

## Observational Study

# Combined value of apparent diffusion coefficient-standardized uptake value max in evaluation of post-treated locally advanced rectal cancer

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## Abstract

**AIM:** To assess the clinical diagnostic value of functional imaging, combining quantitative parameters of apparent diffusion coefficient (ADC) and standardized uptake value (SUV)max, before and after chemo-radiation therapy, in prediction of tumor response of patients with rectal cancer, related to tumor regression grade at histology.

**METHODS:** A total of 31 patients with biopsy proven diagnosis of rectal carcinoma were enrolled in our study. All patients underwent a whole body <sup>18</sup>FDG positron emission tomography (PET)/computed tomography

(CT) scan and a pelvic magnetic resonance (MR) examination including diffusion weighted (DW) imaging for staging (PET1, RM1) and after completion (6.6 wk) of neoadjuvant treatment (PET2, RM2). Subsequently all patients underwent total mesorectal excision and the histological results were compared with imaging findings. The MR scanning, performed on 1.5 T magnet (Philips, Achieva), included T2-weighted multiplanar imaging and in addition DW images with b-value of 0 and 1000 mm<sup>2</sup>/s. On PET/CT the SUVmax of the rectal lesion were calculated in PET1 and PET2. The percentage decrease of SUVmax ( $\Delta$ SUV) and ADC ( $\Delta$ ADC) values from baseline to presurgical scan were assessed and correlated with pathologic response classified as tumor regression grade (Mandard's criteria; TRG1 = complete regression, TRG5 = no regression).

**RESULTS:** After completion of therapy, all the patients were submitted to surgery. According to the Mandard's criteria, 22 tumors showed complete (TRG1) or subtotal regression (TRG2) and were classified as responders; 9 tumors were classified as non responders (TRG3, 4 and 5). Considering all patients the mean values of SUVmax in PET 1 was higher than the mean value of SUVmax in PET 2 ( $P < 0.001$ ), whereas the mean ADC values was lower in RM1 than RM2 ( $P < 0.001$ ), with a  $\Delta$ SUV and  $\Delta$ ADC respectively of 60.2% and 66.8%. The best predictors for TRG response were SUV2 (threshold of 4.4) and ADC2 ( $1.29 \times 10^{-3}$  mm<sup>2</sup>/s) with high sensitivity and specificity. Combining in a single analysis both the obtained median value, the positive predictive value, in predicting the different group category response in related to TRG system, presented R<sup>2</sup> of 0.95.

**CONCLUSION:** The functional imaging combining ADC and SUVmax in a single analysis permits to detect changes in cellular tissue structures useful for the assessment of tumour response after the neoadjuvant therapy in rectal cancer, increasing the sensitivity in correct depiction of treatment response than either method alone.

**Key words:** Advanced rectal cancer; Functional imaging; FDG-PET/CT; Magnetic resonance imaging; Apparent diffusion coefficient; Neoadjuvant treatment; Tumor regression grade

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**Core tip:** In our study we evaluated the combination of changes of glucose metabolism values expressed as SUVmax and the changes of apparent diffusion coefficient (ADC map) values, before and after neoadjuvant therapy, in patients with advanced rectal cancer in order to predict, *in vivo*, the therapy response. The importance of this work consist of the possibility to offer, in the era of positron emission tomography (PET)/magnetic resonance imaging scanner, a new advanced tool that allows the non-invasive evaluation of response to neoadjuvant chemotherapy treatment in patients with

rectal cancer, by adding quantitative value information on diffusion weighted images and on PET/computed tomography imaging.

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## INTRODUCTION

The use of pre-operative chemoradiation treatment (CRT) induces downsizing and downstaging of primary rectal tumors, yielding a pathologic complete response (pCR) in up to 24% of patients<sup>[1]</sup>. A pCR is known to be associated with a favourable oncologic outcome, in regard to both recurrence and patients survival<sup>[2]</sup>.

The trend in treatment of rectal cancer, although is still controversial, to date is toward a more conservative approach in patients identified as complete responders after CRT. Generally, a pCR is determined with histopathologic examination after surgery, but, if the determination of CR before surgery may influence the subsequent treatment decision, an accurate clinical assessment of response becomes essential<sup>[3-5]</sup>.

Recently, diffusion weighted magnetic resonance imaging (DW-MR) after CRT has demonstrated to be more valuable than standard morphologic MR study in differentiation between a pCR and the presence of residual disease. On DW images, the viable neoplastic remnants are more easily defined, since they appear hyperintense in comparison to the low signal intensity (SI) of the surroundings not neoplastic tissues<sup>[6,7]</sup>. Promising results have been shown with quantitative DW imaging analysis by quantifying the apparent diffusion coefficient (ADC) in the evaluation of treatment response to CRT in patients having rectal cancer<sup>[8-14]</sup>.

Even positron emission tomography (PET)/computed tomography (CT) has been suggested to be an accurate imaging modality in the staging of newly diagnosed or in detection of recurrent rectal cancer. Furthermore, qualitative and quantitative assessment of fluoro-deoxyglucose-PET provide helpful information regarding treatment response and prognosis of patients with rectal cancer<sup>[15,16]</sup>.

Both DWI imaging and PET-CT imaging have been used separately in different fields of tumor evaluation, such as detection, characterization and CRT response assessment. As both ADC and standardized uptake value (SUV) have been associated with biological behaviour and treatment response in various tumors types a correlation between SUV values, which reflect metabolic activity and ADC values which reflect cellular density might be found<sup>[17]</sup>.

To date, there have been few comparative studies between ADC and SUVmax to evaluate the tumour response to preoperative CRT in locally advanced rectal cancer (LARC). The aim of this study was, along with brief review of literature, to evaluate the accuracy of combined ADC and SUVmax values in prediction of tumor regression grade (TRG) complete responders in LARC patients, using histological tumor regression grade as standard reference.

## MATERIALS AND METHODS

### Patients

Between June 2009 and April 2012, 53 consecutive patients with diagnosis of rectal cancer were considered for eligibility. Inclusion criteria were: (1) histopathologically proved rectal adenocarcinoma (0 to 15 cm from anal verge, by means of endoscopic biopsy); (2) LARC staged by baseline MR imaging examination ( $\geq$  T3 or positive lymph nodes); (3) absence of distant metastases; (4) neoadjuvant preoperative CRT. The exclusion criteria were: (1) previous CRT for primary rectal carcinoma or tumour in other organ; (2) contraindication to MR imaging study; (3) premature discontinuation of CRT; (4) delayed (more than 8 mo after CRT) or cancelled surgery; and (5) discontinued or non-diagnostic MR imaging examinations during therapy.

A total of 31 patients (22 men and 9 women, mean age of 64.5 years with a range of 42-80) met the study criteria.

This prospective study was approved by our institutional review board, and informed consent was obtained from all patients.

