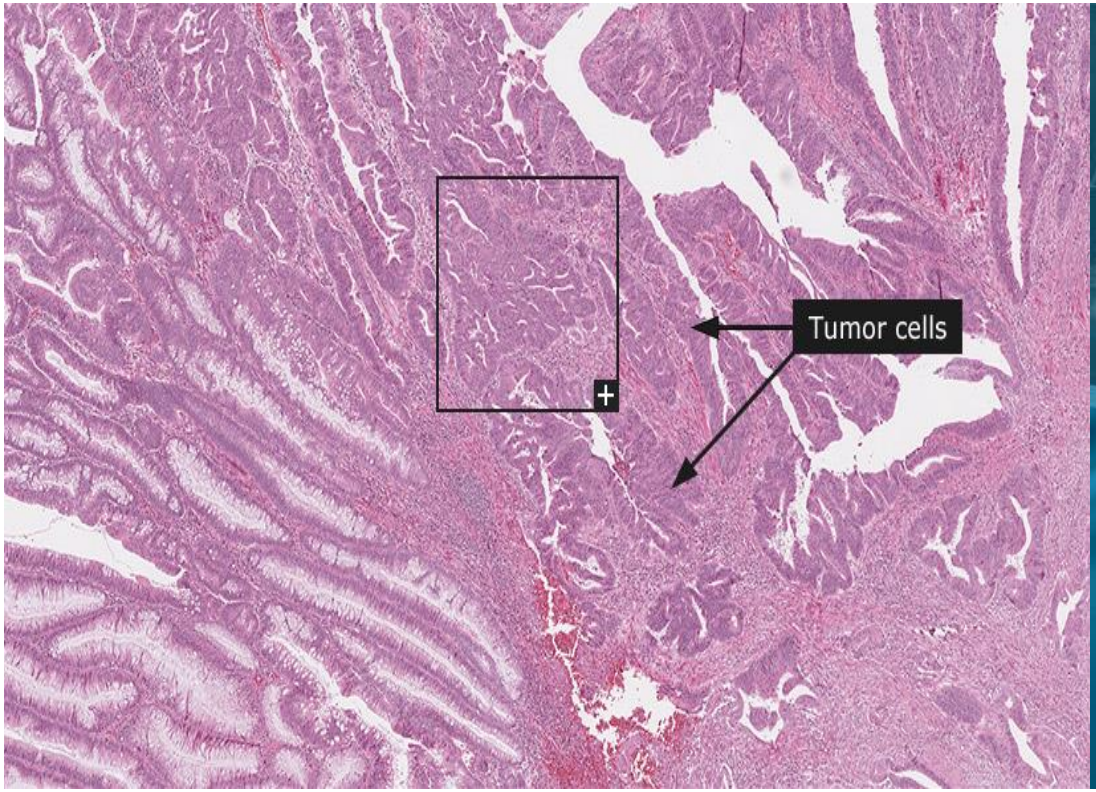
KCE REPORT 260

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

GUIDELINE ON THE MANAGEMENT OF RECTAL CANCER: UPDATE OF CAPITA SELECTA – PART 2: STAGING



KCE REPORT 260
GOOD CLINICAL PRACTICE

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GUIDELINE ON THE MANAGEMENT OF RECTAL CANCER: UPDATE OF CAPITA SELECTA – PART 2: STAGING

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Disclaimer:

- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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ABBREVIATIONS

ABBREVIATION	DEFINITION
AHRQ	Agency for Healthcare Research and Quality
AR	Abdominal resection
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
ELRR	Endoluminal locoregional resection
EMVI	Extramural venous invasion
ERUS	Endorectal ultrasound
ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society for Medical Oncology
FU	Fluorouracil
GDG	Guideline Development Group
GIN	Guidelines International Network
HR	Hazard ratios
IKNL	Integraal Kankercentrum Nederland
KCE	Belgian Health Care Knowledge Centre
LR	Local recurrence
LRFS	Local recurrence free survival
LTME	Laparoscopic total mesorectal excision
MA	Meta-analysis
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network

NICE	National Institute for Health and Care Excellence
NIHDI (RIZIV/INAMI)	National Institute for Health and Disability Insurance
OR	Odds ratio
OS	Overall survival
PET-CT	Positron emission tomography - computed tomography
PICO	Population-intervention-comparator-outcome
PROCARE	Project on Cancer of the Rectum
QoL	Quality of life
RCT	Randomised controlled trial
RQ	research question
RR	Risk ratio
SEER	Surveilllance, Epidemiology and End Results
SR	Systematic review
TAE	Transanal excision
TEM(S)	Transanal endoscopic microsurgery
TME	Total mesorectal excision

SCIENTIFIC REPORT

WHAT IS THE OPTIMAL STAGING STRATEGY USING MAGNETIC RESONANCE IMAGING?

1 INTRODUCTION

This section addresses the role of MRI or endorectal ultrasound (ERUS) in T staging and N staging for rectal cancer. M staging was not included because primary studies usually pool the colon and rectal cancer and an extensive review on this issue was presented in the KCE report on colon cancer.[1] As it is important that MRI is conducted in a proper way, consensus based standards on how to conduct MRI were also put forward by the GDG.

