Assessment of Metabolic Tumor Burden in Primary Staging of Rectal Cancers Using Fdg Pet/ct

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Abstract

INTRODUCTION

The prognostic value of FDG PET/CT metabolic tumor burden has been established in various solid tumors, but its significance in the staging of rectal cancer remains underexplored. This study aimed to investigate the prognostic role of FDG PET/CT metabolic tumor burden in the primary staging of rectal cancer.

METHODS

A retrospective analysis was conducted on 82 consecutive histology-proven rectal cancer patients, including 29 females (37%), with a mean age of 60.8 years. These patients underwent staging FDG PET/CT, and various metabolic tumor burden parameters (hSUVmax, tuMTV, wbMTV, tuTLG, wbTLG) were calculated. The study assessed the correlation between metabolic tumor burden parameters and overall survival (OS), progression-free survival (PFS), as well as histopathology, clinical staging, performance status, bone-mineral indexes, hematology, and therapy management strategies.

RESULTS

The study revealed that metabolic tumor burden, along with the presence of sarcopenia and absence of surgery, were significantly and independently associated with overall survival. Notably, a wbTLG cutoff value of 354 effectively discriminated survivors from non-survivors ($p = 0.0007$) with 83% specificity. Furthermore, higher whole-body tumor burden (wbTLG: $p = 0.0090$) and low body mass index ($p = 0.0231$) were significantly linked to an increased risk of disease progression.

CONCLUSIONS

This research suggests that whole-body tumor burden assessed through staging FDG PET/CT can serve as an independent imaging biomarker for prognostication in rectal cancer patients.

INTRODUCTION

Colorectal cancer is the 3rd most frequent malignant neoplasia in men and the 2nd in women. It is also the 4th cause of death by cancer in men and the 3rd in women [1]. In 2021, it was estimated that there would be approximately 149,500 newly diagnosed cases of colorectal cancer in the United States. Among these cases, approximately 45,230 were expected to be rectal cancers, with 60% occurring in men and 40% in women [2]. Colorectal cancers are nowadays responsible for approximately 10% of cancer-related mortality in Western countries and their incidence is rising due to population aging, inadequate eating habits, smoking, sedentary behavior, and obesity [3]. Colorectal cancers occur mainly above 50 years of age with an age-standardized mortality rate two times higher in developed countries than in developing countries [4]. Rectal cancer accounts for approximately one-third of all colorectal cancers.

Despite the ongoing challenge of improving long-term survival rates in rectal cancer, significant progress has been made in individualized staging techniques that facilitate the implementation of appropriate therapeutic strategies [5–9]. The incorporation of rectal radiotherapy and neoadjuvant and palliative chemotherapy has played a crucial role in enhancing patients' quality of life and extending disease-free and overall survival [10].

Fluorine-18 fluoro-deoxy-glucose (^{18}F-FDG) positron emission tomography combined with computed tomography (FDG PET/CT) has an important role in rectal cancer staging [11–14] when compared to conventional methods, shifting both staging and management in up to one-third of the patients [15, 16]. However, the application of FDG PET/CT metabolic tumor burden parameters (such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG)) to determine its prognostic value on rectal cancer primary staging remains a relatively underexplored field [17–19].

The metabolic tumor burden objective metrics could, potentially, turn the visual findings into tangible data, contributing to better stratification, and personalizing and improving therapeutic decisions. Therefore, unnecessary morbidity could be proscribed, and solid objective arguments could be used to justify the need for invasive procedures.

Therefore, the study aimed to establish if FDG PET/CT metabolic tumor burden parameters have a prognostic role in the primary staging of rectal cancers.

METHODS

Study Design

This study was approved by the local Institutional Review Board (CAEE 03925318.4.0000.5404) and the patient informed consent was waived for this retrospective analysis. We retrospectively reviewed the baseline staging FDG PET/CT images of consecutive patients with rectal cancer between November 2013 and December 2017 and determined the metabolic tumor burden (MTV and TLG) indexes. We compared these metrics with clinical patient data and outcome measures.

The primary endpoints were to correlate whole-body metabolic tumor burden parameters obtained in staging FDG PET/CT with overall survival (OS) and progression-free survival (PFS). OS was established from diagnosis until the date of death from any cause or last follow-up; PFS was established from diagnosis until the date of objective tumor progression, death of any cause, or last follow-up. Objective disease progression was defined clinically, based on imaging findings of new lesions, lesions that increased in size, and physical examination findings leading to a change in current therapy or death during chemotherapy.

The secondary aims were to compare the metabolic tumor burden parameters with histopathology, clinical staging, performance status, bone-mineral indexes, neutrophil-to-leucocyte ratio, platelet ratio, and change in therapy management.

Patient Population

All patients with histopathology-confirmed rectal cancer submitted to an FDG PET/CT study for primary staging between November 2013 and December 2017 were included in the study.

Exclusion criteria consisted of age below 18 years; missing clinical data related to outcome measures; patients with a second primary cancer; patients in which the staging FDG PET/CT study was completely negative because of an emergency tumor removed before imaging.

The data, collected from electronic medical records [20] consisted of clinical parameters (age, sex, performance status at diagnosis, body composition [21], body mass index, weight loss, alcoholism, smoking, clinical stage according to the 8th AJCC cancer manual [22], clinical presence of metastases, sarcopenia as previously described by our group [23], tumor parameters (location, histopathology type, histopathology stage, vascular and neural invasion, resection margins, K-RAS mutation, presence of lymph node metastases), treatment strategies (surgery of the primary lesion, neoadjuvant and adjuvant therapy, metastasectomy) and biochemical laboratory tests at diagnosis (hemoglobin, ANC, lymphocytes, monocytes, platelets, CEA).

FDG PET/CT

Before the injection of fluorine-18 fluoro-deoxy-glucose (^{18}F-FDG), all patients were required to fast for 6 hours (except for stimulated hydration) and the serum glucose levels had to be below 180 mg/dl. FDG PET/CT images were acquired 60 minutes after the injection of 7.77 MBq/kg of ^{18}F-FDG, from the vertex to the thighs on a dedicated PET/CT scanner (Biograph mCT40, Siemens Healthcare, USA®). CT parameters included 5 mm axial reconstruction with the care dose. PET was acquired in 3D mode at 90 seconds/bed. Images were reconstructed and displayed in the transverse, coronal, and sagittal planes.