### MR acquisition protocol

The baseline MR imaging examination (MR1) was performed within a mean of 4.8 wk (I-III quartile: 3.8-6.3 wk) before the treatment for tumour staging, while the second study (MR2) was performed within a mean of 6.6 wk (I-III quartile: 5.3-7.7 wk) after the completion of CRT and before surgery. MRI was performed using a 1.5 T magnet (Philips, Achieva 1.5 T, The Netherlands). The patients were positioned supine and feet first, and scan was performed by using a five-channel high resolution phased-array body coil.

The standard protocol included multiplanar T2- TSE-weighted sequences without fat suppression, applying the following parameters: Repetition time msec/echo time msec 4750/120; slice thickness: 3 mm; slices: 18; matrix: 256  $\times$  256; number of signal acquired (NSA): 4; axial TSE T1-weighted axial sequence Turbo Spin-Echo (TSE) T1-weighted (slice thickness: 3 mm; slice: 20; gap: 3 mm; TR: 612 ms; TE: 14 ms; flip angle: 90°; Field of View (FOV): 180; RFOV: 85; matrix: 272  $\times$  320; NSA: 4.

The images were obtained in three different planes: sagittal, coronal and transverse, with the latter two

orientations angled perpendicularly to the long axis of the tumour according to sagittal images. At the end of the examination, DW images using a Multi-slice Spin Echo Eco-planar Single Shot (SE-EPI-SSH) sequence were obtained in the axial plane with the following parameters: Repetition time msec/echo time 3000/74; slice thickness: 6 mm; slices: 12; matrix: 240  $\times$  256; NSA: 4; b values of 0 and 1000 mm<sup>2</sup>/s; time: 1.30 min; SENSE factor 1.5.

No intravenous contrast medium was injected as part of our routine acquisition protocol for rectal cancer evaluation, according to recent guidelines about clinical management of rectal cancer patients with MRI (recommendations from ESGAR, 2012).

### MR image analysis

MR images were analyzed and ADC measurements were made by one radiologist experienced in abdominal radiology (DI), and who was blinded to the therapeutic response and to the histological results (Figures 1 and 2).

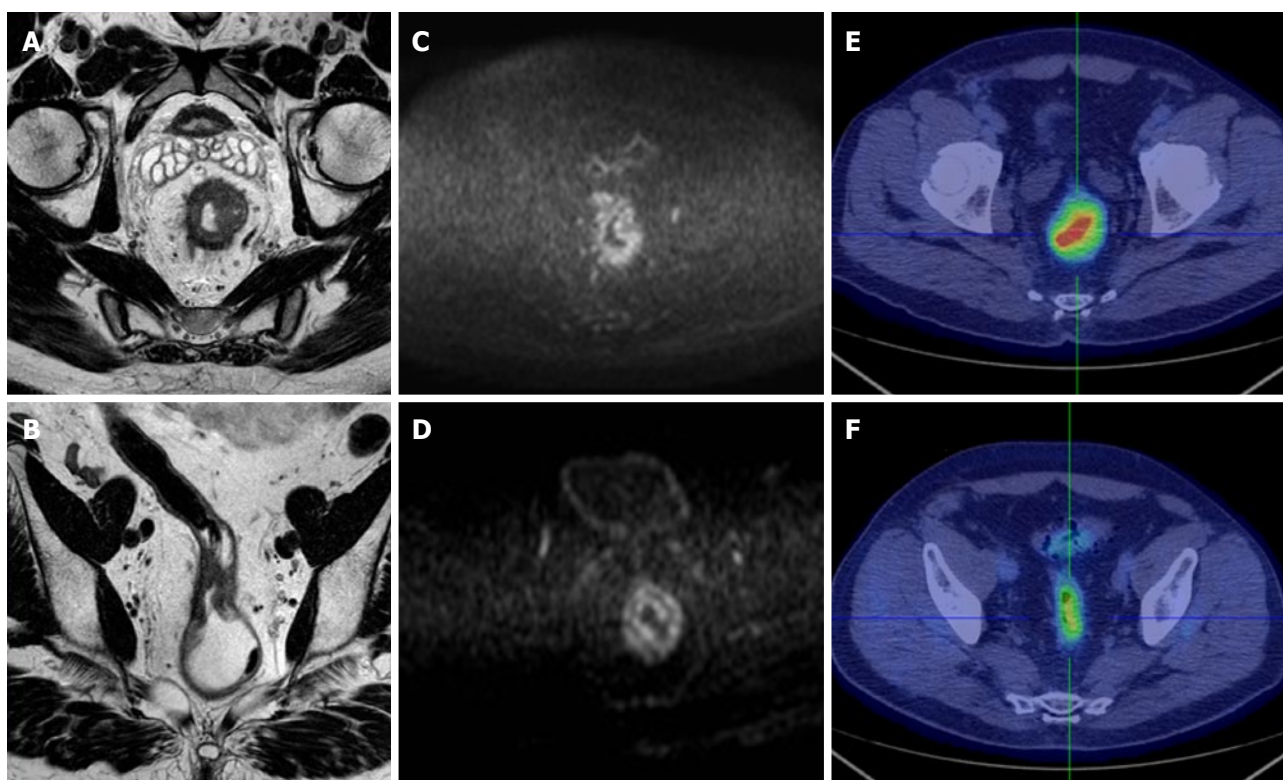
On post-CRT ADC maps, the region of interest (ROIs) were manually drawn on the basis of visual analysis of focal areas of residual high SI on the high-b-value images within the location of the primary tumour site, by comparing pre-CRT examination if needed. When no remaining high SI area could be depicted on the post-CRT DW images, the ROIs were drawn on the rectal wall at the former location of the primary tumour, using pre-CRT DW and T2W images as reference. The lesions were manually contoured along their edge avoiding vessels distortion areas, vessels and motion artefacts. Then, the mean and standard deviation of the ADC values were automatically calculated.

The size of ROI of one section was not less than 20 voxels. Diffusion-weighted images were of diagnostic quality in all patients, and no patients were excluded from the study.

In order to determine percentage variation of ADC before and after CRT, the ADC values in the MR1 (ADC 1) and MR2 (ADC 2) were used also to define delta ADC ( $\Delta$ ADC) as follows:  $\Delta$ ADC = [(ADC2 - ADC1)/ADC2]  $\times$  100.

