

Local staging of rectal carcinoma: endorectal ultrasound *versus* magnetic resonance imaging. Systematic review of literature and meta-analysis

Estadaje local del carcinoma rectal: imágenes de ecografía versus resonancia magnética. Revisión sistemática de la literatura y metaanálisis

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ABSTRACT

New surgical techniques in the treatment of rectal cancer have improved survival mainly by reducing local recurrences. A preoperative staging method is required to accurately identify tumor stage and planning the appropriate treatment. MRI and ERUS are currently being used for the local staging (T stage). In this review, the accuracy of MRI and ERUS with rigid probe was compared against the gold standard of the pathological findings in the resection specimens. Five studies met the inclusion criteria and were included in this meta-analysis. The accuracy was 91.0% to ERUS and 86.8% to MRI ($p=0.27$). The result has no statistical significance but with pronounced heterogeneity between the included trials as well as other published reviews. We can conclude that there is a clear need for good quality, larger scale and prospective studies.

Key words: Rectal cancer; Magnetic resonance imaging; Ultrasonography (source: MeSH NLM).

RESUMEN

Las nuevas técnicas quirúrgicas en el tratamiento del cáncer de recto han mejorado la supervivencia, principalmente mediante la reducción de las recidivas locales. Se requiere un método de estadificación preoperatoria para identificar con precisión el estadio del tumor y planificar el tratamiento adecuado. RNM y EAR actualmente están siendo utilizados para la estadificación local (estadio T). En esta revisión, La exactitud de la RNM y la EAR con sonda rígida se comparo con el patrón oro de los hallazgos patológicos em las muestras de resección. Cinco estudios cumplieron los criterios de inclusión y fueron incluidos en este meta-análisis. La precisión fue 91,0% a 86,8% y EAR a la RNM ($p=0,27$). El resultado no tiene significación estadística pero com heterogeneidad marcada entre los ensayos incluidos, así como otras revisiones publicadas. Podemos concluir que existe una clara necesidad de buena calidad, a mayor escala y estudios prospectivos.

Palabras clave: Cáncer de recto; Imagen por resonancia magnética; Ultrasonografía (fuente: DeCS BIREME).

INTRODUCTION

Rectal cancer is a common cancer and a major cause of mortality in Western countries. The American Cancer Society (ACS) estimates about 39,600 new cases of rectal cancer will occur in 2015⁽¹⁾. Treatment for rectal cancer has advanced greatly over the past decade. Our knowledge of total mesorectal excision has led to improved oncologic outcomes. The concept of extralevatorabdomino-perineal resection shows promise for reducing recurrence rates in tumors of the low rectum and anal canal. Minimally invasive techniques of laparoscopic and robotic surgery are technically feasible, and promise decreased complications in the future. New colonoscopic and endoscopic techniques offer alternatives for those unfit for surgery. Finally the adjuvant therapy with chemotherapy and radiation therapy in addition to surgery improves outcome for patients with carcinomas of the rectum.

The correct staging of rectal cancer plays a central role in prognosis as well as determining the appropriate treatment. The diagnosis is usually established by means of clinical examination (rectal digital examination), endoscopy (sigmoidoscopy and colonoscopy) and histologic confirmation. All of these techniques are poor indicators of the depth of invasion and lymph node involvement, which are both important features for treatment⁽²⁾.

Advances in the management of rectal cancer over the last decade have resulted in an increased application of multimodal therapy with the aim of tailoring neoadjuvant, surgical and adjuvant therapy. The goal of the treatment is to preserve sphincter function while improving tumor resectability. Therefore, a more reliable imaging method would facilitate the design of more effective pre and post-operative treatment strategies⁽³⁾.

Currently, several imaging modalities, including Endorectal Ultrasound (ERUS), Computed Tomography

(CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) or PET-CT, are used to assess preoperative staging. MRI and ERUS are the two standard local anatomical imaging techniques used for the primary staging of rectal cancer (4). The aim of this review was to assess the current evidence for both methods in the local staging of rectal cancer.

METHOD

This was a systematic review of diagnostic test accuracy studies, with meta-analysis and was approved by the local Research Ethics Committee.