2 EVIDENCE DESCRIPTION

Guidelines published from 2012 onwards were searched in the Guidelines International Network (GIN) database and on the Agency for Healthcare Research and Quality (AHRQ) website (guideline clearinghouse and comparative effectiveness reviews). Four potentially suitable guidelines were identified. It was assessed whether the guidelines were based on a systematic search, sound methodology including risk of bias assessment of the primary studies, appropriate pooling and whether the evidence was reported with sufficient detail to judge the relations between evidence and recommendations and to make adaptations if necessary. This rapid assessment refers to the questions 7, 8 and 10 of the AGREE II tool. Monson et al.[2] was based on an appropriate search and method, but reported insufficient details on the results. The 2014 NICE guideline[3] was not updated regarding staging, thus the evidence is up to date until February 2011. IKNL[4] did a systematic search for staging of liver metastases only, in collaboration with KCE.[1] One guideline was selected: the 2014 AHRQ comparative effectiveness review on imaging tests for the staging of colorectal cancer.[5] AMSTAR evaluation was provided in the Appendix 2. The focus of the guideline was on the comparative effectiveness of imaging techniques for pretreatment cancer staging in patients with primary and recurrent colorectal cancer. Test performance for the T and N staging of rectal cancer was reviewed separately from colon cancer. Staging after initial therapy (neoadjuvant) was also evaluated.

Subsequently, the evidence was updated from the search date of the AHRQ review (November 2013) onwards until the 29th of April 2015. Studies comparing at least two diagnostic techniques were retained. Details of the search strategy and flow chart are provided in the **Error! Reference source ot found.** The flowchart and selection process is presented the Appendix.

Four studies were selected. Two were excluded due to quality and reporting issues. The related Quadas evaluation can be consulted in the Appendix. The study by Swarting et al.[6] was excluded because the data necessary to calculate sensitivity and specificity were not provided. The authors only provided accuracy without numbers of false positives and negatives. The study by Kocaman et al.[7] was excluded because of major issues concerning quality of the study: unclear recruitment, assessment of staging and data reporting which made it difficult to extract data.

2.1 Preoperative rectal staging

AHRQ reported on the absolute accuracy of MRI, computed tomography (CT), positron emission tomography computed tomography (PET CT) and ERUS and whenever possible also on the comparative accuracy. Comparative accuracy is evaluated by studies that directly compare different staging modalities, usually reported as an odds ratio (OR). Detailed results can be found in the evidence tables (Table 1 and Table 2). In the AHRQ SR, databases (Embase®, MEDLINE®, PubMed and the Cochrane Library) were searched for the period 1980 through November 2013. All published, English-language, full-length articles for the interventions ERUS, CT, MRI and PET/CT in patients needing N and T staging for colorectal cancer were identified. Eight systematic reviews and 65 primary comparative studies were retrieved. We describe the relevant results for to research question.

Table 1 – AHRQ systematic review: absolute accuracy ERUS, CT and MRI for T staging, N staging

	Sensitivity	Specificity
T staging		
ERUS	To identify:	
T1:	• 87.8% (85.3% to 90.0%)	• 98.3% (97.8% to 98.7%)
T2:	• 80.5% (77.9% to 82.9%)	• 95.6% (94.9% to 96.3%)
T3:	• 96.4% (95.4% to 97.2%)	• 90.6% (89.5% to 91.7%)
T4:	• 95.4% (92.4% to 97.5%)	• 98.3% (97.8% to 98.7%)
CT	For distinguishing T1/T2 from T3/T4: 86% (78% to 92%)	78% (71% to 84%)
MRI	For distinguishing T1/T2 from T3/T4:	
	• 87% (81% to 92%)	• 75% (68% to 80%)
N staging		
EUS	73.2% (70.6% to 75.6%)	75.8% (73.5% to 78.0%)
CT	70% (59% to 80%)	78% (66% to 86%)
MRI	77% (69% to 84%)	71% (59% to 81%)
PET CT	0.61	0.83

Note. The AHRQ review is based on 7 recent (2009 or later) high-quality systematic reviews and 38 primary comparative studies

Table 2 – AHRQ systematic review: comparative effectiveness of the different modalities.

	MRI vs. ERUS	ERUS vs. CT	MRI vs. CT
T staging			
Sensitivity (95% CI) of T1/T2 vs. T3/T4	MRI: 88.9% (79.0% to 94.4%)	insufficient data	insufficient data
	ERUS: 88.0% (80.0% to 93.1%)	insufficient data	insufficient data
Specificity (95% CI) of T1/T2 vs. T3/T4	MRI: 85.3% (70.6% to 93.4%)	insufficient data	insufficient data
	ERUS: 85.6% (65.8% to 94.9%)	insufficient data	insufficient data
Understaging OR (95% CI)	1.571 (0.605 to 4.083)	0.626 (0.438 to 0.894)	0.317 (0.027 to 3.646)
Overstaging OR (95% CI)	1.05 (0.518 to 2.16)	0.472 (0.28 to 0.798)	0.317 (0.028 to 3.653)
N staging			
Sensitivity (95% CI)	MRI: 49.5% (36.0% to 63.1%)	CT: 39.6% (28.1% to 52.4%)	insufficient data
	ERUS: 53.0% (39.7% to 65.5%)	ERUS: 49.1% (34.9% to 63.5%)	insufficient data
Specificity (95% CI)	MRI: 69.7% (51.9% to 83.0%)	CT: 93.2% (58.8% to 99.2%)	insufficient data
	ERUS: 73.7% (43.6% to 91.0%)	ERUS: 71.7% (56.2% to 83.4%)	insufficient data
Understaging OR (95% CI)	0.972 (0.563 to 1.679)	1.453 (0.854 to 2.473)	1.743 (1.028 to 2.957); not robust in sensitivity analysis
Overstaging OR (95% CI)	0.752 (0.457 to 1.237)	1.015 (0.571 to 1.801)	0.498 (0.308 to 0.806)

