

# Monitoring Treatment Response In Patients Undergoing Concurrent Chemoradiotherapy for Locally Advanced Uterine Cervical Carcinoma Using Intravoxel Incoherent Motion Imaging: A Systematic Review And Meta-Analysis

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## Research article

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## Abstract

**Background:** To the best of our knowledge, there are no systematic reviews or meta-analyses on the use of IVIM to assess treatment response of cervical cancer patients undergoing CCRT. Therefore, this study aimed to determine the role and optimal parameters of intravoxel incoherent motion imaging (IVIM) for evaluating treatment response in patients undergoing concurrent chemoradiotherapy (CCRT) for uterine cervical cancer.

**Methods:** We searched the PubMed, PMC, EMBASE, Cochrane Library, and Ovid databases. Two reviewers independently performed data extraction, checked patient inclusion criteria, conducted the imaging protocols and follow-up for treatment response, recorded IVIM parameters, and performed quality assessment.

**Results:** Six studies with 237 patients were included in our meta-analysis. The mean patient age ranged between 47 and 69 years. The International Federation of Gynecology and Obstetrics (FIGO) staging varied from Ib1 to IVb. The pooled mean values of apparent diffusion coefficient (ADC), tissue diffusion (D), and perfusion fraction (f) were 0.51, 0.18, and 6.24, respectively, in the complete response (CR) group, while the values were 0.38, 0.16, and 5.84, respectively, in the non-complete response (non-CR) group. In the subgroup meta-analysis, the ADC and D values in the CR group were higher compared to the non-CR group. Similarly, the incremental increase in f values in the CR group was higher compared to the non-CR groups (3.26, 5.84). All studies had a higher risk of bias in quality assessment due to *study confounding and attrition*.

**Conclusions:** IVIM could be used to monitor the pre- and post-treatment response of cervical cancer patients undergoing CCRT. Early response assessment could begin 1 week after CCRT. However, we were unable to determine the optimal IVIM parameter from our analysis.

## Highlights

Functional evaluation of chemoradiotherapy for treating cervical cancer.

IVIM can monitor the response in patients with cervical cancer undergoing CCRT.

Early monitoring could begin one week after treatment.

## Background

Uterine cervical carcinoma is the fourth most common cancer in women[1]. According to the 2018 World Health Organization (WHO)[2], an estimated 570,000 women have been diagnosed with cervical cancer worldwide and approximately 311,000 women have died from the disease. The standard treatment for International Federation of Gynecology and Obstetrics (FIGO) stage IB-IVA uterine cervical cancer is concurrent chemoradiotherapy (CCRT)[3]. Despite its associated low relapse and increased survival rates, CCRT does not meet the acceptable clinical outcomes in patients with cervical cancer[3]. This may be due to the use of a standardized rather than an individualized treatment regimen. It should be noted that an unsuitable therapeutic protocol can increase morbidity, accelerate tumor growth, and delay treatment[4]. However, evaluating the early treatment response to CCRT makes it possible to adjust therapeutic strategies and increase the patient's survival rate and quality of life.

Solid tumors are generally measured using imaging techniques. Changes in tumor size after treatment are often associated with patient survival. Response Evaluation Criteria in Solid Tumors (RECIST) is determined using magnetic resonance imaging (MRI) and is utilized to assess tumor response in clinical practice and randomized control trials[5, 6]. However, changes in tumor volume after CCRT can lag behind physiological changes[7]. Conventional MRI with soft-tissue resolution imaging approaches can display morphological changes[8], while functional MRI can determine tumor biology[9].

Diffusion-weighted imaging (DWI) is the most common functional imaging modality that can precisely quantify the diffusion capacity of tissues[10, 11]. The apparent diffusion coefficient (ADC) is a measure of the magnitude of diffusion of water molecules within a tissue, which is an index of pathological alterations in tumor cell density[12, 13]. Since cellular traits of a tumor are transformed following chemoradiotherapy, ADC can be a non-invasive indicator of tumor response. Studies have shown that ADC can be used to monitor the treatment reaction of solid tumors, such as brain tumors, head and neck carcinomas, rectal cancers, and prostate carcinoma[14–17]. A systematic review showed that ADC could also be used as a biomarker to monitor CCRT response in patients with cervical cancer[18].

Intravoxel incoherent motion imaging (IVIM) can provide more specific information about tumor proliferation and blood perfusion[19]. Le Bihan et al[20] introduced the IVIM method to discern diffusion and perfusion by fitting the b value to a biexponential model of the signal. In the IVIM model, the clinical-relevant parameters include: D, depicted tissue diffusion; D\*, pseudo-diffusion or perfusion; and f, perfusion fraction. This technology has been used to comprehensively evaluate therapeutic efficacy in patients with head and neck carcinomas[21], esophageal cancer[22], and breast cancer[23]. A series of studies reported that IVIM could also be used to assess treatment response of chemoradiotherapy in patients with locally advanced cervical cancer[7, 24–32].

