Am J Transl Res 2018;10(11):3790-3796
www.ajtr.org /ISSN:1943-8141/AJTR0077946

*Original Article*

# Histogram parameters derived from T2 weighted images are associated with histopathological findings in rectal cancer - a preliminary study

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Received April 15, 2018; Accepted September 1, 2018; Epub November 15, 2018; Published November 30, 2018

**Abstract:** Histogram analysis can better reflect tumor heterogeneity than conventional imaging analysis. The present study analyzed possible correlations between histogram parameters derived from T2 weighted images and histopathological features in rectal cancer. Seventeen patients with histopathological proven rectal adenocarcinoma were retrospectively acquired with prebioptic 3 T MRI and available histopathological specimens. Histogram analysis was performed using an in-house matlab tool conducting a whole lesion measurement. Histopathology was investigated using Ki67 specimens with calculation of Ki67-index as well as cellularity and nucleic areas and CD31 specimens, with estimation of microvessel density. Several histogram parameters correlated with average nucleic area. Skewness showed a moderate correlation with microvessel density (P = 0.54, P = 0.02). None of the parameters correlated with Ki67-index. Skewness derived from T2 weighted images might be used as a surrogate parameter for average nucleic area and microvessel density. However, none of the parameters were associated with proliferation index.

**Keywords:** Rectal cancer, MRI, histogram analysis, microvessel density, Ki67

## Introduction

Rectal adenocarcinoma is one of the most common types of cancer throughout the world [1]. The actual guidelines suggest that treatment decisions should be based on pretreatment magnetic resonance imaging (MRI) due to the high resolution of soft tissue [2]. Therefore, MRI is widely used in clinical practice for tumor staging using conventional sequences.

Numerous reports showed that MRI cannot only provide morphological information regarding tumor spread and local infiltration but also give insight into functional behavior of tumors [3-8]. For example, according to the literature, diffusions-weighted imaging (DWI) is strongly associated with cellularity [3, 4], and dynamic contrast enhanced MRI (DCE-MRI) is associated with microvessel density [9]. This was also shown for rectal cancers [10].

However, there is also increasing evidence that also conventional morphological T1 and T2-weighted images, used in clinical routine, might be able to provide information about tissue composition [11-14]. For instance, it has been shown that parameters of histogram analysis of conventional MR images can reflect tumor cellularity and proliferation index KI67 in cerebral lymphoma and glioblastoma [12, 14]. This method analyzes all voxel within a region of interest (ROI) and issues those into a histogram [15]. Therefore, statistical information regarding frequency and distribution of the voxels within the investigated tissue can be obtained. The calculated statistical parameters comprise percentiles, as well as second order statistics like skewness, kurtosis and entropy. According to the literature, histogram analysis parameters, in particular, histogram analysis of ADC values, were more sensitive in comparison to routinely used mean and/or minimal ADC val-

