Pretreatment Apparent Diffusion Coefficient Cannot Predict Histopathological Features and Response to Neoadjuvant Radiochemotherapy in Rectal Cancer: A Meta-Analysis

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Keywords
Rectal cancer · Diffusion-weighted imaging · Apparent diffusion coefficient · Magnetic resonance imaging

Abstract
Aim: Our purpose was to perform a systemic literature review and meta-analysis regarding use of apparent diffusion coefficient (ADC) for prediction of histopathological features in rectal cancer (RC) and to prove if ADC can predict treatment response to neoadjuvant radiochemotherapy (NARC) in RC. Methods: MEDLINE library, EMBASE, Cochrane, and SCOPUS database were screened for associations between ADC and histopathology and/or treatment response in RC up to June 2020. Authors, year of publication, study design, number of patients, mean value, and standard deviation of ADC were acquired. The methodological quality of the collected studies was checked according to the Quality Assessment of Diagnostic Studies instrument. The meta-analysis was undertaken by using the RevMan 5.3 software. DerSimonian and Laird random-effects models with inverse-variance weights were used to account the heterogeneity between the studies. Mean ADC values including 95% confidence intervals were calculated. Results: Overall, 37 items (2,015 patients) were included. ADC values of tumors with different T and N stages and grades overlapped strongly. ADC cannot distinguish RC with a high- and low-carcinoembryonic antigen level. Regarding KRAS status, ADC cannot discriminate mutated and wild-type RC. ADC did not correlate significantly with expression of vascular endothelial growth factor and hypoxia-inducible factor 1a. ADC correlates with Ki 67, with the calculated correlation coefficient: −0.52. The ADC values in responders and nonresponders overlapped significantly. Conclusion: ADC correlates moderately with expression of Ki 67 in RC. ADC cannot discriminate tumor stages, grades, and KRAS status in RC. ADC cannot predict therapy response to NARC in RC. © 2021 The Author(s)

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Introduction

Rectal cancer (RC) is one of the most frequent cancers worldwide and the second leading cause of oncologic-related mortality around the globe [1]. Magnetic resonance imaging (MRI) plays an important role in staging of RC [2, 3]. For instance, Faletti et al. [4] showed that MRI has a high accuracy for tumoral (T) staging in RC [3].

Furthermore, MRI can not only detect RC but also characterize tumors. Diffusion-weighted imaging (DWI) is a MRI technique based on measure of water diffusion in tissues, and water diffusion is quantified by apparent diffusion coefficient (ADC) [4]. ADC has been shown to inversely correlate with cell count and proliferation activity in benign and malignant lesions [5–7]. Typically, malignant tumors present a higher cell density than benign lesions. Therefore, malignant tumors have lower ADC values in comparison to benign lesions. In fact, ADC can discriminate benign and malignant colorectal lesions [8].

Some authors also indicated that ADC can provide information about immunohistochemical profiling of tumors. So far, ADC has been shown to correlate with expression of hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor (VEGF) in head and neck cancer [9]. In uterine cervical cancer, ADC predicts expression of epidermal growth factor receptor and histone 3 [10]. In RC, it has been published that ADC correlated with expression of Ki 67 [7]. Furthermore, ADC is also associated with expression of epidermal growth factor receptor [11].

Presumably, ADC can also predict treatment outcome in RC. However, the reported data are based on small number of tumors and, therefore, cannot be applied as evident.

The purpose of the present meta-analysis was to analyze associations between ADC and relevant histopathological features like tumor stage, grade, KRAS status, expression of Ki 67, VEGF, and HIF 1a in RC and to question if baseline tumoral ADC can predict response to neoadjuvant radiochemotherapy (NARC) in RC.

Methods

Data Acquisition

MEDLINE library, Cochrane, EMBASE, and SCOPUS databases were screened for associations between ADC parameters and histopathological features (tumor stage, grade, KRAS status, expression of Ki 67, level of carcinoembryonic antigen (CEA), vascular endothelial factor, and HIF 1a) in patients with RC up to June 2020 (Fig. 1). Furthermore, also articles regarding relationships between pretreatment ADC and response to NARC in RC were screened. The following search terms/combinations were used as follows:

“DWI or diffusion weighted imaging or diffusion-weighted imaging or ADC or apparent diffusion coefficient AND rectal cancer OR rectal carcinoma OR rectum cancer OR rectum carcinoma.” In addition, secondary references were manually checked. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used for the research [12].

The primary search identified 2,218 records in PubMed (1,016 records), Cochrane database (n = 8), Scopus database (n = 1,194), and EMBASE database (n = 865). After exclusion of duplicate articles, the abstracts of the remaining 217 items were analyzed according to the following inclusion criteria:

- Data derived from DWI;
- Available mean and standard deviation values of ADC;
- Original studies investigated humans;
- English language.

The following articles were excluded from the analysis:

- Studies unrelated to the research subjects;
- Studies with incomplete data;
- Non-English language;
- Experimental animals and in vitro studies;
- Review, meta-analysis, and case report articles.

Overall, 180 articles were excluded from the analysis, and 37 items meet the inclusion criteria [13–49]. The following data were extracted from the literature: authors, year of publication, study design, number of patients, mean value, and standard deviation of ADC. For analysis of correlation between ADC and histopathological features, a pooled Spearman's correlation coefficient was calculated. The reported Pearson correlation coefficients in some studies were converted into Spearman correlation coefficients according to the previous description [50].

Meta-Analysis

On the first step, the methodological quality of the included 38 studies was checked according to the Quality Assessment of Diagnostic Studies instrument [51] by one observer (A.S.) (Fig. 2). On the second step, the reported DWI values (mean and standard deviation) were acquired. On the third step, the meta-analysis was undertaken by using RevMan 5.3 (RevMan 2014. The Cochrane Collaboration Review Manager Version 5.3). Heterogeneity was calculated by means of the inconsistency index I² [52, 53]. In a subgroup analysis, studies were stratified by tumor type. In addition, DerSimonian and Laird random-effects models with inverse-variance weights were used without any further correction [54] to account for the heterogeneity between the studies. Mean ADC values including 95% confidence intervals were calculated separately for different tumor subgroups.

Results

Studies and Patients

Of the included 37 studies, 20 were retrospective and 17, prospective. In most studies (n = 26, 70%), different 3 T scanners were used. In the remaining 11 studies (30%), MRI was performed on several 1.5 scanners.
Records identified through PubMed database searching ($n = 1,016$)

Additional records identified through other sources
- Scopus database ($n = 1,194$)
- EMBASE ($n = 865$)
- Cochrane database ($n = 8$)

Records after removing of duplicates ($n = 217$)

Records screened ($n = 217$)

Records excluded ($n = 34$) with reasons:
- Review ($n = 25$)
- Non-English language ($n = 6$)
- Case report ($n = 3$)

Full-text articles excluded, with reasons:
- No sufficient results reported ($n = 146$)

Studies included in qualitative synthesis ($n = 37$)

Studies included in quantitative synthesis (meta-analysis) ($n = 37$) comprising 2015 patients with rectal cancer

Fig. 1. PRISMA flowchart of the data acquisition.

