Diagnostic Performance of F-18 FDG PET/CT in the Detection of Recurrent Colorectal Cancer: Correlation with Biochemical Markers and Conventional Imaging Modalities

Jasna Mihailovic *, Jelena Roganovic , Ivana Starcevic , Ivan Nikolic , Natasa Prvulovic Bunovic , Zoran Nikin

Posted Date: 7 May 2024

doi: 10.20944/preprints202405.0308.v1

Keywords: colorectal cancer; recurrence; detection; F-18 FDG PET/CT; CEA; CA 19-9; conventional imaging

Article

Diagnostic Performance of F-18 FDG PET/CT in the Detection of Recurrent Colorectal Cancer: Correlation with Biochemical Markers and Conventional Imaging Modalities

Jasna Mihailović [1,2,*], Jelena Roganović [2], Ivana Starčević [2], Ivan Nikolić [3,4], Nataša Prvulović Bunović [1,5] and Zoran Nikin [6]

[1] Department of Nuclear Medicine, Faculty of Medicine, University of Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia; jasna.mihailovic@mf.uns.ac.rs
[2] Division of Nuclear Medicine, Oncology Institute of Vojvodine, Put dr Goldmana 4, 21.204 Sremska Kamenica, Serbia; mihailovic.jasna@onk.ns.ac.rs; roganovic.jelena@onk.ns.ac.rs; istarcevic97@gmail.com
[3] Department of Internal Medicine, Faculty of Medicine, University of Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia
[4] Clinic for Medical Oncology, Oncology Institute of Vojvodine, Put dr Goldmana 4, 21.204 Sremska Kamenica, Serbia; nikolic.ivan@onk.ns.ac.rs
[5] Centre for Diagnostic Imaging, Oncology Institute of Vojvodine, Put dr Goldmana 4, 21.204 Sremska Kamenica, Serbia; prvulovicn@gmail.com
[6] Department for pathoanatomical diagnostics, Oncology Institute of Vojvodina, Put dr Goldmana 4, 21.204 Sremska Kamenica; nikin.zoran@onk.ns.ac.rs
* Correspondence: jasnam61@gmail.com; Tel.: +381 63 526835

Abstract: Background/Objectives: Although the role of F-18 FDG PET/CT imaging is well established in oncology, its diagnostic value in routine monitoring for recurrent colorectal cancer (CRC) is still controversial. The aim was to evaluate the diagnostic value of FDG PET/CT in detecting recurrent CRC in correlation with CEA, CA 19-9 levels, and conventional imaging modalities (CIM). **Methods:** Between 2009 and 2023, we retrospectively studied 134 CRC patients referred for FDG PET/CT imaging on the suspicion of recurrence based on elevated CEA and/or CA 19-9, and/or equivocal radiological findings. According to the Institutional Tumor Board CRC protocol, after initial treatment which was dependent on TNM stage (neoadjuvant therapy, primary resection or adjuvant treatment), patients underwent a standard 5-year surveillance including CEA and CA 19-9 measurements, CIM, and colonoscopy every 6 months. The statistics including univariate and multivariable analyses were conducted using the IBM SPSS 20.0 statistical software. P-values <0.05 were considered statistically significant. **Results:** Recurrent CRC was confirmed in 54/134 (40.3%) patients with elevated tumor markers. FDG PET/CT shows high diagnostic performance in detecting recurrent CRC with sensitivity, specificity, PPV, NPV, and accuracy of 94.4%, 82.5%, 78.5%, 95.7%, and 87.3%, respectively. The CEA shows a high sensitivity of 98.1%, but both low specificity and accuracy of 15% and 48.5%, respectively. The sensitivity, specificity, and accuracy, for CA 19-9 and CIM for the correct diagnosis in CRC patients were: 44.4%, 67.5%, 58.2%, and 51.9%, 98.8%, 79.9%, respectively. The AUC for FDG PET/CT, elevated CEA levels, CIM, and elevated CA 19-9 levels was 0.885 (95% CI: 0.824-0.946; p<0.001), 0.844 (95% CI: 0.772-0.916; p<0.001), 0.753 (95% CI: 0.612-0.844; p<0.001); and 0.547 (95% CI: 0.442-0.652; p=0.358). Univariate analysis shows that both FDG PET/CT- and CIM-positive results were highly associated with CRC recurrence (p<0.001 and p<0.001, respectively), while gender, mucinous tumor type, presence of initial lymph node metastasis (N+), and presence of initial distant metastasis (M+) have no significance (p=0.211, p=0.158, p=0.583, and p=0.201, respectively). Our multivariate analysis shows that independent predictors for CRC recurrence are: positive FDG PET/CT scans (p<0.001), positive CIM results (p=0.001) and elevated CA19-9 levels (p=0.023). Although CA 19-9 was not detected as a statistically significant predictor in the univariate analysis (p=0.358), in a multivariate analysis it was recognized as a significant predicting factor in detecting CRC recurrence (p=0.023). **Conclusions:** FDG PET/CT shows a high diagnostic efficacy in CRC recurrence detection, in correlation with CEA levels, CA 19-9 levels, and CIM. This imaging modality should be routinely integrated into the postoperative follow-op in patients with elevated tumor markers.

 doi:10.20944/preprints202405.0308.v1

Keywords: colorectal cancer; recurrence; detection; F-18 FDG PET/CT; CEA; CA 19-9; conventional imaging

1. Introduction

Colorectal cancer (CRC) is the third most common neoplasm worldwide. The latest data from cancer statistics in the US estimates new CRC cases for the year 2024 accounting for 8% and 7% in men and in women, respectively. In addition, this malignancy is associated with a high mortality rate reporting 9% of estimated deaths for men and 8% for women in the same year [1]. Radical resection is the initial curative treatment for 80% of non-metastatic CRC patients and results in improved long-term survival. Additional adjuvant or neoadjuvant chemoradiotherapy, as well as, combination treatments depend on the patient's staging and are aimed to provide better outcomes [2,3]. Recurrence rates have been reported in 30-50% of patients during the postoperative monitoring depending on the stage [4-7], with the highest recurrence rate within the first two years [8]. However, recent reports show a declining incidence of CRC recurrence of 15-16% [9,10] and 21-23% [6,7], mostly due to better screening programs and improved treatment options.

Since relapsed CRC has a poor prognosis, detection of recurrence at an early stage when it is potentially curable is essential. According to the European Society for Medical Oncology regular measurements of carcinoembryonic antigen (CEA) levels, computed tomography (CT), a colonoscopy with higher frequencies for the first 3 years after curative surgery and a total duration of 5 years are recommended in patients with non-metastatic CRC [11,12]. Current guidelines for surveillance of CRC patients within 3 or 5 years after treatment with curative intent regular and periodical recommend CT and CEA testing, while frequency depends on stage and risk for recurrence [13-15].

Besides the carcinoembryonic antigen (CEA) some other tumor markers are accepted in routine clinical practice such as carbohydrate antigen (CA 19.9), tissue polypeptide specific antigen (TPS), cancer antigen 125 (CA 125), serum ferritin (SF), tumor-associated glycoprotein-72 (TAG-72), and hematopoietic growth factors (HGF-s) [16,17]. Hence, the CEA is one of the most studied biochemical markers and is considered the most effective in recurrent CRC detection. According to the ASCO and ESMO association, it is a golden standard for monitoring CRC with regular measurements every three months during the first three years and thereafter every six months for subsequent 2-3 years [18,19].

Standard imaging modalities that are performed for the early detection of recurrences include computed tomography (CT) and magnetic resonance imaging (MRI). Although, the fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (F-18 FDG PET/CT) has been shown as a valuable technique in the detection of CRC recurrence, its role is still controversial. This hybrid imaging, i.e. molecular imaging, is a non-invasive scanning technique that can make a distinction between malignant and benign lesions based on differences in their metabolic activities [20]. Despite its ability to provide data on tumor metabolism and whole body image in one scanning, the role of PET/CT imaging is not yet well accepted. Currently, the FDG PET/CT is not officially integrated into the NCCN guidelines for monitoring disease recurrence. However, it has been reported that FDG PET/CT is an efficient imaging modality in CRC with elevated CEA levels for postoperative detection of recurrent and metastatic disease [21,22].

This study aimed to assess the diagnostic accuracy of F-18 FDG PET/CT in the detection of recurrent colorectal cancer and to make a comparison with conventional imaging methods and tumor markers, CEA and CA 19-9.

2. Materials and Methods

2.1. Patients

 doi:10.20944/preprints202405.0308.v1

We retrospectively analyzed 134 CRC patients during the follow-up with increased tumor markers (either only CEA, or only CA 19-9, or both) who underwent FDG PET/CT imaging on the suspicion of recurrent CRC in our institution. All patients underwent whole-body FDG PET/CT at our institution between 2009 and 2023.

The inclusion criteria were as follows: a) histologically confirmed diagnosis of CRC b) all patients have achieved remission of disease after initial treatment for CRC, c) suspicion of recurrent CRC due to at least one or several elevated levels of tumor markers (CEA and/or CA 19-9) above the upper threshold of normal value, and d) results obtained by conventional imaging modalities (CIM) and/or colonoscopy. Patients with a clinical history of another type of malignancy were excluded from the study.

The management of oncological patients in the Oncology Institute of Vojvodina in Sremska Kamenica is provided by the Tumor Board's protocols for different tumors, including CRC. The Tumor Board for CRC is scheduled twice a week and the treatment algorithm is made specifically for every patient (personalized treatment approach). Patients with a tumor localized in the colon underwent primary tumor resection with or without adjuvant chemotherapy depending on the TNM stage. Patients with rectal cancer underwent either tumor resection only or neoadjuvant treatment (chemoradiation), prior to surgical resection of the primary tumor, or additional chemotherapy following neoadjuvant chemoradiation and initial surgery depending on histological report after the initial surgery. After the initial treatment is completed, patients are regularly monitored. According to the protocol of our institution, a standard 5-year protocol for clinical and radiological follow-up includes measurements of tumor markers (CEA and CA 19-9), conventional imaging modalities and colonoscopy periodically at six months.

2.2. Protocol

Patients were referred to FDG PET/CT imaging in case of any sign of recurrence including elevated tumor marker levels (CEA or CA 19-9, or both), and/or abnormal/inconclusive results of conventional imaging modality (CT and/or MRI), or inconclusive result of colonoscopy. Final diagnosis of CRC recurrence was confirmed either using the reference (gold) standard – the postoperative histological report, obtained after the surgical resection or biopsy, or a clinical follow-up including tumor marker measurements, CIM (CT, and/or MRI), and a colonoscopy during at least six months after the FDG PET/CT scan.

Imaging results, as well as, clinical, histopathological, and laboratory data, were extracted from patients' medical records. This study was approved by the Ethics Committee of the Oncology Institute of Vojvodina in Sremska Kamenica.

2.3. Biochemical Markers

The measurement of biochemical (i.e. tumor) markers is a standard measurement for CRC patients during the follow-up according to our institution's Tumor Board CRC protocol. Serum CEA and CA 19-9 measurements were done by an automatic analyzer that uses immune-enzymatic assays (ECLIA, Roshe, Cobas e 411). Normal serum values of CEA and CA 19-9 are <4.70 ng/mL and <39.0 U/mL, respectively. Two consecutively increased values of either CEA or CA 19-9, or both, were considered suspicious of having recurrent CRC. No definite cut-off value was required as a referral for FDG PET/CT.

