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Systematic Review

# The role of diffusion-weighted MRI and $^{18}$F-FDG PET/CT in the prediction of pathologic complete response after radiochemotherapy for rectal cancer: A systematic review

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ABSTRACT

After neoadjuvant radiochemotherapy (RCT) for locally advanced rectal cancer, 15–27% of the patients experience a pathological complete response (pCR). This observation raises the question as to whether invasive surgery could be avoided in a selected cohort of patients who obtain a clinical complete response after preoperative RCT. In this respect, there has been growing interest in functional imaging techniques to improve clinical response assessment. This systematic review focuses on the role of diffusion-weighted imaging (DWI) and $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) in the prediction of pCR after RCT for rectal cancer.

A total of 14 publications on DWI and 25 on $^{18}$F-FDG PET/CT were retrieved. Pooled analysis of individual patient data shows both imaging modalities have a low positive predictive value in the prediction of pCR (mean PPV of 54% and 39% for DWI- and $^{18}$F-FDG PET/CT-based parameters respectively). Especially pre-RCT imaging is unable to predict pCR with overall accuracies of 68–72% for DWI and 44% for $^{18}$F-FDG PET/CT. Qualitative DWI assessment 5–10 weeks after the end of RCT may outperform apparent diffusion coefficient (ADC)-based DWI-parameters (overall accuracy of 87% vs. 74–78%). Although few data are available, early changes in FDG-uptake seem promising in the prediction of pCR and the role of $^{18}$F-FDG PET/CT during RCT should be further investigated. Quantitative and qualitative $^{18}$F-FDG PET/CT measurements are equally effective in the assessment of pCR after RCT.

The major strength of DWI and $^{18}$F-FDG PET/CT lies in the identification of non-responders who are not candidates for organ preservation. Up to now, DWI and $^{18}$F-FDG PET/CT are not accurate enough to safely select patients for organ-sparing strategies. Future research must focus on the integration of functional imaging with clinical data and molecular biomarkers.



Neoadjuvant radiochemotherapy (RCT) followed by total mesorectal excision (TME) surgery is currently the standard treatment for locally advanced rectal carcinoma [1–3]. The tumoral response to this preoperative treatment is very heterogeneous: while 15–27% of the patients achieve a pathological complete response (pCR), a partial response is seen in 54–75% and others show no response at all [4]. Patients who achieve a pCR have a favorable long-term outcome with excellent local control and disease-free survival regardless of their initial T- and N-stages [4–6]. Retrospective studies from Brazil have highlighted the 'wait-and-see' policy in such patients [7]. More recent series support the feasibility of this approach [8,9]. Adopting a non-operative strategy for clinical complete responders will avoid the risks of surgical morbidity and mortality, and will spare them the need for a stoma [10–12]. However, before a 'wait-and-see' policy could be safely implemented, a precise selection of the eligible patients is mandatory.

The gold standard for assessing the tumoral response to preoperative RCT is conventional histopathological analysis. This method, however, is only applicable in the postoperative setting and consequently cannot be used for the preoperative selection for an individualized treatment. Computed tomography (CT), endorectal ultrasound (EUS) and conventional magnetic resonance imaging (MRI) have shown to lack accuracy for restaging after RCT [13–16]. In recent years, there has been growing interest in functional imaging techniques to improve clinical response assessment. These imaging modalities depict the microstructural and metabolic characteristics of the tumor, allowing assessment of treatment-induced changes before morphological changes become apparent. In this

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respect, diffusion-weighted imaging (DWI) and $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) have emerged as powerful tools in the response prediction before, during and after neoadjuvant RCT for rectal cancer.

DWI is a non-invasive imaging modality, providing functional information on the microstructure of tissues through the assessment of differences in water proton mobility [17]. Water diffusion characteristics depend on several factors such as cell density, vascularity, viscosity of the extracellular fluid and cell membrane integrity. By quantifying these properties as the apparent diffusion coefficient (ADC), DWI can be used as an imaging biomarker to monitor and predict tumoral response to RCT [18,19].

$^{18}$F-FDG PET semi-quantitatively assesses tumor glucose metabolic activity through changes in FDG-uptake. A decrease in FDG-uptake after radiotherapy and/or chemotherapy has been correlated with pathological response in several tumor types [20–22].

In this systematic review, we collect the current evidence of the role of DWI and $^{18}$F-FDG PET/CT in the prediction of pCR after preoperative RCT for locally advanced rectal cancer.

## Materials and methods

### *Search strategy and selection criteria*

The MEDLINE and Embase databases were searched for the terms (“rectal cancer” AND “diffusion magnetic resonance imaging” AND “response”) and for (“rectal cancer” AND “positron emission tomography” AND “response”) (29 September 2014) [23]. These initial searches yielded 155 and 222 publications respectively. Only papers published in English, German, and French were included, resulting in 153 and 216 articles. All titles and abstracts were screened and only studies reporting on the role of DWI or $^{18}$F-FDG PET in the assessment of pCR after RCT for locally advanced rectal cancer were retained. Reviews, general overview articles and congress abstracts were excluded. To identify additional relevant studies, the reference lists of the retrieved studies were checked manually. A total of 14 relevant DWI and 25 $^{18}$F-FDG PET/CT papers were identified. Selected studies were evaluated for methodological quality using the quality assessment of diagnostic accuracy studies (QUADAS) criteria [24]. Literature selection results are depicted in Fig. 1. A meta-analysis was not performed due to the wide heterogeneity between the included studies.