Based on the National Comprehensive Cancer Network (NCCN) clinical practice guidelines (2020. V1), MRI is typically performed 3–6 months after the end of treatment in cervical cancer patients, but there has been no consensus regarding the use of MRI for the early evaluation of treatment efficacy. To the best of our knowledge, there is no systematic reviews or meta-analyses on the use of IVIM to assess treatment response of cervical cancer patients

undergoing CCRT. Therefore, this study aimed to investigate the role and optimal parameters of IVIM in evaluating therapeutic response (post-treatment) and early response (during 1 month of treatment) in patients undergoing chemoradiotherapy for cervical carcinoma.

## Methods

### Study Design

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[33]. This review was registered on PROSPERO (CRD42020180661).

### Search Strategy

We conducted a systematic literature search using the Cochrane Library, Embase, PubMed, PMC, and Ovid databases. Additional file 1 describes the search strategy in detail. The search strategy consisted of two keywords, *cervical carcinoma* and *IVIM*, which were combined with the set operator AND. We did not apply language restrictions. We also checked the listing of complete references in the selected articles, as well as the listing of articles included in the prior meta-analysis of the same issues to determine whether there were other references that should be included.

### Selection Of Articles

Two reviewers (Q.L. and H.F.) checked the retrieved articles according to the titles and abstracts. The inclusion criteria were as follows: (1) Studies consisting of no less than five patients with pathologically confirmed cervix carcinoma; (2) Studies assessing treatment response after chemoradiotherapy and data of these items could be extracted from the article; (3) Studies that distinguished between complete responders and non-complete responders; (4) Pathological, clinical follow-up, or other imaging modality used as a reference test; and (5) IVIM parameters and models presented.

The exclusion criteria were as follows: (1) If the publication was a review, meta-analysis, comment, case report, conference article, or letter; (2) If the articles covered information about animal studies; And (3) Articles that did not involve cervical carcinoma IVIM or only IVIM of the primary carcinoma (studies did not include data for assessing therapeutic efficacy).

### Data Extraction

Data extraction was done, in parallel, in a homogenous mode using the predefined data extraction sheets by two researchers, and inconsistencies were determined by consensus.

From each primary study, reviewers independently extracted the following: (a) author and year of publication, (b) journal, (c) research period, (d) country where the study was performed, (e) study department, (f) whether the article was prospective or retrospective, (g) the inclusion and exclusion criteria, (h) the number of patients, (i) patient age, (j) histopathological type, (k) FIGO stage, (l) number of patients with metastases, (m) features on CCRT, (n) magnetic field strength, (o) type of coil, (p) type of spasmolytic drug, (q) type of intravenous contrast agent, (r) examination time, (s) conventional sequences, (t) IVIM sequence, (u) number of reviewers, (v) if more than one reviewer, (w) whether there was a consensus reading or agreement, (x) experience of reviewers, and (y) combining IVIM with one conventional sequence or IVIM alone. The follow-up for therapeutic response characteristic was extracted as follows: (a) the follow-up for therapeutic effect was complete or not; (b) the follow-up strategy, and (c) period between therapy and response evaluation. Data for the interpretation of complete responders and non-complete responders were recorded.

DWI and IVIM parameters including mean ADC, D, D\*, f values standard deviation (SD) or median with inter-quartile range (IQR) was documented for complete or non-complete responders at various time points, such as pretreatment, duration, and post-treatment.

### Quality Assessment

Two researchers appraised the included studies for quality assessment in parallel in a homogenous mode using the predefined data extraction sheets, and inconsistencies were determined by consensus. We extracted the quality characteristics by using the Quality In Prognostic Studies (QUIPS) checklist as a guideline[34].

### Statistical Analysis

The four included studies that were selected for meta-analysis were evaluated using Statistics and Data Science software (Stata, version 15, StataCorp, College Station, TX, USA), and the remaining three studies were analyzed qualitatively. According to the method provided in 16.1.3.2 of the Cochrane Handbook 5.0.2, the mean and SD of ADC, D, D\*, and f values, before and after CCRT, were calculated. Next, we performed a single-arm meta-analysis to determine pooled effect sizes (ES) and used Cohen's method and a random-effects model to calculate the corresponding 95% confidence

interval (CI). We then calculated the  $I^2$  statistic to evaluate the heterogeneity across the studies, and  $p < 0.10$  demonstrated significant heterogeneity. Heterogeneity was divided into none ( $I^2 < 25\%$ ), mild ( $25\% < I^2 < 50\%$ ), moderate ( $50\% < I^2 < 75\%$ ), and high ( $I^2 > 75\%$ ). Begg's publication bias test was used to evaluate whether the research results were selected and oriented to their results. As only one study [27] was conducted in the 1st week after treatment, its data was not included in this meta-analysis. Moreover, the ADC and  $D^*$  values in the 3rd week were not included in the meta-analysis for the same reason.