### <sup>18</sup>F-FDG-PET/CT imaging technique

All patients were investigated by FDG-PET/CT prior to the onset of CRT (PET1) and 4 wk after the completion of the pre-operative treatment (PET2). All studies were performed on a PET scanner coupled with a 8-detector rows CT scanner (Discovery ST - GE Healthcare, Milwaukee, WI, United States), thus allowing one step acquisition of co-registered PET and CT images. According to the acquisition protocol, patients fasted for at least 6 h before the intravenous administration of 3.7 MBq/kg body weight of <sup>18</sup>F-FDG. Blood glucose levels were checked before tracer administration and patients with glucose level above 170 mg/dL were excluded from the study. All patients were orally hydrated (500 mL of water) during the FDG uptake period and were



**Figure 1** A 72-year-old man with pathologically proven proximal rectal cancer, classified as non-responder after chemoradiation treatment. A: Pre-CRT T2-weighted axial MR image shows a circumferential pathological rectal mass, with largest thickening from 12 to 6 o'clock position, narrowing rectal lumen and with corresponding mesorectal fat spread around; B: Post-CRT T2-weighted axial MR image shows incomplete decrease in rectal wall thickening, with irregular and inhomogeneous neoplastic tissue still determining lumen narrow; C: Pre-CRT DWI image shows the presence of hyperintense area at the corresponding level of tumor mass (ADC:  $0.63 \times 10^{-3} \text{ mm}^2/\text{s}$ ); D: Post-CRT DWI image demonstrated partial response, with focal hyperintense area still detectable (ADC:  $1.25 \times 10^{-3} \text{ mm}^2/\text{s}$ ); E: Pre-CRT axial pelvic scan examination image demonstrates a significant radiotracer uptake in the right rectum, corresponding tumor region (SUVmax: 19.4); F: The partial metabolic response is also confirmed by CRT PET/CT scans, in particular a significant tumor uptake is still present (SUVmax: 4.3). CRT: Chemoradiation treatment; DWI: Diffusion weighted imaging; ADC: Apparent diffusion coefficient; SUV: Standardized uptake value.

asked to empty their bladder before positioning for the scan. Sixty  $\pm$  ten minutes after the trace injection, PET/CT study was performed. Unenhanced low-dose CT (LD-CT) was acquired first with the following parameters: 120 kV, 60 mA, gantry rotation time of 0.8 s, section thickness of 3.75 mm and pitch of 1.65. PET emission scanning was performed immediately after LD-CT, with the same coverage volume. All PET studies were acquired in 3D mode, with acquisition time of 3 min per FOV. Images were reconstructed with ordered subsets expectation-maximization algorithm,  $128 \times 128$  matrix size, attenuation, random, and scatter correction. Attenuation correction was performed on the basis of CT scan data. The CT pixel values measured in hounsfield units were transformed into linear attenuation coefficients for the 511-keV energy radiation. CT and PET images were then matched and fused into transaxial, coronal, and sagittal images.

#### Image analysis and quantification of PET data

PET, CT, and fused PET/CT images were displayed on Xeleris workstation (GE Medical Systems, Milwaukee, WI). Images were interpreted by one experienced nuclear medicine physicians (LG) without knowledge of clinical and histological data, but only of the presence

of primary rectal cancer. Lesion uptake was identified as an area of pathologically increased  $^{18}\text{F}$ -FDG uptake, excluding causes of nonspecific or physiologic accumulation of the radio-tracer (Figures 1 and 2). ROIs were drawn over the region of pathological uptake on the baseline scan (PET1) for the calculation of SUV1. At subsequent PET/CT (PET2) images were co-registered with the baseline study by means of the anatomical CT and the ROIs were drawn in the same positions of PET1 in order to calculate SUV2. SUV values were calculated using the maximum activity values within each ROI on the transaxial slices, normalized to the injected dose and patient's body weight, as per ADC values. The SUVmax values in the PET1 (SUV1) and PET2 (SUV2) were used to define  $\Delta\text{SUV}$  in percentage as follows:  $\Delta\text{SUV1} = [(\text{SUV1} - \text{SUV2})/\text{SUV1}] \times 100$ .

#### Histopathologic evaluation and TRG definition

Pathologic response was evaluated on resected specimens by a pathologist, with 15-year experience in gastrointestinal pathology. Each specimen was fixed in 10% buffered formalin for at least 48 h and inked. Serial transversal tissue blocks were cut at 5 mm intervals from the distal portion. Each block, consisting of full thickness of the rectal wall and the mesorectum,

**Table 1** Summarizing table of mean values of standardized uptake value and apparent diffusion coefficient, before and after chemoradiation treatment, and their variation in the overall patients

Variable	Mean $\pm$ SD	P value (Wilcoxon paired)
SUV1	16.3 $\pm$ 8.6	< 0.0001
SUV2	4.5 $\pm$ 2.1	
$\Delta$ SUV (%)	66.8 $\pm$ 20.4	
ADC1	0.83 $\pm$ 0.15	
ADC2	1.33 $\pm$ 0.13	
$\Delta$ ADC (%)	60.2 $\pm$ 23.2	

ADC: Apparent diffusion coefficient; SUV: Standardized uptake value.

was embedded in paraffin. Whole-mount sections were obtained and stained with hematoxylin and eosin. The TRG definition of Mandard *et al.*<sup>[18]</sup> was adopted for clinical response classification. Patients with TRG1-2 scores were considered as responders, while patients with TRG3-5 were classified as non-responders.

### Statistical analysis

Mean and SD of the SUV1, SUV2, ADC1 and ADC2 were calculated and the comparison between SUV1 and SUV2, and between ADC1 and ADC2 was done with Wilcoxon paired test (Table 1). The comparison of the same quantitative parameter was also performed between histopathologic responders and non responders patients with the non parametric Mann-Whitney *U* test (Table 2). The correlation between histological TRG in the resected specimen and the ADC and SUVmax values assessed before and after surgery was analysed with the Pearson correlation test. Multivariate regression model was evaluated including those parameters with significant correlation in univariate regression analysis (Figure 3). The final model incorporated ADC and SUVmax values measured after surgery (ADCpost - SUVpost). Model predictions of histological tumour regression were also compared with true patients' TRG and investigated with scatter diagram (Figure 4).

Receiver operating characteristic (ROC) analysis was performed to define the best accuracy of the metabolic parameters in predicting the response to treatment.

The sensitivity, specificity and overall diagnostic accuracy for each item were calculated under the optimal cut-off value.

Stata software 9.0 (Stata Corporation, College Station, Texas, United States) was used for performing statistical analysis and a *P* < 0.05 was deemed as statistical significant.

## RESULTS

All patients underwent surgical excision within 8-10 wk after CRT completion, *i.e.*, low anterior resection (*n* = 24), abdominoperineal resection (*n* = 6) and extended resection (*n* = 1). The surgical approach was established considering the clinical response to CRT defined at conventional restaging.

