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Prognostic parameters in recurrent colorectal cancer: A role of control or restaging by FDG-PET/CT

Prognostički parametri u rekurentnom kolorektalnom karcinomu: uloga kontrole ili ponovnog određivanja stepena bolesti FDG-PET/CT-om

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Abstract

Background/Aim. Colorectal cancer ranks the third most frequent cancer in the world. Approximately 40% of the disease recurs after surgical resection. Determination of predictive parameters for recurrence may help in stratification of patients and contribute to patient management. There are still very few studies which sought factors to predict the recurrence of colorectal cancer. The aim of this study was to examine the predefined risk factors in metastatic development and evaluate clinical significance of 18F-fluorodeoxyglucose (FDG) uptake. **Methods.** The study was conducted with 56 patients for whom FDG-PET/CT (FDG-positron emission tomography/computed tomography) was requested for the suspicious recurrence or metastasis by routine conventional screening tests. Thirty three patients in whom recurrence/metastases were established with final histopathologic diagnosis formed the malignant group, and 23 patients with no recurrence/metastases formed the benign group. Risk factors [age, serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (Ca 19-9) levels, the maximum standardized uptake volume (SUVmax), tumor size (TS), CT/magnetic resonance imaging (MRI) findings, sex, primary tumor localization, lymphovascular invasion, perineural invasion (PNI), initial neoadjuvant therapy, lymph node initial metastasis (ILNM) excision, stage, tumor differentiation] were compared between these groups. **Results.** CEA, Ca 19-9, SUVmax, TS, PNI, ILNM, FDG uptake pattern, pattern of lesions on CT and tumor differentiation were found statistically significant by univariate analysis. After multivariate analysis, SUVmax and ILNM remained as the main risk parameters impacting recurrence/metastases. Mean SUVmax was 7.25 in the benign group, while it was 11.7 in the malignant group (p = 0.019). ILNM was present in 66.5% of patients in the malignant group, and in 30.5% of patients in the benign group (p = 0.015). For an estimated cut-off value of 6.3 and 12.5, respectively on ROC curve, the calculated specificities were 61% and 87%, respectively. **Conclusion.** ILNM and SUVmax are the main risk factors for recurrence of colorectal cancer and the patients with these factors must be followed up carefully. FDG-PET/CT is very sensitive for the detection of recurrence/metastases of colorectal cancer and SUVmax appears to improve its specificity.

Key words:
colorectal neoplasms; neoplasm staging; prognosis; radiopharmaceuticals; recurrence; sensitivity and specificity; tomography, emission-computed; tomography, x-ray computed.

Apstrakt

Uvod/Cilj. Kolorektalni karcinom se svrstava u treći najčešći karcinom na svetu. Kod približno 40% obolelih bolest se vraća posle hirurške resekcije. Određivanje prediktivnih parametara za relaps može pomoći u stratifikaciji i doprineti vođenju bolesnika. Još uvek je nedovoljan broj studija koje istražuju prediktivne faktore za relaps kolorektalnog karcinoma. Cilj rada bio je da se ispitaju prethodno definisani faktori rizika od razvoja metastaza i proceni klinički značaj preuzimanja 18F-fluorodeoksiglukoze (FDG). **Metode.** Studijom je bilo obuhvaćeno 56 bolesnika kojima je bilo potrebno uraditi FDG-PET/CT (FDG-pozitron emisionu tomografiju/kompjute-rizovanu tomografiju), zbog sumnje na relaps ili metastaze postevljene rutinskim testovima. Od 33 bolesnika kojima su finalnom patohistološkom dijagnozom utvrđeni relaps ili metastaze formirana je grupa sa malignitetima, dok je druga grupa ispitanika bila sa benignim promenama. Između te dve grupe ispitanika poređeni su sledeći faktori rizika: životno doba, serumski nivoi karcinoembrionskog antigena (CEA) i karbohidratni antigen 19-9 (CA 19-9), vrednost maksimalnog standardizovanog preuzimanja (SUVmax), veličina tumora, nalaz CT/magnetna rezonanca

