Title:
Assessing tumor response to neoadjuvant chemoradiation in rectal cancer with rectoscopy and 18F-FDG PET/CT: results from a prospective series

Authors:
Víctor López-López, Jesús Abrisqueta Carrión, Juan Luján, Patricio B. Lynn, Laura Frutos, Akiko Ono, Eduardo Ortiz, José J. López-Espín, José Gil, Pascual Parrilla

DOI: 10.17235/reed.2020.6954/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Assessing tumor response to neoadjuvant chemoradiation in rectal cancer with rectoscopy and 18F-FDG PET/CT: results from a prospective series

Víctor López-López¹, Jesús Abrisqueta¹, Juan Luján¹, Patricio B. Lynn², Laura Frutos³, Akiko Ono⁴, Eduardo Ortiz⁵, José J. López-Espín⁶, José Gil¹ and Pascual Parrilla¹


Received: 18/02/2020
Accepted: 11/04/2020

e-mail: victorrelopez@gmail.com

ABSTRACT

Introduction: rectoscopy and 18F-FDG PET/CT as a diagnostic algorithm for the assessment of tumor response in rectal cancer after neoadjuvant chemoradiation therapy (CRT) is very useful.

Material and methods: this was a prospective longitudinal study in patients with locally advanced rectal cancer treated with neoadjuvant CRT. Patients were assessed after CRT completion with a digital rectal examination, proctoscopy and ¹⁸F-FDG PET/CT. Patients were subdivided as clinical (cCR) or radiologic (rCR) responders and non-responders according to tumor response. Clinical and radiological re-assessment was compared with the surgical specimen. Pathological tumor regression (pCR) grade was determined according to Mandard’s classification. Of the 68 patients included, 15
(22 %) presented pCR in the surgical specimen and tumor persistence (non-PCR) was detected in the remaining 53 (78 %). Clinical assessment (DRE+ rectoscopy) identified 15 patients as cCR and 53 as non-cCR, two were false positives and two were false negatives. The overall accuracy was 94 %. \(^{18}\)F-FDG PET/CT identified 18 patients as rCR and 50 as non-rCR, one was a false positive and four were false negatives. The overall accuracy was 92 %. A combination of clinical findings and \(^{18}\)F-FDG PET/CT resulted in an accuracy of 96 %. The combination of clinical findings + \(^{18}\)F-FDG PET/CT was able to correctly identify all cases of pCR, with the exception of one case that presented a tumor regression of 80 %. In this series, \(^{18}\)F-PET-CT and clinical assessment had excellent accuracies in differentiating PCR from non-PCR after CRT completion. PET-CT combined with clinical assessment had a better accuracy than both modalities independently. \(^{18}\)F-FDG PET/CT is a valid tool that complements the clinical assessment of tumor response.

**Keywords**: Rectal cancer. Chemoradiation therapy. Rectoscopy. \(^{18}\)F-FDG PET/CT. Management.

**INTRODUCTION**

Neoadjuvant chemoradiation therapy (CRT) is one of the preferred approaches for locally advanced rectal cancer, providing excellent rates of local disease control and leading to variable degrees of tumor downsizing and downstaging (1). It has been described that up to 42 % of patients will develop a complete pathologic response (pCR) (2). Cases in which no tumor cells are found in the surgical specimen are associated with excellent oncological outcomes and the role of morbid radical surgery has been questioned in this setting (3). In order to implement alternative approaches to radical surgery, it is fundamental to precisely identify patients that may be candidates for these strategies (4-6). Currently, there is no test that is 100 % accurate. Endorectal ultrasound (EUS), computed tomography (CT) and conventional magnetic resonance imaging (MRI) allow a morphological assessment of tumor extent at the initial diagnosis but have shown disappointing accuracies for restaging after CRT (7,8).
Among the tools available for the reassessment of patients after CRT, rectoscopy and ¹⁸F-FDG PET/CT have shown an accurate correlation between their findings with pCR. Post-CRT rectoscopy with digital rectal exploration (DRE) offers the possibility of direct tumor visualization and, in addition, it enables us to obtain a histopathological sample to establish a close relationship between endoscopy findings and tumor response grade. ¹⁸F-FDG PET/CT is a non-invasive imaging modality that allows the estimation of tumor metabolic activity and is currently used to diagnose, stage, restage and monitor treatment responses in many types of malignancies.