**Table 2** Responders (TRG1-2) vs non responders (TRG3-5)

Variable	Responders (Mean $\pm$ SD)	Not responders (Mean $\pm$ SD)	P value (Mann-Whitney <i>U</i> test)
SUV1	15.1 $\pm$ 8.0	19.5 $\pm$ 9.8	0.151
SUV2	3.6 $\pm$ 1.4	6.6 $\pm$ 2.1	0.0009
$\Delta$ SUV (%)	68.5 $\pm$ 23.2	62.8 $\pm$ 10.5	0.151
ADC1	0.88 $\pm$ 0.19	0.78 $\pm$ 0.09	0.076
ADC2	1.47 $\pm$ 0.22	1.19 $\pm$ 0.2	0.009
$\Delta$ ADC (%)	72.6 $\pm$ 27.1	55.5 $\pm$ 18.5	0.0078

Mann-Whitney *U* test was used to calculate and compare obtained values between SUV1 and SUV2 and between ADC1 and ADC2. ADC: Apparent diffusion coefficient; SUV: Standardized uptake value.

### ADC values analysis

In the whole sample of 31 patients, the mean tumor ADC before CRT in the responder group of 22 patients was  $0.88 \times 10^{-3} \text{ mm}^2/\text{s}$ ; while in the non-responder group (9 patients) was  $0.78 \times 10^{-3} \text{ mm}^2/\text{s}$ . After CRT, the mean tumour ADC in the down-staged group was  $1.47 \times 10^{-3} \text{ mm}^2/\text{s}$ , while in the nondown-staged group was  $1.19 \times 10^{-3} \text{ mm}^2/\text{s}$ .  $\Delta$ ADC showed to be statistically relevant between responders and non responders (*P* = 0.0078), as shown in Table 2.

The regression analysis in comparing the ability of post-CRT ADC,  $\Delta$ ADC values in the identification of response to CRT demonstrates an optimal cut-off point of 1.294 for post-CRT measures [sensitivity = 86.4%, specificity = 66.7%, positive predictive value (PPV) = 86.4%, negative predictive value (NPV) = 66.7%], 0.500 for  $\Delta$ ADC (sensitivity = 63.4%, specificity = 66.7%, PPV = 82.4%, NPV = 42.9%).

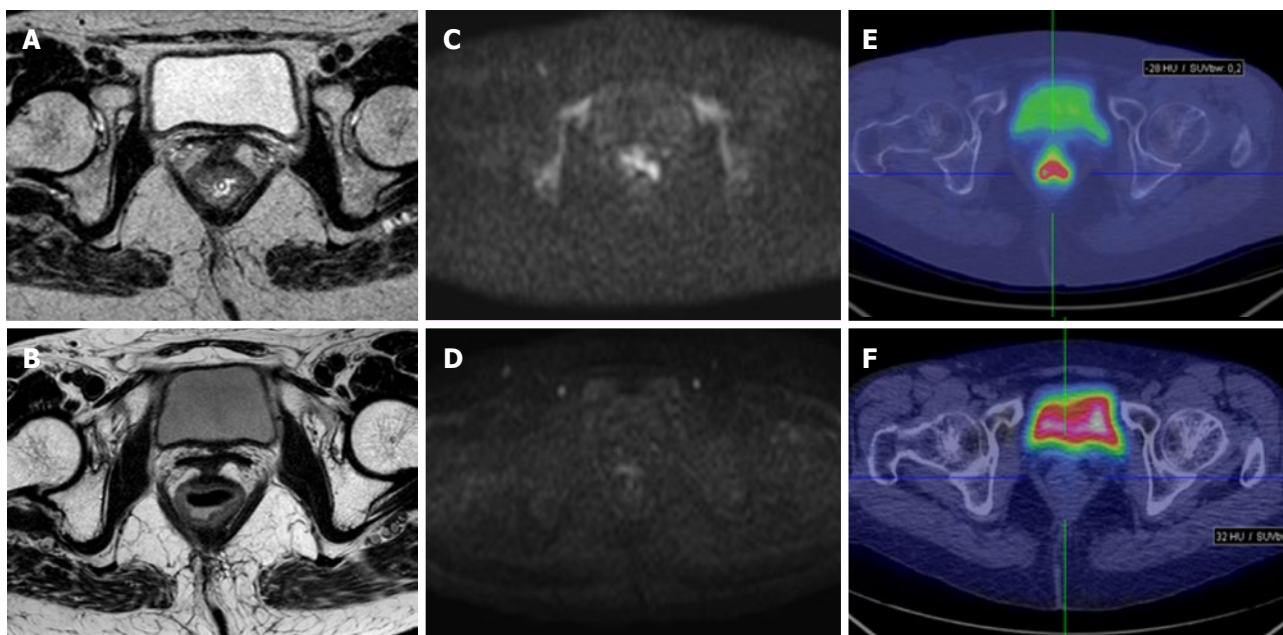
### SUVmax analysis

The mean SUVmax and  $\Delta$ SUV values of the rectal lesion for each PET/CT study are reported (Tables 1 and 2). SUV1 was found significantly higher than SUV2 (*P* < 0.0001). Figure 3 shows the results of univariate and multivariate linear regression analysis comparing metabolic parameters to TRG groups. In the univariate analysis, a statistically significant correlation was found for SUV2 (*P* = 0.009) with TRG (Table 2).

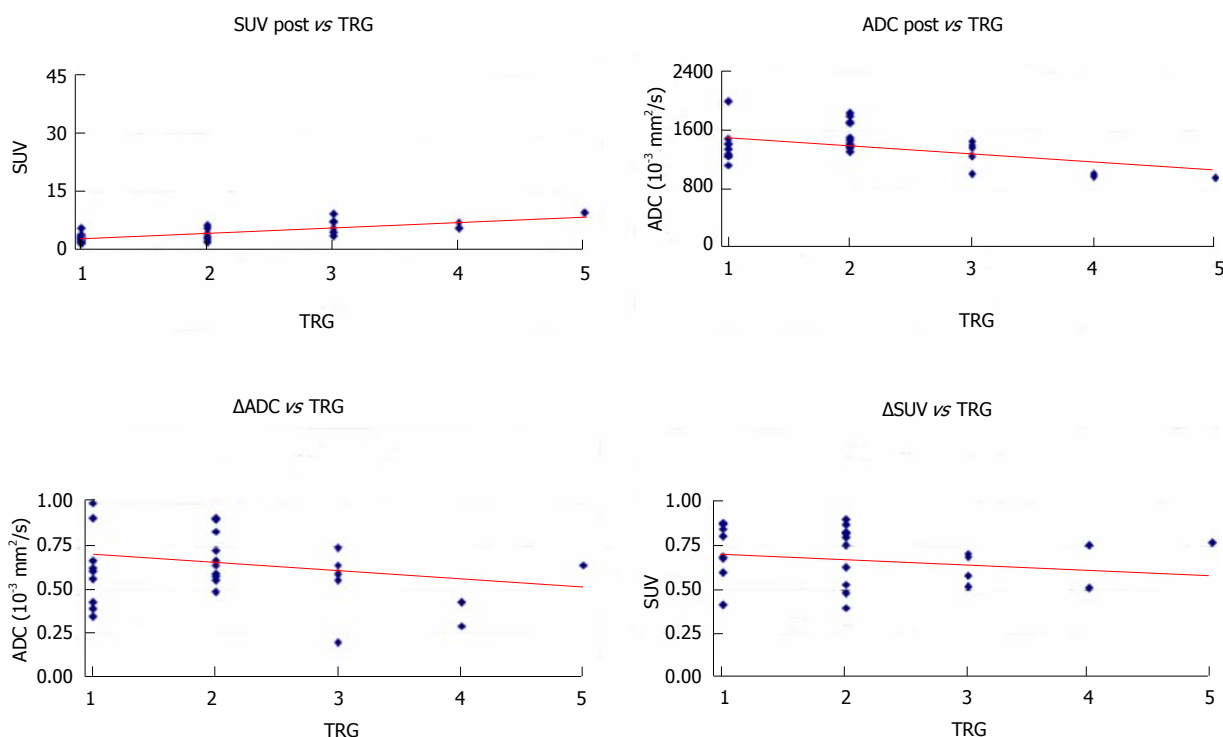
Considering the TRG1-2 patients as responder and TRG3-5 patients as non-responder, the highest accuracy in defining the response to treatment was obtained with a SUV2 cut-off value of 4.4. With this threshold, metabolic response evaluation was true positive in 17 patients, true negative in 8 patients, false positive in 1 patients and false negative in 5 patients, obtaining sensitivity, specificity, accuracy, PPV and NPV of 77.3%, 88.9%, 80.7%, 94.4% and 61.5%, respectively.