## Results

### Search Strategy and Included Studies

The systematic database search identified 591 potential publications, of which 515 remained after removing duplicates. Two reviewers then screened for relevant studies based on titles or abstracts and an additional 205 articles were removed. The final 11 studies were assessed for eligibility. Four studies were excluded due to the non-CCRT treatment regimen ( $n = 1$ ), no correct complete response (CR) or partial response (PR) grouping ( $n = 1$ ), and no extractable IVIM data ( $n = 2$ ). Finally, seven articles containing 237 patients were included in the qualitative evaluation [7, 26, 27, 29-32]. Four studies were included in the quantitative assessment, as the patients belonged to the same research center ( $n = 2$ ) and the study had no original data ( $n = 1$ ). The screening and selection process is outlined in a PRISMA flow chart (Fig. 1).

### Study Design

All included studies were prospective studies. All studies, except one, involved radiology, obstetrics and gynecology, ultrasound, and oncology departments. The study design is summarized in Table 1.

### Patient Population

The study consisted of 237 patients. The number of patients receiving chemoradiation ranged from 17 to 63. All patients had primary squamous cell carcinoma ( $n = 168$ ), except for two studies that did not mention the cancer type. The FIGO staging ranged from Ib to IVb (Ib [ $n = 4$ ], II [ $n = 108$ ], III [ $n = 81$ ], and IV [ $n = 44$ ]). The average age of the patients ranged from 47 to 69 years. Three studies [27, 30, 31] described metastasis. All studies involved CCRT, including a combination of external beam radiotherapy (EBRT), intracavitary brachytherapy (ICR), and chemotherapy. Patient characteristics are described in Table 2.

### MRI Technological Parameters

All the studies included a 3.0T MRI scanner. None of the studies used anti-spasmodics. All studies, except one, used conventional T1 and T2-weighted sequences. The total acquisition time of the IVIM sequence ranged from 3.1 to 10.0 min in the single-shot echo-planar imaging (SS EPI). All articles used the three-parameter models ( $D$ ,  $D^*$ ,  $f$ ) with a fixed  $S_0$ . Details of the technical characteristics of MRI examinations are provided in Supplementary Table 1, Additional file 1.

### MRI IVIM Analysis

All studies, except two, had two reviewers for IVIM analysis and both reviewers reached an agreement through an inter-observer. Details of the IVIM analysis are shown in Table 3.

### Follow-up for Therapeutic Efficacy

All patients completed their follow-up period. Only three studies performed an MRI examination along with pathological histology within 1 - 3 months after treatment [26, 27, 31]. The remaining studies were followed up using MRI. These studies [7] used the European Organization for Research and Treatment of Cancer (EORTC) criteria, and the rest applied RECIST. The descriptions of CR groups and non-complete response groups - PR, stable disease, or progressive disease - are described in RECIST (ver. 1.1). The efficacy results at the last follow-up are shown in Supplementary Table 2, Additional file 1.

### Subgroup Meta-analyses

Changes in IVIM parameters over time in patients in the CR groups and non-CR groups are presented in Supplemental Table 3. The meta-analysis assessed data available from four longitudinal single-arm studies that reported changes in ADC,  $D$ ,  $D^*$ , and  $f$  during and after CCRT for cervical cancer are shown in Table 4 and Supplementary Figures 1-4, Additional file 1.

In the total pooled effect sizes,  $f$  values showed more incremental changes in the CR groups [MD = 6.24 (95% CI: 4.12 to 8.36;  $p = 0.000$ )] and in the non-CR groups [MD = 5.84 (95% CI: 2.92 to 8.75;  $p = 0.000$ )], but the  $I^2$  (94.1%, 91.7%) displayed significant heterogeneity among studies. Similarly, although the numbers are small, the trend indicated an increase in ADC in the CR groups [MD = 0.51 (95% CI: 0.39 to 0.63;  $p = 0.000$ );  $I^2 = 89.0\%$ ] and the non-CR groups [MD = 0.38 (95% CI: 0.15 to 0.62;  $p = 0.001$ );  $I^2 = 96.2\%$ ], and in the  $D$  value in the CR groups [MD = 0.18 (95% CI: 0.16 to 0.21;  $p = 0.000$ );  $I^2 = 99.4\%$ ] and in the non-CR groups [MD = 0.16 (95% CI: 0.13 to 0.20;  $p = 0.000$ );  $I^2 = 98.1\%$ ], respectively.

## Early Therapeutic Response

In the subgroup meta-analysis, ADC and D values showed a significant increase during the 2nd and 4th week after CCRT in the CR groups and the non-CR groups. Although the incremental change was not as large, there were statistically significant incremental changes in f values both in the CR groups [MD = 0.8.42 (95% CI: 2.49 to 14.35;  $p = 0.005$ );  $I^2 = 91.7\%$ ] and the non-CR groups [MD = 3.26 (95% CI: 1.13 to 5.40;  $p = 0.003$ );  $I^2 = 0.0\%$ ] during the 3rd week of treatment. Supplementary Figures 1 – 4, Additional file 1, show details of IVIM parameters assessing the early treatment response.