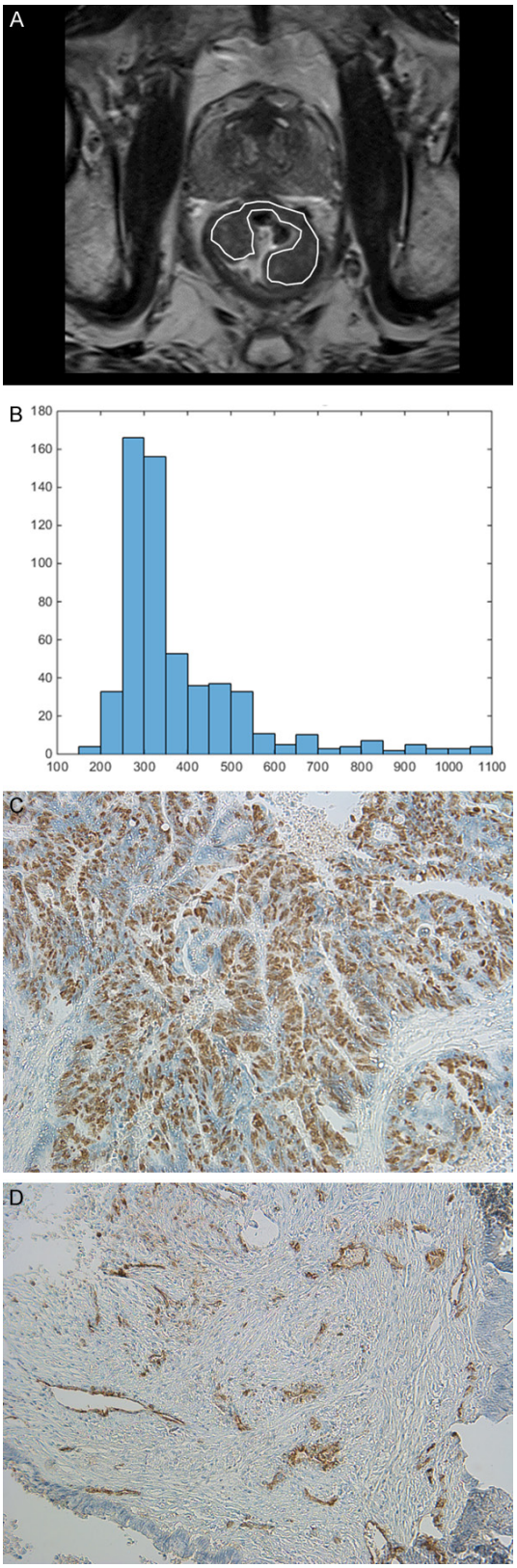


**Figure 1.** Imaging findings and histopathological features in a patient with T3N1M1 rectal cancer. A. Axial T2 weighted image with the ROI placed within the tumor boundaries. The measurement was performed on all slides to obtain a whole lesion measurement. B. Representative histogram of the T2-signal intensity of the lesion. The calculated values are as follows: mean = 3.8, minimum = 1.7, maximum = 6.5, P10 = 3.2, P25 = 3.5, P75 = 4.1, P90 = 4.6, median = 3.7, mode = 3.6, standard deviation = 0.66, kurtosis = 6.34, skewness = 1.48, and entropy = 2.89. C. Immunohistochemical stain (MIB-1 monoclonal antibody). Histopathological parameters are as follows: Ki 67 index = 55%, cell count = 846, total nucleic area = 98778 $\mu m^2$, and average nucleic area = 118 $\mu m^2$. D. Immunohistochemical stain (CD31 monoclonal antibody). The estimated microvessel count was 68.

ues and can provide more data regarding tissue microstructure. Furthermore, heterogeneities reflected by the histogram analysis might also be linked to tumor heterogeneity evaluated by histopathology [15].

Previously, there were very promising results that functional MRI might be able to reflect tumor biology in rectal cancer [10, 16-18]. However, no study investigated, whether morphological images might also be able to reflect tumor microstructure, when analyzed with a histogram based approach.

Therefore, the aim of the present study was to elucidate possible associations between cellularity and perfusion parameters obtained via histopathology and histogram based parameters of T2-weighted (T2w) images in rectal cancer.

## Materials and methods

This retrospective study was approved by the local ethic institutional board and informed content was waived.

### *Patients*

Overall, 17 patients with histologically proven rectal adenocarcinomas were included into the study. One patient was female and 16 were male with a mean age of 68.65 years (median age, 71 years; range, 51-76 years). Well differentiated carcinomas were diagnosed in 2 (12%) cases, moderately differentiated in 10 patients (59%), and poorly differentiated tumors in 5 patients (29%).