Notes. Based on studies that directly compared modalities with each other and verified the results with a reference standard (usually histopathology/intraoperative findings).

Random-effects meta-analyses on the measures of accuracy, over staging, and under staging using a binomial-bivariate normal regression model. Rectal T staging: based on 23 studies of preoperative staging. Six studies compared MRI with ERUS, 13 compared CT with ERUS, 3 compared MRI with CT and 1 study compared CT, MRI, and ERUS. Rectal N staging: based on 19 studies. One study compared MRI with PET/CT, 5 compared MRI with ERUS, 9 compared CT with ERUS and 4 compared MRI with CT.

It was concluded that there is low level of evidence that ERUS is less likely to give an incorrect result (OR = 0.36; 95% CI, 0.24 to 0.54), less likely to under stage (OR = 0.63; 95% CI, 0.44 to 0.89), and less likely to over stage (OR = 0.47; 95% CI, 0.28 to 0.80) rectal cancer than CT in the preoperative T staging setting. There is low level of evidence that MRI and ERUS are similar in accuracy for preoperative rectal T staging.

There is low level of evidence that CT, MRI and ERUS have similar accuracy for preoperative rectal N staging. MRI is less likely than CT to over stage (OR = 0.498; 95% CI, 0.308 to 0.806). The sensitivity of these modalities however is low, ranging from 50% to 70%, depending on the way it is measured.

AHRQ identified two studies reporting on patient management based on MRI or ERUS for preoperative rectal staging. Both studies used a similar design. For each patient, the investigators devised three theoretical treatment strategies: one based solely on MRI information, a second one based solely on ERUS information and a third strategy incorporating clinical information, MRI and ERUS data. Histopathology after surgery was used to identify the "correct" treatment strategy. They pooled the results from both studies in a random-effects meta-analysis and analysed the outcomes "correct treatment," "under-treatment," and "over treatment." All three analyses favoured MRI as the more accurate modality for treatment but none reached statistical significance. The summary OR for incorrect results was 0.326 (95% CI 0.052 to 2.045), the summary OR for over treatment was 0.396 (95% CI 0.129 to 1.216) and the summary OR for under treatment was 0.203 (95% CI 0.011 to 3.847).

The primary study by Granero-Castro et al.[8] prospectively evaluated the accuracy of ERUS and MRI in predicting the pathologic circumferential resection margin in low rectal anterior tumours compared to pathologic examination. An evidence table following the GIN template is provided in the Appendix. Thirty two patients with rectal cancer were included. They concluded that ERUS and MRI have similar accuracy, sensitivity and specificity. For both modalities accuracy was 87.5% (CI: 86.8–88.2), sensitivity 85.7% (CI: 73.6–97.8) and specificity 88.0% (76.7–99.7).

Zhou et al.[9] investigated the accuracy of preoperative CT, MRI and diffusion-weighted imaging with background body signal suppression (DWIBS) in the prediction of nodal involvement in primary rectal carcinoma patients in the absence of tumour invasion into pelvic structures. Fifty-two subjects with primary rectal cancer were assessed preoperatively by CT and MRI at 1.5 T with a phased-array coil. Preoperative lymph node staging with imaging modalities (CT, MRI, and DWIBS) were compared with the final histological findings. Results showed that CT was more sensitive but less specific (sensitivity 18/23 (78.3%); specificity 19/29 (65.5%)) than MRI (13/23 (56.5%); 24/29 (82.8%)). Overall, MRI was more accurate (33/52 (63.5%) vs. 30/52 (57.7%)). Both studies had low sample size and low to moderate quality. Therefore they were not integrated in the meta-analysis by AHRQ because it is was considered unlikely that the conclusions would be altered.

2.2 Interim staging after initial therapy

2.2.1 T staging

AHRQ identified two studies that compared CT, ERUS and MRI. However, due to different data reporting the only measure that could be pooled across the two studies was accuracy (i.e., not specificity, sensitivity, under- or over-staging). There was no difference in accuracy across the various modalities (MRI vs. CT, 0.943 (95% CI: 0.652 to 1.34), MRI vs. ERUS, 0.948 (95% CI: 0.471 to 1.907), CT vs. ERUS, 0.907 (95% CI: 0.41 to 2.011)).