2.4. Data Acquisition, Reconstruction, and Image Interpretation

In our institution FDG PET/CT imaging was performed from 2007, after the installation of a 64-slice hybrid PET/CT scanner (Biograph, True Point 64, Siemens Medical Solutions, Inc. USA), until the end of June 2022 when this machine was shut down. After a couple of weeks, in July 2022, imaging was restarted with a new PET/CT scanner (Discovery MI DR, GE Medical Systems, US).

Patients were instructed to fast at least six hours before the tracer injection and received an intravenous injection (by automatic injector) of 3.7 MBq/Kg of F-18 FDG. Blood glucose level was

 doi:10.20944/preprints202405.0308.v1

measured before FDG injection and was <11 mmol/L in all studied cases. Following F-18 FDG administration, patients rested in a quiet and darkened room without talking in a basal condition, for 60-90 minutes. During this uptake phase, the patients were instructed to drink 1 L of oral contrast dispersion, which ensures a better delineation of lymph nodes and normal bowel. After the resting period, patients underwent a low-dose CT for topographic localization and attenuation correction. That was followed by a PET acquisition (standard whole-body procedure) of the region from the base of the skull to mid-thighs, in a three-dimensional mode.

FDG PET/CT imaging at Biograph, True Point 64, Siemens Medical Solutions, Inc., USA included low-dose non-enhanced CT scans that were acquired (120 kV, 40 mAs, slice thickness 5 mm, pitch 1.5, rotation time 0.5 sec) for topographic localization and attenuation correction. That was followed by PET acquisition (3 minutes per bed, 6–7 beds per patient) in three-dimensional mode. Non-corrected and attenuation-corrected CT, PET, fused PET/CT images, and MIP were analyzed on the Syngo Multimodality Workstation (Siemens AG, Medical Systems, Erlangen, Germany). FDG PET/CT imaging at Discovery MI DR, GE Medical Systems, US, includes a low-dose whole-body CT (Revolution EVO) that was performed in a craniocaudal direction. The first scout (i.e. topogram) was first acquired with the following parameters: 120 kV, 10 mA scout plane 180. The CT scan of the PET/CT scanner consisted of 128 slice-CT (Revolution EVO). A low-dose CT for attenuation was acquired with 64x0.625 mm detectors and 40 mm beam collimation [120 kV, 250 mA, in 0.5 seconds with 512 matrix]. The Display Field Of View (DFOV) was 70 cm. Data are reconstructed with 2.5 mm standard recon type with ASIR 60%. Soon after, CT scanning ended, PET scan was immediately acquired in a three-dimensional mode, from the base of the skull to the mid-thigh, at 2.2 minutes per bed position (bed total depended on a patient's height), 256 matrix, and FOV of 150 mm. PET data were collected in a caudocranial direction. The CT data were matched and fused with the PET data. Reconstruction was performed using the ordered subsets expectation maximization 3D reconstruction method, with VPFX cut-off filter 5 mm, 24 subsets and 2 iterations. Data from both CT and PET were sent to the AW server workstation with installed PET options, GE Healthcare) for clinical evaluation.

Positive FDG PET/CT scan for recurrent CRC was considered when a pathological uptake (focal FDG uptake area greater than the background) was detected after the exclusion of physiologically increased uptake, with or without the corresponding CT lesion. Lesions were analyzed qualitatively and semi-quantitatively. Quantitative measurements of FDG uptake in the lesions were based on the maximum standardized uptake value per focus (SUVmax). This value was calculated at tissue activity (expressed as counts/pixel/s) multiplied by the calibration factor divided by injected 18F-FDG dose (MBq/kilogram of body weight). No absolute cut-off value was used for the diagnosis. Tumor lesions were defined by the volume of interest (VOI) at lesions with high FDG uptake, with a 50% threshold.

Two experienced nuclear medicine physicians and one radiologist independently (i.e. blindly) reviewed all FDG PET/CT images and provided separate diagnoses. The patients were thereby classified as positive or negative for the recurrence. In cases of a discrepancy, the FDG PET/CT images were re-examined and a definitive diagnosis was reached by a consensus. Using the nuclear medicine workstation, the maximum ROIs were drawn over the lesions identified by the nuclear medicine physicians as having the most intense uptake. We selected the highest SUVmax identified for each patient.

True-positive lesions were presented with positive tumor markers, CIM, and FDG PET/CT which were confirmed for malignancy by the reference standard (histology or by the follow-up). Lesions were true-negative if negative tumor markers, CIM, and FDG PET/CT results were confirmed by histology, or by decreasing CEA levels to normal values without imaging evidence of recurrence during the subsequent follow-up. False-positive cases include suspicious lesions with confirmed negative histology for malignancy or lesions that had resolved on the follow-up imaging. Lesions were false-negative if tumor markers, CIM, or FDG PET/CT were negative, but malignancy was confirmed by the reference standard.

2.5. Statistical Analysis

 doi:10.20944/preprints202405.0308.v1

The numbers and percentages were used for the description of categorical data; mean, median, standard deviation, IQR, minimum, and maximum values for continuous data. The association between clinical-pathological variables and CRC recurrence was performed with Mann-Whitney U test (serum CEA and CA 19-9 levels) while Fisher's exact test was used for categorical data.

Receiver operating characteristic (ROC) analysis was used to assess the accuracy of model predictions by plotting sensitivity versus (1-specificity). The area under the ROC curve (AUC) was used to evaluate the accuracy of different diagnostic methods (FDG PET/CT, CIM, CEA, CA 19-9) in detecting CRC recurrence; ROC curve analysis was applied to identify the best-discriminating cutoff values of serum CEA and CA 19-9 levels between patients with recurrence and patients free of disease. The following diagnostic quality parameters were calculated: sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), false positive value (FPV), false negative value (FNV), and overall accuracy (ACC) for F-18 FDG-PET/CT, CIM (CT and/or MRI), and tumor markers (CEA and CA 19-9) for the detection of recurrent CRC.

Multivariable analysis (binary logistic regression model - forward stepwise conditional) was used to find independent predictors for CRC recurrence. The statistical analysis was conducted by using the IBM SPSS 20.0 statistical software. P-values below 0.05 were considered statistically significant.

3. Results

This retrospective study was conducted on 134 patients (mean age 69.6 ± 11.0 years; range, 39-89 years). Patients' demographic, clinical and histopathological characteristics are presented in Table 1. The study included 79 (59%) males and 55 (41%) females, with a mean age of 70.6 ± 11.3 years and 68.2 ± 10.5 years, respectively. All 134 patients had histologically proven CRC, including colon cancer in 99 patients and rectal cancer in 35 patients. Colon cancer was detected at different localization sites including ascending colon (17 patients), caecum (11 patients), transversal colon (12 patients), descending colon (10 patients), sigmoid colon (25 patients), rectosigmoid colon (13 patients), splenic flexure in 6 patients and liver flexure in 3 patients. CRC presented as a single tumor in 132 patients, or as a duplex cancer with combined sites in 2 patients. Out of 134 patients with CRC adenocarcinoma, 22 patients had the mucinous tumor type. The remaining 112 patients with CRC adenocarcinoma were divided into several tumor differentiation grades. The classification of tumor types, differentiation (tumor grade), and initial TNM staging were determined according to the current classifications [23,24]. Patients' demographic and clinical-histopathological characteristics have been summarized in Table 1.

Table 1. Patients' demographic and clinical-histopathological characteristics.

DEMOGRAPHIC CHARACTERISTICS	
Patients	134 (100%)
AGE	
Mean	69.6 ± 11.0 years
Males	70.6 ± 11.3 years
Females	68.2 ± 10.5 years
Range	39-89 years
GENDER	
Males	79 (59%)
Females	55 (41%)
TNM STAGING	
T Stage	
T1	1 (0.75%)
T2	11 (8.21%)

 doi:10.20944/preprints202405.0308.v1

T3	102 (76.12%)
T4	20 (14.92%)
N Stage	
N0	56 (41.79%)
N1	50 (37.31%)
N1a	38 (28.36%)
N1b	9 (6.72%)
N1c	3 (2.23%)
N2	28 (20.90%)
N2a	17 (12.69%)
N2b	11 (8.21%)
M Stage	
M0	122 (93.28%)
M1	9 (6.72%)
TUMOR LOCALIZATION	
Ascending colon	17 (12.69%)
Caecum	11 (8.21%)
Transversal colon	12 (8.95%)
Descending colon	10 (7.46%)
Sigmoid	25 (18.65%)
Rectosigmoid	13 (9.70%)
Rectum	35 (26.12%)
Splenic flexure	6 (4.48%)
Liver flexure	3 (2.24%)
Duplex (caecum + ascending)	1 (0.75%)
Duplex (transversal + descending)	1 (0.75%)
TUMOR HISTOLOGY AND DIFFERENTIATION GRADE	
Non-mucious adenocarcinoma	112 (83.58%)
Well differentiated – G1	16 (11.94%)
Moderately differentiated – G2	81 (60.45%)
Poorly differentiated – G3	15 (11.19%)
Mucinous adenocarcinoma	22 (16.42%)
INITIAL TREATMENT	
Surgery only	19 (14.18%)
Surgery + chemotherapy	8 (5.97%)
Neoadjuvant chemoradiation+surgical resection	4 (2.98%)
Neoadjuvant chemoradiation + surgical resection + chemotherapy	11 (8.21%)
Surgical resection + Adjuvant chemotherapy	86 (64.18%)
Surgical resection + Adjuvant chemoradiation	5 (3.73%)
Surgical resection + Adjuvant radiation therapy	1 (0.75%)

The recurrent CRC was confirmed in 54 (40.3%) patients, histologically in 15/54 (27.8%) patients: after surgery in 13 patients and after biopsy of suspicious lesion in 2 patients. In the remaining 39/54 (72.2%) patients, a definitive diagnosis was based on subsequent follow-up (including CIM,

 doi:10.20944/preprints202405.0308.v1

colonoscopy and clinical/laboratory results). Localization of the recurrent CRC and methods for assessing the final diagnosis are shown in Table 2. Nodal involvement was detected in 11/54 patients; while local-, peritoneal- and locoregional recurrence in 7/54, 5/54 and 4/54 patients, respectively. Distant metastases occurred in the liver and lungs in 9 and 6 patients, respectively. Combined sites of CRC recurrence in most cases appeared in lungs and liver (in 5/54 patients).

Table 2. Patients with recurrent CRC.

Site of recurrence (No of patients)	**Method of recurrence confirmation**		
	Histology (15)		**Follow-up (39)**
	Operation (13)	**Biopsy (2)**	
Local (7)	2	1	4
Regional lymph nodes (11)	0	0	11
Locoregional (4)	0	0	4
Peritoneum (5)	0	0	5
Liver (9)	6	0	3
Lungs (6)	3	0	3
Bone (1)	0	0	1
Combined sites			
Liver + Lungs (6)	0	1	5
Liver + Peritoneum (4)	1	0	3
Liver+ Lungs+ Bone (1)	1	0	0

The FDG PET/CT provided correct diagnosis in 117 out of 134 patients; with true-positive results in 51 patients and true-negative results in 66 patients. A patient with CRC recurrence matched FDG PET/CT and CT imaging (positive FDG PET/CT scan and positive CT scan), is shown in Figure 1.