The aim of this review was to establish the actual role of Endorectal Ultrasonography (ERUS) with rigid probe and Magnetic Resonance Imaging (MRI) in the local staging of rectal cancer. The target condition is rectal cancer. Patients with the diagnosis of primary rectal cancer were included. The exclusion criteria were obstructive tumor, neoadjuvant therapy previous to staging evaluation and patients undergoing emergency surgery or palliative treatment. The reference standard was the pathological examination of the surgical specimen, staged (TNM) according to the guidelines of the American Joint Committee on Cancer and International Union Against Cancer (UICC).

A systematic review of the literature was performed by searching the databases CINAHL, EMBASE, LILACS, MEDLINE, SCISEARCH and The Cochrane Library between 2004 and 2015. Relevant studies on the diagnostic performance comparing endoluminal US (not endoscopic), MR imaging and histopathological analysis in the staging of rectal cancer were identified. The MEDLINE database was searched with the following keywords: (a) "rectal neoplasms" (medical subject heading, or MeSH) and (b) "magnetic resonance imaging" (MeSH) or "ultrasonography" (MeSH) and (c) "specificity" or "false negative" or "accuracy" as text words. The EMBASE, Cochrane, and CANCERLIT databases were also checked for relevant articles by using (a) "rectal cancer" and (b) "magnetic resonance imaging" or "ultrasonography" and (c) "specificity" or "false negative" or "accuracy" as text

words. A hand-search of references from selected articles was also performed to identify additional relevant articles. Data were independently extracted by the reviewers and cross-checked; articles that did not present raw data were excluded.

Studies eligible for inclusion meta-analysis were required to compare, stage for stage with histopathology, MRI and ERUS assessment of T stage of rectal cancer in larger goal.

The methodological quality of the selected studies was critically assessed using the QUADAS-2 tool, a checklist to assess the quality of the diagnostic accuracy of studies (5).

Statistical analysis

The summary thereof was obtained by the weighted sensitivity and specificity and presented graphically by Forest Plot. The likelihood ratios were calculated. The accuracy of the methods was obtained by the SROC curve and was compared using the test differences between proportions.

Meta-analysis of the results was performed using software package Meta-Disc 1.4 (freeware developed by the Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) (6).

RESULTS

With the search strategy the authors chose 104 citations. After careful reading of the titles and abstracts, 26 articles were selected for full-text analysis and critical appraisal. Five were able to meet the inclusion criteria and were included in this meta-analysis (Table 1).

In Table 2 are described the results of each included study and the author's conclusion.

The methodological quality graph (QUADAS-2) presents the percentage of included studies for which the item was rated "low", "high" or "unclear", for each quality assessment domain. The graph shows that the potential area of concern was the description of the patient flow

Table 1. Characteristics of the included studies.

Study	Country	Number of patients	Design	Age - Mean	Outcomereported	Imagingdetails	Risk of bias
Waizer 1991	Israel	13	Cohort Prospective	66 (60 – 80)	Preoperative rectal T staging	Clear	Moderate
Thaler 1994	Italy	34	Cohort Prospective	68.9 (52 – 86)	Preoperative T and N staging accuracy	Clear	Low
Starck 1995	Sweden	35	Cohort Prospective	68 (47 – 84)	Preoperative T and N staging accuracy	Unclear	Moderate
Gualdi 2000	Italy	26	Cohort Prospective	69 (54 – 84)	Preoperative local staging	Clear	Low
Haleflogu 2008	Turkey	34	Cohort Unclear	58,7 (29 – 75)	Preoperative rectal T and N staging accuracy	Clear	Low

Table 2. Characteristics of the included studies.