PET/CT Interpretation and Quantification

FDG PET/CT images were analyzed by two board-certified Nuclear Medicine physicians. Quantitative interpretation (MFS VB20, syngo.via MM Oncology, Siemens Medical Solutions USA®) was performed on all PET/CT images to determine the whole-body tumor burden.

Briefly, the technique consists of placing a rectangular semi-automatic volume of interest (VOI) in the whole-body coronal image with caution to encompass all metastatic sites. After the whole-body VOI was drawn, the cutoff SUVmax was set at ≥ 2.5, and the SUVmax threshold was set at 41% [24].

By establishing the threshold SUVmax value, the VOIs automatically encircled all lesions and excludes all other sites with uptake below the pre-established threshold. Images were then evaluated to manually exclude any sites of high uptake not related to a rectal primary lesion or rectal metastases, such as physiologic uptake or other benign diseases.

Afterward, volumetric parameters of ^{18}F-FDG uptake were automatically acquired from the statistics generated within the final volumetric extraction Fig. 1.

The following parameters were obtained:

1. *h*SUVmax: highest SUVmax among all cancer lesions;
2. *tu*MTV: primary tumor metabolic tumor volume;
3. *tu*TLG: primary tumor total lesion glycolysis;
4. *wb*MTV: whole-body metabolic tumor volume;
5. *wb*TLG: whole-body total lesion glycolysis.

Statistical Analyses

Frequencies and percentages were provided for categorical variables; mean (std.dev) and median (range) were provided for continuous variables.

Cox proportional hazards regression was used to analyze predictors of overall survival and progression-free survival. Initially, a univariate analysis was undertaken with all variables and subsequently the most significant variables were selected in order to perform multivariable analysis.

The ROC curve analysis was used to establish cutoff values in the wbTLG and tuTLG parameters that discriminated survivors from non-survivors.

Statistical analysis was performed using SAS 9.4 for Windows (SAS Institute Inc, 2002–2012, Cary, NC, USA).

The significance level adopted for the study was 5%.

RESULTS

Patient Population Data

A total of 101 patients underwent an ^{18}F-FDG PET/CT study for primary staging in our institution between November 2013 and December 2017. Nineteen patients were excluded because of the following reasons: lost to follow-up; second primary cancer or a biopsy that removed the entire primary lesion. Therefore 82 patients were eligible for subsequent analysis. There were 52 males (63%) and 29 females (37%) with a mean age of 60.8 years.

The clinical stage of the patients was as follows: TxNxM0 = 1 (1.2%); Stage I = 10 patients (12.2%); Stage II = 13 patients (15.8%); Stage III = 33 patients (40.3%); and Stage IV = 25 patients (30.5%). The ECOG status was 0 in 66 (80.5%) patients and 1 in 16 (19.5%) patients. There were no patients in ECOG 2 and 3. Histopathology identified adenocarcinoma in 76 patients (92.7%) and mucinous type in 6 patients (7.3%).

Neural invasion was present in 16 patients and vascular invasion in 15 patients. The demographic data are displayed in Table 1.

Table 1
Clinical and tumor characteristics of 82 rectal cancer patients.

Variables		N	Frequency
Sex	Male	52	63%
	Female	30	37%
Ethnicity	Caucasian	64	78.0%
	Afro	4	4.9%
	Mixed	13	15.9%
	Oriental	1	1.2%
Smoking	Yes	42	51.9%
	No	39	48.1%
Alcoholism	No	55	68.8%
	Yes	25	31.3%
Diabetes	No	71	86.6%
	Yes	11	13.4%
Weight Loss	None	24	29.3%
	< 10%	23	28.0%
	> 10%	35	42.7%
Family History of Rectal Cancer	No	59	74.7%
	Yes	20	25.3%
Familial Polyposis	Yes	0	0.0%
	No	81	100.0%
Rectal tumor location	Low	49	59.8%
	Mid	30	36.6%
	High	3	3.7%
Histology	Adenocarcinoma	76	92.7%
	Mucinous	6	7.3%
ECOG at Diagnosis	0	66	80.5%
	1	16	19.5%
Sarcopenia	No	67	81.7%

	Yes	15	18.3%
Body Mass Index (BMI) in kg/m^2	18.5–24.9	32	39.0%
	25.0-29.9	30	36.6%
	> 30.0	14	17.1%
	< 18.5	6	7.3%
KRAS Mutation	No	5	41.7%
	Yes	7	58.3%
CEA at Diagnosis (ng/mL)	< 5.0	29	37.2%
	> 5.0	49	62.8%
Clinical Stage	I	10	12.2%
	II	13	15.9%
	III	33	40.2%
	IV	25	30.5%
	TxNxM0, Tis, T0N0M0	1	1.2%
Surgery of the Primary Lesion	No	23	28.4%
	Yes	58	71.6%
Pathologic Stage	TisN0M0, TxNxM0	0	0.0%
	I	14	24.1%
	IIA	14	24.1%
	IIB	2	3.4%
	IIC	0	0.0%
	IIIA	1	1.7%
	IIIB	13	22.4%
	IIIC	3	5.2%
	IVA	7	12.1%
	IVB	2	3.4%
	T0N0M0	2	3.4%
Tumor Differentiation	I	12	14.8%
	II	68	84.0%

	III	1	1.2%
Vascular Invasion	No	43	74.1%
	Yes	15	25.9%
Neural Invasion	No	41	71.9%
	Yes	16	28.1%
Negative Resection Margins	No	6	10.9%
	Yes	49	89.1%
Pathologic T stage	T0 / Tis	3	5.3%
	T1	3	5.3%
	T2	12	21.1%
	T3	31	54.4%
	T4a	4	7.0%
	T4b	4	7.0%
Pathologic N stage	N0	37	48.7%
	N1	22	28.9%
	N2	17	22.4%
Clinical M stage	M0	57	70.4%
	M1	24	29.6%
Neoadjuvant Chemotherapy	No	15	18.3%
	Yes	67	81.7%
Adjuvant Chemotherapy	No	50	62.5%
	Yes	30	37.5%
Metastasectomy	No	60	85.7%
	Yes	10	14.3%
Progression	No	48	58.5%
	Yes	34	41.5%

Univariate and multivariable analysis of FDG PET/CT Metabolic Tumor Burden versus Overall Survival

The univariable analysis for OS showed that the increased risk of death was significantly associated with serum levels of CEA (p = 0.0054), hemoglobin (p = 0.0074), absolute neutrophil counts (p = 0.0170),

monocytes ($p = 0.0085$) and platelet counts ($p = 0.0234$) at diagnosis. This risk of death was also increased in patients with the following characteristics at initial staging: the presence of sarcopenia ($p = 0.0499$), lower body mass indexes ($p = 0.0082$), and M-stage disease ($p = 0.0010$). All metabolic tumor burden parameters had a significant relationship with death (tuMTV: $p = 0.0096$; tuTLG: $p = 0.0033$; wbMTV: $p = 0.004$; wbTLG: $p < 0.0001$) (Table 2).

