Original article

Efficacy Of ^{18}FDG-PET/CT In Predicting Response After Neoadjuvant Chemoradiation In Rectal Cancer

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Abstract

Introduction: Neoadjuvant chemoradiation (NACRT) may result in significant response in rectal cancer. Conventional imaging may not be accurate. ^{18}FDG-PET/CT scan has shown promising results for monitoring the response to NACRT. The aim of this study is to evaluate the role of ^{18}FDG-PET/CT scan in predicting pathological response after NACRT in carcinoma rectum.

Methods: Thirty-two consecutive patients with locally advanced rectal cancer were enrolled. Patients underwent NACRT comprising of external beam radiotherapy and concomitant infusional 5-FU based chemotherapy. It was followed 6 weeks later by total mesorectal excision. All patients underwent FDG-PET/CT before and minimum 6 weeks after the completion of NACRT. Maximum standardized uptake (SUV_{max}) value was calculated. The tumor regression grade (TRG) in resected specimen was scored according to the Mandard criteria. TRG 1-2 was considered as responders and TRG 3-5, non-responders. The SUV_{max} within the tumor was correlated to differentiate pathological responders from non-responders.

Results: Fourteen of 30 patients were excluded due to protocol deviation. Following NACRT, 7 (50%) patients were classified as responders (TRG 1-2) and 7 (50%) non-responders (TRG 3-5). There were no significant differences in pre NACRT SUV_{max} between responders (12.05±2.81) and non-responders (17.65±7.20) (p=0.079). The mean post-NACRT SUV_{max} was significantly lower in responders than non-responders (6.4 vs 10.8; p=0.024). To compare the response using ROC curve analysis (AUC=0.83), and considering a cut-off post SUV_{max} as 7.0, the sensitivity was 57.14%, specificity 71.43%, positive predictive value (PPV) 66.67%, negative predictive value (NPV) 62.50%, and the overall accuracy was 64.28% to differentiate pathological responders from non-responders.

Conclusion: These preliminary results suggest that ^{18}FDG-PET/CT could be a potentially useful tool in predicting response after NACRT in locally advanced rectal cancer. Post SUV_{max} of 7.0 appears to be the best predictor tumor response following NACRT.

Keywords: Chemoradiotherapy; PET/CT; Rectal cancer; Tumor regression

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Introduction

The high local disease recurrence rates observed after radical surgery alone has led to the use of additional therapy either before or after surgery in locally advanced rectal tumors (LARC).[1] Hence, multimodality treatment with the combination of radiation therapy, chemotherapy and Total Mesorectal Excision (TME) has been considered the preferred approach for patients with LARC.[2,3]

Presently, assessment of rectal cancer includes clinical assessment of tumor and its response to neoadjuvant therapy with digital rectal examination, proctoscopy and biopsy. Conventional staging modalities includes endorectal ultrasonography, Contrast Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). Although local staging of rectal cancer with these modalities provides accuracy of 70% to 80%, these can be somewhat limiting with respect to reliably establish tumor response to neoadjuvant therapy.4 These tools cannot differentiate between early radiotherapy-induced inflammation or fibrosis from viable tumor cells in residual masses.[5] The accuracy of CT and MRI in predicting response is only 70%.[6]

In this regard, ^{18}FDG-PET/CT has shown to be superior to morphological imaging modalities (CT and MRI) in prediction of response to neoadjuvant approach in patients with LARC.[7-9] The objective of the present study is to assess the role of ^{18}FDG-PET/CT in assessing the tumor response rate to neoadjuvant chemoradiotherapy (CRT) in LARC.

Methods

This prospective study was conducted in Department of General Surgical in collaboration with Department of nuclear medicine, Histopathology and Department of Gastroenterology, from January 2013 to June 2014. [This study is a part of MCh dissertation].Thirty patients of LARC were enrolled after taking informed consent. The inclusion criteria was biopsy proven LARC (T3,T4 and N1/N2 disease). Those patients with synchronous cancer, metastatic disease or contraindication to neoadjuvant treatment were excluded.