Study N patients Author's conclusion	Outcome	ERUS / MRI Reported T stage data
Waizer 1991 13 patients Both have a place in staging	Accuracy Sensitivity Specificity	84.6% / 76.9% 88.9% / 88.9% 75.0% / 75.0%
Thaler 1994 34 patients ERUS is better, except when there is stenosis	Accuracy Sensitivity Specificity	88.2% / 82.3% 92.3% / 76.9% 85.7% / 85.7%
Starck 1995 MRI: 35 patients ERUS: 34 patients ERUS is better; MRI seems to underestimate the extension of rectal tumors	Accuracy Sensitivity Specificity	88% / 66% 92.3% / 76.9% 85.7% / 85.7%
Gualdi 2000 26 patients MRI and ERUS were unable to distinguish neoplastic infiltration from inflammatory tissue; both methods seem to be less accurate in staging tumors of low and upper rectum.	Accuracy Sensitivity Specificity	76.9% / 84.6% 72% / 73% 80% / 66%
Halefoglul 2008 34 patients MRI was slightly superior to ERUS	Accuracy Sensitivity Specificity	85.2% / 89.7% 87.5 / 95.8% 50.0% / 60.0%

and the index test. Figure 1 summarizes the risk of bias and applicability judgments on the five studies included.

The sensitivity and specificity values of ERUS were equal to 86.6% (IC a 95%: 83.3%; 89.5%) and 75.4% (IC a 95%: 71.4%; 79.1%). respectively.

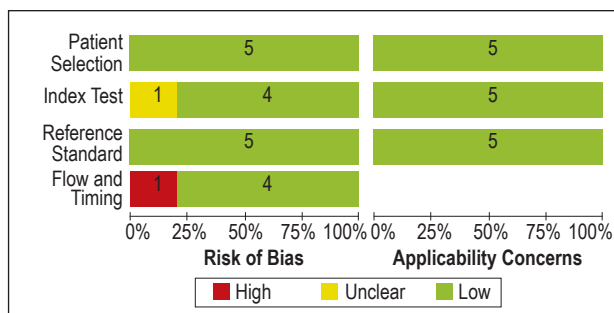
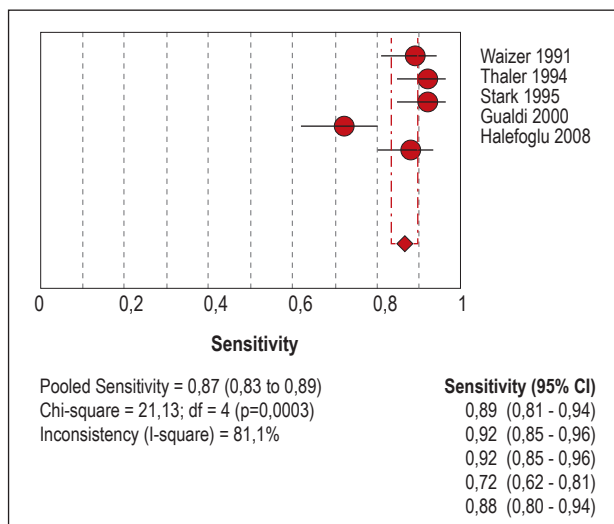


Figure 1. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



For MRI the values of sensitivity and specificity were 82.4% (IC a 95%: 78.8%; 85.6%) and 74.6% (IC a 95%: 70.5%; 78.4%). respectively.

The detailed sensitivity and specificity with 95 % of CI for each individual study were seen in Forest plot (Figures 2 and 3).

Using the fitted summary SROC curve we observed that the area under curve (Accuracy) is 91.0% to ERUS compared to 86.8% to MRI with $p=0.27$ (non-significant). showed in Figures 4 and 5.

DISCUSSION

Pre-operative staging of rectal cancer with accuracy is mandatory in planning the surgical treatment and is the strongest predictor for recurrence ^(7, 8).