### *Data extraction*

We extracted all available data on the performance of following quantitative DWI parameters: pretreatment ADC ($ADC_{pre}$), ADC during RCT ($ADC_{during}$), posttreatment ADC ($ADC_{post}$), change in ADC during RCT ($\Delta ADC_{during}$) and change in ADC after RCT ($\Delta ADC_{post}$). Additionally, volumetric data and data on qualitative DWI assessment were collected. Following $^{18}$F-FDG PET/CT parameters were retained: the mean and maximum standardized uptake value (SUV) measured before ($SUVmean_{pre}$, $SUVmax_{pre}$), during ($SUVmean_{during}$, $SUVmax_{during}$) and after RCT ($SUVmean_{post}$, $SUVmax_{post}$). The absolute change in SUVmax ($\Delta$SUVmax) and the response indices were also extracted (RI $SUV_{mean}$, RI $SUV_{max}$), as was the total lesion glycolysis (TLG) and the metabolic tumor volume (MTV). The visual response score (VRS) was retained as a qualitative parameter.

Some papers used receiver operating characteristic (ROC) analysis to calculate cutoff values for the individual response parameters. A ROC curve plots the true positive rate against the false positive rate at various threshold settings, thereby allowing to calculate optimal cutoff values. If cutoff values were provided, $2 \times 2$ contingency tables were constructed and the sensitivity, specificity, positive and negative predictive values of DWI and $^{18}$F-FDG PET/CT in the prediction of pCR were calculated (Suppl Fig. 1). We defined the sensitivity for pCR prediction as the fraction of patients with pCR that is correctly identified as such by imaging. The specificity is the fraction of patients without pCR correctly identified as such by DWI or $^{18}$F-FDG PET/CT. The positive predictive value (PPV) reflects the probability that a complete response on imaging is confirmed by pathological examination. Conversely, the negative predictive value (NPV) reflects the probability that an incomplete response on imaging is confirmed by pathology. Finally, when available, individual patient data (i.e. true positives, false positives, true negatives and false negatives) were extracted

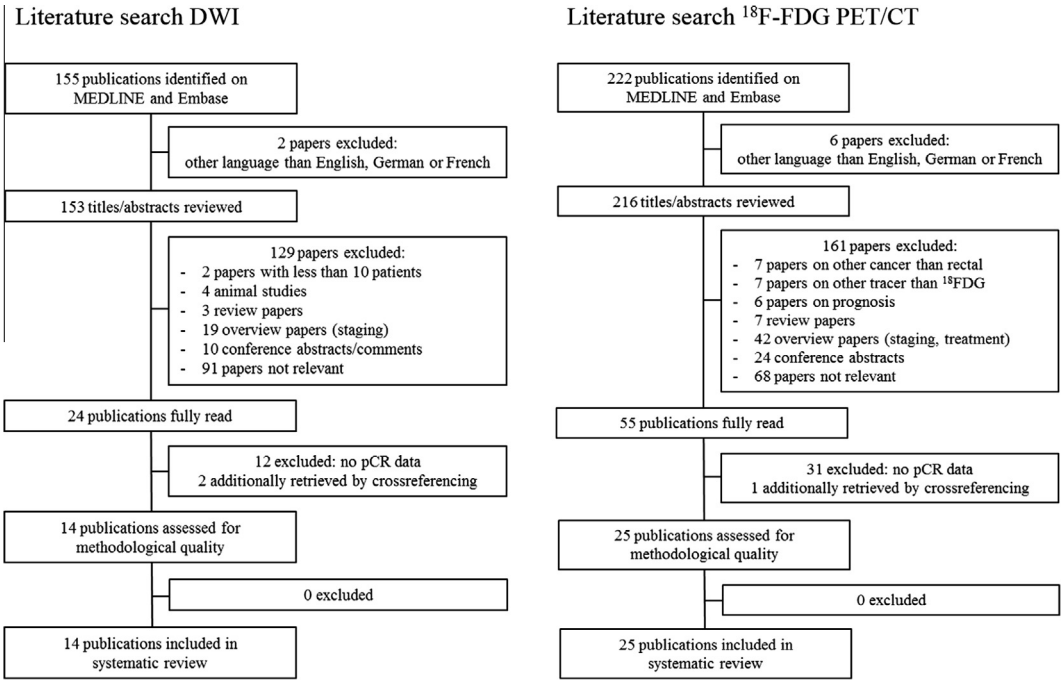


**Fig. 1.** Literature search.

to calculate a pooled accuracy of the retained DWI and $^{18}$F-FDG PET/CT parameters.

## Results

Nine papers reported on the role of $ADC_{pre}$ in the prediction of pCR (Table 1). Three articles found that a low pretreatment ADC significantly correlated with pCR [25–27]. Our group demonstrated that a pretreatment ADC lower than $1.06 \times 10^{-3}$ mm$^2$/s predicted pCR with a sensitivity of 100%, specificity of 86% and overall accuracy of 90% [25]. In a larger patient group, Intven et al. found that a pretreatment ADC lower than $0.97 \times 10^{-3}$ correctly predicted pCR with an overall accuracy of 81%, but with a sensitivity of only 56% [27]. Pooled data show $ADC_{pre}$ predicts pCR with a NPV of 90% and a specificity of 68%, but with a PPV of only 35%. In a study of 20 patients it was demonstrated that the change in ADC after 10–15 fractions of radiation therapy ($\Delta ADC_{during}$) was significantly correlated with pCR [25]. ROC analysis showed an area under the curve (AUC) of 100% at a cutoff point of 50%. Volumetric assessment of DWI prior to RCT has no value in the prediction of pCR, as shown by three papers [29,33,34].

