Diffusion-Weighted Magnetic Resonance Imaging of 103 Patients with Rectal Adenocarcinoma Identifies the Apparent Diffusion Coefficient as an Imaging Marker for Tumor Invasion and Regional Lymph Node Involvement

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Background: This retrospective study included 103 patients diagnosed with rectal adenocarcinoma at a single center in Poland who underwent preoperative diffusion-weighted magnetic resonance imaging (DWI) and aimed to determine whether the apparent diffusion coefficient (ADC) was an imaging marker for tumor invasion and regional lymph node involvement.

Material/Methods: We analyzed primary staging magnetic resonance examinations of the rectum of 103 consecutive patients with histologically proven non-mucinous adenocarcinoma who underwent surgical treatment. In 85 patients, surgery was preceded by long-course chemoradiotherapy (n=18) or short-course radiotherapy (n=67). The following DWI parameters were measured: ADC mean, minimum, maximum, and standard deviation in the region of interest (ADC SD-in-ROI). Values were compared between subgroups based on histological parameters from the report: tumor stage, lymph node stage, differentiation grade, the presence of extranodal tumor deposits, angioinvasion, and perineural invasion. Statistical analysis was performed using the Mann-Whitney U test and the unilateral t test.

Results: ADC mean values were lower for cases in which postoperative histopathological examination lymph node invasion (P=0.04) and tumor deposits were found (P=0.04). Minimal ADC value was higher in cases in which tumor deposits were not found (P=0.009). ADC SD-in-ROI values were lower in cases in which lymph nodes invasion was confirmed (P=0.014). There were no statistically significant differences for other parameters.

Conclusions: The ADC values in pre-treatment DWI in patients with rectal adenocarcinoma were correlated with tumor invasion and regional lymph node metastases. Therefore, ADC values from the pre-treatment MRI may help plan adjuvant therapy in patients with rectal adenocarcinoma.

Keywords: Diffusion Magnetic Resonance Imaging • Rectal Neoplasms • Biomarkers, Tumor

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Background

The incidence of rectal cancer is predicted to increase, both in men and women. This incidence is currently estimated at 125,000 cases per year (15-25 cases in a population of 100,000) in European Union countries [1]. Basic diagnosis involves digital rectal examination followed by endoscopy with biopsy for histopathological confirmation. Other methods, including endorectal ultrasound (ERUS), magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET/CT), are applied in local and distant tumor staging [2]. Both ERUS and MRI are useful for rectal cancer local staging. While ERUS is useful in treatment planning for early detected tumors, MRI has high accuracy in defining regional clinical staging of all rectal tumors [1]. MRI is crucial in primary rectal cancer assessment because of its ability to provide high-resolution images of the tumor and other organs of the pelvis, including mesorectal fascia and peritoneal reflection for primary tumor (T) stage assessment and lymph node visualization for primary lymph node (N) staging [3]. According to prospective multicenter study results, there are features of cancer aggressiveness that proved to predict outcome, including the circumferential resection margin, extramural vascular invasion (EMVI), depth of extramural invasion, extramural tumor deposits, mucin presence, and tumor regression grade to preoperative treatment [4,5]. The presence of these features influences overall and disease-free survival rates [2].

Histopathological examination remains the criterion standard in determining the effectiveness and completeness of treatment as well as in specifying important prognostic factors, and there are no imaging modalities available today that can determine the presence of prognostic factors identified in histopathological examination with 100% certainty [6].

However, the study conducted almost 20 years ago by Brown et al showed that some surgical and pathological prognostic risk factors can be accurately identified by rectal MRI [7]. Technological development of MRI devices brings constant improvement in spatial resolution and signal contrast of new sequences, simultaneously reducing examination time because of shortened sequence duration [3]. Newly designed sequences enable the obtaining of functional or structural data related to a specific tissue [8]. A growing role of diffusion-weighted imaging (DWI), as a standard sequence in MRI of the pelvis, has been noted over the past years [9]. This advanced technique, based on quantifying the movement of water molecules at the cellular level, had been a well-established complement to standard sequences in neurological MRI and is currently also applied in abdominopelvic imaging [10]. In preoperative staging, DWI proved to be effective in detecting lymph nodes [11,12]. During post-radiation reassessment, DWI helps to determine the presence of residual tumor in fibrotic tissues [1]. Over the years, the focus of the role of DWI has moved from the qualitative, visual assessment of rectal cancer for staging or treatment response toward quantitative assessment [13]. Many publications have been devoted to the application of the main DWI measure, the apparent diffusion coefficient (ADC) [14,15].