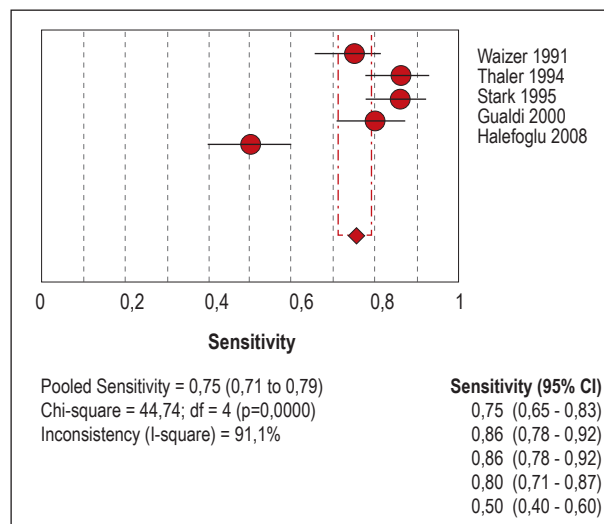


Figure 2. Sensitivity and specificity of ERUS

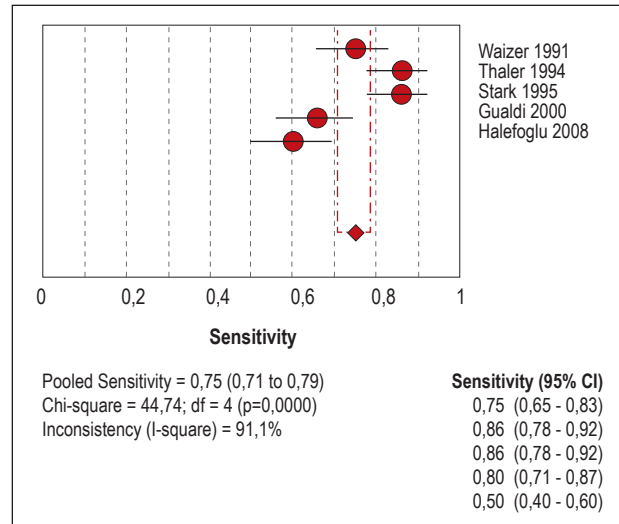
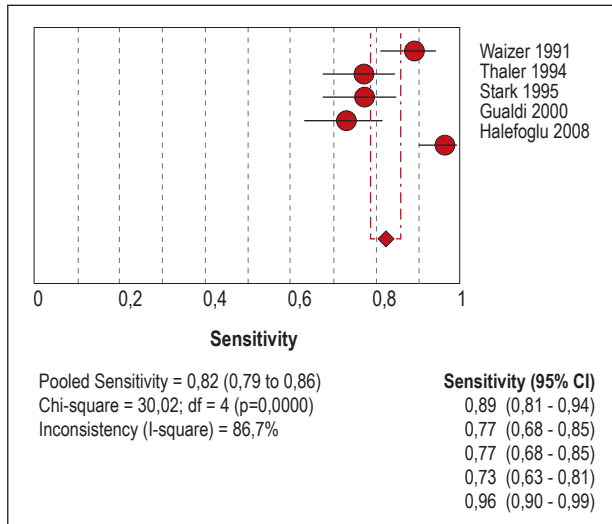


Figure 3. Sensitivity and specificity of MRI.

This review searched the studies comparing Endorectal Ultrasound (ERUS) and Magnetic Resonance Imaging (MRI) with the surgical histopathological analysis for local staging of rectal cancer.

Studies analyzing Endoscopic Ultrasound were not included; despite Colaiácovo *et al.* in 2014 (9) declared that the findings of their study may indicate equivalence in the diagnostic value of both flexible and rigid devices, the reviewers believe there are differences between the methods.

Regarding to the staging the authors understanding that the N stage is another review with proper comments and decided directed the analysis and the results to the T stage - wall invasion.

The results have no statistical significance (p=0.27) and with pronounced heterogeneity between the included trials. The major weakness of this review must be the relatively small number of identified studies, containing small numbers of patients. The significant heterogeneity is an additional weakness. The statistical heterogeneity depends on the clinical and methodological differences within the trials. Inevitably, studies brought together in a systematic review will differ. Further area of concern is the inclusion of many older studies that may have used technology that is now obsolete. Another question mark is the time interval between performance of diagnostic tests and the reference test that should be short. A longer period will lead to a greater change in the disease status and decrease in the discriminatory