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(MR), pol, primarna lokalizacija tumora, limfovaskularna invazija, perineuralna invazija (PNI), inicijalna neoadjuvantna terapija, inicijalna ekscizija metastatskih limfnih čvorova (ILNM), stadijum i diferencijacija tumora. **Rezultati.** Univarijantnom analizom utvrđena je statistička značajnost za CEA, Ca 19-9, SUVmax, veličinu tumora, PNI, ILNM, obrazac preuzimanja FDG, obrazac lezije na CT-u i diferencijacija tumora. Multivarijantnom analizom su SUVmax i ILNM utvrđeni kao glavni parametri rizika koji utiču na metastaze ili relaps. Srednji SUVmax iznosio je 7,25 u grupi bolesnika sa benignim promenama, a 11,7 u grupi sa malignitetima (p = 0,019). U grupi sa malignitetima ILNM je bio prisutan kod 66,5% ispitanika, a u grupi sa benignim promenama kod 30,5% ispitanika (p = 0,015). Za procenjeni *cut-off* od 6,3 i 12,5 na *Receiver Operating Characteristic* (ROC) liniji, izračunata specifičnost iznosila je 61% i 87%, redom. **Zaključak.** Glavni faktori rizika od relapsa kolorektalnog carcinoma su ILNM i SUVmax, zbog čega bolesnici sa tim faktorima rizika moraju biti pažljivo praćeni. Za otkrivanje relapsa ili metastaza kolorektalnog karcinoma FDG-PET/CT je veoma senzitivan test, a SUVmax poboljšava njegovu specifičnost.

Ključne reči:
kolorektalne neoplazme; neoplazme, određivanje stadijuma; prognoza; radiofarmaci; recidiv; osetljivost i specifičnost; tomografija, kompjuterizovana, emisiona; tomografija, kompjuterizovana, rendgenska.

Introduction

Colorectal cancer (CRC) ranks the third most frequent cancer and it was the fourth most frequent cause of cancer-related death in the world. Approximately 40% of the disease recurs after surgical resection of the primary tumor in two years [1]. There are some well-known predefined clinicopathological risk factors for recurrent/metastatic CRC. These are age, serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 levels, tumor depth (invasion), the maximum standardized uptake value (SUVmax) on FDG-PET/CD (18F-fluoro-deoxyglucose – positron emission tomography/computed tomography), tumor size (TS), CT/magnetic resonance imaging (MRI) findings, sex, primary tumor localization (PTL), lymphovascular invasion (LVI), perineural invasion (PNI), initial neoadjuvant therapy (INAT), initial lymph node metastasis (ILNM) excision at primary surgery (ILNM), stage, type of surgery, localization of metastasis (organ), cytogenetic factors, tumor differentiation (DIF). Detecting the recurrence is mandatory for convenient therapy. Different laboratory and imaging tests are handled to identify recurrent and/or metastatic CRC. Most guidelines recommend thoracoabdominal CT, routine serial carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (Ca 19-9) assays to monitor the disease [2].

CEA is expressed by a lot of epithelial tumors and its serum levels may rise in non-malignant disorders [3]. Nearly 70% of patients with CRC display an elevated CEA level at the time of diagnosis. This fact made it a routine monitoring marker for the disease recurrence [4]. Unfortunately, latest meta-analysis studies have declared conflicts about its utility in the detection of the recurrent disease. They are stating roundly sensitivities of 65% and specificities of 90% that can be considered poor for a biomarker [5]. Ca 19-9 assays have also a poor performance. It has been reported that Ca 19-9 was expressed only in 20%–40% of metastatic CRC [6].

Imaging has the key role in postoperative assessment of the metastatic disease. Molecular imaging with FDG-PET combined with CT is the most recent modality for this purpose [7]. The main limitation of CT and other morphological imaging techniques evaluating the recurrence of all types of cancers like CRC is size of the lesion and/or distortion of normal anatomic structures. FDG-PET/CT accomplishes this deficit by the capability to show recurrent CRC as in many other cancers, through pathologically increased tumor metabolism before the appearance of morphological changes [8]. As a glucose analogue, FDG reflects increased glucose consumption of cancer cells and a great majority of CRC are FDG-avid. FDG-PET/CT has been used for primary staging, evaluation of treatment response and restaging in CRC just like in many other cancers. It is more sensitive than conventional tests in patients with suspected recurrence and/or metastasis. But it has some intrinsic limitations. Inflammatory pathologies, fibrosis or edema following irradiation and/or surgery may cause increased FDG uptake [9, 10].

