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Evaluation of pre-treatment F-18 FDG PET/CT according to Mandard classification in locally advanced rectal cancer patients undergoing neoadjuvant chemoradiotherapy

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Abstract

Background This study primarily aimed to assess whether baseline [(18)F] fluorodeoxyglucose (FDG) PET/CT metabolic parameters—including SUVmax, metabolic tumor volume (MTV), and total lesion glycolysis (TLG)—can predict tumor regression grade (TRG) and survival in patients with locally advanced rectal cancer (LARC) undergoing neoadjuvant chemoradiotherapy (nCRT). In addition, secondary analyses were performed to identify other clinical and pathological variables associated with treatment response and prognosis.

Methods This retrospective study included patients diagnosed with LARC who underwent nCRT followed by surgical resection between 2014 and 2023. Pre-treatment staging with F-18 FDG PET/CT was performed for all patients. Postoperative pathological response was assessed using the TRG system. Patients were categorized into two groups: complete responders (TRG1) and incomplete responders (TRG2–5). Demographic characteristics, PET/CT metabolic parameters (SUVmax, MTV, TLG), Carcinoembryonic antigen (CEA), Carbohydrate antigen 19 − 9 (CA19-9), and histopathological features (perforation, lymphovascular invasion [LVI], and perineural invasion [PNI]) were compared between the groups. Statistical analyses included chi-square tests, Mann–Whitney U tests, logistic regression models with odds ratios (ORs), and Kaplan–Meier survival analysis.

Results A total of 151 patients were included. A statistically significant difference was found between TRG1 and TRG2-5 groups regarding family history ($p=0.034$), CEA at diagnosis ($p=0.002$), Ca19.9 after radiotherapy ($p=0.045$), and presence of concurrent chemotherapy (CC) ($p=0.004$). Significant differences were also observed in postoperative pathological features, including perforation ($p=0.045$), LVI ($p=0.023$), PNI ($p=0.031$), and post-operative CEA levels ($p=0.001$). In terms of outcomes, TRG1 was associated with better survival ($p=0.001$), longer disease-free survival ($p=0.001$), and overall survival ($p=0.001$). Logistic regression identified independent predictors of complete response (TRG1): family history (OR: 5.08, $p=0.027$), post-RT CEA (OR: 0.61, $p=0.015$), post-op CEA (OR: 1.13, $p=0.012$), perforation (OR: 20.93, $p=0.033$), LVI (OR: 0.33, $p=0.042$), and PNI (OR: 0.49, $p=0.045$). Kaplan–Meier analysis demonstrated significantly longer overall survival in patients with TRG1 compared to TRG2–5 (log-rank $p=0.001$). Similarly, disease-free survival was significantly better in the TRG1 group (log-rank $p=0.001$). In the multivariate Cox

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regression model, TRG1 (HR: 0.41; 95% CI: 0.26–0.66; $p=0.001$), CC (HR: 0.62; 95% CI: 0.39–0.98; $p=0.039$), and absence of perforation (HR: 0.51; 95% CI: 0.28–0.95; $p=0.034$) were found to be independent predictors of improved survival.

Conclusions Baseline F-18 FDG PET/CT parameters, including SUVmax, MTV, and TLG, were not predictive of TRG or survival in patients with LARC undergoing neoadjuvant chemoradiotherapy. However, clinical and pathological variables such as family history, post-treatment CEA levels, perforation, lymphovascular invasion, and perineural invasion were significantly associated with TRG1. TRG1, histopathological subtype, perforation, and CC were also found to be independent predictors of survival. These findings suggest that while FDG-PET/CT may have limited utility in predicting treatment response, certain clinical and pathological features remain critical for outcome assessment.

Keywords Locally advanced rectal cancer, Neoadjuvant chemoradiotherapy, (18F) FDG PET/CT, Mandard classification

Introduction

Colorectal cancer ranks among the most common cancers globally, and rectal cancer specifically accounts for a significant portion of disease burden. Rectal cancer is the eighth most frequently diagnosed cancer worldwide and causes approximately 340,000 deaths annually [1]. In non-metastatic cases, curative resection is often associated with long-term survival [2]. However, in patients with locally advanced rectal cancer (LARC), the risk of local recurrence remains high, and neoadjuvant chemoradiotherapy (nCRT) has become the standard of care. nCRT may be followed by additional neoadjuvant chemotherapy or adjuvant treatment depending on clinical indications [3]. Despite advancements in treatment protocols, recurrence—either local or systemic—remains a major concern and contributes to poor prognosis. Accurate prediction of prognosis is therefore critical in treatment planning, enabling more individualized care while avoiding overtreatment and minimizing healthcare costs.

While rectal cancer is part of the broader colorectal cancer group, previous studies have often evaluated prognostic factors in heterogeneous cohorts that combine colon and rectal cancers [4–7], which limits the applicability of findings specifically to LARC. Moreover, many earlier studies have suffered from limitations such as small sample sizes, lack of long-term follow-up, or inconsistent methodology. Prognostic factors known to influence outcomes in rectal cancer include tumor stage, age, sex, treatment modality, tumor biology, and serum tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19 – 9 (CA19-9) [8, 9]. In current clinical practice, nCRT for LARC can be administered via long-course conventional radiotherapy or short-course hypofractionated radiotherapy, but the long-term prognostic impact of these differing approaches remains unclear and is underreported in the literature.