Fig. 2. QUADAS-2 quality assessment of the included studies.
| Study or Subgroup | Mean | SE | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|------------------|------|----|--------|--------------------|--------------------|
| **5.1.1 G1**     |      |    |        |                    |                    |
| Akashi 2014 [13] | 0.94 | 0.03 | 3.8%   | 0.94 [0.88, 1.00]  |                    |
| Curvo-Semedo 2012 [20] | 1.31 | 0.01 | 3.8%   | 1.31 [1.29, 1.33]  |                    |
| Elmi 2013 [23]  | 0.89 | 0.03 | 3.8%   | 0.89 [0.83, 0.95]  |                    |
| Gu 2011 [28]    | 0.89 | 0.08 | 3.6%   | 0.89 [0.73, 1.05]  |                    |
| Sun 2014 [43]   | 1.32 | 0.07 | 3.6%   | 1.32 [1.18, 1.46]  |                    |
| Sun 2018 [42]   | 0.65 | 0.02 | 3.8%   | 0.65 [0.61, 0.69]  |                    |
| Surov 2017 [44] | 1.54 | 0.03 | 3.8%   | 1.54 [1.48, 1.60]  |                    |
| Tang 2018 [45]  | 0.79 | 0.04 | 3.7%   | 0.79 [0.71, 0.87]  |                    |
| Xia 2018 [46]   | 0.89 | 0.04 | 3.7%   | 0.89 [0.81, 0.97]  |                    |
| **Subtotal (95% CI)** | 33.6% | 1.02 | 0.80, 1.25 |                    |                    |

- Heterogeneity: Tau² = 0.12; Chi² = 1312.82, df = 8 (P < 0.00001); I² = 99%
- Test for overall effect: Z = 8.89 (P < 0.00001)

| **5.1.2 G2**     |      |    |        |                    |                    |
| Akashi 2014 [13] | 0.91 | 0.02 | 3.8%   | 0.91 [0.87, 0.95]  |                    |
| Curvo-Semedo 2012 [20] | 1.05 | 0.03 | 3.8%   | 1.05 [0.99, 1.11]  |                    |
| Elmi 2013 [23]  | 1.09 | 0.02 | 3.8%   | 1.09 [1.05, 1.13]  |                    |
| Gu 2011 [28]    | 0.84 | 0.08 | 3.6%   | 0.84 [0.68, 1.00]  |                    |
| Sun 2014 [43]   | 1.31 | 0.04 | 3.7%   | 1.31 [1.23, 1.39]  |                    |
| Sun 2018 [42]   | 0.57 | 0.01 | 3.8%   | 0.57 [0.55, 0.59]  |                    |
| Surov 2017 [44] | 1.3 | 0.12 | 3.3%   | 1.3 [1.06, 1.54]   |                    |
| Tang 2018 [45]  | 0.77 | 0.02 | 3.8%   | 0.77 [0.73, 0.81]  |                    |
| Xia 2018 [46]   | 1.13 | 0.03 | 3.8%   | 1.13 [1.07, 1.19]  |                    |
| **Subtotal (95% CI)** | 33.4% | 0.99 | 0.81, 1.18 |                    |                    |

- Heterogeneity: Tau² = 0.08; Chi² = 1135.68, df = 8 (P < 0.00001); I² = 99%
- Test for overall effect: Z = 10.55 (P < 0.00001)

| **5.1.3 G3**     |      |    |        |                    |                    |
| Akashi 2014 [13] | 0.82 | 0.02 | 3.8%   | 0.82 [0.78, 0.86]  |                    |
| Curvo-Semedo 2012 [20] | 1.16 | 0.08 | 3.6%   | 1.16 [1.00, 1.32]  |                    |
| Elmi 2013 [23]  | 0.95 | 0.02 | 3.8%   | 0.95 [0.91, 0.99]  |                    |
| Gu 2011 [28]    | 0.82 | 0.04 | 3.7%   | 0.82 [0.74, 0.90]  |                    |
| Sun 2014 [43]   | 1.2  | 0.08 | 3.6%   | 1.2 [1.04, 1.36]   |                    |
| Sun 2018 [42]   | 0.54 | 0.03 | 3.8%   | 0.54 [0.48, 0.60]  |                    |
| Surov 2017 [44] | 1.07 | 0.13 | 3.2%   | 1.07 [0.82, 1.32]  |                    |
| Tang 2018 [45]  | 0.77 | 0.04 | 3.7%   | 0.77 [0.69, 0.85]  |                    |
| Xia 2018 [46]   | 1.31 | 0.05 | 3.7%   | 1.31 [1.21, 1.41]  |                    |
| **Subtotal (95% CI)** | 33.0% | 0.95 | 0.81, 1.09 |                    |                    |

- Heterogeneity: Tau² = 0.04; Chi² = 259.78, df = 8 (P < 0.00001); I² = 97%
- Test for overall effect: Z = 13.66 (P < 0.00001)

**Total (95% CI)**

100.0% 0.99 [0.87, 1.11]

- Heterogeneity: Tau² = 0.10; Chi² = 3986.62, df = 26 (P < 0.00001); I² = 99%
- Test for overall effect: Z = 16.29 (P < 0.00001)
- Test for subgroup differences: Chi² = 0.35, df = 2 (P = 0.84), I² = 0%

(Figure continued on next page.)
For risk of bias, the quality was variable across each domain. In the patient selection domain, 21 were judged to be at low risk, 5 were considered high risk, and 11 were unclear in risk. In the index test domain, 17 studies were considered low risk, and 20 studies were unclear in risk. For the reference standard domain, 21 were considered low risk, and 16 studies were unclear in risk. In the domain flow and timing, 29 studies had low risk, 2 studies had high risk, and 4 studies had unclear risk.

The acquired 37 studies comprised a total of 2,015 patients with RC. There were 1,142 men and 607 women. In 266 patients, the gender was not given. The calculated mean age of the patients was 60.5 years, range, 49.5–72 years.

**ADC Values and Tumor Grades**

Associations between tumor grade and ADC were reported in 9 studies (477 patients) [13, 20, 23, 28, 42–46]. Grade 1 tumors were identified in 75 cases (15.7%), grade 2 in 321 patients (67.3%), and grade 3 in 81 cases (17%). The calculated mean ADC values (×10⁻³ mm²/s) of RC were 1.02, 95% confidence interval (CI) (0.80, 1.25) for grade 1 lesions, 0.99, 95% CI (0.81, 1.18) for grade 2, and 0.95, 95% CI (0.81, 1.09) for grade 3 carcinomas (Fig. 3a).

The graphical distribution of ADC in different tumor grades is shown in Figure 3b. ADC values of the tumors with diverse differentiating overlapped strongly.

**ADC Values and T Stage**

Relationships between different tumor stages and ADC values were reported in 6 studies (352 patients) [14, 40, 43–46]. There were 29 patients (8.2%) with T1 stage, 141 patients (40.1%) with T2 stage, 145 patients (41.2%) with T3 stage, and 37 patients (10.5%) with T4 stage.

The calculated mean ADC values (×10⁻³ mm²/s) of tumors were as follows: 1.05, 95% CI (0.90, 1.20) in T1 tumors, 1.05, 95% CI (0.84, 1.25) in T2 tumors, 1.03, 95% CI (0.89, 1.18) in T3 tumors, and 0.98, 95% CI (0.76, 1.20) in T4 tumors (Fig. 4a). The graphical distribution of ADC in different tumor grades is shown in Figure 4b.

