Effectiveness of MRI for the Assessment of Mesorectal Fascia Involvement in Patients with Rectal Cancer: A Systematic Review and Meta-Analysis

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Key Words

Rectal cancer · Preoperative staging · Mesorectal fascia · MRI · Meta-analysis

Abstract

Aims: Defining the most appropriate definition of mesorectal fascia involvement (MRF+) by reviewing literature and using new inclusion criteria to re-evaluate the effectiveness of MRI in the assessment of MRF+ for rectal cancer. **Methods:** PubMed, Medline, Embase, and the Cochrane Library databases were electronically searched from 1999 to 2012. The bivariate random effects model was used to estimate the pooled outcomes of each subgroup. The definition of MRF+ in MRI and the influence of neoadjuvant chemoradiotherapy (neo-ChRT) were especially discussed. **Results:** Fourteen studies involving 1,600 patients were included. Different definitions of MRF+ (≤ 1 , ≤ 2 and ≤ 5 mm) in MRI exhibited different pooled sensitivity (76, 79 and 92%), specificity (88, 66 and 48%) and diagnostic odds ratio (DOR) (22.4, 6.6 and 16.0). The definition of MRF+ at ≤ 1 mm showed the highest DOR. The specificity (88 vs. 93%, $p = 0.026$) and DOR (15.5 vs. 39.0, $p = 0.001$) were lower in patients who underwent neo-ChRT than those who did not while using ≤ 1 mm as the definition of MRF+. However, the sensitivity showed no signifi-

cant difference (67 vs. 74%, $p = 0.129$). **Conclusions:** MRI is valuable for the assessment of MRF. The most appropriate definition of MRF+ in MRI is ≤ 1 mm. The effectiveness is higher in patients who did not undergo neo-ChRT.

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Introduction

Since it was first put forward by Heald et al. [1] in 1982, total mesorectal excision (TME) has been used as the standard procedure to treat mid-low rectal cancers with significant local recurrence rate [2–6]. However, some studies revealed an unfavorable local recurrence rate after standardized TME procedures in a small population of patients. Further studies [7, 8] suggested that preoperative mesorectal fascia involvement (MRF+) is an independent risk factor. MRF is defined as the fine linear structure enveloping the mesorectal compartment harboring the rectum perirectal fat [9], and it is considered to be involved if the distance between the tumor tissue and MRF is ≤ 1 mm in histopathology [10]. A meta-analysis by Nagtegaal and Quirke [11] showed the patients with preoperative MRF+ had higher local recurrence and distant metastasis rate, as well as reduced life

expectancy. The main approaches to assess MRF are CT and MRI. Since MRI can achieve better contrast resolution, it is more reliable in the assessment of MRF+ [12, 13]. However, the definition of MRF+ in MRI is still controversial. Three previous meta-analyses have already evaluated the effectiveness of MRI in the assessment of MRF+ for rectal cancer [14–16]. But in their studies, patients who underwent neoadjuvant chemoradiotherapy (neo-ChRT) were not studied. It is generally accepted that a second MRI scan is helpful to identify a potentially involved MRF after neo-ChRT in patients with locally advanced rectal cancer [9]. So it is also important and necessary to study patients who underwent neo-ChRT. Besides, a clear definition of MRF+ was not given in their studies. Studies with the definition like ‘contiguity of tumor and the mesorectal fascial reflection’ were also included (see Appendix 2), which might have influenced the accuracy of outcomes. Based on this, we conducted this meta-analysis to get the most appropriate definition of MRF+ in MRI and to revalue MRI in the assessment of MRF. As far as we know, this is the first meta-analysis to compare the most appropriate definition of MRF+ and to include the influence of neo-ChRT on MRI accuracy in predicting MRF+.

Methods

Criteria for Study Eligibility

Studies were included if they fulfilled the following criteria: (a) histopathology was used as the golden standard, (b) the definition of MRF+ was ≤ 1 mm in histopathology, and ≤ 1 , ≤ 2 or ≤ 5 mm in MRI, (c) original articles (if data were used in more than one article, only the newest paper was included), and (d) original primary data were available to extract or reconstruct 2×2 contingency tables. If not, authors were contacted to request this information.

Studies having any of the following features were not eligible for inclusion: (a) non-English articles, (b) animal experiments, and (c) reports only as abstract, review and lecture.