There are still very few studies which sought factors to predict the recurrence of CRC. The aim of this study was to examine the predefined risk factors in metastatic development and evaluate clinical significance of uptake on FDG-PET/CT during the follow-up after primary curative surgery and/or chemoradiotherapy for recurrence in patients with CRC.

Methods

This retrospective cohort study involved 56 patients treated at the Department of Nuclear Medicine and Department of General Surgery of a tertiary health care hospital between 2009 and 2016. Inclusion criteria were as follows: histopathologically established diagnosis of CRC by surgical specimen after primary surgery, pathological FDG uptake on control (evaluation of treatment response) or restaging by FDG-PET/CT requested for the suspicious recurrence or metastases by routine conventional screening tests in the follow-up, confirmation of all these abnormal uptakes by colonoscopy or histopathology. All cases were treated by surgery and/or chemoradiotherapy. The neoadjuvant chemotherapy was administered to the patients 6 weeks before the primary surgery and consisted of 5-fluorouracil. The files of the patients were retrieved from the archive and looked over retrospectively.

We evaluated the lesions on FDG-PET/CT in 56 patients. Indications for FDG-PET/CT were suspicion of recurrence/metastases (32 patients) and treatment response monitoring (24 patients). Elevated CEA and/or Ca 19-9 levels raised the suspicion of recurrence in 11 cases, conventional imaging in 21. All FDG uptakes were confirmed by colonoscopic

findings or histopathologically. The reference range of Ca 19–9 was 0–35 U/mL; normal range of CEA was < 2.5 ng/mL for nonsmokers, < 5 ng/mL for smokers. Tumors were staged by the seventh edition of the American Joint Committee on Cancer Classification. Predefined risk factors for recurrence were age, serum CEA and Ca 19–9 levels, SUVmax, TS, CT/MRI findings, sex, PTL, LVI, PNI, INAT, ILNM, stage, FDG uptake pattern (FDGP), pattern of lesions on CT (CTP), DIF. PTL was classified as distal rectum (4 cm), middle rectum (5–9 cm), rectosigmoid region, sigmoid (descending) colon and cecum-transverse/right colon. DIF was defined as low grade, moderate differentiation, high grade and mucinous component. FDGP was heterogeneous, diffuse or focal. CTP was soft tissue mass, wall thickening or hypodense lesion. Thirty three patients in whom recurrence/metastases were established with final histopathological diagnosis formed the malignant group, and 23 patients with no recurrence/metastases formed the benign group. The above-mentioned parameters were compared between these two groups.

FDG-PET/CT imaging protocol

Patients were hungry at least for 6 hours and their blood glucose levels were obliged to be below 150 mg/dL before the injection of an activity of 370–555 MBq of FDG calculated according to patient's body weight. Images were acquired one hour later with an integrated PET/CT scanner (Discovery 690-GE Healthcare). Unenhanced low dose CT and PET emission data were obtained from mid-thigh to the vertex of the skull in supine position with the arms raised over head. CT data were collected by an automated dose modulation of 120 kVp (maximal 100 mA) with the collimation of 64 × 0.625 mm, field of view (FOV) of 50 cm, noise index of 20%, reconstruction to images of 0.625 mm transverse pixel size and 3.75 mm slice thickness. PET data acquisition was performed in 3D mode with the scanning period of 2 min per bed position and an axial FOV of 153 mm. The emission data were corrected in a standardized way consisting of random, scatter and attenuation. Iterative reconstruction was done in a matrix size of 256 × 256 by Fourier rebinning and VUE Point FX [3D] with 3 iterations, 18 subsets).

Two nuclear medicine specialists unaware of patient history interpreted FDG-PET/CT images visually. Focally or heterogeneously increased FDG uptake, diffuse or heterogeneously increased FDG uptake and/or soft tissue mass on CT component, hypodense or nodular lesion on CT with or without FDG uptake, diffuse uptake accompanied by wall thickening, consolidation or ambiguous lesions on CT with or without uptake were supposed as pathologic. SUVmax corrected for body weight were computed by a standard protocol on a dedicated Workstation from the activity at the most intense voxel in three-dimensional tumor region from the transaxial whole-body images on attenuation-corrected PET/CT images. The corresponding CT scan of lesions was framed as a guideline if their boundaries were difficult to demarcate for the determination of SUVmax.