Our study showed that all indicators increased following the 1st week of treatment, but the increase in the CR group was greater than that in the non-CR group (Supplemental Table 3, Additional file 1).

## Therapeutic Response Before and After Chemotherapy

We found that the f values demonstrated a statistically significant improvement in evaluating effectiveness before and after therapy in the CR groups [MD = 6.76 (95% CI: 1.78 to 11.74;  $p = 0.000$ );  $I^2 = 91.0\%$ ] and the non-CR groups [MD = 7.61 (95% CI: 3.71 to 11.52;  $p = 0.000$ );  $I^2 = 77.8\%$ ], respectively. Supplementary Figures 1 – 4, Additional file 1, show the values of ADC and D pre- and post-treatment. The D\* values indicated no statistically significant increase or decrease both at pre- and post-treatment.

Begg's publication bias tests for ADC values in the non-CR group showed  $p = 0.024$ , indicating publication bias from heterogeneous sources. Whereas, Begg's publication bias tests for ADC, D, D\*, and f values were quantitatively evaluated to be  $p > 0.05$ , indicating non-publication bias from heterogeneous sources (Table 4).

## Risk of Bias

Supplemental Table 4, Additional file 1, and Figure 2 show the risk of bias analyses. We applied QUIPS for evaluation and obtained the following results. Only one study[30] mentioned the failure of follow-up and its causes. Three studies[27, 30, 31] described other prognostic factors. None of the included studies made an effort to modify probable confounding factors.

## Discussion

To the best of our knowledge, no study to date has analyzed the treatment response of patients with cervical carcinoma undergoing CCRT using IVIM. In this systematic review, we utilized IVIM MRI to evaluate the response of cervical carcinoma during and after CCRT. The pooled mean difference of ADC, D, and f values were used to evaluate the therapeutic response of cervical carcinoma. The incremental increase in values was slightly higher in the CR group compared to the non-CR group, but the heterogeneity was significant. Additionally, ADC, D, and f values were used to evaluate the early therapeutic response, while f values were used for pre-treatment and post-treatment evaluation. However, the D\* was not able to be used to evaluate the efficacy of cervical cancer. Based on these findings, IVIM can be used to monitor the response of cervical carcinoma and after CCRT.

## Early Therapeutic Response

The main finding of this systematic review is that ADC and D values can be used to monitor the early response of cervical cancer after CCRT. Park et al. [16] reported that ADC values could be used to evaluate the early efficacy of concurrent radiotherapy and chemotherapy for cervical cancer. Yang et al. [21] also indicated similar results after using ADC and D values to evaluate adjuvant chemotherapy and concurrent CCRT of nasopharyngeal carcinoma. Fujima et al.[35]confirmed that ADC and D values can be used in the earlthe paranasal sinusesuamous cell carcinoma of paranasal sinuses. In addition, Li et al.[22] reported similar results after using D values to evaluate radiotherapy and chemotherapy for rectal cancer. Lee et al.[18] reported that ADC values be used to evaluate the efficacy of early cervical cancer, but a meta-analysis was not carried out and the effect amount was not calculated due to magnetic field strength of MRI and other reasons.

Similarly, we found that f values could be used to assess therapeutic response in the 3rd week after treatment, and the incremental increase was greater in the CR group compared to the non-CR group. In a study of adjuvant chemotherapy for nasopharyngeal carcinoma, Xiao et al.[35] found that a  $\Delta f$  incomplete response group and non-complete responders followed a similar trend to our findings. Likewise, Che et al.[36] and Ding et al.[37] reported comparable results for early treatment response in breast cancer and oral squamous cell carcinoma. However, in our study, we were not able to compare which parameter might be optimal for assessing early efficacy in patients with cervical cancer due to the smaller number of included studies.

To conclude, in our study, the time points for meaningful early evaluation are weeks 1, 2, 3, and 4 after treatment. Liu et al.[5] and Kuang et al.[38] found that the optimal window for early tumor response was 14 days after starting treatment. However, we did not compare the optimal time points, which might be the best means for assessing early efficacy in patients with cervical cancer.

## Therapeutic Response Before and After Chemotherapy

The main finding of this systematic review is that f values can be used to monitor the post-treatment response of cervical cancer after CCRT. Additionally, the incremental mean of the f value in the CR group was slightly lower compared to the non-CR group.

Similarly, Hauser T et al.[39] reported a significant increase in the f parameter after treatment. Similar results were reported by Che et al.[36], who reported an increased f value after adjuvant chemotherapy for breast cancer. Increased blood perfusion will enhance oxygen delivery to tumors, which is important because oxygenated tumors are more sensitive to radiotherapy and chemotherapy[40, 41]. It has been reported that fibrosis and blood perfusion are significantly reduced compared to baseline with EBRT and ICR after the 5th week of treatment[30]. Therefore, CR groups are more susceptible to developing fibrosis.

