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Role of IVIM MRI in staging and restaging of rectal cancer

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ABSTRACT

Background: IVIM is a noninvasive method that analyses both the mobility of free water particles and the perfusion generated by microcirculation in vivo using a biexponential mathematical model with varied b values**.**

Aim: To evaluate Role of IVIM MRI in staging and restaging of rectal cancer.

Methodology: A comprehensive search was conducted for papers that looked into the role of IVIM MRI in rectal cancer staging and restaging. The pooled specificity, sensitivity, constructed summary receiver - operating characteristic characteristics curve, and positive likelihood ratio were estimated after the data was extracted.

Results: After a full-text review, 11 studies were found to be qualified. Specificity and sensitivity were 81 percent (0.83-0.91) and 86 percent (0.77-0.87), respectively, in the pooled data. The area under the receiver operating characteristic curve using summarized receiver operating characteristics was 0.97.

Conclusions: According to this meta-analysis, IVIM MRI is an accurate, noninvasive diagnostic tool for staging and restaging rectal cancer.

Keywords: *IVIM MRI, rectal cancer, staging, restaging, meta-analysis*

INTRODUCTION

Rectal cancer is the eighth most prevalent malignancy in the world and the ninth largest cause of cancer-related deaths (1). It accounts about 40% of all colorectal cancer cases. The stage of rectal cancer has a direct impact on the prognosis. Prognosis is determined by the tumor's mural (T1-T2) and extramural (T3-T4) dissemination, lymph node spread, mesorectal fascia invasion, and the existence of distant metastases (2).

Magnetic resonance imaging (MRI) is the gold standard for staging and becoming increasingly essential in determining the therapeutic response of local rectal cancer lesions to preoperative treatment (3). After local treatment, MRI is critical for early detection of local recurrence during follow-up (4). Because of its strong soft-tissue contrast, The T and N stages of LARC can be detected using morphologic MRI., but it can't give information how well patients are responding to chemotherapy and radiation (5).

DWI consider a common type of functional imaging that can be used to noninvasively analyse the functional and morphological alterations in case of rectal cancer as well as detect the disease's location (6). On DW imaging, A combined assessment of water molecule mobility (diffusion) and blood circulation in capillaries yields the intravoxel incoherent motion (IVIM) model (perfusion) (7). IVIM is a noninvasive technology that uses a biexponential mathematical model with various b values to analyse both the diffusion of free water molecules and the perfusion induced by microcirculation in vivo.. A biexponential model can be used to analyse DWI data to gain information on both diffusion and perfusion tissue parameters generated from IVIM: the pure tissue coefficient (Dt) that describes water macroscopic motion in the cellular interstitial space, the pseudo- diffusion coefficient (Dp) that describes blood microscopic motion in the vessels, and the pseudo- diffusion coefficient (Dp) that describes blood microscopic motion in the vessels. D (pure diffusion coefficient), D* (pseudodiffusion coefficient), and f are the principal parameters yielded from the biexponential model (perfusion fraction) (8,9). This meta-analysis study aims evaluate Role of IVIM MRI in staging and restaging of rectal cancer.

METHODOLOGY

The related studies were found using a systematic search in PubMed, Google Scholar, Embase, the Cochrane library, and Web of Science. The following search string combinations were used: (“IVIM MRI OR intravoxel incoherent motion MRI OR diffusion weighted imaging”) AND (“staging and restaging”) AND (“rectal cancer OR colorectal cancer OR LARC OR locally advanced rectal cancer”).

STUDY SELECTION

1436 abstracts were reviewed after duplication removal and subsequently the full text of the 110 articles was obtained according to the following inclusion criteria; 1) Included the diagnosis accuracy of conventional MRI alone or with an advance procedure for rectal cancer; 2) findings were from people rather than animals; and 3) results were published in English. 4) included the MRI approach . 5) Included adequate data, and 6) the tumour analysis methodologies.

The following exclusion criteria were used to eliminate 99 studies: 1) they were not relevant to the current meta-analysis; 2) patients had already been treated for rectal cancer; and 3) there was insufficient data to generate a 2x2 contingency table. There were a total of 11 studies included in the analysis.

