectomy in 2015. Post-surgery she was treated with chemotherapy, hormonal therapy and radiotherapy of the pelvis for the metastatic disease in the lymph nodes. In 2019, she was diagnosed with metastatic disease in the liver when the combined HER2 targeted therapy (Perjeta+Herceptin) was prescribed.

Before the study, the patient was asymptomatic and tested negative on RT-PCR SARS CoV-2 performed with 48 hours from the imaging.

A low-dose whole-body PET/CT was performed after the injection of 368,5 MBq of 18F-fluodeoxyglucose intravenously and peroral contrast agent was applied.

Acquisition parameters were determined in accordance with the institutional protocol.

PET/CT images demonstrated in both lungs multiple ground glass opacities that were located peripherally in the parenchyma. All lesions accumulated 18-F fluodeoxyglucose with the low to moderate intensity, SUVmax 3,8.

Described lung lesions were very highly suggestive of the COVID-19 disease, and the patient was isolated and referred for retesting immediately.

PET/CT also demonstrated multiple hypermetabolic lesions in the liver, bones and the local and distant lymph nodes consistent with the metastatic disease.

Repeated RT-PCR SARS-CoV2 testing performed hours from PET/CT imaging proved positive. Continued isolation

Total number of hypermetabolic lesions	85						
	Anatomic region						
	Local recurrence	Regional lymph nodes	Distant lymph nodes	Llver	Lung	Others	Total
SUVmax average	12.56	6.04	8.45	8.46	6.30	5.62	8.17
SUVmax range	7.9 - 17.4	3.4 - 9.8	2.9 - 17.4	5.3 - 13.9	2.7 - 10.7	2.2 - 13.1	2.2 - 17.4
Number of patients with lesions	10	5	13	9	6	11	54
SUVmax ≤2.5	0	0	8	0	0	5	13
SUVmax >2.5/<5.0	0	3	3	6	3	6	21
SUVmax ≥ 5.0	10	2	2	3	3	0	20

Table 1. Distribution of SUVmax (g/ml) per anatomic region

Correlation	r	P
CEA – SUVmax	0.192	0.163
CEA – MTV	0.333	0.014
CEA – TLG	0.678	0.001

Table 2. Correlation between CEA and metabolic PET/CT parameters with Pearson correlation coefficient r

Described lung lesions were very highly suggestive of the COVID-19 disease, and the patient was isolated and referred for retesting immediately. PET/CT also demonstrated extensive hypermetabolic lymphadenopathy (neck, axillary, mediastinal, hilar, retroperitoneal, abdominal, pelvic lymph nodes involvement).

Repeated RT-PCR SARS-CoV2 testing performed hours from PET/CT imaging proved negativ.

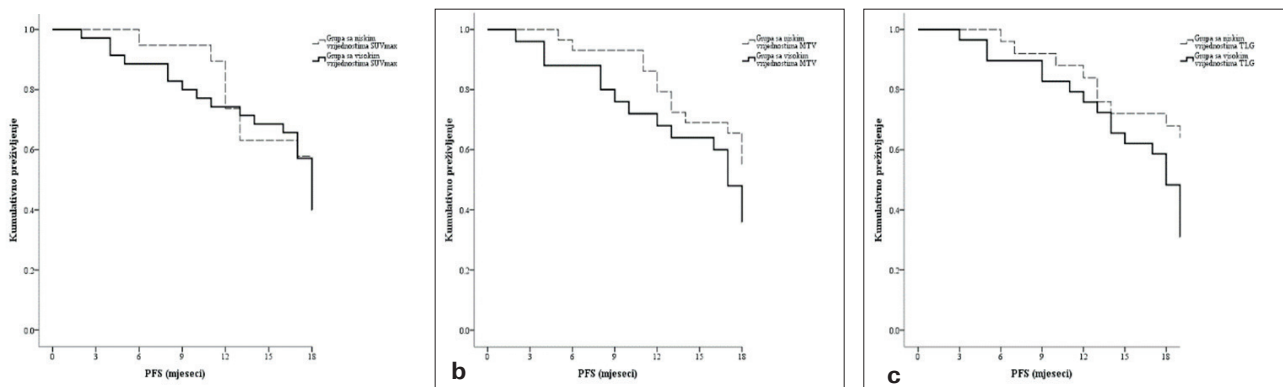


Figure 1. (a,b,c). Kaplan-Meier curves for 18-months PFS in CRC for SUVmax (p=0.214), MTV (p=0.111) and TLG (p=0.028). Patients divided into low-risk and high-risk groups for each metabolic parameter: (a) SUVmax, (b) MTV, (c) TLG

was recommended and the oncology visit was postponed.

Conclusion

A fifty-six-year-old man with Mantle cell lymphoma was referred to a follow-up PET/CT exam due to suspected relapse of the disease.