It should be noted that ADC and D values are not yet well accepted values for monitoring the post-treatment response of cervical cancer after CCRT. However, a systematic review confirmed that ADC values could be used to monitor the efficacy of cervical cancer after CCRT[18]. Similarly, D\* values are not yet considered useful for monitoring treatment efficacy. Consistent with our findings, Liang et al.[42] found that incremental changes in D\* showed no difference between CR and non-CR groups. Zhang et al.[24] further confirmed these results. Thus, the D\* value has technical flaws, such as the noise propagation that causes (incredibly) large variability and large standard deviation, and this instability prevents any significant differences from being detected [28].

In our study, the heterogeneity of each parameter was relatively significant, but we could not perform a heterogeneous test because the number of included studies was small. Moreover, the b values ( $b < 50$  and  $b > 0$ ) were small, and the total number of b values was different between the groups. Hence, further studies are required to determine which b value sets provide optimal discriminatory parameters in evaluating before and after responses to treatment.

We found that the ADC, D, and f values were more effective and sensitive. Because of the small sample size, no comparison between parameters could be performed. We recommend combining ADC, D, and f values to assess therapy response, as they reflect tissue cell density, diffusion, and blood perfusion.

### Study Limitations

Our study has several limitations. First, all patients had squamous cell carcinoma and we did not include other pathological types. The size of cervical cancer was small, and therefore we could not do subgroup analysis for the PR group. Second, as for all meta-analyses, it was impossible to fully control the effectiveness and quality of primary research. Third, there was no long-term follow-up. Finally, the included studies were heterogeneous for the implemented b values.

## Conclusion

In conclusion, this systematic review presents evidence that IVIM can be used to monitor the pre- and post-treatment response in patients with cervical cancer undergoing CCRT. The ADC, D, and f values were effective and sensitive. Furthermore, the time point for early monitoring could begin within 2 weeks of treatment. However, since we were not able to determine the best parameter, it is imperative to conduct a large-scale multicenter cohort study in the future.

## Abbreviations

<b>ADC, apparent diffusion coefficient</b>
CCRT, concurrent chemoradiotherapy
CR, complete response
D, tissue diffusion
D*, pseudo-diffusion or perfusion
F, perfusion fraction
FIGO, The International Federation of Gynecology and Obstetrics
IVIM, Intravoxel incoherent motion imaging
non-CR, non-complete response
MRI, Magnetic resonance imaging
PRISMA, The Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUIPS, Quality In Prognostic Studies
RECIST, Response Evaluation Criteria in Solid Tumors

## Declarations

Ethical approval and consent to participate

The review did not require approval by an Ethical Committee.

### Consent for publication

Not applicable.

### Competing interests

The authors have declared that no competing interest exists.

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### Author's Contribution

LQ drafted and prepared the manuscript for final publication; LQ, FH, SW, YX, and YW reviewed the literature and extracted the data; JML worked performed statistical analyses; LQ and FH drafted the manuscript; JYL performed consultation and revised the manuscript. All authors issued final approval of the version to be submitted.

### Availability of supporting data

Not applicable.

### Acknowledgements

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## Tables

TABLE 1. Results of Study Design Characteristics								
First author	Year	Journal	Study period	Country of origin	Setting (academic and/or other)	Departments Involved	Department of the first author	study design
C. Xu	2019	European journal of radiology	December 2017–December 2018	China	Academic and others	Radiology, Liaoning Provincial Key Laboratory of Medical Imaging	Radiology	prospective
H. Kato	2019	Magnetic resonance in medical sciences : MRMS: an official journal of Japan Society of Magnetic Resonance in Medicine	November 2016–January 2018	Japan	Academic and others	Radiology; High-level Imaging Diagnosis Center; Obstetrics and Gynecology	Radiology	prospective
H. Bian	2019	Medicine (Baltimore)	January 2015–January 2016	China	Other, Hospital	Radiology, Ultrasound	Radiology	prospective
J. Li	2018	Chinese Journal of Radiology (China)	July 2015–December 2016	China	Other, Hospital	Radiology	Radiology	prospective
L. Zhu	2017	J Comput Assist Tomogr	January 2015–March 2016	China	Both, Radiation Oncology and Winship Cancer Institute	Radiology, The Comprehensive Cancer Centre, Radiation Oncology and Winship Cancer Institute	Radiology	prospective
L. Zhu	2017	Scientific reports	January 2014–August 2016,	China	Both, Radiation Oncology and Winship Cancer Institute	Radiology, The Comprehensive Cancer Centre, Radiation Oncology and Winship Cancer Institute	Radiology	prospective
L. Zhu	2016	BMC cancer	December 2013–January 2015	China	Both, Radiation Oncology and Winship Cancer Institute	Radiology, The Comprehensive Cancer Centre, Radiation Oncology and Winship Cancer Institute	Radiology	prospective