Seven papers demonstrated that a high $ADC_{post}$ value significantly correlated with pCR (Table 2). In a retrospective analysis of 40 patients, Kim et al. found that a mean $ADC_{post} > 1.20 \times 10^{-3}$ mm$^2$/s predicted pCR with a sensitivity and overall accuracy of 100% and 85% respectively [35]. The same authors confirmed this in a larger retrospective study of 76 patients, although the optimal cutoff increased to $1.30 \times 10^{-3}$ mm$^2$/s [28]. Conversely, Curvo-Semedo et al. reported a lower $ADC_{post}$ in patients who achieved pCR, although this was not significant [29]. Four papers found that an ADC increase of 41–48% was predictive for pCR [25,27,28,31]. Pooled analysis shows a moderate performance of late quantitative DWI assessment with overall accuracies of 74% and 78% for $ADC_{post}$ and $\Delta ADC_{post}$ respectively. In contrast to pre-RCT DWI, volumetric assessment after RCT might be a valuable tool for pCR prediction [29,33,34]. Pooled analysis demonstrates that volumetric DWI measurements after RCT can predict pCR with a sensitivity and an overall accuracy of 65% and 90%. Relative changes in tumor volume on DWI can predict pCR with a sensitivity and accuracy of 83% and 85% respectively.

Four articles demonstrate that late qualitative DWI assessment can predict pCR with a pooled specificity of 94% and an overall accuracy of 87%, thereby outperforming quantitative DWI measurements [30,36–38].

Thirteen papers reported on the performance of $SUVmax_{pre}$ or $SUVmean_{pre}$ in the prediction of pCR (Table 3). Only one article found a statistically significant correlation between a low $SUVmax_{pre}$ and pCR [39]. Individual patient data from two studies demonstrate that $SUVmax_{pre}$ predicts pCR with a specificity and overall accuracy of only 35% and 44% respectively [42,43]. Early response prediction by $^{18}$F-FDG PET/CT during RCT seems more promising (Table 4). Based on PET data after 10–12 fractions, our group demonstrated that a RI $SUV_{max}$ threshold value of 40% correctly identified all patients who achieved pCR [26]. Recently, Goldberg et al. found that only after one week a decrease in $SUV_{max}$ of more than 32% could predict the achievement of pCR with a sensitivity of 75% and a specificity of 100% [46]. Pooled analysis shows a PPV and overall accuracy of 69% and 88% respectively for SUV measurements during RCT.

We found 14 articles reporting on posttreatment SUV as a semiquantitative parameter for the assessment of pCR (Table 5). $SUVmax_{post}$ tends to be lower in patients without residual tumor cells than in patients with suboptimal treatment response. Optimal cutoff points to discriminate patients who achieve pCR from those who do not, vary between 3.35 and 5.4 [41–45,48,50].

The most studied PET parameter in late response prediction is the relative change in SUV measured before and after RCT (RI $SUVmax_{post}$ and RI $SUVmean_{post}$). A higher decrease in SUV was found predictive for pCR by seven authors [26,41,44,45,50–52]. Optimal cutoff values for RI $SUVmax_{post}$ vary from 45.9% to 76%.

In eleven studies, $^{18}$F-FDG PET/CT scans were interpreted subjectively by visual inspection. Pooled data show qualitative analysis after RCT is able to assess pCR with a negative predictive value of 89% and an overall accuracy of 65%, which is comparable to the quantitative SUV measurements post-RCT. Three articles investigated changes in MTV and TLG as a response parameter, but only Sun and co-workers found a relative decrease in MTV and TLG after 5–7 weeks significantly predictive for pCR [47,49,52].

## Discussion

In this systematic review, we collect the current evidence of the role of DWI and $^{18}$F-FDG PET/CT in the prediction of pCR before, during and after RCT for rectal cancer (Fig. 2).

**Table 1**
Early pCR prediction with DWI.

| Study | N | pCR (%) | *b*-Values (s/mm$^2$), field strength | DWI parameter | Correlation with pCR | *p*-Value | Cutoff* | Sens (%) | Spec (%) | PPV (%) | NPV (%) | Acc (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lambrecht [25] | 20 | 30 | *b*0-50-100-500-750-1000, 1.5 T | $ADC_{pre}$ | Negative | 0.003 | $1.06 \times 10^{-3}$ | 100 | 86 | 75 | 100 | 90 |
| Lambrecht [26] | 22 | 27 | *b*0-50-100-500-750-1000, 1.5T | $ADC_{pre}$ | Negative | 0.002 | $1.06 \times 10^{-3}$ | 100 | 88 | 75 | 100 | 91 |
| Intven [27] | 59 | 15 | *b*0-200-800, 3T | $ADC_{pre}$ | Negative | 0.01 | $0.97 \times 10^{-3}$ | 56 | 86 | 42 | 92 | 81 |
| Kim [28] | 76 | 14 | *b*0-600-1000, 1.5T | $ADC_{pre}$ | Negative | 0.4094 | $0.91 \times 10^{-3}$ | 82 | 39 | 18 | 93 | 45 |
| Curvo-Semedo [29] | 49‡ | 27 | *b*0-500-1000, 1.5T | $ADC_{pre}$ | Negative | 0.61 | $0.97 \times 10^{-3}$ | 39 | 81 | 42 | 78 | 69 |
| | 50 | 28 | | $VDWI_{pre}$ | Negative | 0.16 | 12.5 | 57 | 78 | 50 | 52 | 72 |
| Engin [30] | 30 | 30 | *b*50-400-800, 1.5T | $ADC_{pre}$ | Positive | 0.066 | | | | | | |
| Lee [31] | 38 | 24 | *b*0-1000 | $ADC_{pre}$ | None | 0.972 | | | | | | |
| Genovesi [32] | 28 | 36 | *b*0-400-500-600-800-1000, 3T | $ADC_{pre}$ | Negative | 0.33 | | | | | | |
| Ha [33] | 100 | 35 | *b*0-150-1000, 1.5T | $ADC_{pre}$ | Positive | 0.484 | | | | | | |
| | | | | $VDWI_{pre}$ | Positive | 0.742 | | | | | | |
| Lambregts [34] | 112 | 18 | *b*0-25-50-100-300-500-1000-1100, 1.5T | $VDWI_{pre}$ R1 | Negative | NA | 12.5 | 55 | 71 | 29 | 88 | 68 |
| | | | | $VDWI_{pre}$ R2 | Negative | NA | 12.5 | 70 | 78 | 41 | 92 | 77 |
| **Pooled data** | **226** | **20** | | **$ADC_{pre}$** | | | | **69** | **68** | **35** | **90** | **68** |
| | **274†** | **20** | | **$VDWI_{pre}$** | | | | **61** | **75** | **38** | **89** | **72** |