STATISTICAL ANALYSIS

Before pooling the data, each study's true-positive, false-positive, false-negative, and true-negative results were extracted, and sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and corresponding 95 percent confidence intervals (95 percent CIs) were calculated.. The sensitivity, specificity, PLR, and NLR were summarised using the bivariate random-effects model, and the receiver operating characteristic (ROC) curve and area under the curve (AUC) were summarised using the hierarchical regression model. The Q statistic was used to quantify the heterogeneity of individual studies that contributed to the pooled estimate.

For the Q statistic, a P-value of >0.10 indicated no significant heterogeneity, but a P-value of ≤0.10 indicated considerable heterogeneity. On the basis of sample size, percentage of men, mean age, and subgroup analyses for sensitivity, specificity, PLR, NLR, and AUC were done.

RESULTS

There were 1436 potential article citations in the preliminary literature review (Figure 1). 1326 of these studies were immediately excluded because they were irrelevant, or were published in languages other than English according to the exclusion criteria. The full text of the remaining 110 articles was downloaded for a more thorough examination. Following the full-text reading, 99 articles were eliminated. Eventually, 11 previously published papers were chosen based on the inclusion and exclusion criteria of the present study.

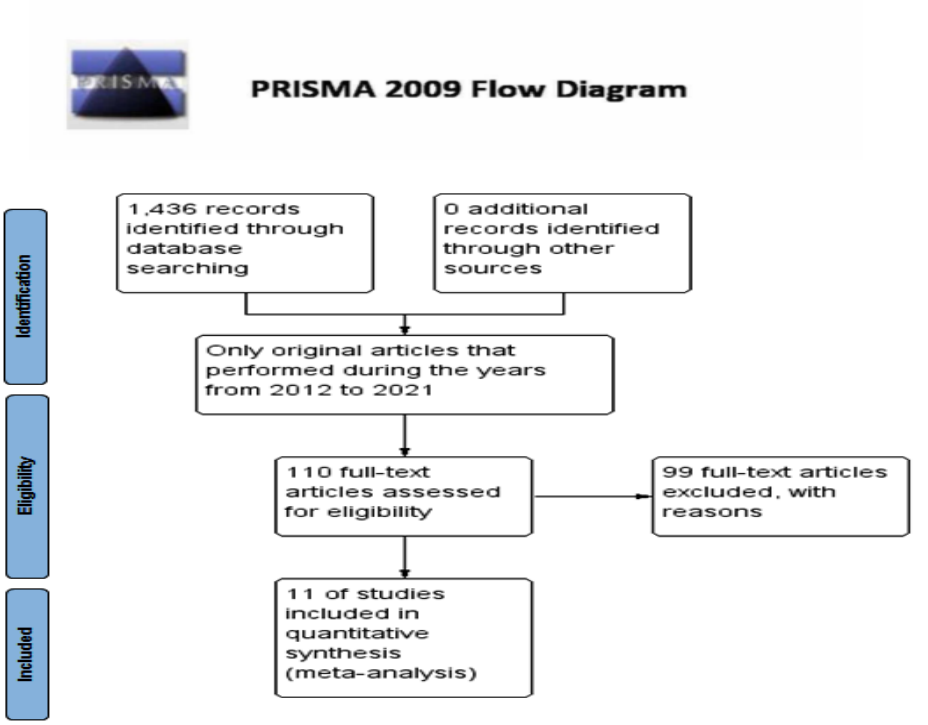

FIGURE 1. Flowchart for determining which papers were included in the metaanalysis. IVIM MRI is used in the staging and restaging of rectal cancer.

As shown in Table (I), raw data of 390 patients were extracted from 11 clinical trials (seven parallel, four cross-over) selected from 1436 articles. FOCUS IVIM - FOCUS IVIM-derived and normalised metrics can be used to predict the histologic grade of rectal cancer., IVIM-DWI parametric map, 5 first-order texture features (Mean, Kurtosis, Skewness, Variance, and Median) and 11 GLCM features were extracted automatically from the VOI by MaZda, including Angular Second Moment (AngScMom), Contrast, Correlat, Difference Entropy (DifEntrp), Difference Variance (Dif- Varnc), Entropy, Inverse Difference Moment (InvDfMom), Sum Average (SumAverg), Sum Entropy (SumEntrp), Sum of Squares (SumOfSqs), and Sum Variance (SumVarnc) - Pretreatment GLCM analysis based on IVIM-DWI might be a promising method for determining LARC's pathological response.

