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The Advantages of Using Endoscopic Ultrasound in Adult Patients With Early Stage Rectal Cancer, A Systematic Review

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Resume:

Contexte:

Le cancer colo-rectal est la deuxième cause de décès, par ordre de fréquence. L'utilisation de l'imagerie dans la stadification du cancer colo-rectal est un élément important de la prise en charge de la maladie. L'échographie endoscopique est une modalité qui permet de préciser la profondeur de l'atteinte néoplasique. Les données probantes concernant la performance diagnostique dans l'identification de cancers peu avancés sont variables.

Objectif :

Effectuer une revue systématique sur la performance diagnostique de l'échographie endoscopique dans l'identification de cancer de stade T1 et T2.

Devis :

Revue systématique.

Sources bibliographiques :

PubMed, EMBASE, Ovid and Cochrane library

Méthodes:

Dans un premier temps, une recherche de revue systématique publiée dans les 15 dernières années fût effectuée sur la précision diagnostique de l'échographie endoscopique dans les banques PubMed, Cochrne et trip database. Deux revues systématiques, publiées en 2008 et 2009 fûrent identifiées. Une deuxième recherche portant sur des études primaires a été effectuée pour la période 2009 à 2016, dans les

mêmes banques bibliographiques. La qualité des études primaires a été évaluée à l'aide de la grille QUADAS2. Les mots clés utilisés étaient échographie endoscopique, EUS, cancer rectal, histo-pathologie, staging.

Sélection d'études :

Les critères d'inclusion : population adulte avec diagnostic de cancer du rectum pas avancé, articles complets publiés dans des revues avec comité de pairs, articles en anglais. Critères d'exclusion : population pédiatrique, cancers avancés avec atteinte métastatique, patients évalués avec d'autres modalités (CT ou IRM) sans échographie endoscopique, absence de confirmation histologique.

Résultats :

Dix articles, publiés depuis 2009, répondaient aux critères d'inclusion. Ces articles furent ajoutés aux articles retenus dans les revues systématiques déjà publiées. Au total,49 articles sont inclus dans cette revue systématique. La performance diagnostique de l'échographie endoscopique a été évaluée en calculant la sensitivité et la spécificité des études regroupées. Pour le stade T1, les valeurs de sensitivité et spécificité étaient 0.84 (CI 0.75-0.91) et 0.93 (CI 0.86–0.97), respectivement. Pour le stade T2 les valeurs de sensitivité et spécificité étaient 0.83 (CI 0.74–0.90) et 0.93 (CI 0.86–0.97), respectivement.

Conclusion:

L'échographie endoscopique présente une performance diagnostique pour l'identification de cancers de stade T1 et T2. Ceci permet d'orienter des patients vers des chirurgies moins invasives avec une survie égale et un taux de complications inférieures comparativement à des chirurgies plus invasives.

Abstract

Background:

Colorectal cancer (CRC) is the second leading cause of death. The use of preoperative imaging in the staging of (CRC) plays a major role in the management.

Endorectal ultrasound (ERUS) is a precise imaging modality to determine the depth of penetration. The data on the precision of (ERUS) to predict early stage of rectal cancer has been variable

Objectives:

To conduct a systematic review, on the diagnostic performance of (ERUS) in the staging of T1 and T2 CRC.

Design:

Systematic review.

Data sources:

A literature search via PubMed, EMBASE, Ovid and Cochrane library.

METHODS:

An initial search for systematic review articles published in the last 15 years on the diagnostic accuracy of EUS in the staging of CRC using PubMed, Cochrane library, and trip database was conducted. After finding two systematic reviews that were published in 2008 and 2009, a second search of original studies published since the systematic reviews were conducted using the same databases from 2009 to 2016. The primary studies included in the systematic reviews and the primary studies published afterwards were included in the review.

Methodological quality was applied using a modified version of the quality assessment of

diagnostic accuracy studies (QUADAS2) tool.

Terms used for search were endoscopic ultrasound, EUS, rectal cancer, histo-pathological finding, and staging.

Study selection:

Inclusion criteria includes adult people diagnosed with early stage CRC, all articles in english language and must be a full manuscripts published in peer-reviews journals.

Exclusion criteria includes any recurrent or metastasis cancer and children with rectal cancer. Patients who were staged preoperatively by other imaging modality (MRI or CT) and no comparison with post operative pathology.