Statistical analysis

The whole data were analyzed by IBM Corporation Released 2013; IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY : IBM Corporation. Number and percentage values were used for the description of categorical data; mean, median, standard deviation (SD), minimum (min) and maximum (max) values for continuous data. Student's *t*-test (age) and Mann-Whitney *U* test (serum CEA and Ca19–9 levels, SUVmax, TS) were performed for categorical variables; Fisher's exact test (CT/MRI findings) and χ^2 test (sex, PTL, LVI, PNI, INAT, ILNM, stage, FDGP, CTP, DIF) for continuous variables in the univariate analysis. The parameters which were found statistically significant in univariate analysis were processed with multivariate analysis. The variables having a value of $p < 0.05$ were accepted as statistically significant. Reciever operating characteristic (ROC) curve was drawn to evaluate the diagnostic value of SUVmax on recurrent disease. Informed consent was deemed as a retrospective study using records, documents and data of patients referred to our clinic for the test. The study was approved by Our Institutional Review Board Committee.

Results

Mean age of the patient population was 58.2 ± 11.1 (30–89) years; 27 (48.2%) of them were males, and 29 (51.8%) females. PTL was distal rectum (11%), middle rectum (18%), rectosigmoid region (27%), sigmoid colon (16%) and cecum-transverse/right colon (28%). Mean serum Ca 19-9 and CEA levels, SUVmax, and TS were: 229.5 U/ml (median, range: 8.5, 0.1–5,548), 6.56 ng/mL (median, range: 2.19, 0.3–71), 9.9 ± 6.3 and 34.7 ± 19.7 mm, respectively. The incidence of LVI, PNI, ILNM were 62.5%, 37.5%, 52%, respectively. 55.5% of the patients were treated by INAT. 11% of the cases were at stage I, 27% at stage II, 37% at stage III, 25% at stage IV. 28.5% of the patients had heterogeneous FDG uptake, 25% diffuse uptake, 37.5% focal uptake and 10% no uptake. Soft tissue mass was seen in 50% of the cases, wall thickening in 34%, hypodense lesion in 16% on CT as CTP. 25% of the tumors were low grade ones, 57% moderately differentiated, 11% were high grade tumors and 7% with mucinous component.

CEA, Ca 19-9, SUVmax, TS, PNI, ILNM, FDGP, CTP and DIF were found statistically significant after the procession of all potential risk factors by univariate analysis. Univariate analysis of predefined potential risk factors (except PTL, FDGP, CTP, DIF) impacting on metastases/recurrence, their mean values and percentages between the benign group and malignant group are shown in Table 1. These factors (LVI was included instead of FDGP) entered multivariate analysis, and SUVmax and ILNM remained as the main risk parameters impacting metastases/recurrence (Table 2). Mean SUVmax was 7.25 in the benign group, while it was 11.7 in malignant group. There was a statistical difference according to SUVmax values between benign and malignant groups ($p = 0.019$). A box-plot graph shows the distribution of SUVmax in benign conditions versus recurrent/metastatic disease (Figure 1).

Table 1

Univariate analysis of some predefined potential risk factors impacting on metastases/recurrence, their mean values and percentages between the benign and malignant groups

Variable	Groups		
	malignant	benign	*p*-value
Mean age (years), mean ± SD	59 ± 11		0.711
Sex, %			
male	45.5	52.2	0.621
female	54.5	47.8	
Serum Ca 19.9 (U/mL), mean (median)	382 (11)	9.7 (7)	0.047
Serum CEA (ng/mL), mean (median)	9.42 (3.5)	2.45 (1.7)	0.009
SUVmax, mean ± SD	11.7 ± 6.2	7.25 ± 5.57	0.019
Mean tumor size (mm, ± SD)	39 ± 21.7	28.5 ± 14.7	0.038
CT/MRI findings, %			
positive	84.8	69.6	0.200
negative	15.2	30.4	
LVI, %			
present	72.7	52.2	0.058
absent	27.3	47.8	
PNI, %			
present	48.5	21.7	0.042
absent	51.5	78.3	
INAT, %			
yes	54.5	56.5	0.884
no	45.5	43.5	
ILNM, %			
present	66.5	30.5	0.015
absent	33.3	69.6	
Stage, %			
I	6.1	17.4	0.253
II	21.2	34.8	
III	45.5	26.1	
IV	27.3	21.7	

Ca – carbohydrate antigen; CEA – carcinoembryonic antigen; SUVmax – maximum standardized uptake value; CT – computed tomography; MRI – magnetic resonance imaging; LVI – lymphovascular invasion; PNI – perineural invasion; INAT – initial neoadjuvant therapy; ILNM – initial lymph node metastasis; SD – standard deviation.