The aim of this study was to report our institutional experience with rectoscopy and ¹⁸F-FDG PET/CT as a diagnostic algorithm for the assessment of tumor response in rectal cancer after CRT.

METHODS

Study design and patients
A prospective longitudinal study was performed at Hospital Clínico Universitario Virgen de la Arrixaca, between May 2012 and January 2017. Patients were included with locally advanced rectal cancer (UICC TNM II-III) with the inferior border located at no more than 12 cm from the anal verge treated with neoadjuvant CRT. The following exclusion criteria were applied: active pregnancy, younger than 18 years, previous rectal treatment (chemotherapy, radiotherapy or surgery), Eastern Cooperative Oncology Group performance status > 2, presence of distant metastases at the time of diagnosis, neoadjuvant therapy contraindications due comorbidity and/or the presence of another synchonic tumor. The study protocol was approved by the Ethics Committee. All the patients were informed of the objective of the study in their native language. Their participation was voluntary and required a signed informed consent. Clinical assessment was performed by board certified surgeons in colorectal surgery. All patients were initially assessed via a complete physical examination, DRE, rigid proctoscopy, complete colonoscopy, ERUS and/or MRI of the pelvis for local pelvic staging. Systemic staging was established via a CT of the chest, abdomen and pelvis and ¹⁸F-FDG PET/CT.
Neoadjuvant chemoradiation protocol

Patients were treated with our institutional protocol consisting of long-course radiation therapy with a total dose of 45 Gy (1.8 Gy per day, five days a week for five weeks) accompanied by concurrent chemotherapy, 5-fluorouracil (425 mg/m²/day) and folinic acid (20 mg/m²/day).

Clinical and endoscopic response assessment

Patients were assessed 12 weeks after CRT completion via DRE and proctoscopy. This examination was identical to the clinical evaluation performed at baseline and was performed by the same investigator. Four tumor biopsies were taken during proctoscopy. Patients were divided into complete clinical responders and non-responders, according to tumor response. Criteria for establishing a complete clinical response (cCR) were as described in the literature. Briefly, these included the disappearance of the original lesion, an area of whitening (scarring) of the mucosa, the presence of telangiectasias, loss of flexibility of the rectal wall harboring the scar and no tumor felt during DRE. All other clinical findings including gross tumor persistence, ulcers, nodules or strictures were considered as non-complete responders (9).

¹⁸F-FDG PET/CT

Patients were evaluated with two ¹⁸F-FDG PET/CT scans, one at diagnosis to complete staging and a second one 12 weeks after CRT completion to evaluate metabolic response. Patients were asked to fast for at least four hours before the ¹⁸F-FDG PET/CT scan. The blood glucose levels were within the normal range (70-120 mg/dl) prior to intravenous injection of 370 MBq (10mCi) of ¹⁸F-FDG, adjusted to body weight. 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 the administration of an 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 was obtained covering the identical transverse field of view. The acquisition time was 3 min per table position. PET image datasets were reconstructed iteratively by applying the CT data for
attenuation correction and co-registered images were displayed on a workstation. Studies were interpreted by qualitative and semi-quantitative analysis and interpreted by nuclear radiologists with a special interest in rectal cancer, who were blinded to the clinical outcome. Lesions were identified as foci with increased tracer accumulation relative to that in comparison to normal contralateral structures and surrounding soft tissues, according to the qualitative visual analysis and based on the normal distribution of \(^{18}\)F-FDG. Tumor 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 (SUV\(_{\text{max}}\), mean ± SD) of the lesions was calculated by manually drawing the regions of interest around the tumor and on all the consecutive transaxial slices that contained tumor, so that the whole lesion was included in the regions of interest. The metabolic response shown on the \(^{18}\)F-FDG PET/CT scan after treatment was visually assessed in terms of the reduction in SUV\(_{\text{max}}\) compared to the baseline scan. SUV measurements were used to determine a complete (pCR) or incomplete response (non-pCR).

**Surgical and pathological examination**
All the patients were scheduled for a total mesorectal excision (anterior resection or abdominoperineal amputation) within two weeks from the time of clinical and radiological re-assessment. Pathological staging was performed according to the American Joint Committee on Cancer/International Union Against Cancer (y)pTNM categories (10). Tumor regression grade was determined according to Mandard’s classification (11). Briefly, grade I corresponds to absence of neoplastic cells (100 % response); grade II, to isolated tumor cells (90 %); grade III, to neoplastic cells, but fibrosis still predominates (50-89 %); grade IV, predominance of neoplastic cells (10-49 %); and grade V, absence of regressive changes (< 10 %). Grade I were considered pCR and grades II-V as non-pCR.

