Diagnostic performance of mono-exponential DWI versus diffusion kurtosis imaging in breast lesions. A meta-analysis

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Abstract

Background: This meta-analysis aimed to explore the diagnostic value of diffusion kurtosis imaging (DKI) compared to mono-exponential diffusion weighted imaging (DWI) in the diagnosis of breast cancer.

Methods: A systematic electronic literature search (up to September 2020) was conducted for published English-language studies comparing the diagnostic values of DKI and DWI for the detection of breast cancer. The data of mean kurtosis (MK), mean diffusivity (MD), and apparent diffusion coefficient (ADC) were extracted to construct 2 × 2 contingency tables. The pooled sensitivities, specificities, and areas under the receiver operating characteristic curve (AUCs) were compared between DKI and DWI in the diagnosis of breast cancer.

Results: Eight studies were finally included, with a total of 771 patients in the same population. Pooled sensitivities were 82.0% [95% confidence interval (95% CI), 78.2–85.3%] for ADC, 87.3% (95% CI, 83.9–90.1%) for MK, and 83.9% (95% CI, 80.2–87.1%) for MD. Pooled specificities were 81.1% (95% CI, 76.7–84.9%) for ADC, 85.1% (95% CI, 81.1–88.5%) for MK, and 83.2% (95% CI, 79.0–86.8%) for MD. According to the summary receiver operator characteristic curve analyses, the AUC was 0.901 for ADC, 0.930 for MK, and 0.918 for MD (ADC vs MK, P = .353; ADC vs MD, P = .611). No notable publication bias was found, while significant heterogeneity was observed.

Conclusions: Although DKI is feasible for identifying breast cancer, MD and MK offer similar diagnostic performance to ADC values. Thus, we recommend that DKI should not be included in the routine evaluation of breast lesions now.

Abbreviations: 95% CI = 95% confidence interval, ADC = apparent diffusion coefficient, AUC = areas under the receiver operating characteristic curve, DKI = diffusion kurtosis imaging, DWI = diffusion weighted imaging, MD = mean diffusivity, MK = mean kurtosis.

Keywords: breast lesions, diagnostic performance, DKI, DWI, meta-analysis

1. Introduction

Breast cancer is the most common cancer in women worldwide. For women with high risk of breast cancer, magnetic resonance imaging (MRI) has been proven to be an important tool for the examination of suspicious breast lesions, as MRI provides multi-directional and multi-sequence imaging along with high soft tissue discrimination ability and can define the nature of the lesions through the blood supply situation around the mass. More importantly, as a functional method of imaging, MRI can reflect the diffusion of water molecules in living tissues by the apparent diffusion coefficient (ADC). Diffusion-weighted imaging (DWI) has been widely used for diagnosis, prognosis, efficacy monitoring and evaluation of recurrence and metastasis.

However, more and more authors indicated that the movement of water molecules in breast tissue was affected by many factors and did not follow the Gaussian distribution in heterogeneous state, and DWI imaging model cannot fully reveal the motion of molecules. Jensen et al first introduced a non-Gaussian diffusion model called diffusion kurtosis imaging (DKI) in 2005. DKI was an extension of mono-exponential DWI, which based on the non-Gaussian properties of tissues, came by diffusing kurtosis information to describe the complex microstructure of tissues, theoretically DKI is more consistent with the reality of human tissues than DWI. Several previous studies also

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have evaluated the diagnostic value of DKI compared to DWI for the differentiation of breast lesions, and some of their results were not consistent. Thus, it’s still uncertain whether DKI can outperform mono-exponential DWI in the diagnosis of breast cancer.

Therefore, the purpose of this study was to compare the diagnostic performance of DKI and DWI, so as to show the possibility of DKI as an alternative method of DWI in the diagnosis of breast cancer.

2. Materials and Methods

2.1. Search strategy

This study did not require ethics approval from our institutional ethics committee, because of the design of this study (meta-analysis).

A systematic literature search on PubMed, Web of Science, and Cochrane Library (Wiley), IEEE, Elsevier, from September 2010 to July 2021, was conducted to identify studies exploring the value of DKI and DWI in the differential diagnosis of breast lesions. The search strategy used the combination of the following medical subject headings terms and keywords: “ADC” AND “DKI OR diffusion kurtosis imaging” AND “breast.” This search was limited to English language publications. The reference lists of finally included articles were assessed for potential inclusion.

2.2. Inclusion and exclusion criteria

Studies were eligible for inclusion if both DKI and DWI were performed in the same population for the differentiation of breast lesions, if raw data was sufficient to complete a 2 × 2 contingency table, and if the diagnosis was finally confirmed at pathology or follow-up. We excluded these types of studies including animal experiments, letters, reviews, case reports, or proceedings.