## DISCUSSION

Recently, a more conservative treatment has been advocated in patients with rectal cancer showing a good or a complete response to neoadjuvant treatments. The



**Figure 2** A 63-year-old woman with pathologically proven cancer in low rectum. It was difficult to evaluate correctly the response after CRT treatment by using only the T2 morphological information. After the additional reading of DWI images, the radiologist changed his evaluation and correctly classified the patient as responder. A: Pre-CRT T2-weighted axial MR image shows a ulcerative narrowing rectal neoplastic lesion from 11 to 3 o'clock position; B: Post-CRT T2-weighted axial MR image shows a residual homogeneous rectal wall thickening, isointense and not clearly definable as fibrotic tissue; C: Pre-CRT axial DWI image shows a focal hyperintense area in the corresponding site of rectal mass (ADC:  $0.84 \times 10^{-3} \text{ mm}^2/\text{s}$ ); D: Post-CRT axial DWI shows no residual hyperintense signal in the corresponding site of rectal wall (ADC:  $1.39 \times 10^{-3} \text{ mm}^2/\text{s}$ ); E: Pre-CRT axial pelvic scan of PET/CT examination image demonstrated a significant focal radiotracer uptake in correspondence of rectal mass (SUVmax: 9.3); F: Post-CRT axial pelvic scan of PET/CT examination image shows no significant uptake (SUVmax: 2.6). CRT: Chemoradiation treatment; DWI: Diffusion weighted imaging; ADC: Apparent diffusion coefficient; SUV: Standardized uptake value.



**Table 3** Overview of studies analysing mean standardized uptake value and delta standardized uptake value values of the rectal lesion for each PET/CT study

Ref.	No. of patients	Mean SUV 1	Mean SUV 2	Mean SUV 3	Sn (%)	Sp (%)	Late cut-off (%)	Sn (%)	Sp (%)	Delta SUV 1 R (%)	Delta SUV 1 NR (%)	Delta SUV 2 R (%)	Delta SUV 2 NR (%)
Bampo <i>et al</i> <sup>[31]</sup>	30	17.5		7.1								73.1	50.2
Cascini <i>et al</i> <sup>[24]</sup>	33	11.2	6	2.7	100	87				62	28		
Guerra <i>et al</i> <sup>[46]</sup>	31	16.3	8.1	4.3	63.2	55.6	60	77.3	55.6	51	43.1	68.5	62.8
Hermann <i>et al</i> <sup>[26]</sup>	28	9.5	5.2	3.1	74	50	45	63	100				
Janssen <i>et al</i> <sup>[25]</sup>	46	16.4	13										
Lambrecht <i>et al</i> <sup>[28]</sup>	22				100	75	76	100	75	59	25	90	63
Rosenberg <i>et al</i> <sup>[27]</sup>	30	9.5	5.5	3.5	74	70	57.5	79	70	44.3	29.6	66	48.3
Shanmugan <i>et al</i> <sup>[29]</sup>	70	10.8		3.8			63	60	84			74	56
Sun <i>et al</i> <sup>[30]</sup>	35	14.7		7.9								57.8	

R: Responders; NR: Non responders; SUV: Standardized uptake value; Sn: Sensibility; Sp: Specificity.

The correlation between therapy-related changes in FDG uptake and tumour response in rectal cancer has been previously reported by several groups. Despite the differences in study set-up, scan type, pathological and metabolic evaluation, the final metabolic response to CRT in rectal cancer with FDG-PET/CT have been demonstrated to correlate with the histopathological response and therefore to be a useful method for early assessment of treatment efficacy in rectal cancer. The different studies provided similar cut-off values, however the above mentioned differences make a direct comparison of the results not possible (Table 3).

Cascini *et al*<sup>[24]</sup> showed that early responder patients, evaluated with PET/CT 12 d after the beginning of therapy, had a higher decrease of SUV than non-responder patients (62% vs 28%, respectively;  $P < 0.0001$ ). Conversely, the pre-surgical PET data did not demonstrate any statistically significant correlation between mean SUV late change and TRG findings ( $P = 0.2$ ) obtaining a low correlation between overall changes and the TRG ( $P = 0.63$ ).

Also Janssen *et al*<sup>[25]</sup> found an early significant decrease of the metabolic activity after the first week of CRT, both in SUVmean and SUVmax, that decreased from respectively  $8.5 \pm 2.8$  (range: 4.0-15.1) and  $16.4 \pm 5.8$  (range: 7.0-28.1) to  $6.9 \pm 2.2$  (range: 4.3-12.7) ( $P < 0.001$ ) and  $13.0 \pm 4.8$  (range: 7.6-27.4) ( $P < 0.001$ ) after the first week of combined treatment. More recently Herrmann *et al*<sup>[26]</sup> found in 28 patients a decrease of mean SUV uptake from 9.5 at baseline to 5.5 ( $P < 0.001$ ) 14 d after the onset of preoperative radiochemotherapy and in the third PET scan (4 wk after completion of treatment), mean SUV decreased to 3.1 ( $P < 0.001$ ).

Rosenberg *et al*<sup>[27]</sup> did not obtain the same result but reported that the percentage of early SUV reduction tended to be higher (44.3%) in responders than in non-responder patients (29.6%;  $P = 0.085$ ). However after the completion of therapy, the reduction of FDG uptake was 66% in histopathologically responding tumors and 48.3% in non responding tumors ( $P = 0.040$ ).