In addition, one study compared CT with MRI for restaging locally advanced cancer after neoadjuvant CRT. MRI had a better accuracy than CT (60.0% correctly staged vs. 41.7%, respectively), equivalent sensitivity for distinguishing between T1/T2 and T3/T4 stages (90%), but a much lower specificity (33.3% vs. 66.7%, respectively). The authors concluded that MRI was not significantly better than CT. Another study that compared CT to ERUS for restaging locally advanced cancer after neoadjuvant CRT. Both modalities were inaccurate for T staging (46.3% correctly staged for CT, 38.3% for ERUS), with high rates of both over- and under staging.

2.2.2 N Staging

AHRQ identified three studies of interim rectal N restaging. One study compared CT with ERUS and two studies compared MRI, CT and ERUS. The study that compared CT with ERUS reported that CT was more sensitive than ERUS (56% vs. 50%, respectively) for detecting affected lymph nodes, but CT had a lower specificity than ERUS (74.5% vs. 81.1%, respectively). The authors concluded that neither modality was good for restaging rectal cancer. The two other studies comparing CT, MRI, and ERUS reported data differently, so that only the accuracy data could be pooled quantitatively in a random-effects meta-analysis. The analysis showed no statistical difference between the three modalities.

The additional search did not yield any relevant studies on restaging after initial treatment using ERUS, CT or MRI.

3 Conclusions and recommendations

The GRADE method is not adequate for diagnostic questions. Therefore recommendations are provided without level of evidence or strength of recommendation.

Conclusions

- ERUS is less likely to give an incorrect result (OR = 0.36; 95% CI, 0.24 to 0.54), less likely to under stage (OR = 0.63; 95% CI, 0.44 to 0.89), and less likely to over stage (OR = 0.47; 95% CI, 0.28 to 0.80) rectal cancer than CT in the preoperative T staging setting.
- MRI and ERUS have similar accuracy for preoperative rectal T staging.
- CT, MRI, and ERUS have similar accuracy for preoperative rectal N staging. MRI is less likely than CT to over stage (OR = 0.498; 95% CI, 0.308 to 0.806). However, the sensitivity of these modalities is low, ranging from 50% to 70%, depending on the way it is measured.
- There was no significant difference in accuracy across ERUS, CT and MRI for interim rectal T and N-staging.
- Only two studies report on patient management based on MRI or ERUS. They show a trend towards better treatment strategy with MRI but differences were not statistically significant.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Correct staging allows to give a more adapted treatment, over staging and under staging may result in under treatment or over treatment. For ERUS, the most common adverse are pain and minor bleeding. Theoretical major adverse events such as bowel perforation were not reported. A supplementary harms search by AHRQ identified a narrative review of complications of endoscopic ultrasound, including ERUS. Harms from MRI appear to be limited to contrast agent reactions. Many of the included studies did not use intravenous contrast and the available data suggests that the use of intravenous contrast does not improve the accuracy of MRI for rectal T or N colorectal staging. Harms from CT include contrast agent reactions and radiation exposure. Many included studies did not use intravenous contrast, and one study suggests that using intravenous contrast does not improve CT's accuracy for rectal T or N staging.

Factor	Comment
Quality of evidence	Very few studies reported on outcomes other than staging accuracy. The studies reporting accuracy outcomes did not find complete cross-classified data (i.e., numbers of patients correctly staged, under staged, and over staged for each stage for all modalities and the reference standard). Many of the studies reporting staging accuracy were quite small and provided limited information on patient characteristics. ERUS is operator dependent and performance is likely to be better in academic and research settings where the validation studies took place, compared to 'real life'. Only a few studies reported how imaging modalities affected patient management, but not whether management changes were deemed appropriate. No studies reported on patient-oriented outcomes such as survival and quality of life. The primary data report accuracies, but it is impossible to estimate from the data in the studies the added value of adding ERUS to MRI or vice versa.
Costs (resource allocation)	The cost was not considered in this report.
Patients values and preferences	No information on patient preferences was found in the literature regarding diagnosis.

Recommendations
• Offer MRI to assess the risk of local recurrence, as determined by anticipated circumferential resection margin, tumour and lymph node staging and extramural venous invasion (EMVI), to all patients with rectal cancer unless it is contraindicated.
• Offer endorectal ultrasound to patients with rectal cancer if MRI shows disease amenable to local excision, additional clinical information is needed, or if MRI is contraindicated.

4 CONSENSUS PROTOCOL FOR STAGING MRI

The GDG insisted that there was a need in Belgium to set a number of standards on how to make optimal use of MRI. Those standards were prepared by a member of the GDG, Didier Bielen, presented at a GDG meeting and to the stakeholders and were approved. The protocol and references is illustrated in Table 3.

Table 3 – Rectal cancer imaging – a 'how-to-do' proposal

Rectal cancer imaging - Rationale

- **Main aim:**
  - Stratify patient's risk of recurrence
  - Selection and treatment planning
    - Early: local resection
    - Medium: short RT + bowel resection (e.g. TME)
    - Late: long RT + extensive surgery
    - Disseminated: palliation (stent)

Pre-treatment planning

- **Diagnosis** [1]
  - Clinical examination
  - Colonoscopy with biopsy
- **Staging**
  - Local: MRI [2-6] and EUS [1, 7]
    - Delineation mesorectal fascia [8, 9]
    - Discrimination between tumour and muscle layer [8, 9]
  - Distant: Abdominal and chest CT [1]

MRI rectum - prerequisites

- **Basic MRI hardware**
  - 1.5T preferable over 3.0T [10]
    - 1.0T is no 1.5 or 3.0T available

- What if no MRI available? Or contra-indicated?