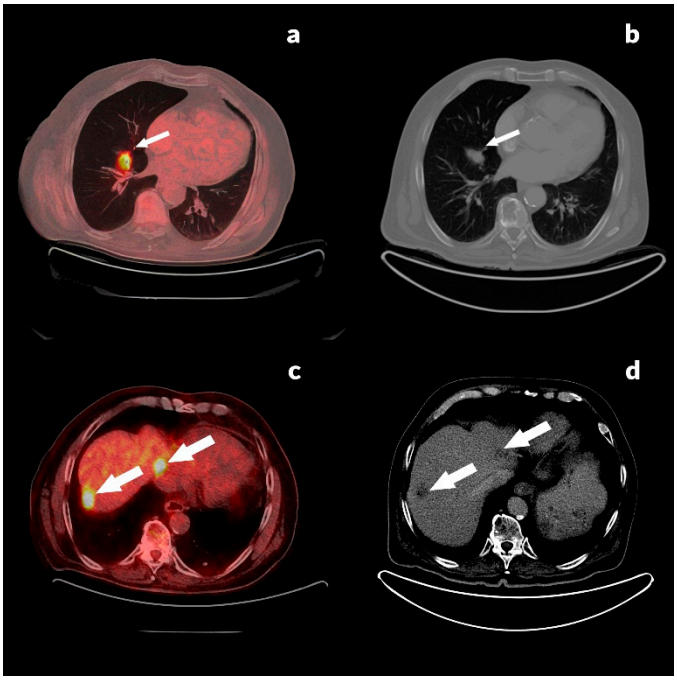

Figure 1. shows P. V., a 88-year-old male with histopathologically confirmed diagnosis of rectal adenocarcinoma, pT3N2aM0, (differentiation tumor gradus, G2), who underwent a primary tumor resection followed by adjuvant therapy; tumor marker values - elevated CEA level (12.6 ng/mL) and normal CA 19-9 level (2.5 U/mL), a) FDG PET/CT axial image detects a focal area of increased FDG uptake in the right pulmonar lobe, segment S4, SUVmax 7.50, corresponding to lung metastasis of

 doi:10.20944/preprints202405.0308.v1

CRC, b) Diagnostic CT scan in axial plane confirms a lesion in the right pulmonar lobe, S4, consistent with a metastatic lesion in the lung, c) FDG PET/CT axial image shows two hypermatbolic lesions in S8 and S2 of the liver, SUVmax 8.9 and in S2, SUVmax 8.0, respectively, corresponding with liver metastases, and d) Diagnostic CT in the axial plane shows two heterodense dominantly hypodense lesions in S8 and S2, consistent with distant metastases in the liver.

FDG PET/CT was able to detect recurrent CRC locally (6/54 patients), in regional lymph nodes (11/54 patients), locoregionally (4/54 patients), peritoneum (4/54 patients), in the liver (9/54 patients), lungs (6/54 patients), bone (1/4 patient), and in combined sites: liver and lungs (6/54 patients), liver and peritoneum (4/54 patients), and liver, lungs and bone (1/54 patient). FDG PET/CT detected CRC recurrence in the liver in 9 patients with elevated tumor markers (elevated CEA levels in 8/9 patients; elevated both, CEA and CA 19-9 in 3/9 patients; while false-negative results of CEA and CA 19-9 were detected in 1/9 and 5/9 patients, respectively); in 7/9 patients FDG PET/CT scan was in agreement with the MRI scan, while remaining 2/9 patients had a false negative CT scan. Detection of recurrent CRC by FDG PET/CT resulted in subsequent management including liver resection in 6 patients and chemotherapy in 3 patients. Lung metastases were detected by positive FDG PET/CT scans in 6/54 patients with CRC recurrence; in 3/6 patients CT was false-negative while in remaining 3 patients CT was in agreement with the positive FDG PET/CT. Based on positive FDG PET/CT result, one patient underwent subsequent surgery, another two patients received surgery followed by chemotherapy, while 3 patients received chemotherapy only.

Seventeen patients were misdiagnosed by FDG PET/CT results including 3 patients with false-negative FDG PET/CT results and 14 patients with false-positive FDG PET/CT scans. The sensitivity, specificity, PPV, NPV, and accuracy of FDG PET/CT in detection of recurrent CRC were 94.4%, 82.5%, 78.5%, 95.7%, and 87.3%, respectively. CRC recurrence was confirmed in three patients with false-negative FDG PET/CT results by a subsequent imaging follow-up: one patient with a mucinous adenocarcinoma underwent MR imaging which detected a bone metastasis in a right pelvic bone (Figure 2), while CECT scan confirmed peritoneal lesion in one and a local recurrence in another patient. Subsequent treatment including chemotherapy was performed in all of these three patients after the confirmation of CRC recurrence.

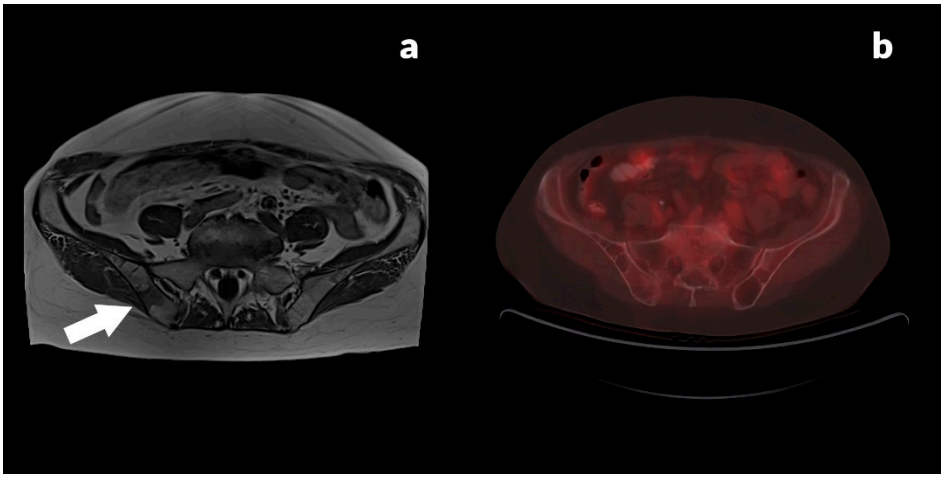

Figure 2. shows M.Z., a 70-year-old female with histopathologically confirmed diagnosis of transversal colon adenocarcinoma, mucinous subtype, pT3N0M0, (differentiation tumor gradus, G1), who received surgical resection only; tumor marker values - elevated CEA level (21.0 ng/mL) and normal CA 19-9 level (2.0 U/mL), a) Axial T1W MR image shows focal T1W hypointense lesion in the right iliac bone coresponding with metastasis, and b) FDG PET/CT axial image does not detect FDG-avid lesion in the region of pelvic bone. .

A case with a false-negative CT scan in whom a recurrent CRC was confirmed by a positive FDG PET/CT scan, is presented in Figure 3.

 doi:10.20944/preprints202405.0308.v1

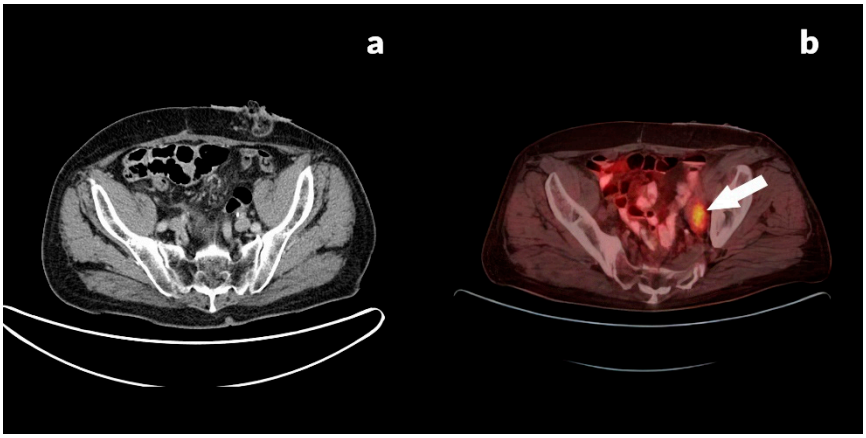

Figure 3. shows K. A. an 84-year-old male with histologically proven diagnosis of rectal adenocarcinoma, pT3N2aM0, (differentiation tumor gradus, G2), after completion of initial treatment, which included surgical resection and a subsequent adjuvant chemoirradiation; tumor marker values – elevated CEA level (18.5 ng/mL) and normal CA 19.9 level (<0.6 U/mL), a) Diagnostic CT in axial plane, shows no lesion in the left pelvic region, and b) FDG PET/CT axial image detects an FDG-avid ovoid lesion in the left obturatory area, SUVmax 7.20, corresponding with lymph node involvement.

Univariate analyses showed that CRC recurrence was not significantly associated with gender (p=0.211), mucinous tumor type (p=0.158), presence of initial regional metastases (N+) (p=0.583), and with a presence of initial distant metastasess (M+) (p=0.201). Positive FDG PET/CT results are higly associated with CRC recurrence (p<0.001) (Table 3).

Table 3. The univariate analysis of predicting factors for CRC recurrence (Fisher's exact test).

Factor	*Whole population (n=134)*	*CRC Recurrence (n=54)*	*Remission (n=80)*	*p-value*
Male gender (%)	79 (59.0 %)	28 (51.9%)	51 (63.8%)	0.211
Mucinous type	22 (16.4 %)	12 (22.2%)	10 (12.5%)	0.158
N (+)	77 (57.5 %)	33 (61.1%)	44 (55.0%)	0.583
M (+)	10 (7.5 %)	6 (11.1%)	4 (5.0%)	0.201
FDG PET/CT (+)	65 (48.5%)	51 (94.4%)	14 (17.5%)	< 0.001
CIM (+)	28 (20.9%)	27 (50.0%)	1 (1.2%)	< 0.001

Male gender; mucinous tumor type; N (+), presence of initial regional metastases; M (+), presence of initial distant metastases; FDG PET/CT (+), positive FDG PET/CT findings; CIM (+), positive CIM findings.

There was no statistically significant difference detected for CA 19-9 levels in a group of patients with recurrence (p=0.358). In contrast, patients without recurrent CRC (10.9 ± 20.4; median 7.56, IQR 4.7) show significantly lower CEA values (p<0.001) than patients with recurrence (92.8 ± 268; median 19.9, IQR 29.2) (Table 4).

Table 4. Serum CEA (ng/mL) and CA 19-9 (U/mL) levels in patients with and without recurrent CRC (Mann-Whitney U test).

Test	*Recurrence*	*N= 134*	*Mean*	*Median*	*Minimum*	*Maximum*	*p-value*
CEA	Yes	54	92.8	19.9	0.9	1.624	<0.001
	No	80	10.9	7.56	1.3	178	

 doi:10.20944/preprints202405.0308.v1

CA 19-9	Yes	54	88.6	18.8	0.5	1.637	0.358
	No	80	30.7	17.0	0.5	194	

FDG PET/CT scans show false-positive results in 14/134 patients with CRC according to the hypermetabolic lesions which were detected at different sites: lymph nodes (8/14 patents), locoregional (2/14 patients), lungs (2/14 patients) and liver (2/14 patients). In 2/14 patients, suspected nodal involvement was histologically confirmed as negative after the biopsy, while the absence of recurrent CRC was confirmed in the remaining 12/14 patients based on follow-up algorithm: decreasing tumor markers and negative, colonoscopy and/or CIM results.