Similarly also Lambrecht *et al*<sup>[28]</sup> found, during CRT, a mean reduction in SUVmax of 59% in patients

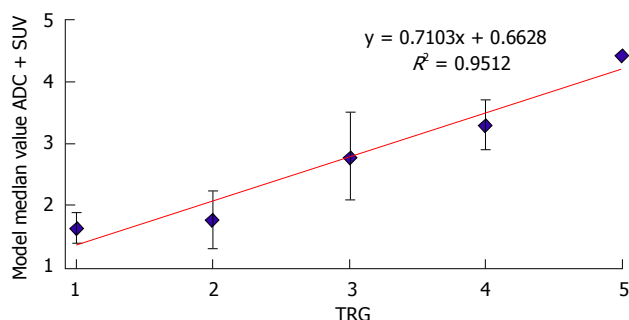
with histopathological complete response vs a mean reduction of SUVmax of 25% in patients without complete response ( $P = 0.0036$ ). Additionally, 5 wk after the completion of CRT, a 90% SUVmax reduction in the first group vs 63% in second group ( $P = 0.013$ ) was found.

Shanmugan *et al*<sup>[29]</sup> recently evaluated seventy patients that underwent pre- and post-CRT PET/CT followed by surgery and found that patients with pCR had a lower median post-CRT SUV compared with those without (2.7 vs 4.5,  $P = 0.01$ ). Median SUV decrease was 63% (7.5%-95.5%) and predicted pCR ( $P = 0.002$ ); the authors concluded that post-treatment SUV and %SUV decrease correlate with pCR.

Similar results were found by Sun *et al*<sup>[30]</sup> in a study group of 53 patients diagnosed with clinical T3- 4 and/or N+ rectal cancer and treated with CRT followed by radical surgery after 6-8 wk. A PET/CT scan was performed before (PET/CT1) beginning of treatment and a second scan (PET/CT2) was performed within 1 wk after the completion of CRT. Thirty-five out of 53 patients also underwent a third (PET/CT3) scan within 1 wk before surgery. When patients were regrouped as having a pCR and a non-pCR significant differences were found in the percentage difference between PET/CT1 and PET/CT3 in SUVmax [ $(\Delta\% \text{ SUVmax}(1-3); 69.17\% \text{ vs } 57.77\%)$ ].

Also Bampo *et al*<sup>[31]</sup> evaluated the possible predictive role of late FDG-PET/CT for the assessment of pathological response in locally advanced rectal cancer following neoadjuvant chemoradiation in 30 patients; significant differences in late SUV value and response index were observed between complete and non-complete pathological responder ( $P = 0.0006$  and  $0.03$ ). Furthermore, with receiver operating characteristic curve analysis, a SUV threshold of 5.4% had 81% sensitivity and 100% specificity, with 90% overall accuracy.

Nevertheless the optimal timing of the post-treatment PET scan, for a proper assessment of early response to CRT, is still unclear. Radiation-induced reduction in glucose intake occurs due to cell loss, which is a prolonged effect<sup>[32]</sup>. However, this can be confounded by two transient processes that occur soon after radio-



**Figure 4** Univariate linear regression analysis of combined model with median value of standardized uptake value post and apparent diffusion coefficient post, in comparison with tumor regression grade. ADC: Apparent diffusion coefficient; SUV: Standardized uptake value; TRG: Tumor regression grade.

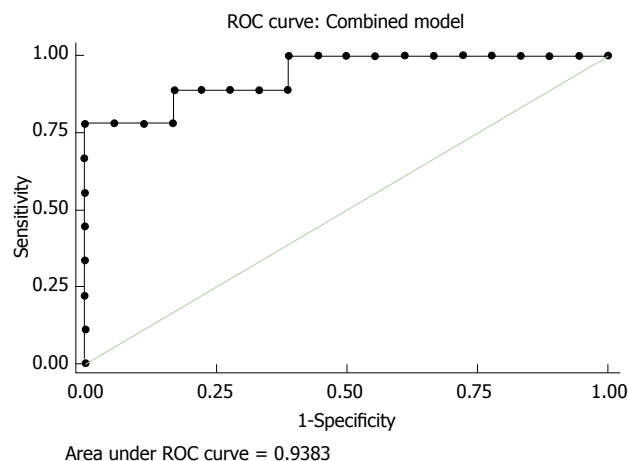
chemotherapy. The first is defined as “stunning” of tumor cells and can lead to a transient reduction in glucose metabolism, increasing false negative results<sup>[33]</sup>. The second one is the possible increase in FDG uptake due to radiogenic inflammatory processes after radiotherapy and can lead to false positive results<sup>[34]</sup>. Increasing time interval between neoadjuvant treatment and PET scan should theoretically lead to a more accurate evaluation. Alternatively, <sup>18</sup>F-FLT PET has been tested to minimize the influence of radiation-induced inflammation<sup>[35]</sup>. In previous animal studies, FLT uptake has been shown to be in inflamed tissue as compared with FDG. However, it has not shown to be a valid tool for a proper CRT response assessment in rectal cancer patients<sup>[36]</sup>.

In Lambrecht *et al.*<sup>[28]</sup> study ROC curve analysis identified a threshold value for  $\Delta$ SUVmax of 40%, for differentiating patients with a complete response after 2 wk, with a sensitivity of 100%, but a specificity of 75% and a PPV of 60%. Similarly using a threshold for  $\Delta$ SUVmax of 76% after CRT and before surgery, is possible to identify complete responders with a sensitivity of 100%, a specificity of 75% and a PPV of 60%.

Considering our results, ROC curves analysis have shown that SUV2 has the best accuracy (80.7%) in predicting response to neoadjuvant treatment with a threshold value of 4.4. Interestingly, to note that in our study the PPV of SUV2 in predicting response was very high (94.4%) suggesting more conservative surgical approaches only in patients with evidence of lower glucose uptake at the end of neoadjuvant treatment.

While evaluating the correlation between the changes of ADC before and after CRT we found that before CRT, the mean tumour ADC in the responder group was  $(0.88 \pm 0.19) \times 10^{-3} \text{ mm}^2/\text{s}$ , while that in the non-responder group was  $(0.78 \pm 0.09) \times 10^{-3} \text{ mm}^2/\text{s}$ . At the end of combined chemoradiation therapy the mean tumor ADC value for responder patients was  $(1.47 \pm 0.22) \times 10^{-3} \text{ mm}^2/\text{s}$ . For non-responder patients the mean ADC value after therapy was  $(1.19 \pm 0.20) \times 10^{-3} \text{ mm}^2/\text{s}$ .

Our results are in line with the previously published by Jung *et al.*<sup>[37]</sup>. Before neoadjuvant CRT, the mean



**Figure 5** Receiver operating characteristic curve of combined model with median value of standardized uptake value post and apparent diffusion coefficient post, in comparison with tumor regression grade. ROC: Receiver operating characteristic.

