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ORIGINAL ARTICLE

The value of ^{18}F-FDG PET/CT for assessing the response to neoadjuvant therapy in locally advanced rectal cancer

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Abstract
Purpose Neoadjuvant radiochemotherapy (RCT) is an accepted treatment for locally advanced rectal cancer (LARC) that improves surgical outcomes. If a pathological complete response is achieved, conservative surgery can be considered. The objective of our study was to assess the reliability of ^{18}F-FDG PET/CT for evaluating the response to neoadjuvant RCT in LARC.
Methods We prospectively studied 41 patients diagnosed with LARC and candidates for neoadjuvant RCT. PET/CT was performed before RCT and again 7 weeks later. A visual and semiquantitative analysis was carried out. The pathological response was classified according to the Mandard tumour regression grade (TRG). We analysed: (a) the relationship between TRG and the result of the posttreatment PET/CT scan, and (b) the correlation between the percentage of pathological response and the percentage decrease in SUVmax according to the response index (RI).
Results The mean SUVmax of the rectal lesions at diagnosis was 13.6 and after RCT 3.96. The mean RI was 65.32 %. Sensitivity was 88.88 %, specificity 92.86 %, positive predictive value 96 %, negative predictive value 81 %. Of the 41 patients, 8 had TRG I (all negative PET/CT); 6 had TRG II (5 negative, 1 positive PET/CT); 16 had TRG III (13 positive, 3 negative PET/CT); 9 had TRG IV (all positive PET/CT); 2 had TRG V (all positive PET/CT). Of the 14 patients classified as responders (TRG I, II), 13 (92.86 %) had negative PET/CT. Of the 27 patients classified as nonresponders (TRG III–V), 24 (88.88 %) had positive PET/CT. Differences were statistically significant ($p<0.0001$). The RI in responders was 79.9 % and in nonresponders was 60.3 %. Differences were statistically significant ($p<0.037$).
Conclusion PET/CT is a reliable technique for assessing response to neoadjuvant RCT in LARC, with a view to considering more conservative surgical treatment. The combination of the visual and semiquantitative analysis increases the diagnostic validity of PET/CT.

Keywords ^{18}F-FDG PET/CT · Locally advanced rectal cancer · Neoadjuvant therapy · Response index

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Introduction

Rectal carcinoma is a highly relevant neoplasia in daily clinical practice and as a consequence it is necessary to constantly develop diagnostic and therapeutic techniques to improve the survival and quality of life of patients with this disease.

Surgery is the fundamental curative approach for rectal carcinoma, so that in its early stage (stage I) a local approach using resection can be enough to avoid the morbidity associated with more extensive resections. In locally advanced stages (II/III) rectal carcinomas are treated using anterior resection with colorectal anastomosis, low anterior resection, or abdominoperineal amputation with resection of the sphincter apparatus and construction of a definitive colostomy.

In recent decades the use of neoadjuvant concomitant radiochemotherapy (RCT) has been encouraged in locally advanced stages [1, 2]. Its main advantages are the reduction in tumour size and stage [3, 4], increased resectability and sphincter conservation, and a lower rate of acute toxicity and local relapse [4–6]. Consequently, in a quite high number of patients, the tumour cells are completely eliminated (in as many as 30 % of patients in some series), a situation known as a pathological complete response [7, 8]. Furthermore, this treatment provides better long-term results with a very low or zero rate of local recurrence or distant relapse [9, 10].

Therefore, in the light of the good prognosis in patients with pathological complete response, new more conservative treatment strategies are being developed to avoid rectal resection. As a consequence, local resection with complete excision of the wall has been reported in patients in whom rectal examination and imaging provide sufficient information [11, 12] to carry out a thorough analysis of the tumour to ensure a pathological complete response. This provides many advantages with a consequent reduction in morbidity and mortality and the preservation of the sphincter apparatus [13, 14].