### *MRI*

In all patients MRI of the pelvis was performed by using a 3.0 T device (Magnetom Skyra,

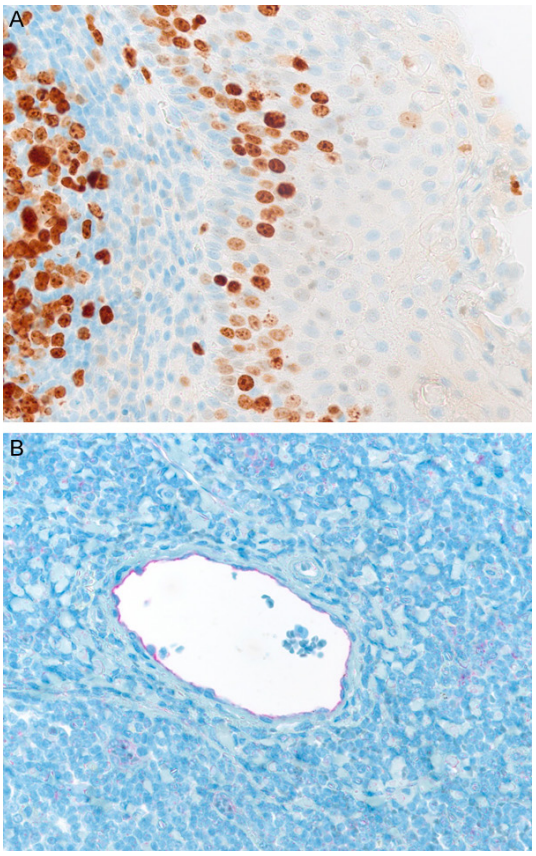


**Figure 2.** A. Control picture of an immunhistochemical staining with Mib-1 (400× magnification). B. Control picture of an immunhistochemical staining with CD-31 (400× magnification).

Siemens, Erlangen, Germany). The imaging protocol included the following sequences: axial and sagittal T2 weighted (T2w) turbo spin echo (TSE) sequences, an axial fat-supressed (fs) short tau inversion recovery (STIR) sequence, an axial T1 weighted turbo spin echo (T1w TSE) images, and an axial T1w TSE sequence with fat suppression after intravenous application of contrast medium (gadopentate dimeglumine, Magnevist, Bayer Schering Pharma, Leverkusen, Germany), in a dosis of 0.1 ml per kilogram of body weight.

For this study, axial T2w TSE images were evaluated. Sequence parameters were as follows: TR/TE: 5000/65 ms, Flip angle: 160°, FoV: 399×399, slice thickness: 3 mm.

*Histogram analysis*

T2w images were transferred in DICOM format and processed with a custom-made MATLAB-based application (The MathWorks, Natick, MA). In every case, the volume of interest (VOI) was created by manually drawing regions of interest (ROIs) on every slide of tumors. **Figure 1** displays an explanatory patient with a drawn ROI and corresponding histopathologic specimen. All measures were performed by one author (AS, 14 years or radiological experience). After setting the VOIs, the following parameters were calculated: the percentiles: 10th, 25th, 75th, and 90th; mean; median; minimum; and maximum values of SI. Furthermore, histogram-based characteristics of the ROI-kurtosis, skewness, and entropy-were also estimated.

*Histopathological analysis*

In all cases the diagnosis of rectal cancer was confirmed histopathologically by endoscopic rectal biopsy. Representative tumor tissue slides from formalin-fixed paraffin-embedded tissue were processed after deparaffinization. The specimens were stained with MIB-1 monoclonal antibody and with CD31 antigen (both from DakoCytomation, Denmark). All stained samples were digitalized by using a research microscope Jenalumar (Zeiss, Jena, Germany), with camera diagnostic instruments 4.2, magnification ×400. Furthermore, the digital histopathological images were transferred as uncompressed TIFF images to ImageJ software (version 1.48v, NIH, Bethesda, MD) with a Windows operating system. Proliferation index Ki67, cell count, and microvessel density were semiautomatically estimated by using the program. Proliferation index (Ki67-index) was calculated as percentage of stained nuclei on the MIB-1 stained specimens, as reported previously [10]. The area with the highest number of positive tumor nuclei was selected for the analysis. Cell count was defined as a number of all nuclei on the MIB-1 stained specimens. Microvessel density was calculated as number of CD31 stained areas according to the description by Weidner et al. [19]. In every case, all histopathological parameters were estimated per two high power fields a 0.16 $mm^2$. **Figure 2** displays control histopathological images.