Table 2
– Univariate and multivariate analysis of death and variables.

Univariable Analysis		**P-value**	**HR**	**CI**
Age at diagnosis (years)		0.1935	1.022	0.989; 1.056
CEA at diagnosis (ng/mL)		**0.0054**	1.003	1.001; 1.005
Hemoglobin at diagnosis (g/dL)		**0.0074**	0.794	0.671; 0.940
ANC at diagnosis (/mcL)		**0.0170**	1.300	1.048; 1.612
Lymphocytes at diagnosis (10^9/L)		0.8259	0.940	0.542; 1.631
Monocytes at diagnosis (10^9/L)		**0.0085**	10.614	1.826; 61.701
Platelets at diagnosis (10^9/L)		**0.0234**	1.004	1.001; 1.007
Metastatic lymph nodes		0.7446	0.960	0.750; 1.228
FDG PET/CT primary tumor burden	tuSUVmax	0.9920	1.000	0.961; 1.040
	tuMTV	**0.0096**	1.018	1.004; 1.031
	tuTLG	**0.0033**	1.002	1.001; 1.003
Whole-body tumor burden	wbMTV	**0.0004**	1.005	1.002; 1.007
	wbTLG	**< .0001**	1.001	1.000; 1.001
Rectal tumor location	Low vs Mid	0.8420	1.083	0.495; 2.370
	Low vs High	0.8600	0.834	0.110; 6.299
Histology	Adeno vs Mucinous	0.8581	0.876	0.206; 3.724
ECOG at Diagnosis	0 vs 1	0.1102	2.043	0.850; 4.911
Sarcopenia	No vs Yes	**0.0499**	2.306	1.000; 5.318
Body Mass Index (BMI) (kg/m^2)	18.5–24.9 vs 25.0–29.9	**0.0096**	3.524	1.359; 9.142
	18.5–24.9 vs > 30.0	**0.0379**	4.811	1.092; 21.200
	< 18.5 vs 18.5–24.9	**0.0082**	4.206	1.451; 12.193
CEA at diagnosis (ng/mL)	< 5.0 vs > 5.0	0.5788	1.271	0.545; 2.967
Tumor Differentiation	I vs II + III	0.9011	1.065	0.397; 2.855
Vascular Invasion	No vs Yes	0.5548	1.455	0.419; 5.053
Neural Invasion	No vs Yes	0.6448	1.338	0.388; 4.614

KRAS Mutation, Clinical Stage and Pathologic T stage excluded from analyses.

Univariable Analysis		**P-value**	**HR**	**CI**
Negative Resection Margins	No vs Yes	0.2546	0.400	0.082; 1.936
Pathologic T stage	N/A	N/A	N/A	N/A
Pathologic N stage	N0 vs N1	0.3431	0.598	0.206; 1.733
Clinical M stage	N0 vs N2	0.4816	1.433	0.526; 3.903
	M0 vs M1	**0.0010**	3.607	1.681; 7.742
Multivariable Analysis		P-value	HR	CI
FDG PET/CT	tuMTV	**0.0096**	1.018	1.004; 1.031
primary tumor burden	tuTLG	**0.0033**	1.002	1.001; 1.003
FDG PET/CT	wbMTV	**0.0004**	1.005	1.002; 1.007
whole-body tumor burden	wbTLG	**< .0001**	1.001	1.000; 1.001
Body Mass Index (kg/m^2)	< 18.5 vs 18.5–24.9	**0.0065**	5.181	1.583; 16.955

KRAS Mutation, Clinical Stage and Pathologic T stage excluded from analyses.

In the multivariable analysis, only the metabolic tumor burden, the presence of low BMI, were associated with reduced overall survival. Because MTV and TLG are highly associated, only using the TLG parameter was evaluated to discriminate the risk of death. Patients with wbTLG above 354 had a significantly (p = 0.0007) increased risk of death (HR = 3.689; 95%CI = 1.732;7.857) (Fig. 2). Likewise, a tuTLG *cutoff* value of 305 also significantly (p = 0.0204) increased risk the of death (HR = 2.599; 95%CI = 1.159;5.826) (Fig. 3).

Univariate and multivariable analysis of FDG PET/CT Metabolic Tumor Burden versus progression-free survival (PFS)

Univariable analysis for PFS demonstrated significantly higher recurrence rates in patients with serum levels of CEA (p = 0.0028), absolute neutrophil counts (p = 0.0052), monocytes (p = 0.0676), and platelets (p = 0.0055) at diagnosis, vascular invasion (p = 0.0109), neural invasion (p = 0.0045). This risk of progression was also increased in patients with the following characteristics at initial staging: lower body mass indexes (p = 0.0008), the presence of metastases (p = 0.0208). The risk of progression was also directly related to *wb*MTV (p = 0.0099) and *wb*TLG (p = 0.0161).

In a multivariable analysis, only whole-body tumor burden (*wb*MTV: p = 0.0478), the presence of low body mass index (p = 0.0231) were independently associated with increased risk of progression (Table 3).

Table 3
– Univariate and multivariate analysis of progression and variables.