Table 2

Multivariate logistic regression analysis of risk factors influencing recurrence in patients with colorectal cancer

Variable	B	Odds ratio	CI	*p*-value
SUVmax	0.136	1.146	1.022–1.284	0.019
ILNM	1.532	4.626	1.351–15.834	0.015

SUVmax – maximum standardized uptake value; ILNM – initial lymph node metastasis; CI – confidence interval.

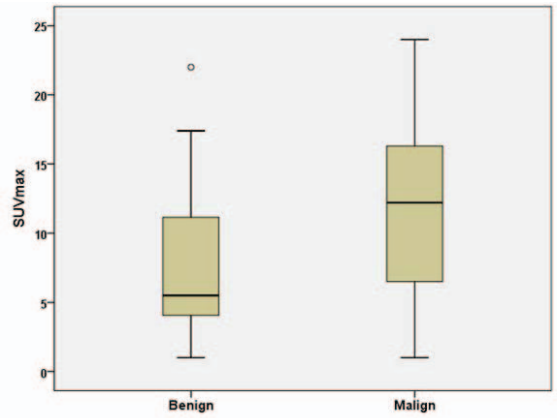

Fig. 1 – Box-plot graph of the distribution of maximum standard uptake value (SUVmax) in the benign conditions versus recurrent/metastatic disease.

ILNM was present in 66.5% of malignant group, 30.5% in benign group and there was a statistical significance between them ($p = 0.015$). A bar graph depicts the presence of ILNM in benign and malignant groups (Figure 2).

There was not a statistically significant difference between the malignant and benign groups according to PTL ($p = 0.944$). FDGP, CTP and DIF were statistically meaningful in the univariate analysis between the malignant and benign groups ($p = 0.014$, $p = 0.006$ and $p = 0.037$, respectively). Focal FDG uptake was present in 81% of recurrence whereas diffuse uptake was seen in 64% of the patients in the benign group. Soft tissue mass on CT was the main pattern (78.5%) in the malignant group, while wall thickening was present in 68.5% of the patients in the benign group. High grade and mucinous component were a clear risk factor for recurrence/metastases. ROC curve for SUVmax was drawn (Fig-

ure 3). AUC (area under curve) was 0.717 [confidence interval (CI): 0.581–0.854] (p = 0.006). Sensitivities and specifities for chosen cut-off values were represented in Table 3.

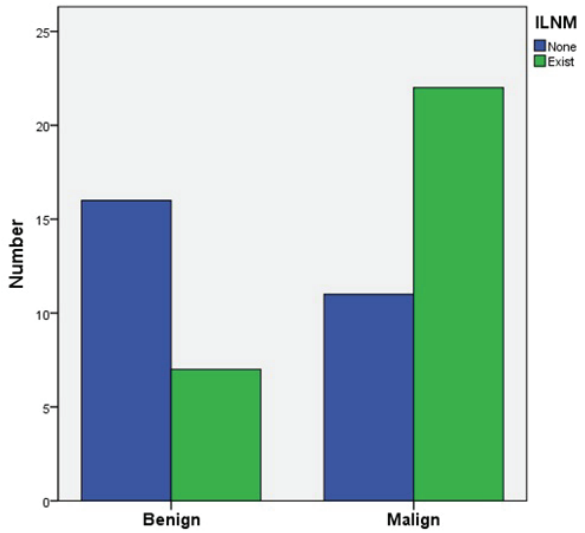

Fig. 2 – Bar graph of initial lymph node metastasis (ILNM) in the benign and malignant groups.

Recurrence and/or metastases developed in 59% of the patients (Figure 4). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FDG-PET/CT for the detection of recurrence and/or metastases were 91%, 56.5%, 75% and 81%, respectively. FDG-PET/CT results and final histopathologic diagnosis are shown in Table 4.