CEA provided a correct diagnosis in 65 patients, with true-positive results in 53 patients, and true-negative results in 12 patients. Sixty nine patients were misdiagnosed by CEA including 1 patient with false-negative results and 68 patients with false-positive results. The sensitivity, specificity, PPV, NPV, and accuracy of CEA in the detection of recurrent CRC were 98.1%, 15%, 43.8%, 92.3%, and 48.5%, respectively. CA 19-9 provided a correct diagnosis in 77 patients, with true-positive results in 23 patients and true-negative results in 54 patients. Fifty six patients were misdiagnosed by CA 19-9, including 31 patients with false-negative results and 26 patients with false-positive results. The sensitivity, specificity, PPV, NPV, and accuracy of CA 19-9 in the detection of recurrent CRC were 44.4%, 67.5%, 48%, 64.3%, and 58.2%, respectively. CIM provided correct diagnosis in 107 patients, with true-positive results in 28 patients and true-negative results in 79 patients. Twenty seven patients were misdiagnosed by CIM including false-negative results in 26 patients and false-positive results in one patient. The sensitivity, specificity, PPV, NPV, and accuracy of CIM in the detection of recurrent CRC were 51.9%, 98.8%, 96.6%, 75.2%, and 79.9%, respectively.

Table 5. shows the diagnostic performance for FDG PET/CT, CIM, CEA, and CA 19-9 in the detection of CRC recurrence.

Table 5. Diagnostic efficacy in detection of CRC recurrence for each performed method, including FDG PET/CT, CIM, CEA and CA 19-9.

Diagnostic method	%	95% CI (confidence interval)	
FDG PET/CT			
SN	94.4	91.2	97.1
SP	82.5	77.1	87.9
PPV	78.5	72.6	84.3
NPV	95.7	92.8	98.5
FPV	21.5	15.7	27.4
FNV	4.3	0.0	7.2
ACC	87.3	82.6	92.0
CIM			
SN	51.9	44.8	58.9
SP	98.8	97.2	100.0
PPV	96.6	94.0	99.1
NPV	75.2	69.1	81.4
FPV	3.4	0.9	6.0
FNV	24.8	18.6	30.9
ACC	79.9	74.2	85.5
CEA			
SN	98.1	96.2	100.0

 doi:10.20944/preprints202405.0308.v1

SP	15.0	9.9	20.1
PPV	43.8	36.8	50.8
NPV	92.3	88.5	96.1
FPV	56.2	49.2	63.2
FNV	7.7	3.9	11.5
ACC	48.5	41.4	55.6
CA 19-9			
SN	44.4	37.4	51.5
SP	67.5	60.8	74.2
PPV	48.0	40.9	55.1
NPV	64.3	57.5	71.1
FPV	52.0	44.9	59.1
FNV	35.7	28.9	42.5
ACC	58.2	51.2	65.2

SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; FPV, false positive value; FNV, false negative value; ACC, accuracy.

Recurrent CRC was diagnosed as a positive result by all 4 performed methods (FDG PET/CT, CIM, elevated CEA, and elevated CA 19-9) in 9 patients (16.7%). Among 54 patients with recurrence, elevated levels of both, CEA and CA 19-9 were detected in 22 (40.7%) patients; elevated CEA levels but normal CA 19-9 levels in 31 patients (57.4%); and elevated CA 19-9 levels but normal CEA only in one patient (1.9%). Imaging methods including both FDG PET/CT and CIM, were positive in 24 (44.4%) of patients; positive FDG PET/CT scans but negative CIM results were obtained in 27 (50.04%) patients, while positive CIM but negative FDG PET/CT scans were detected in only 3 (5.8%) of patients.

In our study, the optimal cutoff values of CEA and CA 19-9 in the detection of CRC recurrence, are shown in Table 6.

Table 6. Optimal cutoff values of CEA and CA 19-9 in detection of CRC recurrence.

	Sensitivity (%)	*Specificity (%)*
FDG PET/CT	94.4	82.5
CIM	51.9	98.8
CEA normal <4.7 ng/mL	98.1	15.0
CEA normal <11.5 ng/mL *	75.9	83.7
CA 19-9 normal <39 U/mL	44.4	67.5
CA 19-9 normal <120 U/mL *	18.5	98.7

*Optimal cutoff from our study.

The ROC curve for FDG PET/CT, CEA, CIM, and CA 19-9 was drawn (Figure 4). AUC (area under curve) was 0.885 (95% CI: 0.824-0.946; p<0.001) for FDG PET/CT, 0.844 (95% CI: 0.772-0.916; p<0.001) for elevated CEA levels, 0.753 (95% CI: 0.612-0.844; p<0.001) for CIM, and 0.547 (95% CI: 0.442-0.652; p=0.358) for elevated CA 19-9 levels.

 doi:10.20944/preprints202405.0308.v1

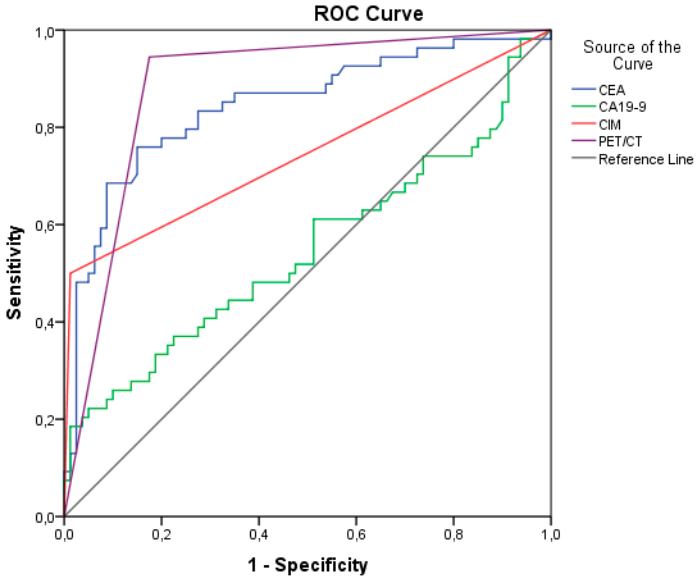

Figure 4. ROC curve of methods for predicting CRC recurrence.

Multivariable analysis (binary logistic regression model) was used to detect whether various demographic, clinical, and histological factors such as gender (male vs. female), CEA and CA 19-9 (normal values vs. elevated levels), histological tumor type (mucinous vs. non-mucinous), initial lymph node metastases (presence or absence), initial distant metastases (presence or absence), FDG PET/CT result (positive vs. negative), and CIM result (positive vs. negative) were associated with the risk of recurrence during the follow-up of patients with colorectal disease. Results of multivariable analysis show that independent predictors for CRC recurrence were: positive FDG PET/CT scans ($p<0.001$), positive CIM scans ($p=0.001$) and elevated CA19-9 levels ($p=0.023$). Although CA 19-9 was not detected as a statistically significant predictor in the univariate analysis ($p=0.358$), in a multivariable analysis this tumor marker was recognized as a significant predicting factor for detection of CRC recurrence ($p=0.023$) (Table 7).

Table 7. Multivariable analysis of factors for predicting CRC recurrence (overall percentage 90.3%).

Factor	*B*	*p*	*Exp (B)*
CEA (+)	5.634	0.107	279
CA 19-9 (+)	2.553	0.023	12.8
CIM (+)	5.759	0.001	317
FDG PET/CT (+)	5.637	<0.001	280
Constant	-11.090	0.007	0.00

FDG PET/CT (+), positive FDG PET/CT scan; CIM (+),positive CT scan; CA 19-9 (+), elevated CA 19-9 levels; CEA (+), elevated CEA levels.

4. Discussion

Since CRC often relapses, regular patient follow-up after the initial treatment is mandatory. Barreiro et al. reported a 5-year cumulative incidence of recurrence of 13.7%, with significantly increased incidence in rectal versus colon cancers ($p=0.024$) and in advanced stage of disease ($p<0.001$). In addition, they have shown that recurrence has a negative impact on prognosis and outcome. Five-year disease-specific mortality increased from 3.8% in CRC recurrence-free patients

 doi:10.20944/preprints202405.0308.v1

one year after the surgery to 33.6% for those who relapsed [9]. Early detection of recurrent CRC is essential for subsequent treatment (surgery or chemo and/or radiation treatment).

Serum markers, carcinoembryonic antigen (CEA), and carbohydrate antigen (CA19-9) have been studied in colorectal cancer for many years. The CEA, a glycoprotein produced by normal fetal gut tissue and by epithelial tumors (specifically large bowel), has been well known since 1965 [25]. However, it is a non-specific biomarker and increased levels are detected in both malignant and benign conditions. CEA is mainly produced by colorectal, gastric, pancreatic, lung, ovarian, and breast cancers. It might be also elevated in different benign diseases including chronic inflammatory bowel disease, diverticulitis, liver disease, and pancreatitis as well as in conditions such as cigarette smoking and alcoholism [26-28]. CA 19-9 is a glycoprotein that has been included in clinical practice since 1979 [29]. It is mostly used in the diagnosis of pancreatic carcinoma, colorectal and gastric cancers. Like CEA, CA 19-9 is not specific for certain histological types of tumors and organ of origin. An increased level of CA 19-9 can also be found in several benign conditions such as endometriosis, bronchiectasis, liver cirrhosis, or acute cholangitis [27,28,30]. There are numerous data of high CEA sensitivity in colorectal carcinoma accounting for 65-74%, in contrast to much lower sensitivity for CA 19-9 ranging from 26-48% only [28, 31,32]. If CA 19-9 measurements are combined with CEA levels, some authors report increased CEA sensitivity [28,33-35]. Since CA 19-9 has low sensitivity, it is not recommended for routine follow-up in CRC patients. Current guidelines include CEA, colonoscopy, and standard imaging techniques (CT and MRI) in postoperative surveillance with an aim to improve recurrence detection [13-15].

If PET was routinely added to the CRC standard monitoring algorithm, although without decreasing the recurrence rate, it ensured earlier detection of a relapse. Sobhani et al, found significant differences when detecting CRC recurrence between randomly divided patients into two different groups during the follow-up - one group received conventional monitoring and another underwent PET imaging (p=0.01) [36]. After many years, the same authors have introduced hybrid imaging, FDG PET/CT, in the study conducted on CRC patients who achieved remission of a disease. They compared two different groups of patients, the control arm group (receiving standard monitoring alone) and the intervention arm group (including additional FDG PET/CT imaging). The authors confirmed the data obtained in the previous study and concluded that CRC recurrence was detected earlier in the FDG PET/CT arm. However, the treatment failure rate (defined as death or unresectable recurrence) did not decrease as expected (29.2% vs. 23.7%, respectively, p=0.34) [37].

According to the guidelines, further use of FDG PET/CT in the detection of CRC recurrence in patients with elevated CEA levels is controversial [38]. However, several authors advocate the high efficacy of FDG PET/CT in detecting tumor recurrence if CEA levels are elevated [21,39-41]. Uzun et al. retrospectively studied 75 patients with CRC during the follow-up suspicious of having recurrence because of elevated CEA levels and/or equivocal/positive findings at conventional imaging modality. They detected recurrence by positive FDG PET/CT results in 77.3% of patients with sensitivity, specificity, and accuracy of 93.1%, 88.2%, and 92%, respectively [21]. Ozkan et al. analyzed 76 CRC patients divided into different groups according to the elevated CEA values. They reported sensitivity and specificity of FDG PET/CT in CRC recurrence detection as 100% and 60%, for CEA levels 5-9.9 ng/mL, while 100% and 75% if CEA levels were 10-14.9 ng/mL. Although without a significant difference among these groups, the specificity of FDG PET/CT was increased in patients with higher CEA levels than in those with lower CEA levels [39]. Ragheb et al. performed FDG PET/CT on 45 CRC patients with elevated CEA levels during the postoperative surveillance. Compared to previous authors, they obtained similar sensitivity, specificity, PPV, and NPV of 96.9%, 83.3%, 94.2%, and 90%, respectively [40]. In addition, Gade et al. reported a high diagnostic performance of FDG PET/CT in recurrent CRC obtained on 73 patients with rising CEA levels. Compared to the results obtained in a previously mentioned study, they detected lower sensitivity of 85.7% and higher specificity of 94.7%, but similar PPV and NPV (93.5 % and 87.8%, respectively) [41]. Spirov et al. reported that significantly more patients with increased CEA had positive FDG PET/CT scan in recurrent CRC, p=0.04 [42]. Our results obtained on 134 CRC patients and elevated tumor markers are in accordance with all mentioned reports. We obtained high diagnostic

 doi:10.20944/preprints202405.0308.v1

performance of FDG PET/CT in the detection of recurrent CRC as follows: 94.4% of sensitivity, 82.5% of specificity, 78.5% of PPV, 95.7% of NPV, and accuracy of 87.3%. In addition, we detected high sensitivity but low specificity for CEA (98.1% and 15%, respectively) in the detection of CRC recurrence. In a meta-analysis including 11 studies with 510 patients with elevated CEA, Lu et al. detected pooled estimated sensitivity of 94.1% and specificity of 77.2% for FDG PET/CT in the detection of CRC recurrence [43]. Our results show similar sensitivity, but better specificity for FDG PET/CT in the detection of tumor recurrence (94.4% versus 82.5%, respectively).

