A meta-analysis on the diagnostic value of diffusion-weighted imaging on ovarian cancer

Guidong Dai*, Kali Liang2*, Zhengyuan Xiao1, Qin Yang2, Shugen Yang1

1Department of Radiography, the Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China; 2Department of Radiography, the Affiliated Hospital (T.C.M) of Southwest Medical University, Luzhou, Sichuan, China.

*Guidong Dai and Kali Liang contributed equally to this work.

Summary

Purpose: This study systematically evaluated the potential influences of diffusion-weighted imaging (DWI) on the initial diagnosis, clinical decision making and diagnostic accuracy of ovarian cancer in the follow-up period.

Methods: Literature on the correlation between DWI and diagnosis of ovarian cancer were searched from PubMed, Embase, Cochrane Library, and Web of Science published before January 1, 2019. References in enrolled eligible literature were manually reviewed. Quality assessment on the diagnostic accuracy was performed using the QUADAS scale. Receiver operating characteristics (ROC) curve was depicted using STATA 12.0. Study heterogeneity and its sources were determined. Sensitivity (SEN), specificity (SPF), positive likelihood ratio (+LR), negative likelihood ratio (-LR) and diagnostic odds ratio (DOR) of eligible studies were calculated for depicting forest plot and summary of ROC curve (SROC). The area under the curve (AUC) was calculated.

Results: A total of 15 articles involving 930 ovarian cancer cases and 832 control cases were enrolled. DWI was identified to exert a certain diagnostic value on ovarian cancer. The 95%CI of the merged SEN (91%, 95%CI=84-95%), SPF (85%, 95%CI=78-90%), +LR (6.18, 95%CI=4.17-9.15) and -LR (4.05, 95%CI=3.30-4.79) were calculated using the random-effects model due to the slight heterogeneity among these studies. AUC was 0.94 (95%CI=0.91-0.96). Subgroup analysis in Asian population obtained the following results: SEN was 85% (95%CI=78-91%), SPF 83% (95%CI=72-90%), +LR 0.18 (95%CI=0.11-0.27), -LR 3.34 (95%CI=2.60-4.09) and DOR 3.34 (95%CI=2.60-4.09); AUC was 0.91 (95%CI=0.88-0.93). In Caucasian population, SEN was 96% (95%CI=83-99%), SPF 89% (95%CI=84-93%), +LR 41.36 (95%CI=5.05-287.48), -LR 0.06 (95%CI=0.02-0.18) and DOR 5.31(95%CI=3.93-6.69); AUC was 0.94 (95%CI=0.91-0.96).

Conclusions: This meta-analysis proved that DWI exerted a relatively high sensitivity and specificity in diagnosing ovarian cancer, especially in the Caucasian population. This conclusion still needs to be further verified in a multi-center study with a large sample size.

Key words: DWI, diagnostic value, ovarian cancer, meta-analysis

Introduction

Ovarian cancer (OC) is a common tumor in gynecology, and its incidence is second only to cervical cancer and endometrial cancer in the reproductive system [1-3]. Due to the deep location of the ovaries in the pelvic cavity and occult early-stage symptoms, over 70% of OC patients are diagnosed in advanced stage accompanied by multiple metastases of the peritoneum. The mortality rate of OC is extremely high, with median survival of 18-24 months [3]. The 5-year recurrence rate of OC is up to 80%, and its cure rate for advanced cases is only 20-50%. Unfortunately, the mortality of OC
remains high and stable even if the therapeutic approaches have made considerable progression [4,5]. OC genesis is a complex process involving genetic factors, estrogen levels and human papillomavirus (HPV) infection. Females with a family history of OC experience a higher onset risk of disease than those without a family history. In addition, long-term estrogen stimulation and immune hypofunction could also lead to the OC tumorigenesis [6,7]. Therefore, post-operative diagnosis of metastatic or recurrent OC as early as possible is particularly important, and imaging examinations provide direct evidence for clinical diagnosis and treatment [8]. Generally speaking, clinical significances of MRI and CT examinations after the second surgery are very limited in diagnosing small recurrent lesions or metastatic loci [9]. Diffusion-weighted imaging (DWI) can reflect the changes of water molecules in the pathological state of the tissues, which undoubtedly promotes the development of non-invasive techniques for identifying tumors [10]. DWI is a functional imaging technique in nuclear magnetic resonance. It examines the movement of water molecules to generate tissue imaging contrast [11,12]. The homogeneity of DWI is varied linearly by a pulsed field gradient. Since movement of water molecules is proportional to the magnet strength, the protons begin to process at different rates, resulting in dispersion of the phase and signal loss. The molecular motion is positively correlated with the phase loss [12,13]. DWI has been widely used in clinical examinations [14,15]. The application of DWI in pelvic tumors contributes to in-depth researches on OC [14,16].

