Diffusion-Weighted Imaging of Different Breast Cancer Molecular Subtypes: A Systematic Review and Meta-Analysis

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Keywords

Meta-analysis · Systematic review · Breast cancer · Diffusion-weighted imaging · Apparent diffusion coefficient

Abstract

Background: Magnetic resonance imaging can be used to diagnose breast cancer (BC). Diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) can be used to reflect tumor microstructure. **Objectives:** This analysis aimed to compare ADC values between molecular subtypes of BC based on a large sample of patients. **Method:** The MEDLINE library and Scopus database were screened for the associations between ADC and molecular subtypes of BC up to April 2020. The primary end point of the systematic review was the ADC value in different BC subtypes. Overall, 28 studies were included. **Results:** The included studies comprised a total of 2,990 tumors. Luminal A type was diagnosed in 865 cases (28.9%), luminal B in 899 (30.1%), human epidermal growth factor receptor (Her2)-enriched in 597 (20.0%), and triple-negative in 629 (21.0%). The mean ADC values of the subtypes were as follows: luminal A: $0.99 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.94–1.04), luminal B: $0.97 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.89–1.05), Her2-enriched: $1.02 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.95–1.08), and triple-negative: $0.99 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.91–1.07). **Conclusions:** ADC values cannot be used to discriminate between molecular subtypes of BC.

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Introduction

Contrast-enhanced magnetic resonance imaging (CE MRI) has become a cornerstone in the diagnosis of breast cancer (BC) [1–4]. It has the highest sensitivity of all imaging modalities but is associated with poor specificity [5]. To overcome this shortcoming, diffusion-weighted imaging (DWI) was additionally introduced into the MRI protocol, which is a functional imaging modality based upon Brownian water movement in tissues [6, 7]. The apparent diffusion coefficient (ADC) derived from DWI is inversely correlated with cellularity, nucleic size, and the proteins of the extracellular matrix. These tissue factors lead to a hindrance of the diffusion of the protons and, consequently, lower ADC values [7–9].

As a result, it was established that benign breast tumors have significantly higher ADC values than malignant tumors, with a threshold of $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ proposed in a recent meta-analysis [10]. However, diagnostic shortcomings have been reported for distinguishing BC subtypes with no clearly significant differences in ADC values [11–13]. These results were predominantly reported by single-center studies with different scanning technologies and partially inconclusive results.

It would be crucial to discriminate different BC subtypes based upon the receptor status, as the prognosis and

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Fig. 1. PRISMA flow chart. An overview of article acquisition. Overall, 28 studies with 2,990 patients were suitable for the analysis.

treatment options differ substantially between types [14, 15]. Her2-enriched BC has a worse prognosis than the hormone receptor-positive types, luminal A and luminal B, but can be treated by human epidermal growth factor receptor (Her2)-targeted antibody therapy [16]. In clinical routine, the receptor status is defined by immunohistochemical staining on biopsy specimens [15]. Possible clinical benefits could be by imaging a defined BC receptor status, as multifocal lesions or metastasized lesions can differ in receptor status [17]. This would result in different clinical decisions based upon functional imaging.

Our purpose was to systematically review the published literature regarding ADC values of BC according to molecular subtype and perform a meta-analysis to establish whether ADC values can discriminate BC subtypes or not.

Materials and Methods

Search Strategy and Selection Criteria

MEDLINE library and Scopus database were screened for associations between ADC values and BC up to April 2020. Two reviewers (H.-J.M. and A.S.) performed the data acquisition.

The following words were used for the search: “DWI” OR “diffusion weighted imaging” OR “diffusion-weighted imaging” OR “ADC” OR “apparent diffusion coefficient” AND “breast cancer” OR “breast carcinoma.” Secondary references were also manually checked and included.

The primary end point of the systematic review was an association between molecular subtypes of BC and ADC values.

Studies (or subsets of studies) were included if they satisfied all the following criteria: (1) patients with BC confirmed by histopathology, (2) pretreatment MRI with DWI, and (3) reported mean and standard deviation of the ADC values.

Fig. 2. QUADAS-2 assessment of the included studies; most showed a low risk of bias.

Only studies with a DWI utilizing 2 *b* values were included. Furthermore, 1.5-T and 3-T MRI scanners were considered appropriate.

An exact definition of immunohistochemical subtype was needed for inclusion. Luminal A tumors were those with positive staining for estrogen receptor (ER) or progesterone receptor (PR), Her2-negative, and low expression (<14%) of the proliferation marker Ki-67. Luminal B tumors were hormone receptor-positive and had high expression (>14%) of Ki-67. Her2-enriched type were defined by Her2 positivity. Tumors were considered Her2-positive only if they scored 3+ on immunohistochemical staining. Triple-negative tumors were those negative for ER, PR, and Her2. In all studies, immunohistochemical analysis was performed on surgical specimens.