However, several authors show that increased CEA levels are not necessary for an FDG PET/CT to detect recurrent CRC [40, 44-47]. In a recent study done by Miloradovic et al, FDG PET/CT imaging was performed on 50 CRC patients with normal or elevated CEA levels, previously treated by initial surgery. The sensitivity and specificity of FDG PET/CT in detecting recurrent CRC were high, 100% and 82.6%, respectively, regardless of the CEA levels. In addition, they report low sensitivity for CEA in the detection of CRC recurrence - only 48.1% [46]. Similar results were obtained by Sanli et al., who evaluated the diagnostic rate for FDG PET/CT on 235 CRC patients with both, normal and elevated CEA levels. They detected recurrence in 64.4% of patients with normal CEA and 88% of patients with increased CEA values, with sensitivity and specificity for both groups of 100% and 85%, versus 97.1% and 95.7%, respectively [47]. In our study, among 54 patients with recurrent CRC, we detect normal CEA level in only 1 patient, while remaining 53 patients with recurrence had elevated CEA levels. In contrast, in recurrent CRC normal levels of CA 19-9 were detected in 31 patients, and elevated levels in 23 patients.

Yao et al, recently published a systematic review and meta-analysis including 18 studies with a total of 1406 CRC patients with normal and elevated CEA levels aimed to analyze the diagnostic performance of FDG PET/CT in the detection of recurrent disease. They concluded that the diagnostic performance of FDG PET/CT was significantly improved in patients with increased CEA levels than those with normal CEA levels; with a reported AUC of 0.97 for the elevated CEA group versus an AUC of 0.88 for the normal CEA group of patients [48]. In another study, Vallam et al. retrospectively analyzed 104 non-metastatic CRC patients who underwent FDG PETCT after surgical resection of the primary tumor followed by adjuvant therapy. FDG PET/CT detected 59.6% recurrent disease with sensitivity, specificity, PPV, and NPV, of 92.7%; 95.2%; 96.2%, and 90.9%, respectively. Increased CEA levels during the patients' follow-up were positive for recurrence in 68% of the secretor arm (baseline level above 5 ng/mL) and in 45% of the non-secretor arm (levels below 5 ng/mL). The likelihood of CRC recurrence was directly proportional to the rising CEA levels. The recurrence was detected in 10%, 45%, 70%, 94%, and 100% of patients if CEA levels were less than 5, 5.1-1, 10.1-15, 15.1-50, and above 50 ng/mL [49].

Morphological imaging modalities (CT and MRI) have limited ability to differentiate recurrence from postoperative inflammatory and post-irradiation changes in CRC patients. With presenting information about tumor metabolism, FDG PET/CT is able to clear the equivocal findings by distinguishing between a scar and a viable tumor [50-53]. Since FDG PET/CT provides biological (functional) information that precedes morphological changes, this imaging modality can detect malignant disease before it is seen on CT and MRI. In CRC patients with elevated CEA levels, several authors obtained better sensitivity and detection recurrence rate for FDG PET/CT if compared to conventional CT scans [39,54-57]. Ozkan et al. made a comparison between two imaging tools in the detection of CRC recurrence in patients with elevated CEA. FDG PET/CT was superior over ceCT and showed better sensitivity and specificity (97% and 61% vs. 51% and 60%), respectively [39]. In a study performed on 50 CRC patients, Metser et al. evaluated recurrent disease by comparing FDG PET/CT imaging versus contrast enhanced 64-MDCT. While FDG PET/CT showed significantly higher sensitivity than MDCT (97.3% vs. 70.3%) on an event-based analysis, the specificity of both techniques was the same (94.4%) [54]. Similarly, Mittal et al. reported a better detection rate of recurrence for PET/CT in comparison to CT scans in postoperative CRC patients with increasing CEA (71% vs. 55%) [55]. Chalabi et al. compared FDG PET/CT and CECT in a prospective study on 100 CRC patients in the detection of recurrence. Diagnostic performance of PET/CT based on lesion analysis shows sensitivity of 95.6%, specificity of 91.4%, PPV of 96.7%, NPV of 88.9%, and diagnostic

 doi:10.20944/preprints202405.0308.v1

accuracy of 94.4% in comparison with 62.6%, 48.6%, 33.3%, 76% and 58% for CECT, respectively [56]. If compared two different imaging methods, based on per lesion analysis, Deleau et al. detected better accuracy for FDG PET/CT than CT for diagnosis of CRC recurrence of 88% vs. 53%, respectively. In regard of both sensitivity and specificity, FDG PET/CT was superior over CT with reported sensitivity of 95% vs. 55%, and specificity of 54% vs. 43%, respectively [57].

Similar results were reported by Choi et al, on a case-based analysis which shows that PET/CT is superior over conventional imaging studies (CIS) in the detection of CRC recurrence (local or distant). They obtained better overall sensitivity, specificity, and accuracy for FDG PET/CT (100%, 97%, and 97.3%, respectively) in comparison to those for CIS (85.1%, 97%, and 95.8%, respectively) [58]. Ince et al. studied 53 CRC patients and reported that FDG PET/CT was superior to CIM (CT or MRI) with sensitivity and specificity of 100% and 52% for FDG PET/CT versus 71% and 87% for CIM, respectively [59]. Results from our study are in accordance with other authors indicating higher sensitivity and accuracy, and slightly lower specificity for PET/CT in regard to CIM (94.4%, 82.5%, 87.3%, and 51.9%, 98.8%, and 79.9%, respectively).

Only a few studies have been done for the evaluation of the diagnostic performance of different diagnostic tools in the detection of CRC recurrence, when combining imaging modalities with tumor marker levels. Odalovic et al. compared diagnostic performance and prognostic significance of FDG PET/CT with MRI and tumor markers (CEA and CA 19-9). They report SN, SP, PPV, NPV, and ACC of FDG PET/CT in detecting CRC recurrence on a patient-based analysis of 92.6%, 75%, 92.6%,75% and 88.6%, compared to those for MRI (65.4%, 66.7%, 85%, 40% and 65.7%), respectively. In addition, CEA and CA 19-9 show overall accuracy in recurrence detection of 48.6% and 64.3%, respectively [60]. In agreement with that study, we also detected a better diagnostic performance for both FDG PET/CT and CIM in detecting CRC recurrence with sensitivity, specificity, PPV, and NPV, of FDG PET/CT (94.4%, 82.5%, 78.5%, 95.7%, and 87.3%, respectively), in contrast to those for CIM (51.9%, 98.8%, 96.6%, 75.2%, and 79.9%, respectively). In addition, we detected accuracy for CEA was the same (46.5% vs. 48.6%), while the accuracy for CA 19-9 was slightly lower in our study (58.2% vs. 64.3%).

In a study performed on a small number of patients, Uzun et al. reported that FDG PET-CT was superior to CEA and CIM in the detection of CRC recurrent disease. They detected a sensitivity of 93.1%, which was similar to our result (sensitivity of 94.4%), whereas their reported specificity of 88.2% and accuracy of 92% were higher than ours (82.5% and 87.3%, respectively). In addition, authors detected sensitivity, specificity, and accuracy for CEA of 72.4%, 64.7% and 87.5%, respectively [21]. In comparison to these results, we obtained a higher sensitivity but lower specificity and accuracy for CEA in CRC recurrent detection (98.1%, 15%, and 48.5%, respectively). Additionally, if CIM was analyzed in detecting the CRC recurrence, compared to the results reported in the previous study, we obtained much better specificity and accuracy (98.8% vs. 52.8%, and 79.9% vs. 72%, respectively), but much lower sensitivity (51.9% vs. 77.5%).

Caglar et al. retrospectively compared the sensitivity and specificity of tumor markers, CT, and FDG PET/CT in 212 CRC patients with suspicious recurrent disease. They detected an area under the ROC curve (AUC) of 0.865, and 0.631 for elevated CEA and elevated CA 19-9 levels, respectively [61]. In our study, AUC was 0.885, 0.844, and 0.547, for FDG PET/CT, CEA, and CA 19-9, retrospectively.

In an univariate analysis, gender, presence of initial nodal, presence of distant metastases, and mucinous tumor type were shown as not statistically significant in the prediction of CRC recurrence ($p=0.211$, $p=0.583$, $p=0.201$, and $p=0.158$, respectively). Both, FDG PET/CT and CEA are significantly associated with recurrence ($p=<0.01$). The results obtained in our study confirm that FDG PET/CT (AUC of 0.885) and elevated CEA levels (AUC of 0.844) are the most accurate methods for detecting CRC recurrence. In comparison, CIM shows less accuracy (AUC of 0.753) while CA 19-9 indicates poor result (AUC of 0.547). Additionally, a multivariate analysis indicates FDG PET/CT as an independent predicting factor for recurrent disease (obtained by binary logistic regression, OR=175). CEA is also shown as a good recurrence predictor in our study (AUC of 0.844; OR=26).

Chiaravalloti et al, retrospectively analyzed the sensitivity and specificity of FDG PET/CT in detecting recurrent disease in 100 patients with CRC, with correlation to CEA and CA 19-9. They

 doi:10.20944/preprints202405.0308.v1

detected a significant association between FDG PET/CT and CEA levels (p=0.001), but not between FDG PET/CT and CA 19-9 (p=0.43). In addition, they recommend the use of FDG PET/CT in patients suspected of having CRC recurrence not only with increased CEA levels but also regardless of CEA values [45]. According to Hancerliogullari et al., the main predicting risk factors for 59% of recurrence in CRC patients are SUVmax and initial nodal involvement, with AUC of 0.717 [95% CI: 0.581-0.854, p=0.006][62].

We report high sensitivity for PET/CT and CEA (94.4% and 98.1%, respectively), but much lower for CIM and CA 19-9 (51.9% and 44.4%, respectively) in the detection of CRC recurrence. The high specificity of FDG PET/CT in CRC patients was high for imaging modalities (98.6% for CIM and 82.5% for FDG PET/CT), in contrast to 67.5% specificity for CA 19-9 and only 15% for CEA. Imaging modalities show significantly better accuracy in CRC recurrence (87.3% for FDG PET/CT versus 79.9% for CIM), in comparison to CA 19-9 and CEA (58.2% and 48.5%, respectively).

