Application of texture analysis based on ADC maps in discriminating different stages of rectal cancer

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Authors: L. Liu; Beijing/CN  
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Purpose

Introduction

In recent years, notable progress has been made in the management of rectal cancer. In particular, the use of neoadjuvant chemoradiotherapy (NAT) for locally advanced rectal carcinoma (stage T3-4 and/or N1-2) has been shown to be associated with 50%-61% reduction in risk of loco-regional recurrence[1, 2]. However, drug toxicity, incontinence and sexual dysfunction are some of the serious side effects of NAT [3-5]. Accurate staging may help in identifying patients who are likely to benefit the most from NAT.

High-resolution magnetic resonance (MR) imaging is broadly accepted as being particularly suited to clinical staging and guiding treatment for rectal cancer. However, differentiation of stage T2 tumors from stage T3 tumors is challenging [6] as the peritumoral inflammatory reaction tends to mimic tumor penetration through the muscular rectal wall. In addition, preoperative detection of nodal involvement is another challenge for radiologists in patients with normal-sized positive lymph nodes [7]. Therefore, improved techniques for clinical staging and risk stratification prior to treatment are key imperatives.

Diffusion-weighted magnetic resonance imaging (DWI) with apparent diffusion coefficient (ADC) is a functional MR imaging technique that can reflect the varying cellularity within a tumor. It has been increasingly used in rectal cancer research because of rapid scanning progress and lack of need of a contrast agent. Recently, several studies have indicated that DWI could improve the accuracy of clinical staging of rectal cancer, and that ADC values had the potential to become an imaging biomarker of tumoral [8, 9].

On the other hand, texture analysis (TA) has been emerging as one of "radiomics" approaches for in-depth interpretation of medical images. It allows for a more objective assessment than a standard morphological analysis of images[10]. Texture analysis allows for a quantitative assessment of the intratumoral heterogeneity which correlates closely with tumor grading and staging[11-13]. To date, some texture parameters of structural or functional images have been successfully used in patients with cancers of breast, kidney, lung and prostate, for differentiating between different tumor grades, and for assessment of cancer aggressiveness [10, 14-16].To the best of our knowledge, use of TA based on ADC maps, for staging of rectal cancer, has not been documented. The purpose of this study was to explore the potential of texture-related attributes on ADC maps in predicting the extent of local invasion (pathological stage T1-2 vs. T3-4) and nodal involvement (N0 vs. N1-2) in patients with rectal cancer.
Methods and materials

Patients

The study was approved by the ethics review board at our hospital. The requirement for informed consent was waived off owing to the nature of study. A search of the hospital electronic cancer registry revealed 112 consecutive rectal cancer patients between September 2014 and July 2015. Inclusion criteria were: patients with pathologically confirmed adenocarcinoma <15cm from anal verge, with preoperative diffusion-weight MR imaging and no preoperative treatment, who underwent radical resection within one month after MRI scan. Forty four patients were excluded for the following reasons: underwent NAT (N=28), MRI scan not performed or with poor image quality (N=5), underwent palliative surgery for primary mass (N=3), underwent endoscopic resection (N=5) or did not undergo surgery (N=3). Finally, 68 eligible patients were included in this study (Figure 1).

MRI Parameters

All pelvic MRI examinations were performed on a 3.0-T magnet with an eight-channel phased-array surface coil. Bowel preparation and intravenous antispasmodic agents were not administered in all cases. An axial diffusion-weighted sequence covering the entire pelvis from abdominal aortic bifurcation up to pubic symphysis was included in MRI examination in all patients. The scan parameters were as follows: TR/TE: 4000/90ms; matrix size: 128x128; FOV: 35-40cm; phase FOV: 0.8-0.9; slice thickness: 5mm; slice interval: 10%; NEX: 4-8; direction: all and b=0 and 1000 sec/mm².

ROI determination and ADC measurement

Parametric ADC maps were created and regions-of-interest (ROI) delineated by a radiologist who had 12 years in performing abdominal MRI examination, on a post-processing workstation. The radiologist was aware of the inclusion criteria for the study but was blinded to other clinical or histopathological findings.