- **Basic rectal MRI protocol**
  - Essential [2, 6, 11, 12]
    - (Rectal distension) [10, 12]
    - Sagittal T2w planning
    - High resolution T2w [6, 12]
      - Long and short axis of the tumour
    - Overview of pelvis
      - LN (T1w/T2w)
    - DWI

    Additional in restaging
    - DWI
    - IV gadolinium

Radiological staging

- **Based on TNM criteria**
  - Staging failures between T2 and borderline T3
    - Desmoplastic extramural reaction
    - Strands of fibrosis extending into perirectal tissues
    - Important: maximal extramural depth (EMD) [6, 9, 13]
      - distance from the outer edge of the longitudinal muscularis propria to the outer edge of the tumour
  - When is the prognosis compromised?
    - Maximal extramural depth (EMD) [9, 13]
      - T3a <1mm T3c 5-15mm
      - T3b 1-5mmT3d >15mm
    - Primary tumour, tumour deposit or positive lymph node abutting mesorectal fascia
      - < 5mm from MRF [14]
      - < 1mm from MRF [15]
  - Nodal disease remains diagnostic challenge for the radiologists
    - Assessment on morphologic criteria [15]

- (Size)
- Shape and aspect

- Metabolic imaging
  - PET: low sensitivity for locoregional nodes
  - USPIO: not clear
  - DWI: after neoadjuvant therapy

MRI reporting *(12, 16, 17)*

- Distance to the anal verge or AR junction?
  - Low (0-5cm), mid (5-10cm), high (10-15cm)
- Depth of tumour growth in the rectal wall and surrounding pelvic structures?
  - T staging
- MRF involved?
  - Good or bad T3
- Nodal status?
  - Nodes other than regional nodes are metastasis
- Extramural vascular invasion (EMVI)?
  - Low level of consensus (10)
- Need for structured reporting (17)
  - Synoptic report improves completeness
- Need for training?
  - Radiologists and radiographic technicians

Conclusion

- MRI essential in imaging rectal cancer
- Optimization of MRI technique required
- Need for structured reporting
- Need for training

Note. This protocol was proposed by D. Bielen; thanks to colleagues E. Dresen, S. Dymarkowski, E. Mussen, K. Op de beeck, D. Vanbeckevoort, V. Vandecaveye, R. Vanslembrouck.
All the references included in this table are reported at the end of the report.

APPENDIX

APPENDIX 1. SEARCH FOR GUIDELINES ABOUT DIAGNOSTICS

We only looked for guidelines published or updated in the last 3 years (2012 to now)

National clearinghouse:

- Key words: colorectal cancer, rectal cancer
- Hits: 104
- Retained: 2

AHRQ evidence reviews: Cancer

- 20 hits, one selected

GIN

- Colorectal cancer
- 77 hits
- Retained

Table 4 – Cochrane database of systematic reviews

Date	05/05/15 17:21:02.949	
Database	Cochrane Database of Systematic Reviews	
Search strategy		
#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	5 583
#2	((rectum or rectal or colorectal) near/4 (cancer* or tumour* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)):ab,ti	7 557
#3	#1 or #2	9 083
#4	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	5 827
#5	mri:ab,ti	4 648
#6	nmr:ab,ti or 'magnetic resonance':ab,ti or mri:ab,ti	9 244

#7	#4 or #5 or #6	10 802
#8	ultrasono*:ab,ti	3 852
#9	Any MeSH descriptor with qualifier(s): [Ultrasonography - US]	7 570
#10	MeSH descriptor: [Ultrasonography] explode all trees	7 969
#11	#8 or #9 or #10	13 498
#12	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	4 164
#13	(ct near/3 scan):ab,ti	901
#14	tomograph*:ab,ti	8 231
#15	('x ray' near/3 (scan or ct)):ab,ti	132
#16	#12 or #13 or #14 or #15	10 734
#17	#7 or #11 or #16	32 630
#18	#17 and #3	441
#19	#18 Publication Year from 2013 to 2015	79
Notes		

Table 5 – Embase

Date	**2015-05-04**	
Database	Embase	
Search strategy		
1	'rectum tumour'/exp	168 913
2	((rectum OR rectal OR colorectal) NEAR/4 (cancer* OR tumour* OR tumour* OR carcin* OR adenocarcin* OR metasta* OR malignan* OR lymphom* OR leiomyosarcom* OR melanom*)):ab,ti	146 206
3	#1 OR #2	191 154
4	'nuclear magnetic resonance imaging'/exp	589 617