**ADC Values and N Stage**

ADC values in RC with different N stages were reported in 8 studies (402 patients) [13, 20, 23, 36, 42–45]. N0 stage was identified in 188 cases (46.8%), and N+ stage was found in 214 patients (53.2%). The calculated mean ADC value (×10⁻³ mm²/s) of RC with N0 stage was 0.98, 95% CI (0.84, 1.11). It was 0.92, 95% CI (0.80, 1.05) for RC with N+ stage (Fig. 5a). Figure 5b shows the graphical distribution of ADC values in N0 and N+ tumors.

**ADC Values and CEA Level**

Comparison of ADC values between tumors with different levels of pretreatment CEA was performed in
### Study or Subgroup

| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI | Mean | SE  | Weight | IV, Random, 95% CI |
|-------------------|------|-----|--------|--------------------|------|-----|--------|--------------------|
| **7.1.1 T1**      |      |     |        |                    |      |     |        |                    |
| Ao 2020 [14]      | 0.92 | 0.04| 5.4%   | 0.92 [0.84, 1.00]  |      |     |        |                    |
| Peng 2018 [40]    | 1.18 | 0.13| 3.8%   | 1.18 [0.93, 1.43]  |      |     |        |                    |
| Sun 2014 [43]     | 1.53 | 0.15| 3.4%   | 1.53 [1.24, 1.82]  |      |     |        |                    |
| Tang 2018 [45]    | 0.8  | 0.06| 5.1%   | 0.80 [0.68, 0.92]  |      |     |        |                    |
| Xia 2018 [46]     | 1.06 | 0.03| 5.5%   | 1.06 [1.00, 1.12]  |      |     |        |                    |
| **Subtotal (95% CI)** | 23.2% | 1.05 | 0.90 [1.20] |        |      |     |        |                    |

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 33.50$, df = 4 ($P < 0.00001$); $I^2 = 88$

Test for overall effect: $Z = 13.65$ ($P < 0.00001$)

### Test for subgroup differences: $\chi^2 = 0.29$, df = 3 ($P = 0.96$), $I^2 = 0$

### 7.1.2 T2

| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI | Mean | SE  | Weight | IV, Random, 95% CI |
|-------------------|------|-----|--------|--------------------|------|-----|--------|--------------------|
| Ao 2020 [14]      | 0.83 | 0.03| 5.5%   | 0.83 [0.77, 0.89]  |      |     |        |                    |
| Peng 2018 [40]    | 1.08 | 0.03| 5.5%   | 1.08 [1.02, 1.14]  |      |     |        |                    |
| Sun 2014 [43]     | 1.38 | 0.03| 5.5%   | 1.38 [1.32, 1.44]  |      |     |        |                    |
| Surov 2017 [44]   | 1.15 | 0.18| 2.9%   | 1.15 [0.80, 1.50]  |      |     |        |                    |
| Tang 2018 [45]    | 0.78 | 0.02| 5.6%   | 0.78 [0.74, 0.82]  |      |     |        |                    |
| Xia 2018 [46]     | 1.11 | 0.03| 5.5%   | 1.11 [1.05, 1.17]  |      |     |        |                    |
| **Subtotal (95% CI)** | 30.5% | 1.05 | 0.84 [1.25] |        |      |     |        |                    |

Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 333.35$, df = 5 ($P < 0.00001$); $I^2 = 99$

Test for overall effect: $Z = 10.03$ ($P < 0.00001$)

### 7.1.3 T3

| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI | Mean | SE  | Weight | IV, Random, 95% CI |
|-------------------|------|-----|--------|--------------------|------|-----|--------|--------------------|
| Ao 2020 [14]      | 0.75 | 0.02| 5.6%   | 0.75 [0.71, 0.79]  |      |     |        |                    |
| Peng 2018 [40]    | 0.96 | 0.02| 5.6%   | 0.96 [0.92, 1.00]  |      |     |        |                    |
| Sun 2014 [43]     | 1.22 | 0.06| 5.1%   | 1.22 [1.10, 1.34]  |      |     |        |                    |
| Surov 2017 [44]   | 1.31 | 0.11| 4.2%   | 1.31 [1.09, 1.53]  |      |     |        |                    |
| Xia 2018 [46]     | 1.03 | 0.02| 5.6%   | 1.03 [0.99, 1.07]  |      |     |        |                    |
| **Subtotal (95% CI)** | 26.0% | 1.03 | 0.89 [1.18] |        |      |     |        |                    |

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 143.52$, df = 4 ($P < 0.00001$); $I^2 = 97$

Test for overall effect: $Z = 13.72$ ($P < 0.00001$)

### 7.1.4 T4

| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI | Mean | SE  | Weight | IV, Random, 95% CI |
|-------------------|------|-----|--------|--------------------|------|-----|--------|--------------------|
| Ao 2020 [14]      | 0.71 | 0.03| 5.5%   | 0.71 [0.65, 0.77]  |      |     |        |                    |
| Peng 2018 [40]    | 0.91 | 0.04| 5.4%   | 0.91 [0.83, 0.99]  |      |     |        |                    |
| Sun 2014 [43]     | 1.19 | 0.11| 4.2%   | 1.19 [0.97, 1.41]  |      |     |        |                    |
| Xia 2018 [46]     | 1.15 | 0.05| 5.3%   | 1.15 [1.05, 1.25]  |      |     |        |                    |
| **Subtotal (95% CI)** | 20.3% | 0.98 | 0.76 [1.20] |        |      |     |        |                    |

Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 69.17$, df = 3 ($P < 0.00001$); $I^2 = 96$

Test for overall effect: $Z = 8.69$ ($P < 0.00001$)

### Total (95% CI)

| Mean | SE  | Weight | IV, Random, 95% CI |
|------|-----|--------|--------------------|
| 1.00 | 0.03| 100.0% | 1.03 [0.95, 1.12]  |

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 613.45$, df = 19 ($P < 0.00001$); $I^2 = 97$

Test for overall effect: $Z = 23.52$ ($P < 0.00001$)

Test for subgroup differences: $\chi^2 = 0.29$, df = 3 ($P = 0.96$), $I^2 = 0$

(Figure continued on next page.)
ADC Cannot Be Used as a Biomarker in Rectal Cancer

6 studies (339 patients) [13, 20, 23, 42, 43, 46]. RC with a CEA level under 5 ng/mL ($n = 209, 61.7\%$) had a calculated mean ADC value ($\times 10^{-3}$ mm$^2$/s) of 0.97, 95% CI (0.82, 1.13) (Fig. 6a). It was 0.93, 95% CI (0.77, 1.09) in RC with a CEA level $>5$ ng/mL ($n = 130, 38.3\%$). ADC values of the tumors with different CEA levels overlapped strongly (Fig. 6b).

**ADC and Histopathological Markers in RC**

Three studies (274 patients) analyzed associations between ADC values and KRAS status in RC [19, 32, 47]. Mutated RC ($n = 124, 45.3\%$) had the calculated mean ADC value ($\times 10^{-3}$ mm$^2$/s) of 1.12, 95% CI (0.93, 1.30) (Fig. 7a). Wild-type RC ($n = 150, 54.7\%$) had the calculated mean ADC value ($\times 10^{-3}$ mm$^2$/s) of 1.24, 95% CI (1.03, 1.33).

In 4 studies with 234 patients, associations between ADC and the proliferation marker Ki 67 were analyzed [14, 38, 43, 44]. The calculated pooled correlation coefficient was $-0.52$, 95% CI ($-0.69, -0.35$) (Fig. 7b).

Furthermore, in 2 studies (102 patients) correlation between ADC and expression of VEGF was studied [38, 44]. The calculated pooled correlation coefficient was $-0.08$, 95% CI ($-0.60, 0.44$) (Fig. 7c).