Acc = accuracy; ADC = apparent diffusion coefficient; DWI = diffusion weighted imaging; N = number of patients; NA = not available; NPV = negative predictive value; pCR = pathologic complete response; PPV = positive predictive value; R = radiologist; Sens = sensitivity; Spec = specificity; T = Tesla; V = volume.

* Cutoff values of ADC are in mm$^2$/s, cutoff values of volumes are in cm$^3$.

‡ In one patient, ADC measurements were not obtained because the tumor had an entirely mucinous aspect.

† To obtain pooled data, N was multiplied by the number of participating radiologists.

**Table 2**
Late pCR assessment with DWI.

| Study | N | pCR (%) | *b*-values (s/mm$^2$), field strength | DWI parameter | Interval RCT-DWI (weeks) | Correlation with pCR | *p*-value | Cutoff* | Sens (%) | Spec (%) | PPV (%) | NPV (%) | Acc (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Quantitative analysis* | | | | | | | | | | | | | |
| Lambrecht [25] | 20 | 30 | *b*0-50-100-500-750-1000, 1.5T | $\Delta ADC_{post}$ (%) | 5–7 | Positive | 0.0011 | 48% | 100 | 93 | 86 | 100 | 95 |
| Intven [27] | 59 | 15 | *b*0-200-800, 3T | $ADC_{post}$ | 4–8 | Positive | 0.047 | | | | | | |
| | | | | $\Delta ADC_{post}$ (%) | | Positive | <0.001 | 41% | 78 | 92 | 64 | 96 | 90 |
| Kim [28] | 76 | 14 | *b*0-600-1000, 1.5T | $ADC_{post}$ | 4–6 | Positive | <0.0001 | $1.30 \times 10^{-3}$ | 100 | 85 | 52 | 100 | 87 |
| | | | | $\Delta ADC_{post}$ (%) | | Positive | <0.0001 | 42% | 100 | 71 | 37 | 100 | 75 |
| Curvo-Semedo [29] | 49‡ | 27 | *b*0-500-1000, 1.5T | $ADC_{post}$ | 6–8 | Negative | 0.48 | $1.41 \times 10^{-3}$ | 46 | 56 | 27 | 74 | 53 |
| | | | | $\Delta ADC_{post}$ (%) | | Negative | 0.96 | 25.3% | 54 | 64 | 35 | 79 | 61 |
| | 50 | 28 | | $VDWI_{post}$ | | Negative | <0.001 | 0.15 | 79 | 100 | 100 | 92 | 94 |
| | | | | $\Delta V_{post}$ (%) | | positive | <0.001 | 97.5% | 86 | 89 | 75 | 94 | 88 |
| Engin [30] | 30 | 30 | *b*50-400-800, 1.5T | $ADC_{post}$ | 6 | Positive | 0.071 | | | | | | |
| Lee [31] | 38 | 24 | *b*0-1000 | $ADC_{post}$ | 6 | Positive | 0.037 | | | | | | |
| | | | | $\Delta ADC_{post}$ (%) | | Positive | 0.026 | | | | | | |
| Genovesi [32] | 28 | 36 | *b*0-400-500-600-800-1000, 3T | $ADC_{post}$ | 8 | Positive | 0.003 | | | | | | |
| Ha [33] | 100 | 35 | *b*0-150-1000, 1.5T | $ADC_{post}$ | NA | Positive | <0.001 | $1.20 \times 10^{-3}$ | 71 | 65 | 52 | 81 | 67 |
| | | | | $VDWI_{post}$ | | Negative | <0.001 | | | | | | |
| | | | | $\Delta V_{post}$ (%) | | Positive | <0.001 | 86.8% | 91 | 80 | 71 | 95 | 84 |
| Lambregts [34] | 112 | 18 | *b*0-25-50-100-300-500-1000-1100, 1.5T | $VDWI_{post}$ R1 | NA | Negative | NA | 0.15 | 60 | 98 | 86 | 92 | 91 |
| | | | | $VDWI_{post}$ R2 | | Negative | NA | 0.15 | 60 | 92 | 63 | 91 | 87 |
| | | | | $\Delta V_{post}$ (%) R1 | | Positive | NA | 97.5% | 80 | 93 | 73 | 96 | 91 |
| | | | | $\Delta V_{post}$ (%) R2 | | Positive | NA | 97.5% | 70 | 82 | 45 | 93 | 79 |
| Kim [35] | 40 | 28 | *b*0-1000, 1.5T | $ADC_{post}$ | 4–6 | Positive | <0.0001 | $1.20 \times 10^{-3}$ | 100 | 79 | 65 | 100 | 85 |
| Song [36] | 50 | 12 | *b*0-100-800-1000, 3T | $ADC_{post}$ | 6 | Positive | <0.0001 | $1.045 \times 10^{-3}$ | 100 | 75 | 35 | 100 | 78 |
| **Pooled data** | **315** | **24** | | **$ADC_{post}$** | | | | | **78** | **72** | **47** | **91** | **74** |
| | **204** | **19** | | **$\Delta ADC_{post}$ (%)** | | | | | **80** | **78** | **46** | **94** | **78** |
| | **274** | **20** | | **$VDWI_{post}$** | | | | | **65** | **96** | **80** | **92** | **90** |
| | **374** | **24** | | **$\Delta V_{post}$ (%)** | | | | | **83** | **86** | **65** | **94** | **85** |
| *Qualitative analysis* | | | | | | | | | | | | | |
| Engin [30] | 30 | 30 | *b*50-400-800, 1.5T | Signal intensity | 8 | | | | 22 | 100 | 100 | 75 | 77 |
| Song [36] | 50 | 12 | *b*0-100-800-1000, 3T | VRS R1 | 6 | | | | 33 | 98 | 67 | 92 | 90 |
| | | | | VRS R2 | | | | | 50 | 91 | 43 | 93 | 86 |
| Lambregts [37] | 120 | 19 | *b*0-1000, 1.5T | VRS R1 | 5–10 | | | | 56 | 94 | 70 | 89 | 86 |
| | | | | VRS R2 | | | | | 64 | 90 | 62 | 90 | 84 |
| | | | | VRS R3 | | | | | 52 | 97 | 81 | 89 | 88 |
| Sassen [38] | 70 | 14 | *b*0-300-1100 ($n$ = 59) | VRS R1 | 6 | | | | 70 | 93 | 64 | 95 | 90 |
| | | | *b*0-500-100 ($n$ = 11), 1.5T | VRS R2 | | | | | 40 | 98 | 80 | 91 | 90 |
| **Pooled data** | **630*** | **18** | | **Qualitative analysis** | | | | | **53** | **94** | **68** | **90** | **87** |