Initial clinical assessment of patients comprised detailed history, complete physical examination, digital rectal examination, and Carcinoembryonic antigen (CEA) level determination. Staging of the disease was performed by Endoscopic Ultrasonography (EUS) and ^{18}FDG-PET/CT. These investigations were repeated 6 weeks after completion of neoadjuvant CRT. Tumor stage T3/T4 and N1/N2 nodal disease was considered as locally advanced.

^{18}FDG-PET/CT reporter was kept blind to the clinical as well as EUS findings. All the patients subsequently underwent TME and additional surgical procedure depending on the location of tumor. Resected specimen was subjected to detailed histopathological examination to confirm the grade and pathological TNM staging.

Neoadjuvant Chemoradiotherapy:

Neoadjuvant radiotherapy consisted of three-dimensional conformal radiotherapy (3DCRT) using linear accelerator and following CT planning in prone decubitus position. The radiation dose was 45 grays (Gy) with daily doses of 1.8Gy (5 fraction/week for 5 week) using 4-field box technique. Concurrently, patients received 5-flurouracil (500mg/m2 daily) and calcium leucovorin (30mg/m2) every week starting from day 1 of radiation therapy till 5 weeks administered by continuous IV infusion.

^{18}FDG-PET/CT:

^{18}FDG-PET/CT scan was obtained after intravenous injection of 370 megabecquerels (MBq) of 2-fluoro-18-FDG. Whole-body imaging was carried out in all patients. Lesions were identified as foci with increased tracer accumulation relative to surrounding soft tissues. Imaging was interpreted by a single experienced observer who will be unaware of the patient clinical assessment status of the tumor response. Standard uptake value (SUV), defined as the uptake of FDG-18 normalized by the administered injected FDG dose and by the weight of the patients, which was recorded pre neoadjuvant CRT and post CRT. SUV_{max} was determined using the maximal pixel value in a region. SUV_{max} more than 3.5 was considered as tumor uptake. Tumor response were assessed according to PERCIST criteria of minimum of 30% decrease in SUV_{max} value.10

Pathologic Assessment:

Pathologic tumor, node, metastases (TNM) staging was performed on the surgical specimen. Additionally circumferential resecton margin, proximal and distal resection margin, lymphovascular invasion were assessed. The tumor response was determined by using Mandard Tumor Regression grade (TRG), which classifies the tumor into 5 histological grades.[11]

TRG 1: 100% pathological response
TRG 2: 90% pathological response
TRG 3: 50-89% pathological response
TRG 4: 10-49% pathological response
TRG 5: <10% pathological response

According to TRG, the patients were divided into responders (TRG 1 and 2) and nonresponders (TRG 3 to 5)

Statistical Analysis:

Statistical evaluation was carried out using the statistical package SPSS for Windows (Version 17.0; SPSS Inc, Chicago,IL). P values ≤ 0.05 was considered statistically significant. To evaluate the correlations between the different metabolic parameters and tumor regression grade, the Kruskal-Wallis test was used. The numerical data were reported as mean±standard deviation, and qualitative variables with frequencies and percentages. A receiver-operating characteristics (ROC) curve was plotted to identify the cut-off value with highest accuracy for predicting pathological response. The cut-off value was defined by the point on the ROC curve with the minimum distance from the 0% false-positive rate and

