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Monitoring early changes in rectal tumor morphology and volume during 5 weeks of preoperative chemoradiotherapy – An evaluation with sequential MRIs

Doenja M.J. Lambregts [a,*], Ahmed Bani Yassien [b], Max J. Lahaye [a], Anja Betgen [b], Monique Maas [a], Geerard L. Beets [c,d], Uulke A. van der Heide [b], Baukelien van Triest [b], Regina G.H. Beets-Tan [a,d]

[a] Department of Radiology, Netherlands Cancer Institute; [b] Department of Radiation Oncology, Netherlands Cancer Institute; [c] Department of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands; [d] GROW School for Oncology and Developmental Biology – University of Maastricht, Maastricht, The Netherlands

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ABSTRACT

Purpose: To assess early changes in rectal tumor volume and morphology on sequential MRIs performed during 5 weeks of chemoradiotherapy.

Materials and methods: Thirteen patients underwent weekly T2W-MRI during 5 weeks of preoperative radiotherapy (total 50 Gy), starting after the first week of radiation. Two radiologists visually evaluated tumor volume and morphology and one reader manually segmented tumors for each time point to quantitatively calculate tumor volumes. Evolution in tumor volume/morphology was assessed over time and compared between good responders (tumor regression grade (TRG) 1–2) and poor responders (TRG 3–5).

Results: Tumor volumes decreased significantly during radiation. Early signs of response were also visually apparent: in the majority of good responders an early fibrotic transformation (week 2–3) as well as a visually estimated early volume reduction of >1/3 (week 1–2), was observed while these early changes only occurred in a minority of poor responders.

Conclusion: Results of this exploratory pilot study suggest that changes in rectal tumor morphology (fibrosis) and volume can already be observed early during radiation, both when measured quantitatively and when assessed visually. These changes appear to be indicative of the final treatment outcome.

Introduction

According to current guidelines, standard treatment for locally advanced rectal cancer (LARC) consists of a long course of neoadjuvant chemoradiotherapy (CRT) followed by surgical resection. In recent years there has been increasing attention for the concept of 'organ preservation', in particular 'watchful waiting'. In a watchful waiting policy, patients who have a clinical complete tumor regression after CRT are deferred from surgery and followed intensely. In case of a tumor regrowth, patients may still undergo salvage TME, whereas in patients that show a sustained complete response, surgery can be definitively evaded thereby avoiding complications and morbidity related to resection [1–4]. A pooled analysis of >3000 patients showed that approximately 15% of LARC patients achieve a complete response after routine CRT with a radiation dose of 45–50.4 Gy [5], indicating that only a minority of patients will be potential candidates for watchful waiting. In order to increase these numbers and ultimately offer more patients the benefits of organ preservation, efforts are being undertaken to maximize response rates by optimizing neoadjuvant treatment schemes, for example by means of radiation dose escalation to the tumor ('boosting'). A meta-analysis showed that an escalated preoperative dose of ≥60 Gy may lead to increased pCR rates of over 20% [6].

Two important challenges to allow meaningful adaptive neoadjuvant treatment are to identify the right patients and determine the proper timing to alter or intensify treatment in order to maximize therapeutic effects. Patients who show a response to routine CRT are more likely to benefit from further dose escalation to increase the chance of a complete response. Conversely, for patients who do not respond or respond very poorly to routine CRT, an extra dose will unlikely lead to therapeutic benefit while patients are still subjected to added toxicity. To discriminate between these patient groups, an early assessment of how well patients will respond to treatment would be of great value. Moreover, knowledge of the timeline of early tumor regression

* Corresponding author at: Department of Radiology, Netherlands Cancer Institute, P.O. Box 90203, 1006 BE Amsterdam, The Netherlands.
E-mail address: d.lambregts@nki.nl (D.M.J. Lambregts).

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can be used to determine the best time point to perform an early response evaluation.

Although numerous studies have focused on the use of imaging to evaluate response after completion of long course CRT, limited data are available on imaging for early response assessment. Several reports have evaluated the use of Positron Emission Tomography (PET) to measure response 1–2 weeks after onset of treatment, showing that early changes in tumor glucose metabolism may be useful for early response assessment [7,8]. PET is, however, not routinely used in clinics for the local staging and response assessment of rectal tumors. MRI is to date the most widely used imaging modality. There is some evidence that functional MRI (e.g. diffusion-weighted and dynamic contrast-enhanced MRI) performed early during treatment can aid in predicting the final treatment response [9–12], but so far only a few studies have investigated the use of routine morphological MRI and mainly at one or two time points during treatment [10,13,14]. One previous report by van de Begin et al. calculated gross tumor volumes on multiple sequential MRIs performed before, during and after preoperative chemoradiotherapy and concluded that rectal tumor regression mainly occurs during the first half of the preoperative CRT course [15].