LARC itself is a biologically and clinically heterogeneous disease. The development of individualized treatment strategies based on tumor biology and predicted response has driven interest in tools that allow better prognostication. In recent years, **organ-preserving strategies**, such as "watch-and-wait" approaches for patients with pathological complete response (pCR), have been increasingly favored to reduce long-term morbidity and improve quality of life [10–15].

F-18 FDG PET/CT has emerged as a valuable imaging modality in the management of rectal cancer. It enables the evaluation of metabolic activity, thereby assisting in staging, treatment planning, and response assessment. In the pre-treatment setting, PET/CT provides functional information that may complement anatomical imaging modalities, particularly in detecting nodal or distant metastases. After neoadjuvant chemoradiotherapy, PET/CT has shown promise in evaluating treatment response by quantifying metabolic parameters such as standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) [16, 17]. These metabolic markers may help in predicting pathological response and survival outcomes. However, despite growing evidence, there is still no consensus on the prognostic value of PET/CT-derived parameters in LARC. This study aims to explore the relationship between initial PET/CT metabolic values and the Mandard tumor regression grade (TRG), as well as their predictive significance on survival outcomes [18–20].

Given this background, the present study primarily aimed to evaluate the prognostic utility of pre-treatment F-18 FDG PET/CT metabolic parameters (SUVmax, MTV, and TLG) in predicting pathological tumor regression grade (TRG) and survival in LARC patients undergoing nCRT. Recognizing the multifactorial nature of treatment response, we also performed secondary exploratory analyses on clinical and pathological variables (e.g., CEA levels, lymphovascular invasion) to better understand their potential contributions in the absence of significant PET/CT associations.

Patients and methods

Study design and participants

This retrospective cohort study was approved by the Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (Approval date: 23.11.2022;

Approval number: 1582), and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of diagnosis and treatment initiation.

A total of 151 patients diagnosed with LARC who presented to the Radiation Oncology and Medical Oncology Clinics of Manisa City Hospital between January 2014 and December 2023 were included in the study. All patients underwent standardized neoadjuvant chemoradiotherapy (nCRT), followed by pre-treatment F-18 FDG PET/CT imaging as part of baseline staging, and curative-intent surgical resection. Treatment response was assessed histopathologically using the Mandard TRG system. No interim or post-treatment PET/CT scans were included in the analysis.

Inclusion criteria were: (1) histopathologically confirmed LARC; (2) standardized neoadjuvant chemoradiotherapy (nCRT); (3) pre-treatment F-18 FDG PET/CT imaging; (4) curative-intent surgical resection; (5) available histopathological evaluation using the Mandard TRG classification; and (6) complete clinical, laboratory, imaging, pathological, and survival follow-up data.

Exclusion criteria included: presence of metastatic disease at diagnosis, incomplete or non-standard treatment protocols, insufficient or missing PET/CT data, prior malignancies or chemotherapy history, or inadequate follow-up information. These strict criteria were applied to minimize data heterogeneity and ensure the validity of statistical comparisons, although we acknowledge that this may limit generalizability.

All patients received treatment under a unified institutional protocol. Radiation therapy was delivered as long-course conventional radiotherapy (50.4 Gy in 28 fractions), and concurrent chemotherapy was administered using either oral capecitabine or infusional 5-FU/leucovorin (FUFA). No significant differences in chemotherapy regimens existed between departments. Patients who received non-standard chemotherapy or radiation protocols were excluded to minimize potential confounding.

Clinical, imaging, and pathological data were collected retrospectively from electronic medical records. The following variables were obtained:

- Clinical: age, sex, comorbidities, smoking status, alcohol use, family history;
- Imaging: SUVmax, metabolic tumor volume (MTV), total lesion glycolysis (TLG) from baseline F-18 FDG PET/CT;
- Pathological: TRG grade, presence of perforation, lymphovascular invasion (LVI), and perineural invasion (PNI);
- Laboratory: baseline and post-RT CEA and CA19-9 levels;
- Outcome: survival status, overall survival (OS), disease-free survival (DFS), date of last follow-up or death.

Postoperative pathological tumor regression was evaluated using the Mandard Tumor Regression Grade (TRG) system, which classifies tumor response into five categories based on the extent of fibrosis and residual tumor cells. TRG1 indicates complete regression with fibrosis and no residual tumor, while TRG5 denotes no regression. All pathological evaluations were conducted by experienced gastrointestinal pathologists at our institution. Although interobserver agreement analysis (e.g., kappa statistics) was not performed, assessments were based on established criteria and consistent institutional standards. This limitation is acknowledged in the manuscript.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro–Wilk and Anderson–Darling tests. Levene's test was employed to evaluate the homogeneity of variances. Variables with normal distribution were expressed as mean ± standard deviation (SD), while non-normally distributed variables were reported as median with interquartile range (IQR) or as median (minimum–maximum) where appropriate. Categorical variables were presented as frequencies and percentages. Comparisons between the TRG1 and TRG2–5 groups were performed using the independent samples t-test or Mann–Whitney U test for continuous variables, depending on the distribution. Pearson's chi-square test or Fisher's exact test was used for categorical variables, and the Kruskal–Wallis test was applied when ordinal variables were evaluated. To determine the independent predictors of complete pathological response (TRG1), multivariate logistic regression analysis was used, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Survival outcomes were analyzed using the Kaplan–Meier method, and differences between survival curves were compared using the log-rank test. Cox proportional hazards regression was applied to identify variables independently associated with overall survival (OS) and disease-free survival (DFS), with results expressed as hazard ratios (HRs) and 95% CIs. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