For these reasons, it is necessary to reliably establish tumour response to neoadjuvant therapy. However, conventional imaging techniques (endorectal ultrasonography, CT and MRI), which have been confirmed as indispensable tests for staging these patients, have not proven to be reliable predictors of response to neoadjuvant treatment, given that they tend to overestimate local tumour extension after treatment (fibrotic changes, oedema, etc.) [15, 16]. In contrast, functional imaging with ^{18}F-FDG based on tumour glucose metabolism has proven to be capable of reliably predicting treatment response in showing greater certainty in detecting residual tumours [17–19], and in providing patients in full remission with the option of more conservative surgery. It also helps to identify the absence of neoadjuvant response, allowing the clinician to replace RCT protocols with more aggressive alternatives. In this regard, the degree of ^{18}F-FDG uptake reduction after neoadjuvant treatment compared to its baseline value in the pretreatment stage has been proposed as an index for the early prediction of regression in tumours treated with RCT [20, 21].

The objective of the present study was to assess the reliability of ^{18}F-FDG PET/CT for evaluating response to neoadjuvant therapy in locally advanced rectal cancer, comparing tumour glucose metabolism in pretreatment and posttreatment scans and its correlation with the level of pathological response.

Material and methods

Patients

We carried out a prospective longitudinal study in 41 patients (25 men and 16 women, mean age 66 years) diagnosed with locally advanced rectal adenocarcinoma (stages II/III) in our hospital between January 2009 and September 2011, and who were candidates for neoadjuvant therapy with RCT. The following exclusion criteria were applied: pregnancy, neoadjuvant therapy contraindicated due to comorbidity, presence of another synchronic tumour, suspicion of an inherited condition (familial adenomatous polyposis), and inflammatory bowel disease.

All the patients followed conventional diagnostic/staging procedures for characterizing the rectal lesion (location and size, distance from the sphincter apparatus, circumferential resection margin, its relationship with neighbouring organs, infiltration of the mesorectum, and the existence of adenopathies) through the usual techniques of rectal examination, endorectal ultrasound-guided biopsy, complete colonoscopy and pelvic MRI. In addition, staging of distant disease was performed by ^{18}F-FDG PET/CT and a thoracoabdominopelvic CT scan.

Neoadjuvant radiochemotherapy

Neoadjuvant radiotherapy (RT) consisted of three-dimensional conformal RT following CT planning in the prone decubitus position, using three fields (one anterior and two lateral). The RT dose was 46–50 Gy to the whole risk volume, followed by an overdose of 4–8 Gy to the macroscopic tumour volume with a margin of 1–1.5 cm. Approximate treatment duration was five and a half weeks. Chemotherapy (capecitabine, 825 mg/m^2 twice daily) was administered concomitantly.

^{18}F-FDG PET/CT scan and image analysis

Two PET/CT scans were carried out, one after the initial diagnosis to complete disease staging, and another 7 weeks after completion of neoadjuvant treatment to evaluate the metabolic response. The patients were asked to fast for at least 4 h before the ^{18}F-FDG PET/CT scan. Their blood glucose levels were within the normal range (70–120 mg/dL) prior to intravenous injection of 370 MBq (10 mCi) of ^{18}F-FDG. Data were acquired on an integrated PET/CT system (Gemini GXL-Philips) within 60–90 min of

injection. The procedure for data acquisition was as follows: CT scanning was performed first without administration of oral or intravenous contrast agent from the head to the pelvic floor with 120 kV, 100 mA and a 5-mm section thickness. Immediately after CT scanning, a PET emission scan covering the identical transverse field of view was obtained. The acquisition time was 3 min per table position. PET image datasets were reconstructed iteratively by applying the CT data for attenuation correction, and coregistered images were displayed on a workstation.

Studies were interpreted by qualitative and semiquantitative analysis. According to the qualitative visual analysis and on the basis of the normal biodistribution of ^{18}F-FDG, lesions were identified as foci with increased tracer accumulation relative to that in comparable normal contralateral structures and surrounding soft tissues. Tumour metabolic activity was quantified in terms of the standardized uptake value (SUV) normalized to the injected dose and to body weight. The maximum single-pixel SUV (SUVmax, mean±SD) of the lesions was calculated drawing manually the regions of interest around the tumour and on all the consecutive transaxial slices that contained the tumour so that the whole tumour was included in the regions of interest. We considered SUVmax greater than 2.5 to be positive.