Finally, in 2 studies (102 patients) correlation between ADC and expression of HIF 1a was analyzed [38, 44]. The calculated pooled correlation coefficient was $-0.07$, 95% CI ($-0.63, 0.50$) (Fig. 7d).

**ADC Values and Response to NARC**

In 21 studies, comprising pretreatment ADC values (mean and standard deviation) were reported in regard to therapy response. Egger’s test revealed a significant publication bias ($p < 0.001$) among these studies (Fig. 8).

The collected 21 articles contained 964 patients. Of the 964 patients, 380 (35.6\%) were reported as responders and 584 (64.4\%) as nonresponders to the NARC. The pooled calculated pretreatment mean ADC value of RC in responders was 0.96 (95% CI $= [0.91; 1.01]$) (Fig. 9a). In nonresponders, it was 1.04 (95% CI $= [0.95; 1.12]$) (Fig. 9a). Figure 8b shows the graphical distribution of ADC values in responders and nonresponders. The ADC values of the groups overlapped strongly.

On the next step, cumulative mean ADC values were calculated in dependence on scanner type (Tesla strength). Overall, 348 patients were investigated on 1.5 T scanners and 578 patients on 3.0 T scanners. In the subgroup investigated by 1.5 T scanners, 150 patients were reported as responders and 198 patients as nonresponders to the NARC. In the subgroup investigated by 3.0 T scanners, 221 patients were reported as responders and 357 patients as nonresponders. The pooled calculated pretreatment mean ADC values of RC did not differ strongly between the subgroups (Fig. 10a, b).

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**Fig. 4. a** Forest plots of ADC values reported for RCs with different tumor stages. **b** Graphical distribution of ADC values of RCs with different tumor stages. ADC, apparent diffusion coefficient; RC, rectal cancer; CI, confidence interval.
Fig. 5. a Forest plots of ADC values reported for RCs with different nodal stages. b Graphical distribution of ADC values of RCs with different nodal stages. ADC, apparent diffusion coefficient; RC, rectal cancer; CI, confidence interval.
## Study or Subgroup

| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|------|-----|--------|-------------------|-------------------|
| **4.1.1 CEA < 5ng/ml** |      |     |        |                   |                   |
| Akashi 2014 [13]  | 0.9  | 0.02| 8.4%   | 0.90 [0.86, 0.94] |                   |
| Curvo-Semedo 2012 [20] | 1.07 | 0.03| 8.3%   | 1.07 [1.01, 1.13] |                   |
| Elmi 2013 [23]   | 0.89 | 0.01| 8.5%   | 0.89 [0.87, 0.91] |                   |
| Sun 2014 [43]    | 0.59 | 0.02| 8.4%   | 0.59 [0.55, 0.63] |                   |
| Sun 2018 [42]    | 1.31 | 0.04| 8.2%   | 1.31 [1.23, 1.39] |                   |
| Xia 2018 [46]    | 1.1  | 0.03| 8.3%   | 1.10 [1.04, 1.16] |                   |
| **Subtotal (95% CI)** | 1.0  | 0.01| 50.1%  | 0.97 [0.82, 1.13] |                   |

Heterogeneity: \( \tau^2 = 0.04 \); \( \chi^2 = 420.45, \text{df} = 5 \) \( P < 0.00001 \); \( I^2 = 99\% \)

Test for overall effect: \( Z = 12.37 \) \( P < 0.00001 \)

**4.1.2 CEA >= 5ng/ml**

| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|------|-----|--------|-------------------|-------------------|
| Akashi 2014 [13]  | 0.89 | 0.02| 8.4%   | 0.89 [0.85, 0.93] |                   |
| Curvo-Semedo 2012 [20] | 1.04 | 0.04| 8.2%   | 1.04 [0.96, 1.12] |                   |
| Elmi 2013 [23]   | 0.75 | 0.01| 8.5%   | 0.75 [0.73, 0.77] |                   |
| Sun 2014 [43]    | 0.56 | 0.01| 8.5%   | 0.56 [0.54, 0.58] |                   |
| Sun 2018 [42]    | 1.29 | 0.05| 8.0%   | 1.29 [1.19, 1.39] |                   |
| Xia 2018 [46]    | 1.07 | 0.03| 8.3%   | 1.07 [1.01, 1.13] |                   |
| **Subtotal (95% CI)** | 1.0  | 0.01| 49.9%  | 0.93 [0.77, 1.09] |                   |

Heterogeneity: \( \tau^2 = 0.04 \); \( \chi^2 = 667.18, \text{df} = 5 \) \( P < 0.00001 \); \( I^2 = 99\% \)

Test for overall effect: \( Z = 11.13 \) \( P < 0.00001 \)

**Total (95% CI)**

| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|------|-----|--------|-------------------|-------------------|
| **Total (95% CI)** | 1.0  | 0.01| 100.0% | 0.95 [0.84, 1.07] |                   |

Heterogeneity: \( \tau^2 = 0.04 \); \( \chi^2 = 1389.30, \text{df} = 11 \) \( P < 0.00001 \); \( I^2 = 99\% \)

Test for overall effect: \( Z = 16.41 \) \( P < 0.00001 \)

Test for subgroup differences: \( \chi^2 = 0.16, \text{df} = 1 \) \( P = 0.69 \); \( I^2 = 0\% \)

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**Fig. 6.**

**a** Forest plots of ADC values reported for RCs with different CEA levels. **b** Graphical distribution of ADC values of RCs with different CEA levels. ADC, apparent diffusion coefficient; RC, rectal cancer; CEA, carcinoembryonic antigen; CI, confidence interval.
| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI |
|-------------------|------|-----|--------|-------------------|
| Cui 2019 [19]    | 1.18 | 0.02| 17.5%  | 1.18 [1.14, 1.22] |
| Jo 2019 [32]     | 0.95 | 0.03| 17.2%  | 0.95 [0.89, 1.01] |
| Xu 2018 [47]     | 1.26 | 0.1 | 13.7%  | 1.26 [1.06, 1.46] |
| Subtotal (95% CI)| 48.4%|     | 1.12 [0.93, 1.30] |

Heterogeneity: \( \tau^2 = 0.02; \ Chi^2 = 42.90, \text{df} = 2 (P < 0.00001); I^2 = 95% \)

Test for overall effect: \( Z = 11.71 (P < 0.00001) \)

### 1.1.2 Wild type

| Study or Subgroup | Mean | SE  | Weight | IV, Random, 95% CI |
|-------------------|------|-----|--------|-------------------|
| Cui 2019 [19]    | 1.33 | 0.02| 17.5%  | 1.33 [1.29, 1.37] |
| Jo 2019 [32]     | 0.96 | 0.03| 17.2%  | 0.96 [0.90, 1.02] |
| Xu 2018 [47]     | 1.43 | 0.04| 16.9%  | 1.43 [1.35, 1.51] |
| Subtotal (95% CI)| 51.6%|     | 1.24 [0.97, 1.50] |

Heterogeneity: \( \tau^2 = 0.05; \ Chi^2 = 129.67, \text{df} = 2 (P < 0.00001); I^2 = 98% \)

Test for overall effect: \( Z = 9.18 (P < 0.00001) \)

Total (95% CI): 1.18 [1.03, 1.33]

Heterogeneity: \( \tau^2 = 0.03; \ Chi^2 = 208.31, \text{df} = 5 (P < 0.00001); I^2 = 98% \)

