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Editorial Musings

Multi-parametric MRI of rectal cancer – Do quantitative functional MR measurements correlate with radiologic and pathologic tumor stages?

U.I. Attenberger[a], L.R. Pilz[b], J.N. Morelli[c], D. Hausmann[a,*], F. Doyon[d], R. Hofheinz[e], P. Kienle[d], S. Post[d], H.J. Michaely[a], S.O. Schoenberg[a], D.J. Dinter[a]

[a] Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Germany
[b] Medical Faculty Mannheim, University of Heidelberg, Germany
[c] Scott & White Memorial Hospital and Clinic, Temple, TX, USA
[d] Department of Surgery, University Medical Center Mannheim, Germany
[e] Department of Oncology, University Medical Center Mannheim, Germany

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ABSTRACT

Purpose: The purpose of this study is two-fold. First, to evaluate, whether functional rectal MRI techniques can be analyzed in a reproducible manner by different readers and second, to assess whether different clinical and pathologic T and N stages can be differentiated by functional MRI measurements.
Materials and methods: 54 patients (38 men, 16 female; mean age 63.2 ± 12.2 years) with pathologically proven rectal cancer were included in this retrospective IRB-approved study. All patients were referred for a multi-parametric MRI protocol on a 3 Tesla MR-system, consisting of a high-resolution, axial T2 TSE sequence, DWI and perfusion imaging (plasma flow –s PF_{Tumor}) prior to any treatment. Two experienced radiologists evaluated the MRI measurements, blinded to clinical data and outcome. Inter-reader correlation and the association of functional MRI parameters with c- and p-staging were analyzed.
Results: The inter-reader correlation for lymph node (ρ 0.76–0.94; $p < 0.0002$) and primary tumor (ρ 0.78–0.92; $p < 0.0001$) apparent diffusion coefficient and plasma flow (PF) values was good to very good. PF_{Tumor} values decreased with cT stage with significant differences identified between cT2 and cT3 tumors (229 versus 107.6 ml/100 ml/min; $p = 0.05$). ADC_{Tumor} values did not differ significantly. No substantial discrepancies in lymph node ADC_{Ln} values or short axis diameter were found among cN1-3 stages, whereas PF_{Ln} values were distinct between cN1 versus cN2 stages ($p = 0.03$). In the patients without neoadjuvant RCT no statistically significant differences in the assessed functional parameters on the basis of pathologic stage were found.
Conclusion: This study illustrates that ADC as well as MR perfusion values can be analyzed with good interobserver agreement in patients with rectal cancer. Moreover, MR perfusion parameters may allow accurate differentiation of tumor stages. Both findings suggest that functional MRI parameters may help to discriminate T and N stages for clinical decision making.

1. Introduction

Magnetic resonance imaging (MRI) has achieved broad acceptance for local staging of primary rectal cancer prior to treatment [1]. The accuracy of MRI in discriminating tumor stage 2 (T2) and 3 (T3) tumors has been established. This distinction is critical with respect to treatment planning as stage T3 tumors generally are treated with neoadjuvant radio- or radiochemotherapy, whereas stage T2 tumors are managed surgically, typically without neoadjuvant treatment [2–4]. Moreover, MRI reliably predicts infiltration depth into perirectal fat and tumor infiltration of the mesorectal fascia (MRF) [5–8], an important marker for local recurrence. Primary tumor extent and distance to the MRF is generally evaluated on high-resolution T2 axial TSE scans as recommended by the American Joint Committee on Cancer staging guidelines [1]. However, a recent publication by Al-Sukhni et al. questions the value of MRI, as currently performed and interpreted, in the preoperative staging. According to this publication, fewer than 40% of MRI reports included critical staging information such as the T stage, the involvement of the circumferential margin, and lymph node involvement, all essential factors to be considered in treatment decisions [9].

* Corresponding author. Tel.: +49 621 383 2067; fax: +49 621 383 4065.
E-mail address: daniel.hausmann@medma.uni-heidelberg.de (D. Hausmann).

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Recently, several authors have demonstrated the additional value of functional MRI parameters such as apparent diffusion coefficients on primary rectal cancer staging accuracy [10] and as markers for tumor clearance from the MRF in locally advanced rectal cancer [11]. In addition to ADC values, MR perfusion may play a role as an imaging-based biomarker for the prediction of therapeutic response as indicated in a previous study by Oberholzer et al. [12]. These studies suggest that functional MRI parameters may be helpful in improving the accuracy of primary tumor (T) and lymph node (N) staging by MRI. To further evaluate this possibility, the correlation between functional parameters and clinical (c) and histopathologic (p) T and N staging must be established. To our knowledge, no study to date has explored this correlation. For successful clinical implementation of functional MRI techniques, the reliability, reproducibility, and efficacy of such techniques must be established. Thus, it is important to assess such techniques relative to pathologic staging and to determine levels of inter-observer agreement.

Therefore the aim of this study is two-fold. First, to evaluate, whether functional rectal MRI techniques can be analyzed in a reproducible manner by different readers and second, to assess whether different clinical and pathologic T and N stages can be differentiated by functional MRI measurements.