TABLE 1. Summary of the patient cohorts and characteristics of MRI protocols for the included studies IVIM MRI.

Author	Year	Country	No. of patient	MRI field, T	Aim	Conclusion
1-Cheng et al.	2021	China	88	3T	We obtained FOCUS DWI and FOCUS IVIM.	The normalised and FOCUS IVIM-derived values are beneficial for predicting the histologic grade in the rectal area.
2-Fusco et al.	2019	Italy	34	1.5T	a comparison between DCEMRI, intravoxel incoherent motionand diffusion kurtosis imaging-derived parameters.	SIS is a hopeful DCE-MRI angiogenic biomarker to assess preoperative treatment response after SCR with delayed surgery. Furthermore, an important prognostic role was obtained by VARPRO Fp mean value pre-treatment and by a decision tree composed by diffusion. parameters derived by DWI and DKI to assess pathological complete response.
3-Xu et al.	2021	Italy	-	,,	future trends of Methods based on MRI in evaluating complete response in rectal cancer.	some interesting MR criteria for measuring rectal cancer full response. And the development of new techniques, such as MRI-derived textural analysis, radiomics analysis, and deep learning, may enhance diagnostic performance, which incorporate the clinical features which may help MRI become a non- invasive and reliable decision-making tool in evaluating complete response of rectal cancer.,
4-Petrillo et al.	2017	Italy	35	1.5T	to assess preoperative Short Course Radiotherapy (SCR) tumor response in locally advanced rectal cancer (LARC) through Standardized Index of Shape (SIS) by DCE-MRI, apparent diffusion coefficient (ADC) and intravoxel incoherent motion-derived parameters by DW-MRI.	SIS is a hopeful DCE-MRI angiogenic biomarker to assess preoperative treatment response after SCR with delayed surgery, and it permits to discriminate pCR allowing to direct surgery for tailored and conservative treatment.

5-Liu et al.	2019	China	41	1.5T	investigate the performance of the mean parametric values and texture features based on (IVIM-DWI) on identifying pathological complete response (pCR) to neoadjuvant chemoradiotherapy (nCRT) in (LARC).	Pretreatment GLCM analysis based on IVIM-DWI may be a potential approach to identify the pathological response of LARC.
6-Hu et al.	2020	China	50	3T	to ascertain the diagnostic effectiveness of (IVIM). on evaluating patients with locally advanced rectal cancer's response to neoadjuvant chemoradiation (nCRT)	The dIVIM-DWI technology may be useful in identifying pCR and GR patients who should be treated with nCRT for LARC.
7-Xu et al.	2018	China	51	3T	identify whether IVIM parameters derived from whole-tumor volume (WTV) before and after NACT could accurately assess pCR in patients with LARC.	The IVIM-derived D value is a promising tool in predicting the pCR status before therapy. The percentage changes in D values after therapy may help assess the pCR status prior to surgery.
8-Yang et al.	2021	China	42	3 T	evaluate the role of IVIM and diffusion kurtosis imaging (DKI) in identifying pathologic complete response (pCR) and T stages after neoadjuvant chemoradiotherapy (nCRT) in locally advanced rectal cancer (LARC).	IVIM parameters could provide more information when evaluating pCR and T stages after nCRT. In particular, the diagnostic performance of the MD values was more valuable than ADC values in being able to determine pCR.
9-Schurink et al.	2019	Amsterdam	-	-	reviewing current applications and clinical utility of diffusion-weighted imaging (DWI) for rectal cancer and in addition provides a brief overview of more recent developments (including intravoxel incoherent motion imaging.	The role of DWI for further clinical tumour and nodal staging is less well-defined.Novel methods of DWI analysis and post-processing are still being developed and optimized; the clinical potential of these tools remains to be established in the upcoming years.
10-Nougaret et al.	2016	France	31	1.5T	determine the diagnostic performance of IVIM parameters and apparent diffusion coefficient (ADC) to assess response to combined chemotherapy and radiation therapy (CRT). in patients with rectal cancer by using histogram analysis derived from whole-tumor volumes and single-section regions of interest (ROIs).	Median D and ADC values obtained after CRT were useful for discrimination between good and poor responders. Histogram metrics did not add to the median values for assessment of tumor response. Volumetric analysis demonstrated better interobserver reproducibility when compared with single-section ROI analysis.
11-Ganten et al.	2013	Germany.	18	3 T	Using the IVIM model, define and explain the therapy-induced changes in diffusion parameters in rectal cancer during chemoradiotherapy (CRT).	Contrary results in the literature on apparent diffusion coefficient (ADC) changes in rectal cancer during CRT for patients displaying T-downstaging are unlikely to be attributed to perfusion effects, according to the IVIM model. Our findings back up the idea that an increase in D/ADC can be seen with successful therapy.