**Statistical analysis**
The data were analyzed using the SPSS 24.0 statistical package for Windows (SPSS, Chicago, IL). For each imaging test and rectoscopy, sensitivity (S), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated, with confidence intervals of 95%. Reduction in SUVmax compared to the baseline scan was expressed as mean ± standard deviation. Descriptive numeric variables were expressed as median and interquartile range and qualitative variables as frequencies and percentages.

**RESULTS**

During the study period, a total of 75 patients underwent neoadjuvant CRT and seven patients were excluded (no surgery = 4, local excision = 2, lost to follow up = 1). The remaining 68 patients underwent surgical treatment and were included in the final analysis. The median age was 63.5 years (34-88), 32 patients were female and median distance from the anal verge was 7 cm (1-12). Fifty-seven patients (83%) were staged with a baseline PET/CT and all patients completed a second $^{18}$F-FDG PET/CT 12 weeks after CRT completion (Fig. 1).

Of the 68 patients included, 15 (22%) presented pCR in the surgical specimen and tumor persistence (non-pCR) was detected in the remaining 53 (78%). Clinical assessment (DRE + rectoscopy) identified 15 patients as cCR and 53 as non-cCR, two were false positives and two were false negatives. The overall accuracy was 94%. $^{18}$F-FDG PET/CT identified 18 patients as rCR and 50 as non-rCR. There were one false positive and four false negatives; the overall accuracy of the test was 92%. The combination of clinical findings and $^{18}$F-FDG PET/CT resulted in an accuracy of 96% (Table 1). In fact, the combination of clinical findings and $^{18}$F-FDG PET/CT was able to correctly identify all cases of pCR, with the exception of one case that presented tumor regression of 80%.

$^{18}$F-FDG PET/CT as predictor of response

There were no differences in demographic characteristics, clinical staging, tumor size and location between pCR and non-pCR patients (Table 2). Furthermore, no differences were observed in the initial SUVmax, post-treatment SUVmax as well as a
percentage decrease in SUVmax between the studies. Surprisingly, pT3 tumors presented the greatest decrease in SUVmax (Table 3). A ROC curve was constructed with the % decrease in SUVmax values in order to find a suitable cut-off value to predict PCR. Unfortunately, the area under the curve was not good enough (0.52) to consider this parameter independently. With regard to the ability to identify nodal disease after treatment, 18F-FDG PET/CT also showed disappointing results with a sensitivity of 0.43 (0.22-0.64), specificity of 0.83 (0.72-0.94), PPV of 0.53 (0.29-0.77) and NPV of 0.76 (0.65-0.88).

DISCUSSION

The results of this study show that 18F-FDG PET/CT improves the accuracy of the clinical/endoscopic assessment of tumor response in rectal cancer at 12 weeks from CRT completion. Unfortunately, no 18F-FDG PET/CT predictors were found that could be used to identify cCR. Furthermore, the accuracy of this modality to identify residual nodal disease was somewhat disappointing. Both clinical/endoscopic assessment and 18F-FDG PET/CT showed excellent accuracies for the detection of pCR. In fact, the combined use of both modalities resulted in an increased accuracy and only one patient was incorrectly identified as a cCR with tumor persistence in the pathology examination.

A decade ago, the European Organization for Research and Treatment of Cancer (EORTC) established the 18F-FDG PET/CT criteria for tumor response assessment in rectal cancer after neoadjuvant CRT (12). Since then, many studies have shown the utility of different parameters of this diagnostic modality. Two recent meta-analysis analyzed this subject. One study based on 26 studies showed that 18F-FDG-PET or 18F-FDG PET/CT sensitivity, specificity, PPV and NPV were 81 %, 77 %, 78 % and 80 %, respectively (13). A second one from 2015 including 29 studies reported a pooled sensitivity of 71 % and a pooled specificity of 76 % for complete response (AUC 0.8) (14). The present results compare favorably with these meta-analyses, reinforcing the importance of 18F-FDG PET/CT as a valid tool.

