ACTA ONCOLOGICA
2019, VOL. 58, NO. 9, 1246–1249
https://doi.org/10.1080/0284186X.2019.1622774

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LETTER TO THE EDITOR



# Quantitative analysis of 18-FDG-PET/MRI to assess pathological complete response following neoadjuvant radiochemotherapy in locally advanced rectal cancer. A prospective preliminary study

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## Background

Pathologic complete response (pCR) is observed in 8–24% of the cases of patients with locally advanced rectal cancer (LARC) treated with neoadjuvant radiochemotherapy (RCT) before curative surgery [1,2]. Accurate restaging modalities after RCT are of paramount importance to be able to individualize the most appropriate treatment, as preserving surgical techniques can be offered to selected patients [3]. In the literature, MRI with diffusion (DWI) protocol is proven to be the most accurate imaging technique to assess local therapy response [4] and to restage patients with colorectal cancer [5]. FDG-PET/CT has been shown to improve the accuracy of malignant lymph node detection compared with CT and MRI [6]. However, no definite consensus on optimal imaging modality has yet been established, and more specific and sensitive methods are needed [7,8]. In recent years 18-FDG-PET/MRI has emerged as a new imaging technique that combines simultaneous positron emission tomography. MRI can add anatomic and quantitative strengths of MR imaging to physiologic information obtained from PET [9–11].

The aim of this study is to report our clinical experience with 18-FDG-PET/MRI to assess the response to neoadjuvant treatment in patients with LARC.

## Materials and methods

### Patients

Patients with locally advanced rectal cancer who completed a full cycle of neoadjuvant RCT were prospectively enrolled from January 2014 to January 2018. 18-FDG-PET/MRI was performed to restage all patients eight weeks after completing neoadjuvant RCT, and each examination included whole-body PET/MRI and a dedicated pelvic PET/MRI.

This prospective study was conducted at Sanchinarro University and was approved by the institution; all patients provided written informed consent. Inclusion criteria were: histologically proven rectal carcinoma, staged T3-4 and/or with positive regional lymph-node, age> 18 years, complete RCT followed by surgery.

Exclusion criteria were: contraindication to PET/MRI imaging examination; delayed surgery (more than eight months after CRT) and distant metastases.

### Neoadjuvant radiochemotherapy

Radiotherapy consisted of 50.4 Gy divided into 28 sessions (5 days a week) of 1.8 Gy; this regimen was associated with capecitabine (825mg/m2) twice daily.

### Imaging technique

F-FDG was established depending on body weight. Post-injection median uptake time was 40–50 min for the pelvic imaging study and 60–70 min for the whole body imaging study.

### Image analysis

PET/MRI data sets were reviewed on a commercially available workstation (Syngo.Via, Siemens Healthcare, Erlangen, Germany) by a radiologist and a nuclear medicine physician, both with more than 10 years' experience in MRI and PET/CT, respectively. For all tumors, maximum SUV was analyzed in the PET dataset of the rectum plotting an isocontour volume of interest (VOI) around the tumor ($SUV_{max}$ threshold 40%) by the nuclear medicine physician. ADC maps were automatically generated by the implemented software. After a qualitative evaluation of the ADC map, two regions of interest (ROI) in two different slices were manually drawn on this map in the area with the minimal signal intensity inside the tumor. In all lesions, two minimal ADC values ($ADC_{min}$), were registered.

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### Histopathological examination

The histopathological examination was performed by expert colorectal pathologists. Pathologic tumor staging (ypTNM) and TRG scores of the surgical specimens were established with the seventh guidelines of the American Joint Committee on Cancer [12]. TRG0 indicates a pathological complete response, TRG1 (moderate response) consists of single cells or small groups of cancer cells, TRG2 (minimal response) indicates residual cancer outgrown by fibrosis, and TRG3 (poor response) shows extensive residual cancer. Circumferential resection margin (CRM) is considered negative if the distance between the tumor and CRM is more than 1 mm.

### Statistical analysis

Continuous variables are reported as medium with interquartile range and categorical variables as absolute frequency and percentage. Variables are compared with the Wilcoxon rank-sum test and chi-square for quantitative and qualitative data, respectively.

The area under the receiver operating characteristic curve (AURC) was used to measure the accuracy of detecting the pathologic complete response. For the statistical analysis, SPSS software (version 10, IBM SPSS, Chicago, IL, USA) was used and all the tests were considered statistically significant if the value of $p \leq .05$.

## Results

### Patient population

We enrolled 30 patients: 23 male and 7 female with a median age of 61.5 (±10.06). Demographics and preoperative characteristics are shown in Table 1.

After performing TME (total mesorectal excision) in 26 patients, a colon rectal mechanical anastomosis was performed while two patients received a coloanal anastomosis, and in two patients an AAP was required. The CRM and distal resection margins were free of invasion in all the patients.

pCR occurred in 23,3% (7/30). Tumor regression grade 1 (TRG 1) was obtained in 40% (12/30), TRG 2 and TRG 3 were observed in 23.3% (7/30) and in 6.7% (2/30), respectively.