Results:

The search identified 420 articles, 97 articles were duplicate and excluded, and 232 refined articles were screened for title and abstract, reviewed. Thirty-two full text studies were assessed for eligibility, and ten published as full text and met the inclusion criteria; they were added to the articles identified in the earlier systematic reviews a total of 49 articles. Results of the evaluation of the accuracy of ERUS analyzed according to the diagnostic measures of sensitivities and specificities calculated for each study.

The pooled sensitivity and specificity of EUS for stage T1 CRC was 0.84 (CI 0.75-0.91) and 0.93 (CI 0.86–0.97), and for T2 was 0.83 (CI 0.74–0.90) and 0.93(CI 0.86–0.97) respectively.

Conclusion:

The range of sensitivity and specificity values suggest that EUS performs well in accurately staging T1 and T2 cancers.

Further advancement in this technology will lead to an improved diagnosis, clinical

decision-making, and reduce the over staging drawback.

Keywords.· Endorectal ultrasonography,rectal cancer,cancer staging,diagnostic accuracy endorectal echography,sensitivity and specificity, rectum carcinoma,rectum tumor histopathology and early staging

Table of Contents

List of tables

List of figures

List of abbreviation:

CRC: Colorectal cancer.

ERUS : Endorectal ultrasound.

CT: Computed tomography (CT)

MRI: Magnetic resonance imaging

PET: positron emission tomography

FAP: Familial adenomatous polyposis (FAP)

HNPCC: Hereditary non polyposis colorectal cancer

IBD: Inflammatory bowel disease (IBD).

RCT: Randomized control study

TEM : Transanal endoscopic microsurgery

TME : Total mesorectal excision.

LAR: Lower anterior resection.

LN: Lymph nodes

QUADAS: Quality Assessment of Diagnostic Accuracy Studies.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

CHUM: The Centre hospitalier de l'Université de Montréal

To my loving parents, my precious husband and to my adorable children

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Reaching the goals of my research would not have been possible without the help of members of the health technology master; I am very grateful and thankful to all of them.

Chapter I

Introduction

1.1-Description of the condition:

Colorectal cancer (CRC) is a common cancer and is considered the second most diagnosed cancer in the world [1].

The incidence rate increases with age and peaks in the seventh decade of life (mean age 60-65 years). Approximately 30-40% of colorectal cancer begins in the rectum, which is defined as the distal margin of the tumor within 15 cm of the anal verge [2, 3].

Given the vitality of the difficult anatomy of the rectum within the pelvis and surrounding visceral structures, accurate preoperative staging by suitable imaging modality is essential to determine the consequent treatment.

Staging rectal cancer by a multidisciplinary team and accurate diagnostic imaging helps provide the best care for patients by offering treatment modalities, by guiding patients for either pre-operative chemo-radiotherapy or surgical management and assessment of prognosis of the tumor.

The multidisciplinary team includes colorectal surgeons, gastroenterologists and both radiation and medical oncologists.

Adequate surgical resection is considered the mainstay of treatment for rectal cancer; further, in the early stage of rectal cancer, the five-year survival rate is more than 90%, while for advanced-stage rectal cancer, the five-year survival rate is less than 10% [4].

Endorectal ultrasound (ERUS) has become the most prevalent diagnostic imaging modality for the local staging of rectal cancer; it is safe and less expensive [5, 6].

The muscularis propria of the rectum is a layer of muscle tissue considered the most important anatomic structure for physicians. It helps them decide whether the lesions are suitable for local excision if muscularis propria is not at the infiltrated stage (T1), or if extensive surgery is necessary if muscularis propria seems to be at the infiltrated stage (T2) or (T3). The accuracy and precision of muscularis propria involvement by the ERUS are superior compared to other existing imaging modalities [6].

Transanal local excision or endoscopic microsurgery is the modality of treatment for stage T1 or lower [7, 8], while a total mesorectal surgery would be used for stages T2 and T3.

Early detection in curable stages and accurate diagnosis can influence the therapeutic strategy and improve outcome. There is a consensus regarding the role of ERUS in local staging rectal cancer and how commonly it is used due to lower costs and patient accessibility to the equipment.

The focus of this review is to perform a systematic assessment that analyzes the accuracy and limits of the endorectal ultrasound (ERUS) method in early-stage CRC in comparison to the histopathology findings of the subsequent surgical specimen, and that highlights the impact of the ERUS value in staging CRC.

Developing systematic reviews that are applicable for clinical practice stances a major challenge, and requires strong idea about the possibility and purpose of the review.

