Diffusion-weighted imaging for rectal cancer response monitoring after neo-adjuvant radiochemotherapy: a good correlation with pathological response.

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Introduction
Radiochemotherapy (RCT) is the standard of care pre-operative treatment in primary irresectable rectal cancer. After neo-adjuvant RCT, a pathological complete response rate of 10-30% is found. This questions the use of surgery in complete responders because surgery is associated with substantial morbidity and even mortality (1). Retrospective studies by the group of Habr-Gama showed that omission of surgery is safe in patients with complete clinical response after neo-adjuvant RCT (2,3). However, to enable safe omission of surgery reliable pathological response prediction is needed. Diffusion-weighted MR imaging (DWI) reflects the microanatomy in tissues and is frequently used in oncology for tissue characterisation and response assessment. In this study, we analysed rectal cancer response after neo-adjuvant RCT with DWI.

Patients and Methods
Fourteen patients (4 women, 10 men) with histologically proven adenocarcinoma of the rectum received neo-adjuvant RCT followed by surgical rectum resection irrespective of the response. Pre-operative therapy consisted of radiotherapy with a delivered irradiation dose of 50 Gy in 2 Gy fractions over 5 weeks combined with oral 5-fluorouracil 2 dd 825 mg/m2 (capecitabine®) daily.
MRI images were acquired before RCT and 6-8 weeks after RCT just before the surgical procedure on a 3 Tesla MRI scanner (Achieva, Philips Medical Systems, Best, The Netherlands). DWI was performed in axial plane using single shot spin echo -echo planar imaging (ssSE-EPI) sequence with b values of 0, 200 and 800 s/mm^2 (TR: 7.6 s, TE : 63 ms, slice thickness: 4 mm, slice gap: 0 mm, no slices: 45, EPI factor: 63, matrix size: 132 x 120, resolution: 2.5 x 2.5 mm^2, fat suppression: SPAIR). Apparent diffusion coefficient (ADC) maps were generated from the DWI with b-values of 200 and 800 s/mm^2 by a linear regression after a logarithmic transformation of the signal intensity (lnS), $lnS = lnA - b\ ADC$, where A is the relative amplitude. Additionally, two anatomical scans were included: a multislice transverse and sagittal T2-weighted (T2w) turbo spin echo sequence (TR: 3.8s, TE: 80 ms, matrix size: 800 x 736, resolution: 0.45 x 0.45 mm^2, slice thickness: 4 mm, no slices: 30, turbo factor: 20). Further, the difference in ADC before and after RCT was calculated and referred to as ΔADC.
For data analysis, the circumference of the rectum was delineated in suspected areas on the pre-therapy T2w MRI scan. The rectal circumference from T2w imaging was copied to the ADC map and adjusted to correct for motion and geometrical distortions. The delineation on the pre-RCT scan was manually registered to the post-RCT scan and here the same length of rectum was delineated. Thus, the selected regions of interest (ROI) consisted of both rectal tumour and normal rectal wall tissue with exclusion of intrarectal air. Patients were classified according their pathological response that was defined as the Rectal Cancer Regression Grade (RCRG) method proposed by Wheeler *et al*. RCRG 1 indicates good responsiveness, that is the tumour is either sterilized or only microscopic foci of adenocarcinoma remain. RCRG 2 or moderate response reflects marked fibrosis with macroscopic tumour still present and RCRG 3 indicates poor response with little or no fibrosis in the presence of abundant macroscopic tumour (4,5).
Statistical analysis was performed using GraphPad Prism (Graphpad Prism 4.00. 2003: Graphpad Software Inc). ADC and ΔADC values between RCRG groups were compared using a Mann-Whitney test and pre-RCT and post-RCT ADC values in both groups were compared using a paired student-*t* test

Results
Six patients (43%) were classified as RCRG 1. The other patients were all classified as RCRG 2 because of a remaining tumour focus and abundant marks of the pre-operative therapy at pathology.
Similar ADC values before RCT were found, 1.10*10^{-3} mm^2/s and 1.06*10^{-3} mm^2/s for the RCRG 1 group and RCRG 2 group respectively (p = 0.606). After RCT, a significant difference (p = 0.008) was found in ADC values of 1.23*10^{-3} mm^2/s for the RCRG 1 group and 1.36*10^{-3} mm^2/s for the RCRG 2 group respectively. No difference was found between pre-RCT and post-RCT ADC values in the RCRG 1 group (p = 0.189) in contrast to the difference between pre-RCT and post-RCT ADC values in the RCRG 2 group (p<0.001).
A significant difference (p = 0.003) in ΔADC between pre-RCT and post-RCT values were found respectively 0.093*10^{-3} mm^2/s for the RCRG 1 group and 0.306*10^{-3} mm^2/s for the RCRG 2 group (figure 1). The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was 0.9583 (95% confidence interval 0.8583 to 1.058) (figure 2).

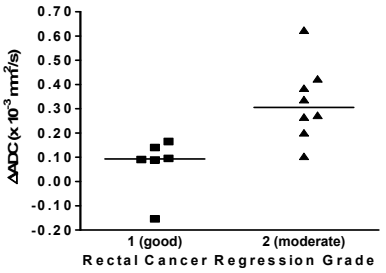

Figure 1: ΔADC for the rectal cancer regression grade 1 and 2 group. The horizontal line represents the median value. (p= 0.003)

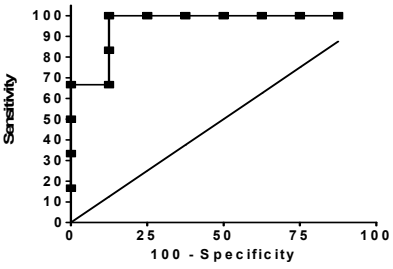

Figure 2: Receiver operating characteristic (ROC) for ΔADC. Area under the curve 0.9583 (95% confidence interval 0.8583 to 1.058)

Discussion
In this study, we analysed rectal cancer response after neo-adjuvant RCT with DWI. Unexpectedly, we found that low post-RCT ADC values and low ΔADC values were correlated with good pathological response when compared with a moderate response. ROC curve showed a good correlation between ΔADC values and pathological response.
Kremser *et al* found in a similar study no difference of mean pre-RCT ADC values between pathological response groups (6). Recently, Kim *et al* reported that high post-RCT ADC values were correlated with good pathological response, whereas in our study high post-RCT ADC values were correlated with moderate pathological response (7).
The interpretation of the low ΔADC found in the ROI in the good responders compared to the moderate responders is hypothetical. We propose that the low ΔADC in good responders might be attributed to the replacement of the tumour by fibrosis 6-8 weeks after treatment. In moderate responders, there might be vascular oedema in the remaining tumour tissue causing higher post-RCT ADC values and higher ΔADC.
A limitation to our study was the use of pathological reports from different pathologists with different protocols. To overcome inaccurate pathological complete responses, we used the pathological staging system of Wheeler *et al.* To prevent misinterpretation of the post-RCT DWI, an ROI including both rectal tumour and surrounding rectal wall tissue was delineated instead of tumour tissue alone. For the ROC curve no cut-off value, sensitivity or specificity was calculated due to limited number of patients.

Conclusions
Unexpectedly, low post-RCT ADC values and low ΔADC correlated with a good pathological response after neo-adjuvant radiochemotherapy. Future studies are needed with standardized pathology to confirm our results for larger groups of patients and determine the predictive value of DWI.

References
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