The findings of this series are also in line with the results reported by Pérez et al. (15), in the sense that 18F-FDG PET/CT improves the accuracy of clinical/endoscopic
examination. The combined accuracy of PET/CT and clinical findings in the Pérez et al.
study was the same as that reported here, which was 96%. Nevertheless, \(^{18}\text{F-FDG}\)
PET/CT as an isolated tool showed a worse performance in their study compared to
ours (85% vs 92% accuracy). All of our patients underwent TME and thus have a
pathologic staging even though our study had a smaller sample size compared to the
aforementioned one, whereas 16% of the patients in the other study did not undergo
surgery and were enrolled in a “Watch and Wait” protocol. Only one local recurrence
was reported in their study during a three-year follow-up. This enforces the good
oncological outcomes of this approach. However, late local recurrences, although rare,
have been described and those numbers might change.

Tumors that presented a pCR had lower initial and post-CRT SUVmax values (8.8 vs
10.8 and 1.6 vs 4.2) as well as a bigger drop in the % decrease of SUVmax values
between the initial and post-CRT \(^{18}\text{F-FDG}\) PET/CTs. Nevertheless, none of these
parameters were statistically significant (Table 3). The association between SUVmax
and rectal cancer response has been previously reported. The majority of studies used
response to CRT as the main outcome, grouping microscopic residual disease and pCR
as “good” responses, when oncological outcomes of these groups are different and
require different treatments (16-20). The percentual decrease of SUVmax measured in
two sequential PET/CT studies using pCR as the primary outcome has also been
studied, yielding cut-off values of 66-77% (14,21-25). Unfortunately, our ROC curve
had an AUC of 0.54, which prevented further analysis.

One of the strengths of our study is that tumor assessment and \(^{18}\text{F-FDG}\) PET/CT were
performed at least 12 weeks from CRT completion. Tumor response is a time-
dependent phenomenon and the peak in response is obtained when the assessment is
performed at least 12 weeks from CRT completion (23). Many of the aforementioned
studies used shorter waiting periods to assess response, which may be valid when
looking for predictors of early response, but lead to suboptimal results if the final
response is to be assessed (14,16-24) 12 weeks from CRT completion

This study has several limitations. First, the number of patients is rather small and
given the nature of the study (observational and time-limited), no power calculation
was made to prove any given outcome. Second, not all the included patients completed a baseline PET/CT, which limited the conclusions that could be drawn. However, most of the series on PET/CT and rectal cancer response are small, with only a handful of studies with more than 68 cases (14,22-26).

Alternative metabolic imaging modalities such as diffusion weighted magnetic resonance imaging and dynamic contrast enhanced magnetic resonance imaging are also being studied in this setting and promising results have been reported (27-29). Future prospective and properly powered studies comparing PET/CT with these other modalities are warranted and accuracies and costs should be considered.

CONCLUSIONS

In this series, 18F-FDG PET-CT and clinical assessment both had excellent accuracies in differentiating PCR from non-PCR at 12 weeks from CRT completion (92 % and 94 %). The use of 18F-FDG PET-CT combined with clinical assessment had a better accuracy than both modalities considered independently (96 %). We were unable to identify predictors of PCR in 18F-FDG PET/CT. In LARC, 18F-FDG PET/CT is a valid tool that complements the clinical assessment of tumor response to CRT.

REFERENCES


4. Kim HJ, Song JH, Ahn HS. Wait and see approach for rectal cancer with a clinically complete response after neoadjuvant concurrent chemoradiotherapy. Int J


14. Leccisotti L, Gambacorta MA, De Waure C, et al. The predictive value of 18F-FDG PET/CT for assessing pathological response and survival in locally advanced rectal...


Table 1. Comparison of the clinical findings, $^{18}$F-FDG PET/CT and combined modality as diagnostic tools