1.2-Description of the intervention:

The endorectal ultrasound (ERUS) technique is the best diagnostic tool for the pre-treatment staging of rectal cancer; it examines the thickness of the rectal wall, assesses the depth of tumor invasion and helps in distinguishing between tumors localized to the rectal wall and tumors with transmural invasion [9]. A combination of imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and/or endorectal ultrasound (ERUS) are used to accurately measure the extent of rectal cancer. Endorectal ultrasound (ERUS) is considered the first choice for diagnostic modality; in ERUS, a tiny ultrasound transducer is installed on the tip of the endoscope to allow the transducer to get closer to the body's organs to achieve high-quality ultrasound images, thus providing enhanced details about the organs inside the body. ERUS probes are available in different lengths, diameters, and frequencies. The higher the ultrasound frequency, the better the resolution, with an accuracy range from 85-95% for assessing the depth of rectal cancer invasion, published in many articles [10, 11, 12, 13, 14, 15].

It is the only method that has the capability to show images of the layers of the bowel wall, which can discriminate between T1 and T2 tumors [10]. ERUS indicated a better accuracy than other imaging modalities to assess the depth of invasion. The range for CT scans is between 65-75% and 75-85% for MRIs [16, 17, 18].

ERUS is a simple procedure usually done as an outpatient; most patients undergo ERUS simultaneously through the same colonoscopy session with conscious sedation.

Before the procedures start, a digital rectal examination will be performed to describe the tumor size, location, and distance from the anal verge. The patient will be in a left lateral position and the trans-anal probe covered in a water-filled balloon to allow for

visualization of the rectum and perirectal area and avoid compression of the tumor by the ultrasound probe, which leads to overstating. This probe is inserted into the rectum above the level of the tumor, then slowly withdrawn until it reaches the tumor level for complete evaluation of the tumor and lymph node and to assess the degree of rectal invasion [19].

The higher frequency (2, 12.5, 15, 20, 25 and 30 MHz) ultrasound allows for better resolution of the rectal wall layers and inspection of stenotic lesions, while the lower ultrasound frequencies are used for assessment of lymph nodes and perirectal tissue invasion [20, 21]. Digital ultrasound images are saved on a computer file.

The probe is inserted into the rectum above the level of the tumor, and then slowly withdrawn until it reaches the tumor level for complete evaluation of the tumor and lymph node and to assess the degree of rectal invasion [14]. Ultrasound can visualize the five layers of the rectum; usually they alternate between hyperechoic (white) and hypoechoic (dark) layers. Two are hypoechoic, three are hyperechoic and carcinomas are usually hypoechoic; the degree of penetration of the rectal wall layers suggests local or advanced-stage disease [22]. The first hyperechoic layer resembles a water-filled balloon; the mucosa represents the second hypoechoic layer while the third hyperechoic layer corresponds to submucosa. Muscularis propria, the fourth layer (hypoechoic) and the fifth layer (hyperechoic) relate to the interface between muscularis propria and perirectal fat [23, 24]. EUS is the only method that has the capability of imaging the layers of the bowel wall, which can discriminate between a lesion on the sub mucosa and muscularis propria (T1-T2 rectal tumors) [10].

1.3-How systematic review will contribute to our understanding of the problem addressed:

Systematic reviews are used to review a clearly formulated question with careful consideration of a review's methodological approach. It identifies all evidence and analyzes data from the studies that would decide which research could be included or excluded based on inclusionary eligibility criteria to answer a specific research question. [25,26]. In this thesis, the systematic review approach will be conducted to answer a certain question in relation to the advantage of ultrasound diagnostic imaging in early-stage rectal cancer.

The result of this thesis may improve the guidelines with respect to the added value of using an ultrasound in clinical practice for diagnosing early-stage rectal cancer and identifying further research needs by providing and synthesizing more reliable findings from the included studies about this specific research topic so as to aid in decision-making.

In addition, systematic review can perform an assessment of the validity of the review's outcomes, for example, evaluation of the risk of bias and confidence in cumulative estimates.

The PRISMA-P was followed in this review, which consists of checklist items divided into three parts: administrative information, introduction, and methods [27].

This checklist was designed to improve the conduct of systematic reviews, provide readers with a complete acceptance of evidence from existing studies, and

help in the evaluation of the effects of interventions in early-stage rectal cancer.

See Appendix.