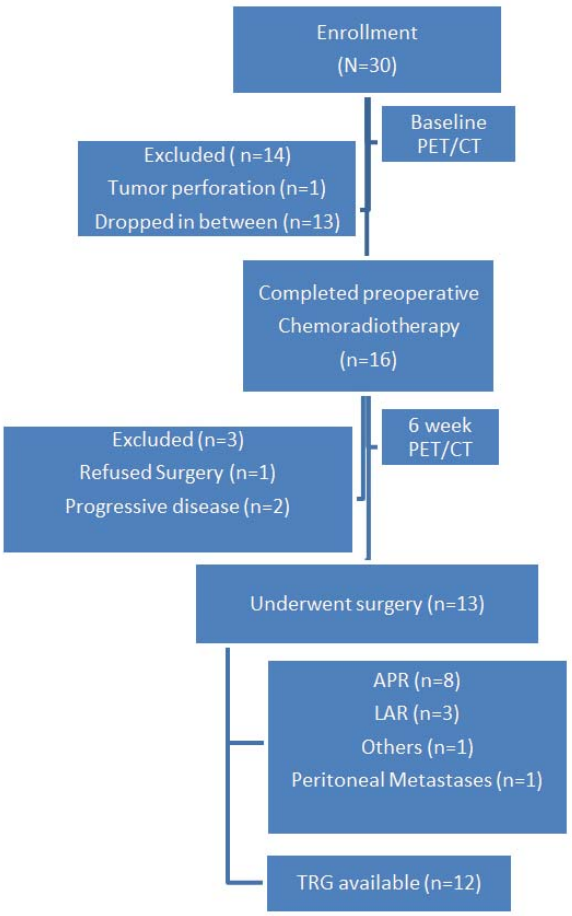

Figure 1. Flow-chart of study patients

100% true-positive rate. The higher ROC area under the curve (AUC) indicates a better discriminatory power. An AUC of 0.50 indicates that the test is as good as random chance for discriminating an outcome, whereas an AUC of 1.0 indicates perfect discrimination of the test (sensitivity and specificity of 100%). The sensitivity, specificity, and the positive and negative predictive values of ^{18}FDG-PET/CT were calculated using standard formulas.

Results

Patients characteristics:

The study consecutively enrolled 30 patients. Eighteen patients were excluded from the study for the reasons mentioned. Finally twelve patients had completed the treatment protocol. The mean age was 50 yr (range; 18-70 years) and the M:F ratio was 10:2. The main clinical features of the patients are described in **Table 1**.

During the neoadjuvant chemoradiation, thirteen patients droppped out of the study as they did not want to continue chemoradiotherapy and another patient had chemoradiation related tumor perforation who underwent Hartmann's procedure. Hence, a total sixteen patients completed neoadjuvant chemoradiation. They were subsequently evaluated after 6 week by PET/CT scan for the assessment of the response. Three patients were further excluded as two developed progressive disease (multiple liver metastases) and one refused surgery (**Figure 1**).

Overall, thirteen patients underwent surgery at a mean of 56 days (range: 37-66 days) after completion of neoadjuvant chemoradiation. Resectional surgery was performed after

Table 1. Patients Demographics

Patient characteristics (n=12)	Mean±SD
Age(yr)	50 (18-70)
Sex (Male:Female)	10:2
Symptoms:	
1. Bleeding PR	9 (75%)
2. Loose stool	6 (50%)
3. Tenesmus	4 (33.33%)
4. Pain	3 (25%)
Tumor distance from anal verge (cm)	
1. Upper third (>10cm)	2 (16.66%)
2. Middle third (7-10cm)	2 (16.66%)
3. Lower third (0-6cm)	8 (66.66%)
Fixed tumor	12 (100%)
Circumferencial involvement	
1. <50%	7 (58.33%)
2. 50-75%	3 (25%)
3. 75-100%	2 (16.66%)
Average size (cm)	4.75 (range:2-6)
Pretreatment clinical cT stage :no. (%)	
T3	9 (75%)
T4	3 (25%)
Pretreatment clinical cN stage	
N0	0
N1	100%
Operation: no. (%)	
APR	8 (66.66%)
LAR	3 (25%)
Others	1(8.33%)
Pathological (ypT) category: no.(%)	
ypT0	4 (33.33%)
ypT2	2 (16.66%)
ypT3	4 (33.33%)
ypT4	2 (16.66%)
Pathological (pN) category: no.(%)	
pN0	9 (75%)
pN1	2 (16.66%)
pN2	1 (8.33%)
Histopathology: no.(%)	
Adenocarcinoma	10 (83.33%)
Signet-ring cell carcinoma	2 (16.66%)

a median of 10 days (range: 5-21 days) of repeat PET/CT scan. One patients with middle-third signet ring cell rectal cancer had diffuse peritoneal metastases on exploration, hence was excluded from study. Finally twelve patients underwent definitive surgery alongwith TME as follows:

1. Abdominal perineal resection (APR): 8 (66.66%)
2. Low anterior resection (LAR): 3 (25%)
3. Total colectomy with APR: 1(8.33%)

Assessment of response to NACRT

Clinical: After neoadjuvant CRT, there was significant subjective improvement in symptoms, however, loose stool and pain persisted in 2 (16.66%) patients each. On objective assessment, the average tumor size decreased from 4.75 cm to 4.08 cm. In one (8.33%) patient, there was gross disapperance of tumor leaving behind only rectal thickening which was consistent with complete clinical response (cCR). In rest of the eleven patients tumor persisted as in pre neoadjuvant CRT state.