Defining the factors that indicate a high risk of fast progression or low treatment responsiveness poses another challenge. The search for new markers which may facilitate infiltration character recognition, prediction of treatment response, recurrence risk, tendency to adjacent tissue invasion, and probability of distant metastasis is ongoing [16]. The present study investigated the significance of ADC values as imaging markers to identify aggressive rectal cancer, defined as a tumor with metastatic potential (lymph node metastasis and tumor deposits in adjacent fat tissue), and evaluated whether ADC values contribute to predicting lymph node metastasis.

The quantification of rectal tumor diffusion by measuring the ADC has proven reliable as an imaging biomarker [17,18]. Sun et al evaluated ADC as a potential imaging biomarker that reflects the biological features of rectal cancer, such as tumor stage, extranodal tumor deposits, and pre-treatment CEA or CA19-9 levels [17]. Curvo-Semedo et al [18] and Rao et al [19] also verified the usefulness of DWI in rectal cancer and evaluated whether ADC can be used as a noninvasive marker of tumor aggressiveness.

We conducted this study to determine if the ADC values of mean, minimum, maximum, and standard deviation in the region of interest (ADC SD-in-ROI) depend on the features defined in a histopathological examination of postoperative material, namely histological tumor and node stage, histological grade, the presence of extranodal tumor deposits, angioinvasion, perineural invasion, and the depth of mesorectal invasion for T3 tumors.

Our study is similar to previous studies; however, we conducted this study in a larger group of patients and measured the additional ADC values of minimum, maximum, and ADC SD-in-ROI. We performed our measurement manually, without additional software. Therefore, our observations can be easily and widely applied in clinical practice. In contrast to previous studies, we also checked if there is a relationship of ADC values with perineural invasion and the depth of mesorectal invasion of over 5 mm for stage T3 tumors.

This retrospective study included 103 patients diagnosed with rectal adenocarcinoma who underwent preoperative DWI at a single center in Poland and aimed to determine whether the ADC was an imaging marker for tumor invasion and regional lymph node involvement.
Material and Methods

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki. Ethics approval from the Bioethical Committee at the Regional Medical Chamber in Rzeszów was obtained on May 24, 2021. Informed consent was obtained from all participants involved in the study.

Study Design and Patient Selection

This was a single-center retrospective study. Clinical and imaging data were retrieved from the patient database. MRI images were obtained from the picture archiving and communication system. The medical records of 205 patients who underwent an MRI examination of the rectum between 2014 and 2020 were analyzed. Patients with incomplete MRI data (motion artifacts, lack of DWI sequences) or histopathological analyses were excluded. A total of 112 consecutive patients diagnosed with rectal cancer by colon biopsy who were surgically treated and had available histopathological specimen analysis results were selected.

Rectal cancer was defined as cancer that arose below the sigmoid take-off and in the distal 15 cm of the intestinal tract, as measured to or from the anal verge. Patients with cancers other than adenocarcinoma (n=2) and rectosigmoid cancers (n=4) were excluded from the study. We also excluded 3 patients with mucinous adenocarcinoma because of the controversial use of DWI in mucinous tumors [20]. Finally, statistical analysis was performed in the group of 103 consecutive patients with histologically proven non-mucinous adenocarcinoma of the rectum, including 64 men (62%) and 39 women (38%). Most patients were over 60 years old (71%), with a median age of 64 years (range, 39-84 years).

