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Locally advanced rectal cancer: Qualitative and quantitative evaluation of diffusion-weighted MR imaging in the response assessment after neoadjuvant chemo-radiotherapy

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ABSTRACT

Purpose: to investigate the added value of qualitative and quantitative evaluation of diffusion weighted (DW) magnetic resonance (MR) imaging in response assessment after neoadjuvant chemo-radiotherapy (CRT) in patients with locally advanced rectal cancer (LARC).
Methods: 31 patients with LARC (stage ≥ T3) were enrolled in the study. All patients underwent conventional MRI and DWI before starting therapy and after neoadjuvant CRT. All patients underwent surgery; pathologic staging represented the reference standard. For qualitative analysis, two radiologists retrospectively reviewed conventional MR images and the combined set of conventional and DW MR images and recorded their confidence level with respect to complete response (ypCR). For quantitative analysis, tumor's apparent diffusion coefficient (ADC) values were measured at each examination. ADC pre-CRT, ADC post-CRT and Δ ADC post−ADC pre of the three groups of response (ypCR, partial response ypPR, stable disease ypSD) were compared. Receiver-operating characteristics (ROC) curve analysis was employed to investigate the discriminatory capability for ypCR, responders (ypCR, ypPR) and ypSD of each measure.
Results: addition of DWI to conventional T2-weighted sequences improved diagnostic performance of MRI in the evaluation of ypCR. A low tumor ADC value in the pre-CRT examination, a high ADC value in the post-CRT examination, a high Δ ADC post−ADC pre [>0.3 ($\times 10^{-3}$ mm^2/s)] were predictive of ypCR.
Conclusions: DW sequences improve MR capability to evaluate tumor response to CRT. Nevertheless, no functional MR technique alone seems accurate enough to safely select patients with ypCR.

1. Introduction

Rectal cancer is one of the most frequent neoplasias, with an incidence of 40 in 100,000 [1]. Over the last two decades its treatment has undergone many changes and innovation, thus more precise preoperative evaluation leaded to refined patient selection for appropriate treatment strategies. The tumor stage determines whether radiation and chemotherapy should be used in addition to surgery. In particular, T1-T2 N0 tumors are managed surgically, without neoadjuvant treatment whereas neoadjuvant chemo-radiotherapy (CRT) followed by total mesorectal excision (TME) surgery represents the standard treatment for locally advanced rectal carcinoma (≥T3; any T, N+) [2].

According to literature data 15–27% of the patients treated with CRT achieve a pathological complete response (ypCR), a partial response is seen in 54–75% and others show no response at all [3].

In view of these advances of CRT, alternative approaches to radical surgery have been proposed. Therefore, staging rectal cancer before and after CRT and assessing tumor response have become a very critical issue and imaging studies play a key role with relevant implications in patients' management.

On one hand response assessment during CRT could possibly re-orientate non-responding patients to a different treatment

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modality (*e.g.* early surgery) or to treatment intensification (*e.g.* dose escalation or addition of targeted agents); on the other hand response assessment before surgery may enable physicians to offer patients who achieve a clinical complete response less extensive surgery, such as sphincter-saving local excision [4], or even a 'wait-and-see' policy [5,6].

According to the European guidelines, magnetic resonance (MR) imaging is the most accurate technique for predicting tumor stage [5,7]. Nevertheless, MRI, as a morphologic imaging modality, has inherent limitations in the differentiation of residual viable tumor from diffuse fibrotic change; therefore, conventional MRI sequences cannot be used to predict complete response to CRT [8,9].

The reported overall accuracy of MRI in predicting the pathologic stage of nonirradiated rectal cancer is 71–91% (mean 85%) for T staging and 43–85% (75%) for N staging; on the other hand the reported overall accuracy of MRI in predicting the pathologic stage of irradiated rectal cancer is 47–54% (50%) for T staging and 64–68% (65%) for N staging [7,10].

Since conventional MR sequences are insufficient for reliably assessing these critical issues there is considerable enthusiasm for employing functional imaging techniques such as diffusion-weighted (DW) MR imaging [11], which may depict microstructural and metabolic treatment-induced changes of the tumor before morphological changes become apparent. DWI allows to perform quantitative measures such as apparent diffusion coefficient (ADC); it may be used as a noninvasive imaging biomarker of tumor aggressiveness [12,13] and to monitor and predict tumor response to CRT [14].

In recent years different imaging tools either volumetric (tumor volume reduction rate [15], magnetic resonance volumetry [16]) or functional [6] have been investigated as potential imaging-based biomarker of treatment response; in particular, the role of qualitative and quantitative DWI findings for prediction of tumor response to CRT has been evaluated.