The risk of bias in the included trials was summarized in Figure (2). The red bar denotes a high risk of bias; the yellow bar denotes a risk of bias that is uncertain; and the green bar denotes a low risk of bias. Details of the quality evaluation were displayed in the lower section. The green circle with a '+' suggests a low risk of bias or a low worry for applicability; the yellow circle with a '?' indicates an uncertain risk of bias or concern for applicability; and the red circle with a " indicates a high risk of bias or a low concern for applicability. In terms of study heterogeneity, the 11 included studies showed considerable "heterogeneity with P0.00001 using the X2 test. The sensitivity heterogeneity (I2 of 92) was larger than the specificity heterogeneity (I2 of 92). Furthermore, no threshold impact was discovered (correlation,.0.36; % of heterogeneity owing to threshold).

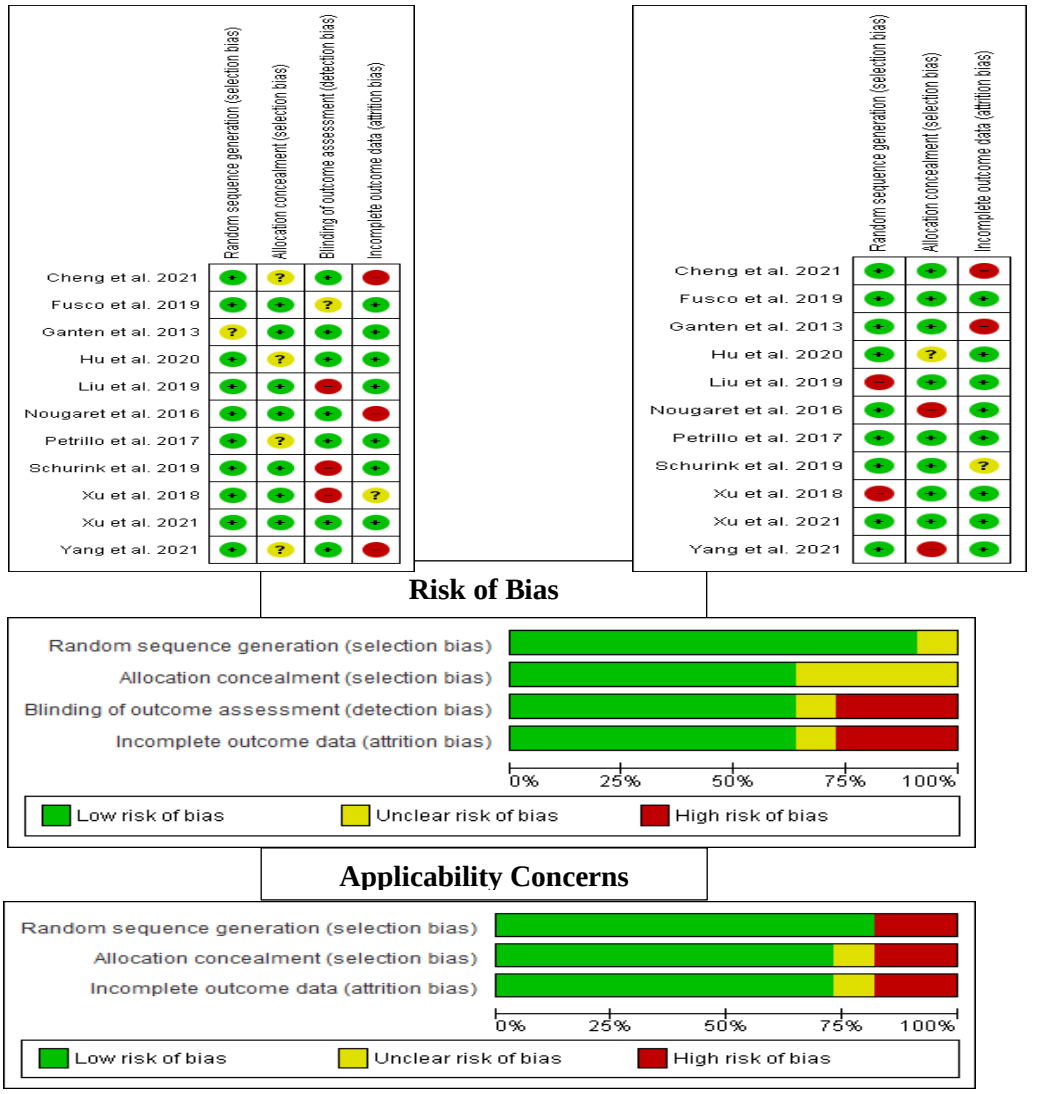

FIGURE 2. Quality assessment of the included studies using the Quality Assessment of Diagnostic Accuracy Studies.

As shown in Figure (3) and Figure (4 The forest plots of sensitivity and specificity are shown in the Synthesis of General Diagnostic, Comparison of the diagnostic performance of IVIM MRI, The pooled sensitivity and specificity were (0.74%) and (0.86%), respectively, There was (0.96%), Accuracy.

Funnel plot of comparison

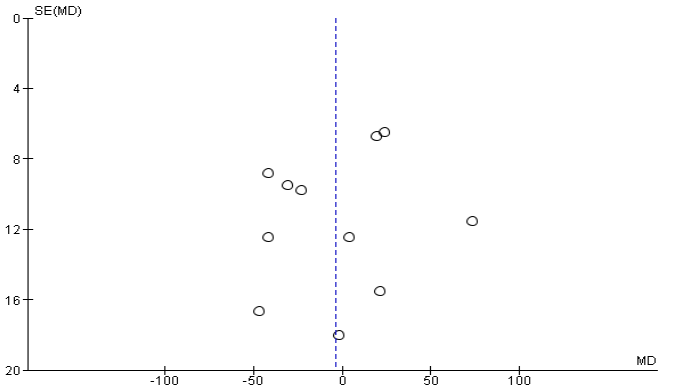

FIGURE 3. The funnel plot of Deeks is used to analyse publication bias. If the computed P0.05, there is a possibility of publishing.