When comparing clinical responders with non-responders, the difference in SUV_{max} value and response index were in negative values of 0.5 and 5.88 respectively. This patient subsequently had pCR. Similarly, the 11 patients of clinical non-responders mean differences in SUV_{max} and response index were 7.16±8.16 and 49.23±23.00 respectively. On tumor regression analysis, they subsequently had 5 pathological responders (TRG1-2) and 6 non-responders (TRG4-5). Hence clinical response was not correlating with pathological response on TRG analysis.

FDG-PET/CT was done after completion of chemoradiotherapy in all twelve patients. The overall mean post SUV_{max} was 8.17 ± 3.78 (4.0-14.9) which was significantly lower than the pre SUV_{max} value14.69 ± 6.46 (8.4-28.5) (p= 0.017) **Table 2**.

The differences in SUV_{max} (ΔSUV_{max}) assumed negative values (post SUV_{max} higher than preSUV_{max}) in three patients, probably due to postradiotherapy inflammatory changes.

Four patients (33.33%) who had pathological compete response (pCR) had lower mean post SUV_{max} (5.62±2.28 vs 9.16±1.57 p= 0.055) compared with those without the response (5.6 vs 9.1). Similarly, on basis of TRG, the mean Response Index (RI) among tumor responders were 46.33±22.65 (range: 5.9-71.7), while among non-responders mean value was 45.13±45.13 (5.9-80.7). Hence, both responders and non-responders are showing similar percentage fall in SUV_{max} after CRT.

Histopathological regression:

The pathological T stage as per AJCC, TNM 7th edition was T0 in 4 (33.33%) patients, T2 in 2 (16.66%), T3 in 4 (33.33%), T4 in 2 (16.66%) patients, and no patients were T1. The pathological N stage was N0 in 9 (75%) patients, N1 in 2 (16.66%) and N2 in 1 (8.33%) patients

Table 2. Overview of stage, SUV_{max}, CEA and TRG before and after neoadjuvant CRT

	Pre CRT	Post CRT	Differences (Δ)	P value*
AJCC				
Stage 0	-	4 (33.33%)	-	
Stage I	-	1 (8.33%)		
Stage II	-	4 (33.33%)		
Stage III	12 (100%)	3 (25%)		
SUV_{max} (mean±SD)	14.69 ± 6.46	8.17 ± 3.78	6.52 ± 8.09	0.017
Minimum	8.4	4.0		
Maximum	28.5	14.9		
Response Index (RI): (%)- mean±SD				
Responders	-	-	46.33 ±22.65	0.939
Non-responders	-	-	45.13 ±29.85	
CEA (ng/ml) (mean±SD)	5.10 (±2.92)	2.99 (±2.09)	-1.79 (±3.81)	0.570
Tumor regression grade (TRG)				
1		4 (33.33%)		
2		2 (16.66%)		
4		3 (25%)		
5		3 (25%)		

**Paired t-test*

(Table 1). Proximal, distal and circumferential resection margins were free of tumor. Lymphovascular emboli (LVE) were present in 2 (16.6%) patients. There was tumor downstaging in 9 patients (75%) from stage III to stage 0 in 4 patients (33.33%), stage I in 1 patients (8.33%) and stage II in 4 patients (33.33%). Three patients (25%) was not downstaged and remained in stage III. Four patients (33.33%) had compete pathological response (pCR).