TABLE 2. Results of Patients Characteristics									
First author	Year	Journal	Inclusion & Exclusion Criteria	Number of patients included	Age (mean + SD or median)	Distribution of the histological type	FIGO staging	Number of patients with metastasis	Treatment (surgery, radiotherapy, chemotherapy, etc.)
C. Xu	2019	European journal of radiology	The inclusion criteria: (1) all CCRT treatment options were consistent and (2) all patients with cervical cancer underwent integrated PET-MR scans 3 times	41	49.8 (range 32–66)	-	II (n=18);III (n=20);IV (n=3)	-	EBRT 46-56 Gy, chemotherapy (cisplatin 30 to 40 mg/m <sup>2</sup> or nedaplatin 50 mg/week), intracavitary brachytherapy 30 Gy
H. Kato	2019	Magnetic resonance in medical sciences : MRMS : an official journal of Japan Society of Magnetic Resonance in Medicine	The inclusion criteria: pathologically confirmed of the uterine cervix underwent IVIM MR imaging before and during CRT	17	69.1 (range, 28–94)	SCC (n=17)	IB (n=3);IIA (n=1);IIB (n=3);IIIA (n=3);IIIB (n=4);IVA (n=2);IVB (n=1)	-	Radiotherapy (n = 7) and CCRT (n = 10)
H. Bian	2019	Medicine (Baltimore)	The inclusion criteria : primary cervical cancer, no surgery before and after concurrent CCRT, and no contraindication to magnetic resonance imaging (MRI) Exclusion criteria were discontinuation of treatment (n = 1, due to radiation related intestinal fistula) or withdraw of follow-up MRI scans (n = 2)	28	47.78 (range, 31–69)	-	IB (n=1), IIB(n=26), and IIIB (n=1)	2	EBRT (5040c Gy/28 fractions), chemotherapy(cisplatin,40 mg/m <sup>2</sup> ),ICR (3000c Gy/5 fractions)
J. Li	2018	Chinese Journal of Radiology (China)	Inclusion criteria: (1) diagnosed with advanced stage ( $\geq$ IB) cervical cancer by clinical and imaging examinations; (2) completed concurrent CCRT plan without any other treatment before; (3) pelvic MRI follow-up review during treatment (During treatment and end of treatment). Exclusion criteria: poor MRI image quality and incomplete review data	63	51 ( $\pm$ 11, range 23–81)	SCC (n=63)	II(n = 15),III (n =27), IVa (n=21)	-	EBRT (60Gy/30fractions), chemotherapy(cisplatin,40 mg/m <sup>2</sup> ), intracavitary brachytherapy (30 Gy/5 fractions)
L. Zhu	2017	J Comput Assist Tomogr	Inclusion criteria: biopsy-proven untreated	37	51.4 (range 24–77)	SCC(n=37)	II (n=19);III	4	EBRT 45-50 Gy, chemotherapy (nedaplatin/week or

			advanced cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stage IIB–IVB) for whom CCRT was on schedule ; Exclusion criteria: contraindications for MR imaging and ineligibilities for CCRT ; inability to take part in all follow-up MR examinations for personal reasons (n=29) and considerable degradation of their MR images (n=12)				(n=11);IV (n=7)		nedaplatin plus paclitaxel/docetaxel/ biweek ), intracavitary brachytherapy 30-40 Gy
L. Zhu	2017	Scientific reports	Inclusion criteria: patients with histologically confirmed untreated cervical cancer (FIGO IIA ~ IVB) and prearranged to undergo CCRT The exclusion criteria: age < 18 yrs, or contraindications for MR scanning or CCRT (pacemaker implantation, drug allergy, etc.)	30	51.1 (range 24-76)	SCC(n=30)	II (n=15);III (n=9);IV (n=6)	5	EBRT 40-50 Gy, chemotherapy (nedaplatin/week or nedaplatin plus paclitaxel/docetaxel/ biweekly ), intracavitary brachytherapy 30-40 Gy
L. Zhu	2016	BMC cancer	Inclusion criteria: patients with histologically confirmed untreated cervical cancer (FIGO IIA ~ IVB) and prearranged to undergo CCRT The exclusion criteria: age < 18 yrs, or contraindications for MR scanning or CCRT (pacemaker implantation, drug allergy, etc.)	21	49.6 ( range 24–76)	SCC(n=21)	II (n=11);III (n=6);IV (n=4)	4	EBRT 40-50 Gy, chemotherapy (nedaplatin/week or nedaplatin plus paclitaxel/docetaxel/ biweekly ), intracavitary brachytherapy 30-41 Gy