The metabolic response shown on the PET/CT scan after treatment was assessed visually and in terms of the reduction in SUVmax compared to the baseline scan, and the percentage difference in SUVmax or the response index (RI) between the initial PET/CT scan and the scan after treatment calculated according to the formula:

RI = [(pretreatment SUVmax − posttreatment SUVmax)/(pretreatment SUVmax)] × 100

Surgery and histopathological study

Surgical treatment was carried out during the 8th week after neoadjuvant treatment. The postsurgical histopathological stage and the percentage of pathological response were determined by analysis of a surgical specimen using the Mandard tumour regression grade (TRG) [22, 23], which classifies the tumour into five histological grades: TRG I is the absence of cancer cells/complete regression (100 % pathological response); TRG II is the presence of isolated tumour cells scattered throughout the fibrosis (90 %); TRG III is an increase in the number of cancer cells but with fibrosis still predominating (50–89 %); TRG IV is residual cancer outgrowing the fibrosis (10–49 %); TRG V is the absence of regression (<10 %). According to TRG the patients were divided into two groups: responders (TRG I and II) and nonresponders (TRG III to V).

Table 1 Patient characteristics and results

	Number	Minimum	Maximum	Mean	Standard deviation
Age (years)	41	44	85	66.0	11.02
SUVmax					
Before neoadjuvant treatment	41	2.4	39.0	13.6	7.61
After neoadjuvant treatment	41	1.0	16.0	3.96	2.74
Percent fibrosis	41	10	100	70.65	29.9
RI	41	−3.8	93.7	65.32	22.84

Neoadjuvant response was analysed from two perspectives:

1. The relationship between TRG and the result of the posttreatment PET/CT scan.
2. The correlation between the percentage pathological response and the percentage decrease in SUVmax.

Statistical analysis

The numerical data are reported as means±standard deviation, and the qualitative variables with frequencies and percentages. For the comparative study of the means we used nonparametric tests (Kruskal-Wallis). To contrast the qualitative variables we used the chi-squared test. All results with a confidence level of 0.05 were considered positive. The statistical analysis was carried out using the SPSS program v. 18.0.

Results

^{18}F-FDG PET/CT detected the primary tumour in all patients. The mean SUVmax of the rectal lesions at diagnosis was 13.6. After neoadjuvant treatment the mean SUVmax was 3.96. The mean RI was 65.32 %. The mean percentage fibrosis in the histopathological samples after neoadjuvant treatment was 70.65 % (Table 1).

Table 2 Comparison between PET/CT after neoadjuvant treatment and histopathological results

PET/CT scan result	Histopathology result		Total
	Positive (nonresponders: TRG III, IV and V)	Negative (responders: TRG I and II)	
Positive	24	1	25 (60.97 %)
Negative	3	13	16 (39.03 %)
Total	27 (65.85 %)	14 (34.15 %)	41 (100 %)

Table 3 Comparison between posttreatment PET/CT scan result and TRG

PET/CT scan result	TRG grade					Total
	I	II	III	IV	V	
Positive	0	1	13	9	2	25
Negative	8	5	3	0	0	16
Total	8	6	16	9	2	41

Of the 41 patients studied, in 25 (60.97 %) the PET/CT scan was positive after neoadjuvant treatment (24 true-positive and 1 false-positive), and in 16 (39.03 %) the scan was negative (13 true-negative and 3 false-negative). The test had high diagnostic effectiveness ($p < 0.0001$), with a sensitivity of 88.88 %, a specificity of 92.86 %, a positive predictive value of 96 % and a negative predictive value of 81 % (Table 2).