Acc = accuracy; ADC = apparent diffusion coefficient; DWI = diffusion weighted imaging; N = number of patients; NA = not available; NPV = negative predictive value; pCR = pathologic complete response; PPV = positive predictive value; R = radiologist; RCT = radiochemotherapy; Sens = sensitivity; Spec = specificity; T = Tesla; V = volume; VRS = visual response score.

* Cutoff values of ADC are in mm$^2$/s, cutoff values of volumes are in cm$^3$.

‡ In one patient, ADC measurements were not obtained because the tumor had an entirely mucinous aspect.

**Table 3**
Early pCR prediction with $^{18}$F-FDG-PET/CT.

| Study | N | pCR (%) | PET parameter | Correlation PET and pCR | *p*-Value | Cutoff | Sens (%) | Spec (%) | PPV (%) | NPV (%) | Acc (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Perez [39] | 99 | 7 | $SUVmax_{pre}$ | Negative | 0.043 | | | | | | |
| Konski [40] | 53 | 30 | $SUVmax_{pre}$ | Positive | 0.71 | | | | | | |
| Capirci [41] | 81 | 27 | $SUVmax_{pre}$ | Positive | 0.097 | 13.9 | | | | | |
| Palma [42] | 50 | 22 | $SUVmax_{pre}$ | Negative | 0.149 | 10.14 | 46 | 74 | 33 | 83 | 68 |
| Martoni [43] | 80 | 20 | $SUVmax_{pre}$ | Negative | NA | 27 | 100 | 11 | 20 | 100 | 29 |
| Hur [44] | 37 | 35 | $SUVmax_{pre}$ | Negative | 0.838 | | | | | | |
| Shanmugan [45] | 70 | 26 | $SUVmax_{pre}$ | Positive | 0.6 | | | | | | |
| Goldberg [46] | 19 | 21 | $SUVmax_{pre}$ | Positive | 0.617 | | | | | | |
| Guillem [47] | 121 | 21 | $SUVmax_{pre}$ | NA | n.s. | | | | | | |
| | | | $SUVmean_{pre}$ | NA | n.s. | | | | | | |
| Kim [48] | 151 | 13 | $SUVmax_{pre}$ | Negative | 0.064 | | | | | | |
| Lee [49] | 81 | 6 | $SUVmax_{pre}$ | Negative | 0.675 | | | | | | |
| | | | $SUVmean_{pre}$ | Negative | 0.675 | | | | | | |
| Bampo [50] | 30 | 30 | $SUVmax_{pre}$ | Negative | 0.08 | | | | | | |
| Van Stiphout [51] | 114 | 21 | $SUVmax_{pre}$ | Negative | 0.29 | | | | | | |
| **Pooled data** | **130** | **21** | **$SUVmax_{pre}$** | | | | **78** | **35** | **24** | **86** | **44** |

Acc = accuracy; NPV = negative predictive value; N = number of patients; NA = not available; n.s. = not significant; pCR = pathologic complete response; PET = positron emission tomography; PPV = positive predictive value; Sens = sensitivity; Spec = specificity; SUV = standardized uptake value.