Exclusion criteria were (1) reviews, (2) case reports, (3) studies without data of pretreatment dynamic CE MRI, (4) studies with histopathology performed after treatment, (5) non-English language studies, and (6) experimental (xenograft or animal model) studies.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for the analysis [18]. The paper acquisition is summarized in Figure 1.

In total, 28 studies were suitable for the analysis and were thus included [19–46].

Quality Assessment

The methodological quality of the acquired studies was independently evaluated by 2 readers (A.S. and H.-J.M.) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument [47]. The QUADAS-2 assessment results are shown in Figure 2.

Statistical Analysis

The meta-analysis was performed using RevMan v5.3 (2014; Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was calculated by means of the inconsistency index I^2 [48, 49]. Finally, DerSimonian and Laird [50] random-effect models with inverse-variance weights were performed without any further correction.

Results

Risk of Bias

Patient selection was generally well defined within the respective methodology; however, several studies did not report the inclusion criteria clearly, which may account for potential bias.

All studies clearly reported methodology of the index test and were thus not considered a significant source of potential bias. The reference test in all studies was histopathology with immunohistochemical staining.

There was a total of 2,990 breast tumors in 28 studies; 6 studies (21.4%) had a prospective design and 22 (78.6%) a retrospective design. Different 1.5-T scanners were used in 6 studies (21.4%), 3-T scanners in 20 studies (71.5%) studies, and both 1.5-T and 3-T scanners in 2 studies (7.1%). Regarding *b* values, most studies ($n = 19$, 67.9%) used *b* values 0 and ≥ 800 s/mm². In 3 studies (10.7%), *b* values 0 and 750 s/mm² were used; in 2 studies (7.1%), *b* values 0 and 600 s/mm² were used. All studies used a clinically used single-shot echo-planar sequence.

Regarding ADC measurements, 5 studies (17.9%) took whole-lesion measurements and 23 studies (81.1%) single-slide measurements.

Luminal A type was diagnosed in 865 cases (28.9%), luminal B in 899 cases (30.1%), Her2-enriched in 597 cases (20.0%), and triple-negative in 629 cases (21.0%).

The mean ADC values of the tumors were as follows:

Luminal A type: 0.99×10^{-3} mm²/s (95% CI 0.94–1.04, $\tau^2 = 0.01$, $\chi^2 = 310.71$, $df = 14$, $I^2 = 95\%$); luminal B type: 0.97×10^{-3} mm²/s (95% CI 0.89–1.05, $\tau^2 = 0.02$, $\chi^2 = 715.49$, $df = 12$, $I^2 = 98\%$); Her2-enriched type: 1.02×10^{-3} mm²/s (95% CI 0.95–1.08, $\tau^2 = 0.02$, $\chi^2 = 641.08$, $df = 22$, $I^2 = 97\%$); triple-negative type: 0.99×10^{-3} mm²/s (95% CI 0.91–1.07, $\tau^2 = 0.03$, $\chi^2 = 962.41$, $df = 20$, $I^2 =$

Fig. 3. Forest plots. **a** Mean ADC values of the luminal A type. The pooled mean ADC value was $0.99 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.94–1.04, $\tau^2 = 0.01$, $\chi^2 = 310.71$, $df = 14$, $I^2 = 95\%$). **b** Mean ADC values of the luminal B type. The pooled mean ADC value was $0.97 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.89–1.05, $\tau^2 = 0.02$, $\chi^2 = 715.49$, $df = 12$, $I^2 = 98\%$). **c** Mean ADC values of the Her2-enriched type. The pooled mean ADC value was $1.02 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.95–1.08, $\tau^2 = 0.02$, $\chi^2 = 641.08$, $df = 22$, $I^2 = 97\%$). **d** Mean ADC values of the triple-negative type. The pooled mean ADC value was $0.99 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.91–1.07, $\tau^2 = 0.03$, $\chi^2 = 962.41$, $df = 20$, $I^2 = 98\%$).

98%) (Fig. 3). Figure 4 displays these results as a box plot graph. The ADC values of the BC groups overlapped significantly, with no clear proposed threshold to distinguish between types.

Discussion

According to this analysis, there were no differences in ADC values between the investigated BC types. Therefore, ADC cannot predict the hormone receptor status of BC. This finding is very important.