The patient was diagnosed with Mantle cell lymphoma after neck lymph node biopsy in 2016. He was treated with systemic therapy (chemotherapy) and the last chemotherapy cycle was in 2018. During follow-up period he noticed neck lymph node enlargement.

Before the study, the patient was asymptomatic and tested negative on RT-PCR SARS CoV-2 performed with 48 hours from the imaging.

A low-dose whole-body PET/CT was performed after the injection of 362,5 MBq of 18F- fluodeoxyglucose intravenously and peroral contrast agent was applied.

Acquisition parameters were determined in accordance with the institutional protocol.

PET/CT images demonstrated peripheral lung consolidation in both lungs.

All lesions accumulated 18-F fluodeoxyglucose with high intensity, SUVmax 7.8.

4. RESULTS

Study included 100 patients, 45 (45,0%) males and 55 (55,0%) females, age range 36-81 years, mean age 61,4 years. Cancer site was colon in 56% and rectum in 44%. Men were predominantly diagnosed with rectal, and women with colon cancer, predominantly sygma. PET/CT was positive in 54, and negative in 46 patients. A total of 85 hypermetabolic lesions were analyzed and stratified into local recurrence, regional lymph nodes, distant lymph nodes, liver, lungs and other rarely affected organs (e.g. bones, peritoneum, subcutis, ovaries), as shown in Table 1.

Sensitivity, specificity, PPV and NPV of 18F-FDG PET/CT in detection of recurrent or metastatic CRC was 95%, 73%, 70% and 95%. Serum CEA was normal in 74, and elevated in 26 patients with the range of 0,48-821,0. Sensitivity, specificity, PPV and NPV of CEA in detection of recurrent or metastatic CRC was 58%, 96%, 91% and 78%, respectively. Out of 54 patients with positive PET/CT, 24 had elevated CEA, while 30 (55,5%) had normal CEA values. In 46 patients with negative PET/CT, only 2 (4,3%) had elevated CEA.

Correlation studies revealed positive correlation between CEA and all metabolic 18F-FDG PET/CT parameters, very

weak for CEA-SUVmax, weak for CEA-MTV and significant for CEA-TLG (Table 2).

In evaluation of the prognostic values of metabolic parameters in CRC, the prognostic models were created with 18-month PFS as an endpoint. Receiver operating characteristic (ROC) curves were generated according to SUVmax, MTV and TLG values and PFS of 18 months, and the cut-off values for each parameter were determined. The cut-off value for SUVmax was 7.25 g/ml (AUC 0.521, 95%CI (0.36-0.680)), MTV 13.25 cm³ (AUC 0.534, 95%CI (0.376-0.692)) and TLG 42.55 (AUC 0.571, 95%CI (0.411-0.731)). Patients were then divided into the low and high-risk groups according to the cut-off value for each parameter, and Kaplan-Meier survival curves were generated for each parameter. Log rank test was used to compare PFS for 18 months between the two groups for each parameter. The low and high-risk groups for SUVmax, MTV and TLG included 19 and 35 patients, 29 and 25 patients and 25 and 29 patients, respectively. The 18-months PFS rates in the low and high SUVmax, MTV and TLG groups were 58% and 40%, 55% and 36% and 64% and 31%. PFS for 18 months between the low risk and high risk group significantly differed only for TLG, where the low risk group had 55% lower risk of progression of disease in 18 months in comparison to the high risk group (HR=0.45, 95%CI=0.21-0.99, p=0.228). In univariate analysis with SUVmax (p=0.214), MTV (p=0.111) and TLG (p=0.028), only TLG was considered statistically significant as a prognostic marker for PFS for 18 months.

5. DISCUSSION

The role of PET/CT in CRC is to offer precise and timely answers to clinical questions in order for clinicians to make optimal decisions on the therapeutic modalities. In a meta-analysis of 11 studies by Huebner et al (18), it was concluded that PET performed after conventional radiologic studies changed clinical management in about 30% of patients with CRC. This could be attributed to the ability of PET/CT to early detect metabolic changes that appear before the structural ones, and also imaging of the whole body (19).

Since the introduction of PET/CT into clinical practice, a plethora of studies evaluated diagnostic accuracy of 18F-FDG PET/CT in the follow-up of CRC. Studies demonstrated high sensitivity of 80-100% and somewhat lower, but clinically accepted specificity of 60-85% (20-22). In this research, sensitivity, specificity, PPV and NPV were 95%, 73%, 70% and 95%, respectively. High sensitivity was caused by molecular features of CRC affecting glucose hypermetabolism, so that tumor tissue could be delineated from the background. Lower specificity was caused by potential FDG accumulation in non-tumor tissues (inflamed subcutaneous tissue, normal bowel lumen and wall, inflamed sacroiliac joints and reactive distant lymph nodes). In a previous study of 50 patients by the same authors (23), sensitivity and specificity were 100% and 82,6%, respectively.

