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MRI in esophageal cancer

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

Peter S.N. van Rossum [a,b], Astrid L.H.M.W. van Lier [a], Marco van Vulpen [a], Onne Reerink [a], Jan J.W. Lagendijk [a], Steven H. Lin [c], Richard van Hillegersberg [b], Jelle P. Ruurda [b], Gert J. Meijer [a,*,1], Irene M. Lips [a,1]

[a] Department of Radiotherapy; [b] Department of Surgery, University Medical Center Utrecht, The Netherlands; and [c] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, United States

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ABSTRACT

Purpose: To explore the value of diffusion-weighted magnetic resonance imaging (DW-MRI) for the prediction of pathologic response to neoadjuvant chemoradiotherapy (nCRT) in esophageal cancer.

Material and methods: In 20 patients receiving nCRT for esophageal cancer DW-MRI scanning was performed before nCRT, after 8–13 fractions, and before surgery. The median tumor apparent diffusion coefficient (ADC) was determined at these three time points. The predictive potential of initial tumor ADC, and change in ADC (ΔADC) during and after treatment for pathologic complete response (pathCR) and good response were assessed. Good response was defined as pathCR or near-pathCR (tumor regression grade [TRG] 1 or 2).

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 vs. non-pathCR patients (34.6% ± 10.7% [mean ± SD] vs. 14.0% ± 13.1%, $p = 0.016$), as well as in good vs. poor responders (30.5% ± 8.3% vs. 9.5% ± 12.5%, $p = 0.002$). The ΔADC_{during} was predictive of residual cancer at a threshold of 29% (sensitivity of 100%, specificity of 75%, PPV of 94%, and NPV of 100%), and for poor pathologic response at a threshold of 21% (sensitivity of 82%, specificity of 100%, PPV of 100%, and NPV of 80%).

Conclusions: In this exploratory study, the treatment-induced change in ADC during the first 2–3 weeks of nCRT for esophageal cancer seemed highly predictive of histopathologic response. Larger series are warranted to verify these results.

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The addition of neoadjuvant chemoradiotherapy (nCRT) to surgery for the treatment of resectable esophageal cancer has improved locoregional control and overall survival rates [1,2]. Neoadjuvant chemoradiotherapy can induce significant tumor downstaging before surgery, even resulting in a pathologic complete response (pathCR) in approximately 30% of patients [2]. This complete disappearance of viable tumor cells is associated with a favorable long-term prognosis and it is speculated that surgery might be safely omitted in this selected group of patients with a complete response [3–7]. In rectal cancer studies, authors have reported encouraging results with regard to feasibility and outcome of such a wait-and-see policy that includes omission of surgery and close clinical follow-up [8,9]. On the other hand, patients with a poor pathologic response to nCRT may benefit less from nCRT but are exposed to its toxicity. Accurate identification of poor responders before or early during treatment could potentially allow for early modification or discontinuation of nCRT. However, in order to safely and effectively guide patient-tailored strategies in the management of esophageal cancer, a reliable tool that accurately assesses response to treatment is warranted first.

All studied modalities – including endoscopy with or without biopsy, endoscopic ultrasonography (EUS), computed tomography (CT), and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) – yield unsatisfactory results in the assessment of response to nCRT so far [10–13]. Therefore, guiding neoadjuvant

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* Corresponding author at: Department of Radiotherapy, Q00.3.11, University Medical Center Utrecht, PO Box 85500, 3508GA Utrecht, The Netherlands.
E-mail addresses: P.S.N.vanRossum-2@umcutrecht.nl (P.S.N. van Rossum), G.J.Meijer@umcutrecht.nl (G.J. Meijer).

[1] Both authors contributed equally to this manuscript.

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treatment decisions based on treatment response monitoring remains unjustified in current practice. The inability of size-related (dimensional) criteria to detect small tumor masses or underlying submucosal extent of residual tumor, and the difficulty of differentiating residual tumor mass from inflammation and fibrosis result in a low negative predictive value (NPV) [13]. Metabolic and functional imaging modalities allow for biological and microstructural characterization of tumors and may visualize treatment-induced changes before volumetric changes become apparent [14,15]. Two meta-analyses on the value of FDG-PET(/CT) for response evaluation suggested that the decrease in mean or maximum metabolic activity within the first two weeks of nCRT is the best available predictor of pathCR so far, although still insufficient, with pooled sensitivities and specificities of 67–70% (95% confidence intervals ranging from 62% to 76%) [10,11].

Diffusion-weighted MRI (DW-MRI) is a functional imaging modality that allows for tissue characterization by deriving image contrast from variations in the free diffusion (i.e. random mobility or Brownian motion) of water molecules between tissues which is a marker for microstructural density [16]. The apparent diffusion coefficient (ADC) can be calculated to quantify these differences in diffusion or microstructural density in a certain volume of interest [14]. The ADC is inversely correlated with tissue cellularity and as chemoradiotherapy can result in the loss of cell membrane integrity, tumor response can be detected as an increase in tumor ADC [17]. The predictive value of ADC in the assessment of response to (chemo)radiotherapy has previously been described in several malignancies including brain, head-and-neck, breast, prostate, and rectal cancer with promising results [15,18–23].