According to several publications, FDG PET/CT has no role in the imaging of mucinous CRC. Very low or negligible FDG uptake is influenced by a hypocellularity of these tumors caused by the presence of mucin [63,64]. Some authors advocate that mucinous adenocarcinoma was the most common cause of false-negative scans of CRC recurrence accounting for two-quarters of false-negative studied patients [65,66]. A lower efficacy of FDG PET/CT for the detection of mucinous adenocarcinoma has been reported; showing the sensitivity of FDG PET/CT imaging that was significantly lower than in non-mucinous tumor types (58% versus 92%, respectively; p=0.05) [66]. Similar results were obtained in the study by Berger et al. who reported sensitivity of 59% for FDG PET/CT in the detection of mucinous CRC with 41% of false-negative results. They stated that the failure of PET to reveal tumor foci significantly correlated with low tumor cellularity (p=0.011) and overall abundance of mucin (p=0.009) [67]. Some authors recommend that in mucinous adenocarcinoma with negative FDG PET scans, other imaging modalities should be performed to establish the final diagnosis [68]. Our results are in agreement with the authors who reported previous data. In our study, there are only 3 false negative FDG PET/CT results; one patient with mucinous adenocarcinoma who was misdiagnosed due to already known low sensitivity of PET/CT to detect malignant tissue in this particular type of adenocarcinoma. FDG PET/CT scan omitted small peritoneal lesions in one patient probably due to resolution limitation, and a local recurrence in the third patient.

Colorectal cancer very often metastasizes in the liver (in about 50-60%), while initially diagnosed patients with liver metastases account for approximately 30 % of patients [69]. Early detection of liver metastasis is of essential importance to allow proper restaging and further patient selection for surgery (liver resection). It is well known that MRI is established as the most sensitive diagnostic tool for diagnosing liver metastasis in CRC [70]. However, several authors reported FDG PET/CT as highy sensitive in the detection of liver metastases in patients with CRC [71,72]. If compared to CECT, FDG PET/CT is superior, in particular for the detection of occult metastases [40,42]. Results obtained in a study of Cinar et al. are in line with previous reports. They present FDG PET/CT as more successful than CT in detecting CRC recurrence, with better sensitivity and specificity for PET/CT than for CT (88% and 92% vs. 80% and 76%, respectively) [73].

The lung is another common site for colorectal cancer metastases. In our study, FDG PET/CT shows high accuracy in the detection of distant metastases in the liver (being consistent with MRI results in all cases) and lung metastases (having agreement with CT scan only in 50% of cases due to false-negative CT results). Recurrence detection led to changed patients' management and resulted in surgery for 6 patients with liver metastases and one patients with lung metastases; chemotherapy in 6 patients (including 3 patients with lungs and 3 with liver metastases), while two patients with lung metastases received surgery followed by chemotherapy.

In our study FDG PET/CT results falsely diagnosed recurrence due to high FDG uptake in benign lesions (liver hemangioma in 2 patients, lung granulomatous and lung inflammatory lesions in the remaining two patients, respectively). Suspicious locoregional lesion in two patients, as well as suspected regional lymph nodes in 8 patients were falsy interpreted due to inflammatory changes. It has been previously described in the literature that pelvic anatomy is altered in CRC patients as a

 doi:10.20944/preprints202405.0308.v1

result of surgery and radiation therapy that might result in compromised findings due to false–positive results [50,74].

We detected the value of 11.5 ng/mL as an optimal cut-off value for CEA and the value of 120 U/mL as an optimal cut-off value for CA 19-9 in detecting recurrent CRC on our patients' cohort. The sensitivity and specificity, according to the standard cut-off values for CEA and CA 19-9 (4.7 ng/mL and 39 U/mL respectively), were 98.1% and 15.0% for CEA; and 44.4% and 67.5% for CA 19-9, respectively. The sensitivity and specificity, according to the optimal cutoffs from ROC analyses obtained in our study (11.5 ng/mL for CEA and 120 U/mL for CA 19-9), were 75.9% and 83.7% for CEA; and 18.5% and 98.7% for CA 19-9, respectively. Caglar et al. performed a similar study with an aim to determinate the optimal cutoff level for tumor markers, CEA and CA 19-9. In contrast to our data, they reported different results as following: CEA cutoff level of ≥5.7 ng/mL (in comparison to normal value of <4.7 ng/mL) and CA 19-9 cutoff level of ≥15.37 U/mL (in comparison to normal value of <39 U/mL) yielding a sensitivity of 70.6% and 66.7% and a specificity of 94.4% and 66.7%, respectively [61]. In another study, Tan et al. suggested a cutoff of 2.2 μg/L to show high specificity of 90% and limited sensitivity of 64% for the recurrent CRC detection [75]. We did not find any significant difference in CA 19-9 levels in patients with recurrence compared to those without CRC recurrence (p=0.358). However, the difference in CEA levels in patients with recurrent CRC versus patients without recurrent CRC shows a statistically significant difference (92.8 ± 268; median 19.9, IQR 29.2, and 10.9 ± 20.4; median 7.56, IQR 4.7, respectively; p<0.001).

The results of univariate analysis in our study show that CRC recurrence was not significantly associated with gender (p=0.211), mucinous component (p=0.158), and presence of initial lymph node metastasis (N+) (p=0.583), as well as presence of initial distant metastasis (M+) (p=0.201). However, positive FDG PET/CT scan and positive CIM findings (p<0.001) were highly associated with CRC recurrence (p<0.001). In addition, our multivariate analysis shows that independent predictors for CRC recurrence were: positive FDG PET/CT scans (p<0.001), positive CIM scans (p=0.001) and elevated CA 19-9 levels (p=0.023). Although CA 19-9 was not detected as a statistically significant predictor in the univariate analysis (p=0.358), in a multivariate analysis this tumor marker was recognized as a significant predicting factor in detecting CRC recurrence (p=0.023).

There are several limitations to our study. The FDG PET/CT imaging in Serbia is available at only two Nuclear Medicine Centers, one of them being our institution. Moreover, CRC patients suspected of having recurrence were referred from different centers in the country. CIM and tumor marker results were not standardized since they were obtained from different centers and laboratories. Moreover, we were not able to evaluate the clinical impact of FDG PET/CT results in all patients because some of them were subsequently monitored and treated at their referral institutions. The histopathological confirmation of CRC recurrence was directly obtained in only 27.8% of patients, while in the 72.2% of the remaining patients it was obtained through subsequent clinical and imaging follow-up. In addition, due to retrospective analyses of patients' data, we were unable to change the diagnostic algorithm as necessary. Furthermore, we did not classify patients into smokers and non-smokers which may have had an impact on increased CEA levels and been a bias in the determination of diagnostic performance. Another bias could have been be due to patient selection and a relatively short follow-up period. Future prospective studies with longer patient surveillance, standardized lab analysis, and imaging tools are necessary to improve current diagnostics in detection of recurrent CRC.

5. Conclusions

FDG PET/CT shows a high diagnostic efficacy in CRC recurrence detection. Compared to conventional imaging modalities, FDG PET/CT shows a higher sensitivity and accuracy but slightly lower specificity in detecting CRC recurrence in patients with elevated tumor markers. In our cohort of patients with elevated tumor markers (CEA, CA 19-9), FDG PET/CT seems to be the best method in the detection of CRC recurrence. FDG PET/CT should be routinely integrated into the postoperative follow-op of patients with CRC.

Author Contributions: Conceptualisation, J.M.; methodology, J.M., I.N. and Z.N.; software, J. M.; validation, I.N., N.P.B., and Z.N.; formal analysis, J.M., I.S. and J.R.; investigation, I.N. and Z.N.; data curation, I.S., J.R., and J.M.; writing—original draft preparation, J.M.; writing—review and editing, J.M.; supervision, I.N., N.P.B., and Z.N.; project administration, J.M., I. S. and J.R. All authors have read and agreed to the published version of the manuscript.

Funding: This article was supported by the Republic of Serbia, Autonomous Province of Vojvodina, Provincial Secretariat for High Education and Scientific Research, grant nos. 142-451-3489/2023-02.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Oncology Institute of Vojvodina in Sremska Kamenica (protocol code 4/24/1-1316/2-7, 9April 2024).

Informed Consent Statement: Patient consent was waived since only retrospective patient data were used for the study.

Data Availability Statement: Data presented in this study are available on request from the corresponding author. Data are not publicly available due to patients' privacy.

Acknowledgments: The authors would like to thank Zoran Potić for his assistance in statistical analyses.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Siegel, R.L.; Giaquinto, A.N.; Jemal, A. Cancer statistics, 2024. *CA. Cancer. J. Clin*. **2024**, *74*, 12-49. Erratum in: *CA. Cancer. J. Clin*. **2024**, *74*, 203. doi: 10.3322/caac.21820
2. Sargent, D.; Sobrero, A.; Grothey, A.; O'Connell, M.J.; Buyse, M.; Andre, T.; Zheng, Y.; Green, E.; Labianca, R.; O'Callaghan, C.; et al. Evidence for cure by adjuvant therapy in colon cancer: Observations based on individual patient data from 20,898 patients on 18 randomized trials. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2009**, *27*, 872-877. doi: 10.1200/JCO.2008.19.5362
3. Shah, M.A.; Renfro, L.A.; Allegra, C.J.; Andre, T.; de Gramont, A.; Schmoll, H.J.; Haller, D.G.; Alberts, S.R.; Yothers, G.; Sargent, D.J.; et al. Impact of Patient Factors on Recurrence Risk and Time Dependency of Oxaliplatin Benefit in Patients with Colon Cancer: Analysis from Modern-Era Adjuvant Studies in the Adjuvant Colon Cancer End Points (ACCENT) Database. *J. Clin. Oncol.* **2016**, *34*, 843-853. doi: 10.1200/JCO.2015.63.0558
4. Riihimäki, M.; Hemminki, A.; Sundquist, J.; Hemminki, K. Patterns of metastasis in colon and rectal cancer. *Sci. Rep*. **2016**, *6*, 29765. doi: 10.1038/srep29765
5. Nikolic, N.; Radosavljevic, D.; Gavrilovic, D.; Nikolic, V.; Stanic, N.; Spasic, J.; Cecev, T.; Castellvi-Bel, S.; Cavic, M.; Jankovic, G. Prognostic factors for post-recurrence survival in stage II and III colorectal carcinoma patients. *Medicina* **2021**, *57*, 1108. doi: 10.3390/medicina57101108.
6. Sonoda, H.; Yamada, T.; Matsuda, A.; Ohta, R.; Shinji, S.; Yokoyama, Y.; Takahashi, G.; Iwai, T.; Takeda, K.; Ueda, K.; et al. Elevated serum carcinoembryonic antigen level after curative surgery is a prognostic biomarker of stage II-III colorectal cancer. *Eur J Surg Oncol*. **2021**, *47*, 2880–2887. doi: 10.1016/j.ejso.2021.05.041
7. Furuke, H.; Arita, T.; Kuriu, Y.; Shimizu, H.; Kiuchi, J.; Yamamoto, Y.; Konishi, H.; Morimura, R.; Shiozaki, A.; Ikoma, H.; et al. The survival after recurrence of colorectal cancer: A retrospective study focused on time to recurrence after curative resection. *Surg. Today* **2021**, *52*, 239–250. doi: 10.1007/s00595-021-02336-z.
8. Henne-Bruns, D.; Dürig, M.; Kremer, B. *Chirurgie,* 3rd ed.; Thieme: Leipzig, Germany, 2008. ISBN: 978-313-125-293-7.
9. Balboa-Barreiro, V.; Pértega-Díaz, S.; García-Rodríguez, T.; González-Martín, C.; Pardeiro-Pértega, R.; Yáñez-González-Dopeso, L.; Seoane-Pillado, T. Colorectal cancer recurrence and its impact on survival after curative surgery: An analysis based on multistate models. *Dig. Liver. Dis*. **2023** *11*, S1590-8658(23)01074-5. doi: 10.1016/j.dld.2023.11.041
10. Qaderi, S.M.; Galjart, B.; Verhoef, C.; Slooter, G.D.; Koopman, M.; Verhoeven, R.H.A.; de Wilt, J.H.W.; van Erning, F.N. Disease recurrence after colorectal cancer surgery in the modern era: a population-based study. *Int. J. Color. Dis*. **2021**, *36*, 2399-2410. doi: 10.1007/s00384-021-03914-w.
11. Glynne-Jones, R.; Wyrwicz, L.; Tiret, E.; Brown, G.; Rodel, C.; Cervantes, A.; Arnold, D.; Committee, E.G. Corrections to: Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2018**, *29*, IV263. doi: 10.1093/annonc/mdy161
12. Argiles, G.; Tabernero, J.; Labianca, R.; Hochhauser, D.; Salazar, R.; Iveson, T.; Laurent-Puig, P.; Quirke, P.; Yoshino, T.; Taieb, J. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2020**, *31*, 1291–1305. doi: 10.1016/j.annonc.2020.06.022.
13. NICE 2020. National Institute for Health and Clinical Excellence. Colorectal cancer. Jan 29, 2020. NICE guideline [NG151]. Available online: https://www.nice.org.uk/guidance/ng151 (accessed on 6 April 2024)

14. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon cancer. Version 1.2024 — January 29, 2024. Available online: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed on 28 April 2024)
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal cancer. Version 1.2024 — January 29, 2024. Available online: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed on 28 April 2024)
16. Świderska, M.; Choromańska, B.; Dąbrowska, E.; Konarzewska-Duchnowska, E.; Choromańska, K.; Szczurko, G.; Myśliwiec, P.; Dadan, J.; Ładny, J.R.; Zwierz, K. The diagnostics of colorectal cancer. *Contemp. Oncol.* **2014**, *18*, 1–6. doi: 10.5114/wo.2013.39995
17. Gao, Y.; Wang, J.; Zhou, Y.; Sheng, S.; Qian, S.Y.; Huo, X. Evaluation of serum CEA, CA19-9, CA72-4, CA125 and ferritin as diagnostic markers and factors of clinical parameters for colorectal cancer. *Sci. Rep.* **2018**, *8*, 2732. doi: 10.1038/s41598-018-21048-y
18. Locker, G.Y.; Hamilton, S.; Harris, J.; Jessup, J.M.; Kemeny, N.; Macdonald, J.S.; Somerfield, M.R.; Hayes, D.F.; Bast, R.C. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J. Clin. Oncol*. **2006**, *24*, 5313–5327. doi: 10.1200/JCO.2006.08.2644
19. Schmoll, H.J.; Van Cutsem, E.; Stein, A.; Valentini, V.; Gliemelius, B.; Haustermans, K.; Nordlinger, B.; van de Velde, C.J.; Balmana, J.; Regula, J.; et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. *Ann. Oncol*. **2012**, *23*, 2479–2516. doi: 10.1093/annonc/mds236
20. Bailey, C.E..; Hu, C.Y.; You, Y.N.; Kaur, H.; Ernst, R.D.; Chang, G.J. Variation in positron emission tomography use after colon cancer resection. *J. Oncol. Pract*. **2015**, *11*, e363-372. doi: 10.1200/JOP.2014.001933.
21. Uzun, A.K.; Güveli, T.K.; Özülker, F.; Özülker, T. The Efficacy of 18F-FDG PET/CT in Detecting Colorectal Cancer Recurrences. *Eur. Arch. Med. Res*. **2021**, *37*, 236–243. DOI: 10.4274/eamr.galenos.2021.52533
22. Laurens, S.T.; Oyen, W.J. Impact of flurodeoxyglucose PET/computed tomography on the management of patients with colorectal cancer. *PET Clin*. **2015,** *10*, 345–360. doi: 10.1016/j.cpet.2015.03.007
23. Digestive System Tumours: WHO Classification of Tumours (Medicine) 5th Edition. WHO Classification of Tumours Editorial Board. World Health Organization, **2019**.
24. Amin, M.B.; Edge, S.B.; Greene, F.L.; Byrd, D.R.; Brookland, R.K.; Washington, M.K.; Gershenwald, J.E.; Compton, C.C.; Hess, K.R.; Suillivan, D.C.; et al. *American Joint Committee on cancer. AJCC Cancer Staging Manual*, Eight edition; American College of Surgeons: Chicago, US, **2018**; pp. 237-275.
25. Gold, P.; Freedman, S.O. Demonstration of Tumor-Specific Antigens in Human Colonic Carcinomata by Immunological Tolerance and Absorption Techniques. *J. Exp. Med*. **1965**, *121*, 439–462. doi: 10.1084/jem.121.3.439
26. Lech, G.; Słotwiński, R.; Słodkowski, M.; Krasnodębski, I.W. Colorectal cancer tumour markers and biomarkers: Recent therapeutic advances. *World. J. Gastroenterol.* **2016**, *22*, 1745–1755.
27. Jelski, W.; Mroczko, B. Biochemical Markers of Colorectal Cancer–Present and Future. *Cancer. Manag. Res*. **2020**, *12*, 4789-4797. doi: 10.2147/CMAR.S253369
28. Lakemeyer, L.; Sander, S.; Wittau, M.; Henne-Bruns, D.; Kornmann, M.; Lemke, J. Diagnostic and Prognostic Value of CEA and CA19-9 in Colorectal Cancer. *Diseases.* **2021**, *9*, 21. doi: 10.3390/diseases9010021
29. Koprowski, H.; Steplewski, Z.; Mitchell, K.; Herlyn, M.; Herlyn, D.; Fuhrer, P. Colorectal carcinoma antigens detected by hybridoma antibodies. *Somat. Cell Genet*. **1979**, 5, 957–971. doi: 10.1007/BF01542654
30. Kim, S.; Park, B.K.; Seo, J.H.; Choi, J.; Choi, J.W.; Lee, C.K.; Chung, J.B.; Park, Y.; Kim, D.W. Carbohydrate antigen 19-9 elevation without evidence of malignant or pancreatobiliary diseases. *Sci. Rep*. **2020**, *10*, 8820. doi: 10.1038/s41598-020-65720-8
31. Yakabe, T.; Nakafusa, Y.; Sumi, K.; Miyoshi, A.; Kitajima, Y.; Sato, S.; Noshiro, H.; Miyazaki, K. Clinical significance of CEA and CA19-9 in postoperative follow-up of colorectal cancer. *Ann. Surg. Oncol.* **2010**, 17, 2349–2356. doi: 10.1245/s10434-010-1004-5.
32. Bagaria, B.; Sood, S.; Sharma, R.; Lalwani, S. Comparative study of CEA and CA19-9 in esophageal, gastric and colon cancers individually and in combination (ROC curve analysis). *Cancer. Biol. Med.* **2013**, *10*, 148–157. doi: 10.7497/j.issn.2095-3941.2013.03.005
33. Zhang, S.-Y.; Lin, M.; Zhang, H.-B. Diagnostic value of carcinoembryonic antigen and carcinoma antigen 19-9 for colorectal carcinoma. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 9404–9409.
34. Abe, S.; Kawai, K.; Ishihara, S.; Nozawa, H.; Hata, K.; Kiyomatsu, T.; Tanaka, T.; Watanabe, T. Prognostic impact of carcinoembryonic antigen and carbohydrate antigen 19-9 in stage IV colorectal cancer patients after R0 resection. *J. Surg. Res*. **2016**, *205*, 384–392. doi: 10.1016/j.jss.2016.06.078
35. Thomsen, M.; Skovlund, E.; Sorbye, H.; Bolstad, N.; Nustad, K.J.; Glimelius, B.; Pfeiffer, P.; Kure, E.H.; Johansen, J.S.; Tveit, K.M.; et al. Prognostic role of carcinoembryonic antigen and carbohydrate antigen 19-9 in metastatic colorectal cancer: A BRAF-mutant subset with high CA 19-9 level and poor outcome. *Br. J. Cancer.* **2018**, *118*, 1609–1616. doi: 10.1038/s41416-018-0115-9