Literature Search and Data Extraction

A literature search was performed for relevant publications in PubMed, Medline, Embase and Cochrane Central (1.1.1999–30.6.2012). We retrieved 132 studies in PubMed, 249 in Embase and Medline, and 8 in Cochrane Central (see Appendix 1). Reference lists of these retrieved articles were also searched manually to identify relevant studies and 3 studies were identified. By reading abstracts of all these studies independently by two veteran reviewers, a total of 149 studies that may fit the inclusion criteria were identified.

Assessment of Methodological Quality

Quality was assessed using the checklist of Quality Assessment of Diagnostic Accuracy Studies (QUADAS), which is recommend-

ed by Cochrane Collaboration [17]. Each quality item was scored as ‘yes’, ‘no’ or ‘unclear’. Two reviewers independently reviewed the studies to evaluate the 11 different quality indexes of each study. In case of disagreement, it was resolved by discussion or consulting with a third reviewer. According to Whiting et al. [18], we did not calculate the summary scores because of its problematic interpretation.

Statistical Analysis

In this study, bivariate random effects model [19, 20] was used to generate the summary estimates of sensitivity, specificity, and diagnostic odds ratio (DOR) through Stata software (Stata SE 12). RevMan 5 (Review Manager software 5.0) was used to draw the summary of receiver-operating characteristic (SROC) curves. In covariate analyses, t test was used and the p value was calculated. The pooled sensitivity, specificity and DOR were compared in patients who underwent neo-ChRT (MRI after neo-ChRT vs. histopathology) and who did not (baseline MRI vs. histopathology) when analyzing the influence of neo-ChRT.

Investigations of Heterogeneity

Heterogeneity could be caused by the following factors: (a) whether patients underwent neo-ChRT, (b) definition of MRF+ in MRI, (c) tumor location, (d) tumor stage, (e) QUADAS items 1, 3 and 7, (f) types of operation, (g) patients’ age and sex, (h) tumor differentiation, (i) different parameters of MRI, (j) different time intervals between MRI and surgery, and (k) treatments by different surgeons, pathologists and radiologists.

Results

Literature Search and Selection of Studies

The literature search identified 389 references and a total of 149 full studies were retrieved, of which 14 were considered relevant for this meta-analysis (fig. 1) [21–34].

Study Characteristics

A total of 14 studies and 1,600 patients were included in this study (table 1), including 8 prospective, 4 retrospective and 2 undefined studies. Among the 14 studies, 2 did not have neo-ChRT and 12 did. All 14 studies used ≤ 1 mm as the definition of MRF+, but 3 of them [26, 32, 34] also used other definitions (≤ 2 and ≤ 5 mm). A total of 10 studies and 1,286 patients (636 of whom had neo-ChRT) were included when discussing the influence of neo-ChRT (table 2). Four studies [29, 32–34] were excluded because they were not available to extract or reconstruct 2×2 contingency tables of patients who had neo-ChRT and those who did not separately. From table 2 we can see 7 of the 10 included studies had neo-ChRT and they all had second MRI and were compared with the final histopathology.

Fig. 1. Flowchart of search results.

Table 1. Characteristics of the included studies

Study	Year	Design	n	Sen	Spe	Tesla of MRI	Using DWI of MRI	Used meta-static lymph node? ^a	Neo-ChRT: NOT ^b	1 mm ^c	2 or 5 mm ^c	T stage		Distance from the anal verge, cm		
												T0-2	T3-4	0-5	5-10	10-15
Giusti [21]	2012	retrospective	96	1.000	0.850	1.5	no	? ^d	48:48	yes	no	46	50	?	?	?
Nougaret [22]	2012	retrospective	58	0.667	0.796	1.5	yes	?	58:0	yes	no	34	24	42	16	0
Pomerri [23]	2011	retrospective	68	0.500	0.900	1.0	no	yes	68:0	yes	no	?	?	?	?	?
Taylor [24]	2011	prospective	374	0.642	0.907	?	no	?	216:158	yes	no	?	?	113	261 ^e	
Kim [25]	2009	prospective	66	0.942	0.571	1.5	no	?	0:66	yes	no	22	44	10	56	?
Tytherleigh [26]	2008	prospective	46	0.286	0.795	1.0	no	yes	46:0	yes	yes	?	?	?	?	?
Kulkarni [27]	2008	prospective	80	0.538	0.866	1.0	no	no	80:0	yes	no	36	44	?	?	?
Strassburg [28]	2007	retrospective	68	1.000	1.000	1.0 or 1.5	no	yes	23:45	yes	no	22	46	17	31 ^f	20 ^f
Videhult [29]	2007	prospective	91	0.800	0.864	1.0 or 1.5	no	?	?	yes	no	20	71	18	?	?
MERCURY Study Group [30]	2006	prospective	408	0.593	0.924	?	no	yes	97:311	yes	no	136	272	139	145	101
Ferri [31]	2005	?	22	1.000	0.900	1.5	no	?	0:22	yes	no	?	?	?	?	?
Brown [32]	2003	prospective	98	0.810	0.974	1.5	no	yes	?	yes	yes	28	70	13	85 ^e	
Martling [33]	2003	retrospective	99	0.800	0.725	1.5	no	yes	?	yes	no	?	?	?	?	?
Blomqvist [34]	1999	?	26	0.875	0.778	1.5	no	?	24:2	yes	yes	?	?	?	?	?