Magnetic Resonance Imaging

All patients underwent a primary staging MRI with a 1.5T MRI machine (Avanto, Siemens) using a phased-array body coil. The patients did not receive any bowel preparation. To reduce artifacts from peristaltic movement, an intravenous bolus injection of 20 mg of butylscopolamine was administered. The standard imaging protocol included 2-dimensional T2-weighted image (T2WI) fast spin-echo sequences in 3 orthogonal planes. The tumor axis was identified on the sagittal scan. The transverse images were angled perpendicularly, and the coronal images were parallel to the tumor axis. An axial echo-planar imaging DWI sequence was angled on the same plane as the transverse T2WI. The DWI sequence was performed with spectral attenuation recovery fat suppression with b values of 0, 300, 700, and 1000 s/mm²; TR/TE of 6000/86 ms; number of slices 30 to 35; and slice thickness 5 mm. ADC maps were automatically generated by the operating system using a mono-exponential decay model including all 4 b values.

ADC Value Measurement

The assessment of radiological images was done independently by 2 experienced radiologists and a radiology trainee. Medixant RadiAnt DICOM Viewer (version 2020.2.3) software was used. No additional specialized software was needed for our measurements. The readers were blinded to the patients’ clinical data and pathology report results. The following DWI parameters were measured: ADC mean, minimum, maximum, and SD-in-ROI. The interobserver agreement was very good, and the deviations in measured values between observers did not exceed 5%. The almost perfect agreement between radiologists using DWI was reported in the study by Rosa et al [21]. To simplify the calculations and statistical analysis, the mean of the measured values were assumed.

T2WIs were used for anatomical reference. To measure the ADC mean, maximum, and SD-in-ROI values on an MRI, the round ROI of about 1 cm² (26-28 px) was drawn within the inner border of the tumor on the single axial DWI ADC map. Radiologists selected the appropriate cross-section to fit the entire ROI circle within the tumor tissue and to achieve the lowest possible SD value. The process is presented in Figure 1, where MRI T2WI shows the thickened rectal wall in the axial and sagittal planes. Axial DWI b=1000 s/mm² images and corresponding ADC maps show restriction of water diffusion, the sign of malignancy. The ROI is placed within the tumor tissue and the ADC values are shown.

The region of minimum ADC was visually determined as the brightest region of the tumor on the axial (b=1000 s/mm²) image and by radiologists and was covered with a round- or oval-shaped ROI. Axial T2WIs were used to confirm the location within the tumor borders. The software automatically mapped the ROI onto the corresponding ADC map for minimum ADC value reading. The b value of 1000 s/mm² was the highest available value for the pre-defined study protocol for rectal for our MRI system. Figure 2 presents the ROI placed within the tumor tissue in the visually indicated brightest tumor region. Software mapped the ROI onto the ADC map. The location within the tumor was confirmed on the sagittal T2WI. The methods of measurement used in our study were similar to those used by other investigators [18,22].

Histopathological Analysis

Histological examination of the resected surgical specimens was used as the standard evaluation for confirmation of tumor type, tumor grade, and as part of the staging process. In
each case, the pathology reports were reviewed to confirm the tumor (T) and node (N) stage, differentiation grade, peritumoral-intravascular cancer emboli, the presence of extranodal tumor deposits, angioinvasion, and perineural invasion. The pathological TN-metastasis (M) stage was determined according to the 8th American Joint Committee on Cancer, with the assessment of the depth of mesorectal infiltration (T3 substages). Patients with stage T3 were divided into 2 groups based on whether the depth of mesorectal invasion exceeds 5 mm (T3 a/b vs c/d). Subclassification of T3 rectal cancer was obtained from the European Society for Medical Oncology guidelines [1] but was not validated or incorporated in any TNM versions. Based on histopathological analysis, the rectal cancers were divided into well- (G1), moderately (G2), and poorly (G3) differentiated.

