Diffusion-weighted magnetic resonance imaging for the prediction of response to neoadjuvant chemoradiotherapy in esophageal cancer.

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Target audience Radiologists, radiation oncologists, medical physicists, medical oncologists, and oncologic surgeons interested in the fields of MRI and/or esophageal cancer.

Purpose Neoadjuvant chemoradiotherapy (nCRT) can induce significant tumor downstaging before surgery, even resulting in a pathologic complete response (pathCR) in approximately 30% of patients.[1] It is speculated that surgery might be safely omitted in this selected group of patients with a complete response.[2-4] On the other hand, patients with a poor pathologic response to nCRT may benefit less from nCRT but are exposed to its toxicity. The aim of this study was to explore the value of diffusion-weighted magnetic resonance imaging (DW-MRI) for the prediction of response to nCRT in patients with esophageal cancer.

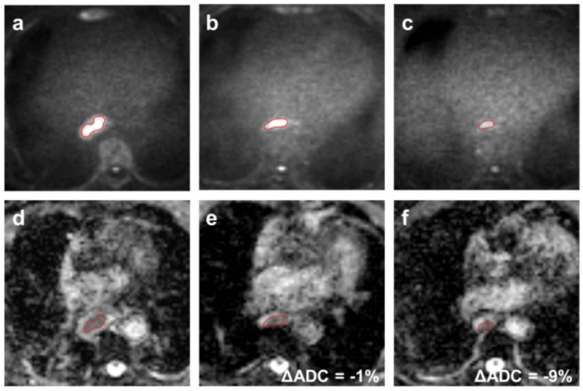

Figure 1 Patient with an adenocarcinoma of the distal esophagus with a poor histopathologic response to treatment (TRG 4) (*red contours*). High b-value (b=800 s/mm^2) DW images (a,b,c), and corresponding ADC maps (d,e,f) before nCRT (a,d), during nCRT (b,e), and after nCRT (c,f).

Methods This prospective study was approved by our institutional review board and patients provided written informed consent. Patients presented at our center from May 2013 until May 2014 with newly diagnosed esophageal cancer that were planned to receive nCRT followed by surgery were included. Patients underwent MRI scanning with T2-weighted and DW-MRI sequences within two weeks before nCRT (MRI_{pre}), after 8-13 radiotherapy fractions (MRI_{during}), and three to nine weeks after completion of nCRT, prior to surgery (MRI_{post}). The MRI examinations were performed on one 1.5T scanner equipped with a 16-element phased-array receive coil for thoracic imaging (Achieva; Philips Medical Systems, Best, The Netherlands). Transverse DW-MR images were acquired using three different diffusion-sensitizing gradients (b = 0, 200 and 800 s/mm^2). The primary tumor was manually delineated on the high b-value DW-MR images before, during, and after nCRT (*Figure 1*). From the drawn volumes of interest (VOIs), the median ADC per VOI was extracted. The predictive potential of initial tumor ADC, and change in ADC (ΔADC) during and after treatment for pathologic complete response (pathCR) and good response (GR) was assessed. Good response was defined as pathCR (tumor regression grade [TRG] 1) or near-pathCR (TRG 2).[5]

Results A pathCR after nCRT was found in 4 of 20 patients (20%), and 8 patients (40%) showed a good response to nCRT. The ΔADC_{during} was significantly higher in pathCR patients compared to patients without pathCR (34.6%±10.7% [mean±SD] vs. 14.0%±13.1%, p=0.016), as well as in good responders compared to poor responders (30.5%±8.3% vs. 9.5%±12.5%, p=0.002) (*Figure 2*). Initial tumor ADC and ΔADC_{post} were not significantly related to pathologic response (*Table 1*). ROC analysis for ΔADC_{during} resulted in an area under the curve (AUC) of 0.90 for discriminating pathCR from no pathCR. An optimal cut-off value of 28.9% yielded a sensitivity of 100%, specificity of 75%, accuracy of 95%, PPV of 94%, and NPV of 100% for predicting residual cancer. For discriminating good from poor responders, ΔADC_{during} showed an AUC of 0.92 with an optimal cutoff value of 20.7% resulting in a sensitivity of 82%, specificity of 100%, accuracy of 89%, PPV of 100%, and NPV of 80%.

Table 1 Association between ADC measurements and histopathologic tumor regression. Values are means ± SD.

MRI measurement	PathCR (n=4)	No pathCR (n=16)	*p* value	GR (n=8)	No GR (n=12)	*p* value
Initial ADC (*10^{-3} mm^2/s)	1.71 ± 0.32	1.84 ± 0.24	0.299	1.75 ± 0.29	1.86 ± 0.24	0.316
ΔADC_{during} (%)	34.6 ± 10.7	14.0 ± 13.1	**0.016***	30.5 ± 8.3	9.5 ± 12.5	**0.002***
ΔADC_{post} (%)	38.9 ± 45.7	18.9 ± 34.6	0.258	36.3 ± 34.3	12.3 ± 37.3	0.178

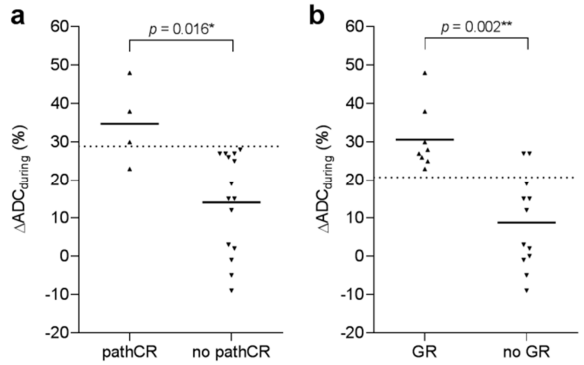

Figure 2 Scatter plots demonstrating the percentage of change in tumor ADC during nCRT (ΔADC_{during}) in pathologic complete responders (*pathCR*) versus pathologic non-complete responders (*no pathCR*) (a), and in good responders (*GR*) versus poor responders (*no GR*) (b).

Discussion The high sensitivity and NPV of ΔADC_{during} for predicting residual cancer are particularly promising when considering a patient-tailored wait-and-see approach with omission of surgery in the future. The high specificity and PPV of ΔADC_{during} for predicting poor response are particularly promising for future considerations regarding modification or discontinuation of nCRT early during treatment.

Conclusion The treatment-induced change in ADC as determined on DW-MRI during the first 2-3 weeks of nCRT for esophageal cancer allows for accurate early prediction of histopathologic response.

References 1. van Hagen P, et al. N Engl J Med 2012;366(22):2074-84. 2. Oppedijk V, et al. J Clin Oncol 2014;32(5):385-91. 3. Berger AC, et al. J Clin Oncol 2005;23(19):4330-7. 4. Stahl M, et al. J Clin Oncol 2005;23(10):2310-7. 5. Mandard AM, et al. Cancer 1994;73(11):2680-6.