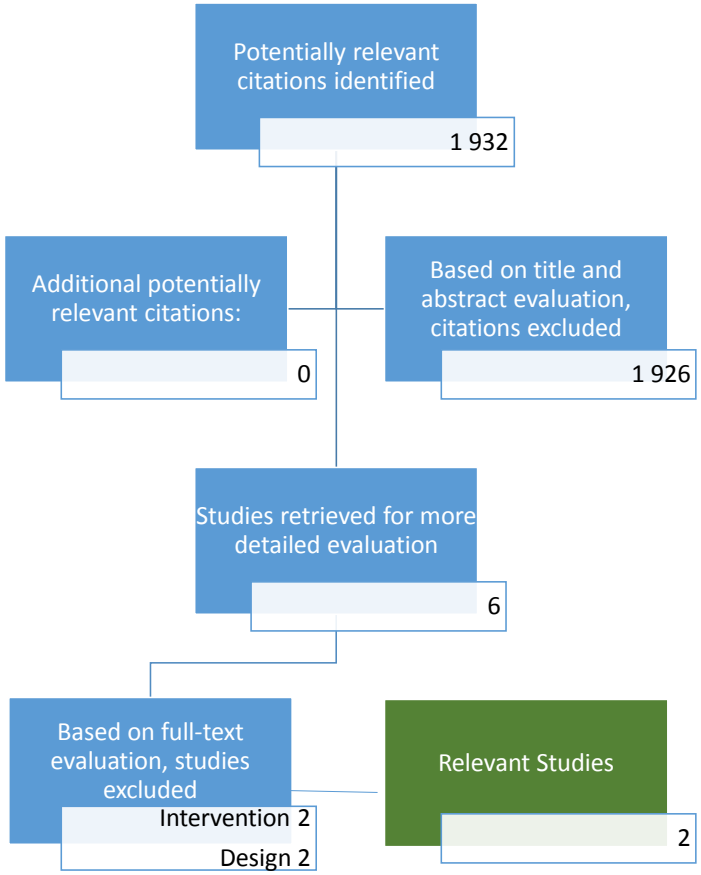
5	mri:ab,ti	238 976
6	nmr:ab,ti OR 'magnetic resonance':ab,ti OR mri:ab,ti	550 016
7	#4 OR #5 OR #6	797 058
8	ultrasono*:ab,ti	107 685
9	'echography'/exp	552 604
10	#8 OR #9	580 366
11	'computed tomography scanner'/exp	12 869
12	(ct NEAR/3 scan):ab,ti	65 596
13	tomograph*:ab,ti	323 443
14	('x ray' NEAR/3 (scan OR ct)):ab,ti	7 276
15	#11 OR #12 OR #13 OR #14	380 891
16	#7 OR #10 OR #15	1 578 869
17	#3 AND #16	14 209
18	#17 NOT [medline]/lim	5 095
19	#18 AND [1-11-2013]/sd NOT [29-4-2015]/sd	1 693
20	#19 AND [editorial]/lim	15
21	#19 NOT #20	1 678
22	#21 AND [animals]/lim	105
23	#21 AND [humans]/lim	1 607
24	#22 NOT #23	26
25	#21 NOT #24	1 652
26	#21 NOT #24 AND ([article]/lim OR [article in press]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)	776
Notes		

Table 6 – Medline Ovid SP

Date	2015-05-04	
Database	Medline OvidSP	
Search strategy		
1	exp Colorectal Neoplasms/	153 914
2	((rectum or rectal or colorectal) adj4 (cancer* or tumour* or tumour* or carcin* or adenocarcin* or metasta* or malignan* or lymphom* or leiomyosarcom* or melanom*)).ab,ti.	105 182
3	1 or 2	178 464
4	Magnetic resonance imaging/	293 237
5	mri.ab,ti.	152 374
6	(nmr or "magnetic resonance" or mri).ab,ti.	422 145
7	4 or 5 or 6	544 265
8	us.fs.	206 251
9	ultraso*.ab,ti.	263 183
10	exp ultrasonography/	257 686
11	8 or 9 or 10	465 989
12	exp Tomography, X-Ray Computed/	316 022
13	(CT adj3 scan).ab,ti.	40 849
14	tomograph*.ab,ti.	270 311
15	(x-ray adj3 (scan or ct)).ab,ti.	5 074
16	12 or 13 or 14 or 15	483 867
17	7 or 11 or 16	1 317 612
18	3 and 17	13 091
19	limit 18 to ed=20131101-20150429	1 289

20	exp animal/ not humans/	4 025 936
21	19 not 20	1 258
22	21 not editorial.pt.	1 244
Notes		

Figure 1 – Flowchart update guidelines on staging



APPENDIX 2. QUALITY APPRAISALS

Table 7 – AMSTAR evaluation of the AHRQ systematic review: Imaging Tests for the Staging of Colorectal Cancer

1. Was an 'a priori' design provided?	Yes
2. Was there duplicate study selection and data extraction?	Yes
3. Was a comprehensive literature search performed?	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Unclear
5. Was a list of studies (included and excluded) provided?	Yes
6. Were the characteristics of the included studies provided?	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes
10. Was the likelihood of publication bias assessed?	Yes
11. Was the conflict of interest included?	No

Table 8 – QUADAS 2 Granero-Castro et al.[8]