First Author	Year	Journal	Number of Reviewers	Consensus or Interviewer agreement	Experience of Reviewers	MRI data analyses <sup>a</sup>
C. Xu	2019	European Journal of Radiology	2	interobserver agreement	both more than 10 yrs of experience in radio diagnosis	IVIM +CS (referring to T2W imaging)
H. Kato	2019	Magnetic resonance in medical sciences: MRMS: an official journal of Japan Society of Magnetic Resonance in Medicine	1	-	19 yrs of post-training experience in interpreting genitourinary images	IVIM +CS (referring to T2WI)
H. Bian	2019	Medicine (Baltimore)	1	-	5 yrs' experience in pelvic MRI imaging,	IVIM+CS (referring to T2WI)
J. Li	2018	Chinese Journal of Radiology (China)	2	interobserver agreement	5 and 10 yrs of experience in clinical MRI	IVIM +CS (referring to T2W images)
L. Zhu	2017	J Comput Assist Tomogr	2	interobserver agreement	6 and 8 yrs of experience in gynecologic imaging	IVIM +CS (referring to T2W images and contrast-enhanced-T1W imaging)
L. Zhu	2017	Scientific reports	2	interobserver agreement	8 and 12 yrs of experience in gynecologic imaging	IVIM +CS (referring to other MR sequences)
L. Zhu	2016	BMC cancer	2	interobserver agreement	8 and 12 yrs of experience in gynecologic imaging	IVIM +CS (referring to other MR sequences)

a: IVIM + conventional or IVIM or IVIM alone  
CS: conventional sequences

**TABLE 4. Summary of the Longitudinal Meta-analysis**

IVIM parameters	Number of studies	Groups	Number of patients	Total Effect Size(95% CI)	Total Effect Size p Value	Heterogeneity		Begg's Test p value
						I <sup>2</sup>	p value	
ADC value	2	CR	31	0.51(0.39, 0.63)	<b>0.000</b>	89.00%	<b>0.000</b>	0.707
		N-CR	16	0.38(0.15,0.62)	<b>0.001</b>	96.20%	<b>0.000</b>	0.024
D value	4	CR	81	0.18(0.16, 0.21)	<b>0.000</b>	99.40%	<b>0.000</b>	0.900
		N-CR	35	0.16(0.13, 0.20)	<b>0.000</b>	98.10%	<b>0.000</b>	0.706
D* value	2	CR	31	0.05(-0.06,0.16)	0.344	89.20%	<b>0.000</b>	0.707
		N-CR	16	0.07(0.01, 0.14)	<b>0.019</b>	73.50%	<b>0.002</b>	0.339
f value	4	CR	81	6.24(4.12, 8.36)	<b>0.000</b>	94.10%	<b>0.000</b>	0.063
		N-CR	35	5.84(2.92, 8.75)	<b>0.000</b>	91.70%	<b>0.000</b>	1.000