Relationship between TRG and result of posttreatment PET/CT scan

Of eight patients with complete regression (TRG I), all had a negative PET/CT scan. Of six patients with isolated tumour cells (TRG II), five had a negative PET/CT scan and one a positive scan. Of 16 patients with more residual cancer cells but with fibrosis predominating (TRG III), 13 had a positive PET/CT scan and 3 a negative scan. Of nine patients with residual cancer outgrowing fibrosis (TRG IV), all had a positive PET/CT scan. Finally, of two patients with absence of regression (TRG V), all had a positive PET/CT scan. Overall, of the 14 patients classified as responders (TRG I and II), 13 (92.86 %) had a negative PET/CT scan and 1 (7.14 %) a positive scan. Of the 27 patients classified as nonresponders (TRG III, IV and V), 24 (88.88 %) had a positive PET/CT scan and 3 (11.11 %) a negative scan. The differences between the level of pathological response and the result of the PET/CT scan were significant ($p<0.0001$; Table 3).

Figures 1 and 2 show two representative cases of a nonresponder and a false-negative patient, respectively.

Relationship between pathological response and decrease in SUVmax according to the RI

In the TRG I patients, the mean RI was 71.7 %, in the TRG II patients, the mean RI was 79.16 %, and in the TRG III, IV and V patients, the mean RIs were 72.97 %, 47.59 % and 30.8 %, respectively. The differences between the level of pathological response and the RI were significant ($p=0.013$). Overall, the mean RI in the responders was 79.9±4.69 %, and the mean RI in the nonresponders was 60.3±4.6 % ($p<0.037$; Table 4).

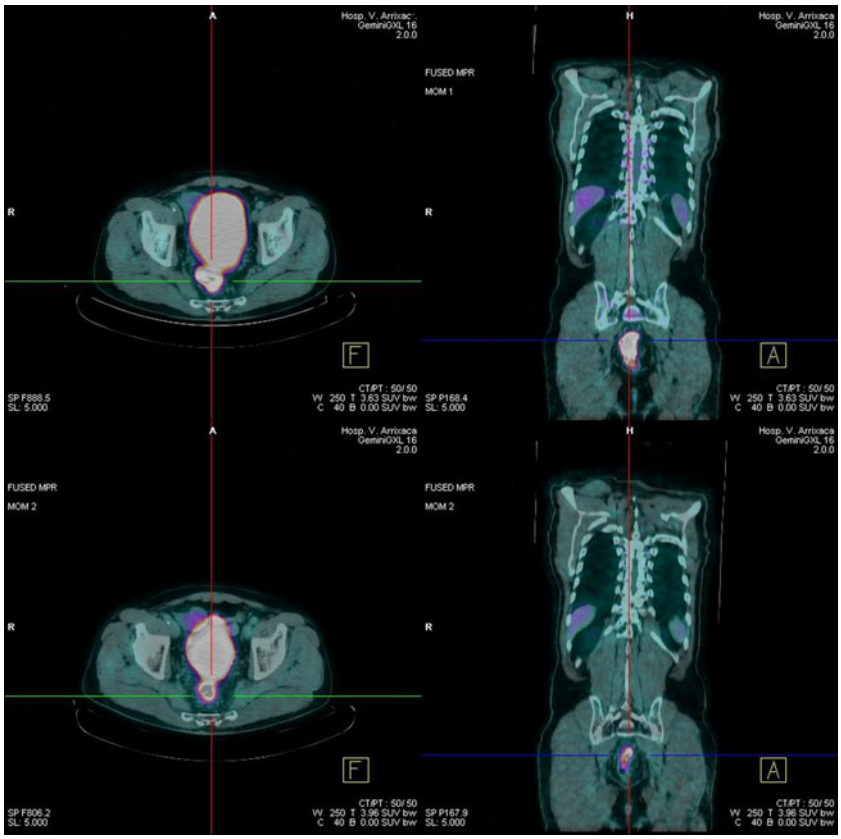

Fig. 1 ^{18}F-FDG PET/CT scan in a nonresponder. In the baseline scan (*upper row*) there is increased ^{18}F-FDG uptake in the middle third of the rectum (SUVmax 12.8), and in the scan after neoadjuvant treatment (*lower row*), tumour uptake is still present (SUVmax 6.8) revealing residual vital tumour tissue. The postsurgical TRG was IV (20 % pathological response), and the patient was classified as true-positive