*Statistical analysis*

For statistical analysis the SPSS statistical software package was used (SPSS 20, SPSS Inc., Chicago IL, USA). Collected data were eval-

**Table 1.** Correlations between histogram parameters derived from T2 weighted images and histolopathologic features

| | | Cell Count | Total nucleic area | Average nucleic area | Ki67-index | Weidner Count |
|---|---|---|---|---|---|---|
| T2_Mean | ρ (rho) | 0.294 | 0.032 | -0.412 | 0.085 | -0.201 |
| | P | 0.252 | 0.903 | 0.101 | 0.746 | 0.439 |
| T2_Min | ρ (rho) | 0.015 | 0.365 | 0.245 | 0.250 | 0.181 |
| | P | 0.955 | 0.149 | 0.343 | 0.332 | 0.486 |
| T2_Max | ρ (rho) | 0.294 | -0.015 | -0.478 | -0.092 | -0.154 |
| | P | 0.252 | 0.955 | 0.052 | 0.725 | 0.554 |
| T2_P10 | ρ (rho) | 0.319 | 0.137 | -0.262 | 0.036 | -0.012 |
| | P | 0.213 | 0.599 | 0.309 | 0.892 | 0.963 |
| T2_P25 | ρ (rho) | 0.270 | 0.108 | -0.319 | 0.145 | -0.184 |
| | P | 0.295 | 0.680 | 0.213 | 0.579 | 0.480 |
| T2_P75 | ρ (rho) | 0.397 | 0.076 | **0.502** | 0.000 | -0.208 |
| | P | 0.115 | 0.772 | **0.040** | 1.000 | 0.422 |
| T2_P90 | ρ (rho) | 0.419 | 0.078 | **0.517** | -0.090 | -0.164 |
| | P | 0.094 | 0.765 | **0.034** | 0.732 | 0.529 |
| T2_Median | ρ (rho) | 0.328 | 0.074 | -0.429 | 0.102 | -0.255 |
| | P | 0.198 | 0.779 | 0.086 | 0.697 | 0.323 |
| T2_Mode | ρ (rho) | 0.418 | 0.163 | -0.383 | 0.135 | -0.271 |
| | P | 0.095 | 0.532 | 0.130 | 0.605 | 0.293 |
| T2_SD | ρ (rho) | 0.260 | -0.145 | **0.637** | -0.182 | -0.343 |
| | P | 0.314 | 0.580 | **0.006** | 0.485 | 0.178 |
| T2_Kurtosis | ρ (rho) | -0.112 | -0.281 | 0.076 | -0.388 | 0.246 |
| | P | 0.670 | 0.275 | 0.772 | 0.124 | 0.340 |
| T2_Skewness | ρ (rho) | -0.350 | 0.118 | **0.608** | -0.113 | **0.544** |
| | P | 0.168 | 0.653 | **0.010** | 0.666 | **0.024** |
| T2_Entropy | ρ (rho) | 0.289 | 0.431 | 0.034 | 0.430 | -0.088 |
| | P | 0.260 | 0.084 | 0.896 | 0.085 | 0.736 |

Significant associations are highlighted in bold. ρ: Spearman's rho. P: significance for 95% CI.

uated by means of descriptive statistics (absolute and relative frequencies). Categorical variables were expressed as percentages. Group comparisons were performed by means of two sided Mann-Whitney-U-tests. Spearman's correlation coefficient was used to analyze the association between histogram parameters and histological parameters. *P*-values < 0.05 were taken to indicate statistical significance in all instances.

## Results

The **Table 1** summarizes results of the correlation analysis. None of the histogram analysis parameters correlated statistically significant with tumor cellularity. Only P90 and mode tended to correlate with cell count. Similarly, there were no significant correlations between the imaging parameters and Ki67.

Significant correlations were identified between average nucleic area and P75 (P = 0.50, P = 0.04), P90 (P = 0.52, P = 0.03), standard deviation (P = 0.64, P = 0.006) as well as skewness (P = 0.61, P = 0.01).