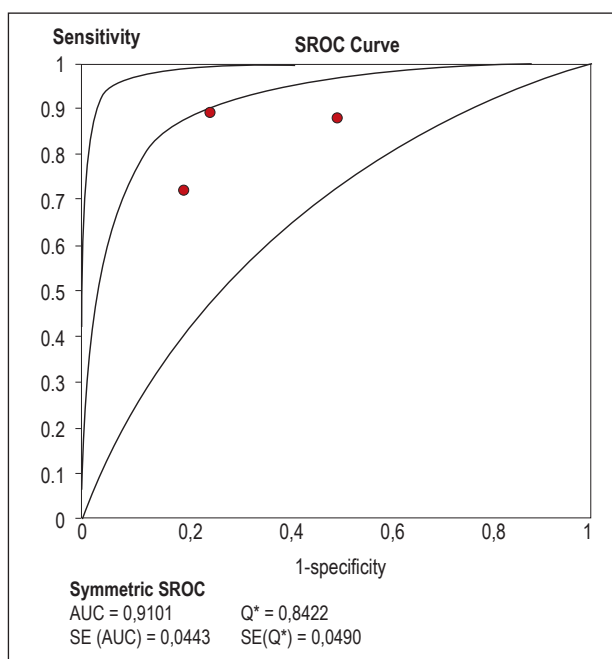


Figure 4. ERUS - SROC curve.

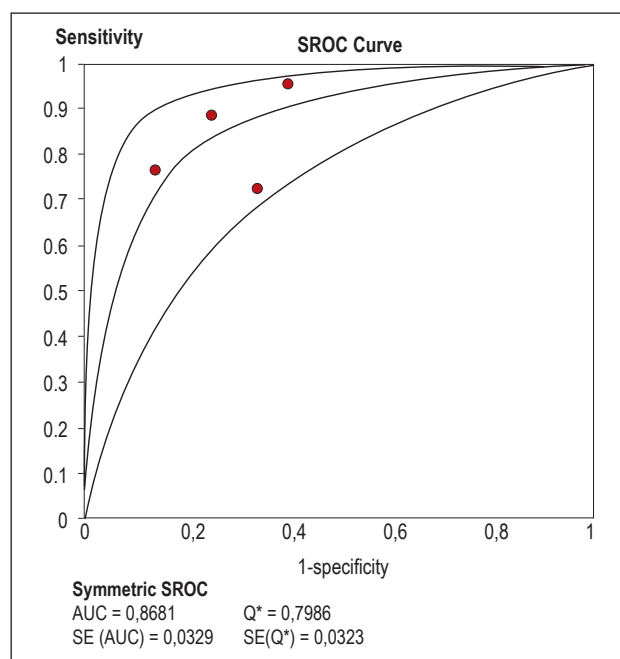


Figure 5. MRI - SROC curve.

power of the diagnostic test. In all of the studies, this time period was not described; however a large interval is not likely, given the disease under consideration.

To address the question data were abstracted by the included studies and supplemented this analysis with information from narrative reviews and other sources (e.g., FDA alerts, National Guidelines).

A large number of features are involved in the staging of rectal cancer and also important for diagnostic accuracy:

1. Patient characteristics: disease stage, age, or sex distribution. Anatomic landmarks for identification of the most inferior portion of the peritoneal membrane were tip of seminal vesicles in men and the utero-cervical angle in women, but some limitations can occur as postoperative status or retroversion of the uterus for example. It is difficult to position the ultrasound probe and visualize high with stenosing tumors, resulting in inconclusive results in >10% of patients ⁽¹⁰⁾.

2. The importance of rectal cancer imaging protocols on interpretation accuracy has been reported ⁽¹¹⁾. In a review for U.S. Department of Health and Human Services, Bruening *et al.* ⁽¹²⁾ consulted a Technical Expert Panel who determined, after discussion and consensus, that transabdominal ultrasound and MRI using endorectal coils are obsolete for staging rectal cancer. New protocols includes a pelvic phased-array multichannel coils and larger-FOV imaging for MRI ⁽¹³⁾ or 2D or 3D with 360°rotating anorectal transducers featuring high frequency and between 6-16 MHz, focal distance between 2.8 and 6.2-cm, and automatic image acquisition without manual movement of the transducer for anorectal ultrasonography ⁽¹⁴⁾. The accuracy of three-dimensional ERUS in the assessment of the infiltration depth of rectal cancer is comparable to conventional ERUS ⁽¹⁵⁾. But the 3D volume can be freely rotated, rendered, tilted and sliced to allow the operator to infinitely vary the different section parameters and visualize the lesion at different angles and in different planes (coronal, frontal, axial) to get the most information from the data and may be helpful for the planning of surgery in the future ⁽¹⁶⁾.