**Table 4**
pCR prediction during RCT with $^{18}$F-FDG-PET/CT.

| Study | N | pCR (%) | PET parameter | Correlation PET and pCR | Timing PET | *p*-Value | Cutoff | Sens (%) | Spec (%) | PPV (%) | NPV (%) | Acc (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lambrecht [26] | 22 | 27 | RI $SUVmax_{during}$ | Positive | After 10–12 fractions | 0.0036 | 40% | 100 | 75 | 60 | 100 | 82 |
| Goldberg [46] | 19 | 21 | $SUVmax_{during}$ | Positive | After 8 days | 0.841 | | | | | | |
| | | | RI $SUVmax_{during}$ | Positive | After 8 days | 0.046 | 32% | 75 | 100 | 100 | 94 | 95 |
| Bampo [50] | 30 | 30 | $SUVmax_{during}$ | Negative | After 2 weeks | 0.32 | | | | | | |
| | | | RI $SUVmax_{during}$ | Positive | | 0.23 | | | | | | |
| **Pooled data** | **41** | **24** | **RI $SUVmax_{during}$** | | | | | **90** | **87** | **69** | **96** | **88** |

Acc = accuracy; NPV = negative predictive value; N = number of patients; pCR = pathologic complete response; PET = positron emission tomography; PPV = positive predictive value; RCT = radiochemotherapy; RI = response index; Sens = sensitivity; Spec = specificity; SUV = standardized uptake value.

**Table 5**
Late pCR assessment with $^{18}$F-FDG-PET/CT.

| Study | N | pCR (%) | PET parameter | Correlation PET and pCR | Interval RCT-PET (weeks) | *p*-Value | Cutoff | Sens (%) | Spec (%) | PPV (%) | NPV (%) | Acc (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Quantitative analysis* | | | | | | | | | | | | |
| Lambrecht [26] | 22 | 27 | RI $SUVmax_{post}$ | Positive | 5 | 0.013 | 76% | 100 | 75 | 60 | 100 | 82 |
| Perez [39] | 99 | 7 | $SUVmax_{post}$ | Negative | 6 | 0.23 | | | | | | |
| | | | $SUVmax_{post}$ | Negative | 12 | 0.15 | | | | | | |
| | | | RI $SUVmax_{post}$ | Negative | 6 | 0.87 | | | | | | |
| | | | RI $SUVmax_{post}$ | Negative | 12 | 0.96 | | | | | | |
| Konski [40] | 53 | 30 | $SUVmax_{post}$ | Positive | 3–4 | 0.18 | | | | | | |
| | | | RI $SUVmax_{post}$ | Positive | 5–6 | 0.08 | | | | | | |
| Capirci [41] | 81 | 27 | $SUVmax_{post}$ | Negative | | <0.0001 | 5.2 | | | | | |
| | | | RI $SUVmax_{post}$ | Positive | | <0.0001 | 45.90% | | | | | |
| | | | ΔSUVmax | Positive | | 0.296 | 6.4 | | | | | |
| Palma [42] | 50 | 22 | $SUVmax_{post}$ | Negative | 5–7 | 0.013 | 4.07 | 64 | 74 | 41 | 88 | 72 |
| | | | RI $SUVmax_{post}$ | Positive | | 0.354 | 69.67% | 46 | 74 | 33 | 83 | 68 |
| | | | ΔSUVmax | Negative | | 0.594 | | | | | | |
| Martoni [43] | 80 | 20 | $SUVmax_{post}$ | Negative | 6–7 | NA | 5 | 88 | 34 | 25 | 90 | 45 |
| | | | RI $SUVmax_{post}$ | Positive | | NA | 66.10% | 94 | 31 | 25 | 95 | 44 |
| Hur [44] | 37 | 35 | $SUVmax_{post}$ | Negative | 4 | <0.001 | 3.35 | 85 | 79 | 69 | 91 | 81 |
| | | | RI $SUVmax_{post}$ | Positive | | 0.009 | 75.00% | 69 | 83 | 69 | 83 | 78 |
| | | | ΔSUVmax | Positive | | 0.404 | | | | | | |
| Shanmugan [45] | 70 | 26 | $SUVmax_{post}$ | Negative | 4 | 0.01 | 4 | 78 | 58 | 39 | 88 | 63 |
| | | | RI $SUVmax_{post}$ | Positive | | 0.002 | 63.00% | 83 | 60 | 42 | 91 | 66 |
| Guillem [47] | 121 | 21 | RI $SUVmax_{post}$ | NA | 4–6 | n.s. | | | | | | |
| | | | RI $SUVmean_{post}$ | NA | | n.s. | | | | | | |
| Kim [48] | 151 | 13 | $SUVmax_{post}$ | Negative | 5–7 | <0.001 | 3.55 | 74 | 64 | 23 | 94 | 65 |
| | | | RI $SUVmax_{post}$ | Positive | | 0.19 | | | | | | |
| | | | ΔSUVmax | Negative | | 0.312 | | | | | | |
| Bampo [50] | 30 | 30 | $SUVmax_{post}$ | Negative | 6 | 0.01 | 5.4 | 100 | 81 | 69 | 100 | 87 |
| | | | RI $SUVmax_{post}$ | Positive | | 0.035 | | | | | | |
| Van Stiphout [51] | 114 | 21 | $SUVmax_{post}$ | Negative | | <0.001 | | | | | | |
| | | | RI $SUVmax_{post}$ | Positive | | <0.001 | | | | | | |
| Sun [52] | 35 | 31 | RI $SUVmax_{post}$ | Positive | 1 | 0.932 | | | | | | |
| | | | RI $SUVmax_{post}$ | Positive | 5–7 | 0.045 | | | | | | |
| | | | RI $SUVmean_{post}$ | Positive | 1 | 0.444 | | | | | | |
| | | | RI $SUVmean_{post}$ | Positive | 5–7 | 0.019 | | | | | | |
| Huh [53] | 181 | 14 | RI $SUVmax_{post}$ | Positive | 5 | NA | 63.60% | 73 | 65 | 26 | 94 | 66 |
| **Pooled data** | **418** | **21** | **$SUVmax_{post}$** | | | | | **80** | **61** | **35** | **92** | **65** |
| | **440** | **20** | **RI $SUVmax_{post}$** | | | | | **77** | **60** | **42** | **91** | **64** |
| *Qualitative analysis* | | | | | | | | | | | | |
| Lambrecht [26] | 22 | 27 | VRS | | 5 | | | 50 | 88 | 60 | 82 | 77 |
| Song [36] | 50 | 12 | VRS | | 6 | | | 83 | 43 | 17 | 95 | 48 |
| Guillem [47] | 121 | 21 | VRS | | 4–6 | | | 54 | 66 | 30 | 84 | 64 |
| Capirci [54] | 81 | 35 | VRS | | 4 | | | 79 | 45 | 43 | 80 | 57 |
| Kalff [55] | 30 | 20 | VRS | | 3–4 | | | 83 | 50 | 29 | 92 | 57 |
| Vliegen [56] | 20 | 10 | VRS | | 6.3 | | | 50 | 94 | 50 | 94 | 90 |
| Kristiansen [57] | 30 | 27 | VRS | | 7 | | | 75 | 46 | 33 | 83 | 53 |
| Kalff [58] | 63 | 16 | VRS | | 4–5 | | | 80 | 62 | 29 | 94 | 65 |
| Cho [59] | 30 | 13 | VRS | | 6 | | | 75 | 85 | 43 | 96 | 83 |
| Mak [60] | 20 | 35 | VRS | | 3–6 | | | 71 | 85 | 71 | 85 | 80 |
| Murcia Duréndez [61] | 41 | 20 | VRS | | 7 | | | 100 | 76 | 50 | 100 | 81 |
| **Pooled data** | **508** | **22** | **VRS** | | | | | **72** | **63** | **35** | **89** | **65** |