		P-value	HR	CI
Age at diagnosis (years)		0.4732	0.990	0.963;1.018
CEA at diagnosis (ng/mL)		**0.0028**	1.003	1.001;1.005
Hemoglobin at diagnosis (g/dL)		0.4543	0.937	0.790;1.111
ANC at diagnosis (/mcL)		**0.0052**	1.324	1.088;1.611
Lymphocytes at diagnosis (10^9/L)		0.7062	1.094	0.684;1.750
Monocytes at diagnosis (10^9/L)		**0.0676**	4.771	0.893;25.489
Platelets at diagnosis (10^9/L)		**0.0055**	1.004	1.001;1.008
Metastatic lymph nodes		0.7465	1.020	0.907;1.146
FDG PET/CT primary tumor burden	tuSUVmax	**0.0418**	0.958	0.919;0.998
	tuMTV	0.1528	1.011	0.996;1.027
	tuTLG	0.7817	1.000	0.999;1.002
Whole-body tumor burden	wbMTV	**0.0099**	1.003	1.001;1.005
	wbTLG	**0.0161**	1.000	1.000;1.001
Rectal tumor location	Low vs Mid	0.2296	1.538	0.762;3.106
	Low vs High	0.3276	2.079	0.480;8.998
Histology	Adeno vs Mucinous	0.4358	0.566	0.135;2.367
ECOG at Diagnosis	0 vs 1	0.8332	0.903	0.348;2.339
Sarcopenia	No vs Yes	0.3892	1.442	0.627;3.319
Body Mass Index (BMI) (kg/m^2)	18.5–24.9 vs 25.0–29.9	**0.0008**	4.360	1.839;10.337
	> 30.0 vs 18.5–24.9	0.0768	0.427	0.167;1.096
	< 18.5 vs 18.5–24.9	0.3806	1.753	0.500;6.143
KRAS Mutation	No vs Yes	0.8874	0.897	0.199;4.040
CEA at diagnosis (ng/mL)	< 5.0 vs > 5.0	0.4933	1.288	0.624;2.658
Surgery of Primary Lesion	No vs Yes	0.4668	0.752	0.349;1.620
Tumor Differentiation	I vs II + III	0.6278	1.295	0.455;3.687

Clinical Stage and Pathologic Stage excluded from analyses.

		P-value	HR	CI
Vascular Invasion	No vs Yes	**0.0109**	2.873	1.275;6.473
Neural Invasion	No vs Yes	**0.0045**	3.134	1.426;6.889
Negative Resection Margins	No vs Yes	0.2476	0.527	0.178;1.560
Pathologic T stage	N/A	N/A	N/A	N/A
Pathologic N stage	N0 vs N1	0.7674	1.133	0.495;2.596
	N0 vs N2	0.1174	1.935	0.847;4.419
Clinical M stage	M0 vs M1	**0.0208**	2.297	1.135;4.648
Multivariable Analysis		P-value	HR	CI
FDG PET/CT	wbMTV	**0.0478**	1.003	1.000; 1.006
whole-body tumor burden	wbTLG	**0.0090**	1.000	1.000; 1.001
Body Mass Index (kg/m^2)	< 18.5 vs 18.5–24.9	**0.0231**	6.944	1.304; 36.964
Clinical Stage and Pathologic Stage excluded from analyses.				

DISCUSSION

In rectal cancer patients, whole-body metabolic tumor burden on a staging FDG PET/CT is an independent predictor of overall survival and progression-free survival. The use of PET/CT for primary staging may strategically help establish the best treatment options. Each unit increase of the wbTLG significantly augmented 3.6 times the risk of death ($p < 0.0007$).

There is a scarce amount of data evaluating specifically whole-body metabolic tumor burden for rectal cancer staging. Most of the available investigations are related to colorectal cancer, not specifically rectal cancer, and quantify the metabolic tumor burden of the primary tumor, not the whole-body metabolic tumor burden. Nevertheless, our data are consistent with a few investigations related to colorectal cancer, such as the study by Xu et al [25]. The authors performed FDG PET/CT for the primary staging of colorectal cancer and determined the metabolic tumor volume of the primary tumor. They showed that MTV has a strong relationship with prognosis; patients with low MTV had a significantly better prognosis. The authors also found that a SUVmax cutoff value of 19 separates patients with better from worst prognoses. The difficulty of studying CRC is the heterogeneity of the population and the presence of multiple variables, such as KRAS. Oner et al [26] evaluated patients that underwent FDG PET/CT for primary staging of colorectal cancer and showed that although both KRAS mutation and MTV of the primary tumor demonstrated prognostic power, MTV could not predict the presence of KRAS mutation.

In our study, both whole-body and primary tumor MTV and TLG values were significantly associated with overall survival and progression-free survival. Rectal cancer tumor volume itself is not a predictor of overall survival. More important to determine survival is the presence of local invasion and lymph node metastases, which is elegantly performed with MRI for local staging [27]. However, for the identification of synchronous tumors and distant metastases in advanced rectal cancer, FDG PET/CT has been increasingly indicated.

Interestingly, although the association of volume and metabolism had some prognostic power, still wbTLG and tuTLG played a significantly more important role in rectal cancer prognosis compared to wbMTV and tuMTV, similar to other tumor types such as lung cancer and lymphoma [28, 29]. In rectal cancer, it seems that the metabolism of the disease is a more important prognostic indicator than the volume of the disease.

For example, patients with patients with stages III and IV and low wbMTV had a better outcome (Fig. 4), whereas early-stage disease (I and II) presenting with a large metabolic volume of the tumor had a dismal outcome (Fig. 5). The patient example was classified as stage II disease but had high wbMTV on the staging FDG PET/CT; the patient died after 10 months. Therefore, whole-body metabolic tumor burden may be more powerful than tumor staging. Likewise, in patients presenting lymph node metastasis (especially pelvic and abdominal lymph nodes) with low-grade uptake (uptake below the automatic selection SUVmax threshold), there was no significant change in wbMTV compared to lower-stage patients and consequently their prognoses were similar to patients without lymph node metastases although these metastatic lesions lead to upstaging. Contrarily, patients with a highly metabolically active voluminous primary tumor, even with negative N and M in primary staging, were more likely to develop worse outcomes compared to patients with tumors that had a low metabolism and volume even with higher TNM stage.

Patients with mucinous-type tumors and localized disease, in general, present a relatively good prognosis while the mucinous type tumors with metastatic disease have dismal outcomes, especially when located in the rectum, because of their poorer response to chemotherapy and radiotherapy compared to adenocarcinomas [30–34].