# Figures

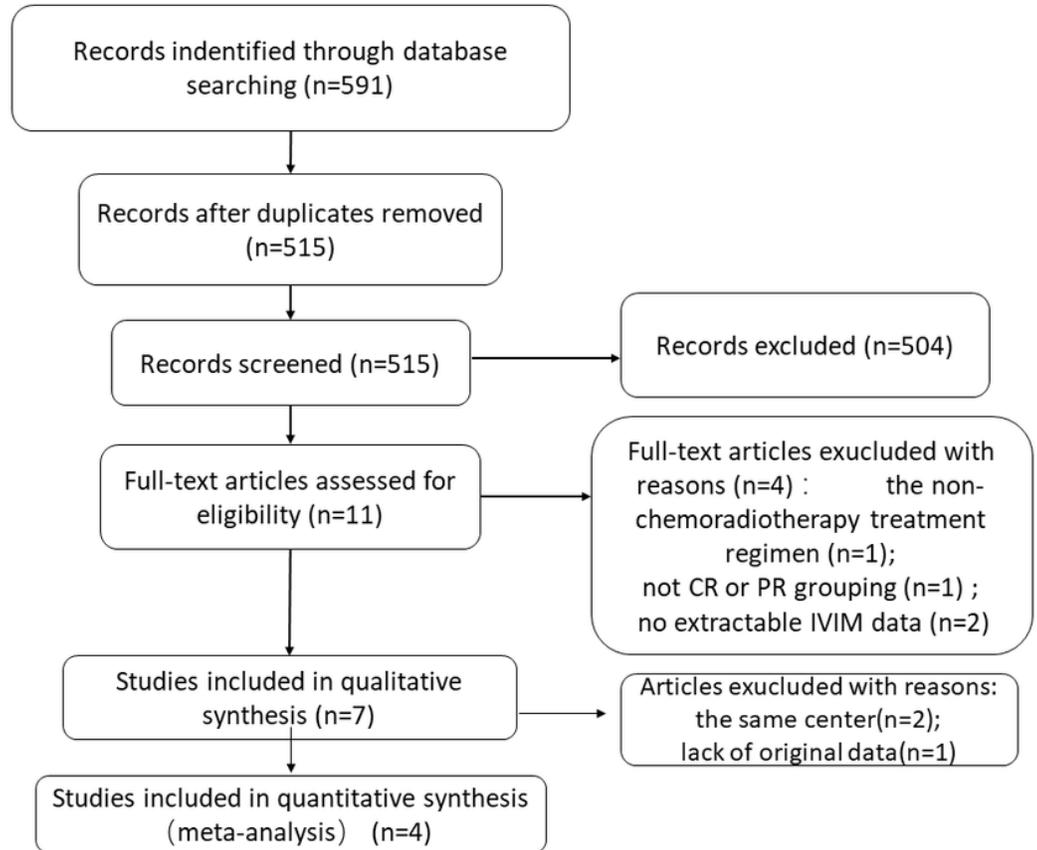
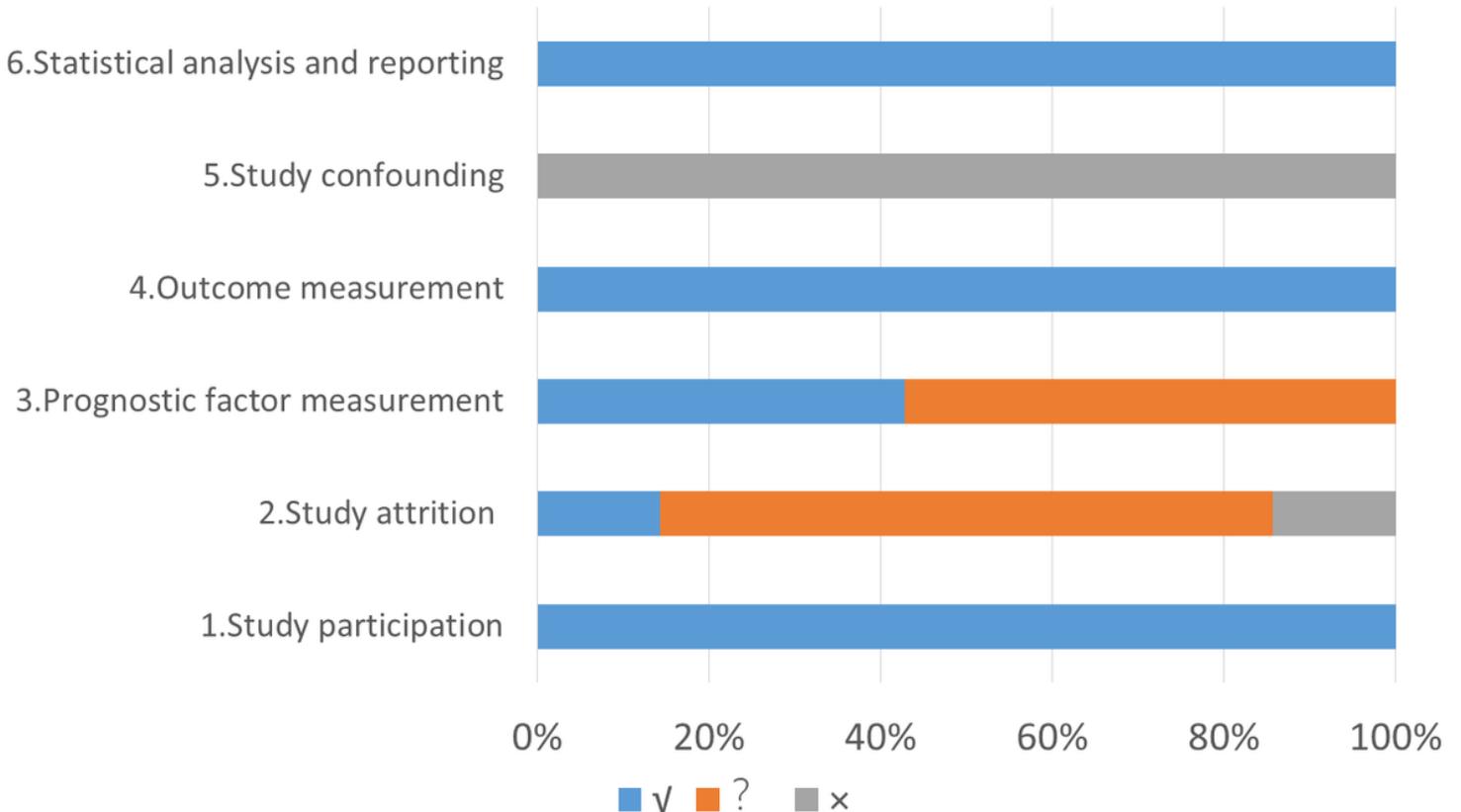


Figure 1

Study selection procedure (Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines)



## Figure 2

Bias of risk assessment

## Supplementary Files

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