The primary aim of this study was to explore the value of diffusion-weighted magnetic resonance imaging (DW-MRI) for the prediction and assessment of pathologic response to neoadjuvant chemoradiotherapy (nCRT) in patients with esophageal cancer. In order to elaborate on our understanding of the biological meaning of the ADC value in esophageal tumors a secondary aim was to study the relation between pre-treatment DW-MRI measurements and histopathologic tumor characteristics.

Materials and methods

Study population

This prospective study was approved by our institutional review board and all patients provided written informed consent. Patients presented at our tertiary referral center from May 2013 to May 2014 with newly diagnosed biopsy-proven esophageal cancer that were planned to receive nCRT followed by surgery were eligible for inclusion. In the Netherlands, neoadjuvant chemoradiotherapy is currently considered the standard of treatment with curative intent, rather than neoadjuvant chemotherapy, for both adenocarcinomas and squamous cell carcinomas [2]. Patients with contraindications for MRI were excluded. Besides endoscopy with biopsy, the diagnostic work-up consisted of EUS, ultrasonography of the neck, and either standalone diagnostic CT or integrated FDG-PET/CT scan for clinical staging.

Treatment protocol

The neoadjuvant treatment regimen consisted of weekly intravenous administration of carboplatin (area under the curve of 2 mg/mL per minute) and paclitaxel (50 mg/m^2 body-surface area) for 5 weeks with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy) [2]. Here, the gross tumor volume (GTV) was defined by the primary tumor and any suspicious regional lymph nodes determined using all available information (physical examination, endoscopy, EUS, CT-thorax/abdomen, and FDG-PET if available). The clinical target volume (CTV) was created by expanding the GTV with a proximal and distal margin of 3 cm – in case of tumor extension into the stomach a distal margin of 2 cm was chosen – and a radial margin of 5 mm adjusted for anatomical structures. The planning target volume (PTV) consisted of the CTV plus a margin of 1 cm in all directions. All patients were treated with an IMRT technique obeying the following constraints for the heart and lung tissue: $V_{heart}40\ Gy \leqslant 30\%$ and $V_{lung}20\ Gy \leqslant 35\%$. Five to ten weeks after completion of nCRT (median: 8.6 weeks) all patients underwent transhiatal or transthoracic esophagectomy with en-bloc two-field lymphadenectomy and gastric conduit reconstruction with cervical anastomosis.

Image acquisition

Patients underwent MRI scanning with anatomical T2-weighted and functional DW-MRI sequences within two weeks (median: 4 days) before nCRT (MRI_{pre}), after 8–13 radiotherapy fractions at 10–15 days after initiation of treatment (median: 8 fractions or 10 days after initiation of treatment) (MRI_{during}), and three to nine weeks (median: 5.7 weeks) after completion of nCRT, prior to surgery (MRI_{post}). The timing of the scan in the second or third week after initiation of nCRT was based on FDG-PET studies in esophageal cancer demonstrating a potentially superior diagnostic accuracy at this time point as opposed to a pre- and post-treatment assessment only [11,24]. These studies proposed that the second or third week may be an optimal time point in which significant tumor regression can already be found in responders while the image interpretation may not yet be influenced by radiation esophagitis, which generally occurs after the first few weeks of treatment.

The MRI examinations were performed on one 1.5-T scanner equipped with a 16-element phased-array receive coil for thoracic imaging (Achieva; Philips Medical Systems, Best, The Netherlands). Patients were scanned in supine position. No anti-peristaltic agents were administered. Sagittal and transverse T2-weighted images were obtained with a navigator that monitors the position of the diaphragm using a fast 1D-MRI acquisition in order to trigger scanning exclusively during the expiration position of the diaphragm [25]. Transverse DW images were obtained under free breathing conditions. Diffusion-weighted images were acquired using three different diffusion-sensitizing gradients ($b = 0$, 200 and 800 s/mm^2). Detailed scan parameters are presented in Supplementary Table 1.

Image analysis

ADC calculation and measurements

Imaging analysis including primary tumor delineations and automatic calculation of tumor ADC values was performed using our image analysis software package Volumetool developed in-house [26]. The DW-MR images with b-values of 0, 200, and 800 s/mm^2 were used to generate ADC maps [16]. ADC values were calculated using a linear regression for the logarithmically transformed signal intensity (S_b) obtained with a certain diffusion-weighting b, according to the following equation: $ln(S_b) = ln(S_0) - b * \mathrm{ADC}$, where S_0 is the signal intensity without diffusion-weighting.

The whole primary tumor was manually delineated on the DW-MR images with a b-value of 800 s/mm^2 before, during, and after nCRT by one reader (P.S.N.v.R.). The reader was blinded to patient-related characteristics and clinical outcome in terms of histopathologic response. The scans performed at different time points were registered per patient using mutual information, allowing for direct comparison of the delineated volumes. In case no residual tumor was identified on the post-treatment images,