Acc = accuracy; NPV = negative predictive value; N = number of patients; NA = not available; n.s. = not significant; pCR = pathologic complete response; PET = positron emission tomography; PPV = positive predictive value; RCT = radiochemotherapy; RI = response index; Sens = sensitivity; Spec = specificity; SUV = standardized uptake value; VRS = visual response score.

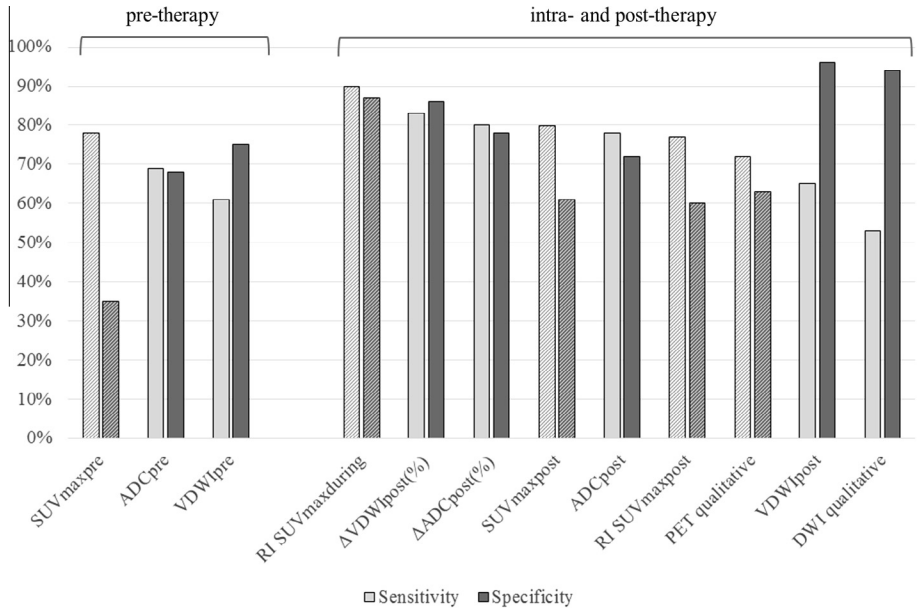


**Fig. 2.** Overview of the sensitivity and specificity of DWI and $^{18}$F-FDG PET/CT in the prediction of pathological complete response. Solid bars represent DWI-based parameters, while $^{18}$F-FDG PET/CT parameters are depicted by hatched bars. Parameters based on pre-RCT imaging and those based on imaging during or after RCT are depicted on the left and the right side respectively. Parameters are represented in the order of decreasing sensitivity in the prediction of pathological complete response.

Response assessment during RCT could possibly re-orientate non-responding patients to a different treatment modality (e.g. surgery) or to treatment intensification (e.g. dose escalation or addition of targeted agents) [62]. Some authors found that a low pretreatment ADC was correlated with a good response to treatment. Similar findings have been reported in brain tumors [63] and in hepatic metastases of colorectal cancer [64]. The association between the pretreatment ADC and tumor response is hypothesized to be correlated to the presence of necrotic areas (characterized by a high ADC), in which tumor cells are exposed to a more acidic and hypoxic environment, diminishing the effectiveness of radiation therapy and chemotherapeutic agents [64,65]. However, coagulative necrosis without cell liquefaction may not increase ADC and this might be the reason why tumors do not respond well to neoadjuvant RCT, although they have a low pretreatment ADC. It should be stressed however that this hypothesis has not yet been confirmed by radiological-pathological correlative studies. While baseline $^{18}$F-FDG PET/CT itself has limited value in response prediction, the relative change in SUVmax during RCT seems more promising. A higher decrease in FDG-uptake represents a smaller amount of metabolically active tumor cells, indicating response to treatment.