3. A drawback of ERUS compared to cross-sectional imaging techniques is that it is highly operator-dependent and requires a learning curve before optimal diagnostic performance can be obtained ^(10,17).

4. Some authors questioned the cost-effectiveness for MRI. Brown *et al.* ⁽¹⁸⁾ conducted a study cohort and showed that MRI results in significant treatment cost benefits that are very likely to offset the costs of the procedure itself.

Bipat *et al.* in 2004 ⁽¹⁹⁾ conducted a review and metaanalysis comparing Computed Tomography (CT)

with ERUS and MRI and declared that endoluminal US seems to be a better diagnostic imaging test for local staging than are CT and MRI imaging but they cited that ERUS has several limitations: operator dependency; limitation to tumors located 8–10 cm from the anal verge when a rigid probe is used; and no assessment of stenotic tumors.

The authors of one exclusion study ⁽²⁰⁾ concluded that both methods are still complementary techniques but their use is influenced by the operator experience, the availability of instruments and methods in the diagnosis centers. Unfortunately it was not possible to include this article since we could not clarify the data.

Arezzo *et al.* ⁽²¹⁾ in an Italian guideline propounded that ERUS can distinguish layers within the rectal wall. It provides the most accurate assessment of the depth of tumour penetration for early rectal cancer, and perirectal spread. It is recommended as the best modality for the staging. The use of 3D ERUS could potentially further increase the accuracy. MRI is recommended as the technique of first choice for the overall primary staging of rectal cancer. Differentiation between T1 and T2 tumours is not possible with MRI. Endorectal ultrasound remains the imaging method of first choice to differentiate between T1 and T2 tumours if local resection is being considered.

Kolev *et al.* ⁽²²⁾ declared that the results from their study and the literature review show that 3-D ERUS is the diagnostic modality of choice in staging of cancer penetration in the rectal wall. In accordance with them Kwok *et al.* ⁽²³⁾ also found ERUS to be the most accurate modality in the assessment of wall penetration.

The main strength of MRI is the evaluation of large T3 tumours that penetrate the muscular rectal wall and T4 tumours invading adjacent organs. MRI, however, is known to have difficulties in differentiating between superficial T1 and T2 tumours. As opposed to EUS, with MRI it is not possible to separately appreciate all three layers of the rectal wall. The submucosal layer of the rectal wall is not visualized on phased-array MRI (except when there is oedema). Hence, differentiation between a T1 tumour limited to the submucosa and a T2 tumour penetrating the *muscularis propria* is not feasible ⁽¹⁰⁾. Rafaelsen *et al.* ⁽²⁴⁾ evaluating the agreement between transrectal ultrasound (TRUS) and magnetic resonance imaging (MRI) in classification of \geq T3 rectal tumors concluded there was very good inter modality agreement between TRUS and MRI in classification of tumors as early and advanced \geq T3.

Recently, innumerable reviews, guidelines and articles discussing the role of the different imaging modalities for local staging of rectal cancer were conducted. The definitive results are very resembling ⁽²⁵⁻²⁹⁾.

Conclusion

We will ask permission to Nielsen and Wille-Jørgensen⁽³⁰⁾ and finalize our conclusion: “despite much knowledge, there is no international consensus for the staging of rectal cancer”.

Implications for practice

For rectal T staging, ERUS and MRI appear to not be statistically significantly different in accuracy. Rectal wall layers were reliably demonstrated with both methods, but with some restrictive condition: (a) the difference between T1 and T2 tumours remaining a point of obstacle to MRI despite the news technologies; (b) ERUS has lack of capacity with obstructive tumours due to the probe is unable to reach the upper limit of the tumor.

Implications for research

There is a clear need for good quality, larger scale prospective studies analyzing MRI and ERUS (with rigid probe), compared with pathological surgery specimen as a reference standard. Collaborative, properly designed trials that involve a large, representative number of individuals, with explicit clinical inclusion and exclusion criteria, description of the interval between the anatomical imaging techniques and the reference test.

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