Test for overall effect: \( Z = 15.28 (P < 0.00001) \)

Test for subgroup differences: \( \chi^2 = 0.54, \text{df} = 1 (P = 0.46), I^2 = 0% \)

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### b Correlation

| Study or Subgroup | Correlation | SE   | Weight | IV, Random, 95% CI |
|-------------------|-------------|------|--------|-------------------|
| Ao 2020 [14]     | -0.69       | 0.06 | 34.0%  | -0.69 [-0.81, -0.57] |
| Meng 2016 [38]   | -0.48       | 0.08 | 30.3%  | -0.48 [-0.64, -0.32] |
| Sun 2014 [43]    | -0.32       | 0.13 | 21.5%  | -0.32 [-0.57, -0.07] |
| Surov 2017 [44]  | -0.49       | 0.19 | 14.1%  | -0.49 [-0.86, -0.12] |

Total (95% CI): 100.0% -0.52 [-0.69, -0.35]

Heterogeneity: \( \tau^2 = 0.02; \ Chi^2 = 9.13, \text{df} = 3 (P = 0.03); I^2 = 67% \)

Test for overall effect: \( Z = 5.87 (P < 0.00001) \)

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### c Correlation

| Study or Subgroup | Correlation | SE   | Weight | IV, Random, 95% CI |
|-------------------|-------------|------|--------|-------------------|
| Meng 2016 [38]   | -0.29       | 0.1  | 62.2%  | -0.29 [-0.49, -0.09] |
| Meyer 2018 [11]  | 0.26        | 0.29 | 37.8%  | 0.26 [-0.31, 0.83] |

Total (95% CI): 100.0% -0.08 [-0.60, 0.44]

Heterogeneity: \( \tau^2 = 0.10; \ Chi^2 = 3.21, \text{df} = 1 (P = 0.07); I^2 = 69% \)

Test for overall effect: \( Z = 0.31 (P = 0.76) \)

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### d Correlation

| Study or Subgroup | Correlation | SE  | Weight | IV, Random, 95% CI |
|-------------------|-------------|-----|--------|-------------------|
| Meng 2016 [38]   | -0.3        | 0.1 | 60.6%  | -0.30 [-0.50, -0.10] |
| Meyer 2018 [11]  | 0.29        | 0.29| 39.4%  | 0.29 [-0.28, 0.86] |

Total (95% CI): 100.0% -0.07 [-0.63, 0.50]

Heterogeneity: \( \tau^2 = 0.13; \ Chi^2 = 3.70, \text{df} = 1 (P = 0.05); I^2 = 73% \)

Test for overall effect: \( Z = 0.24 (P = 0.81) \)

(For legend see next page.)
Discussion

The question of imaging, in particular DWI/ADC, can reflect histopathological features in oncology is very important. In fact, if so, then ADC can be recommended as surrogate markers for tumoral biology.

Previously, some reports suggested that ADC values can reflect tumor grade and stage in several tumors [55–57]. For example, in meningioma, ADC can discriminate benign and high-grade lesions [55]. Similar results were reported also for uterine cervical cancers [56]. In prostatic cancer, ADC correlates with the Gleason score [57]. Furthermore, more interestingly, ADC correlates also with presence/absence of nodal and distant metastases [58, 59]. So far, in breast cancer, some reports indicated that ADC values of nodal metastasized tumors were statistically significant lower in comparison with nonmetastasized tumors [58, 59].

In RC, however, the reported data are controversial. For instance, Akashi et al. [13] showed that mean tumor ADC values were different when comparing groups stratified by histologic differentiation grades \( p = 0.0192 \). There was no significant difference in mean ADCs when stratifying patients according to CEA levels, T stage, N stage, and the presence of lymphangiovascular invasion [13]. Curvo-Semedo et al. [20] also found that mean tumor ADCs differed between the several groups of histological differentiation grades \( p = 0.025 \). However, they mentioned that N0 versus N+ cancers had different ADC values \( p = 0.011 \) [20]. In the study of Sun et al. [43], RC with different tumor differentiation did not show statistically significant differences of ADC values. Furthermore, higher T-stage values correlated with lower ADC values [43].

The present analysis provides evident data regarding relationships between ADC and histopathology in RC based on a large sample. Summarizing the published literature so far, this meta-analysis found no evidence to support that ADC values varied according to T and N stages, tumor grading, as well as KRAS mutation. Furthermore, ADC does not correlate with expression of VEGF and HIF 1a and does not correlate with CEA plasma level. Our findings suggest that ADC cannot predict relevant histopathological features in RC. ADC does correlate with proliferation index of Ki 67 only. Therefore, ADC cannot be used as a surrogate parameter for tumor histopathology in RC.

Independent on associations with histopathology, a key question is, if pretreatment ADC can predict response to NARC in RC or not. The possibility to stratify tumors regarding response to NARC is very important in clinical practice. This stratification may guide individualization of patient treatment in order to maximize therapeutic outcomes and minimize treatment toxicity. NARC often leads to excellent response. In fact, according to the literature, in approximately 24% of patients treated with NARC, no residual tumor tissue is present in the resection specimen (complete tumor response) [60]. Patients with complete response have a better prognostic outcome. Therefore, in these patients, organ-saving treatment may be applied [60–63]. Also, pretreatment selection of nonresponders to NARC is even very important.

The published data about the role of ADC in prediction of response to NARC are contradictory. While some authors found an association between pretreat-
Test for overall effect: Z = 36.62 (P < 0.00001)
Heterogeneity: Tau² = 0.03; Chi² = 2482.49, df = 41 (P < 0.00001); I² = 98%

Test for overall effect: Z = 24.09 (P < 0.00001)
Heterogeneity: Tau² = 0.04; Chi² = 1803.97, df = 20 (P < 0.00001); I² = 99%

Musio 2013 [39]
Lee 2013 [35]
Jung 2012 [33]
Ippolito 2015 [31]
Hu 2017 [29]
Foti 2016 [26]
Genovesi 2013 [27]
Hu 2017 [29]
Iancicelli 2016 [30]
Ippolito 2015 [31]
Jung 2012 [33]
Lee 2013 [35]
Lu 2017 [36]
Lu 2017 [37]
Muzio 2013 [39]
Quaia 2016 [41]
Sun 2014 [43]
Yu 2017 [48]
Zhu 2016 [49]

Heterogeneity: Tau² = 0.01; Chi² = 335.07, df = 20 (P < 0.00001); I² = 94%
Test for overall effect: Z = 39.08 (P < 0.00001)