FDG-PET/CT was true positive in 45% of the patients with normal Ca 19-9 and/or CEA levels and true negative in 12% of cases with elevated Ca 19-9 and/or CEA levels according to histopathologic confirmation or colonoscopy findings. In the follow-up, CT or MRI detected suspicious malignancy in 50% of the patients (28/56) and further examination with FDG-PET/CT was true negative in 32% of these cases (9/28) according to histopathology.

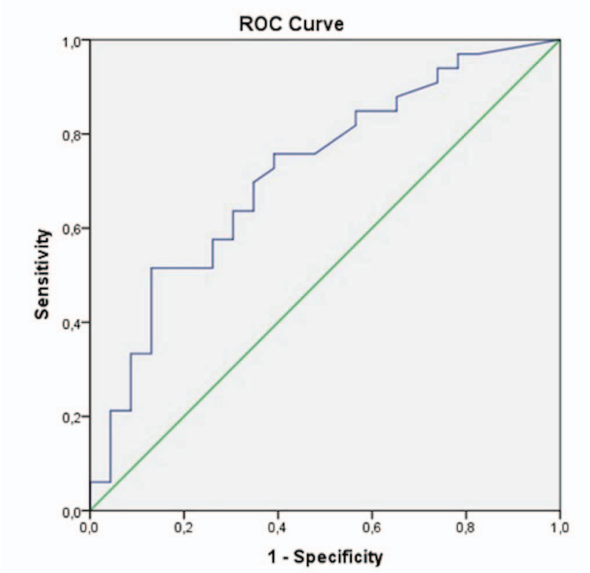

Fig. 3 – Recieved operating characteristic (ROC) curve for the maximum standardized uptake value (SUVmax).

Table 3

Cut-off values, related sensitivities and specificities of SUVmax for recurrence

Cut-off values	Sensitivity (%)	Specificity (%)	Area under curve (95% confidence interval)
12.5	51	87	0.717 (0.581–0.854)
6.3	76	61	

SUVmax – maximum standardized uptake value.

Table 4

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FDG-PET/CT according to final histopathologic diagnosis

Histopathologic diagnosis	FDG-PET/CT results						
	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Total (n)
Malignant (n)	TP = 30	FN = 3					33
Benign (n)	FP = 10	TN = 13					23
Total (n)	40	16	91%	56.5%	75%	81%	56

TP – true positive; FP – false positive; FN – false negative; TN – true negative; FDG – 18F-fluoro-deoxyglucose; PET – positron emission tomography; CT – computed tomography.