Kim et al. [8] demonstrated that in patients with locally advanced rectal cancer, adding DW MR imaging to conventional MR imaging yields better diagnostic accuracy than use of conventional MR imaging alone in the evaluation of complete response to neoadjuvant CRT.

Other studies [6] have investigated the role of ADC measurements (potential markers of response being pre-CRT, post-CRT ADC measures and ΔADC) for prediction of treatment outcome and for early detection of tumor response in patients with locally advanced rectal cancer. Sometimes, however the obtained results are discordant and DWI seems not accurate enough to safely select patients for organ preservation.

The aims of our study were:

- to investigate the added value of qualitative DW MRI evaluation in the response assessment after neoadjuvant CRT in patients with locally advanced rectal cancer;
- to evaluate the diagnostic performance of rectal cancer's ADC measurements, the quantitative parameter of diffusion, for the assessment of therapeutic response to CRT.

2. Materials and methods

2.1. Patients

This was a single institution retrospective cohort study. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and in accordance with recommendations of the local ethic committee. Informed consent was waived due to the retrospective study design.

Between October 2011 and May 2015, 47 patients with diagnosis of rectal cancer were considered for eligibility.

Inclusion criteria were as follows: histologically proven rectal carcinoma, staged on rectal MRI with DWI T3-4 and/or with positive regional lymph-node, neoadjuvant CRT, post-CRT rectal MRI with DWI, subsequent surgery.

Exclusion criteria were: previous CRT for primary rectal carcinoma or tumor in other organ (n = 1); contraindication to MR imaging examination (n = 2); delayed (more than 8 months after CRT), cancelled surgery or surgery performed in other institution (n = 2); insufficient quality of MR examination (*e.g.* owing to metal implants or movement artifacts) (n = 2); distant metastases (n = 4); lack of follow-up MR examination (n = 5).

All patients underwent a staging protocol before preoperative CRT, that included: digital rectal examination, complete blood tests, colonoscopy, contrast enhanced computed tomography (CT) of the chest and the abdomen, external pelvic phased-array MR examination and transrectal ultrasound.

2.2. Reference standard

Pretreatment stage (cT cN) was compared with pathologic stage (ypT ypN). Pathologic staging represented the reference standard and was based on the TNM staging system (VII ed.).

The response was graded as follows. No response to treatment was defined as stable disease (ypSD). A partial response (ypPR) to treatment was defined as downstaging, or reduction of at least one level in T or N staging between the baseline MR exam and histopathological staging. Pathological complete response (ypCR) was defined as the absence of any residual tumor cells detected in the operative specimen (ypT0 ypN0).

2.3. Neoadjuvant CRT treatment plan

CRT was performed by means of integration between an initial induction chemotherapy (ICT) and a subsequent concurrent radiochemotherapy (CRCT), over a period of 9 weeks.

During the ICT phase, all patients received a FOLFOX 4 chemotherapy schedule for two cycles, with Oxaliplatin 85 mg/m^2 in 3 h i.v. infusion (on day 1), 5-Fluoruracil 400 mg/m^2 i.v. bolus, Folinic acid 200 mg/m^2, 5-Fluoruracil 600 mg/m^2 continuous intravenous infusion over 22 h (on day 1 and 2). The cycle was repeated after 14 days, by previous clinical and haematological examination.

A CT radiotherapy simulation was conducted during the ICT phase, in order to prepare the treatment plan.

The CRCT phase requires a continuous i.v. infusion of 5-Fluoruracil at 250 mg/m^2 daily during all radiotherapy treatment period. Radiation therapy was conducted with patient in prone position, by means of a belly board position system, in order to reduce the dose to the small bowel.

Radiotherapy was planned using a 3D-Conformal technique (Fig. 1), to ensure a coverage of the whole pelvis, including rectum, mesorectum, common iliac, internal and external iliac lymph nodes, obturator lymph nodes. This volume was defined as CTV 1 (Clinical Target Volume 1) and was irradiated to a dose of 45 Gy, with a conventional fractionation of 1,8 Gy/day. A second volume, called CTV2, was also defined to give a boost to the site of the primary tumor in the rectum, by means of a concomitant irradiation during the last six fractions, after an interval of 6 h from the first fraction. This volume received a dose of 9 Gy, with a fractionation of 1,5 Gy/day.

Using the above described concomitant-boost technique, a total dose of 54 Gy is given to the primary tumor. This dose is at least 10% higher than that conventionally used in the currently accepted protocols for neoadjuvant irradiation of rectal cancer.