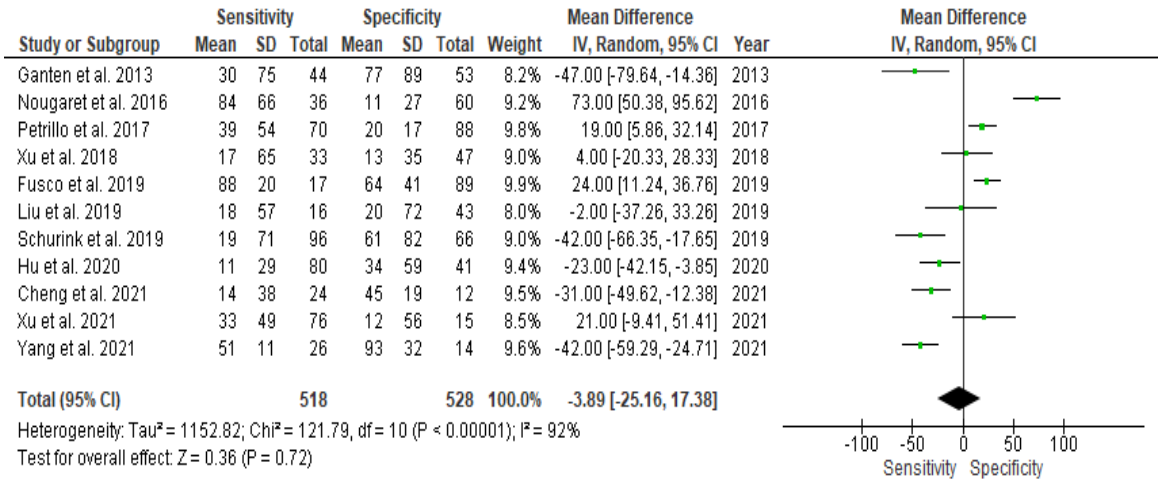

FIGURE 4. For the studies that were included, a forest plot of the pooled sensitivity and specificity was created. The 95 percent confidence intervals (CIs) for each study are shown in black solid horizontal lines. The aggregated sensitivity or specificity for all 11 trials is indicated by a red dashed line. The sensitivity or specificity of each investigation is shown by the grey boxes with centre black dots.

To assess the sensitivity, specificity, positive predictive value, negative predictive value, and diagnosis of each parameter accuracy, the receiver operating curve (ROC) was used to evaluate the predictive strength of each parameter (sensitivity, 1-specificity). The difference is statistically significant if it is less than 0.05.

Based on ROC curve analysis, the diagnostic performance of the IVIM-MRI parameters in identifying pathological responses were shown in Figure (4). To discriminate Pcr from non-pCR, Ä%T had the highest area under the curve (ADC) (0.817), had the best sensitivity and negative predictive value, whereas had the lowest sensitivity and negative predictive value with an (ADC of 0.849).

Figure (5) predicting response to neoadjuvant chemoradiation, the Receiver Operating Characteristic Curve (ROC) was shown to be effective (nCRT). For ROC curves, the area under the curve (ADC) was computed, as well as sensitivity and specificity. The ADC is a measurement of precision. The more closely the curve follows the ROC space's upper-left border, the more accurate the test. The closer the curve gets to the ROC space's 45° diagonal, the better.

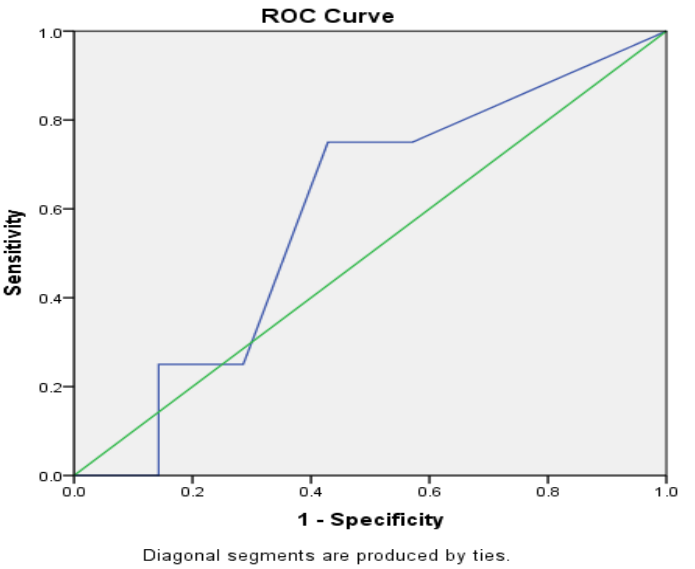

FIGURE 5: ROC, to be precise. The ellipsoid 95 percent confidence zone in ROC space for the summary point estimate of diagnostic performance is represented by the confidence region (smaller circle with dashed line). ROC stands for receiver operating characteristics summary. ADC stands for area under the curve; PEC stands for specificity; SENS stands for sensitivity.

Table 2. Larger values of the test result variable(s) indicate stronger evidence for a positive actual state.

Case Processing Summary	
Type of study[a]	**Valid N (listwise)**
Positive[b]	4
Negative	7

a. The test result variable(s): Age has at least one tie between the positive actual state group and the negative actual state group.
b. The positive actual state is Prospective.

Colorectal cancer screening and staging commonly use imaging studies. According to a recent meta-analysis, MRI outcomes for restaging rectal cancer following neoadjuvant treatment were inconsistent. Demonstrates the Roc Curve of sensitivity and specificity, Comparison of the diagnostic performance of IVIM MRI, The pooled sensitivity and specificity were 81% (0.83-0.91) and 86% (0.77-0.87), respectively, Table (III).

TABLE 3. Subgroup analysis and meta.regression IVIM MRI.