151 patients were included in our study. Socio-demographic findings and tumor characteristics of the patients are shown in Table 1. The median age of all patients was 62 (28–85) years. 42% (n: 63) of the patients were female

Table 1 Socio-demographic findings and tumor characteristics of the patients (tumor regression grade: TRG)

Characteristic	All patients* (*n* = 151) n (%)	TRG1 (*n* = 44) *n* (%)	TRG2–TRG5 (*n* = 107) n (%)	*P**
Gender				
Female	63 (42%)	22	41	0.187
Male	88 (58%)	22	66	
Age	62 (28–85)	59 (28–82)	63 (37–85)	0.140
History				
None	104 (69%)	35	69	0.058
HT	7 (4%)	1	6	
DM	10 (7%)	4	6	
HT + DM	9 (6%)	1	8	
Cardiac	10 (7%)	2	8	
Others	11 (7%)	1	10	
Family history				
None	131 (86%)	37	94	**0.034**
Meme Ca	2 (1%)	1	1	
GİS Ca	7 (5%)	0	7	
Others	11 (8%)	6	5	
Smoking				
No	95 (63%)	32	63	0.124
10 packs/year and below	11 (7%)	2	9	
10–20 packs/year	30 (20%)	7	23	
20 packs/year and above	15 (10%)	3	12	
Alcohol				
No	141 (93%)	42	99	0.512
Yes	10 (7%)	2	8	

Bold values indicate statistical significance ($P < 0.05$)

*Chi-Square and Mann–Whitney test

and 58% (n: 51) were male. 31% of the patients ($n = 47$) had at least 1 accompanying disease in their medical history. 14% ($n = 14$) of the patients had a family history of cancer. 37% of the patients were smokers and 7% were alcohol users. TRG1 and TRG2-5 groups were statistically similar in terms of age, gender, personal history, smoking and alcohol use ($p > 0.05$). There was statistical significance between TRG1 and TRG2-5 in terms of family history ($p = 0.034$) (Table 1).

Tumor characteristics, blood parameters and treatments administered before surgery are shown in Table 2. The histopathological diagnosis of 95% of the patients ($n = 144$) was adenocarcinoma. The histopathological grade of 84% of the patients ($n = 127$) was II. The median primary tumor size was 6.0 (1–47) mm and 5.0 (1–15) cm. 82% of the patients ($n = 125$) had advanced TNM stage (IIIB and IIIC). PET SUVmax median value of the patients was 14.3 (7–31), TLG value was 174 (27–590), MTV value was 20 (3-100), carcinoembryonic antigen (CEA) value was 9.97 ± 17.9, and Ca19.9 value was 35.17 ± 98.2. There was statistical significance between TRG1 and TRG2-5 in terms of CEA and Ca19-9 values

Table 2 Tumor characteristics, blood parameters, and treatments administered before surgery (tumor regression grade: TRG)

Characteristic	All patients* (*n* = 151) n (%)	TRG1 (*n* = 44)	TRG2–TRG5 (*n* = 107)	*P**
Histopathological diagnosis				
Adenocarcinoma	144 (95%)	41	103	0.356
Signet-ring cell	3 (2%)	1	2	
Mucinous Carcinoma	4 (3%)	2	2	
Histopathologic grade				
I	7 (5%)	3	4	0.186
II	127 (84%)	38	89	
III	17 (11%)	3	14	
Primary Tumor Size (mm)	6.0 (1–47)	5.8 (1–13)	6.0 (1–47)	0.716
Primary Tumor Location (Distance from anal canal) (cm)	5.0 (1–15)	5.0 (1–12)	5.0 (1–15)	0.386
TNM stage				
IIA (T3N0	24 (16%)	7	17	0.862
IIB (T4aN0)	1 (1%)	0	1	
IIC (T4bN0)	1 (1%)	0	1	
IIIB (T3-T4a/N1, T2-T3N2a)	98 (65%)	29	69	
IIIC (T4aN2a, T3-T4aN2b, T4bN1-N2)	27 (17%)	8	19	
PET SUVmax	14.3 (7–31)	12.7 (7–28)	14.4 (7–31)	0.259
Total lesion glycolysis (TLG)	174 (27–590)	159 (29–494)	177 (27–590)	0.309
Metabolic tumor volume (MTV)	20 (3-100)	16 (7–25)	21 (3–70)	0.125
Carcinoembryonic antigen (CEA)	9.97 ± 17.9	2.4 (0–80)	4.5 (1-109)	**0.002**
Carbohydrate antigen 19 – 9 (Ca19.9)	35.17 ± 98.2	12 (1-146)	13 (0-700)	0.152
Concurrent chemotherapy (CC)				
No	8 (5%)	0	8	**0.004**
Yes	143 (95%)	44	99	
Concurrent CC Regime				
FUFA	38 (25%)	11	27	0.126
Oral Capecitabine	105 (75%)	33	72	
After radiotherapy (RT) (6–8 weeks)				
CEA	4.21 ± 6.3	1.88 (1–57)	2.84 (1–28)	0.706
Ca19.9	15.9 ± 21.9	9.2 (0–35)	12 (0-164)	**0.045**

Bold values indicate statistical significance ($P < 0.05$)

*Chi-square and Mann–Whitney test

after CC (weeks 6–8) ($p = 0.002$, $p = 0.004$, and $p = 0.045$, respectively) (Table 2).