Sen = Sensitivity; Spe = specificity. ^a Whether metastatic lymph node was used for measuring the closest distance to the MRF. ^b Neo-ChRT = The number of patients who had neo-ChRT. NOT = The number of patients who did not have neo-ChRT. ^c Whether 1, 2 or 5 mm was used as the definition of MRF+ in MRI. ^d Character '?' means 'unclear' in this table. ^e This study did not subdivide between 5–10 and 10–15 cm. ^f This study divided the group as 0–6, 6–12 and 12–16 cm.

Quality Assessment

The quality of included studies is summarized in table 3. It shows that the main disagreement is in 3 out of the 11 quality indexes (items 1, 3 and 7). In this study, item 1 indicates that studies should include all kinds of rectal cancer including upper, middle, lower and T1–T4 rectal cancers. Only 5 studies met this criterion. Item 3 is

defined as follows: if the patient underwent neo-ChRT the surgery should be performed in 5–10 weeks, otherwise the surgery should be performed in 8 weeks after neo-ChRT. Only 6 studies met this criterion. Item 7 indicates that histologists did not know the results of MRI when they were analyzing the specimens. Twelve studies did not describe this practice.

Table 2. Characteristics of 10 studies included in discussing the influence of neo-ChRT

Study	n	Sen	Spe	Neo-ChRT			Without neo-ChRT			Second MRI after neo-ChRT	DWI	Time of interval, days ^a
				n	Sen	Spe	n	Sen	Spe			
Giusti [21]	96	1.000	0.850	48	1.000	0.667	48	1.000	1.000	yes	no	≤14
Nougaret [22]	58	0.667	0.796	58	0.667	0.800	0	/	/	yes	yes	6–14
Pomerri [23]	68	0.500	0.900	68	0.500	0.900	0	/	/	yes	no	14–21
Taylor [24]	374	0.642	0.907	216	0.375	0.990	158	0.862	0.783	yes	no	?
Kim [25]	66	0.942	0.571	0	/	/	66	0.942	0.571	/	no	/
Tytherleigh [26]	46	0.286	0.795	46	0.286	0.795	0	/	/	yes	no	≤2
Kulkarni [27]	80	0.538	0.866	80	0.538	0.866	0	/	/	yes	no	21
Strassburg [28]	68	1.000	1.000	23	1	1	45	1	1	yes	no	?
MERCURY												
Study Group [30]	408	0.593	0.924	97	0.944	0.734	311	0.417	0.978	yes	no	30
Ferri [31]	22	1.000	0.900	0	/	/	22	1.000	0.900	/	no	/
Total	1,286	/	/	636	0.67	0.88	650	0.74	0.93	/	/	/

Sen = Sensitivity; Spe = specificity. ^a Time of interval between surgery and second MRI after neo-ChRT.

Fig. 2. SROC curve of MRI for assessment of MRF in rectal cancer, with 95% confidence region (dotted lines) for all subgroups. Each confidence region has a summary point (dots) which represents the most likely values of true summary sensitivity and specificity.

Data Analysis

From table 4, we can see the different definitions of MRF+ (≤ 1 , ≤ 2 and ≤ 5 mm) in MRI exhibited different pooled sensitivity (76, 79 and 92%, respectively), specific-

ity (88, 66 and 48%, respectively) and DOR (22.4, 6.6 and 16.0, respectively). The definition of MRF+ at ≤ 1 mm showed the highest DOR. Table 5 shows the details of each outcome and figure 2 shows each SROC curve when using ≤ 1 mm as the definition of MRF+. Summary estimates of sensitivity, specificity and DOR were produced with 95% confidence interval (CI).