### Statistical Analysis

MRI results were compared with the histopathology results. Values were compared between subgroups based on the statistical analysis, which was performed with Statistica software (version 13.3, TIBCO Software Inc). Depending on the presence of a specific feature, patients were divided into subgroups. First, conformity of particular variables to a normal distribution was tested. Normality was verified with the Kolmogorov-Smirnov and Shapiro-Wilk tests. The results are presented in Table 1. If the distribution appeared to be not normal (P≤0.05), nonparametric methods were applied to test hypotheses (variable comparison). The Mann-Whitney U test was used to define the relationships between ADC minimal values, ADC SD-in-ROI, and selected parameters. Values were compared between subgroups based on histological parameters obtained from the report. The unilateral t test was used to determine the relationship between mean ADC values. Due to heterogeneity of variances in particular groups, to verify the hypothesis of the relationship of ADC mean values with a histopathological grade of lesion, the Kruskal-Wallis test was used as a condition for the application of variance analysis. Statistical significance was defined as a P≤0.05.
Results

Initial Staging

Rectal cancer was diagnosed and treated with primary or secondary surgery in 103 patients. The initial tumor stage on MRI was cT1-2 in 30 (29%) patients, cT3 in 56 patients (54%), and cT4 in 17 patients (17%). Thirty-eight patients (37%) had stage cN0 and 65 (63%) had cN+. Fourteen patients (14%) had distant metastases. The MRI presence of EMVI was observed in 33 (32%) patients.

Patients Treatment and Histopathological Results

Within the group, 85 patients with non-locally advanced tumors underwent surgery without neoadjuvant treatment (33 patients) or, immediately after surgery, received a short course of radiotherapy 5×5 Gy (52 patients). Eighteen patients with locally advanced disease underwent a long course of conformal radiotherapy (28×1.8 Gy radiotherapy with 2×825 mg/m²/d capecitabine). All 103 patients included in the study underwent surgery: 44 patients underwent the Miles procedure and 57 underwent the Hartmann/Dixon procedure. Histopathological

Table 1. Conformity of particular variables to normal distribution. Apparent diffusion coefficient, the standard deviation in the region of interest. Microsoft Corporation, Microsoft Word 2013 (version 15.0.5389.1000).

| Variable                  | Kolmogorov-Smirnov test | Shapiro-Wilk test | Variable distribution |
|---------------------------|-------------------------|-------------------|-----------------------|
| ADC mean value            | d=0.07, p>0.2           | W=0.98, p=0.21    | Normal                |
| ADC SD-in-ROI             | d=0.11, p<0.15          | W=0.95, p=0.0006  | Not normal            |
| ADC minimum value         | d=0.07, p>0.2           | W=0.97, p=0.017   | Not normal            |
| ADC maximum value         | d=0.09, p>0.2           | W=0.96, p=0.008   | Not normal            |

ADC – apparent diffusion coefficient; SD-in-ROI – standard deviation in the region of interest.

Figure 2. Magnetic resonance (MRI) scans in a 63-year-old woman with rectal cancer. A thickened rectal wall on (A) axial MRI T2-weighted image (arrow). High signal on (B) diffusion weighted image b=1000 s/mm², and (C) low signal on corresponding apparent diffusion coefficient (ADC) map indicates the presence water diffusion restriction, the feature of malignancy. The visually determined brightest region within the tumor on (B) axial b=1000 s/mm² image (the circle) and (C) the reading of minimum ADC value on corresponding ADC map in the region of interest (ROI) (black arrow). Medixant, RadiAnt DICOM Viewer (version 2020.2.3).
analysis revealed that 35 (34%) patients had grade G1, 61 (59%) patients had grade G2, and 7 (7%) patients had grade G3. Perineural invasion on histopathology was found in 31 (30%) patients. Angioinvasion was diagnosed in 32 (31%) patients. Positive lymph nodes were found in 42 (41%) patients, while tumor deposits were present in 33 (32%) patients. Cancer T stage was determined as pT1 in 5 (5%) patients, pT2 in 25 (24%) patients, pT3 in 59 (57%) patients, and the highest, pT4, in 14 (14%) patients. For pT3 patients, depth of mesorectal invasion exceeding 5 mm was diagnosed in 22 (21%) patients, while it was lower than 5 mm in 37 (36%) patients.

**Relationship of ADC Values with Histopathological Findings**

The analysis revealed a statistically significant relationship in which ADC mean values were lower for patients in whom postoperative histopathological examination tumor deposits were found (unilateral t test, median±SD, 758.74±122.94×10⁻³ mm²/s vs 804.81±117.91×10⁻³ mm²/s, P=0.04). ADC mean values were also lower for the patients with lymph node metastasis (unilateral t test, mean±SD, 767.71±115.57×10⁻³ mm²/s vs 809.97±121.52×10⁻³ mm²/s, P=0.04).