Response assessment before surgery enables physicians to offer patients who achieve a clinical complete response less extensive surgery or even a 'wait-and-see' policy. Pooled analysis showed that qualitative DWI assessment had a higher accuracy in pCR prediction than quantitative analysis (87% vs. 74–78%). However, with respect to sensitivity, ADC measurements outperformed subjective visual assessment (78–80% vs. 53%), indicating that quantitative analysis is more accurate in detecting patients with pCR. Quantitative and qualitative $^{18}$F-FDG PET/CT evaluations are equally performant in the preoperative assessment of complete response.

Most studies suffer from a retrospective design and a low number of patients. In an attempt to assess the performance of the different imaging parameters, we pooled the available individual patient data. Most authors provide cutoff values based on ROC analysis, which aims at the maximal accuracy of response prediction. However, this maximal accuracy may not necessarily represent the most desirable clinical parameter. For instance, we believe a high PPV and specificity are mandatory if alteration of the surgical strategy is considered. A low specificity and PPV may correlate with many false positives, corresponding to residual tumor on pathology whereas the DWI or $^{18}$F-FDG PET/CT images show no evidence of disease. In general, DWI and $^{18}$F-FDG PET/CT had a high NPV in the prediction of pCR, making these functional imaging techniques potential valuable tools to deselect patients for a conservative treatment approach. Unfortunately, both imaging modalities lack the specificity and PPV needed to safely select patients for a 'wait-and-see' policy.

The combination of different functional imaging techniques at different time points may increase the specificity for pCR prediction. Our group previously showed that the combination of early and late RI SUVmax$_{post}$ thresholds increased the specificity in the prediction of pCR (75% for the individual threshold values vs. 94% when combined) [26]. We also demonstrated that the combination of $^{18}$F-FDG PET/CT with pretreatment DWI may further increase the specificity of response assessment. Although this study only included 22 patients, the combination of different imaging modalities at different time intervals is at least hypothesis-generating and deserves further investigation. Combined PET/MRI cameras might make these evaluations logistically less cumbersome. Van Stiphout et al. demonstrated that the integration of functional imaging and clinical data might also contribute to the accuracy of pCR assessment [51]. This group developed and validated a nomogram for pCR prediction by collecting population-based databases of 953 patients from 4 different institutes. These databases were divided into three groups: clinical factors (762 patients), pre-RCT $^{18}$F-FDG PET-CT (151 patients) and post-RCT $^{18}$F-FDG PET-CT (162 patients). The model's performance was evaluated by ROC analysis. The AUC increased from 0.68 to 0.86 when post-RCT PET data were added to the clinical and pre-RCT PET variable set. The integration of blood and tissue biomarkers appears also useful in pCR prediction after RCT for rectal cancer [66–68].

The ability of functional imaging to predict pCR is affected by the interval between the end of RCT, the post-treatment scan and surgery. In most studies, post-treatment $^{18}$F-FDG PET/CT and DWI scans were performed 4–8 weeks after the end of RCT. A longer time interval between the end of RCT and surgery has shown to increase pCR rates [69,70]. However, Perez et al. reported that not all patients benefit from this prolonged interval [65].

These authors showed that the increase between early (1 h) and late (3 h) SUVmax at 6-weeks $^{18}$F-FDG PET/CT scans was a significant predictor of poor response. Patients who have such an increase in SUVmax do not benefit from a longer time interval between RCT and surgery. It is known that the interpretation of functional imaging scans during and early after the end of RCT can be confounded by treatment-induced tissue alterations. This is especially the case for $^{18}$F-FDG PET/CT in which RCT-induced inflammation can cause FDG-uptake.

A number of limitations of this analysis must be recognized. Most papers report on a limited number of patients, yielding large 95% confidence intervals around the diagnostic accuracy parameters, thereby providing cutoff thresholds that are not sufficiently robust for clinical use. Few papers provided enough data to construct individual $2 \times 2$ contingency tables. However, by pooling individual patient data, we were able to evaluate the performance of DWI and $^{18}$F-FDG PET/CT in a larger patient group. Because of the heterogeneity within the included studies with respect to patient selection, neoadjuvant treatment and imaging protocols and analyses, this pooled analysis should be regarded as an indicator of the general performance of DWI and $^{18}$F-FDG PET/CT in the prediction of pCR. Furthermore, the results on functional imaging prediction are restricted to monocentric studies conducted in ultra-specialized centers. Validation and implementation in a multicenter setting are still awaited. Standardization through protocols for both image acquisition and data analysis is necessary to ensure reproducibility of the results and enable widespread implementation.

In conclusion, data on the role of $^{18}$F-FDG PET/CT and DWI in response prediction before, during and after RCT for locally advanced rectal cancer are emerging. In general, a low pretreatment ADC, an increase in ADC and decrease in SUV are associated with better response to RCT. Pooled analysis shows qualitative DWI assessment 5–10 weeks after the end of RCT outperforms ADC-based DWI-parameters. Although little data are available, early changes in FDG-uptake seem promising and the role of $^{18}$F-FDG PET/CT during RCT should be further investigated. Multicenter studies using large patient populations are needed to validate the role of functional imaging in order to identify those patients who may benefit from a less aggressive therapeutic approach after RCT. Up to now, DWI and $^{18}$F-FDG PET/CT are not accurate enough to safely select patients for organ preservation. Future research must focus on the integration of functional imaging with clinical data and molecular biomarkers.

## Conflict of interest

None declared.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.11.026.

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