3.1.1 Responder
Bakke 2017 [15] 0.74 0.06 2.3% 0.74 [0.62, 0.86]
Blazic 2015 [16] 0.88 0.02 2.5% 0.88 [0.84, 0.92]
Cao 2020 [17] 1.65 0.07 2.2% 1.65 [1.51, 1.79]
Chen 2016 [18] 0.86 0.01 2.6% 0.86 [0.84, 0.88]
de Felice 2017 [21] 0.81 0.03 2.5% 0.81 [0.75, 0.87]
Delli Pizzi 2017 [22] 0.96 0.04 2.4% 0.96 [0.88, 1.04]
Ekhbaatar 2018 [24] 1.07 0.04 2.4% 1.07 [0.99, 1.15]
Foti 2016 [26] 0.78 0.02 2.5% 0.78 [0.74, 0.82]
Genovesi 2013 [27] 1.01 0.02 2.5% 1.01 [0.97, 1.05]
Hu 2017 [29] 0.83 0.02 2.5% 0.83 [0.79, 0.87]
Iancicelli 2016 [30] 0.94 0.05 2.4% 0.94 [0.84, 1.04]
Ippolito 2015 [31] 0.88 0.04 2.4% 0.88 [0.80, 0.96]
Jung 2012 [33] 0.93 0.02 2.5% 0.93 [0.89, 0.97]
Lee 2013 [35] 1.17 0.15 1.5% 1.17 [0.88, 1.46]
Lu 2017 [36] 1.07 0.05 2.4% 1.07 [0.97, 1.17]
Lu 2017 [37] 1.2 0.06 2.3% 1.2 [0.98, 1.32]
Muzio 2013 [39] 0.87 0.06 2.3% 0.87 [0.75, 0.99]
Quaia 2016 [41] 0.94 0.03 2.5% 0.94 [0.88, 1.00]
Sun 2014 [43] 1.07 0.03 2.5% 1.07 [1.01, 1.13]
Yu 2017 [48] 1 0.03 2.5% 1.0 [0.94, 1.06]
Zhu 2016 [49] 0.89 0.02 2.5% 0.89 [0.85, 0.93]

Subtotal (95% CI) 50.6% 0.96 [0.91, 1.01]

Heterogeneity: Tau² = 0.01; Chi² = 335.07, df = 20 (P < 0.00001); I² = 94%
Test for overall effect: Z = 39.08 (P < 0.00001)

3.1.2 Non Responder
Bakke 2017 [15] 0.61 0.04 2.4% 0.61 [0.53, 0.69]
Blazic 2015 [16] 0.87 0.01 2.6% 0.87 [0.85, 0.89]
Cao 2020 [17] 1.75 0.07 2.2% 1.75 [1.61, 1.89]
Chen 2016 [18] 0.9 0.01 2.6% 0.9 [0.88, 0.92]
de Felice 2017 [21] 1.05 0.3 0.6% 1.05 [0.48, 1.64]
Delli Pizzi 2017 [22] 1.16 0.04 2.4% 1.16 [1.08, 1.24]
Ekhbaatar 2018 [24] 1.15 0.02 2.5% 1.15 [1.11, 1.19]
Foti 2016 [26] 0.91 0.04 2.4% 0.91 [0.83, 0.99]
Genovesi 2013 [27] 1.3 0.01 2.6% 1.3 [1.28, 1.32]
Hu 2017 [29] 0.86 0.03 2.5% 0.86 [0.80, 0.92]
Iancicelli 2016 [30] 0.87 0.02 2.5% 0.87 [0.83, 0.91]
Ippolito 2015 [31] 0.78 0.03 2.5% 0.78 [0.72, 0.84]
Jung 2012 [33] 1.03 0.02 2.5% 1.03 [0.99, 1.07]
Lee 2013 [35] 1.17 0.09 2.0% 1.17 [0.99, 1.35]
Lu 2017 [36] 1.13 0.09 2.0% 1.13 [0.95, 1.31]
Lu 2017 [37] 1.25 0.02 2.5% 1.25 [1.21, 1.29]
Muzio 2013 [39] 0.75 0.05 2.5% 0.75 [0.65, 0.85]
Quaia 2016 [41] 0.91 0.03 2.5% 0.91 [0.85, 0.97]
Sun 2014 [43] 1.19 0.03 2.5% 1.19 [1.13, 1.25]
Yu 2017 [48] 1.14 0.06 2.3% 1.14 [1.02, 1.26]
Zhu 2016 [49] 1.06 0.01 2.6% 1.06 [1.04, 1.08]

Subtotal (95% CI) 49.4% 1.04 [0.95, 1.12]

Heterogeneity: Tau² = 0.04; Chi² = 1803.07, df = 20 (P < 0.00001); I² = 99%
Test for overall effect: Z = 24.09 (P < 0.00001)

Total (95% CI) 100.0% 1.00 [0.95, 1.06]

Heterogeneity: Tau² = 0.03; Chi² = 2482.49, df = 41 (P < 0.00001); I² = 98%
Test for overall effect: Z = 36.62 (P < 0.00001)
Test for subgroup differences: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.1%

(Figure continued on next page.)
ment ADC and pathologic response scores after NARC in RC, others did not.

The present analysis based on a large cohort shows that pretreatment DWI cannot predict treatment outcome in BC because baseline ADC values of responders to NAC and nonresponders did not differ and overlapped significantly. Furthermore, this result is independent from Tesla strength. Our finding is in agreement with those of Amedo et al. [64], who also showed that pretreatment ADC values did not differ significantly. Therefore, ADC does not play a prognostic role in patients with RC underwent NARC.

The present study has several limitations. It is based on published results in the literature with a known publication bias. Unfortunately, only a small number of studies met the inclusion criteria for this analysis, and several studies were excluded because some data, for example, ADC mean values and/or standard deviation were missing. Furthermore, only publications in English language were included. Therefore, the subgroups with analyses of associations between histopathological features like tumor stage, grade, and expression of relevant biomarkers include a small number of articles and small number of patients/tumors. Furthermore, different study designs, different MR techniques like Tesla strength, DWI sequences, and \( b \) values, and the use of different reference standards among studies are also limitations of the present analysis. Therefore, a high heterogeneity among the collected studies is shown in some subgroups. Also, some collected studies show high bias and/or are unclear in risk, especially for the domains patient selection and index test. Finally, publication bias is shown among the studies regarding associations between ADC and therapy response.

These facts may relativize our results. However, the identified methodological constellation represents a real clinical situation about data acquisition and technical details. Furthermore, the results of the present metaanalysis are based on a large cohort and provide evident data regarding the current state of ADC in RC.

ADC correlates moderately with expression of Ki 67 in RC. ADC cannot discriminate tumor stages, grades, and KRAS status in RC. ADC cannot predict therapy response to NARC in RC.

**Statement of Ethics**

All the procedures in the study involving human material and data were performed in accordance with World Medical Association’s Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subject. Patients’ informed consent and Ethical Committee approval were not needed.
Study or Subgroup | Mean | SE | Weight | IV, Random, 95% CI | Mean |
|------------------|------|----|--------|-------------------|------|
| 12.1.1 Tesla 3   |      |    |        |                   |      |
| Chen 2016 [18]   | 0.86 | 0.01| 5.6%   | 0.86 [0.84, 0.88] |      |
| de Felice 2017 [21] | 0.81 | 0.03| 5.2%   | 0.81 [0.75, 0.87] |      |
| Delli Pizzi 2017 [22] | 0.96 | 0.04| 4.9%   | 0.96 [0.88, 1.04] |      |
| Enkhbaatar 2018 [24] | 1.07 | 0.04| 4.9%   | 1.07 [0.99, 1.15] |      |
| Genovesi 2013 [27] | 1.01 | 0.02| 5.5%   | 1.01 [0.97, 1.05] |      |
| Hu 2017 [29]     | 0.83 | 0.02| 5.5%   | 0.83 [0.79, 0.87] |      |
| Jung 2012 [33]   | 0.93 | 0.02| 5.5%   | 0.93 [0.89, 0.97] |      |
| Liu 2017 [36]    | 1.07 | 0.05| 4.6%   | 1.07 [0.97, 1.17] |      |
| Musio 2013 [39]  | 0.87 | 0.06| 4.3%   | 0.87 [0.75, 0.99] |      |
| Yu 2017 [48]     | 1.00 | 0.03| 5.2%   | 1.00 [0.94, 1.06] |      |
| Zhu 2016 [49]    | 0.89 | 0.02| 5.5%   | 0.89 [0.85, 0.93] |      |
| **Subtotal (95% CI)** | 0.93 | 0.03| 56.7%  | 0.93 [0.88, 0.98] |      |