The ADC minimal value was higher when tumor deposits were found in postoperative specimens than when tumor deposits were not found (Mann-Whitney U test=2.625, median 564.50×10⁻³ mm²/s vs 521.00×10⁻³ mm²/s, P=0.009). Higher ADC minimal values were associated with a smaller probability of tumor deposit presence. A subsequent relationship observed was that ADC SD-in-ROI values were lower in patients in whom lymph node invasion was confirmed (Mann-Whitney U test=-2.460, median 95.00 vs 114.00, P=0.014). The relationships described above are presented in **Figure 3A-3D**.

**Figure 3.** Statistically significant relationship between (A) apparent diffusion coefficient (ADC) mean and the presence of tumor deposits, (B) ADC mean and lymph node metastases, (C) ADC minimum value and the presence of tumor deposits, and (D) standard deviation in region of interest (SD-in-ROI) and lymph nodes metastases. TibCO Software Inc, Statistica (version 13.3).

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There were no other statistically significant differences in ADC mean, maximum, minimum, and ADC SD-in-ROI values for other investigated parameters. We did not find a dependence between ADC values and lesion histopathological grade (Figure 4A, 4B).

Lower ADC mean values within a distinguished part of the tumor were related to the presence of histopathological features considered as adverse prognostic factors. Such a relationship occurred with vascular invasion (angioinvasion diagnosed on histopathological examination and EMVI diagnosed on MRI) and the invasion of the mesorectum of over 5 mm beyond the rectal wall for T3 cancers. In patients with perineural invasion, ADC mean values and ADC minimal values were higher than in patients in whom such a feature was not found. However, the difference was not statistically significant.

Based on ROC analysis, it can be stated that the ADC mean value may be used for prediction of mesorectal invasion status and cancer stage pT1-2 vs pT3-4 (P=0.041). When the ADC mean value was below $776 \times 10^{-3}$ mm$^2$/s, cancers of a higher stage were recognized with 60% sensitivity, 67.2% specificity, and 64.1% accuracy, with an area under the ROC curve (AUC) of 0.615. Based on maximum and minimum ADC values, and in accordance with ROC analysis, verification of lesion malignancy degree was not possible (P>0.09). The results are presented in Table 2.

**Discussion**

The results of our study suggest that ADC values of rectal cancer can be used as imaging markers to predict the presence of tumor deposits and lymph node metastases. ROC analysis results suggest that the ADC values can be used for prediction of T stage and mesorectal invasion status. Several studies have shown that new MRI techniques can provide morphological and functional parameters that can be correlated with measurements of tumor biology [23-25]. DWI for rectal cancer has been the subject of many scientific studies over the last 10 years, with over 150 publications pertaining to this issue. While some publications focused entirely on the technical aspects, others described the results of diverse studies, ranging from pre-clinical to major multicenter clinical cohort studies [13].
Incorporating DWI into clinical practice has been a growing topic in recent years. The routine application of DWI for rectal cancer restaging has been recommended by the expert consensus guidelines of the European Society of Gastrointestinal Abdominal Radiology (ESGAR) [9]. Currently, the most significant benefits of DWI use in practice are evident in the visual assessment of residual tumors in post-radiation fibrosis [13,26]. Based on the evidence available to date, there are no clear additional benefits of DWI for other indications, such as primary T staging, (y)N staging, assessment of mesorectal fascia involvement, and EMVI. Nevertheless, some ESGAR experts claimed that DWI sequences can be beneficial for individual cases and thus should be performed [9]. Currently, as there are no standardized protocols and approved thresholds, the DWI images (and ADC maps) are assessed only qualitatively in clinical practice. While the use of DWI has been undergoing a rapid evolution in the last years, the first promising results have been reported for quantitative DWI analysis, but they should be confirmed on a larger number of patients [27,28]. The numerical values obtained with DWI can be used to predict the response to neoadjuvant treatment and overall tumor behavior. However, to be used in routine rectal cancer assessment, the protocols need to be standardized. It seems that the level of disruption of free water movement at the cellular level correlates with tumor aggressiveness. Lower ADC values were observed in cancers demonstrating histopathologic features considered as adverse prognostic factors. A study by Peng et al indicates that reduced field of view using a 3T magnetic field can differentiate the histologic malignancy grade of rectal carcinomas [29]. In the present study, we did not find a statistically significant relationship between ADC values and histological grade. In contrast, our study was performed on an older 1.5T device using standard DWI sequences. A very recent study conducted by Nerad et al investigated the differences between the mean ADC value of advanced vs early colon cancers. The ADC value of the primary tumor can be used to predict advanced cancer with distant metastases and lymph nodes with a sensitivity and specificity of 81% and 86%, respectively, an AUC of 0.83, and a cut-off value of 1179×10^{-3} mm²/s [14]. The present study shows, based on ROC analysis, that ADC mean value could also be used for the prediction of mesorectal invasion and was able to predict cancer stage of pT1-2 vs pT3-4. Unfortunately, the sensitivity and specificity in the present study were lower than those presented by Nerad et al [14], which may have been caused by single-slice analysis in contrast to a whole tumor volume measurement.