ADC of responders and non-responders were  $(0.93 \pm 0.09) \times 10^{-3} \text{ mm}^2/\text{s}$  and  $(1.03 \pm 0.08) \times 10^{-3} \text{ mm}^2/\text{s}$ , respectively. After neoadjuvant CRT the mean post-CRT ADC in responders was higher than in non-responders ( $P = 0.009$ ), being respectively  $(1.29 \pm 0.13) \times 10^{-3} \text{ mm}^2/\text{s}$  and  $(1.18 \pm 0.08) \times 10^{-3} \text{ mm}^2/\text{s}$ . Using a post-CRT ADC of  $1.18 \times 10^{-3} \text{ mm}^2/\text{s}$  as cut-off value for discriminate between the responders and non-responders, the highest accuracy (77.1%) was obtained, with the following diagnostic predictive values: Sensitivity 91.3%, specificity 50.0%, positive predictive value 77.8%, and negative predictive value 75.0%.

Similarly Kim *et al.*<sup>[6]</sup> reported that the mean ADC after CRT in the responders group  $[(1.62 \pm 0.36) \times 10^{-3} \text{ mm}^2/\text{s}]$  differed significantly from the one in the non-responders group  $[(1.04 \pm 0.24) \times 10^{-3} \text{ mm}^2/\text{s}]$ . Moreover, when an ADC value of  $1.20 \times 10^{-3} \text{ mm}^2/\text{s}$  was used as cut-off, the authors obtained an accuracy of 85% with the following diagnostic predictive values: sensitivity 100%, specificity 79%, positive predictive value 65%, and negative predictive value 100%.

Recently, other studies<sup>[38-40]</sup> revealed similar data. Ha *et al.*<sup>[38]</sup> comparing the mean post-CRT ADC for the RC group vs the non-CR group  $[(1.33 \pm 0.25) \times 10^{-3} \text{ mm}^2/\text{s}$  vs  $(1.13 \pm 0.32) \times 10^{-3} \text{ mm}^2/\text{s}]$  found a significant increased ( $P = 0.001$ ) of ADC value. When a post-CRT ADC of  $1.20 \times 10^{-3} \text{ mm}^2/\text{s}$  was used as a cut-off value for discriminating CR, the accuracy was 67%, sensitivity was 52.1%, specificity of 80.8%, positive predictive value of 71.4%, and negative predictive value of 64.6%.

Even the best timing to perform the follow-up MR study for the assessment of response to CRT is still debated. Some Authors performed the diffusion-MR also during the first 15 d of the combined treatment. Sun *et al.*<sup>[12]</sup> evaluated the ADC only one week after the beginning of CRT. Before CRT the mean tumour ADC value in the down-staged group was lower than that in

**Table 4** Overview of studies analysing mean apparent diffusion coefficient and delta apparent diffusion coefficient values of the rectal lesion for each MR study

Ref.	n of patients	Pre ADC mean R	Pre ADC mean NR	Post ADC mean R	Post ADC mean NR	ROC curve (highest accuracy)
Ippolito <i>et al</i> <sup>[45]</sup>	30	0.88 ± 0.19	0.78 ± 0.09	1.47 ± 0.22	1.19 ± 0.20	1.28 (80%)
Kim <i>et al</i> <sup>[41]</sup>	34	0.90 ± 0.06	0.94 ± 0.03			
Jung <i>et al</i> <sup>[37]</sup>	35	0.93 ± 0.09	1.03 ± 0.08	1.29 ± 0.13	1.18 ± 0.08	1.18 (77.1%)
Kim <i>et al</i> <sup>[6]</sup>	40			1.62 ± 0.36	1.04 ± 0.24	1.20 (85%)
Curvo Semedo <i>et al</i> <sup>[43]</sup>	50	1.07 ± 0.15	1.10 ± 0.19	1.39 ± 0.24	1.45 ± 0.28	1.41 (53%)
Ha <i>et al</i> <sup>[38]</sup>	100	0.59 ± 0.29	0.49 ± 0.22	1.33 ± 0.25	1.13 ± 0.32	1.20 (67%)
Genovesi <sup>[44]</sup>	28	1.01 ± 0.06	1.29 ± 0.02	1.79 ± 0.51	1.37 ± 0.43	29.5 (91.3%)
Cai <i>et al</i> <sup>[39]</sup>	15	0.659	0.885	0.713	1.027	
Birlik <i>et al</i> <sup>[40]</sup>	43	0.66 ± 0.10	0.72 ± 0.14	1.22 ± 0.26	0.95 ± 0.20	1.20 (60%)

R: Responders; NR: Non responders; ADC: Apparent diffusion coefficient.

the nondown-staged group ( $1.07 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.13$  vs  $1.19 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.15$ ,  $F = 6.91$ ,  $P = 0.013$ ). At the end of the first week, the mean tumour ADC increased significantly to  $1.32 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.16$  ( $F = 37.63$ ,  $P < 0.001$ ) in the down-staged group, while there was no significant ADC value increase in the nondown-staged group ( $F = 1.18$ ,  $P = 0.291$ ).

Also Kim *et al*<sup>[41]</sup> reported that the mean percentage of tumour ADC change in the responder group after 2 wk of CRT was higher in comparison with that of the non-responder group, even if not statistically significant. Seierstad *et al*<sup>[42]</sup> found an increase in tumour ADC values on day 11 after the beginning of CRT.

Cai *et al*<sup>[39]</sup> obtained an increase in the mean tumour ADC during the course of neoadjuvant CRT, especially at the 2<sup>th</sup> week ( $P = 0.004$ ), with a significant increase in the mean ADC at the 2<sup>th</sup> week of neoadjuvant therapy in the T down-stage and tumour regression group ( $P = 0.011$ ;  $0.004$ ). They also found a strong negative correlation between the mean pretreatment tumour ADC and tumour regression after neoadjuvant CRT ( $P = 0.0021$ ).

Hypotizing that disrupted membranes increase the extracellular volume since they demonstrated higher permeability, Authors concluded that the ADC values changes in this early phase of CRT are probably the result of irreparable radiation induced DNA damage. However considering the variability among the results obtained in the recent literature (Table 4), actual evidence suggests that DWI-MR performed early after the beginning of therapy could not provide accurate and reproducible results for the evaluation of early tumour response to CRT. Hence the attention should be focused on ADC values obtained after the end of the treatment.

As well as for SUV values, in order to evaluate the prognostic value of pretreatment MR, several authors assessed<sup>[6,7,38-40,43,44]</sup> the pre-CRT ADC, obtaining controversial results. Curvo-Semedo *et al*<sup>[43]</sup> demonstrated that lower pre-CRT ADC values were associated with a more aggressive tumour profile: in their study mean ADCs were significantly different for mesorectal fascia tumour free (MRF) vs MRF-invaded ( $P = 0.013$ ), mrN0 vs mrNp ( $P = 0.011$ ), and for the different

tumour differentiation grades at histology ( $P = 0.025$ ). Particularly tumours with involved MRFs, nodal-positive disease and those of less differentiated showed lower ADC values. Furthermore, a significant positive correlation ( $r = 0.374$ ;  $P = 0.019$ ) between ADC values and the distance of the tumour from the MRF was found.

