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Original article

Dynamic contrast-enhanced MRI for treatment response assessment in patients with oesophageal cancer receiving neoadjuvant chemoradiotherapy ☆

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ABSTRACT

Purpose: To explore and evaluate the potential value of dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) for the prediction of pathologic response to neoadjuvant chemoradiotherapy (nCRT) in oesophageal cancer.

Material and methods: Twenty-six patients underwent DCE-MRI before, during (week 2–3) and after nCRT, but before surgery (pre/per/post, respectively). Histopathologic tumour regression grade (TRG) was assessed after oesophagectomy. Tumour area-under-the-concentration time curve (AUC), time-to-peak (TTP) and slope were calculated. The ability of these DCE-parameters to distinguish good responders (GR, TRG 1–2) from poor responders (noGR, TRG $\geqslant$ 3), and pathologic complete responders (pCR) from no-pCR was assessed.

Results: Twelve patients (48%) showed GR of which 8 patients (32%) pCR. Analysis of AUC change throughout treatment, $AUC_{per\text{-}pre}$, was most predictive for GR, at a threshold of 22.7% resulting in a sensitivity of 92%, specificity of 77%, PPV of 79%, and a NPV of 91%. $AUC_{post\text{-}pre}$ was most predictive for pCR, at a threshold of −24.6% resulting in a sensitivity of 83%, specificity of 88%, PPV of 71%, and a NPV of 93%. TTP and slope were not associated with pathologic response.

Conclusions: This study demonstrates that changes in AUC throughout treatment are promising for prediction of histopathologic response to nCRT for oesophageal cancer.

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Worldwide, oesophageal cancer is the eighth most common cancer and the incidence rate is rapidly increasing [1]. Oesophageal cancer has a poor prognosis with 5-year overall survival rates ranging from 15% to 25% [2]. Oesophagectomy with en-bloc lymphadenectomy for patients with resectable non-metastatic disease results in 5-year survival rates of 34% to 36% [3,4]. Neoadjuvant chemoradiotherapy (nCRT) increases these rates by approximately 13% as was consistently shown in recent trials and a meta-analysis [3,5,6]. Therefore nCRT is currently considered as the standard treatment with curative intent for both adenocarcinomas (AC) and squamous cell carcinomas (SCC). However, not all patients benefit equally, as patient outcome depends heavily on the response to chemo(radio)therapy [5,7,8]. In 29% of the patients pathologic complete response (pCR) to nCRT is found, with increased 5-year overall survival rates up to 48–65% [3,7,9,10].

With accurate response prediction before surgery the treatment strategy could potentially be improved. Depending on patient outcome, adaptive approaches could be explored such as an organ-preserving wait-and-see approach, modification of nCRT or termination of neoadjuvant therapy to initiate surgery sooner [11].

Endoscopic biopsy and/or ultrasonography and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) have been extensively studied for neoadjuvant treatment response assessment in oesophageal cancer [12–16]. Unfortunately, these imaging modalities yield insufficient accuracies in the prediction of pathologic response [17,18]. Among the studied modalities ^{18}F-FDG-PET seems the best so far. Two meta-analyses on treatment response monitoring, found that scans from the first two weeks of

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nCRT were most predictive for pathologic response, showing similar or superior diagnostic accuracy as opposed to pre- and post-treatment scanning only [13,14,19]. Accordingly, investigators proposed that the second week might be optimal, because significant tumour regression can already be found in responders while the image interpretation may not yet be influenced by radiation esophagitis [14]. Overall pooled sensitivities and specificities were, however, still insufficient to justify changes in clinical decision-making with values ranging from 67% to 70% [13,14]. Also non-image based methods using molecular biomarkers and clinical parameters have shown potential for response prediction [20–22].

Recently, diffusion-weighted magnetic resonance imaging (DW-MRI) was described as a potential method for treatment response monitoring and prediction in oesophageal cancer [18,23]. It was reported that the change in apparent diffusion coefficient (ADC) measured prior and during nCRT is predictive for response. The reported sensitivity and specificity were higher than for the aforementioned methods, showing the potential of MRI-based techniques for early treatment response assessment and prediction.

Pilot studies on dynamic contrast-enhanced (DCE-)MRI demonstrated the feasibility for oesophageal cancer imaging [24,25]. However, the use of DCE-MRI to measure (early) response of oesophageal tumours to nCRT with histopathology as reference standard has not previously been described. Therefore, the purpose of this study was to investigate the potential of nonparametric analysis of DCE-MRI for the (early) prediction of pathologic response to nCRT in patients with oesophageal cancer. Since DCE-MRI visualizes different physiological properties (perfusion and vascular permeability in tumour microenvironment) compared to DW-MRI (diffusion in tissues), it could potentially provide complementary information beyond DW-MRI. In this exploratory study not only pre- and post-treatment measurements were obtained, but also approximately two weeks after initiation of treatment, enabling comparison of the predictive potential of perfusion parameters at three different time points.