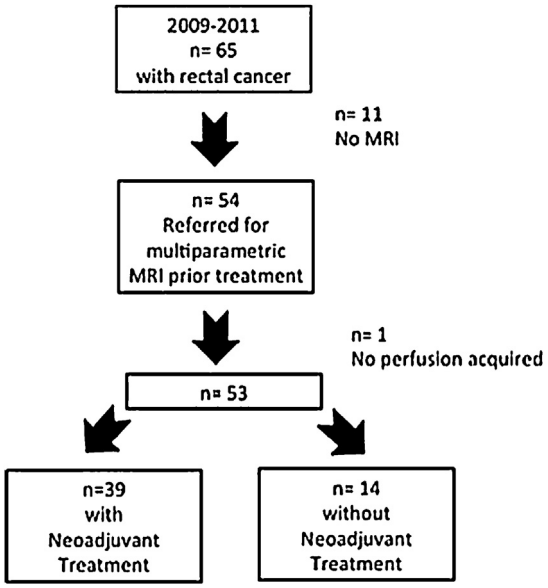

Fig. 1. Criteria of patient selection for this retrospective study are detailed.

2. Materials and methods

2.1. Patients

From 2009 to 2011 a total of 54 consecutive patients (38 men, 16 female; mean age 63.2 ± 12.2 years) were included in this retrospective, IRB approved analysis. Every patient was referred for a multiparametric rectal MRI at 3 T as part of an institutional standard work up in order to identify risk factors for local recurrence such as infiltration of the mesorectal fat (revealing at least a T3 stage) and a distance between the mesorectal fat and fascia of less than 1 mm—factors which would necessitate neoadjuvant radio-chemotherapy (RCT) prior to surgery. 39 out of this group (74%) presented with features on rectal endoscopic ultrasound and standard high-resolution T2-weighted images (see below) warranting neoadjuvant radio-chemotherapy (RCT) prior to surgery. These patients underwent multi-parametric MRI before and after RCT; however, since RCT alters tumor cellularity and perfusion, only pre-operative functional MR values were utilized in the subsequent comparisons. For patients who did not undergo RCT, pre-operative functional MRI parameters were compared to histopathological tumor stage (pT). Based on current treatment guidelines, these patients ($n = 14$) had all been classified as T2 tumor stage on the basis of endoscopic rectal ultrasound and high resolution T2-weighted MR images. Rectal cancer was histopathologically proven in all patients. One patient for whom clinical data was not available was excluded. Fig. 1 details patient selection for this retrospective study.

2.2. c- and p-staging

The clinical T and N stages were determined by the results of rectal endoscopic ultrasound as well as the results of a standard T2 high-resolution MRI examination, as part of the multiparametric MRI protocol, given in detail below. Infiltration into the mesorectal fat was taken as indicator for a T3 tumor. Infiltration of neighboring organs such as the vagina or bladder was rated T4. Any lymph nodes visible within the mesorectal fascia were included in this analysis. In case of discrepant cT or cN stages, the worst case scenario was assumed for clinical decision making. The oncologists were blinded to the results of the functional MRI examination at the time at which the tumor stage was diagnosed. Pathologic stage (pT and pN status) was established following surgical removal of the tumor.

2.3. MRI protocol

MR was performed on a clinical 3 T MR-system (TimTrio, Siemens Healthcare Sector, Erlangen, Germany) utilizing a standard 6-element body-matrix coil centered over the pelvis in combination with the inbuilt 32-element spine-matrix coil. 50 mL of ultrasound gel was inserted into the rectal vault of each patient prior to the initial MRI procedure. After localizer sequences, standard T2w TSE scans were acquired in axial, coronal and sagittal planes for anatomic orientation. The axial and coronal T2-weighted sequences were angulated perpendicular and parallel to the tumor axis. A high-resolution T2 TSE axial scan (TR/TE/FA 4000 ms/101 ms/150°, FoV 200 × 200 mm^2, matrix 320 × 310), parallel imaging (GRAPPA) factor 2 as well as DWI (TR/TE/FA 5000 ms/73 ms/90°, FoV 284 × 379 mm^2, matrix 115 × 192, $b = 50/400/800/1000$, parallel imaging (GRAPPA) factor 2) were acquired. An additional echo-shared, high spatial and temporal resolution, time-resolved MR-examination with interleaved stochastic trajectories (TWIST-MR) (TR/TE/FA 3.6/1.4/15 ms/ms/°, FoV 350 × 187 mm^2, matrix size 192 × 144, slice thickness 3.6 mm, temporal resolution 4.9 s) in an axial oblique slice orientation was acquired for the perfusion analysis. A Gd-based 0.5 M macrocyclic contrast agent (Dotarem, Guerbet, France) was injected at a dose of 0.1 mmol/kg bw and at a rate of 2.5 ml/s, followed by 40 ml of saline flush, injected at the same rate.

2.4. Post-processing

Parametric ADC maps were calculated automatically by the scanner. ADC analysis was performed offline on an OsiriX workstation (3.7.1, OsiriX Foundation Geneva, Switzerland). The readers evaluated perfusion data offline utilizing an in-house built software plug-in for OsiriX [13]. After defining a region-of-interest for the arterial input function, a de-convolution model was applied and parametric maps of plasma flow (PF, ml/100 ml/min), mean transit time (MTT, s) and plasma volume (ml) were automatically

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