The surgical and pathological features of the patients are shown in Table 3. Perforation was present in 3% ($n = 4$), LVI in 7% ($n = 11$), and PNI in 7% ($n = 11$). At the time of analysis, 59% ($n = 89$) of the patients were alive. Median disease-free survival was 34.5 (4-130) months, and median overall survival was 40.0 (4-132) months.

Table 3 Characteristics of the patients during and after surgery (tumor regression grade: TRG)

Characteristic	All patients* (*n* = 151) n (%)	TRG1 (*n* = 44)	TRG2–TRG5 (*n* = 107)	*P**
Perforation				
Yes	4 (3%)	1	3	**0.045**
No	147 (97%)	43	104	
Lymphovascular invasion (LVI)				
Yes	11 (7%)	1	11	**0.023**
No	140 (93%)	43	96	
Perineural invasion (PNI)				
Yes	11 (7%)	1	10	**0.031**
No	140 (93%)	43	97	
Post-op				
CEA	1.61 (0.4-243.3)	0.8 (0.4–243)	2.0 (0.5–29)	**0.001**
Ca19-9	9.26 (0.2–526.0)	8.5 (1–25)	11 (0-526)	0.117
Adjuvant CT				
Yes	128 (85%)	40	88	0.134
No	23 (15%)	4	19	
Survive status				
Alive	89 (59%)	38	51	**0.001**
Ex	62 (41%)	6	56	
Disease-Free Survival Time (Months)	34.5 (4-130)	65 (4-125)	25 (4-130)	**0.001**
Overall Survival Duration (Months)	40.0 (4-132)	65 (5-125)	35 (4-132)	**0.001**

Bold values indicate statistical significance ($P < 0.05$)

*Chi-square and Mann–Whitney test

There was statistical significance between TRG1 and TRG2-5 in terms of perforation, LVI, and PNI ($p = 0.045$, $p = 0.023$, and $p = 0.031$, respectively). There was statistical significance between TRG1 and TRG2-5 in terms of post-op CEA value ($p = 0.001$). There was statistical significance between TRG1 and TRG2-5 in terms of survival status, disease-free survival time, and overall survival time ($p = 0.001$, $p = 0.001$, and $p = 0.001$, respectively) (Table 3).

Table 4 The effect of parameters in predicting complete response (TRG1) in Mandard scoring (tumor regression grade: TRG)

Variable	Odds ratio	95% CI	*P**
Histopathological diagnosis (Adenocarcinoma)	0.398	0.05–2.92	0.365
Family history (No)	5.081	1.20-21.38	**0.027**
SUVmax at diagnosis (low)	1.158	0.94–1.41	0.149
Total lesion glycolysis (TLG) (low)	1.002	0.97-1.00	0.439
Metabolic Tumor Volume (MTV) (low)	1.046	0.98–1.11	0.145
CEA at diagnosis (low)	1.016	0.98–1.04	0.258
Ca19.9 at diagnosis (low)	1.006	0.99–1.01	0.236
CEA after RT (low)	0.614	0.41–0.91	**0.015**
Post-op CEA (low)	1.129	1.02–1.24	**0.012**
Perforation (No)	20.934	1.2-345.1	**0.033**
Lymphovascular invasion (No)	0.331	0.02–3.9	**0.042**
Perineural invasion (No)	0.496	0.03–5.9	**0.045**

Bold values indicate statistical significance ($P < 0.05$)

*Multiple logistic regression analysis

Representative individual cases are shown in Fig. 1, and the reported values (SUVmax, MTV, TLG) are specific to these single patients, not to the group averages (Fig. 1).

The effect of parameters in predicting TRG1 in Mandard scoring is shown in Table 4. The risk factors were found to be significantly associated with TRG1 in the logistic regression analysis included family history ($p = 0.027$), post-RT CEA ($p = 0.015$), post-op CEA ($p = 0.012$), perforation ($p = 0.033$), LVI ($p = 0.042$), and PNI ($p = 0.045$) (Table 4).