Jung *et al*<sup>[37]</sup> recently reported that the mean pre-CRT ADC obtained with a 3 Tesla MR of responders was lower than that of non-responders ( $P = 0.034$ ). Other authors<sup>[39,40]</sup>, obtained similar results with 1.5 T MR. For instance, in the study of Birlik *et al*<sup>[40]</sup>, before CRT the mean tumour ADC in the responder group was significantly lower than that in the nonresponder group ( $P < 0.001$ ).

Other authors, however, reported that pre-treatment ADC values were not statistically different for responders and non-responders and that may be limited in predicting treatment outcome<sup>[6,38,41,44,45]</sup>. For instance, Kim *et al*<sup>[41]</sup> reported that, predicting the treatment outcome based on TRG, there were no significant differences among responder and non-responder groups when comparing pre-CRT ADCs and early tumour ADC increase rates: As the tumour responds to treatment, ADC values will probably rise at first, due the initial disruption of cell membranes, and then decrease at the end of the treatment, for the post-irradiation ingrowth of fibrosis restricting water mobility.

Considering these results and according to recent literature, the best reproducibility was obtained by studies that evaluated a post-treatment cut-off value of ADC and SUV; being the most promising and precise way of applying functional techniques in the clinical practice.

Moreover, as evaluated in our series of patients, combining in a single analysis the mathematical model of median values of ADC and of SUV values, the power of both functional technique improves, gaining a strictly and significant relationship with TRG system staging by linear regression analysis with  $R^2$  of 0.95 (Figure 5).

In the era of PET/MRI scanner, the future approach should be represented by the combination of PET imaging with MRI not only to increase anatomical resolution but also for cell and molecular imaging, improving

the accuracy in the assessment of tumour response. Moreover, the synchronous acquisition of both technique is critical in order to avoid differences in patient position, organ motion, and tumor growth.

In conclusion, the combined functional analysis of MRI and PET imaging, by the quantitative analysis of ADC map on DW-MR imaging and glucose uptake by  $^{18}\text{F}$ -FDG-PET, can contribute to the management of patients with locally advanced rectal cancer increasing the overall accuracy and sensitivity for treatment response evaluation in one step, since they permit to detect changes in cellular tissue structures useful in prediction the different group category response in relation to TRG system.

## COMMENTS

### Background

The treatment of locally advanced rectal cancer has shifted in recent years toward a more conservative policy for patients identified as complete responders after chemoradiation treatment (CRT). Therefore the determination of CR before surgery would influence the subsequent treatment choice, an accurate clinical assessment of response becomes essential. Conventional imaging modalities cannot distinguish fibrosis or scar from viable tumour cells in residual masses after chemoradiotherapy; therefore, these methods have a negligible impact on the prediction of pathologic findings. For these reasons, in recent years, the functional imaging studies are increasingly being conducted to add information about changes in tumour pathophysiology.

### Research frontiers

$^{18}\text{F}$ fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG PET) is a non-invasive tool to detect tumour metabolic activity and can be used to assess changes in tumour glucose metabolism after a CRT treatment. The semiquantitative assessment of glucose metabolism by evaluating the standardized uptake value (SUV) has been shown to have clinical relevance in several tumour types, since a strong relationship between  $^{18}\text{F}$ -FDG SUV changes and pathological response has been proved in different types of cancer. DW-MRI enables noninvasive characterization of biologic tissues on the basis of their water diffusion properties (Brownian motion) microcirculation. Due to the restricted motion of water molecules, the diffusion coefficients obtained by quantitative DWI differ from the free diffusion values and are called apparent diffusion coefficients (ADC), and it can be measured. ADCs tend to decrease with increased tissue cellularity or cell density. Conversely, the cell density may be indicative of tumor aggressiveness; increased metastatic capacity of tumors with high cellularity.

### Innovations and breakthroughs

The importance of this work consist of the possibility to offer, in the era of PET/MRI scanner, a new advanced quantitative tool that allows the non-invasive evaluation of response to neoadjuvant chemotherapy treatment in patients with rectal cancer, by adding quantitative value information on DW images and on PET/CT imaging, combined in a single analysis. Moreover in this manuscript the authors reviewed and commented the recent literature findings on this field by using the two different techniques modalities [*i.e.*, PET/CT and magnetic resonance imaging (MRI)].

### Applications

Considering the variability among the results obtained in the recent literature, in rectal cancer post-therapy imaging assessment, the actual evidence suggests that DWI-MR and PET/CT performed early after the beginning of therapy could not provide accurate and reproducible results for the evaluation of early tumour response to CRT. Hence the attention should be focused on functional quantitative evaluation of ADC and SUVmax obtained after the end of the treatment.

### Terminology

DWI: Diffusion MRI (or dMRI) is a MRI method which allows the mapping of the diffusion process of molecules, mainly water, in biological tissues, *in vivo* and non-invasively. Molecular diffusion in tissues is not free, but reflects interactions with many obstacles, such as macromolecules, fibers, and membranes. Water molecule diffusion patterns can therefore reveal microscopic details about tissue architecture, either normal or in a diseased state. ADC is a measure of the magnitude of diffusion (of water molecules) within tissue, and is commonly clinically calculated using MRI with diffusion weighted imaging, the extent of tissue cellularity and the presence of intact cell membrane help determine the impedance of water molecule diffusion. This impedance of water molecules diffusion can be quantitatively assessed using the ADC value. This assessment can be done using different b values via changing gradient amplitude. ADC values are calculated automatically by the software and then displayed as a parametric map that reflects the degree of diffusion of water molecules through different tissues. Then, by use of a dedicated workstation, ADC measurements are recorded for a given region by drawing regions of interest (ROIs) on the ADC map. SUVmax: The SUV is often used in PET imaging for a simple semiquantitative analysis. Its use is particularly common in the analysis of  $^{18}\text{F}$ -FDG images of cancer patients. It can also be used with other PET agents especially when no arterial input function is available for more detailed pharmacokinetic modeling. The SUV represents the ratio of the image derived radioactivity concentration found in a selected part of the body at a certain time point, and as reference the radioactivity concentration in the hypothetical case of an even distribution of the injected radioactivity across the whole body.

### Peer-review

This study is well designed and well described. The conclusion that MRI and PET imaging including the quantitative analysis of ADC map on DW-MR imaging and glucose uptake by  $^{18}\text{F}$ -FDG-PET can contribute to the management of patients with locally advanced rectal cancer is helpful in clinical practice.

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