On MRI, the primary tumor was recognized as a focal mass or an area of abnormal wall thickening showing high signal intensity on DWI (b1000) and intermediate signal intensity on T2-weighted MRI. Each free-hand ROI was drawn along the border of the high signal of the primary tumor on the single slice of DWI (b1000) that showed the largest tumor dimension, and automatically co-localized on the corresponding ADC map. Axial T2-weighted imaging was used for reference in order to ensure accurate positioning of ROI (Figure 2). Care was taken to cover the entire tumor area and avoid areas with
obvious necrosis sac (long diameter >10mm) and lumen contents. After determining the ROI on the ADC map, the mean, minimum and maximum ADC values (ADC_{mean}, ADC_{min}, ADC_{max}) for each patient were automatically calculated and recorded.

**Image texture analysis**

Each delineated two-dimensional (2D) ROI was extracted from the original ADC map by using an image processing software and later transferred to a Matlab platform for TA using implemented feature algorithms (Figure 2). This TA model could generate 135 texture parameters for each ROI. We chose five of these that could reflect regional heterogeneity and were frequently used in previous studies. Skewness and kurtosis were derived by using first order statistics, while entropy, contrast and correlation were calculated by using grey level co-occurrence matrix (GLCM).

**Surgery and clinical-pathological assessment**

Within one month of the MRI study, radical surgery was performed following the principles of total mesorectal excision (TME). The specimens were fixed in formalin solution for at least 48 hours, and were then transversely sliced (perpendicular to the long axis of the rectum) at a thickness of three micrometers. Pathological T (pT) stages and nodal status (pN) were documented. More than twelve lymph nodes were examined in each specimen. Staging was performed according to the 7th edition of the tumor-node-metastasis (TNM) staging system[17].

**Statistical Analysis**

Histopathological findings were used as a reference standard. Normal distribution of variables was verified by the Kolmogorov-Smirnov test. ADC measurements and texture parameters were compared between pT1-2 and pT3-4 stages, and between pN0 and pN1-2 stages using the student t test or the Mann-Whitney test. Multivariate logistic regression analysis was used to identify independent predictors for (pN1-2). Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic efficacy of the selected logistic models for detection of high-T stage tumor and positive nodal status. In addition, the parameters were compared among overall stage group I, II, III, and IV by using Analysis of Variance (ANOVA) with post hoc test (LSD), or the Kruskal-Wallis test. Spearman correlation analysis was performed to assess correlation between each parameter and the tumor stages.
Consecutive rectal cancer patients between September 2014 and July 2015 (n=112)

With pretreatment pelvic MRI including DWI (n=107)

Patient underwent radical surgery according to the principles of TME (n=96)

Underwent NAT after MRI scan (n=28)

Eligible patients (n=68)

Fig. 1: Schematic illustration of case selection criteria

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Fig. 2: Image analysis in a 57-year-old woman with rectal cancer a) T2-weighted MR image used as a reference for delineation of the ROI. b) ROI drawn on a diffusion-weighted image showing the largest diameter of the tumor, c) ROI synchronously co-localized on the corresponding ADC map and the traditional ADC metric values calculated. d) ROI with magnification extracted from the ADC map by Image J software, and texture features generated on a Matlab platform. MR, Magnetic resonance; ROI, region of interest; ADC, Apparent diffusion coefficient

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Results

Patient characteristics
The mean age of patients was 59.6±9.6 years (range, 31 - 88 years). Six (8.8%) patients had synchronous isolated distant metastasis (liver: 5 patients; lung: 1 patient) and underwent synchronous or heterochronous resection of the same. The average time interval between MRI scan and surgery of the primary mass was 19 ± 5 days (range, 12 - 29 days).