The clinical importance of different BC molecular subtypes cannot be disputed [14]. There are distinctive differences in prognosis and therapy for each immunohistochemically determined BC subtype [14]. The BC type with expression of ER and PR and low expression of Ki-67, i.e.,

the luminal A type, has the best prognosis with a 5-year overall survival rate of 95.1 versus 78.5% with the triple-negative type [14, 51]. This is also caused by the possibility of endocrine hormone therapy as a treatment option. Luminal B type is defined by the presence of ER and PR, with a high proliferation rate compared to Luminal A. Her2-enriched type is defined by the expression of the oncogene, Her2, which stimulates proliferation and inhibits apoptosis; importantly, this receptor can be targeted by antibody treatment, i.e., trastuzumab, showing its utter importance [52]. Lastly, the triple-negative type is defined by the absence of any of these receptors, resulting in the worst prognosis and limited treatment options [14].

Previously, it was shown that ADC values are associated with cellularity and tumor microstructure [6, 7]. Beyond sole cellularity, ADC values are associated with important histopathology parameters, reflecting prolifera-

Fig. 4. Box plots of the mean ADC values according to BC molecular subtype. The ADC values of the BC groups overlapped significantly, with no clear threshold value to distinguish between subtypes.

tion potential (Ki-67) and tumor suppressor genes (p53) [53, 54]. However, some immunohistochemical features of angiogenesis were not found to be associated with ADC values [55]. In short, there is ongoing debate about which features of tumors can be predicted from imaging.

The published results are conflicting about whether ADC values can also reflect immunohistochemical features in BC. For clarification, in some single-center studies, there were reports that Her2-positive tumors have slightly higher ADC values than Her2-negative tumors [56]. However, Choi et al. [57] could not identify any influence of the Her2 status on ADC values. In another study by Montemezzi et al. [38], the luminal A type showed the highest ADC values of all subtypes. According to other authors, the triple-negative type shows the highest ADC values [29, 42]. In a first multicenter study comprising 661 patients, no significant differences were reported between BC subtypes; this is corroborated by our present results [11].

Presumably, the differences reported by previous investigations were due to different scanner technologies and patient samples. For example, it is a known fact that mucinous carcinoma alone has distinctively higher ADC values, due to the histopathological type which seems to be more important than the immunohistochemical subtype [58]. Beyond this, DWI is biased by several technical factors. Thus, the measurement of a region of interest (ROI) can have an influence, depending on whether a sin-

gle-slide or whole-lesion measurement has been taken. Another important factor is the choice of b values to fit the ADC values [59]. Higher b values result in slightly lower ADC values and small b values in higher ADC values, based upon the fitting model. There might be an influence caused by contrast media application with yet inconclusive results. Non-mass lesions may produce different ADC values; it is a known fact that DWI and ADC values have a limited diagnostic accuracy in non-mass lesions [60]. All of these features can influence the ADC values and therefore an imaging modality that cannot yet be standardized. We could not further address these heterogeneities in subgroup analyses as the groups were too small.

Our analysis can harmonize these reported differences, i.e., that no significant differences of ADC values between molecular subtypes of BC can be assumed.

ADC values are reflective of tumor microstructure, with a moderate inverse correlation of the cellularity of tumors [6–9]. Presumably, the histopathologic differences of the molecular subtypes are not strong enough that they can be reliably predicted by DWI.

There are other reports highlighting the importance of necrosis for ADC values, with this being the only independent factor found to influence ADC values [31]. This association resulted in the highest ADC values being documented in triple-negative BC, i.e., due to the high rate of necrosis in this subtype.

Our results are in agreement with a recently published meta-analysis that stated that ADC cannot predict the outcome of neoadjuvant radiochemotherapy of BC [61]. There is nevertheless clear evidence that ADC values can aid in differentiating between benign and malignant tumors, as shown in a recent meta-analysis [10]. Most importantly, ADC values can aid important clinical decision-making despite the current negative results.

There were some inherent limitations to this study. Firstly, the meta-analysis was based on results published in the literature. There could thus be a certain publication bias due to the trend of reporting only positive or significant results, with studies with insignificant or negative results often being rejected or not even submitted for publication. Secondly, the search was restricted to English language papers only. Thirdly, the study investigated the widely used DWI technique using 2 *b* values. However, more advanced MRI sequences, such as intravoxel incoherent motion and diffusion kurtosis imaging, may have greater accuracy in discriminating BC phenotypes [62, 63]. Unfortunately, only a few studies have reported on the use of these sequences, so a comprehensive analysis could not be made.

Conclusions

Our systematic review and meta-analysis identified that ADC values cannot discriminate immunohistochemical molecular subtypes of BC.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors made substantial contributions to the study conception and design; acquisition, analysis and interpretation of data; and all agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A.S. and A.W. were involved in drafting the manuscript, revising it critically for important intellectual content, and approving the final version to be published.

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