ADC parameters can be acquired either from a single slice of the tumor, a tumor sample, or the whole tumor volume [22]. Delineation of the tumor margins can be performed manually and automatically. According to Schurink et al, manual segmentation of rectal tumors is labor-intensive and time-consuming and often requires a high level of experience [13]. The measurements in our study were performed on a single slice instead of the whole tumor volume. A study from Lambregts et al demonstrated that ADC values obtained from the whole tumor volume provide the most reproducible results. Based on the observations from their study, the small sample ROI may have resulted in lower ADC values, which can be caused by the inclusion of only the most viable solid parts of the tumor, skipping the regions of necrosis [22].

Interobserver agreement between radiologists was an important factor which required consideration when planning our study. However, the differences in values measured by the independent radiologists did not vary more than 5%. Rosa et al also found that DWI results in a high level of agreement between observers [21].

Several studies have shown that the ADC values used in the quantitative assessment of rectal tumor diffusion can be considered imaging biomarkers. Also, ADC values could be beneficial in predicting prognostic factors such as nodal stage, mesorectal fascia involvement, and histological differentiation grade [18,19].

The next factor to consider is the use of an ultrahigh b value (b=2000 s/mm²). Delli Pizzi et al [30] stated that ultrahigh values can improve rectal cancer interobserver agreement and conspicuity, maintaining comparable diagnostic accuracy to a standard b=1000 s/mm² value DWI. They found ultrahigh b values offered a lower mean signal intensity of the surrounding tissues and a more uniform signal of tumor and healthy structures.

Yiqun Sun et al also evaluated the ADC as a potential imaging marker reflecting the biological features of rectal cancers [17]. In their study, 49 patients with rectal cancer who received surgical resection without neoadjuvant therapy were selected and underwent primary MRI and DWI. ADC values were determined and correlated with biochemical biomarkers (such as pre-treatment CEA or CA19-9 levels), and/or the histological and immunohistochemical properties of the tumor. The mean ADC value was significantly lower in the case of extranodal tumor deposits (P=0.006) and lymph node involvement between N0, N1, and N2 categories (P=0.055). The authors also evaluated the relationship between ADC mean values, histological grade, angioinvasion, and perineural invasion, and the differences were not significant (P=0.515, P=0.061, and P=0.890, respectively). Their results agree with the results of the present study.