Materials and methods

Study population

This prospective study was approved by the local medical ethics committee and written informed consent was obtained from all patients. Patients with contraindications for MRI with contrast agent were not eligible for inclusion. Six patients who participated in the study but did not receive all three MRI scans due to patient's wish of discontinuation ($n = 5$) or urgent non-elective surgery ($n = 1$), were excluded. In addition, one patient was excluded due to a technical failure during MR acquisition. Twenty-six consecutive patients with biopsy-proven oesophageal cancer who received nCRT followed by surgery, and completed all three MRI studies in our institutes (University Medical Center Utrecht [UMCU], $n = 19$; and the Netherlands Cancer Institute [NKI], $n = 7$) from August 2013 to January 2015, were included. One patient with severe pneumonia on the initial MRI, with an infiltrate adjacent to the tumour, was excluded for further analysis.

All patients received five weeks of neoadjuvant treatment, involving weekly intravenous administration of carboplatin (area under the curve of 2 mg/mL per minute) and paclitaxel (50 mg/m^2 body-surface area) with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy) [3]. Five to ten weeks after completion of nCRT all patients underwent oesophagectomy with en-bloc two-field lymphadenectomy and gastric conduit reconstruction with cervical anastomosis. After resection, pathologic assessment of the resection specimen included determination of the tumour regression grade (TRG) according to Mandard, using an identical protocol in both institutes [26].

MRI acquisition

MR images were acquired at the following three time points: prior to treatment (pre), after 8–13 fractions nCRT (per) and 3–9 weeks after completion of treatment, prior to surgery (post). All MR images were acquired with 1.5T systems Philips Achieva or Philips Ingenia (Best, the Netherlands), using the Torso coil (16 channel) or Anterior/Posterior (28 channel) receive coils, respectively. For anatomical verification, a T_2-weighted scan was performed with a multi-slice turbo spin echo sequence (TR/TE = 1983/100 ms, resolution = $0.67 \times 0.67 \times 4$ mm^3), using a navigator for respiratory triggering [18]. A DCE-MRI series of 62 images was acquired using a three-dimensional spoiled gradient echo sequence (TR/TE = 3.43/1.53 ms, flip angle = 20°, matrix size = $432 \times 432 \times 33$, reconstructed image voxel size = $1.18 \times 1.18 \times 3$ mm^3), with a 3-s interval. After the 10th image, the contrast agent (CA) gadobutrol (Gd-BT-DO3A, Gadovist; Schering AG, Berlin, Germany) was injected at a dose of 0.1 mmol/kg of body weight with an automatic syringe pump at a flow rate of 1 ml/s followed by saline injection. The scanned volume included the heart in order to prevent artefacts in the aorta due to pulsatile flow. In both institutes the same imaging protocol was used. However, at the NKI a different CA was used, Dotarem (Gadoteric acid, 0.5 mM; Guerbet, Paris, France), with a fixed dose of 7.5 mmol for each patient.

Prior to the dynamic series, five acquisitions for varying flip angles ($\alpha = 2°/6°/10°/12°/16°$) with identical scanning properties were acquired for determination of pre-contrast T_1 values. This flip angle series was chosen to be sensitive to a large range of tissue T_1 values. Additionally, DW-MRI scans were acquired with b-values of 0, 200 and 800 s/mm^2 (STIR fat suppression, resolution = $3.5 \times 3.5 \times 4$ mm^3) [18].

Image processing

Delineation of the primary tumour on the T_2-weighted scans was divided over two clinicians (P.S.N.v.R and I.M.L.). The delineation was adapted in the scans obtained during and after nCRT to account for tumour alterations. For definition of the craniocaudal tumour length the DW-MRI with $b = 800$ s/mm^2 was used. A radiation oncologist (O.R.), with over 10 years of experience, verified all delineations. To account for breathing motion within the DCE-MRI series, scans were rigidly registered to a scan after contrast-enhancement, which led to the best retrospective motion compensation [27] (Supplementary Fig. 1). Finally, the delineation was cropped with an isotropic margin of 2 mm to account for the conversion from T_2-weighted scan to the DCE-MRI, residual motion and partial volume effects.

Image analysis

In order to enable comparison of scans between different sessions in time, independent of MRI scaling settings, institute, MRI scanner or CA, the image intensity was converted to concentration. For this purpose, T_1 pre-contrast relaxation times were calculated with in-house developed software using multiple flip angle sequences. Relaxivity values of 4.7 and 3.6 L mmol^{-1} s^{-1} for Gadovist and Dotarem, respectively, were used [28].

A nonparametric approach was chosen for the analysis of DCE-MRI throughout time, as studies in different tumour sites indicate that this approach has an increased prognostic ability compared to parametric measures [29]. No analysis was performed per tumour subtype, as the subgroups of SCC and adenosquamous carcinoma

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