Tumor Regression:

Mandard criteria: The pathologist were blinded for the results of PET-CT findings. According to Mandard criteria, tumor response was classified as TRG 1 in 4 (33.33%) patients, TRG 2 in 2 (16.66%), TRG 4 in 3 (25%) patients and TRG 5 in 3 (25%) patients. No TRG 3 was observed. According to the prognostic values of TRG score, we have classified them into two groups. Responders (TRG1-2; 50% patients) and non-responders (TRG 3-5; 50% patients).On analyzing the tumor stage response with responders, the improvement in tumor stage was collaborating with TRG in 5/6 patients (83.33%). On contrary, improvement in tumor stage in 4/6 (66.66%) patients was not collaborating with tumor regression in non-responders, may be because these group also show tumor regression from 10-49%, although

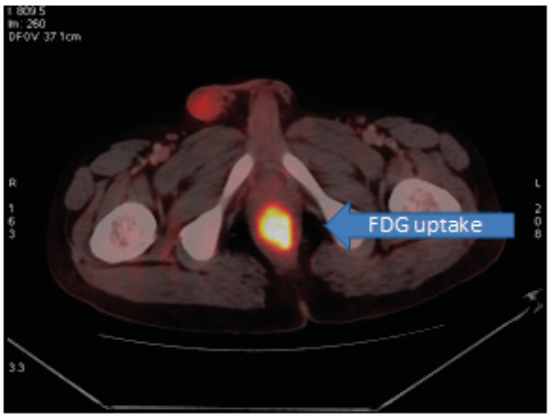

Figure 2. PET/CT scan of patient before CRT showing increased uptake in lower third of rectum (SUV_{max} 16.3)

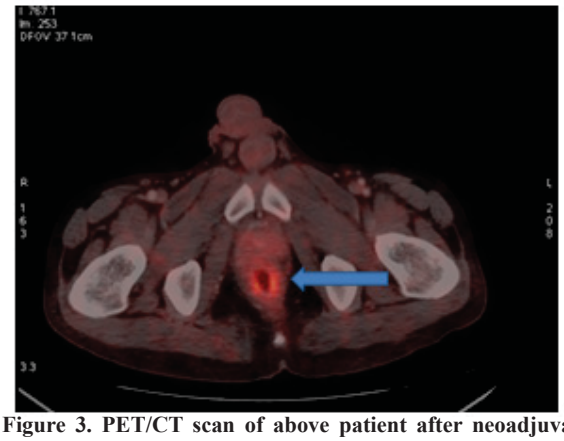

Figure 3. PET/CT scan of above patient after neoadjuvant CRT, tumor uptake (SUV_{max} 4.6). The TRG was 1

being categorized as non-responders based on mandard regression.

On analysis, the mean post SUV_{max} (6.00±1.82 vs 12.5±2.69: p=.001) and mean difference in SUV_{max} (10.57±6.43 vs 2.47±2.73: p= 0.039) were significantly lower in responders than nonresponders (**Table 3**). In addition, the fall in SUV_{max} was higher in responders than nonresponders (16.57 to 6.00 vs 11.46 to 12.5).

Table 3. Comparision of response (>30% change) by PET/CT with SUV_{max}

	Responders (n=8)	Non-responders (n=4)	P value*
Mean pre SUV_{max}	16.57 ±7.06	11.46 ±2.75	.162
Mean post SUV_{max}	6.00 ±1.82	12.5 ±2.69	.001
Mean ΔSUV_{max}	10.57 ±6.43	2.47 ±2.73	.039
Mean Response Index (RI)	60.30 ±13.29	16.57 ±15.26	.000

**Paired t-test*

FDG-PET/CT findings and TRG

Based on the Mandard criteria, 6 (50%) were divided into responders (TRG1-2) and 6 (50%) patients non-responders (TRG 4-5). When regrouping the population into responders and non-responders, the mean post SUV_{max} values were lower in responders (6.08±1.93 vs 10.25±4.16; p=0.051). Similarly, both the responders and nonresponders had similar decrease in response index (46.33 vs 45.13). Although there was higher fall in CEA value after neoadjuvant CRT in responders, the change was nonsignificant (2.46±2.87 vs 1.12±4.76; p=0.57).