Our study showed that mucinous adenocarcinomas had a similar risk of death when compared to non-mucinous adenocarcinomas ($p = 1.0000$), despite the low number of patients with the latter histology type. Although some studies show that mucinous adenocarcinomas tend to be less FDG-avid than adenocarcinomas [35], we did not see this pattern in our study group. The patients with mucinous tumors in our cohort presented with highly avid lesions as has been shown in the study by Anjos et al. [36]. Furthermore, a frequent problem encountered in mucinous tumors is a relative delay in diagnosis and treatment onset [37]. This outcome was seen in our population as there was an elevated risk of death in patients with mucinous tumors because 6 out of 7 were stage IIIB or IV, with a delay in diagnosis and thus in treatment onset.

The major strength of this study was demonstrating that specifically in rectal cancer, whole-body tumor burden on a staging PET/CT study is a strong independent diagnostic imaging biomarker of prognosis. There is a scarce amount of data evaluating specifically whole-body metabolic tumor burden for rectal cancer staging. Most of the available investigations are related to colorectal cancer, not specifically rectal cancer, and the majority quantify the metabolic tumor burden solely of the primary tumor, not the metabolic tumor burden of the whole body.

Although other clinical variables were also independently associated with overall survival and progression-free survival these variables do not account for the possibility of evaluating through imaging the prediction of outcome.

One major limitation of our study was that 70% of our patients were stages III or IV because our institution is a public tertiary reference hospital in a developing country and therefore treats mostly advanced rectal cancer patients as there is a delay of referral from primary and secondary institutions. Therefore, our study has major demographic and clinical differences compared to worldwide statistics and other studies [25, 38].

Even with these limitations, our investigation may allow us to take the next step in helping better stratify rectal cancer patients. Although laboratory data (hemoglobin, ANC, monocytes, and platelet levels), the presence of sarcopenia, and low BMI, and clinical staging are also associated with prognosis, these variables are incapable of independently discriminating prognosis in localized tumors with aggressive behavior or vice versa.

CONCLUSION

In rectal cancer patients, in addition to the conventional TNM staging and diagnostic work-up, FDG PET/CT may be useful to stratify patients. Whole-body tumor burden on FDG PET/CT may be an independent imaging biomarker of prognosis and help discriminate survivors from non-survivors thus improving treatment strategies and surveillance. A larger sample size, a longer follow-up period, and a balance among staging groups are required to confirm our findings.

Declarations

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Ethics approval: This observational study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Campinas (UNICAMP) under the grant number: CAEE 03925318.4.0000.5404. The patient informed consent was waived for this retrospective analysis.

References

1. Sung H, Ferlay J, Siewgel R et al (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. Cancer J Clin 71:209–249
2. Siegel RL, Miller KD, Fuchs HE, Jemal A, Cancer Statistics (2021) CA Cancer J Clin 2021; 71: 7–33
3. Kuipers EJ, Grady WM, Lieberman D et al (2015) Colorectal cancer Review Nat Rev Dis Primers 1:65
4. Draft C et al (2015) Global, regional and national levels of age-specific mortality and 240 causes of death, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 385:1990–2013
5. Papamichael D et al (2014) Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 26:463–476
6. Hurwitz H et al (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335–2342
7. Fujii H, Matsuhashi N, Kitahora M et al (2019) Bevacizumab in Combination with TAS-102 Improves Clinical Outcomes in Patients with Refractory Metastatic Colorectal Cancer: A Retrospective Study. Oncologist 10.1634/theoncologist.2019 – 0541
8. Stucky CC, Pockaj BA, Novotny PJ et al (2011) Long-term follow-up and individual item analysis of quality of life assessments related to laparoscopic-assisted colectomy in the COST trial 93-46-53 (INT 0146). Ann Surg Oncol 18:2422–2431
9. Green BL, Marshall HC, Collinson F et al (2013) Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 100:75–82
10. Keller DS, Berho M, Perez RO et al (2020) The multidisciplinary management of rectal cancer. Nat Rev Gastroenterol Hepatol 17:414–429
11. Gallamini A, Zwarthoed C, Borra A (2014) Positron Emission Tomography (PET) in Oncology. Cancers (Basel) 6:1821–1889
12. Antoch G, Saoudi N, Kuehl H et al (2004) Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. J Clin Oncol 22:4357–4368
13. Chowdhury FU, Shah N, Scarsbrook AF, Bradley KM (2010) [18F] FDG PET/CT imaging of colorectal cancer: a pictorial review. Postgrad Med J 86:174–182
14. Abdel-Nabi H, Doerr RJ, Lamonica DM et al (1998) Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings.

Radiology 206:755–760

15. O'Connell JB, Maggard MA, Ko CY (2004) Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst 96:1420–1425
16. Petersen RK, Hess S, Alavi A, Høilund-Carlsen PF (2014) Clinical impact of FDG-PET/CT on colorectal cancer staging and treatment strategy. Am J Nucl Med Mol Imaging 4:471–482
17. Ozis SE, Soydal C, Akyol C et al (2014) The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the primary staging of rectal cancer. World J Surg Oncol 12:26
18. Sasaki K, Kawasaki H, Sato M et al (2017) Impact of Fluorine-18 2-Fluoro-2-Deoxy-D-Glucose Uptake on Preoperative Positron Emission Tomography/Computed Tomography in the Lymph Nodes of Patients with Primary Colorectal Cancer. Dig Surg 34:60–67
19. Vijayaragavan M, Marco K, Sze TL et al (2012) Prognostic Ability of ^{18}F-FDG PET/CT in the Assessment of Colorectal Liver Metastases. J Nucl Med 53:1345–1351
20. Harris PA, Taylor R, Minor BL et al (2019) The REDCap Consortium: Building na International Community of Software Platform Partners. J Bio Med Inform 95:103208
21. Pozzuto L, Silveira MN, Mendes MCS et al (2021) Myosteatosis Differentially Affects the Prognosis of Non-Metastatic Colon and Rectal Cancer Patients: An Exploratory Study. Front Oncol 11:762444
22. Amin MB, Greene FL, EdgeSB, Cancer et al (2017) J Clin 67:93–99
23. da Cunha LP, Silveira MN, Mendes MCS et al (2019) Sarcopenia as an independent prognostic factor in patients with metastatic colorectal cancer: A retrospective evaluation. Clin Nutr ESPEN 32:107–112
24. Boellaard R et al (2015) FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging ; 328–354
25. Xu J, Li Y, Hu S, Lu L, Gao Z, Yuan H (2019) The significant value of predicting prognosis in patients with colorectal cancer using $_{18}$F-FDG PET metabolic parameters of primary tumors and hematological parameters. Ann Nucl Med 33:32–38
26. Oner AO, Budak ES, Yıldırım S, Aydın F, Sezer C (2017) The value of ^{18}FDG PET/CT parameters, hematological parameters and tumor markers in predicting KRAS oncogene mutation in colorectal cancer. Hell J Nucl Med 20:160–165
27. Liu Z, Meng X, Zhang H et al (2020) Predicting distant metastasis and chemotherapy benefit in locally advanced rectal cancer. Nat Commun 11:4308
28. Ventura L, Scarlattei M, Gnetti L et al (2020) ; 030089162090440. doi: 10.1177/0300891620904404. Online ahead of print.
29. Gupta N, Singh N (2020) To evaluate prognostic significance of metabolic-derived tumour volume at staging 18-flurodeoxyglucose PET-CT scan and to compare it with standardized uptake value-based response evaluation on interim 18-flurodeoxyglucose PET-CT scan in patients of non-Hodgkin's lymphoma (diffuse large B-cell lymphoma). Nucl Med Commun 41:395–404

