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Correlation Between Minimum Apparent Diffusion Coefficient (ADC_{min}) and Tumor Cellularity: A Meta-analysis

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Abstract. *Background/Aim: Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique based on measure of water diffusion that can provide information about tissue microstructure, especially about cell count. Increase of cell density induces restriction of water diffusion and decreases apparent diffusion coefficient (ADC). ADC can be divided into three sub-parameters: ADC minimum or ADC_{min}, mean ADC or ADC_{mean} and ADC maximum or ADC_{max}. Some studies have suggested that ADC_{min} shows stronger correlations with cell count in comparison to other ADC fractions and may be used as a parameter for estimation of tumor cellularity. The aim of the present meta-analysis was to summarize correlation coefficients between ADC_{min} and cellularity in different tumors based on large patient data. Patients and Methods: For this analysis, MEDLINE database was screened for associations between ADC and cell count in different tumors up to September 2016. For this work, only data regarding ADC_{min} were included. Overall, 12 publications with 317 patients were identified. Spearman's correlation coefficient was used to analyze associations between ADC_{min} and cellularity. The reported Pearson correlation coefficients in some publications were converted into Spearman correlation coefficients. Results: The pooled correlation coefficient for all included studies was ϱ=–0.59 (95% confidence interval (CI)=–0.72 to –0.45), heterogeneity Tau^2=0.04 (p<0.0001), I^2=73%, test for overall effect Z=8.67 (p<0.00001). Conclusion: ADC_{min} correlated moderately with tumor cellularity. The calculated correlation coefficient is not stronger in comparison to the reported coefficient for ADC_{mean} and, therefore, ADC_{min} does not represent a better means to reflect cellularity.*

Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique based on measuring water diffusion in tissues (1). DWI can provide additional information about tissue microstructure, especially about cell count (1-5). Previously, some clinical and experimental studies investigated associations between apparent diffusion coefficient (ADC) and cellularity in several benign and malignant lesions (2-5). In most reports, statistically significant correlations between the parameters were identified (2-5). It has been shown that increase of cell density induced restriction of water diffusion and decreased ADC (2-5). Furthermore, according to the literature, ADC can be divided into three sub-parameters: ADC minimum or ADC_{min}, mean ADC or ADC_{mean} and ADC maximum or ADC_{max} (6-9). Some studies have suggested that ADC_{min} shows stronger correlations with cell count in comparison to other ADC fractions and, therefore, may be used as a parameter for estimation of tumor cellularity (6, 8). Onishi *et al*. reported that, in breast cancer, the correlation coefficient for ADC_{min} and cellularity was –0.537 (p=0.022), whereas for ADC_{mean} it was –0.412 (p=0.09) (8). However, other authors did not confirm these results (7, 9). For instance, in the study of Chen *et al*., investigated DWI findings in lung cancer demonstrated that the correlation coefficient between cellularity and ADC_{min} was –0.47 (p<0.01), and between ADC_{mean} and cellularity –0.6 (p<0.01) (7).

The aim of the present meta-analysis was to estimate the correlation coefficient between ADC_{min} and cellularity in different tumors based on large patient data.

Patients and Methods

Data acquisition and proving. For this analysis, MEDLINE database was screened for associations between ADC and cell count in different tumors up to September 2016. The following search criteria

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Key Words: Minimum apparent diffusion coefficient, tumor cellularity, meta-analysis.

Table I. *Studies involved in the meta-analysis.*

Study	Year	Country	Number of patients	Tumors	Correlation coefficient
Chen *et al.* (7)	2014	China	60	Lung cancer	–0.451
Doskaliyev *et al.* (11)	2010	Japan	24	Brain tumors	–0.582
Han *et al.* (12)	2015	China	17	Medulloblastoma	–0.669
Kikuchi *et al.* (13)	2009	Japan	10	Ganglioglioma	–0.659
Onishi *et al.* (8)	2015	Japan	17	Mucinous breast cancer	–0.788
Onishi *et al.* (8)	2015	Japan	17	Invasive ductal breast carcinoma	–0.519
Schnappauf *et al.* (14)	2009	Germany	31	Muscle sarcoma	–0.87
Schob *et al.* (15)	2016	Germany	21	Cerebral lymphoma	–0.13
Schob *et al.* (16)	2016	Germany	14	Thyroid cancer	–0.20
Sugahara *et al.* (17)	1999	Japan	20	Glioma	–0.76
Surov *et al.* (18)	2015	Germany	49	Meningioma	–0.44
Surov *et al.* (9)	2016	Germany	11	Head and neck cancer	0.05
Yamashita *et al.* (19)	2009	Japan	26	Posterior fossa tumors	–0.73

were used: "DWI or diffusion-weighted imaging or diffusion-weighted imaging or ADC or apparent diffusion coefficient AND cellularity or cell density or cell count or cell number". Secondary references were also recruited. We extracted only publications in English and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) (10).

As a next step, duplicates and papers without information regarding associations between DWI and cellularity were excluded. Thereafter, 494 publications were involved into further analysis. For this work, only data regarding ADC_{min} were included. Exclusion criteria were as follows: Papers that did not contain correlation coefficients between ADC_{min} and cell count; Data retrieved from diffusion tensor imaging; Data regarding DWI parameters other than ADC_{min}, such as ADC_{max} and ADC_{mean}; Experimental animals and *in vitro* studies.

Overall, 482 publications were excluded and, therefore, our analysis comprises 12 publications with 317 patients (7-9, 11-19). One study (8) contained two patient samples, therefore 13 patients samples were included. The following data were extracted from the literature: authors, year of publications, number of patients, tumor type and correlation coefficients (Table I).