This study analyzed the relevant literature on reporting the application of DWI in diagnosing OC and our aim was to evaluate the diagnostic value of DWI in OC.

Table 1. Characteristics and methodology assessment of individual studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Design</th>
<th>Reference standard</th>
<th>No. of lesions</th>
<th>Age (y)</th>
<th>Case</th>
<th>Control</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>QUADAS score</th>
</tr>
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<tbody>
<tr>
<td>Michielsen, 2017</td>
<td>Belgium</td>
<td>Caucasian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>NA</td>
<td>61</td>
<td>50</td>
<td>44</td>
<td>47</td>
<td>1</td>
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<td>12</td>
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<td>Michielsen, 2016</td>
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<td>Caucasian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>NA</td>
<td>63</td>
<td>48</td>
<td>3</td>
<td>47</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Kovac, 2015</td>
<td>Serbia</td>
<td>Caucasian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>162</td>
<td>60.6</td>
<td>124</td>
<td>58</td>
<td>124</td>
<td>6</td>
<td>0</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Fan, 2015</td>
<td>China</td>
<td>Asian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>88</td>
<td>46.7</td>
<td>58</td>
<td>30</td>
<td>54</td>
<td>5</td>
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<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Malek, 2014</td>
<td>Iran</td>
<td>Asian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>56</td>
<td>36.5</td>
<td>27</td>
<td>29</td>
<td>24</td>
<td>10</td>
<td>3</td>
<td>19</td>
<td>12</td>
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<tr>
<td>Zhang, 2014</td>
<td>China</td>
<td>Asian</td>
<td>Prospective</td>
<td>Histopathology</td>
<td>144</td>
<td>NA</td>
<td>41</td>
<td>103</td>
<td>38</td>
<td>11</td>
<td>3</td>
<td>92</td>
<td>12</td>
</tr>
<tr>
<td>Cappabianca, 2013</td>
<td>Italy</td>
<td>Caucasian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>91</td>
<td>NA</td>
<td>35</td>
<td>56</td>
<td>35</td>
<td>11</td>
<td>0</td>
<td>45</td>
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</tr>
<tr>
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<td>USA</td>
<td>Caucasian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>57</td>
<td>NA</td>
<td>9</td>
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<td>3</td>
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<td>25</td>
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<td>Takeuchi, 2015</td>
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<td>Asian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>40</td>
<td>55</td>
<td>27</td>
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<td>Caucasian</td>
<td>Retrospective</td>
<td>Histopathology</td>
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<td>Asian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>202</td>
<td>56.5</td>
<td>128</td>
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<td>85</td>
<td>7</td>
<td>43</td>
<td>67</td>
<td>13</td>
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<tr>
<td>Li, 2012</td>
<td>China</td>
<td>Asian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>131</td>
<td>NA</td>
<td>85</td>
<td>46</td>
<td>77</td>
<td>5</td>
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<td>41</td>
<td>11</td>
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<tr>
<td>Takeuchi, 2010</td>
<td>Japan</td>
<td>Asian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>49</td>
<td>59</td>
<td>39</td>
<td>10</td>
<td>29</td>
<td>2</td>
<td>10</td>
<td>8</td>
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</tr>
<tr>
<td>Low, 2009</td>
<td>USA</td>
<td>Caucasian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>19</td>
<td>NA</td>
<td>9</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>3</td>
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<td>10</td>
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<tr>
<td>Fujii, 2008</td>
<td>Japan</td>
<td>Asian</td>
<td>Retrospective</td>
<td>Histopathology</td>
<td>123</td>
<td>52</td>
<td>42</td>
<td>81</td>
<td>36</td>
<td>37</td>
<td>6</td>
<td>44</td>
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</table>

NA: not available, QUADAS: quality assessment of diagnostic accuracy studies
Methods

Literature search

Literature on the correlation between DWI and the diagnosis of OC were searched from PubMed, Embase, Cochrane Library and Web of Science published before January 1, 2019. Keywords were as follows: “diffusion weighted imaging”, “DWI” and “ovarian cancer” and “diagnosis”, “detection”. References of enrolled eligible literature were manually reviewed. Keywords were adjusted in each database and mainly divided into three parts: target disease, evaluated trials and diagnostic accuracy.