2.3. Data extraction and quality assessment

Retrieved hits were evaluated for possible inclusion in the study independently by 2 researchers. Any disagreements were resolved through discussion with a third researcher. The included studies were assessed for the required data. First, characteristics were extracted from each study in a standard format: author, year of publication, number of patients. Then true-positive (predicted to be malignant, actually malignant), false-negative (predicted to be benign, actually malignant), false-positive (predicted to be malignant, actually benign), and true-negative (predicted to be benign, actually benign) results of ADC, mean kurtosis (MK), and mean diffusivity (MD) were extracted or calculated to build the 2 × 2 contingency tables. The quality of the included studies was assessed by the Quality Assessment of diagnostic accuracy studies tool-2 [20] using Review Manager Version 5.3.

2.4. Statistical analysis

Heterogeneity among included studies was indicated by value calculated by Q statistic of the chi-square test. If there was notable heterogeneity, the pooled sensitivity and specificity were calculated using the random-effect model. The positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were also calculated as outlined above. Summary receiver operating characteristic (SROC) curves were built to calculate areas under the receiver operating characteristic curve (AUCs), which were used to evaluate the diagnostic performance of ADC, MK and MD. The Z test was performed to compare the difference of statistical significance in AUCs value, and further to assess diagnostic value of DKI and DWI in the diagnosis of breast cancer.

The threshold effect analysis, subgroups analysis and meta-regression analysis were used to explore potential sources of heterogeneity. The threshold effect was assessed by the Spearman correlation coefficient between Logit (sensitivity) and Logit (1-specificity), and P value < 0.05 suggested a threshold effect. Publication bias was evaluated by using Deek funnel plot, and P value < 0.05 could indicate the existence of publication bias. The above statistical analyses were carried out in Meta-DiSc (version 1.4).

3. Results

3.1. Literature search

We identified 30 abstracts through the initial literature search, and 12 abstracts were removed before the full text assessment. During the full text assessment, 10 studies were eliminated due to lack of sufficient data of DKI and DWI (n = 5), other organs included (n = 3), radiomics based on DKI (n = 1), and lack of malign lesions (n = 1) (Fig. 1). Baseline characteristics of the included studies were summarized in Table 1. The quality of the included studies was good according to the diagnostic accuracy studies tool-2 results (Fig. 2).

3.2. Quantitative synthesis

With the absence of threshold effect, we used the random-effect model to pool the sensitivity, and specificity outcomes. Pooled sensitivities were 82.0% (95% CI, 78.2–85.3%) for ADC, 87.3% (95% CI, 83.9–90.1%) for MK, and 83.9% (95% CI, 80.2–87.1%) for MD. Pooled specificities were 81.1% (95% CI, 76.7–84.9%) for ADC, 85.1% (95% CI, 81.1–88.5%) for MK, and 83.2% (95% CI, 79.0–86.8%) for MD (Table 2, Fig. 3). According to the summary receiver operator characteristic curve analyses, the AUC was 0.901 for ADC, 0.930 for MK, and 0.918 for MD (ADC vs MK, P = .333; ADC vs MD, P = .611). As shown in Table 2 and Figure 4.

3.3. Meta-regression and subgroup analysis

The meta-regression analysis indicated that field strength (1.5T vs 3.0T) contributed significantly to the heterogeneity for MD among the included studies (P = .04). Then we performed subgroup analyses between different study characteristics such as study design, field strength, maximum b-value, number of b-values, and estimation method. As shown in Table 3, the subgroup analysis showed that studies with fewer b-values (≤5) had higher AUC than that of studies with 6 or 7 b-values (P = .047 for MD, no statistical significance for MK). The studies with a maximum b-values of 2000–2500 s/mm² had higher AUC than those with a maximum b-value > 2500 s/mm², with no statistical significance.

3.4. Publication bias

Publication bias was assessed visually by using a scatter plot of the inverse of the square root of the effective sample size versus the diagnostic log odd ratio. The Deeks funnel plot regression showed that publication bias was not statistically significant for ADC (P = .46), MK (P = .59), and MD (P = .68).

4. Discussion

The findings of our study have shown that DKI was a valuable tool in differentiating malignant from benign breast lesions. Compared with ADC values, the MK and MD values showed higher AUC. However, there were no statistically significant differences, which yielded that neither technique was superior to the other.
Theoretically, DKI, which quantifies non-Gaussian diffusion, is believed to better characterize tissue micro-structure than mono-exponential DWI. DKI model potentially better reflects water diffusion in tissues at ultra-high b-values. Some studies have compared DKI with DWI in the qualitative diagnosis of breast lesions, but the results are inconsistent. Therefore, it is of great significance to summarize the published research results for evaluating the ability of DKI and making a comprehensive comparison with DWI in the diagnosis of breast cancer.