	Granero-Castro			
Index test	MRI compared to ERUS			
Reference test	surgery and pathology			
Name of appraiser	JOR			
Item	**Yes**	**No**	**Unclear**	**Comments**
Was the spectrum of patients representative of the patients who will receive the test in practice?	x			

Were selection criteria clearly described?	x		They only considered patients where both MRI and ERUS were performed.
Is the reference standard likely to correctly classify the target condition?	x		
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	x		
Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	x		
Did patients receive the same reference standard regardless of the index test result?	x		
Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	x		
Was the execution of the index test described in sufficient detail to permit replication of the test?	x		
Was the execution of the reference standard described in sufficient detail to permit its replication?	x		
Were the index test results interpreted without knowledge of the results of the reference standard?	x		
Were the reference standard results interpreted without knowledge of the results of the index test?	x		
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	x		
Were uninterpretable/ intermediate test results reported?	x		
Were withdrawals from the study explained?	x		

Table 9 – Quadas 2 Kocaman et al.[7]

	Kocaman			
Index test	MDCT, MRI or EUS			
Reference test	surgery and pathology			
Name of appraiser	JOR			
Item	**Yes**	**No**	**Unclear**	**Comments**
Was the spectrum of patients' representative of the patients who will receive the test in practice?			x	mix of patients that underwent neoadjuvant and no neoadjuvant
Were selection criteria clearly described?		x		unclear how patients were included
Is the reference standard likely to correctly classify the target condition?	x			
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?		x		neoadjuvant may confound staging confirmation by surgery
Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	x			
Did patients receive the same reference standard regardless of the index test result?		x		staging after neoadjuvant likely to give different results
Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	x			
Was the execution of the index test described in sufficient detail to permit replication of the test?	x			
Was the execution of the reference standard described in sufficient detail to permit its replication?	x			
Were the index test results interpreted without knowledge of the results of the reference standard?			x	
Were the reference standard results interpreted without knowledge of the results of the index test?			x	

Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	x			
Were uninterpretable/ intermediate test results reported?	x			
Were withdrawals from the study explained?		x		

Table 10 – Quadas 2 Zhou et al.[9]

	Zhou			
Index test	CT, MR, and DWIBS			
Reference test	surgery and pathology			
Name of appraiser	JOR			
Item	**Yes**	**No**	**Unclear**	**Comments**
Was the spectrum of patients representative of the patients who will receive the test in practice?	x			
Were selection criteria clearly described?	x			
Is the reference standard likely to correctly classify the target condition?	x			
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	x			
Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	x			
Did patients receive the same reference standard regardless of the index test result?	x			
Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	x			
Was the execution of the index test described in sufficient detail to permit replication of the test?	x			

Was the execution of the reference standard described in sufficient detail to permit its replication?	x	
Were the index test results interpreted without knowledge of the results of the reference standard?	x	
Were the reference standard results interpreted without knowledge of the results of the index test?		x
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	x	
Were uninterpretable/ intermediate test results reported?	x	
Were withdrawals from the study explained?	x	

APPENDIX 3. EVIDENCE TABLES

Table 11 – Evidence table Granero-Castro et al.[8]

HEADINGS	DESCRIPTION
Bibliographic citation	Granero-Castro, P., E. Munoz, M. Frasson, A. Garcia-Granero, P. Esclapez, S. Campos, B. Flor-Lorente and E. Garcia-Granero (2014). "Evaluation of mesorectal fascia in mid and low anterior rectal cancer using endorectal ultrasound is feasible and reliable: a comparison with MRI findings." Dis Colon Rectum 57(6): 709-714.
Sources of funding and competing interest	Funding/Support: Dr Granero-Castro is the recipient of the 2012 European Colorectal Fellowship Grant by Covidien. Financial Disclosure: None reported.
Setting	Specialized colorectal multidisciplinary team at a tertiary teaching Hospital Spain
Objective(s) of the study	Evaluate the accuracy of ERUS in predicting the pathologic circumferential resection margin in low rectal anterior tumours and to compare it with MRI findings
Questions addressed	Accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of endorectal ultrasound and MRI according to tumour location
METHODS	
Study design (cited by author or actual)	Transectional
Reference standard test	Surgery and pathology
Diagnostic test(s) evaluated	The surgeon who performed ERUS and the radiologist who interpreted MRI findings were not aware of the results of the other examination. ERUS and MRI staging were compared with the pathologic findings, considered as the gold standard. The pathologist was blinded to the preoperative CRM staging by ERUS and MRI.
Time interval and treatment(s) administered between the tests	Not reported but surgery followed immediately
Investigator(s) and assessor(s) training	Not reported
Study population expected	mid to low non-metastatic rectal cancer
RESULTS	
Numbers	Thirty-two patients were excluded for the following reasons: 1) treated by tumour local excision (pathologic analysis of the whole specimen was not possible; 12 patients), 2) incomplete ERUS for tumour stenosis (12 patients), and 3) impossibility to perform MRI because of claustrophobia or presence of a pacemaker (8 patients). Moreover, we excluded 83 patients who received preoperative