30. Dai D, Zhou B, Zhong Y, Jin H, Wang X (2019) Survival of patients with resected primary colorectal mucinous adenocarcinoma: A competing risk nomogram analysis. Oncol Lett 18:6594–6604
31. Hyngstrom JR, Hu CY, Xing Y et al (2012) Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. Ann Surg Oncol 19:2814–2821
32. Catalano V, Loupakis F, Graziano F et al (2009) Mucinous histology predicts for poor response rate and overall survival of patients with colorectal cancer and treated with firstline oxaliplatin and/or irinotecanbased chemotherapy. Br J Cancer 100:881–887
33. Negri FV, Wotherspoon A, Cunningham D, Norman AR, Chong G, Ross PJ (2005) Mucinous histology predicts for reduced fluorouracil responsiveness and survival in advanced colorectal cancer. Ann Oncol 16:1305–1310
34. Sengul N, Wexner SD, Woodhouse S et al (2006) Effects of radiotherapy on different histopathological types of rectal carcinoma. Colorectal Dis 8:283–288
35. Au-Yeung AW, Luk WH, Lo AX (2012) Imaging features of colorectal liver metastasis in FDG PET-CT: a retrospective correlative analysis between CT attenuation and FDG uptake. Nucl Med Commun 33:403–407
36. Dos Anjos DA, Habr-Gama A, Vailati BB et al (2016) (18)F-FDG uptake by rectal cancer is similar in mucinous and nonmucinous histological subtypes. Ann Nucl Med 30:513–517
37. Zhang R, Zhao J, Xu J, Chen Y (2020) Long-term outcomes and prognostic factors of young patients with mucinous and signet-ring cell colorectal cancer. Archives of Medical Science 16:359–365
38. Key statistics for colorectal cancer. American Cancer Society website. https://www.cancer.org/cancer/types/colon-rectal-cancer/about/key-statistics.html

Figures

A B C D

Figure 1

Example of quantitative PET/CT to determine the whole-body tumor burden in a patient with colorectal cancer (A) presenting lung, liver, and bone metastases. (B) Initially, a rectangular semi-automatic volume of interest (VOI) in the whole-body coronal image is placed encompassing all metastatic sites. (C) The cutoff SUVmax was set at ≥ 2.5 and the SUVmax threshold was set at 41%. (D) VOIs automatically encircle metastases and exclude all other sites with uptake below the pre-established threshold and any sites of high uptake not related to a rectal primary lesion or rectal metastases.

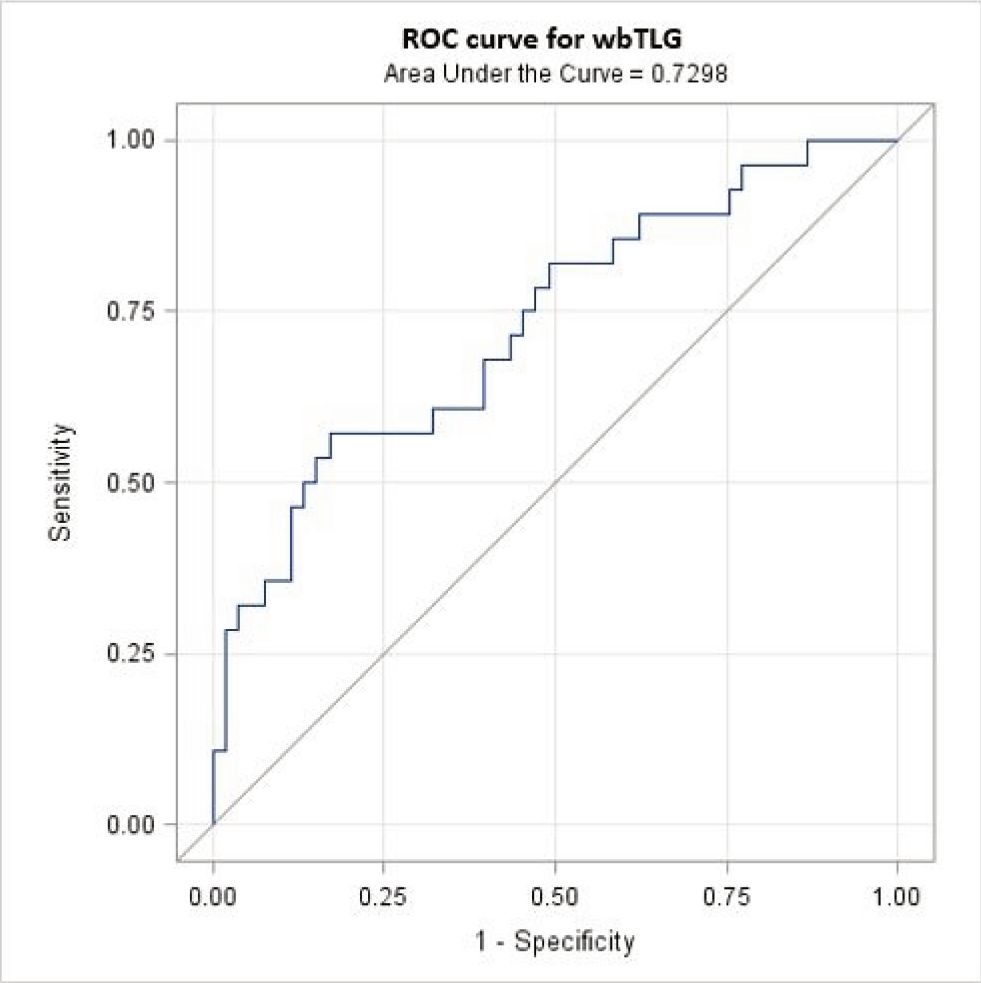

Figure 2

The ROC curve of the wbTLG parameter to determine the risk of death showed that the *cutoff* value=354 significantly discriminated survivors from non-survivors (p = 0.0007) with a specificity of 83%. The risk of death was 3.6 times higher (HR=3.689; 95%CI = 1.732;7.857).

