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REVIEW ARTICLE

Diagnostic performance of diffusion-weighted MRI for detection of pelvic metastatic lymph nodes in patients with cervical cancer: a systematic review and meta-analysis

G SHEN, MD, H ZHOU, MD, Z JIA, MD and H DENG, MD

Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Address correspondence to: Dr Zhiyun Jia
E-mail: zhiyunjia@hotmail.com

Guohua Shen and Huijun Zhou contributed equally to this work.

ABSTRACT

In recent years, diffusion-weighted (DW) MRI has emerged as a new technique for detecting the pelvic lymph metastases in patients with cervical cancer. The aim of this meta-analysis was to assess the diagnostic value of DW imaging (DWI) for benign/malignant discrimination of pelvic lymph nodes (LNs). Studies about DWI for the detection of metastatic LNs were searched in the PubMed, EMBASE, Web of Science, EBSCO, the Cochrane Library and three Chinese databases. Based on the extracted data, we determined pooled sensitivities, specificities and diagnostic odds ratios (DORs) across studies, calculated positive and negative likelihood ratios (LRs) and constructed summary receiver operating characteristic curves with area under the curve (AUC) and Q^* obtained. We also analysed the heterogeneity between studies based on subgroup analysis, threshold effect and publication bias. In total, 15 studies involving 1021 patients met the inclusion criteria. The pooled sensitivity, specificity and DOR of DWI were 0.86 [95% confidence interval (CI), 0.84–0.89], 0.84 (95% CI, 0.83–0.86) and 47.21 (95% CI, 25.67–86.81), respectively. LR syntheses yielded overall positive LR of 6.55 (95% CI, 4.77–9.01) and negative LR of 0.17 (95% CI, 0.12–0.23). The AUC and Q^* index were 0.9384 and 0.8754, respectively. The heterogeneity was relatively high between studies; however, there was no evidence for threshold effect and publication bias. DWI is beneficial in the pelvic nodal assessment in patients with cervical cancer. Large-scale, high-quality trials with standard protocols are required to evaluate its clinical value for discrimination of metastatic from non-metastatic pelvic LNs in patients with cervical cancer. Advances in knowledge include providing evidence to assess the role of DWI in nodal staging of cervical cancer.

Cervical cancer is one of the most common gynaecological malignancies, which takes third place among female genital malignancies in the world, following the uterine body and ovarian cancers.^{1,2} During the past few decades, there has been an obvious decline in the death rate and incidence of cervical cancer in developed countries observed, but this has not been mirrored by a similar decline in developing countries.³

The extent of lymph node (LN) metastasis is an important prognostic factor, and the survival rates of patients with nodal metastases are significantly lower than those of patients without such metastases.^{4–9} Surgical LN assessment is the gold standard for the diagnosis of LN metastasis;¹⁰ however, it increases the time and cost of diagnosis with an increased risk of immediate and delayed complications to the patient. Therefore, a non-invasive

technique that accurately identifies LN metastasis would be valuable.

CT and MRI are widely used to assess metastatic LNs of patients with cervical cancer, which is based on the measurement of node size. However, the sensitivity of these imaging techniques for the detection of LN metastasis in uterine cervical cancer is between only 30% and 73%, while the specificity is between 44% and 93%.^{11–17} Fluorine-18 fludeoxyglucose positron emission tomography/CT is considered to be a useful technique in the detection of LN metastasis for tumour with high sensitivity and specificity, especially as it could provide diagnostic information of the entire body, but so far it has not been widely used for clinical application owing to high cost. Diffusion-weighted imaging (DWI) is sensitive to the diffusion of water molecules in tissue,

which can make subtle abnormality more obvious and can provide better characterization of tissue and their pathological processes at microscopic level.¹⁸ Additionally, the quantitative assessment can be performed by the measurement of the apparent diffusion coefficient (ADC).¹⁹ Of late, DWI has been introduced for the differentiation of benign and malignant lesions in extracranial organs, especially for diagnosis of abdominal and pelvic organs.^{20,21} Although multiple previous studies have discussed the feasibility of DWI in detecting and diagnosing cervical cancer,^{22–24} the findings are inconclusive or conflicting. Thus, we undertook a meta-analysis to evaluate the possible benefit of DWI to differentiate metastatic from non-metastatic LNs in uterine cervical cancer.