Covariate Analyses

Based on the heterogeneity investigations, we performed covariate analysis of items a, b, e, and i. Though items c, d, j and k also have very important influences on the results, covariate analysis was not performed due to insufficient data.

As shown in table 5, sensitivity, specificity and DOR of patients who underwent neo-ChRT were 67% (95% CI 43–85%), 88% (95% CI 77–95%) and 15.5 (95% CI 6.5–37.0). The specificity and DOR were much lower ($p = 0.026$ and 0.001) and the sensitivity showed little difference ($p = 0.1286$), comparing with the patients who did not undergo neo-ChRT.

The full details of pooled sensitivity, specificity and DOR of the other subgroups are listed in table 5. The sensitivity, specificity and DOR were all much higher ($p \leq 0.05$) when MRI was performed on 1.5-tesla (T) instruments compared with 1.0-T instruments. The type of studies (retrospective vs. prospective) had marked influence on the sensitivity ($p \leq 0.01$), but not on the specificity and DOR.

Table 3. Methodological quality of the included studies

Study	Year	QUADAS item										
		1	2	3	4	5	6	7	8	9	10	11
Giusti [21]	2012	unclear	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes
Nougaret [22]	2012	no	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes
Pomerri [23]	2011	no	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes
Taylor [24]	2011	yes	yes	unclear	yes	yes	yes	unclear	yes	yes	yes	yes
Kim [25]	2009	no	yes	unclear	yes	yes	yes	unclear	yes	yes	yes	yes
Tytherleigh [26]	2008	unclear	yes	no	yes	yes	yes	unclear	yes	yes	yes	yes
Kulkarni [27]	2008	no	yes	no	yes	yes	yes	unclear	yes	yes	yes	yes
Strassburg [28]	2007	yes	yes	unclear	yes	yes	yes	unclear	unclear	unclear	yes	yes
Videhult [29]	2007	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
MERCURY Study Group [30]	2006	yes	yes	no	yes	yes	yes	unclear	yes	yes	yes	yes
Ferri [31]	2005	unclear	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Brown [32]	2003	yes	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes
Martling [33]	2003	unclear	yes	unclear	yes	yes	yes	unclear	yes	unclear	yes	yes
Blomqvist [34]	1999	unclear	yes	unclear	yes	yes	yes	unclear	yes	yes	yes	yes

1 = Representative spectrum, in this meta-analysis it means tumors from all levels of rectum (upper, mid, low; T1–T4). 2 = Acceptable reference standard. 3 = Acceptable delay between tests, in this meta-analysis it means time period ≤ 8 weeks between MRI and surgery (≤ 2 weeks if patient received pre-RCT) [9]. 4 = Partial verification avoided. 5 = Differential verification avoided. 6 = Incorporation avoided. 7 = Index test results blinded. 8 = Reference standard results blinded. 9 = Relevant clinical information. 10 = Uninterruptable results reported. 11 = Withdrawals explained.

Table 4. Sensitivity, specificity and DOR for different definitions of MRF+

Definition	Sensitivity, % (95% CI)	Specificity, % (95% CI)	DOR (95% CI)
≤ 1 mm	76 (63–85)	88 (82–92)	22.4 (11.4–43.8)
≤ 2 mm	79 (66–88)	66 (61–71)	6.6 (3.4–12.6)
≤ 5 mm	92 (83–97)	48 (43–53)	16.0 (1.2–219.2)

Discussion

For the definition of MRF+ in histopathology, ≤ 1 mm was recommended by the National Comprehensive Cancer Network (NCCN) [10], and this study adopted this definition. There is much debate about the definition of MRF+ in MRI. We consider ≤ 1 mm to be the most appropriate definition in MRI. The reasons are as follows: in the studies of our initial search, there were 4 types of definitions of MRF+ (≤ 1 , ≤ 2 , ≤ 5 mm and no specific distance) (see Appendix 2) and ' ≤ 1 mm' is the most frequently used one. 17 of the articles used ' ≤ 1 mm' as the definition, 14 were included in this study and 3 [35–37] were excluded due to lack of data. Previous articles showed the distances