	RCT, because a comparison between preoperative CRM and pathologic CRM was not possible. For the present subanalysis, 27 patients were excluded because the tumour was posterior or posterolateral and, therefore, CRM could not be evaluated by ERUS because of the absence of neighbouring structures, such as vagina, seminal vesicles, or prostate. The present analysis therefore includes 49 patients with medium (7–10 cm from anal verge) or low (≤6 cm from anal verge) rectal tumours located at the anterior circumferential position treated by TME surgery without neoadjuvant RCT.				
Patients and disease characteristics	Age, median ± SD (range), y 69.3 ± 12.3 (23–90) Sex, men 37 (75.5) Tumour location by rectoscopy Medium rectum (7-10 cm from anal verge) 17 (34.7) Lower rectum (≤6 cm from anal verge) 32 (65.3)				
Accuracy		Accuracy			
	All patients(N=49)	ERUS	83.7	(73.4–94.0)	
		MRI	91.8	(84.1–99.5)	
	Low rectum (N=32)	ERUS	87.5	(86.8–88.2)	
		MRI	87.5	(86.8–88.2)	
		Sensitivity			
	All patients(N=49)		85.7	(75.9–95.5)	
			85.7	(75.9–95.5)	
	Low rectum (N=32)		85.7	(73.6–97.8)	
			85.7	(73.6–97.8)	
		Specificity			
	All patients(N=49)		83.3	(72.9–93.7)	
			92.8	(85.4–99.8)	
	Low rectum (N=32)		88.0	(76.7–99.7)	
			88.0	(76.7–99.7)	
Reproducibility	Not reported				
Cut-Off determination	NA				
Comparison of two or more tests					

Adverse effects	Not reported

CRITICAL APPRAISAL OF THE STUDY QUALITY	
Authors conclusion	Report the authors' conclusion
Results validity	Discuss the validity of the results and potential bias present: Internal validity: study design, sample size, blinding, appropriateness of the reference standard test as a gold standard, limitations of the reference standard test (i.e. incomplete reference standard test), interpretation of the results (taking into account the study hypotheses), comment on patients lost to follow-up (if applicable), use of inappropriate statistical analysis, etc. External validity: setting, population involved, test used, etc. General comments, including own conclusion of the reviewer, if possible.
Other /Addendum Optional	Further comments made by the reviewer

Table 12 – Evidence table Zhou et al.[9]

HEADINGS	DESCRIPTION
Bibliographic citation	Zhou, J., S. Zhan, Q. Zhu, H. Gong, Y. Wang, D. Fan, Z. Gong and Y. Huang (2014). "Prediction of nodal involvement in primary rectal carcinoma without invasion to pelvic structures: accuracy of preoperative CT, MR, and DWIBS assessments relative to histopathologic findings." PLoS ONE 9(4): e92779.
Sources of funding and competing interest	Funding: This study was supported by a grant from the Science and Technology Commission Foundation of Shanghai Municipality (NO, 10411952300) in China. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Competing Interests: The authors have declared that no competing interests exist.
Setting	Shuguang Hospital, Shanghai University of Traditional Chinese Medicine
Objective(s) of the study	Evaluate the accuracy of ERUS in predicting the pathologic circumferential resection margin in low rectal anterior tumours and to compare it with MRI findings accuracy of preoperative computed tomography (CT), magnetic resonance (MR) imaging and diffusion-weighted imaging with background body signal suppression (DWIBS) in the prediction of nodal involvement in

	primary rectal carcinoma patients in the absence of tumour invasion into pelvic structures
Questions addressed	Accuracy, sensitivity, specificity
METHODS	
Study design (cited by author or actual)	Transectional
Reference standard test	Surgery and pathology
Diagnostic test(s) evaluated	preoperative CT,MRI imaging and diffusion-weighted imaging
Time interval and treatment(s) administered between the tests	Surgery followed within 2 weeks
Investigator(s) and assessor(s) training	Not reported
Study population expected	mid to low non-metastatic rectal cancer
RESULTS	
Numbers	52
Patients and disease characteristics	A total of 52 patients (29 males with a mean age of 62+-10 years, 23 females with a mean age of 65610 years) with histologically confirmed primary rectal carcinoma were recruited between March 2010 and May 2013. Inclusion criteria were: 1) a suspected diagnosis of rectal carcinoma following colonoscopy or rectal CT and MR, from which clear images without apparent artifacts were obtained; 2) total mesorectal excision (TME) surgery within two weeks after radiological examinations; and 3) no preoperative chemoradiotherapy or other tumour treatment.
Accuracy	Methods Sensitivity % Specificity % Accuracy % CT 18/23 78.3% 19/29 65.5% 30/52 57.7% MRI 13/23 56.5% 24/29 82.8% 33/52 63.5% DWIBS 23/23 100% 19/29 65.5% 21/52 40.4%
Reproducibility	Not reported
Cut-Off determination	NA
Comparison of two or more tests	
Adverse effects	Not reported
CRITICAL APPRAISAL OF THE STUDY QUALITY	
Authors conclusion	In conclusion, MRI is relatively more accurate than CT in predicting nodal involvement in patients with primary rectal carcinoma in the absence of tumour cell invasion to pelvic issues.

Results validity	No blinded assessment of reference test may create bias. Small sample.
Other /Addendum Optional	

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