METHODS AND MATERIALS

Literature search

The PubMed, EMBASE, Web of Science, EBSCO, the Cochrane Library and three Chinese databases—CNKI, VIP and WanFang—were searched for eligible studies about the diagnostic performance of DWI-MR for the pelvic nodal assessment in patients with cervical cancer. The search strategy was based on the combination of the following key words: (“Diffusion Magnetic Resonance Imaging” or “Diffusion MRI” or “Diffusion Weighted MRI” or “DWI” or “diffusion-weighted magnetic resonance imaging” or “MRI DWI” or “diffusion-weighted imaging” or “diffusion-weighted-MRI”) and (“Uterine Cervical Neoplasms” or “Cervical Neoplasms” or “Cervical cancer” or “cervical carcinoma” or “cervix cancer” or “Cervix Neoplasms” or “Cervix carcinoma”). In addition, reference lists of included studies were manually screened for additional eligible studies.

Study selection

Two reviewers independently judged the eligibility with disagreements resolved by discussion and consensus. The inclusion criteria were as follows: (1) DWI was identified to detect pelvic LN metastasis of cervical cancer; (2) histopathology results and/or clinical follow-up were used as the reference standard; (3) only studies with absolute numbers of true-positive (TP), false-positive (FP), false-negative (FN) and true-negative (TN) extracted could be included; (4) the studies were based on a per-lesion analysis; (5) when data or subsets of data were presented in more

than one article, the article with the most details or the most recent article was chosen. Because of non-sufficient information, the reviews, letters, conference abstracts and case reports were excluded. The studies consisting of no more than 10 patients were also excluded.

Data extraction and quality assessment

From the studies finally selected, the same investigators independently extracted relevant data including basic description of studies (first author, publication year, original country), study population (sample, age, type of primary cancer), study design (prospective *vs* retrospective, patient enrolment and blindness), technique parameters (magnetic strength, *b*-value and scanning sequence) and reference standard. Obviously, TP, FP, FN and TN results were also recorded for further analysis. In addition, the quality assessment of included studies was performed with Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tools, which comprised 14 questions, and each item was answered by “yes”, “no” or “unclear”.²⁵ Score 12 was used as the cut-off of high and low quality.

Statistical analyses

We conducted all analysis based on a per-region/node data analysis. The pooled sensitivity, specificity and diagnostic odds ratio (DOR) with 95% confidence intervals (CIs) were calculated based on the bivariate analysis.²⁶ In addition, likelihood ratios (LRs) that were the combination of sensitivity and specificity in the calculation were also obtained. The discrimination ability was better with higher DOR, higher positive LR and lower negative LR. Furthermore, we also constructed the summary receiver operating characteristic (SROC) curves with area under the curve (AUC) and Q^* estimate obtained.

With regard to the heterogeneity between studies, we used the inconsistency index (I^2) test to examine it. A fixed model was used if I^2 value was $>50\%$, which reflected substantial heterogeneity; otherwise, a fixed model was used. To explain the source of heterogeneity, we performed the subgroup analysis according to the study design, patient enrolment, blindness, QUADAS score and the reference standard. In addition, the meta-regression and publication bias analysis were also performed. All statistical analyses were conducted using Meta-Disc v. 1.4 (XI Cochrane Colloquium; Barcelona, Spain) and STATA v. 12.0 (StataCorp LP; College Station, TX).

RESULTS

Study selection and description

We initially identified 520 articles after electronic search and excluded 455 articles after reviewing the title and abstract. The remaining 65 articles were screened in full text, and 15 articles^{22,23,27–39} were finally included for further analysis. The selection process and reasons for exclusion were shown in Figure 1. In total, 1021 patients involving 3134 LNs were enrolled in this meta-analysis. Of all studies, only two studies^{27,28} enrolled patients prospectively, another six studies^{22,23,29,31,38,39} were retrospectively designed and the remaining were unknown. Patients were enrolled consecutively in five articles.^{28,29,31–33}

Figure 1. Flowchart for study selection.

Table 1. Principal characteristics of eligible studies included in this meta-analysis