Inclusion and exclusion criteria

Published literature on the diagnostic value of DWI in OC was searched. Inclusion criteria were applied as follows: (1) Publication in English language; (2) Literature reporting the diagnostic value of DWI in OC; (3) Prospective or retrospective study; (4) Sample size ≥ 20 cases; (5) DWI was performed for each subject; (6) Complete or latest data were enrolled if data were overlapping; and (7) True positive (TP), false positive (FP), true negative (TN) and false negative (FN) were directly provided or relative data were provided to calculate these parameters.

Exclusion criteria were applied as follows: (1) Literature on evaluating OC only; (2) Other examinations rather than DWI; (3) Abstracts, reviews, reports, and low-quality literature.

Data extraction

Data acquisition was independently carried out by two reviewers, and a third reviewer was responsible for re-evaluating disagreements. Baseline data acquisition included: first author, study type, sample size, year of publication, region, examinations, outcome parameters.

Evaluation of QUADAS

The enrolled literature consisted of diagnostic trials. Diagnostic quality was evaluated by the QUADAS scale, with 71% (11/14) as the boundary to distinguish high from low scores [17].

Statistics

Statistical analyses were performed using Stata software (version 12.0, Stata Corporation, College Sta-
Figure 2. Forest plots of sensitivity (A), specificity (B), positive predictive value (C) and negative predictive value (D) by diffusion-weighted imaging as a diagnostic technique for ovarian cancer including both Asian and Caucasian populations in the studies included for meta-analysis. Each solid circle represents an eligible study. The size of the solid circle reflects the sample size of each eligible study. Error bars represent 95% CI.

Figure 3. Forest plots of sensitivity (A), specificity (B), positive predictive value (C) and negative predictive value (D) by diffusion-weighted imaging as a diagnostic technique for ovarian cancer in Asian population. Each solid circle represents an eligible study. The size of the solid circle reflects the sample size of each eligible study. Error bars represent 95% CI.
Results

Characteristics of the studies

A total of 15 articles involving 930 ovarian cancer cases and 832 control cases were enrolled [18-20]. Baseline characteristics and prognostic parameters are displayed in Table 1 [21-32]. The searching and selection process is depicted in Figure 1. The enrolled literature graded over 11 points of QUADAS score suggested that it was of high quality.

Quantitative synthesis results

This study came to the conclusion that DWI elevates the diagnostic efficacy of OC. Here, $I^2=82.04\%$ of the merged SEN and the random-effects model was utilized. The merged SEN was calculated as 91% (95%CI=84-95%). Also, if $I^2=85.77\%$ of the merged SPF we also used the random-effects model for analysis. The merge SPF was 85% (95%CI=78-90%). The merged +LR (6.18, 95%CI=4.17-9.15) and -LR (4.05, 95%CI=3.30-4.79) were calculated (Figure 2). The merged DOR was 4.05 (95%CI=3.30-4.79, Figure 5A). After depicting SROC, AUC was 0.94 (95%CI=0.91-0.96, Figure 6A).

Subgroup analysis in Asian population obtained the following results: SEN was 85% (95%CI=78-91), SPF was 85% (95%CI=72-90), +LR was 0.18 (95%CI=0.11-0.27), -LR was 3.34 (95%CI=2.60-4.09) and DOR was 3.34 (95%CI=2.60-4.09); AUC was 0.91 (95%CI=0.88-0.93) (Figure 3, 5B and 6B).

In Caucasian population, SEN was 96% (95%CI=83-99), SPF was 89% (95%CI=84-93), +LR was 41.36 (95%CI=5.95-287.48), -LR was 0.06 (95%CI=0.02-0.18) and DOR was 5.31(95%CI=3.93-6.69); AUC was 0.94 (95%CI=0.91-0.96) (Figure 4, 5C and 6C).