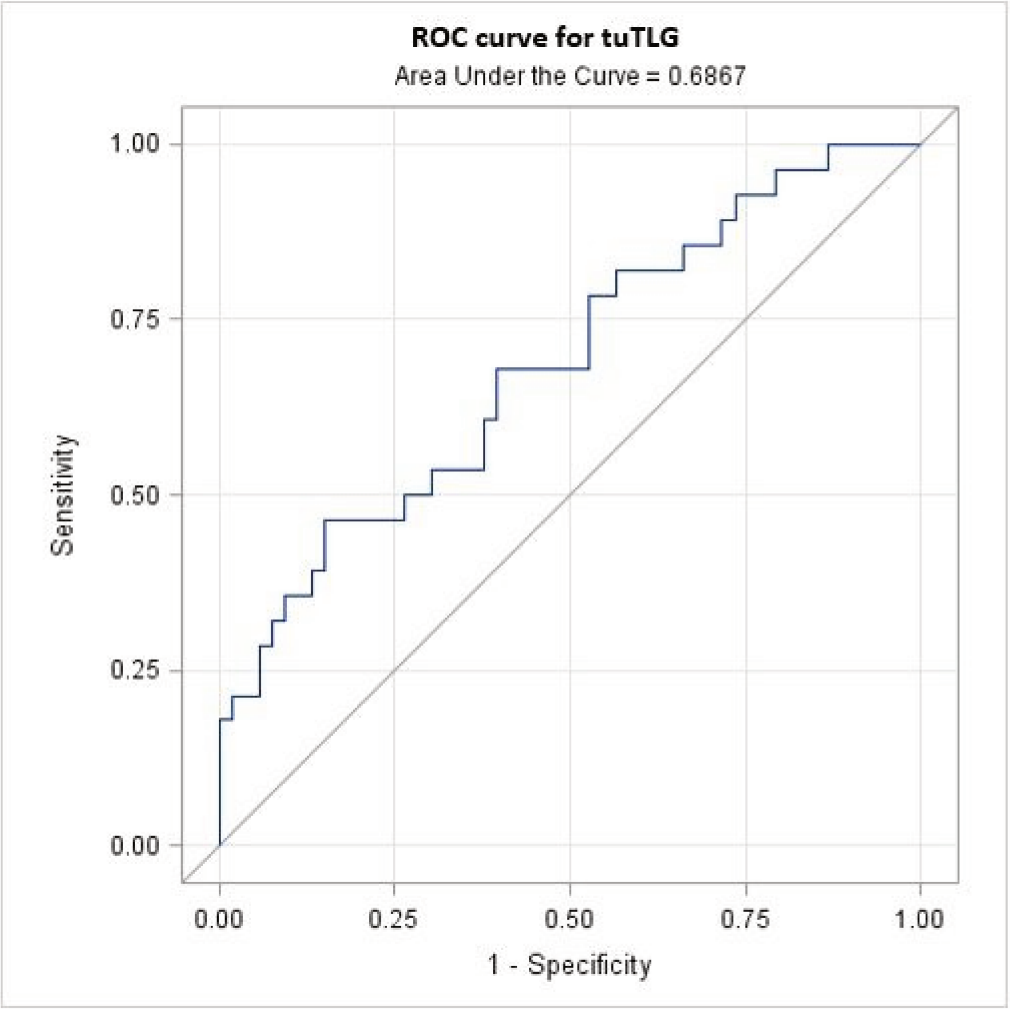

Figure 3

The ROC curve of the tuTLG parameter to determine the risk of death showed that the *cutoff* value=305 increased significantly (p = 0.0204) the risk of death (HR=2.599; 95%CI = 1.159;5.826) with a specificity of 84.9%.