ADC measurements and texture parameters: stage pT1-2 vs. stage pT3-4 tumors
There were statistically significant differences between pT1-2 and pT3-4 tumors with respect to skewness (P=0.015), entropy (P=0.004) and contrast (P=0.017). All the three texture features were significantly lower in stage T1-2 as compared to that in stage T3-4 tumors (skewness, 0.166 vs. 0.476; entropy, 3.212 vs. 3.441; contrast, 10.773 vs. 13.596). However, no significant inter-group differences were observed with respect to ADC_mean, ADC_min, ADC_max, kurtosis or correlation. Distribution of statistically significant parameters within different T categories is shown in Figure 3 (a, b, c).

Skewness, entropy and contrast were used as input variables for multiple logistic regression analysis. Higher skewness (Odds ratio [OR], 3.608; 95% Confidence Interval [CI], 1.060-12.766; P=0.047) and higher entropy (adjusted OR, 10.230; 95% CI, 1.449-69.881; P=0.018) were found to be independent predictors of extramural invasion of the tumor (pT3-4). Using a logistic regression model that incorporated two texture attributes to differentiate pT3-4 tumors from pT1-2 tumors, we achieved a moderate accuracy (Area under the curve [AUC], 0.743; 95% CI, 0.622-0.841) with a sensitivity of 80.9% and specificity of 61.9%.

ADC measurements and texture parameters: stages pN0 vs. pN1-2
Between pN0 and pN1-2 tumors, significant differences were found with respect to ADC_mean (P=0.023), ADC_max (P=0.005) and entropy (P=0.015). pN0 tumors had significantly higher ADC_mean and ADC_max, and lower entropy as compared to that in pN1-2 tumors (1.157 vs. 1.041; 1.686 vs. 1.445; 3.299 vs. 3.486). There were no significant inter-group differences with respect to ADC_min, skewness, kurtosis, contrast or correlation. The distribution of various statistically significant parameters within different N categories is shown in Figure 3 (d, e, f).

On multivariate logistic regression analysis, lower ADC_max (adjusted OR, 0.086; 95% CI, 0.014-0.532) and higher entropy (adjusted OR, 9.421; 95% CI, 1.399-63.449) were found
to be independent predictors of positive nodal status. The use of the logistic regression model for differentiation between pN1-2 and pN0 tumors showed a moderate accuracy, with an AUC of 0.750 (95% CI, 0.630-0.847), sensitivity of 96.2% and specificity of 45.2%.

**ADC measurements and texture parameters among overall stages**

The ADC values and texture features of and IV tumors are summarized in. ADC_{mean}, skewness, entropy and contrast were significantly different between different overall stages. Entropy proved to be significantly different between stage I and III, between stage I and IV, between stage II and IV as well as between stage II and IV. However, no significant difference was found with respect to ADC_{min}, ADC_{max}, kurtosis and correlation. The distribution of significant parameters within different stages is shown in Figure 3 (g, h, i, j).
Fig. 3: Box-plots for distributions of statistically significant parameters within different stage groups. Distributions of skewness (a), entropy (b) and contrast (c) of ADC maps between pT1-2 and pT3-4 tumors. Distributions of ADCmean (d), ADCmax(e) and entropy (f) between pN0 and pN1-2 tumors. Distributions of ADCmean (g), skewness (h), entropy (i) and contrast (j) among overall-stage I, II, III and IV.
Conclusion

Texture features based on ADC maps may prove to be valuable in the diagnosis of locally advanced rectal cancer. In particular, entropy and skewness were independent predictors of higher tumor stage and extramural invasion in this study. Further, entropy was an independent predictor of positive nodal status. Our findings suggest that TA, together with other imaging techniques, may help identify patients who are likely to benefit from NAT.
Personal information

Liheng Liu, M.D. Yi Zhang, B.S. Erhu Jin, M.D. Zhenchang Wang, M.D. Zhenhan Yang, Ph.D. Department of Radiology, Beijing Friendship Hospital, Capital Medical University, No.95, Yongan Road, Beijing, CN. Zip code: 100050.

Email of Liheng Liu: Email: llh9821@163.com