Heterogeneity: \( \tau^2 = 0.01; \ Chi^2 = 113.18, \text{df} = 10 (P < 0.00001); I^2 = 91\% \)
Test for overall effect: \( Z = 38.35 (P < 0.00001) \)

**12.1.2 Tesla 1.5**

| Study or Subgroup | Mean | SE | Weight | IV, Random, 95% CI | Mean |
|------------------|------|----|--------|-------------------|------|
| Bakke 2017 [15]  | 0.74 | 0.06| 4.3%   | 0.74 [0.62, 0.86] |      |
| Blazic 2015 [16] | 0.88 | 0.02| 5.5%   | 0.88 [0.84, 0.92] |      |
| Cao 2020 [17]    | 1.65 | 0.07| 3.9%   | 1.65 [1.51, 1.79] |      |
| Foti 2016 [28]   | 0.78 | 0.02| 5.5%   | 0.78 [0.74, 0.82] |      |
| Ianielli 2016 [30] | 0.94 | 0.05| 4.6%   | 0.94 [0.84, 1.04] |      |
| Ippolito 2015 [31] | 0.88 | 0.04| 4.9%   | 0.88 [0.80, 0.96] |      |
| Lu 2017 [37]     | 1.20 | 0.06| 4.3%   | 1.20 [1.08, 1.32] |      |
| Quaia 2016 [41]  | 0.94 | 0.03| 5.2%   | 0.94 [0.88, 1.00] |      |
| Sun 2014 [43]    | 1.07 | 0.03| 5.2%   | 1.07 [1.01, 1.13] |      |
| **Subtotal (95% CI)** | 1.00 | 0.04| 43.3%  | 1.00 [0.89, 1.12] |      |

Heterogeneity: \( \tau^2 = 0.03; \ Chi^2 = 218.00, \text{df} = 8 (P < 0.00001); I^2 = 96\% \)
Test for overall effect: \( Z = 17.07 (P < 0.00001) \)

**Total (95% CI)**

| Mean | SE | Weight | IV, Random, 95% CI |
|------|----|--------|-------------------|
| 100.0% | 0.96 | 91.0% | 0.96 [0.91, 1.01] |

Heterogeneity: \( \tau^2 = 0.01; \ Chi^2 = 331.86, \text{df} = 19 (P < 0.00001); I^2 = 94\% \)
Test for overall effect: \( Z = 38.66 (P < 0.00001) \)
Test for subgroup differences: \( \text{Chi}^2 = 1.16, \text{df} = 1 (P = 0.28), I^2 = 13.8\% \)

**Fig. 10.** a) Forrest plots of ADC reported for RCs responded to NARC in dependency on Tesla strength. b) Forrest plots of ADC reported for RCs nonresponded to NARC in dependency on Tesla strength. ADC, apparent diffusion coefficient; RC, rectal cancer; NARC, neoadjuvant radiochemotherapy; CI, confidence interval.

*(Figure continued on next page.)*
### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

A.S. and A.W.: conceived and designed the study; A.S., M.P., M.P., and K.W.: collection and analysis of data; all authors: manuscript writing; and M.P. and A.W.: critical revision of the manuscript. All the authors approved the final manuscript submitted.
Surov A, Meyer HJ, Wienke A. Correlation between apparent diffusion coefficient (ADC) and cellularity is different in several tumors: a meta-analysis. *Dis Colon Rectum*. 2016;59(8):789–99.

Faletti R, Gatti M, Arezzo A, Stola S, Benedini MC, Bergamasco L, et al. Preoperative staging of rectal cancer using magnetic resonance imaging: comparison with pathological staging. *Minerva Chir*. 2018;73(1):13–9.

Le Bihan D. Apparent diffusion coefficient and beyond: what diffusion MR imaging can tell us about tissue structure. *Radiology*. 2013; 268(2):318–22.

Surov A, Meyer HJ, Wienke A. Correlation between apparent diffusion coefficient (ADC) and histopathological features including expression of EGFR, VEGF, p53, noninvasive marker of tumor aggressiveness. *Int J Clin Exp Med*. 2015; 8(10):17333–42.

Meyer HJ, Leifers L, Hamerla G, Höhn AK, Surov A. ADC-histogram analysis in head and neck squamous cell carcinoma. *Acta Radiol*. 2016; 57(7):1000097.

Meyer HJ, Höhn M, Surov A. Histogram analysis of ADC in rectal cancer: associations with different histopathological features including expression of EGFR, VEGF, patchy, PD1, and KI 67. *Cancer Imaging*. 2018;18(9):18510–7.

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.

Akashi M, Nakahusa Y, Yakabe T, Egashira Y, Koga Y, Sumi K, et al. Assessment of aggressiveness of rectal cancer using 3-T MRI: correlation between the apparent diffusion coefficient as a potential imaging biomarker and histologic prognostic factors. *Acta Radiol*. 2014;55(5):524–31.

Ao W, Bao X, Mao G, Yang G, Wang J, Hu J. Value of apparent diffusion coefficient for assessing preoperative T staging of low rectal cancer and whether this is correlated with Ki-67 expression. *Can Assoc Radiol J*. 2020; 71(1):5–11.

Bakke KM, Hole KH, Dueland S, Groholt KK, Flatmark K, Ree AH, et al. Diffusion-weighted magnetic resonance imaging of rectal cancer: tumour volume and perfusion fraction predict chemoradiotherapy response and survival. *Acta Oncol*. 2017; 56(6):813–8.

Bläsić I, Maksimović R, Gajčić M, Saranović D. Apparent diffusion coefficient measurement covering complete tumor area better predicts rectal cancer response to neoadjuvant chemoradiotherapy. * Croat Med J*. 2015;56(5):460–9.

Cao W, Li B, Gong J, Hu M, Li W, Pan X, et al. Diffusion-weighted magnetic resonance imaging of mucin pools in locally advanced rectal mucinous adenocarcinoma predicts tumor response to neoadjuvant therapy. *Eur J Radiol*. 2020;125:108890.

Chen YG, Chen MQ, Guo YL, Li SC, Wu JX, Xu BH. Apparent diffusion coefficient predicts pathology complete response of rectal cancer treated with neoadjuvant chemoradiotherapy. *PLoS One*. 2016;11(4):e0153944.

Cui Y, Cui X, Yang X, Zhuo Z, Du X, Xin L, et al. Diffusion kurtosis imaging-derived histogram metrics for prediction of KRAS mutation in rectal adenocarcinoma: preliminary findings. *J Magn Reson Imaging*. 2019;50(3):930–9.

Curvo-Semedo L, Lambregts DM, Maas M, Beets GL, Caseiro-Alves F, Beets-Tan RG. Diffusion-weighted MRI in rectal cancer: apparent diffusion coefficient as a potential noninvasive marker of tumor aggressiveness. *J Magn Reson Imaging*. 2012;35(6):1365–71.

De Felice F, Magnante AL, Musio D, Ciolina M, De Cecco CN, Rengo M, et al. Combined value of diffusion-weighted magnetic resonance imaging in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. *Eur J Surg Oncol*. 2017;43(7):1324–9.