of the tumor to MRF revealed by MRI and histology was in good agreement [38–40]. Brown et al. [39] pointed out that specimen fixation or processing had no appreciable effect on the measurement of distance from tumor to MRF. This observation implies the distance of the tumor to MRF measured in MRI and histopathology had little difference. Because the definition of MRF+ in histopathology is ≤ 1 mm [10], using ≤ 1 mm as the definition of MRF+ in MRI appears to be the most appropriate. Though Beets-Tan et al. [41] found that a tumor-free MRF of at least 1.0 mm can be predicted with a high degree of certainty when the measured distance on MRI is at least 5.0 mm, that difference in distance between MRI and histopathology had already been reduced [22] with consistent use of a high-resolution technique and the improved skills of radiologists. Nowadays, Beets-Tan and colleagues [42] also use ≤ 1 mm for invasion and ≤ 2 mm which they call high risk. In addition, we found that in the 3 subgroups concerning MRF+ (≤ 1 , ≤ 2 and ≤ 5 mm), ' ≤ 1 mm' group exhibited the highest DOR (table 4). Recently, a multicenter study suggests that using the definition of ≤ 1 mm did not decrease the accuracy of MRI in predicting MRF status compared with the definition of ≤ 2 mm or even ≤ 5 mm. On the contrary, it would reduce overtreatment that could achieve only minimal gain based on very low

Table 5. Sensitivity, specificity and DOR for MRF+ (≤ 1 mm) in different subgroups

Subgroups	Sensitivity, % (95% CI)	Specificity, % (95% CI)	DOR (95% CI)
All studies	76 (63–85)	88 (82–92)	22.4 (11.4–43.8)
Exclude two studies ^a	77 (67–85)	86 (81–90)	21.6 (13.3–35.2)
Exclude Blomqvist et al. ^b	75 (62–85)	88 (82–92)	22.4 (10.9–46.2)
Studies used 1.5 T ^c	87 (78–93)	83 (72–91)	35.0 (14.5–84.7)
Studies used lymph node ^d	68 (50–82)	93 (81–97)	27.2 (5.7–129.3)
Patients have neo-ChRT ^e	67 (43–85)	88 (77–95)	15.5 (6.5–37.0)
Patients did not have neo-ChRT ^f	74 (49–90)	93 (79–98)	39.0 (18.9–80.5)
p value	0.129	0.026	0.001
Retrospective studies	97 (20–100)	89 (64–98)	288.1 (0.7–113,857)
Prospective studies	72 (58–83)	88 (82–92)	19.0 (10.3–35.0)
p value	0	0.366	0.161

^a Two studies: only one study [27] has the highest accuracy and the other [25] has the lowest accuracy.

^b Blomqvist et al. [34]: MRI scan was performed on the specimen (in vitro) in this study. ^c Studies used 1.5 T: the studies which used 1.5 T of MRI in all patients (7 studies, details in table 1). ^d Studies used lymph node: studies in which metastatic lymph node was used for measuring the closest distance to the MRF (6 studies, details in table 1). ^e Sensitivity, specificity and DOR were calculated by comparing MRI after neo-ChRT with histopathology.

^f Sensitivity, specificity and DOR were calculated by comparing baseline MRI with histopathology.

local recurrence (89 of 216 additional patients would have been treated to prevent seven potential local recurrences when using ≤ 5 mm as the definition) [24]. For all these discussed reasons, we consider ≤ 1 mm to be the best definition of MRF+ in MRI.

From table 4, we can see the sensitivity, specificity and DOR are 76%, 88% and 22.4, respectively, when we adopt ≤ 1 mm as the definition. It is much lower compared with the results by Al-Sukhni et al. [16] (77%, 94% and 56.1, respectively), which is the latest study and also has the largest amount of patients among the three previous meta-analyses [14–16]. The following factors could have caused these differences: first, neo-ChRT is probably the most important factor; second, we only included studies that used a definition of MRF+ at ≤ 1 mm both in MRI and histopathology, and third, we have included studies that were published after Al-Sukhni's study [21–24].