Study	Nation	Patients	Lesions	Mean age (range)	Study design	Patient enrolment	Blind	Review	Type of cervical cancer	Diffusion-weighted imaging parameters (<i>b</i> -values s mm ⁻²)	Cut-off (×10 ⁻³ mm s ⁻²)	Reference standard
Hu et al ³³	China	26	77	44.6 ± 7.5 (26–58)	ND	C	Y	2	SCC (23), AC (1), ASC (1), SCLC (1)	1.5 T SE-EPI (0,800)	1.14	HP
Liao and Chen ³⁴	China	53	108	45 (25–59)	ND	ND	Y	2	SCC (45), AC (4), ASC (4)	1.5 T SE-EPI (0,800)	1.11	HP
Ling et al ³⁵	China	36	86	45 ± 12	ND	ND	ND	ND	SCC (32), AC (4)	1.5 T SE-EPI (0,500,1000)	ND	HP
Liu et al ³⁶	China	49	116	44 (27–75)	ND	ND	Y	2	SCC (44), AC (3), ASC (2)	3 T SE-EPI (0,600,1000)	0.778	HP
Liu et al ³⁷	China	36	159	44.1 (32–62)	ND	ND	ND	ND	SCC (26), AC (9), CS (1)	1.5 T ASSET/SE-EPI (0,1000)	0.983	HP
Ren et al ³⁸	China	42	188	43.16 ± 8.95	R	ND	Y	2	SCC (93), AC (18)	1.5 T SS-EPI (0,800)	0.879	HP
Zhang et al ³⁹	China	65	392	45.6 ± 6.5 (35–73)	R	ND	Y	2	ND	1.5 T SS-EPI (0,800)	0.881	HP
Chen et al ²⁸	China	61	153	46 (25–60)	P	ND	ND	2	SCC (52), AC (5), ASC (4)	1.5 T SE-EPI (0,800)	1.15	HP
Chen et al ²⁷	China	26	77	35 (26–58)	P	C	ND	2	SCC (23), AC (1), ASC (1), SCLC (1)	1.5 T STIR-EPI (0,800)	1.14	HP
Choi et al ²⁹	Republic of Korea	163	339	52 ± 13 (28–75)	R	C	Y	2	ND	1.5 T SS-SE-EPI (0,1000)	0.864	Clinical and imaging follow-up;
Xue et al ³²	China	24	66	37.9	ND	C	ND	2	AC (5), epitheliums (19)	1.5 T STIR-EPI (800)	0.921	HP

(Continued)

Table 1. (Continued)

Study	Nation	Patients	Lesions	Mean age (range)	Study design	Patient enrolment	Blind	Review	Type of cervical cancer	Diffusion-weighted imaging parameters (<i>b</i> -values s mm ⁻²)	Cut-off (×10 ⁻³ mm s ⁻²)	Reference standard
Kim <i>et al</i> ²²	Republic of Korea	125	250	48 ± 12	R	ND	Y	2	ND	1.5 T SS-EPI (0,1000)	0.862	HP
Kim <i>et al</i> ²³	Republic of Korea	143	680	48 ± 11 (24–73)	R	ND	Y	2	ND	1.5 T SE-EPI (0,1000)	0.911	HP
Liu <i>et al</i> ³⁰	China	42	188	45.3 (30–62)	ND	ND	Y	2	ND	1.5 T SS-SE-EPI/ASSET (0,1000)	0.881	HP
Park <i>et al</i> ³¹	Republic of Korea	130	255	49 ± 14	R		Y	2	ND	1.5 T SS-SE-EPI (0,1000)	0.790	HP

AC, adenocarcinoma; ASC, adenosquamous carcinoma; ASSET, array spatial sensitivity encoding technique; C, consecutive; CS, carcinosarcoma; HP, histopathology; ND, not documented; P, prospective; R, retrospective; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; SE-EPI, spin echo echoplanar imaging; SS, single shot; SS-EPI, SS echo-planar imaging; STIR-EPI, short tau inversion recovery echoplanar imaging; Y, yes (blind).

The principal characteristics of included studies were presented in [Table 1](#).

Assessment of study quality and publication bias

The results of quality assessment were shown in [Table 2](#). All studies fulfilled 11 or more of the 14 items in QUADAS tool. Common weaknesses were concentrated in the time interval between tests (Item 4) and the blindness between the reference standard and index test (Items 10 and 11). Based on the results of Deeks' funnel plot asymmetry test ($p = 0.329$), no publication bias was found ([Figure 2](#)).

Diagnostic accuracy of diffusion-weighted imaging

The pooled sensitivity, specificity and DOR of DWI were 0.86 (95% CI, 0.84–0.89), 0.84 (95% CI, 0.83–0.86) and 47.21 (95% CI, 25.67–86.81), respectively. LR syntheses demonstrated an overall positive LR of 6.55 (95% CI, 4.77–9.01) and negative LR of 0.17 (95% CI, 0.12–0.23). The SROC curves showed very good diagnostic performance overall for DWI with AUC and Q* index obtained (0.9384 for AUC and 0.8754 for Q* index) ([Figure 3](#)).