Table 4 SUVmax and RI in relation to TRG

	TRG grade				
	I (8 patients)	II (6 patients)	III (16 patients)	IV (9 patients)	V (2 patients)
SUVmax before neoadjuvant treatment					
Mean	11.66	12.16	16.23	11.64	13.5
Standard deviation	9.05	2.73	8.38	5.42	4.5
SUVmax after neoadjuvant treatment					
Mean	1.95	5.7	3.86	6.02	8.45
Standard deviation	0.8	0.27	1.4	3.95	0.45
RI (%)					
Mean	71.7	79.16	72.97	47.59	30.8
Standard deviation	8.01	2.71	4.06	8.17	19.7

Discussion

We consider several aspects of the characteristics of the sample, methodology and results of our study, and confirm that the population under study did not differ from those in other similar studies. All the patients were in the same evolutionary stage, and by including only patients with stages II/III and not those with stage IV, we ensured that the final results were unaffected by the worse prognosis that the presence of distant metastases would have conferred. There is unanimity [24] over the better results obtained with the concomitant use of RCT (in terms of toxicity, control of local disease, local recurrence and survival) rather than the exclusive use of RT. This has made it possible to standardize a common neoadjuvant treatment protocol in different institutions allowing a certain amount of variability for optimizing treatment in an individual patient. The treatment used in our patients was no different from the commonly accepted method. Similarly, the interval between the adopted procedures was that recommended by the World Health Organization [25]: a late PET/CT scan 7 weeks after neoadjuvant therapy, and early surgery 1 week later.

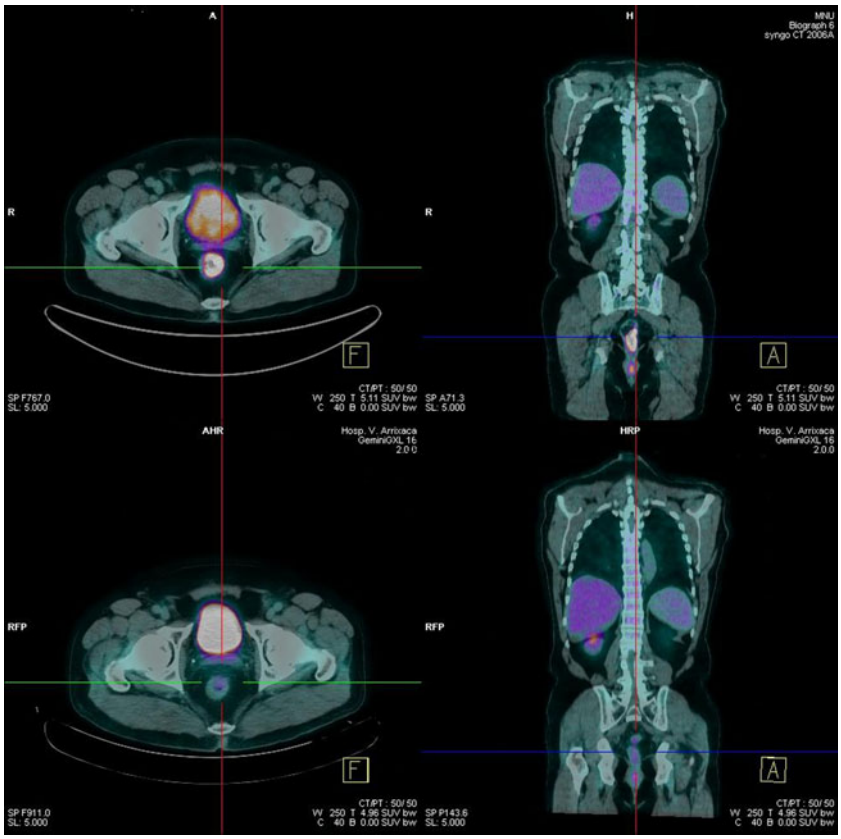

Fig. 2 ^{18}F-FDG PET/CT scan in a false-negative patient. In the baseline scan (*upper row*) there is increased ^{18}F-FDG uptake in the middle third of the rectum (SUVmax 15), and normal distribution in the scan after neoadjuvant treatment with a SUVmax of 2.3 (*lower row*). The histopathological examination revealed residual cancer cells with 85 % pathological response (TRG III)