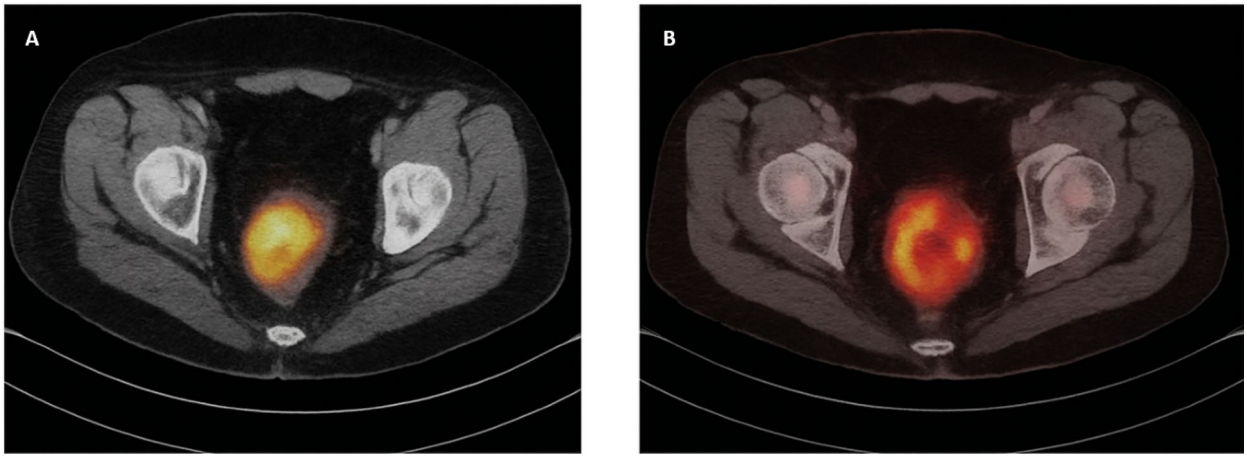

Fig. 1 **A** Pre-treatment axial F-18 FDG PET/CT image of a patient with TRG1 (complete pathological response). The primary lesion in the rectum shows moderate FDG uptake (SUVmax: 12.3; MTV: 18 mL; TLG: 156). **B** Pre-treatment axial F-18 FDG PET/CT image of a patient with TRG5 (poor response). The lesion demonstrates intense FDG uptake (SUVmax: 22.7; MTV: 38 mL; TLG: 435)"

The effect of parameters in predicting survival is shown in Table 5. The risk factors were found to be significantly associated with survival in the logistic regression analysis included TRG1, histopathological diagnosis (OR: 19,930, $p = 0.001$), and perforation (OR: 8,100, $p = 0.045$), and presence of concurrent CC (OR: 3.714, $p = 0.009$) (Table 5; Fig. 2.).

Kaplan–Meier analysis demonstrated significantly longer overall survival in patients with TRG1 compared to TRG2–5 (log-rank $p = 0.001$). Similarly, disease-free survival was significantly better in the TRG1 group (log-rank $p = 0.001$). In the multivariate Cox regression model, TRG1 (HR: 0.41; 95% CI: 0.26–0.66; $p = 0.001$), CC (HR: 0.62; 95% CI: 0.39–0.98; $p = 0.039$), and absence of perforation (HR: 0.51; 95% CI: 0.28–0.95; $p = 0.034$) were found to be independent predictors of improved survival (Fig. 3.).

Table 5 The effect of parameters in predicting survival (Tumor regression grade: TRG)

Variable	Odds ratio (OR)	95% CI	P*
Mandard classification (TRG1)	6.954	2.71–17.81	**0.001**
Histopathological diagnosis (Adenocarsinom)	19.930	18.20-21.14	**0.001**
Family history (No)	1.514	0.36–6.31	0.327
SUVmax at diagnosis (low)	0.960	0.91–1.10	0.960
Total lesion glycolysis (TLG) (low)	0.995	0.99-1.00	0.051
Metabolic Tumor Volume (MTV) (low)	1.010	0.97–1.04	0.521
CEA at diagnosis (low)	0.991	0.97–1.01	0.343
Ca19.9 at diagnosis (low)	0.998	0.99–1.02	0.286
CEA after RT (low)	0.955	0.89–1.01	0.155
Post-op CEA (low)	0.923	0.81–1.05	0.225
Perforation (No)	8.100	0.87–74.8	**0.045**
Lymphovascular invasion (No)	2.432	0.67–8.47	0.163
Perineural invasion (No)	1.974	0.53–7.23	0.304
Concurrent chemotherapy (CC) (Yes)	3.714	1.36–10.07	**0.009**

Bold values indicate statistical significance ($P < 0.05$)

*Multiple logistic regression analysis

Discussion

This study evaluated the association between pre-treatment F-18 FDG PET/CT parameters and pathological TRG, as well as their prognostic impact on survival in patients with LARC undergoing nCRT. Our main findings indicate that baseline metabolic PET parameters—SUVmax, MTV, and TLG—were not significant predictors of TRG1 or survival outcomes. In contrast, clinical and pathological parameters such as family history, post-treatment CEA levels, perforation, LVI, and PNI were significantly associated with treatment response and overall survival.

Nowadays, it is important to determine the role of Mandard classification, which is increasingly used in determining tumor response after nCRT in LARC, and its role in predicting complete response and predicting survival. In a study by Avallone et al., it was reported that among the values measured on F-18 FDG PET/