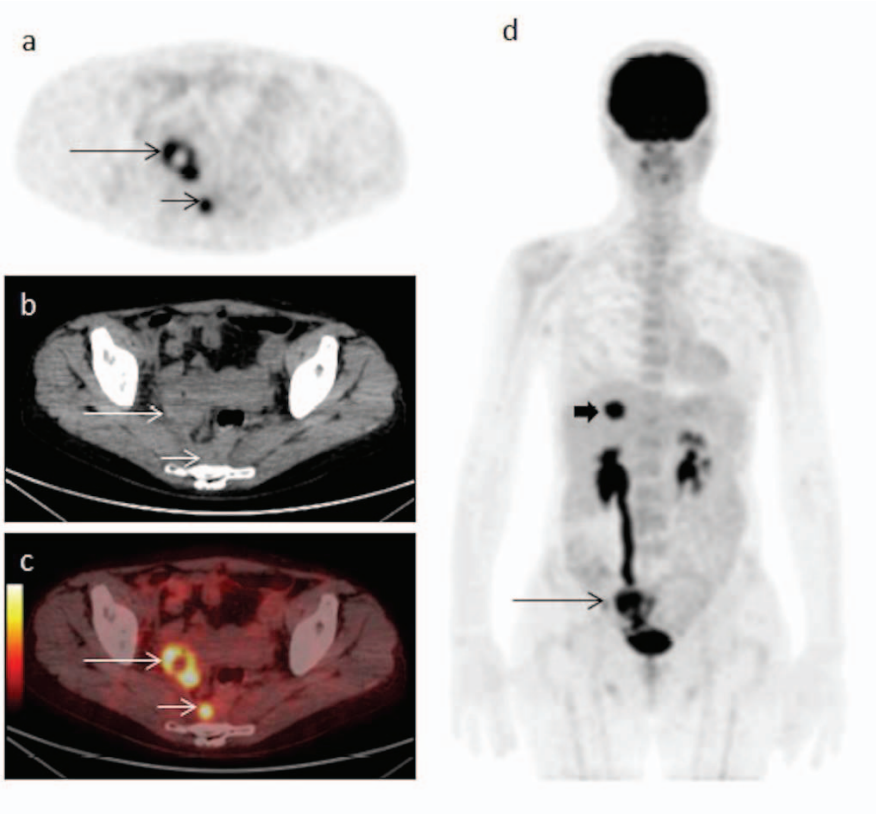

Fig. 4 – A female patient aged 67 years with rectal cancer was operated and treated by chemoradiotherapy. Her axial PET (A), CT (B), fusion (C) and maximum intensity projection (MIP) (D) images on FDG-PET/CT exhibited circular FDG uptake in the rectum (long arrow) with a SUVmax of 10.1 and TLG of 154 accompanied by wall thickening on the CT component. Besides, there was focal FDG uptake in the presacral area (short arrow) which was considered as metastatic lymph node (SUVmax: 9.6). These uptakes raised the suspicion of a probable recurrence and histopathology confirmed both of them as malignant. In whole body MIP images there was a metastatic foci in the liver showing FDG uptake (thick arrow) (SUVmax: 8.8).
PET – positron emission tomography; CT – computed tomography; FDG – 18F-fluoro-deoxyglucose; SUVmax – maximum standardized uptake value; TLG – total lesion glycolysis.

Discussion

Recurrent disease is seen in 30%–50% of patients with CRC after curative resection [11]. The recurrence rate was 59% in our study and it is higher than those described in literature. The most frequently encountered location of recurrence occurs in the area of surgery [12] and our findings were in agreement with this. Primary aim of follow-up surveillance is to identify recurrences at the earliest moment for an immediate cure. Most of the relapsed cases are not operable at the time of diagnosis and 1/3 of the patients with isolated locoregional or distant metastases survive 5 years [13]. Determination of predictive parameters for recurrence may help in stratification of patients and contribute to patient management with intense follow-up. FDG-PET/CT finding may be a prognostic factor and change treatment planning in CRC [14].

Mean age of CRC patients fluctuates around 60 years and younger ages are accepted as a risk factor for recurrence in literature [11]. Average age of our patient population was 58 years and this is in accordance with previous studies. But we observed that age is not a risk factor in our study. Many articles explained stage and LVI as having association with recurrent CRC. Kobayashi et al. [15] evaluated stage of the disease in 5,230 consecutive patients and found advanced stage a risk factor. Ryuk et al. [1] found high postoperative Ca 19-9 level, LVI, ILNM and advanced stage as risk factors for recurrence. Interestingly, we did not identify stage and LVI as statistically significant in the univariate analysis ($p = 0.253$ and $p = 0.058$, respectively). This is possibly due to undersampling or inconvenient data for statistics and not important clinically. PTL is a risk factor in many papers and recurrence in right colon is more incident [16]. However, PTL was not a meaningful prognosticator in our study and this is contrary to previous reports.

High serum CEA and Ca 19-9 levels assayed at follow-up after curative resection are prognostic factors for CRC [17]. They were also risk factors in our study ($p = 0.009$ and $p = 0.047$, respectively). But FDG-PET/CT yielded true positive results at a rate of 45% in patients whose Ca 19-9 and/or CEA levels were normal while it was true negative just in 12% of the cases with elevated Ca 19-9 and/or CEA levels according to histopathological confirmation. The relationship of recurrence with the use of neoadjuvant therapy is still unclear [18]. It was not a significant parameter in our study. Tsai

et al. [19] determined PNI as the most important factor in their study on 778 patients. Tsai et al. [20] showed that DIF, ILNM, LVI, PNI were risk factors in their study on 259 patients. Our findings are in agreement with them, except for LVI.