Mammography is the traditional method of breast examination, which is sensitive to calcification. Mammography depends on the density difference between the lesion and the normal breast tissue to observe the overall morphology and characteristics of the lesion, but it cannot expose the fine structure and blood supply of the lesion. While functional magnetic resonance imaging can reveal the characteristics of tissues from the molecular level, MK represented the average diffusion kurtosis of each ladder direction in space. It was an index to measure the complexity of...
organizational structure. MK value was proportional to the complexity of the organizational process, and the more complex the structure, the greater the MK value. MD represented the apparent diffusion coefficient value corrected by non-Gaussian distribution. ADC value quantified the extent to which molecular dispersion was restricted. Although radiomics and deep learning methods were applied in mammography research, MRI still shows more advantages in the diagnosis of breast disease.

For the applications of body DKI, the number and maximum value of b-values varied from each other in previous study. Theoretically, at least 3 b-values were suggested for clinical applications in body DKI. In fact, it may be advantageous to avoid acquiring an excessive number of b-values. The subgroup analysis (number of b-values) in this study showed that the group with 3 - 5 b-values had higher AUC than that of 6 or 7 b-values for MD ($P = .047$). Moreover, the excessive number of b-values might increase the overall scan time, both increasing the likelihood of motion artifact and hindering incorporation of DKI into clinical protocols.

In the DKI studies of brain, it is suggested that the maximum b-value is 2000-2500 s/mm$^2$. The use of such a high b-value in other organs outside the brain is limited by the signal-to-noise ratio and faster signal decay of the transverse relaxation. Compared with head coil, the lower sensitivity of flexible surface coil also leads to lower signal-to-noise ratio in tissues. We found that these studies (maximum b-value: 2000–2500 s/mm$^2$) had higher AUC than studies with maximum b-value > 2500 s/mm$^2$, which was not statistically significant. Therefore, considering the examination time and equipment requirements, it may not be necessary to use an ultra-high b-value of 2500–3000 s/mm$^2$.

Although some published papers suggested that DKI was superior to DWI in diagnostic and therapeutic evaluation of tumors, Li et al (in ovarian tumors), Roethke et al (in prostate), Tamura et al (in lung), and Yang L et al (in liver) didn’t report the additional value of DKI superior to DWI. For our results, large-scale prospective studies were needed to further verify our findings in the diagnosis of breast cancer.

5. Limitations
Some limitations of this meta-analysis should be noted. First, a small number of studies were included. Our meta-analysis was aimed to assess the role of DKI compared to DWI in breast. Therefore, only studies including both DKI and DWI were evaluated. In addition, studies that didn’t have enough data to construct a $2 \times 2$ contingency table were removed, even if they included the 2 imaging methods mentioned above. Secondly, we compared the diagnostic value of DKI and DWI in the differential diagnosis of breast lesions, but we did not evaluate other important issues, such as tumor grade or prediction of invasion due to the small number of related papers.

6. Conclusion
In conclusion, DKI and DWI showed comparable diagnostic performance for the differentiation of breast lesions. On the basis of current evidence, we do not recommend including DKI in routine clinical assessment of breast lesions for the moment. However, considering the advantages and potential of DKI, we still expect further studies with standardized method and optimized imaging protocols to improve the performance of DKI in the diagnosis of breast lesions.

Author contributions
Formal analysis: Yumei Jin. Methodology: Yewu Wang, Jun Zhang. Software: Mou Li, Shaoyu Wang, Huapeng Zhang. Supervision: Bin Song. Validation: Bin Song. Writing – original draft: Yumei Jin.
Figure 3. Pooled sensitivity and specificity of ADC, MK, MD. ADC = apparent diffusion coefficient, MD = mean diffusivity, MK = mean kurtosis.

Figure 4. ROC analyses of ADC, MK, MD. ADC = apparent diffusion coefficient, MD = mean diffusivity, MK = mean kurtosis, ROC = receiver operator characteristic curve.
The results of the meta-regression and subgroup analyses in this meta-analysis.

| Characteristic                  | No. of Studies | ADC | AUC | P     | SPEC | SENS | P     | AUC | P     |
|--------------------------------|----------------|-----|-----|-------|------|------|-------|-----|-------|
| Study design                   | Retro          | 2   | 0.25| 0.04  | 0.93 | 0.87 | 0.91  | 0.92| 0.92  |
| Field strength                 | 1.5 T          | 6   | 0.04| 0.87  | 0.85 | 0.82 | 0.93  | 0.92| 0.92  |
| Maximum value (s/mm²)          | 1500 ≤ b ≤ 2000| 4   | 0.04| 0.87  | 0.85 | 0.82 | 0.93  | 0.92| 0.92  |
| Number of VOIs                  | 1≤5            | 4   | 0.04| 0.87  | 0.85 | 0.82 | 0.93  | 0.92| 0.92  |
|                              | >5             | 5   | 0.04| 0.87  | 0.85 | 0.82 | 0.93  | 0.92| 0.92  |

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