36. Sobhani, I.; Tiret, E.; Lebtahi, R.; Aparicio, T.; Itti, E.; Montravers, F.; Vaylet, C.; Rougier, P.; André, T.; Gornet, J.M.; et al. Early detection of recurrence by 18FDG-PET in the follow-up of patients with colorectal cancer. *Br. J. Cancer* **2008**, 98, 875–880. doi: 10.1038/sj.bjc.6604263
37. Sobhani, I.; Itti, E.; Luciani, A.; Baumgaertner, I.; Layese, R.; André, T.; Ducreux, M.; Gornet, J.-M.; Goujon, G.; Aparicio, T.; et al. Colorectal cancer (CRC) monitoring by 6-monthly 18FDG-PET/CT: An open-label multicentre randomised trial. *Ann. Oncol.* **2018**, *29*, 931–937. doi: 10.1093/annonc/mdy031
38. Benson, A.B., 3rd; Venook, A.P.; Bekaii-Saab, T.; Chan, E.; Chen, Y.J.; Cooper, H.S.; Engstrom, P.F.; Enzinger, P.C.; Fenton, M.J.; Fuchs, C.S.; et al. Colon cancer, version 3.2014. *J. Natl. Compr. Canc. Netw.* **2014**, *12*, 1028–1059. doi: 10.6004/jnccn.2014.0099
39. Ozkan, E.; Soydal, C.; Araz, M.; Kir, K.M.; Ibis, E. The role of 18F-FDG PET/CT in detecting colorectal cancer recurrence in patients with elevated CEA levels. *Nucl. Med. Commun.* **2012**, *33*, 395-402. doi: 10.1097/MNM.0b013e32834f7dbe
40. Ragheb, S.R.; Sharara, S.M. Can PET/CT detect recurrence in post-operative colorectal carcinoma patients with elevated CEA level? *Egypt. J. Radiol. Nucl. Med.* **2020**, *51*, 1-9. doi: 10.1186/s43055-020-00170-w
41. Gade, M.; Kubik, M.; Fisker, R.V.; Thorlacius-Ussing, O.; Petersen, L.J. Diagnostic value of (18)F-FDG PET/CT as first choice in the detection of recurrent colorectal cancer due to rising CEA. *Cancer. Imaging.* **2015**, *15*, 11. doi: 10.1186/s40644-015-0048-y
42. Spirov, G.;, Kocev, S.B.; Matveeva, N.; Spirov, V.; Ugrinska, A. The value of PET/CT in detecting colorectal canbcer recurrence in patients with negative CT findings. *J.M.S.* **2021**, *4*, 57-65.
43. Lu, Y.-Y.; Chen, J.-H.; Chien, C.-R.; Chen, W.T.-L.; Tsai, S.-C.; Lin, W.-Y.; Kao, C.-H. Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: A systematic review and meta-analysis. *Int. J. Colorectal. Dis.* **2013**, *28*, 1039–1047. doi: 10.1007/s00384-013-1659-z.
44. Lee, J.H.; Park, S.G.; Jee, K.N.; Park, D.G.; Namgung, H.; Song, I.H. Performance of FDG PET/CT in postoperative colorectal cancer patients with a suspected recurrence and a normal CEA level. *Nucl. Med. Commun.* **2010**, *31*, 576-582. doi: 10.1097/MNM.0b013e32833845b7.
45. Chiaravalloti, A.; Fiorentini, A.; Palombo, E.; Rinino, D.; Lacanfora, A.; Danieli, R.; Di Russo, C.; Di Biagio, D.; Squillaci, E.; Schillaci, O. Evaluation of recurrent disease in the re-staging of colorectal cancer by 18F-FDG PET/CT: Use of CEA and CA 19-9 in patient selection. *Oncol. Lett.* **2016**, *12*, 4209-4213. doi: 10.3892/ol.2016.5143.
46. Milardovic, R.; Beslic, N.; Sadija, A.; Ceric, S.; Bukvic, M.; Dzananovic, L. Role of 18F-FDG PET/CT in the Follow-up of Colorectal Cancer. *Acta Inform Med.* **2020**, *28*, 119-123. doi: 10.5455/aim.2020.28.119-123
47. Sanli, Y.; Kuyumcu, S.; Ozkan, Z.G.; Kilic, L.; Balik, E.; Turkmen, C.; Has, D.; Isik, G.; Asoglu, O.; Kapran, Y.; et al. The utility of FDG-PET/CT as an effective tool for detecting recurrent colorectal cancer regardless of serum CEA levels. *Ann. Nucl. Med.* **2012**, *26*, 551–558. doi: 10.1007/s12149-012-0609-0
48. Yao, J.; Zhang, S.; Liang, J.; Li, H. The diagnostic performance of 2-[18F]FDG PET/CT for the recurrent colorectal cancer in patients with elevated CEA versus normal CEA: a systematic review and meta-analysis. *Clin. Transl. Imaging.* **2023**, *11*, 209-223. doi: 10.1007/s40336-022-00536-2
49. Vallam, K.C.; Guruchannabasavaiah, B.; Agrawal, A.; Rangarajan V.; Ostwal V.; Engineer R.; Saklani A. Carcinoembryonic antigen directed PET CECT scanning for postoperative surveillance of colorectal cancer. *Colorectal Dis.* **2017**; *19*: 907-991. doi: 10.1111/codi.13695
50. Ogunbiyi, O.A.; Flanagan, F.L.; Dehdashti, F.; Siegel, B.A.; Trask, D.D.; Birnbaum, E.H.; Fleshman, J.W.; Read, T.E.; Philpott, G.W.; Kodner I.J. Detection of recurrent and metastatic colorectal cancer: comparison of positron emission tomography and computed tomography. *Ann. Surg. Oncol.* **1997**, *4*, 613–620. doi: 10.1007/BF02303744
51. Kantorová, I.; Lipská, L.; Bêlohlávek O.; Visokai, V.; Trubaĉ, M.; Schneiderová , M. Routine (18)F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. *J. Nucl. Med.* **2003**; *44*, 1784–1788.
52. Schlag, P.; Lehner, B.; Strauss, L.G.; Georgi, P.; Herfarth, C. Scar or recurrent rectal cancer. Positron emission tomography is more helpful for diagnosis than immunoscintigraphy. *Arch. Surg.* **1989**, *124*, 197–200. doi: 10.1001/archsurg.1989.01410020067011
53. de Geus-Oei, L.F.; Ruers, T.J.M.; Punt, C.J.A.; Leer, J.W.; Corstens, F.H.M.; Oyen, W.J.G. FDG-PET in colorectal cancer. *Cancer Imaging* **2006**, *6*, S71–S81. doi: 10.1102/1470-7330.2006.9014
54. Metser, U.; You, J.; McSweeney, S.; Freeman, M.; Hendler, A. Assessment of tumor recurrence in patients with colorectal cancer and elevated carcinoembryonic antigen level: FDG PET/CT versus contrast-enhanced 64-MDCT of the chest and abdomen. *Am. J. Roentgenol.* **2010**, *194*, 766–771. doi: 10.2214/AJR.09.3205
55. Mittal, B.R.; Senthil, R.; Kashyap, R.; Bhattacharya, A.; Singh, B.; Kapoor, R.; Gupta, R. 18F-FDG PET-CT in evaluation of postoperative colorectal cancer patients with rising CEA level. *Nucl. Med. Commun.* **2011**, *32*, 789-793. doi: 10.1097/MNM.0b013e3283477dd7

56. Chalabi, N.A.M.; Bassiouny, R.H.; El Sedek, M.A. FDG-PETCT versus contrast-enhanced computed tomography in diagnosis of post-therapeutic colorectal cancer recurrence and metastases. *Egypt. J. Radiol. Nucl. Med*. **2020**, *51*, 1–9. doi: 10.1186/s43055-019-0083-y
57. Deleau, C; Buecher, B.; Rousseau, C; Kraeber-Bodéré, F.; Flamant, M.; des Varannes, S.B.; Frampas, E.; Galmiche, J.P.; Matysiak-Budnik, T. Clinical impact of fluorodeoxyglucose-positron emission tomography scan/computed tomography in comparison with computed tomography on the detection of colorectal cancer recurrence. *Eur. J. Gastroenterol Hepatol.* **2011**, *23*, 275-281. doi: 10.1097/MEG.0b013e328343eaa0.
58. Choi, E.K.; Yoo, IeR.; Park, H.L.; Choi, H.S.; Han, E.J.; Kim, S.H.; Chung, S.K.; O, J.H. Value of Surveillance (18)F-FDG PET/CT in Colorectal Cancer: Comparison with Conventional Imaging Studies. *Nucl. Med. Mol. Imaging.* **2012**, *46*, 189-195. doi: 10.1007/s13139-012-0145-9
59. Ince, S.; Okuyucu, K.; Hancerliogulları, O.; Alagoz, E.; San, H.; Arslan, N. Clinical Significance of Fluorine-18-fluorodeoxyglucose Positron Emission Tomography/computed Tomography in the Follow-up of Colorectal Cancer: Searching off Approaches Increasing Specificity for Detection of Recurrence. *Radiol. Oncol*. **2017**, *51*, 378-385. doi: 10.1515/raon-2017-0045.
60. Odalovic, S.; Stojiljkovic, M.; Sobic-Saranovic, D.; Pandurevic, S.; Brajkovic, L.; Milosevic, I.; Grozdic-Milojevic, I.; Artiko, V. Prospective study on diagnostic and prognostic significance of postoperative FDG PET/CT in recurrent colorectal carcinoma patients: comparison with MRI and tumor markers. *Neoplasma*. **2017**, *64*, 954-961. doi: 10.4149/neo_2017_613.
61. Caglar, M.; Yener, C.; Karabulut, E. Value of CT, FDG PET-CT and serum tumor markers in staging recurrent colorectal cancer. *Int. J. Comput. Assist. Radiol. Surg*. **2015**, *10*, 993-1002. doi: 10.1007/s11548-014-1115-8
62. Hancerliogullari, O.; Okuyucu, K.; Ince, S.; Peker, S.; Arslan, N. Prognostic parameters in recurrent colorectal cancer: A role of control or restaging by FDG-PET/CT. *Vojnosanit. Pregl*. **2020**, *77*, 201-208. doi: 10.2298/VSP170817065H
63. Borello, A.; Russolillo, N.; Lo Tesoriere, R.; Langella, S.; Guerra, M.; Ferrero, A. Diagnostic performance of the FDG-PET/CT in patients with resected mucinous colorectal liver metastases. *Surgeon.* **2021**, *19*, e140-e145. doi: 10.1016/j.surge.2020.09.004
64. Elia, R.Z.; Elbastawessy, R.A.; Abdelmgeguid, H.A.; Bassiouny, A.M.. FDG PET/CT in follow UP patients with colorectal carcinoma after adjuvant chemotherapy. *Egypt. J. Radiol. Nucl. Med*. **2021,** *52*, 289. doi: 10.1186/s43055-021-00655-2
65. Borasio, P.; Gisabella, M.; Bille, A.; Righi, L.; Longo, M.; Tampellini, M.; Ardissone, F. Role of surgical resection in colorectal lung metastases: Analysis of 137 patients. *Int. J. Colorectal Dis*. **2011**, *26*, 183–190. doi: 10.1007/s00384-010-1075-6
66. Whiteford, M.H.; Whiteford, H.M.; Yee, L.F.; Ogunbiyi, O.A.; Dehdashti, F.; Siegel, B.A.; Birnbaum, E.H.; Fleshman, J.W.; Kodner, I.J.; Read, T.E. Usefulness of FDG-PET scan in the assessment of suspected metastatic or recurrent adenocarcinoma of the colon and rectum. *Dis. Colon. Rectum.* **2000**, *43*, 759–767. doi: 10.1007/BF02238010
67. Berger, K.L.; Nicholson, S.A.; Dehdashti, F.; Siegel, B.A. FDG PET evaluation of mucinous neoplasms: Correlation of FDG uptake with histopathologic features. *Am. J. Roentgenol*. **2000**, *174*, 1005–1008. doi: 10.2214/ajr.174.4.1741005
68. Zhang, Y.; Feng, B.; Zhang, G.L.; Hu, M.; Fu, Z.; Zhao, F.; Zhang, X.L.; Kong, L.; Yu, J.M. Value of 18F-FDG PET-CT in surveillance of postoperative colorectal cancer patients with various carcinoembryonic antigen concentrations. *World J Gastroenterol*. **2014**, *20*, 6608-14. doi: 10.3748/wjg.v20.i21.6608
69. Kitajima, K.; Nakajo, M.; Kaida, H.; Minamimoto, R.; Hirata, K.; Tsurusaki, M.; Doi, H.; Ueno, Y.; Sofue, K.; Tamaki, Y.; et al. Present and future roles of FDG-PET/CT imaging in the management of gastrointestinal cancer: An update. *Nagoya J. Med. Sci.* **2017**, *79*, 527–543. doi: 10.18999/nagjms.79.4.527
70. Renzulli, M.; Clemente, A.; Ierardi, A.M.; Pettinari, I.; Tovoli, F.; Brocchi, S.; Peta, G.; Cappabianca, S.; Carrafiello, G.; Carrafiello, G. Imaging of Colorectal Liver Metastases: New Developments and Pending Issues. *Cancers. (Basel.* **2020**, *12*, 151. doi: 10.3390/cancers12010151
71. Agarwal, A.; Marcus, C.; Xiao, J.; Nene, P.; Kachnic, L.A.; Subramaniam, R.M. FDG PET/CT in the management of colorectal and anal cancers. *Am. J. Roentgenol.* **2014**, *203*, 1109–1119. doi: 10.2214/AJR.13.1225
72. Ali, S.A.; Abd Elkhalek, Y.I. Value of integrated PET/CT in detection of hepatic metastatic deposits. *Egypt. J. Radiol. Nuclear. Med*. **2016,** 47, 459–465. doi: 10.1016/j.ejrnm.2016.03.006
73. Çinar, A.; Gencoglu, E.A. The Impact Of F-18 FDG PET/CT In the restaging of colorectal cancer in patients with suspected recurrence. *J. Med. Palliat. Care.* **2022,** *3*, 16-21. doi: 10.47582/jompac.1053300

 doi:10.20944/preprints202405.0308.v1

74. Even-Sapir, E.; Parag, Y.; Lerman, H.; Gutman, M.; Levine, C.; Rabau, M.; Figer, A.; Metser, U. Detection of recurrence in patients with rectal cancer: PET/CT after abdominoperineal or anterior resetion. *Radiology*. **2004**, *232*, 815–822. doi: 10.1148/radiol.2323031065.
75. Tan, E.; Gouvas, N.; Nicholls, R.J.; Ziprin, P.; Xynos, E.; Tekkis, P.P. Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer. *Surg. Oncol.* **2009**, *18*, 15–24. doi: 10.1016/ j.suronc. 2008.05.008