With regard to the threshold effect, a Spearman's rank correlation test was performed and was determined to be 0.38 ($p = 0.162$), which indicated the absence of threshold effect. The subgroup analyses were performed based on patient enrolment, blindness and quality assessment. The results were presented in [Table 3](#), which showed there were no significant differences among those subgroups ($p > 0.05$). In addition, the heterogeneity between studies was highly significant ($I^2 > 50\%$); thus, we should interpret the results with care.

The differences in ADC measurements between metastatic LNs and non-metastatic LNs were statistically significant, with no overlapping of the 95% CIs [0.85 (95% CI, 0.84–0.87) vs 1.04 (95% CI, 1.04–1.05), $p < 0.05$]. This is illustrated in [Figure 4](#).

DISCUSSION

Compared with the surgical LN assessment that is the gold standard for the diagnosis of LN metastasis, a non-invasive technique would be of great benefit to the patients with cervical cancer, which will reduce the time and cost of diagnosis, as well as the risk of immediate and delayed complications.^{10,40} Traditional size criteria that the short-axis diameter of 10 mm was commonly used as the cut-off for benign and malignant lesions revealed a relevantly low sensitivity.^{12,41} DWI that provides information about the integrity of cell membranes and tissue consistency is non-invasive and enables the radiologist to move from morphological to functional assessment of diseases. Furthermore, quantitative assessment is possible by the ADC values, which could be measured by DWI.⁴² As a result of technical developments and recent research, DWI has emerged as a promising tool for detecting and characterizing gynaecologic tumours, determining the anatomic extent of disease, understanding lesion pathophysiology and predicting and monitoring treatment outcome.^{10,25,26}

DWI has been reported to be capable of distinguishing metastatic from benign LNs in patients with uterine cervical

Table 2. Evaluation of quality of included studies using Quality Assessment of Diagnostic Accuracy Studies tool

Study	Item														Total score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Hu et al ³³	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14
Liao and Chen ³⁴	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	13
Ling et al ³⁵	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	11
Liu et al ³⁶	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14
Liu et al ³⁷	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	12
Ren et al ³⁸	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14
Zhang et al ³⁹	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14
Chen et al ²⁸	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	11
Chen et al ²⁷	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	11
Choi et al ²⁹	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	12
Xue et al ³²	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	11
Kim et al ²²	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14
Kim et al ²³	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	12
Liu et al ³⁰	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	13
Park et al ³¹	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14

U: unclear, 0 score; Y: yes, 1 score.

cancer. Chen et al²⁸ reported that DWI with ADC measurements could differentiate metastatic from hyperplastic nodes with a sensitivity of 83.3%, specificity of 74.7% and accuracy of

78.4%. In another study, Liu et al³⁰ used the minimum ADC as a cut-off, and the sensitivity and specificity for differentiating metastatic from non-metastatic LNs were 95.7% and 96.5%,

Figure 2. Results of Deek's funnel plot of asymmetry test for publication bias for diffusion-weighted imaging. The non-significant slope indicated that no significant bias was found ($p = 0.329$). ESS, effective sample size.

Figure 3. Summary receiver operating characteristic (SROC) curves for diffusion-weighted imaging in nodal assessment of cervical cancer. The middle line was the summarized ROC curve, and the two beside were 95% confidence intervals. AUC, area under the curve; SE, standard error.

respectively. Kim et al²² and Choi et al²⁹ demonstrated the similar conclusion that DWI was feasible for differentiating metastatic from non-metastatic LNs of uterine cervical cancer. However, owing to the presence of relatively small sample size and variations in study design, it is necessary to perform a meta-analysis to have a comprehensive assessment of DWI in the diagnosis of pelvic LNs of cervical cancer.

The present meta-analysis identified 15 studies that involve the diagnostic accuracy of DWI for metastatic LNs of cervical cancer. To our knowledge, this is the first meta-analysis that evaluates the role of DWI for nodal assessment in pelvic imaging. The recent meta-analysis performed by Hou et al⁴⁰ investigated the diagnostic performance of DWI for differentiating normal cervical tissue from tumour tissues, not for nodal assessment. Our meta-analysis demonstrated that the pooled estimates were 0.86 (95% CI, 0.84–0.89) for sensitivity and 0.84 (95% CI, 0.83–0.86) for specificity, which indicated that DWI with ADC values could be helpful for the diagnosis of metastatic LNs. However, the heterogeneity between studies was relatively notable, and it was necessary to explore reasons for heterogeneity.