Test of heterogeneity

ROC curve was not in the shoulder-brachial distribution, suggesting that there was no heterogeneity due to threshold effects. Heterogeneity judgment caused by non-threshold effect was evaluated by DOR forest map. DOR on the individual
study and the merged DOR were not distributed along the same straight line, indicating heterogeneity in the enrolled literature (Figure 6).

Publication bias

Publication bias in this study was assessed by depicting Deek’s funnel. The systematic shape of the funnel diagram indicated no significant publication bias (p=0.462).

Discussion

OC is a challenging gynecological tumor. Typical symptoms of OC are occult in early stage and gradually become apparent during advanced stages. Females should be vigilant about abdominal pain, bloating, increased abdominal circumference, loss of appetite, and a sense of satiety more than 12 times per month [1-5]. Therefore, early diagnosis,
precise treatment and recurrence prevention of OC have been well concerned [7,8]. Recent studies have identified the diagnostic potential of DWI in multiple types of diseases, which markedly elevates the diagnostic efficacy of OC [16]. Diagnostic efficacy of DWI on OC, as well as its sensitivity and specificity, should be well explored to enhance the clinical outcomes of OC patients.

DWI examination can quantitatively evaluate tissue structure and cell component, and it accurately determines the lesion location, size and nature as well as the chemotherapy outcomes [10-12]. DWI provides evidence for clinical diagnosis and complements morphology and biochemical examinations [13]. DWI images are generated based on the degree of molecular motion limitation and attenuation, which indirectly reflects the microstructure. Two factors greatly influence DWI: The first is the diffusion sensitivity factor (b value), the magnetic diffusion gradient [14,15]. The more attenuated the image is at a given position, the greater diffusion there is in the direction of the diffusion gradient. The second factor is the strength of the diffusion gradient [13-15]. DWI exerts a certain clinical importance in diagnosing OC.

DWI differentiates benign and malignant tumors according to the biological metabolism of tumor cells. The working principle of DWI is essentially different from that of CT and MRI. DWI detects small recurrent or metastasis lesions earlier, thus improving the early-stage diagnostic rate [15,16]. Nevertheless, DWI examination is expensive and could not be applied as a routine examination item for diagnosis or follow-up [14,15]. This study focused on searching the most optimal method for diagnosing OC with the highest sensitivity and specificity. Our results identified that DWI exerted certain advantages in diagnosing OC. A total of 15 articles involving 930 ovarian cancer cases and 832 control cases were enrolled. DWI was identified to exert a certain diagnostic value on OC. The data revealed that the merge SEN was 91%, SPF 85%, +LR 6.18, -LR 4.05 and AUC 0.94. Subgroup analysis in Asian population obtained the following results: SEN was 85%, SPF 83%, +LR 0.18, -LR 3.34, DOR 3.34 and AUC 0.91. In Caucasian population, SEN was 96%, SPF 89%, +LR 41.36, -LR 0.06, DOR 5.31 and AUC 0.94.

Some limitations should be noteworthy. Firstly, the gold standard for diagnosing OC remained different in the enrolled literature, which may influence the accuracy of our results. Secondly, we did not explore the in-depth correlation between DWI and CA125 level, tumor location and tumor size of recurrent lesions owing to the limited sample size. Thirdly, pathogenic factors vary a lot in different ethnicities and may result in differences in diagnosis. This study only focused on the Asian and Caucasian populations. We were unclear whether the diagnostic potential of DWI in OC is different in other populations. Fourthly, unpublished literature and those published in other languages (English language was limited here) could lead to publication biases.

To sum up, this study identified accurate diagnostic potential in OC. However, this conclusion still needs to be further validated in a multi-center study with a large sample size. Gene-environment impact on diagnosing OC should also be fully explored.

Conclusions

This meta-analysis proved that DWI exerted a relatively high sensitivity and specificity in diagnosing OC, especially in Caucasian population.

Conflict of interests

The authors declare no conflict of interests.

References


32. Zhang H, Zhang GF, He ZY, Li ZY, Zhang GX. Prospective evaluation of 3T MRI findings for primary adnexal lesions and comparison with the final histological diagnosis. Arch Gynecol Obstet 2014;289:357-64.