In the pathologic specimen ypT1, ypT2, ypT3,ypT4 were detected in 6.7% (2/30), 16.6% (5/30), 46.7% (14/30) in 3.3% (1/30) patients, respectively. A pT0N1 was observed. ypT + N0 occurred in 73.3% (22/30) and ypT + N1 in 23.3% (7/30) patients.

### Diagnostic performance of post-RCT PET/MRI

In Table 2 the diagnostic performance of PET/MRI is reported (Pearson Chi-Square $p < .01$).

For the identification of pCR patients, post-CRT PET/MRI had a sensitivity of 0.91 (95% CI: 0.72 to 0.99), specificity of 0.85 (95% CI: 0.42 to 0.99), positive predictive value of 0.95 (95% CI: 0.77 to 0.99), and negative predictive value of 0.75% (95% CI: 0.43 to 092). The overall accuracy was 0.90 (95% CI: 0.73 to 0.99).

**Table 1.** Demographic characteristics.

| Characteristics | Total | pCR | no PCR | *p* |
|---|---|---|---|---|
| Sex | | | | |
| Male | 23 | 5 | 19 | >.05 |
| Female | 7 | 2 | 4 | |
| Age | 62.2 | 60 | 62.8 | >.05 |
| BMI | 23.1 | 22.8 | 23.4 | >.05 |
| ASA | | | | >.05 |
| I | 4 | 1 | 3 | |
| II | 26 | 6 | 20 | |
| III | 0 | 0 | 0 | |
| T stage | | | | |
| 2 | 2 | 0 | 2 | >.05 |
| 3 | 28 | 7 | 21 | |
| 4 | 0 | 0 | 0 | |
| N stage | | | | >.05 |
| 0 | 10 | 5 | 5 | |
| 1 | 12 | 1 | 11 | |
| 2 | 8 | 1 | 7 | |
| Overall stage | | | | >.05 |
| IIA | 10 | 5 | 5 | |
| IIIA | 2 | 0 | 2 | |
| IIIB | 9 | 1 | 8 | |
| IIIC | 9 | 1 | 8 | |
| Distance from anal verge | | | | >.05 |
| < 5 cm | 8 | 1 | 7 | |
| 5–8 cm | 11 | 3 | 8 | |
| > 8 cm | 11 | 3 | 8 | |
| Approach | | | | |
| Laparoscopic | 20 | 5 | 13 | >.05 |
| Robotic | 10 | 2 | 8 | |
| Type of resection | | | | >.05 |
| TME | 28 | 7 | 21 | |
| AAP | 2 | 0 | 2 | |
| Operation time | 291 | 283 | 295 | >.05 |
| Hospital stay | 11.9 | 12.3 | 11.5 | >.05 |

**Table 2.** Treatment response evaluation to neoadjuvant chemotherapy using (18)F-FDG PET/MRI.

| | Pathology | | |
|---|---|---|---|
| | No- pCR | pCR | Total |
| PET MRI | | | |
| Positive | 21 | 1 | 22 |
| Negative | 2 | 6 | 8 |
| Total | 23 | 7 | 30 |

Correlation between finally pathologic examination and PET MRI finding demonstrate a statistically correlation (Pearson Chi-Square $p < .01$).

### Quantitative aspects of PET/MRI

The $ADC_{min}$ median value was $0.87 \pm 0.33\ 10^{-3}$ $mm^2/s$ and the $SUV_{max}$ median value was $6.2 \pm 3.01$.

The pCR $ADC_{min}$ median value was $1.22 \pm 0.25 \times 10^{-3} mm^2/s$ and the No pCR $ADC_{min}$ median value was $0.75 \pm 0.27 \times 10^{-3}$ $mm^2/s$ (un-paired *t* test, $p < .01$). The pCR $SUV_{max}$-median value was $4.17 \pm 2.13$. The No pCR $SUV_{max}$ median value was $6.81 \pm 2.99$ (un-paired *t* test, $p < .05$) (Figure 1(a)).

$ADC_{min}$ and post-CRT $SUV_{max}$ values were significantly different in TRG classes ($p < .0001$). Analyzing the distribution of the post-CRT $ADC_{min}$ and post-CRT $SUV_{max}$ and the TRG in the final histological examination, we found a significant statistical correlation between them, indicating a negative high correlation for $ADC_{min}$ (Spearman's Rho = −0.695) and a