Characteristic	NO. OF studies	Pooled sensitivity (CI)	P‑value	Pooled specificity (CI)	P‑value
MRI field, T			0.72		0.84
3.0	5	0.86 (0.77-0.88)		0.80 (0.85-0.95)	
1.5	4	0.81 (0.83-0.91)		0.82 (0.78-0.86)	
Country of origin			0.66		0.91
China	5	0.77 (0.81-0.88)		0.79 (0.81-0.94)	
Italy	3	0.76 (0.79-0.86)		0.76 (0.77-0.89)	
Amsterdam	1	0.73 (0.88-0.91)		0.75 (0.83-0.91)	
France	1	0.73 (0.84-0.94)		0.74 (0.80-0.90)	
Germany	1	0.72 (0.81-0.90)		0.74 (0.81-0.88)	
Study design			0.43		0.89
Prospective	5	0.91 (0.89-0.98)		0.81 (0.84-0.96)	
Retrospective	4	0.89 (0.79-0.87)		0.80 (0.79-0.89)	
narrative review	2	0.84 (0.75-0.89)		0.78 (0.79-0.86)	
IVIM MRI			0.39		0.77
positive	4	0.81 (0.83-0.91)		0.81 (0.77-0.87)	
Negative	7	0.84 (0.86-0.95)		0.86 (0.82-0.97)	

DISCUSSION

The IVIM MRI is a popular approach for cancer staging before surgery. It has a high degree of accuracy in terms of tumour localization and diagnosis, tumour infiltration depth judgement, and resection range determination. The main disadvantage of morphological analysis is that it can only indicate intuitive alterations in cancer rather than accurately representing information at the cell and molecular level. Staging of (81%), and restaging of (84%). For the distinction between T1 and T2 tumors, MRI is not accurate; so IVIM MRI could be used for this specific purpose (10).

In the present meta-analysis, more than 75% of the studies were of low risk of bias regarding the random sequence generation (selection bias), while more than 50% of the studies were of low risk of bias regarding the allocation concealment (selection bias) (11-16) and incomplete outcome data (attrition bias) (17,18).

In this meta-analysis, for the assessment of the function of IVIM MRI in staging and restaging of rectal cancer, the pooled sensitivity of 81 percent (CI 0.83-0.91) and specificity of 86 percent (CI 0.77-0.87) from the 11 included studies was calculated. AUC >0.80 suggests a good test when it is between 0.50 and 1.00.

And, using a summary receiver operating characteristic curve, we obtained an AUC of 0.97, which was much higher than the expected 0.80. As a result, the IVIM MRI performed exceptionally well in rectal cancer staging and restaging.

This meta-analysis revealed significant heterogeneity in some of the pooled estimates. Although the threshold effect could be a contributing factor, there was no substantial threshold effect, and the form of the ROC is not characteristic of a "shoulder arm" pattern. The probability of publication bias as a source of heterogeneity was considered. Deeks' funnel tests, on the other hand, revealed no publication bias (P = 0.72).

Subgroup analysis was used to go further into the source of heterogeneity. The results revealed that there was no significant improvement in homogeneity in subgroups classified by state, b-value, imaging techniques, and other factors. There is a significant improvement in homogeneity in the subgroup excluding the studies of Xu et al. (2021) and Schurink et al. (2019) whose patient spectrum was not particularly appropriate. Xu et al. (2021) and Schurink et al. (2019) both have the drawback of being narrative reviews with no definite number of patients and no specific MRI field (T) found. Sensitivity and specificity were 0.74 and 0.86 percent, respectively (Chl2=121.79, P=<0.00001), I2=92%), according to the subgroup analysis.

As a result, heterogeneity lowers dramatically compared to the initial pooled results. Although several factors such as MRI field (T), MRI imaging strategy, and analysis method may still create small heterogeneity in the subgroup analysis, our meta-analysis has a relatively desirable homogeneity.

CONCLUSION

In conclusion, all available data suggests that IVIM MRI is a reliable, noninvasive, and non-radiative imaging approach for rectal cancer staging and restaging.

Wide-ranging randomised control trials will be required in the future to further confirm the clinical utility of IVIM MRI and set measurement, analysis, and diagnosis cut-off values.

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