Only skewness was associated with microvessel density (P = 0.54, P = 0.02).

## Discussion

This present study found that histogram parameters derived from T2w images are associated with average nucleic size and microvessel density in rectal cancers. To the best of our knowledge, no previous reports compared directly histopathology with imaging parameters retrieved from conventional sequences in rectal cancer to date.

As mentioned above, there is increasing evidence that MRI cannot only provide morphological information regarding tumor localization, infiltration of the adjacent structures and possible metastatic spread but it can also give insight into tumor microstructure, such as cellularity, perfusion and other, clinically important histopathological parameters [10].

For example, it was shown that ADC values were moderately associated with cellularity and Ki67 index in various tumors [3, 4, 10]. Furthermore, DCE-MRI can reflect microvessel density [9]. Additionally, some reports suggested that other clinically relevant histopathological parameters, such as Hif1-alpha, VEGF and Her2-status can also be reflected by DWI and DCE-MRI [20-22].

It is not thought that MRI, analyzed by histogram or texture analysis, can replace histopathology but it might be the only modality that can display the whole tumor, whereas histopathology is obtained only by small bioptic specimens and, therefore, might not reflect the whole lesion. Moreover, MRI can be obtained sequentially and non-invasively, contrary to histopathology. Based upon these facts, MRI might play a greater role in oncologic routine in the future. Previously, most reports studies studied histogram analysis parameters retrieved from ADC maps in different malignant and benign lesions. For example, it has been shown that ADC histogram analysis can provide detailed information about tumor behavior and, therefore, can be used for prognosis assessment [23].

To date, only few reports investigated histogram and texture analysis of conventional MR images in rectal cancer [24-28]. For example, Kluza et al. investigated T2w signal intensities of rectal cancers with a histogram based approach [26]. A high accuracy could be identified for prediction of treatment response to radiochemotherapy for several histogram parameters [26]. Furthermore, the authors found that the calculated histograms were progressively negatively skewed after radiochemotherapy [26]. In another study, which used texture analysis derived from T2w images for prediction of treatment response to radiochemotherapy, skewness was the only significant parameter in the univariate analysis for prediction of overall survival, emphasizing its possible importance as a novel biomarker [24]. Furthermore, texture analysis could better identify T-stages in rectal cancer [27] and can be used for prognosis [28].

The present study showed that T2w histogram parameters might be able to reflect the underlying histopathology in rectal cancer. At the first time, our study identified associations between skewness derived from T2w images and microvessel density. According to the literature, microvessel density is a prognostic factor in colorectal cancer and is significantly related to sensitivity for chemoradiotherapy [29, 30]. Therefore, prediction of this parameter by MRI is very important.

Furthermore, we identified that P75, P90, standard deviation and skewness correlated with average nucleic area. In addition, P90 and mode tended to correlate with tumor cellularity. Finally, entropy tended to correlate with expression of KI67. Previously, only few studies analyzed associations between signal intensity on T1w and/or T2w images and histopathology in several tumors. For example, in cerebral lymphomas, maximum signal intensity of FLAIR sequence was associated with cell count [14]. Moreover, several texture analysis parameters of T1- and T2w images correlated with Ki67 index, p53 expression and nucleic areas in thyroid cancer [13].

There are several limitations of the present study. Firstly, it is a retrospective study with possible known bias. However, the histopathology and imaging analysis was conducted independently and blinded to each other. Secondly, the patient sample is relatively small. Thirdly, the MRI was performed as a whole lesion measurement, whereas the histopathology was investigated by a bioptic specimen, which might not be representative for the whole tumor.

In conclusion, this study showed that different parameters of histogram analysis of T2w images can reflect several histopathological features in rectal cancer. Skewness canpredict microvessel density. Furthermore, P75, P90, standard deviation and skewness correlated with average nucleic area. In addition, P90 and mode tended to correlate with tumor cellularity. Finally, entropy tended to correlate with expression of KI67.

## Disclosure of conflict of interest

None.

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