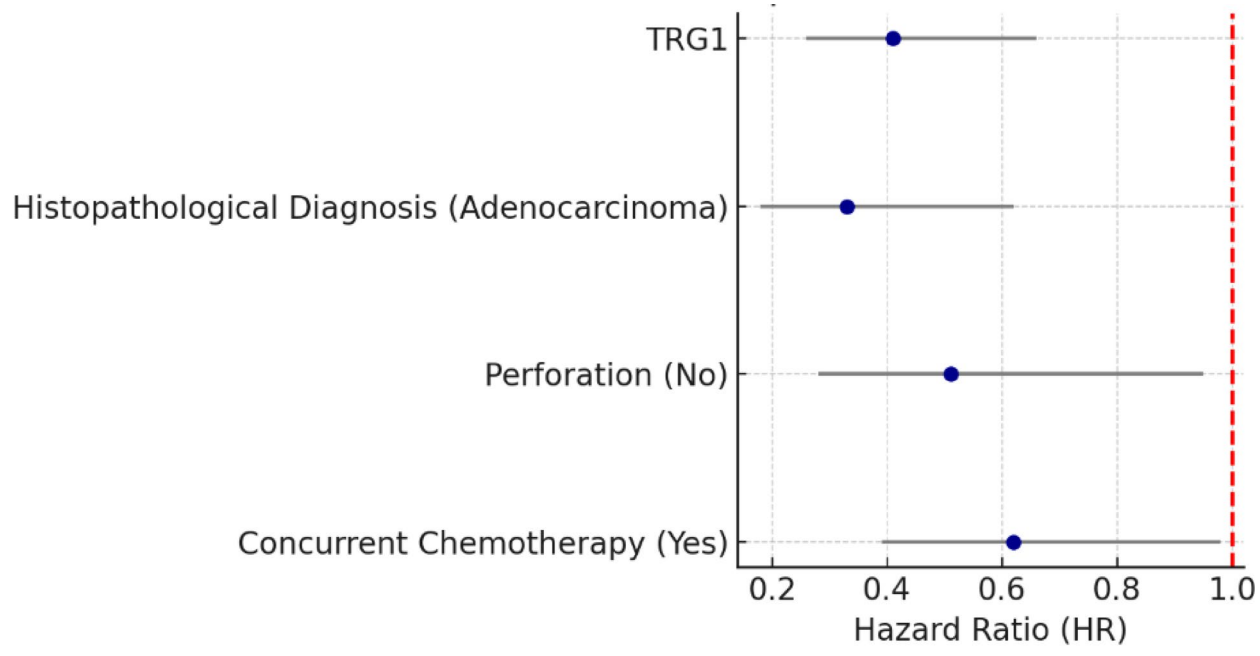

Fig. 2 Forest plot of multivariate Cox regression analysis for overall survival. Hazard ratios (HR) and 95% confidence intervals (CI) are shown for independent predictors

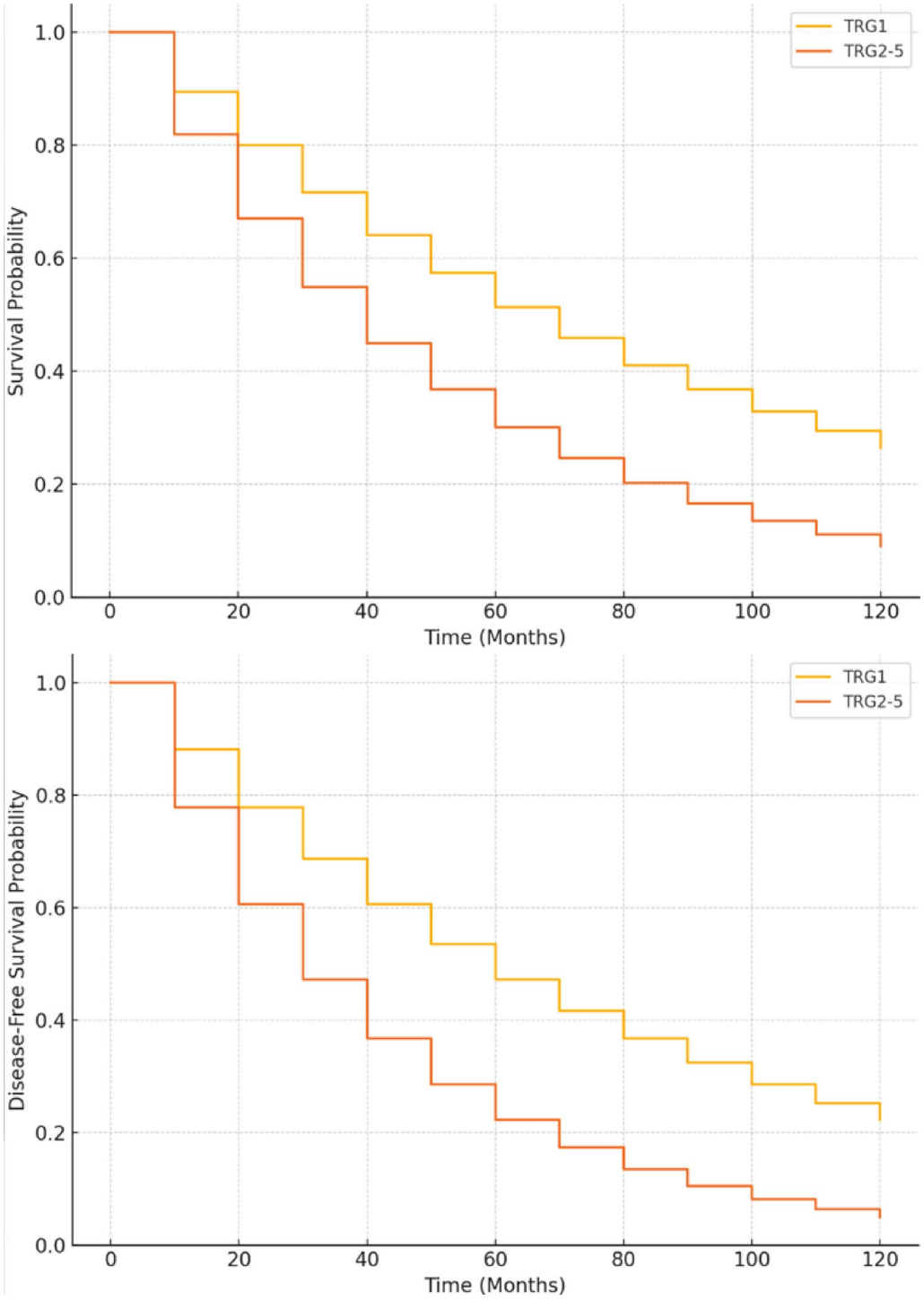

Fig. 3 Kaplan–Meier curves for overall and disease-free survival according to tumor regression grade (TRG)