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95 % CI)</th>
<th>Specificity (95 % CI)</th>
<th>PPV (95 % CI)</th>
<th>NVP (95 % CI)</th>
<th>Accuracy (%)</th>
<th>CP+ (95 % CI)</th>
<th>CP- (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical findings</td>
<td>0.96 (0.91-1.01)</td>
<td>0.87 (0.69-1.04)</td>
<td>0.96 (0.91-1.01)</td>
<td>0.87 (0.69-1.04)</td>
<td>94</td>
<td>7.22 (1.98-26.25)</td>
<td>0.04 (0.01-0.17)</td>
</tr>
<tr>
<td>$^{18}$F-FDG PET/CT</td>
<td>0.92 (0.85-1.0)</td>
<td>0.93 (0.81-1.06)</td>
<td>0.98 (0.94-1.2)</td>
<td>0.78 (0.59-0.97)</td>
<td>92</td>
<td>13.87 (2.08-92.27)</td>
<td>0.08 (0.03-0.21)</td>
</tr>
<tr>
<td>Clinical+</td>
<td>0.98 (0.94-1.02)</td>
<td>0.76 (0.56-0.97)</td>
<td>0.93 (0.86-1.06)</td>
<td>0.93 (0.79-1.06)</td>
<td>96</td>
<td>4.17 (1.77-9.83)</td>
<td>0.03 (0-0.18)</td>
</tr>
<tr>
<td>$^{18}$F-FDG PET/CT</td>
<td>1.02</td>
<td>0.97</td>
<td>1.06</td>
<td>0.97</td>
<td>9.83</td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; PPV: positive predictive value; NVP: negative predictive value; CP+: positive probability coefficient; PN-: negative probability coefficient.
Table 2. Comparison between pCR and non-PCR

<table>
<thead>
<tr>
<th></th>
<th>pCR ($n = 15$)</th>
<th>Non-pCR ($n = 53$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>65 (35-87)</td>
<td>63 (34-88)</td>
<td>0.33</td>
</tr>
<tr>
<td>Gender, M:F, n (%)</td>
<td>5:10 (33.3:66.7)</td>
<td>31:22 (58.5:41.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Initial tumor size, cm, median (range)</td>
<td>3 (1.5-5.2)</td>
<td>5 (1.4-10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Distance from AV, cm median (range)</td>
<td>6 (3-12)</td>
<td>7 (3-12)</td>
<td>0.14</td>
</tr>
<tr>
<td>CEA, ng/ml median (range)</td>
<td>2.8 (1-53)</td>
<td>3.9 (0.5-147)</td>
<td>0.3</td>
</tr>
<tr>
<td>Initial T staging</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>T2</td>
<td>5 (33.3)</td>
<td>6 (11.3)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>9 (60)</td>
<td>42 (79.2)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>1 (6.7)</td>
<td>5 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Initial N staging</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>N0</td>
<td>4 (26.6)</td>
<td>10 (18.9)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>11 (73.4)</td>
<td>43 (81.1)</td>
<td></td>
</tr>
<tr>
<td>Initial SUVmax, median (range)</td>
<td>8.8 (2-16.5)</td>
<td>10.8 (5.6-49.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Post-CRT SUVmax, median (range)</td>
<td>1.6 (0-8.6)</td>
<td>4.2 (0-10.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>% Decrease SUVmax, median (range)</td>
<td>70 (35-91)</td>
<td>61.5 (0-93)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Table 3. % SUVmax decrease between baseline and 12 week ¹⁸F-FDG PET/CTs according to tumor and nodal staging

<table>
<thead>
<tr>
<th>pTN</th>
<th>Pre-CRT SUV</th>
<th>Post-CRT SUV</th>
<th>% decrease SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT4</td>
<td>21.86 ± 9.6</td>
<td>4.8 ± 0.9</td>
<td>56.7 ± 18.2</td>
</tr>
<tr>
<td>pT3</td>
<td>14 ± 1.3</td>
<td>5.3 ± 0.4</td>
<td>72.7 ± 17.2</td>
</tr>
<tr>
<td>pTis + T1 + T2</td>
<td>13.2 ± 2</td>
<td>3.8 ± 0.5</td>
<td>61.4 ± 6.3</td>
</tr>
<tr>
<td>pCR</td>
<td>8.7 ± 1.19</td>
<td>2.4 ± 0.5</td>
<td>67.4 ± 4</td>
</tr>
<tr>
<td>TxN+</td>
<td>11.4 ± 2.5</td>
<td>4.5 ± 0.4</td>
<td>58.1 ± 6.5</td>
</tr>
</tbody>
</table>

pTN: pathological tumor and nodal stage; pCR: complete pathologic response, CRT: chemoradiation; SUV: standard uptake value; Tx: tumor cannot be assessed; Tis: carcinoma in situ; N+: lymph nodes metastasis.
Fig. 1. Relationship between rectoscopy and $^{18}$F-FDG PET/CT at diagnosis before neoadjuvant chemoradiation (A) and 12 weeks after neoadjuvant chemoradiation completion (B).