Using best cut off threshold value of post SUV_{max} of 7.0, the area under the receiver operating characteristic curve (AUC =0.833; p=0.055) for defining response to therapy, it was possible to discriminate with sensitivity of 66.66%, specificity of 66.66%, positive predictive value (PPV) and negative predictive value (NPV) of 66.66% and 66.66% respectively and the accuracy of 66.6% as shown in ROC analysis and curve. Similarly, using 56.25% as the cut-off threshold for the response index (RI) values, area under the receiver operating characteristic curve (AUC=0.542: p=0.810) for defining response, sensitivity of 66.67%, specificity of 50%, PPV and NPV of 57.14% and 60% respectively were seen. The accuracy was 58.33%.

Discussion

Functional imaging, such as ^{18}FDG-PET/CT is a promising approach for evaluating tumor response.[7,12,13] There is some evidence indicating that ^{18}FDG-PET/CT may be more accurate than morphological imaging, but the optimal method for quantitative analysis has yet to be determined. SUV_{max} is the most commonly studied metabolic parameters for semiquantitative analysis of glucose metabolism with PET/CT. Most studies have indicated the SUV_{max} is a promising predictor of response to neoadjuvant CRT.[14,15]

Although there is no universal consensus on percentage decrease in SUV_{max}, 36% reduction in SUV uptake is considered as response to CRT in rectal cancer.[16] In our study, assuming 30% reduction as a criteria of response we could correlate PET/CT response with histological response. Similarly, for rectal cancer, reported response index (RI) values range from 50% to 60%. Only one study has reported a much higher RI of 83%.[7] Although the European Organisation for Research and Treatment of Cancer (EORTC) defined a change in SUV_{max} >36% as an indicator of therapeutic response, the optimal cut-off for RI to predict response is not well known.[16] In the present study using 30% as cut-off for ΔSUV_{max}, there were 8 responders (66.66%) vs 6 nonresponders (50%) patients on the basis of TRG. But our ROC analysis defined a 56.25% decrease in SUVmax as the cut-off value for defining tumor response (TRG) to therapy with 66.67% sensitivity and 50% specificity which is in the range as shown by previous studies.

Although the validity of ^{18}FDG PET/CT for monitoring the effects of neoadjuvant therapy is recognized, its capacity

to predict TRG according to differences in uptake intensity between before and after treatment is not generally accepted. The diagnostic validity found in our study was low and close to those previous studies. Most studies on PET/CT seem to show a high sensitivity, specificity, positive and negative predictive value of post-CRT PET scans. Contrary to these studies, however, Kristiansen et al,[17] showed the sensitivity was 44%, specificity was 64%, PPV and NPV was 58% and 50% respectively. Similarly, Janssen et al,[18] reported on 30 patients with LARC treated with preoperative CRT. PET scans were performed on days 8 and 15 during CRT. Pathologic response was assessed using the TRG scale. The investigators found that the day 15 PET scan correlated better with histologic response, and a response index (RI) of >43% for SUVmax showed a sensitivity of 77% and a specificity of 93%.

In the present study, the post SUV uptake increased in two patients suggesting that they did not respond to CRT and the tumor appeared progression as confirmed by histopathology. Lone patient despite showing complete pathological response there was high post SUV_{max}.The possible explanation may be due to the radiotherapy-induced inflammation which could increase FDG uptake up to 25% in inflammatory cells.[12]

In the present study, downstaging was predicted with 66.66% sensitivity and 66.66% specificity using post SUV_{max} of 7.0 as the cut-off value. Because below this 7.0 cut-off value of post SUV_{max}, tumor was showing histopathological response. Inspite of dramatic decrease in post SUV_{max} from 17.65 to 10.25 and mean response index (RI) of 45% in non-responders, there were no pathological tumor response in 4/6 (66.66%) patients. The possible explanation for this decrease post SUV_{max} may be a temporary reversible reduction in tumor FDG uptake caused by the so-called "stunning" of tumor cells.[13]

In the present study, there was high drop out rate of 25% (5/ 20) , which was much higher than 7% (6/ 87).[14] Reason is our patients were low BMI, high incidence of radiation induced toxity, financial constraint and fear of permanent stoma . Moreover, the patients in whom there is excellent clinico pathological response, they consider it as a sign of cure and do not come back for surgery.

The results of this study were limited by the small number of patients. Another shortcoming of this study is that we have used only index for assessment of tumor response whereas in the literature most studies used various quantifiers, such as clinical pathological response, total lesion glycolysis (TLG), tumor regression grade, visual response score and metabolic tumor volume (MV) on ^{18}FDG-PET scans.