Al-Sukhni et al. [16] excluded patients who had neo-ChRT, because they considered neo-ChRT administered after MRI might downstage the tumor so that final histopathology no longer represented an appropriate reference standard for the original MRI. However, we still considered MRI valuable in the assessment of MRF of neo-ChRT patients for the following reasons: first, when we calculate the influence of neo-ChRT, all studies (table 2) did a second MRI after neo-ChRT and were compared with the final histopathology, thus reducing the differ-

ences; second, studies showed that preoperative short-course radiotherapy or radiochemotherapy has little influence on MRF+ [11, 43, 44], and third, not all patients' MRI before neo-ChRT could be gained. In this situation, the MRI after neo-ChRT became the only data we could use.

Table 5 shows that the DOR and specificity were much lower when patients had neo-ChRT, because there was much fibrosis and tumor 'scar', which made it difficult to distinguish from treated tumor [29, 30, 32]. Studies show that MRI using diffusion-weighted imaging (DWI) can increase the accuracy in patients who had neo-ChRT. One of the reasons is that DWI provides information that reflects tissue cellularity and the integrity of cellular membranes and it is sensitive to intratumoral changes induced by chemoradiation therapy, so it is easier to discriminate between fibrosis and residual tumor [45–51]. Park et al. [46] showed that the accuracy improved from 0.4 (0.69 in observer 2) to 0.89 (0.93 in observer 2). In our 14 included studies, only 1 used DWI (table 1), so we did not analyze the influence of using DWI.

Apart from DWI, other instruments of MRI can also influence the estimates of MRI, especially the different magnetic strength (T). Al-Sukhni et al. [16] found 3.0 T MRI had much higher specificity than 1.0 or 1.5 T on T staging, but Maas et al. [52] showed no difference between 3 and 1.5 T MRI for the T staging. In our analysis,

no study used the 3.0 T MRI, but the 1.5 T MRI showed higher sensitivity, specificity and DOR than 1.0 T MRI (table 5). But it was influenced by considerable heterogeneity caused by neo-ChRT, the use of DWI and the individual differences of radiologists and surgeons. So, RCT studies with larger samples are needed to establish the influence of different tesla.

The location of tumor is also an important factor that can influence the accuracy of MRI for the assessment of MRF. Studies found that MRI had lower accuracy to assess MRF in anterior tumors than in posterior tumors [25, 30, 52]. The anterior perirectal fat is usually very thin, which makes it more difficult to delimit the anterior MRF or Denonvilliers' fascia in MRI. Besides, it is less reliable to predict MRF in lower rectal tumor than in middle and upper rectal tumors by MRI because lower rectal tumor is much closer to the horizontal position and anteriorly closer to the seminal vesicles in male patients and to the posterior vaginal wall in female patients. Glimelius et al. [53] proposed that in low tumors that are below the levator muscles, where the MRF cannot be defined, the relationship to the sphincters should be described. In our meta-analysis, the proportions of tumors arising from different locations were varied among each article (table 1). Due to lack of data we did not perform a detailed analysis. This may be one limitation of our study. Recently, in order to enhance the accuracy of MRI in staging low rectal cancer, some studies proposed a novel MRI staging technique, which was based on the relationship of the tumor to the levators and individual components of the sphincter complex [53–55]. However, the benefit of the new staging technique is not clear and larger prospective studies are needed to confirm its benefit.

There are other factors affecting the accuracy of MRI for the assessment of MRF, such as the tumor stage and the histological type of tumor. Kim and colleagues [56] found T3 tumor was related to the incorrect prediction of MRF. Different types of tumor can also influence the accuracy. Studies showed mucinous tumors would increase the error for the assessment of MRF in neo-ChRT patients, because mucinous tumors had higher signal intensity after chemoradiation therapy than non-mucinous tumors, which made it difficult to differentiate residual tumor from inactive mucin pools [38, 40].

According to NCCN, the definition of MRF+ in histopathology includes both secondary to metastatic lymph node and direct tumor extension [10]. In the 14 included studies, only 6 [23, 26, 28, 30, 32, 33] gave a positive instruction on whether metastatic lymph node was used for measuring the closest distance to MRF (table 1). This may

be another limitation of our study. We analyzed these 6 studies and found that they had a lower sensitivity and higher specificity when MRF is positive and when metastatic lymph node was present (table 5).