CT in 61 LARC patients, only the TLG value was significantly lower in patients with a complete response (TRG1). In multiple regression analysis, it was shown that only TLG value was significant in predicting metabolic TRG1 [21]. In a study conducted by Deantonio et al. in 100 LARC patients, it was shown that the SUV, MTV, and TLG values measured in F-18 FDG PET/CT were similar in the TRG1 and TRG2-5 groups. In the comparison made between TRG1-2 and TRG 3–5 groups, it was reported that only the MTV value was significantly lower in the TRG1-2 group [22]. In a study by Sakin et al., it was reported that among the values measured on F-18

FDG PET/CT, only the MTV value predicted both complete response and survival in 51 LARC patients receiving nCRT [23]. In a study conducted by Karahan Sen et al. in 51 LARC patients receiving nCRT, it was reported that MTV and TLG values, among the values measured in F-18 FDG PET/CT, were significantly lower in patients with complete response in 51 LARC patients receiving nCRT [24]. Other studies have supported the use of the TLG value in distinguishing TRG1 and TRG2-5 [25, 26]. In a study conducted by Guido et al., in 80 LARC patients receiving nCRT, F-18 FDG PET/CT results showed that SUV, MTV, and TLG values were significantly lower in patients with complete response [27]. In a study by Asabella et al., it was reported that the SUV value and TNM stage measured after nCRT were significant in predicting TRG1 in 56 LARC patients receiving nCRT [28]. In current study, baseline SUVmax, MTV, and TLG values were similar to the TRG2-5 group, although they were numerically lower in the TRG1 group. However, it was found that SUVmax, MTV, and TLG values at the time of diagnosis were not significant in predicting TRG1 and survival. Our findings suggested that F-18 FDG PET/CT cannot distinguish TRG1 and TRG2-5.

In the literature, sociodemographic (to be deleted), patient-specific and pathological data such as blood values, perforation, LVI and PNI, which predict early metabolic complete response (TRG1), were used. In a study by Avallone et al., it was reported that there was no statistical significance between TRG1 and TRG2-5 in terms of age, gender, TNM stage, smoking-alcohol use, distance from the anal canal, and baseline CEA [21]. In the study conducted by Sakin et al., it was reported that there was no statistical significance between TRG1 and TRG2-5 in terms of sociodemographic data, presence of comorbidities, family history, perforation, LVI, PNI, except TNM stage, in 51 LARC patients receiving nCRT [23]. In a study by Lai et al., it was reported that there was no statistical significance between TRG1 and TRG2-5 in terms of sociodemographic data, pre-CEA, post-CEA in 93 LARC patients receiving nCRT [29]. On the contrary, in our study, there was statistical significance between family history, presence of CC, post-RT Ca19-9 values, perforation formation in the post-operative pathological specimen, presence of LVI and PNI in TRG1 and TRG2-5. In multiple regression analysis, among these values, family history, post-RT CEA, and post-operative CEA values were significant in predicting TRG1. These findings emphasize the importance of simple, non-invasive methods that can be used in determining treatment response and monitoring patients.

In many studies, parameters such as SUV, MTV, TLG, TRG, histopathological diagnosis, family history, presence of CC and tumor markers are used to evaluate survival in LARC patients. In the study conducted by Sakin et al., it was reported that TRG1 and MTV values were significant in predicting survival [23]. In the study of Li et al., consisting of 326 LARC patients who received nCRT, TRG1, TNM stage, and adjuvant CT were found to be significant in predicting survival [30]. In Li et al.'s study on 326 LARC patients receiving nCRT, TRG1, TNM stage, and presence of CC were found to be significant in predicting survival [31]. In another study by Lu et al., consisting of 269 LARC patients receiving nCRT, post-CEA value and TNM stage were identified to be significant in predicting survival [32]. In a study conducted by Laohawiriyakamol et al. in 104 LARC patients receiving nCRT, intraoperative tumor perforation, poor differentiation, and perineural invasion were found to be significant in predicting survival [18]. In a study by Li et al., smoking history, TRG, LVI, and pre-Ca19.9 values were found to be significant in predicting survival in 324 LARC patients receiving nCRT [31]. In our study, TRG1, histopathological diagnosis, perforation, and the presence of CC were found to be significant in predicting survival. It should be kept in mind that it would be more valuable to carefully select important parameters in the evaluation of metabolic complete response and survival and predict survival. It should not be forgotten that these findings may contribute to the determination of clinical factors that should be taken into consideration during the planning and follow-up of patients' treatment.

While PET/CT remains indispensable for initial staging, its prognostic utility in predicting TRG and survival may be limited unless standardized and combined with other parameters. Clinical features such as CEA dynamics and pathological indicators like LVI and PNI offer accessible, reproducible metrics that can inform treatment planning, surveillance intensity, and candidacy for organ-preservation strategies.

The timing of PET/CT imaging plays a critical role in its prognostic performance. In our study, only baseline PET/CT scans performed before nCRT were analyzed. This decision was based on our aim to investigate the predictive value of pre-treatment metabolic burden. However, it is important to acknowledge that interim or post-nCRT PET/CT assessments may provide more accurate representations of tumor response. Several studies have shown that changes in SUV, MTV, or TLG after treatment better correlate with TRG or survival. Thus, our findings should be interpreted within the context of baseline imaging only, and future studies incorporating serial PET/CT imaging may help establish more dynamic and responsive prognostic models.