Conclusion

It may be concluded that more than 30% reduction in SUV uptake after CRT was moderately co related with pathological response. The stunning phenomenon and radiation induced fibrosis were the possible factors responsible for poor response prediction. Larger studies may be needed to improve the prediction of response following chemoradiotherapy in primary rectal cancer.

References

1. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351(17):1731–40.
2. Folkesson J, Birgisson H, Pahlman L, et al. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23(24):5644–50.
3. Tjandra JJ, Kilkenny JW, Buie WD, et al. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 2005;48(3):411–23.
4. Schaffizin DM, Wong WD. Endorectal ultrasound in the preoperative evaluation of rectal cancer. Clin Colorectal Cancer 2004;4(2):124-132.
5. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage O distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240(4):711-7.
6. Zerhouni EA, Rutter C, Hamiton SR, et al. CT and MR imaging in the staging of colorectal carcinoma: report of the Radiology Diagnostic Oncology Group II. Radiology 1996;200(2):443-451.
7. Capirci C, Rampin L, Erba PA, et al. Sequential FDG-PET/CT reliably predicts response of locally advanced rectal cancer to neo-adjuvant chemo-radiation therapy. Eur J Nucl Med Mol Imaging 2007;34:1583–1593.
8. Rau B, Hunerbein M, Barth C, et al. Accuracy of endorectal ultrasound after preoperative radiochemotherapy in locally advanced rectal cancer. Surg Endosc. 1999;13:980–4.
9. Guillem JG, Puig-La Calle Jr J, Akhurst T, Tickoo S, Ruo L, Minsky BD, et al. Prospective assessment of primary rectal cancer response to preoperative radiation and chemotherapy using 18-fluorodeoxyglucose positron emission tomography. Dis Colon Rectum. 2000;43:18–24.
10. Richard L, Heather J, Lodge Martin et al. From RECIST to PERCIST : Evolving consideration for PET response criteria in solid tumors. J Nucl Med. 2009;50: 122S-150S
11. Mandard AM, Dalibard F, Madard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiation therapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994;73:2680–6.
12. Cascini GL, Avallone A, Delrio P, et al. 18F-FDG PET is an early predictor of pathologic tumor

response to preoperative radiochemotherapy in locally advanced rectal cancer. J Nucl Med 2006;47:1241–1248.
13. Chongjial Li, Xiaoli Lan, Hui Yuan, et al. 18FDG PET predicts pathological response to preoperative chemoradiotherapy in patients with primary rectal cancer: a meta-analysis. Ann Nucl Med 2014;28:436-446.
14. Capirici C, Rubello D, Pasini F, et al. The role of Dual-time combined 18Fluorodeoxyglucose positron emission tomorgaphy and computed tomography in the staging and restaging workup of locally advanced rectal cancer, treated with preoperative chemoradiation therapy and radical surgery. Int J radiation Oncology Biol Phys 2009;74(5):1461-1469.
15. Caruso R, Vicente E, Quijano Y, Duran H, Fabra I, Diaz E, Malave L, Agresott R, Cañamaque LG, Ielpo B, Ferri V. Role of 18F-PET-CT to predict pathological response after neoadjuvant treatment of rectal cancer. Discov Oncol. 2021 May 18;12(1):16.
16. Di Fabio F, Pinto C, Ceccarelli C, et al. Correlation between FDG-PET and pathological response in patients with rectal cancer treated with neo-adjuvant chemoradiotherapy: First results of the Bologna Project. ASCO 2005;Abs. n. 3623.
17. Kristiansen C, Loft A, Berthelsen AK, Graff J, et al. PET/CT and histopathologic response to preoperative chemoradiation therapy in locally advanced rectal cancer Dis Colon Rectum 2008;51:21-25.
18. Janssen MH, Ollers MC, Riedl RG, et al. Accurate prediction of pathological rectal tumor response after weeks of preoperative radiochemotherapy using 18Fluorodeoxyglucose-positron emission tomography-computed tomography imaging. Int J Radiat Oncol Biol Phys 2010;77:392-399.