The assessment of N staging remains one of the biggest challenges for radiologists [24]. According to meta-analyses and population data, N staging using only node size >10 mm as a criterion for the node-positive disease has been shown to be inaccurate, despite using ERUS, CT, and MRI combined [7]. Currently, the standard procedure involves determining lymph nodes with a sensitivity and specificity of 81% and 86%, respectively, an AUC of 0.83, and a cut-off value of 1179×10^{-3} mm²/s [14].
node size and morphological features, such as shape, borders, and homogeneity. Although diffusion imaging is characterized by high sensitivity in lymph node detection, it is not always able to differentiate between normal and infectious lymph nodes and those containing cancer cells [31]. Therefore, the search for biomarkers that can predict lymph node invasion is ongoing. For example, in the study conducted by Chen et al [32], the DWI-based value was identified as an independent risk factor for lymphovascular invasion (odds ratio [OR], 1.207; \( P=0.005 \)) and lymph node metastasis (OR, 1.420; \( P=0.005 \)) [32].

Our analysis revealed a statistically significant relationship: ADC mean values were lower for patients in whom postoperative histopathological examination of lymph node invasion and tumor deposits were found (\( P=0.04 \) for both relationships). Our results are similar to those obtained by Schurink et al and indicate the potential of the assessment of the nodal component in tumor staging [13]. We also found that when tumor deposits were found in postoperative specimens, the minimal ADC value was statistically significantly higher than in those in which tumor deposits were not found (\( P=0.009 \). Therefore, higher ADC minimal values indicated a smaller probability of incidence of tumor deposits. These results agree with the observations of Sun et al [17]. In the present study, we also found that there was a higher incidence of perineural invasion in patients with higher mean ADC values. Despite the low statistical importance of this relationship, we can assume with some likelihood that higher ADC values and the related increase in uninhibited movement of water molecules (lower cellularity) may be a predisposition to perineural invasion rather than to lymphovascular invasion and angioinvasion.

Mean and median ADC values are the most commonly used ADC parameters [23]. Unfortunately, because of rectal tumor heterogeneity, these values might not always be representative. Histogram analysis is a novel analysis tool which allows for the assessment of the entire spectrum of ADC values within a tumor, enabling not only mean (or median) values, but also parameters such as the minimum and maximum, standard deviation, and different percentile ranges to be obtained [33]. The novel, advanced analysis of the whole tumor parameters, such as the diffusion kurtosis MRI histogram, shows the positive relationship between ADC values and some prognostic factors, such as nodal involvement and presence of lymphangiovascular invasion [17]. Unfortunately, based on the limited available evidence, Lu W et al emphasized that most investigators stated that histogram parameters did not significantly outperform median or mean ADC values [23].

New MRI techniques provide novel radiological biomarkers that can be valuable tools for response prediction and for overall tumor prognostication, further improving the selection of tailored treatment. ADC tumor values can help identify patients potentially eligible for neoadjuvant treatment using not only qualitative but also quantitative biomarkers. Post-processing tools and analysis methods are still being developed to improve the precision of evaluation. The predictive values and the usefulness of biomarkers are continually being checked. The role of these tools remains to be established.

Limitations

There are several limitations in our study. First, it was a single-center study conducted on a relatively small group of patients. For routine use, the results need to be confirmed in a larger group of patients. Second, the measurements were performed on a single slice of tumor. The evaluation of the whole tumor volume would provide higher accuracy and repeatability across centers. Although our measurement method was simple, widely available, and easy to implement, it was operator-dependent, and thus result bias is possible. To ensure reproducible results, the study should be performed with automated tools. Third, our study group was heterogeneous and comprised patients who varied in terms of sex, age, and T stage. In the future, it would be worth checking if the results are consistent in a selected group of patients. Fourth, our study was a retrospective design, and the data availability was limited. A prospective study would allow for more MRI sequences to be performed; for example, the DWI sequence in the coronal plane. Finally, the length of time between MRI and surgery varied among patients. Some patients underwent surgical treatment a few days after preoperative examination, whereas others underwent neoadjuvant radiotherapy or radiochemotherapy. Only a few patients had MRI examinations for restaging after neoadjuvant treatment; therefore, the data for assessing the relationship between ADC values and treatment response, for example, was not available.

Conclusions

The findings from this retrospective study from a single center in Poland showed that ADC values in pre-treatment DWI in patients with rectal adenocarcinoma were correlated with tumor invasion and regional lymph node metastases. Therefore, ADC values from pre-treatment MRI may help plan adjuvant therapy in patients with rectal adenocarcinoma.

Department and Institution Where Work Was Done

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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