The methodological quality of the 12 included studies was independently checked by two observers (A.S. and H.J.M.) using the Quality Assessment of Diagnostic Studies (QUADAS) instrument (20, 21). The results of QUADAS proving are shown in Table II.

Statistical analysis. Spearman's correlation coefficient was used to analyze associations between ADC_{min} and cellularity. The reported Pearson correlation coefficients in some publications were converted into Spearman correlation coefficients as reported previously (22).

The meta-analysis was undertaken by using software RevMan 5.3 (Computer program, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was calculated by means of the inconsistency index I^2 (23, 24). In a subgroup analysis, studies were stratified by tumor type. Furthermore, DerSimonian and Laird random-effects models with inverse-variance weights were used without any further correction (25).

Table II. *Methodological quality of the included studies according to the Quality Assessment of Diagnostic Studies (QUADAS) criteria.*

	Yes (%)	No (%)	Unclear (%)
Patient spectrum	13 (100)		
Selection criteria	9 (69.23)	2 (15.38)	2 (15.38)
Reference standard	13 (100)		
Disease progression bias	13 (100)		
Partial vertification bias	13 (100)		
Differential vertification bias	13 (100)		
Incorporation bias	13 (100)		
Text details	13 (100)		
Reference standard details	7 (53.85)	6 (46.15)	
Text review details	6 (46.15)	7 (53.85)	
Diagnostic review bias	13 (100)		
Clinical review bias	13 (100)		
Uninterpretable results	12 (92.31)		1 (7.69)
Withdrawals explained	12 (92.31)	1 (7.69)	

Results

The pooled correlation coefficient for all included studies (Figure 1) was ϱ=–0.59 (95% confidence interval (CI)=–0.72 to –0.45), heterogeneity Tau^2=0.04, (p<0.0001), I^2=73%, test for overall effect Z=8.67 (p<0.00001).

Discussion

The present analysis provided the correlation coefficient between ADC_{min} and cellularity in a large cohort.

The search for imaging parameters, which can reflect tissue composition of several tumors, has a high clinical relevance. They can be used as biomarkers for tumor

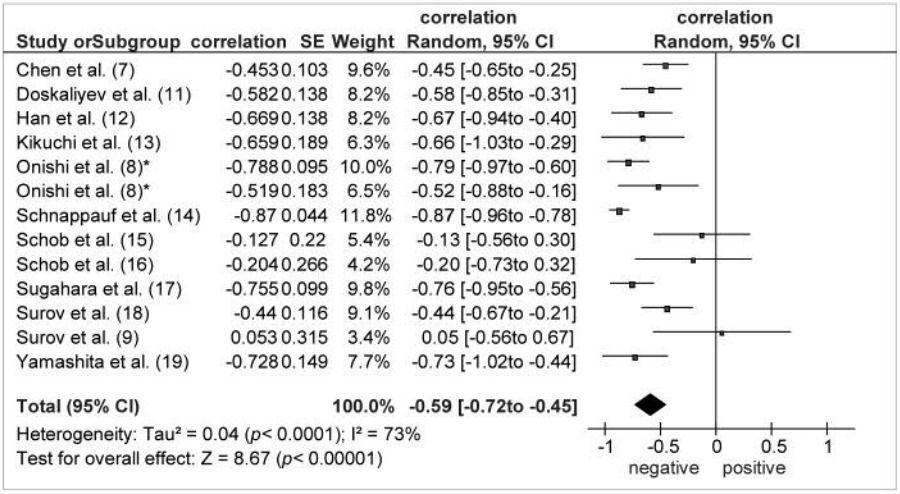

Figure 1. *Forest plots of correlation coefficients between minimum apparent diffusion coefficient (ADC_{min}) and cellularity in patients from all involved studies. SE, Standard error; CI, confidence interval. *Different patient samples in one study.*

cellularity, proliferation potential and, therefore, also predict tumor behavior. Previously, numerous studies investigated relationships between different imaging features and histopathology in benign and malignant lesions (26, 27). Especially ADC has been reported to have a great potential (7, 27). Furthermore, as mentioned above, ADC consists of different fractions: ADC_{min}, ADC_{mean} and ADC_{max}, which may reflect different histopathological features (9, 19, 27). It has been reported that ADC_{min} correlated statistically significant with cell count but not with proliferation index Ki-67, whereas ADC_{mean} correlated well with Ki-67 but not with cell count (27). Moreover, both parameters correlated well with total nucleic areas (27). In addition, ADC_{max} correlates slightly with cell count but not with Ki-67 and nucleic areas (27). However, other authors have indicated that none of ADC parameters correlated with cellularity (15). The main problem of the reported data was that they were based on small number of investigated lesions. This fact and controversial results question the use of ADC parameters in clinical practice and highlight the need for studies based on larger samples and/or systematic analysis of the published data. Recently, a meta-analysis regarding associations between ADC_{mean} and cellularity in different tumors was reported (28). It has been shown that the cumulative correlation coefficient was –0.56 (28). Furthermore, it ranged significantly in different tumors (28). As seen, the cumulative correlation coefficient between cellularity and ADC_{min} calculated in the present analysis does not differ significantly from the reported coefficient for ADC_{mean}. Therefore, in contrast to previous reports (6, 8, 18, 27), we postulate that ADC_{min} does not represent a better means to reflect cellularity. However, further studies are needed to investigate this association in larger groups and, more importantly, also in different tumors. It may be possible that, in some tumors, ADC_{min} correlates stronger with cell count.

In conclusion, ADC_{min} correlated moderately with tumor cellularity. The calculated correlation coefficient is not stronger in comparison to the reported coefficient for ADC_{mean} and, therefore, ADC_{min} does not better reflect cellularity as expected.

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