Although the validity of ^{18}F-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. Therefore, we investigated this aspect in our sample as one of the objectives of the study. ^{18}F-FDG PET/CT detected the primary tumour in all patients. In addition, statistical significance was found between the PET/CT and histopathological results in terms of TRG, grouping the patients into responders (TRG I and II) and nonresponders (TRG III, IV and V; $p<0.0001$), and also between the PET/CT results and the five categories of pathological response ($p<0.0001$). The diagnostic validity found in our study was high (sensitivity 88.88 %, specificity 92.86 %, positive predictive value 96 % and negative predictive value 81 %) and greater than that obtained in previous studies [26, 27], regardless of whether the authors used visual analysis or a semiquantitative method. We used a combined analysis that was not mutually exclusive involving visual and semiquantitative analyses through the SUVmax. This combined analysis was especially useful in those patients in whom the posttreatment SUVmax was around the strict cut-off point of 2.5, because the visual analysis helped define a positive or negative result. In this regard, 11 patients had a SUVmax of 2.5 or very close to 2.5, and the two methods provided consistent findings (PET positive or negative) in nine patients and discrepant findings in two, who were ultimately classified according to the visual evaluation of the PET scan. Thus, either the PET/CT result or the pathological tumour response was true-negative and the other true-positive, a situation that would not have occurred if only SUVmax had been used for the evaluation, in which case they would have been false-positive and false-negative, respectively.

In this study we used the TRG after histopathological examination of the total residual tumour mass, thus eliminating the possibility of an incomplete histological analysis which could have led to a wrong interpretation such as finding a patient to be false positive who was really true positive. One patient had a SUVmax of 2.5 (a negative value in strict terms), but a positive visual evaluation, so was classified as false-positive because the patient was TRG II (isolated tumour cells). It is unlikely that there were sufficient tumour cells to account for the uptake (uptake by these cells would have been below the level of detection by PET), or that discrete inflammatory activity could have accounted for the uptake (we tried to avoid this by carrying out a late posttreatment PET/CT scan when the inflammatory tissue caused by the RT should have disappeared). However, the false-positive finding in this patient did not affect the statistical significance of the results. In contrast, we found three false-negative TRG III patients (tumour with fibrosis predominating) with SUVmax values of 1, 1.6 and 2.3, respectively, and with a negative visual evaluation. This finding could have been due to the residual tumour being less than 10 mm in these patients, because it is widely believed that the detection capacity of PET is limited in this regard. Alternatively, the lesion could have been larger but with a low metabolic rate due to cell disruption induced by treatment, and therefore was not shown by PET. Disease progression as a cause of these false-negative findings is ruled out in our study because of the short time between the posttreatment PET/CT scan and surgery.

All patients except one, in whom there was an increase in posttreatment SUVmax, showed a decrease in SUVmax after neoadjuvant treatment. The mean pretreatment SUVmax was 13.6 and the mean posttreatment SUVmax was 3.96, representing a decrease of 71 %. Regarding our second objective (to compare the level of pathological response with the RI), there were statistically significant differences ($p<0.037$) between responders with a mean RI of 79.9± 4.69 % and nonresponders with a mean RI of 60.3±4.6 % (the mean RI of the whole population was 65.32 %). These values are somewhat higher than those found in previous studies in responders and nonresponders (approximately 60 %) [25, 28–30], and the previous studies also showed a good overall response to neoadjuvant treatment.

We conclude that ^{18}F-FDG PET/CT is a reliable technique for evaluating response to neoadjuvant therapy in locally advanced rectal cancer, with a view to considering more conservative surgical treatment, although more precise studies are needed to support these results. Furthermore, the combination of the visual and semiquantitative analysis of the PET data increases the diagnostic validity of the examination. Our patients also responded very satisfactorily to neoadjuvant treatment, according to the mean RI.

Conflicts of interest None.

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