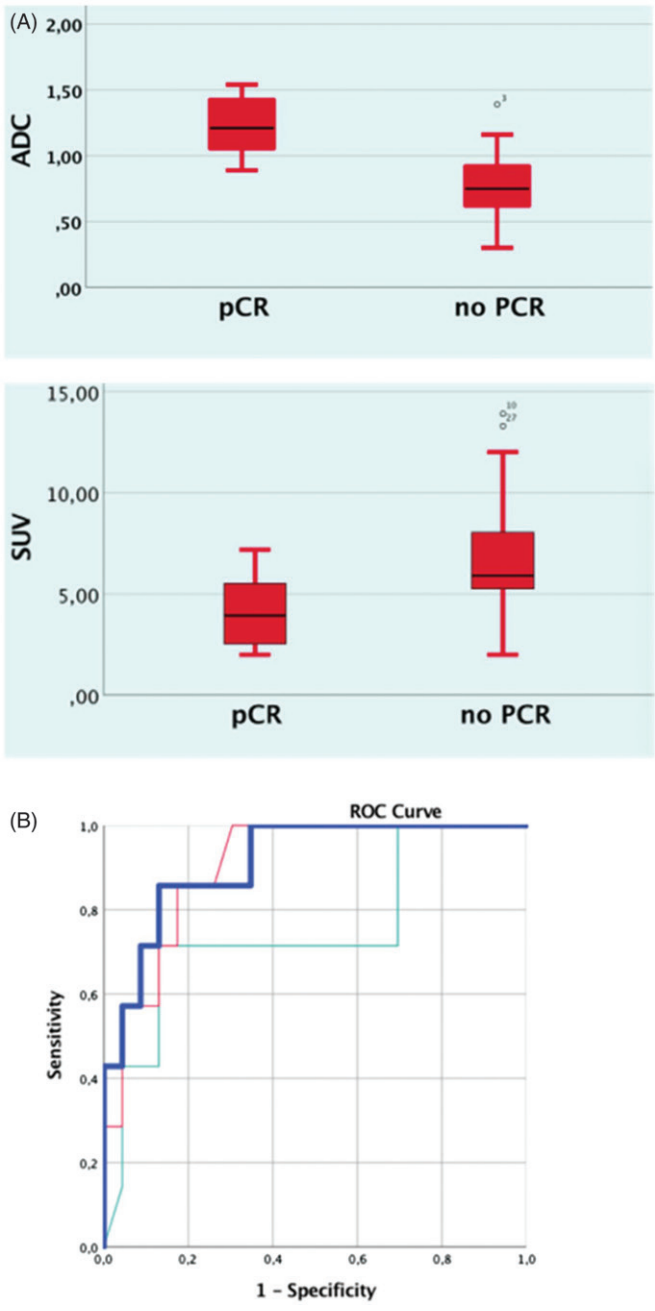


**Figure 1.** Quantitative analysis. (A) ADC and SUV values representation with respect to the final histological examination. (B) ROC curve for ADC, SUV and ADC + SUV.

positive moderate correlation for $SUV_{max}$ (Spearman's Rho + 0.529); (95% confidence interval −0.75 to −0.24).

Using the post-CRT $ADC_{min}$ and $SUV_{max}$ values, the ROC curve was constructed (Figure 1(b)). The ROC curve for $ADC_{min}$, $SUV_{max}$ and the hybrid curve of $ADC_{min}$+$SUV_{max}$ were able to predict the PCR with an area under the curve (AUC) of 0.904, 0.748 and 0.913.

## Discussion

Early studies suggest that FDG-PET/MRI may be more accurate than CT, MRI or FDG-PET/CT [11,13] in restaging LARC after RCT. In 2015 Paspulati described a case series of 12 patients studied with PET/MRI, before and after neoadjuvant treatment, reporting a high diagnostic accuracy of PET/MRI in T staging of rectal cancer compared with PET/CT [14]. In 2018 Bailey [15] described a high performance of PET/MRI in lymphonodal staging after RCT.

PET/MRI may offer more accurate information with respect to PET/CT when a metastatic disease is suspected; in fact, MRI offers a better characterization of liver lesions and detection of small metastases and peritoneal implants, which has an impact on treatment planning [16,17].

Our initial experience shows a high-diagnostic accuracy of PET/MRI in restating LARC after RCT with a sensitivity rate of 91%, a specificity of 85.7% and an overall accuracy of 90%. In the quantitative analysis, post-CRT values of ADC and SUV were significantly different between patients with pCR and those in whom the tumor was identified in the specimen. Moreover, the ADC and SUV values post CRT showed a statistically positive correlation with TRG, suggesting that this ADC increase and SUV decrease reflects the local necrosis and sensitivity of tumors to treatment. Finally, in the ROC curve analysis, the hybrid curve of combined values of ADC and SUV had a superior AUC compared with separate ADC and SUV curves, although no statistical significance was observed.

To the best of our knowledge, this is the first study that explores both the quantitative and qualitative aspects of this imaging technique. However, this study does have several limitations. First, results are based on a small number of patients. Second, a comparison with a restaged image technique, such as a standard MRI, has not been performed. Third, it has focused on the search for possible associations between ADC, SUV and histopathologic results. The differentiation between T and N pathologic responses should be also analyzed. Finally, future studies are required in order to compare SUV and ADC variations before and after RCT.

## Conclusion

In conclusion, 18-FDG-PET/MRI shows high accuracy in detecting a response to RCT in LARC. Furthermore, ADC and SUV values show statistically significant correlations in the grade of response to neoadjuvant treatment, and can be used as complementary prediction factors for the detection of pCR. Larger studies are needed to validate these preliminary results.

## Ethical approval

This study was approved by the Ethics Committee of the Sanchinarro Hospital, San Pablo University.

## Disclosure statement

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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