It has been reported that FDG-PET/CT is more accurate than CT or MRI for establishing recurrence in several studies. Odalovic et al. [21] found FDG-PET/CT more sensitive and specific than MRI. Scott et al. [22] showed that FDG-PET/CT detected 45 additional lesions in a multicenter prospective trial conducted on 93 patients. Detection of a lesion on CT/MRI was not a risk factor ($p = 0.200$) and FDG-PET/CT was more sensitive than CT/MRI findings at the follow-up in our study. It was true negative in 32% (9/28) of the cases on whose CT or MRI were seen lesions which were suspicious of malignancy according to histopathology. TS and DIF (undifferentiated high grade tumors and mucinous component) are clear risk factors for recurrence/metastases [23]. It is well-known that malignant lesions usually appear as focal FDG uptake with a soft tissue mass on FDG-PET/CT whereas diffuse uptake accompanied by wall thickening on CT component is mostly the main pattern in benign conditions [24]. Recurrences tend to occur in large and high grade tumors with usually focal FDG uptake accompanied by a soft tissue mass on CT component. FDGP, CTP and DIF were statistically meaningful in the univariate analysis between the malignant and benign groups in the study ($p = 0.014$, $p = 0.006$ and $p = 0.037$, respectively). ILNM is a strong predictor for recurrence in almost every study and it was the cutest factor together with SUVmax in the univariate analysis ($p = 0.008$ and $p = 0.006$, respectively). At the same time, they came out from the multivariate analysis as the only predictors impacting recurrence/metastases amongst all risk factors ($p = 0.015$ and $p = 0.019$, respectively). All our results are in line with these ones.

The use of FDG-PET/CT in the follow-up of CRC is controversial. Recent data recommend no indication except inconclusive CT with suspicion of distant metastases or in the presence of negative CT and serial CEA increase [12]. Many studies declared that FDG-PET/CT is very sensitive, but not so specific for the detection of recurrence of CRC. It has some limitations. FDG is accumulated in cancer cells at a relatively higher rate during glucose metabolism. However, cancer cells are not the only metabolically hyperactive ones. Inflammatory, infectious and some non-neoplastic diseases can have increased FDG accumulation causing a low specificity for CRC [25] as it was also seen in our study. The benign pathologies in our study consisted of granulation tissue, fibrin and inflammation, fibrosis, pyelonephritis, ulceration of colonic mucosa, fibrosis and inflammation, polyps, secondary changes to radiotherapy or operation. Lots of benign conditions like ours and physiologic FDG uptakes exhibiting focal or diffuse FDG accumulations in gastrointestinal tract can be seen in patients with CRC during the follow-up and confused with true pathologic lesions. It is essential to distinguish them by colonoscopic biopsy. Previously some quantitative parameters based on volume-of-interest FDG uptake were introduced to augment its diagnostic accuracy in several cancers. SUVmax is the first one. Determination of a cut-off level of SUVmax which differentiates between benign conditions and recurrence would certainly be helpful in CRC.

We investigated the value of SUVmax for the discrimination between the benign and malign conditions. Gade et al. [7] found a lower mean SUVmax of 8.6, Marcus et al. [26] of 7.3 in recurrent CRC when compared to our mean SUVmax of 12.7. Shamim et al. [27] found a significant increase of mean SUVmax in recurrence (11.8 for recurrence versus 3.7 for benign conditions) in a study on 32 patients with CRC. These values were 11.7 for the recurrence against 7.2 for the benign group in our study and this difference was statistically significant. Our results revealed that SUVmax was very helpful in the differentiation of the recurrent disease from benign conditions and it improved the diagnostic accuracy of FDG-PET/CT. For an estimated cut- off value of 6.3 and 12.5 on ROC curve, the calculated specificities were 61% and 87%, respectively. According to our findings, SUVmax was very beneficial for increasing the specificity when compared with that of FDG-PET/CT alone (56.5%).

Several studies reported that neighboring organ invasion and depth of tumor infiltration were significant prognostic factors for postoperative recurrence and survival rate in patients with CRC undergoing curative resection [23]. Although the depth of wall invasion by the primary tumor is an important prognostic factor, we could not research it due to lack of sufficient data and this was a limitation in our study. Small patient number and study design were also inevitable limitations. Ideally, prospective studies with large numbers are needed. There was a slight selection bias for our patient population. Lack of some other risk factors (type of surgery, localization of metastasis, especially cytogenetic factors) affecting recurrence/metastases are the other limitations.

Conclusion

ILNM and high SUVmax values on the control or restaging FDG-PET/CT are the main risk factor in recurrent CRC and patients with these risk factors must be followed up carefully. FDG-PET/CT is very sensitive for the detection of recurrence/metastases and SUVmax appears to improve its specificity.

Conflict of Interest

No conflict of interest was declared by the authors.

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