Aim of this study was to add to these limited previous data and explore (in a pilot analysis) how rectal tumor morphology and volume change early during radiation treatment with sequential 'routine' T2-weighted MRIs performed during 5 weeks of radiotherapy in order to obtain a better understanding of early morphological signs of rectal tumor regression

Materials and methods

This study was approved by the local institutional review board. All patients provided written informed consent.

Patients

From October 2013 till May 2015, thirteen patients with locally advanced rectal cancer (cT3-4 and/or cN+), scheduled to undergo a long course of preoperative chemoradiotherapy were prospectively enrolled to undergo weekly MRI during their 5 weeks of radiation treatment. Inclusion criteria consisted of biopsy proven rectal adenocarcinoma and routine long course neoadjuvant treatment which according to our institutional guideline consisted of 50 Gy in 25 fractions on weekdays for 5 weeks combined with Capecitabine 825 mg/m2 BID on radiation treatment days.

MR imaging

As part of the study protocol patients underwent weekly MRIs (5 in total) during the 5 weeks of radiation treatment using a standardized protocol. The first MRI was performed on the first weekday after the first week of radiation, the following MRIs were routinely done on the first weekday of radiation (before the start of treatment), with the final MRI performed after completion of the fifth week of radiation. Images were acquired on a 3.0 T MRI system (Achieva, Philips Medical Systems, Best, The Netherlands) using a phased array surface coil. The MR sequences used for the current study consisted of 2D T2-weighted TSE sequences in 3 orthogonal directions (true sagittal, transverse and coronal plane) with the following scan parameters (for the transverse sequence): TR ± 3200-6200 (shortest), TE 120 msec, 90° flip angle, 30 echo train length, 1 NSA, $0.80 \times 0.84 \times 3.0$ mm acquired voxel size, 27-49 slices, 2:26-4:22 minutes acquisition time. Outside the scope of the study, patients also underwent a primary staging MRI before treatment and a restaging MRI after completion of CRT (and a waiting interval) as part of routine clinical diagnostic procedures. These clinical MRI examinations were partly performed elsewhere (in referring hospitals) and not according to the standardized study protocol.

Visual evaluation

Two expert radiologists (DL and ML; each with >8 years of specific experience in reading rectal MRI) in consensus visually assessed the size/volume and morphology of the rectal tumor for each patient on the primary staging MRI performed before treatment and studied their evolution over time for the 5 study scans performed during radiation treatment. The two readers evaluated:

- the morphology of the primary tumor before onset of treatment (solid vs. mucinous, polypoid vs. (semi)circular, regular vs. irregular tumor boundaries)
- when, i.e. in which week of treatment, a fibrotic transformation became visually apparent (see Fig. 1). Fibrotic transformation was defined as a reduction in signal on T2-weighted MRI occurring within the rectal wall / tumor bed.
- when, i.e. in which week of treatment, a substantial volume reduction (i.e., a visually estimated decrease of ± 1/3 or more in tumor volume) became apparent (see Fig. 1).

When there was any disagreement between the two readers, a third expert with >15 years of rectal MRI experience (RB-T) was consulted to reach a final decision.

Quantification of tumor volumes

One of the readers (DL) manually delineated the tumor boundaries on each consecutive slice containing tumor (see Fig. 2) in order to calculate whole tumor volumes. Delineations were performed using the free open source platform 3D Slicer (www.slicer.org) [16].

Data analyses

Statistical analyses were performed using IBM SPSS version 22 (IBM® Corps., Darmonk, NY, USA). The main outcome was the final tumor response as assessed at histopathology after surgery using the tumor regression grade (TRG) of Mandard [17]. Patients with a TRG 1–2 were classified as good responders; patients with a TRG 3–5 were considered poor responders. Initial tumor morphology and the timeline of response (as visually assessed) were compared between good and poor responders using descriptive statistics. Absolute tumor volumes (± standard deviations) as well as the percentage volume decrease after each week were plotted and compared between the five different time points as well as between patients from the poor vs. good response group using non-parametric paired and independent tests respectively (because data were not normally distributed). *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

Nine patients were male, 4 were female. Median age at the time of diagnosis was 65 years (range 49–75). TRG scores were available in 10/13 patient (TRG1-2 in $n = 3$; TRG 3–5 in $n = 7$). For three patients, the TRG was not available. Two of these three patients were classified as poor responders (1 underwent palliative care after CRT due to progressive metastasized disease with obvious signs of vital residual tumor on the final post-CRT MRI, 1 had a yT2N1 residual tumor at histopathology with a clear residual tumor mass on the final post-CRT MRI performed just before

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