With regard to the threshold effect, the result (Spearman's correlation coefficient, 0.38; $p > 0.05$) indicated that no significant threshold effect existed. Based on the subgroup analysis, patient enrolment, blindness or quality assessment did not contribute to the observed heterogeneity. Although we did not perform the subgroup analysis based on the study design mainly owing to limited data, the study design might be a potential source of heterogeneity. In general, retrospective studies had higher diagnostic performance than prospective studies, for the risk that imaging observers had known the histopathological results before DWI assessment. We have examined the publication bias using Deek's funnel plot, and there was no publication bias existing. However, all of our included studies were performed in Asia, which was a potential bias.

Table 3. Diagnostic accuracy of diffusion-weighted imaging in the evaluation of lymph node staging in patients with cervical cancer

Study	Number	Pooled sensitivity	I^2 (%)	Pooled specificity	I^2 (%)	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio
Overall	15	0.86 (0.84–0.89)	57.0	0.84 (0.83–0.86)	89.1	6.55 (4.77–9.01)	0.17 (0.12–0.23)	47.21 (25.67–86.81)
Consecutive	5	0.85 (0.80–0.90)	33.2	0.89 (0.86–0.91)	88.0	10.05 (4.76–21.23)	0.18 (0.13–0.25)	69.70 (24.77–196.13)
Inconsecutive ^a	10	0.87 (0.83–0.90)	65.8	0.83 (0.81–0.85)	89.4	5.81 (3.99–8.46)	0.16 (0.10–0.25)	40.46 (18.40–89.00)
Blinded	10	0.85 (0.81–0.88)	55.4	0.84 (0.82–0.85)	91.4	6.14 (4.24–8.89)	0.19 (0.13–0.27)	37.12 (18.55–74.30)
Unblinded ^b	5	0.90 (0.85–0.94)	57.7	0.88 (0.84–0.91)	80.9	8.13 (3.91–16.89)	0.12 (0.06–0.24)	97.39 (22.68–418.26)
High quality	11	0.86 (0.82–0.89)	57.3	0.84 (0.83–0.86)	91.0	6.52 (4.52–9.40)	0.18 (0.12–0.26)	42.58 (21.29–85.16)
Low quality	4	0.89 (0.83–0.93)	63.2	0.85 (0.80–0.90)	83.1	7.37 (3.13–17.34)	0.14 (0.07–0.28)	81.35 (15.04–440.13)

^aInconsecutive or unclear.

^bUnblinded or unclear.

Figure 4. Forest plot: apparent diffusion coefficient (ADC) values for metastatic lymph nodes and non-metastatic lymph nodes. CI, confidence interval; ES, effect size; ID, identification.

Currently, there was no standard optimal protocol for DWI scanning; thus, the differences in the instrument manufacturers, magnetic field strength and sequences could have been a main cause of the between-study heterogeneity. For example, the most commonly used magnetic field strength was 1.5 T. Some studies^{27,28,32} used b -values of 0 and 800 s mm⁻²; others^{22,23,31} used 0 and 1000 s mm⁻². With a low b -value, signals were significantly affected by perfusion effects, which led to an inaccurate reflection of water diffusion motion. However, high b -values have the risk of distortion and susceptibility artefacts.^{12,41} All of the above factors were capable of affecting ADC measurements, which led to variability in cut-off values ranging from 0.778 to 1.150. Furthermore, with regard to ADC measurements, the minimum ADC, the mean ADC or relative ADC was used as the reference standard.

The DOR, which is calculated by the combination of sensitivity and specificity, is a single indication of test accuracy.⁴² It ranges from zero to infinity, with higher values indicating better diagnostic performance. The pooled DOR was 47.21, which suggested high total diagnostic accuracy of DWI. In addition, both positive LR and negative LR were calculated and served as our measurements of diagnostic performance. The results (6.55 for positive LR and 0.17 for negative LR) revealed that using DWI alone is not accurate enough to rule in or out the disease.

We should acknowledge some limitations in this meta-analysis. First, the exclusion of reviews, conference abstracts and letters may lead to potential publication bias. Although it can be tested by funnel plots, the limited sample of included studies in this meta-analysis might decrease the examination power of publication bias. Second, we did not perform meta-regression analysis owing to insufficient data. The present explanation for the heterogeneity was insufficient; there were too many variables in the scanning method and acquisition protocol to conduct the subgroup analysis based on these variants. Third, most of the included studies were retrospective in design. The retrospective nature of studies can be considered a limitation, which potentially affected the diagnostic performance of DWI.

In conclusion, DWI is useful for differentiation between metastatic and benign LNs in patients with uterine cervical cancer. Large, multicentre and prospective studies with strict standardization of DWI protocols are required to evaluate its diagnostic performance for further development as a routine clinical application in the near future.

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