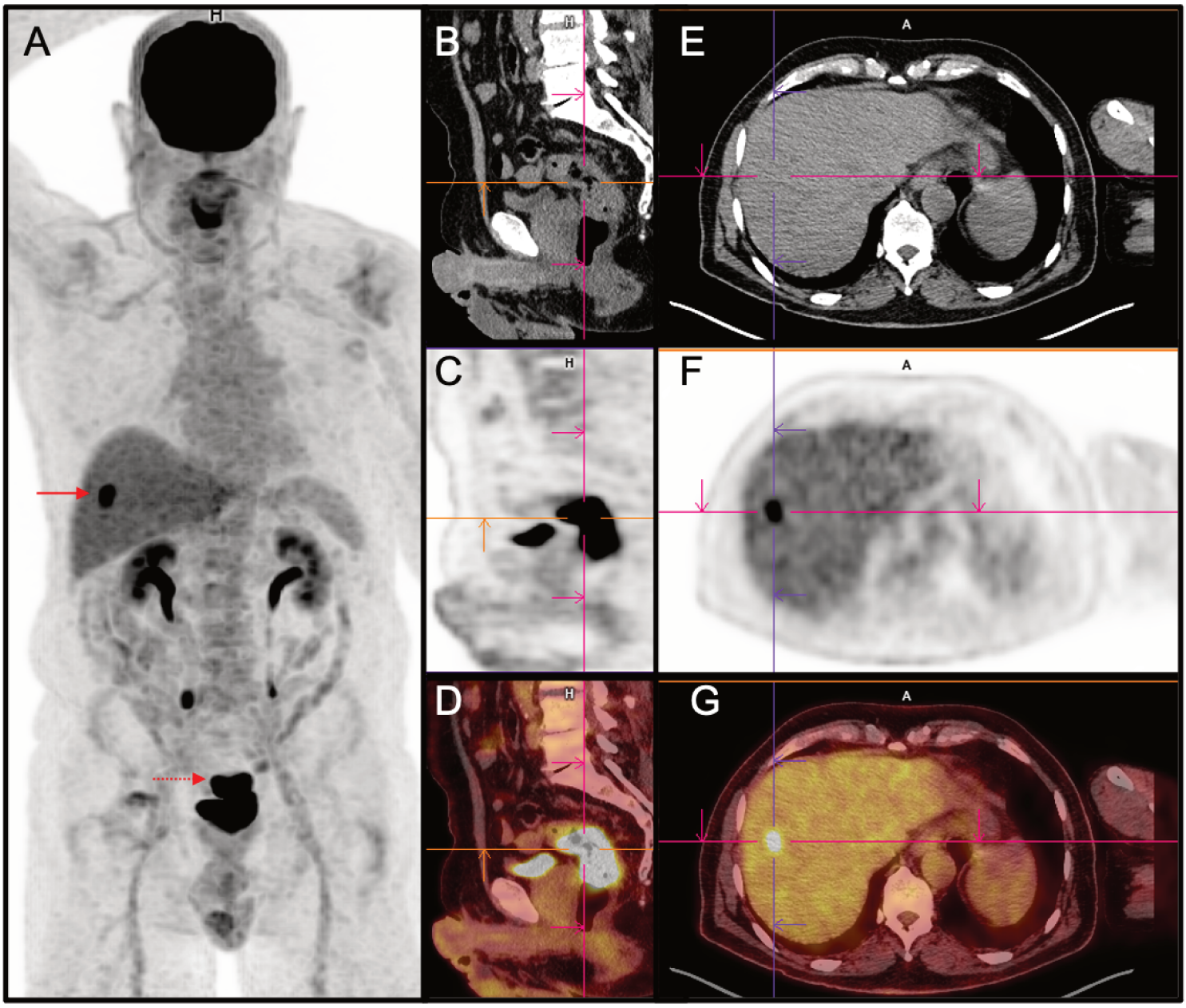

Figure 4

FDG PET/CT study for primary staging of a patient with stage IV rectal cancer and favorable outcome, (A) The MIP anterior view image shows a liver metastasis (arrow) and the rectal cancer (dotted arrow). no signs of distant metastases. The rectal cancer is better displayed in the pelvic delayed images after hyperhydration, diuretics and voiding in the sagittal view (B,C,D). The liver metastasis is noted also in the CT (E), PET (F) and PET/CT (G) images. The metabolic tumor burden of the patient was quite low (wbTLG = 119.64), despite the liver metastasis.

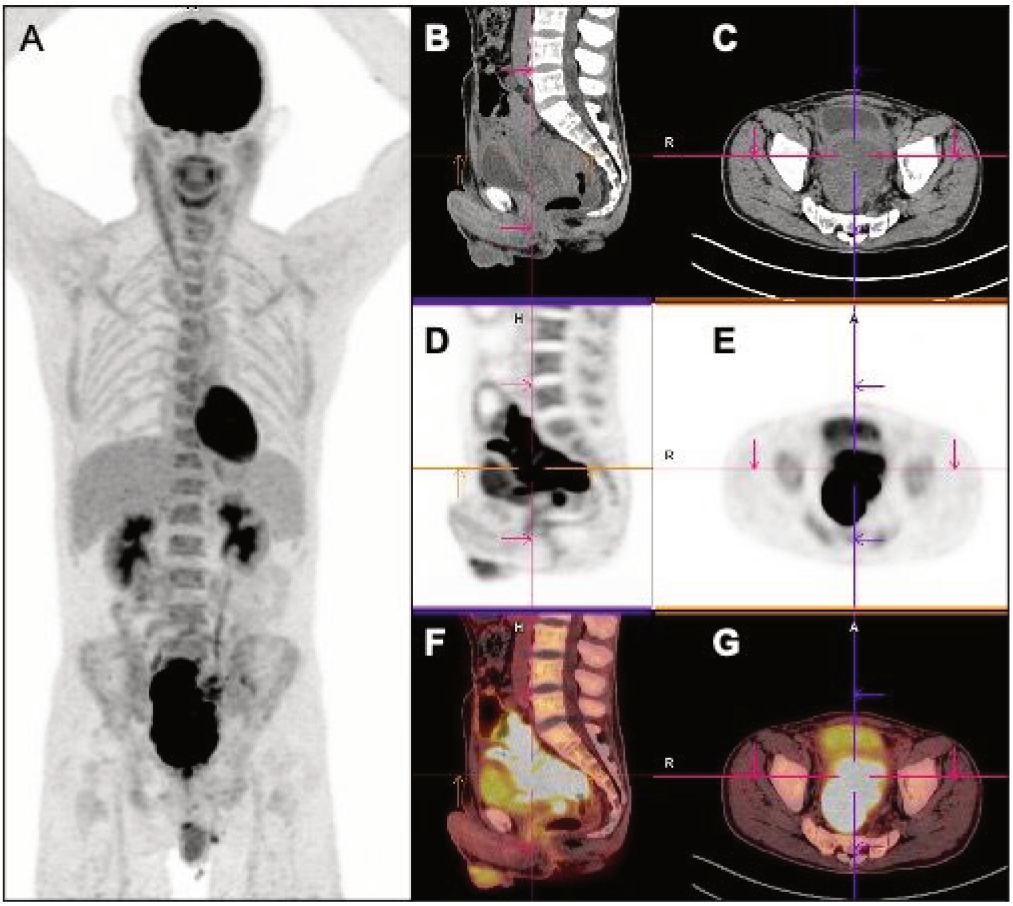

Figure 5

FDG PET/CT study for primary staging of a patient with a stage II rectal cancer however with unfavorable outcome. (A) MIP anterior view image shows no signs of distant metastases. (B) The CT (B, C), PET (D, E) and Fused (F, G) delayed images in the sagittal and transaxial views after hyperhydration, diuretics and voiding shows extensive tumor with intense hypermetabolism and high metabolic tumor burden (wbTLG = 1462.35). Despite the low stage (II), the patient died after 10 months.