There are several other limitations in our study. First and also the most important one is the bias caused by the quality of surgery. Quirke et al. [57] found that surgery was achieved in the mesorectal plane in only 52% patients (34% in intramesorectal plane and 13% in muscularis propria plane), and the ratio was lower in abdominoperineal excision compared with anterior resection, but similar in primary surgery and surgery after neo-ChRT. Besides, Martling et al. [33] thought that the surgeon was aware of the findings on preoperative MRI, which may have influenced the surgical approach, thus leading to extended resection in patients with a predicted involved MRF. These non-standard TME surgeries with extended or contracted resection reduce the accuracy of MRI. Second, we restricted our search to the studies published in English, which may lead to language bias. Third, 3 studies [35–37] that could not be used to extract or reconstruct 2×2 contingency tables were excluded. The exclusion of these data may influence our results. Fourth, in our study, the time interval between second MRI and surgery was different (table 2), and as we know, changes in disease status can occur in this time frame [58]. However, van der Paardt et al. [59] described a group with a maximum 6-week interval between second MRI and surgery, and found that they had a difference but which was not statistically significant. So in our opinion, the different time intervals were another source of bias, but during a certain time frame. How to clearly define this interval and its relationship with the results needs further investigation. Fifth, considerable heterogeneity was observed in this meta-analysis and did not appear to diminish when the 2 studies with lowest and highest accuracy were excluded. The heterogeneity was probably caused by variations in study design, patient characteristics, different MRI parameters, and the individual differences of radiologists, surgeons and pathologists.

In conclusion, MRI has a favorable specificity in the assessment of preoperative MRF for rectal cancer, but its sensitivity remains to be further investigated. Our meta-analysis found that the definition of ≤ 1 mm is the most appropriate in MRI, and neo-ChRT has marked influence on the effectiveness of MRI in assessing MRF.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

Appendix 1

Search strategies

Database	Search strategies	Papers, n
PubMed	<p>#1 rectal neoplasms [MeSH Terms]</p> <p>#2 (((cancer* [Text Word]) OR carcinoma* [Text Word]) OR neoplas* [Text Word]) OR malignan* [Text Word]</p> <p>#3 rectal*</p> <p>#4 (#2) AND #3</p> <p>#5 (#1) OR #4</p> <p>#6 (((((((circumferential resection margin* [Text Word]) OR circumferential margin* [Text Word]) OR mesorectal fascia* [Text Word]) OR resection margin* [Text Word]) OR radial resection margin* [Text Word]) OR meso-rectal margin* [Text Word]) OR circumferential margin involvement* [Text Word])</p> <p>#7 magnetic resonance imaging [MeSH Terms]</p> <p>#8 (((MRI [Text Word]) OR magnetic resonance imaging [Text Word]) OR magnetic resonance [Text Word]) OR magnetic resonance imag* [Text Word]</p> <p>#9 (#7) OR #8</p> <p>#10 (diagnosis [MeSH Terms]) OR sensitivity and specificity [MeSH Terms]</p> <p>#11 (((((((((((likelihood functions [MeSH Terms]) OR likelihood ratio [Text Word]) OR likelihood [Text Word]) OR sensitivity [Text Word]) OR specificity [Text Word]) OR accura* [Text Word]) OR false positive rate [Text Word]) OR false negative rate [Text Word]) OR predictive value [Text Word]) OR Youden's index [Text Word]) OR kappa statistic [Text Word]) OR reliability [Text Word])</p> <p>#12 (#11) OR #10</p> <p>#13 (((#5) AND #6) AND #9) AND #12 Filters: Publication date from 1999/01/01 to 2012/06/30; Humans; English</p>	132
The Cochrane Central Register of Controlled Trials	<p>#1 (cancer*): ti,ab,kw or (carcinom*): ti,ab,kw or (neoplas*): ti,ab,kw or (malignan*): ti,ab,kw</p> <p>#2 MeSH descriptor Rectal Neoplasms explode all trees</p> <p>#3 (rectal*): ti,ab,kw</p> <p>#4 (#1 AND #3)</p> <p>#5 (#4 OR #2)</p> <p>#6 MeSH descriptor Magnetic Resonance Imaging explode all trees</p> <p>#7 (MRI): ti,ab,kw or (magnetic resonance imaging): ti,ab,kw</p> <p>#8 (#6 OR #7)</p> <p>#9 (circumferential resection margin*): ti,ab,kw or (circumferential margin*): ti,ab,kw or (mesorectal fascia*): ti,ab,kw or (radial resection margin*): ti,ab,kw or (resection margin*): ti,ab,kw or (circumferential margin involvement*): ti,ab,kw</p> <p>#10 (sensitivity): ti,ab,kw or (specificity): ti,ab,kw or (accura*): ti,ab,kw or (Youden's index): ti,ab,kw or (kappa statistic): ti,ab,kw</p> <p>#11 (false positive rate): ti,ab,kw or (false negative rate): ti,ab,kw or (predictive value): ti,ab,kw or (likelihood ratio): ti,ab,kw or (likelihood): ti,ab,kw</p> <p>#12 (#10 OR #11)</p> <p>#13 MeSH descriptor Likelihood Functions explode all trees</p> <p>#14 MeSH descriptor Diagnosis explode all trees</p> <p>#15 MeSH descriptor Sensitivity and Specificity explode all trees</p> <p>#16 (#13 OR #14 OR #15 OR #12)</p> <p>#17 (#5 AND #8 AND #12 AND #16), from 1999 to 2012</p>	8