Although our main finding—that baseline PET/CT metabolic parameters such as SUVmax, MTV, and TLG are not predictive of pathological response or survival—is consistent with several prior studies, our study provides additional value through its methodological

comprehensiveness and clinical relevance. With a relatively large single-institution cohort and long-term follow-up, we integrated imaging metrics with clinical, pathological, and biochemical variables to construct a multidimensional analysis of treatment response. Notably, we identified that non-imaging factors such as family history, post-treatment CEA levels, and pathological indicators including LVI, PNI, and perforation had stronger predictive value for TRG1 and survival than PET-based measures. These findings suggest that reliance solely on baseline PET/CT metrics may be insufficient for prognostic stratification, and underscore the importance of combining metabolic, pathological, and clinical markers to guide treatment planning and surveillance strategies in patients with LARC. Our results may support more personalized and clinically pragmatic approaches, particularly in selecting candidates for organ-preserving treatments.

The lack of predictive association between baseline F-18 FDG PET/CT parameters and TRG or survival observed in our study warrants further interpretation. One key factor may be the timing of imaging. Our study evaluated PET/CT parameters obtained exclusively prior to neoadjuvant chemoradiotherapy. In contrast, several studies demonstrating predictive value have focused on intra-treatment or post-treatment changes in metabolic activity, suggesting that dynamic response may be more informative than static baseline values. Furthermore, SUVmax, MTV, and TLG are influenced by a variety of technical and biological factors, including scanner calibration, patient preparation, and tumor heterogeneity. These metrics reflect a composite of metabolic burden but may not capture crucial elements of tumor biology, such as hypoxia, perfusion, or immune infiltration, which can strongly influence response to therapy.

Another consideration is that standardized imaging protocols and robust interobserver reliability are essential for ensuring reproducibility of metabolic parameters, which was not the focus of this retrospective study. These limitations underscore the need for future prospective trials that evaluate sequential PET/CT assessments, explore advanced radiomic features, and integrate molecular biomarkers (e.g., KRAS/NRAS/BRAF mutation status or circulating tumor DNA) to develop more nuanced prediction models. As metabolic imaging becomes increasingly sophisticated, combining FDG-PET/CT with clinical, pathological, and molecular data may yield improved stratification of responders and help identify optimal candidates for organ-preservation strategies.

Limitations

In addition to the retrospective, single-center design and associated selection and survival bias, several further limitations warrant consideration. First, we could not retrieve detailed information regarding treatment-related side effects, variations in chemoradiotherapy protocols, or the presence of common mutations such as *KRAS*, *NRAS*, and *BRAF*, due to incomplete or unavailable records. These molecular and treatment-related variables may significantly influence both treatment response and survival outcomes. Second, the interpretation of pathological TRG scoring and PET/CT metabolic values is inherently subjective and may vary between observers. The absence of standardized criteria across institutions and reliance on individual reader expertise may introduce interobserver variability. In our study, neither blinded scoring nor interobserver agreement assessment (e.g., kappa analysis) was performed, which represents a methodological limitation.

Furthermore, the use of ROC analysis to define optimal cut-off values, without external validation or adjustment for multiple comparisons, introduces a risk of overfitting and false discovery. These threshold values should therefore be interpreted as exploratory and hypothesis-generating rather than definitive. Additionally, the exclusion of patients with incomplete imaging, pathology, or follow-up data may have introduced selection bias, potentially affecting the generalizability of our findings. Lastly, the study lacked adjustment for potential confounding variables such as differences in tumor biology (e.g., mucinous vs. non-mucinous histology), radiation dose heterogeneity, and treatment interval variation, all of which may influence treatment response and survival but could not be fully accounted for due to limitations in the dataset. Future prospective, multicenter studies incorporating molecular profiling, standardized imaging protocols, dynamic metabolic monitoring, and comprehensive clinical data collection are warranted to validate and expand upon these findings.

Conclusions

Our study investigated the predictive value of pre-treatment F-18 FDG PET/CT parameters for TRG and survival in patients with locally advanced rectal cancer undergoing nCRT. The results revealed that baseline SUVmax, MTV, and TLG values were not significantly associated with TRG1 or survival outcomes, suggesting that these PET-based parameters may have limited utility in predicting pathological response in this clinical context. Conversely, clinical and pathological factors such as family history, post-RT and post-op CEA levels, perforation, LVI, and PNI were significantly associated with TRG1. Moreover, TRG1, histopathological subtype, perforation status, and CC were independent predictors of survival. These findings highlight the importance of integrating clinical and histopathological features rather than relying solely on baseline PET/CT data for response assessment. Further multicenter, prospective studies are

warranted to explore the standardization and prognostic potential of FDG-PET/CT in rectal cancer.

Abbreviations

FDG	(18)F] fluorodeoxyglucose
PET	Positron emission tomography
CT	Computed tomography
TRG	Mandard's tumor regression grade
LARC	Locally advanced rectal cancer
nCRT	Neoadjuvant chemoradiotherapy
CC	Concurrent chemotherapy
CEA	Carcinoembryonic antigen
CA19-9	Carbohydrate antigen 19-9
LVI	Lymphovascular invasion
PNI	Perineural invasion

Author contributions

The authors equally contributed to the conception, design of the study, definition of intellectual content, data collection, analysis and interpretation as well as manuscript writing. All the authors gave approval for the final submitted version of this article.

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Data availability

The datasets used for this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the decision of University Faculty of Medicine Health Sciences Ethics Committee (Date: 23.11.2022 and approval no: 1582. Informed consent to participate was obtained from all participants in the study. The Declaration of Helsinki protocol was followed in the research protocol. Our study is a retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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