Delli Pizzi A, Cianci R, Genovesi D, Esposito G, Timpani M, Tavoletta A, et al. Perforation in locally advanced rectal cancer: a comparison with conventional diffusion-weighted imaging. *Oncotarget*. 2017;8(43):75597–606.

Enkhbaatar NE, Inoue S, Yamamura H, Kawada S, Miyakawa M, Nakamura N, et al. MR imaging with apparent diffusion coefficient histogram analysis: evaluation of locally advanced rectal cancer after chemotherapy and radiation therapy. *Radiology*. 2018; 288(1):129–37.

Fornell-Perez R, Vivas-Escalonaa V, Aranda-Sanchez J, Gonzalez-Dominguez MC, Rubio-Garcia J, Aleman-Florese P, et al. Primary and post-chemoradiotherapy MRI detection of extramural venous invasion in rectal cancer: the role of diffusion-weighted imaging. *Eur J Radiol*. 2020;125(6):522–30.

Foti PV, Privitera G, Piana S, Palmucci S, Spatola C, Bevilacqua R, et al. Locally advanced rectal cancer: qualitative and quantitative evaluation of diffusion-weighted MR imaging in the response assessment after neoadjuvant chemoradiotherapy. *Eur J Radiol Open*. 2016;3:145–52.

Genovesi D, Filippone A, Ausili Céfarò G, Trignani M, Vinciguerra A, Augurio A, et al. Diffusion-weighted magnetic resonance for prediction of response after neoadjuvant chemoradiation therapy for locally advanced rectal cancer: preliminary results of a monoinstitutional prospective study. *Eur J Surg Oncol*. 2013;39(10):1071–8.

Gu J, Khong PL, Wang S, Chan Q, Law W, Zhang J. Quantitative assessment of diffusion-weighted MR imaging in patients with primary rectal cancer: correlation with FDG-PET/CT. *Mol Imaging Biol*. 2011;13(5):1020–8.

Hu F, Tang W, Sun Y, Wan D, Cai S, Zhang Z, et al. The value of diffusion kurtosis imaging in assessing pathological complete response to neoadjuvant chemoradiation therapy in rectal cancer: a comparison with conventional diffusion-weighted imaging. *Oncotarget*. 2017;8(43):75597–606.

Iannicelli E, Di Pietropaolo M, Pilozzi E, Osti MF, Valentino M, Masoni L, et al. Value of diffusion-weighted MRI and apparent diffusion coefficient measurements for predicting the response of locally advanced rectal cancer to neoadjuvant chemoradiotherapy. *Abdom Radiol*. 2016;41(10):1906–17.

Ippolito D, Fior D, Trattenero C, Ponti ED, Drago S, Guerra L, et al. Combined value of apparent diffusion coefficient-standardized uptake value max in evaluation of post-treat-ed locally advanced rectal cancer. *World J Radiol*. 2015;7(12):509–20.

Jo SJ, Kim SH. Association between oncogenic RAS mutation and radiologic-pathologic findings in patients with primary rectal cancer. *Quant Imaging Med Surg*. 2019;9(2):238–46.

Jung SH, Heo SH, Kim JW, Jeong YY, Shin SS, Soung MG, et al. Predicting response to neoadjuvant chemoradiation therapy in locally advanced rectal cancer: diffusion-weighted 3 Tesla MR imaging. *J Magn Reson Imaging*. 2012;35(1):110–6.
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34 Kim YC, Lim JS, Keum KC, Kim KA, Myoung S, Shin SJ, et al. Comparison of diffusion-weighted MRI and MR volumetry in the evaluation of early treatment outcomes after preoperative chemoradiotherapy for locally advanced rectal cancer. J Magn Reson Imaging. 2011;34(3):570–6.

35 Lee EM, Hong YS, Kim KP, Lee JI, Kim SY, Park YS, et al. Phase II study of preoperative chemoradiation with S-1 plus oxaliplatin in patients with locally advanced rectal cancer. Cancer Sci. 2013;104(1):111–5.

36 Liu L, Liu Y, Xu L, Li Z, Lv H, Dong N, et al. Application of texture analysis based on apparent diffusion coefficient maps in discriminating different stages of rectal cancer. J Magn Reson Imaging. 2017;45(6):798–808.

37 Lu W, Jing H, Ju-Mei Z, Shao-Lin N, Fang C, Xiao-Ping Y, et al. Intravoxel incoherent motion diffusion-weighted imaging for differentiating the pathological response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer. Sci Rep. 2017;7(1):8496.

38 Meng X, Li H, Kong L, Zhao X, Huang Z, Zhao H, et al. MRI In rectal cancer: correlations between MRI features and molecular markers Ki-67, HIF-1α, and VEGF. J Magn Reson Imaging. 2016;44(4):594–600.

39 Musio D, De Felice F, Magnante AL, Ciolina M, De Cocco CN, Rengo M, et al. Diffusion-weighted magnetic resonance application in response prediction before, during, and after neoadjuvant radiotherapy in primary rectal cancer carcinoma. Biomed Res Int. 2013;2013:740195.

40 Peng Y, Li Z, Tang H, Wang Y, Hu X, Shen Y, et al. Comparison of reduced field-of-view diffusion-weighted imaging (DWI) and conventional DWI techniques in the assessment of rectal cancer at 3.0 T: image quality and histological T staging. J Magn Reson Imaging. 2018;47(4):967–75.

41 Quaia E, Gennari AG, Ricciardi MC, Ulcigrai F, et al. Readout-segmented echo-planar diffusion-weighted MR for the evaluation of aggressive characteristics of rectal cancer. Sci Rep. 2018;8(1):12554.

42 Xu Y, Xu Q, Sun H, Liu T, Shi K, Wang W. Could IVIM and ADC help in predicting the KRAS status in patients with rectal cancer? Eur Radiol. 2018;28(7):3059–65.

43 Yu J, Xu Q, Song JC, Li Y, Dai X, Huang DY, et al. The value of diffusion kurtotic magnetic resonance imaging for assessing treatment response of neoadjuvant chemoradiotherapy in locally advanced rectal cancer. Eur Radiol. 2017;27(5):1848–57.

44 Zhu HB, Zhang XY, Zhou KH, Li XT, Liu YL, Wang S, et al. Assessment of pathological complete response to preoperative chemoradiotherapy by means of multiple mathematical models of diffusion-weighted MRI in locally advanced rectal cancer: a prospective single-center study. J Magn Reson Imaging. 2017;46(1):175–83.

45 Chalkidou A, Landau DB, Odell EW, Cornelius VR, O’Doherty MJ, Marsden PK. Correlation between Ki-67 immunohistochemistry and 18F-fluorothymidine uptake in patients with cancer: a systematic review and meta-analysis. Eur J Cancer. 2012;48(18):3499–513.

46 Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUA-DAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.

47 Leeﬂang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. Ann Intern Med. 2008;149(12):889–97.

48 Zamora J, Abraira V, Muriel A, Khan K, Coopr;rasany A, Meta-DisC: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006;6:31.

49 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.

50 Surow A, Ginat DT, Sanverdi E, Lim CC, Hakyem B, Yogi A, et al. Use of diffusion weighted imaging in differentiating between malignant and benign meningiomas. A multicenter analysis. World Neurosurg. 2016;88:598–602.

51 Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM. Systematic reviews of diagnostic test accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.