CEA is considered a long established diagnostic and prognostic marker in CRC. A study by Metser et al (24) concluded that in about 90% of patients, postoperatively elevated CEA was caused by the recurrence. Our results for sensitivity, specificity, PPV and NPV in detection of recurrent CRC were 58%, 96%, 91% and 78%, respectively. Such results are concordant

with the results of multiple studies (24-26). Lower sensitivity may be attributed to the fact that CEA is nonspecific and may be elevated in other malignant and some benign conditions of different nature, including smoking. In our study, out of 54 patients with positive PET/CT, 24 had elevated CEA, while 30 (55,5%) had normal CEA values. In 46 patients with negative PET/CT, only 2 (4,3%) had elevated CEA. As the works of Park et al (27) and Bu et al (25) suggest, about 30% of primary CRC and their metastases do not produce CEA.

One of the objectives of the study was to evaluate the routine use of volumetric PET/CT parameters (MTV, TLG) together with SUVmax in PET/CT reporting in order to increase the specificity of PET/CT study. Calculation of both MTV and TLG is easily available in our software as well as reproducible. Hypothesized was that the volumetric PET/CT parameters as measures of tumor burden and tumor aggressiveness, independently or in correlation with other markers (CEA, SUVmax) might offer additional information on pathological lesions and thus increase the specificity.

Correlation between PET/CT metabolic parameters and CEA revealed that all metabolic parameters (SUVmax, MTV, TLG) positively correlated with CEA, with the correlation coefficients of 0,19, 0,33 and 0,67, respectively. We concluded only CEA-TLG correlation to be significant. Such results are in agreement with the results of other authors, emphasizing the paucity of similar studies in the present literature. Caglar et al (28) demonstrated the moderate correlation for all parameters with the coefficients of 0,45, 0,44 and 0,49, respectively. Oh et al suggested a combined approach using SUVmax and MTV for differentiation of benign and malignant lesion with a diagnostic accuracy of 90% (29). Ozkan et al (22) established no correlation between CEA and SUVmax, whatsoever. It is concluded that the routine use of MTV and TLG would be of limited value, and that by increasing the specificity of PET/CT studies to some extent. As volumetric parameters, MTV and TLG could play roles in the evaluation of treatment response, but further studies are required.

In order to assess the prognostic role of metabolic 18F-FDG PET/CT parameters in recurrent and metastatic CRC, the prognostic models were created. The current literature on such roles is scarce, while the existing studies had different designs and objectives, making the direct comparisons impossible. The studies of other cancers demonstrated that volumetric parameters (MTV and TLG) had predictive role in risk stratification in SCLC, anal cancer and pancreatic cancer (19,30). Marcus et al (31) proved a significant correlation between PET metabolic volume parameters and overall survival (OS), where prognostic role was proven by a combined approach, using SUVmax and MTV. In our study, only the regression model created for TLG established a statistically significant distribution in 18-month PFS for the low-risk and the high-risk group (Table 3). Such results are partly in agreement with the results of Ince et al (19) from the study on 53 patients, who concluded that both MTV and TLG had prognostic roles, while TLG was a better predictor of the CRC recurrence. In a study by Jo et al (32) on 73 patients, it was concluded that MTV, TLG, tumor stage, lymph nodes, and a positive surgical margin were all prognostic factors for OS, but none of them for recurrence-free survival (RFS). Our study is only partly in agreement with such results, and only

in a part related to TLG, considering the PFS a surrogate end-point for OS. Geus-Oei et al (33) studied a predictive role of SUVmax in metastatic CRC and concluded that SUVmax of metastatic lesions was a significant predictor for OS, and the higher values were noted in post-chemotherapy patients compared to the ones with metastasectomy. As our results failed to prove a prognostic role for SUVmax, they are in disagreement with the study of Geus-Oei et al. Once again, different designs of the studies rendered direct comparisons impossible. Ogawa et al (34) evaluated 325 patients with CRC and concluded that after curative resection of CRC, patients with high MTV and TLG had poorer outcomes in a five-year survival.

Our study indicated that TLG, but not SUVmax and MTV could predict outcome in recurrent and metastatic CRC. The cause of such a discriminatory ability could be attributed to its inherent features: being a mathematical product, it conveys the metabolic information about the cancer cells reflected in the glycolytic level, and also volumetric information, which are then distributed and harmonized for the entire tumor. Stratification of patients based onto the risks from the prognostic models could aid in selection of the most optimal therapeutic modalities in the light of their aggressiveness, such as single vs. combined therapy. Prognostic models could also be created for different clinical scenarios and different population subgroups, such as the candidates for radiotherapy. Limitations of the study were its retrospective-prospective design, high variability of some parameters (CEA), inability to use only pathohistology as the gold standard, and using a surrogate end-point marker (PFS) instead of OS.

6. CONCLUSION

It is considered that some metabolic 18F-FDG PET/CT parameters may have the prognostic value in CRC, but further multicentric prospective studies are required for validation.

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