Appendix 1 (continued)

Database	Search strategies	Papers, n
Medline and Embase	#1 'rectal tumor'/exp #2 cancer* OR carcinom* OR neoplas* OR malignan* #3 rectal* #4 (#2 AND #3) #5 (#1 OR #4) #6 'nuclear magnetic resonance imaging'/exp #7 'mri'/exp OR 'magnetic resonance imaging'/exp #8 (#6 OR #7) #9 'circumferential resection margin' OR 'resection margin' OR 'circumferential margin' OR 'mesorectal fascia' OR 'radial resection margin' OR 'circumferential margin involvement' #10 'diagnosis'/exp #11 'sensitivity and specificity'/exp #12 sensitivity OR specificity OR 'false positive rate' OR 'false negative rate' OR 'predicative value' OR 'Youden index'/exp OR 'likelihood ratio' OR 'likelihood function' OR 'kappa statistic'/exp #13 accura* #14 (#10 OR #11 OR #12 OR #13) #15 (#5 AND #8 AND #9 AND #14) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim) AND [English]/lim AND [humans]/lim AND [1-1-1999]/sd NOT [30-6-2012]/sd	249

Appendix 2

Sixteen studies which were excluded because of different definitions of MRF+

Study	Year	Journal	Definition of MRF+ in MRI	Definition of MRF+ in histopathology	2 × 2 contingency tables
Park	2011	Radiology	≤2 mm	≤2 mm	yes*
Akasu	2009	Ann Surg Oncol	unclear	unclear	yes
Kim	2009	J Magn Reson Imaging	≤2 mm	≤2 mm	yes*
Salerno	2009	Dis Colon Rectum	tumor on MRI invading into the intersphincteric plane or laying within 1 mm of levator muscle or tumor invading into the external anal sphincter and infiltrating or extending beyond the levators with or without invading an adjacent organ	≤1 mm	yes
Youssef	2009	Colorectal Dis	unclear	≤1 mm	no
Kim	2008	Eur J Surg Oncol	≤2 mm	≤2 mm	no
Vliegen	2008	Radiology	≤2 mm	≤2 mm	yes*
Allen	2007	AJR Am J Roentgenol	≤2 mm	≤2 mm	no
Rao	2007	World J Gastroenterol	≤2 mm	≤2 mm	yes
Taylor	2007	Abdom Imaging	≤5 mm	≤5 mm	yes
Oberholzer	2005	J Magn Reson Imaging	≤2 mm	≤2 mm	no
Peschaud	2005	Dis Colon Rectum	≤2 mm	≤2 mm	yes
Vliegen	2005	Radiology	diffuse stranding from the tumor into the mesorectal fascia, a nodular tumor mass encroaching the mesorectal fascia, or a tumor deposit or suspected lymph node in direct contact with the mesorectal fascia	≤1 mm	yes
Branagan	2004	Dis Colon Rectum	contiguity of tumor and the mesorectal fascial reflection	unclear	yes

Appendix 2 (continued)

Study	Year	Journal	Definition of MRF+ in MRI	Definition of MRF+ in histopathology	2 × 2 contingency tables
Mathur	2003	Colorectal Dis	tumor was seen to involve or encroach upon the mesorectal envelope	unclear	yes
Botterill	2001	Colorectal Dis	tumor in broad contact with lateral edge of mesorectum coupled with signal change in surrounding tissue	unclear	yes

* Studies which had two reviewers to evaluate the value of MRI in the assessment of preoperative MRF for rectal cancer, and have two sets of data. In our meta-analysis, we separated the data as if they were from two different studies.

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