1.4-Gap of the evidence:

Early and accurate diagnosis can influence the therapeutic strategy and improve the outcome. Agreement exists regarding the role of ERUS in the local staging of rectal cancer and how commonly it is used due to lower costs and patient accessibility to the equipment. However, some studies showed inferior results from the EUS due to the experience of effects of the results.

A systematic review is necessary to highlight the value of the diagnostic test accuracy of ERUS imaging in staging preoperative rectal cancer (CRC) and to determine the efficacy of evaluating the depth of colorectal cancer invasion.

In a review of the Cochrane database, Medline indicated two previous reviews performed in 2008-2009, which covered the diagnostic accuracy of EUS in the early staging of CRC.

1.5-HTA in diagnostic test:

Various details exist between diagnostic technologies evaluation and medical therapeutics. The most significant detail is that diagnostic test results influence outcomes but cannot determine health outcomes in patients. Tests performed on a person who has a symptom or sign of illness are usually termed diagnostic. Diagnostic tests are a critical component of health care; clinicians and patients usually have several questions regarding diagnostic tests, such as: What is the test used for? Does it improve the outcome? Is the test recommended in practice guidelines? How are the test results interpreted?

Imaging techniques allocate the generic features of all diagnostic tests; however, several issues are abnormal when imaging tests: 1-the test results are frequently multidimensional, 2-clear-cut points are rarely established, 3-images can reveal signs of different diseases, 4-imaging techniques may be associated with the risk of radiation-induced side effects, leading to a clinical tradeoff between benefit and harm, 5-image quality increases with improved resolution and 6-many emerging imaging tests are expensive.

Finally, an important feature of the evaluation of a diagnostic procedure is that different readers can assess images at different times, which allows us to analyze intra- and inter observer agreement.

There are six levels of diagnostic efficacy assessment: (a) technology, (b) diagnostic accuracy, (c) diagnostic thinking, (d) therapeutic planning, (e) patient outcomes and (f) society.

Level one is the domain of physicists and engineers who develop and refine an imaging technology before its clinical implementation and testing.

Level two is sensitivity and specificity, positive and negative predictive values or receiver operating characteristic (ROC) curves.

Level three, or "diagnostic thinking efficacy," is used to measure the effect of diagnostic test results on the thinking of physicians.

The likelihood ratio represents the ratio of the frequency of a certain test result in patients with a disease to its frequency in patients without the disease. The likelihood ratio can be used to judge the usefulness of a particular test in a given clinical situation [28]. Advocates of evidence-based medicine have also recommended the use of likelihood

ratios in the evaluation of diagnostic technologies [29].

Level four is known as “therapeutic planning efficacy. Level five, or “patient outcome efficacy,” can really be assessed only in a prospective RCT, in which only some of the patients undergo the test and patient outcomes in the two groups (test vs. no test) are compared.

Level six, or “societal efficacy,” asks whether the societal benefit associated with the test is acceptable in relation to its cost [30].

Technology description of any diagnostic test is highly dependent on the population, disease and other features of the setting in which it are used.

In the absence of clinical data, diagnostic tests are estimated based on test accuracy – the ability of the test to correctly determine the disease status of an individual. Test accuracy is not a measure of clinical effectiveness and improved accuracy does not necessarily result in improvement.

Diagnostic tests are used to monitor therapeutic measures. Ideally, an evaluation should assess the clinical utility of a test. This evaluation was presented in two measures, namely sensitivity and specificity, to describe the characteristics of a diagnostic test.

A positive test result might lead to the induction of therapy when it otherwise might not have been considered. A negative test might lead to the decision not to initiate therapy when it otherwise would have been given [31].

1.6-Measures of diagnostic accuracy:

Sensitivity

Specificity

Positive and negative predictive value

The area under a receiver operator characteristic (ROC) curve

Likelihood ratios of positive and negative test results

Diagnostic odds ratios

Why are we doing diagnostic test accuracy?

Studies are easy to undertake; answers can be achieved quickly; required sample sizes are feasible and results do not depend much on human and health service factors.

Figure 1: The 2x2 contingency table

		Reference standard	
		Positive	**Negative**
Index test	**Positive**	TP	FP
	Negative	FN	TN

Sensitivity = $\frac{TP}{TP + FN}$

The proportion of people with the target condition who have a positive test result.

How good is this test at identifying people with the condition?

Specificity = $\frac{TN}{TN + FP}$

The proportion of people without the target condition who have a negative test result.

How good is this test at correctly excluding people without the condition?

Chapter 2

Rectal cancer

2.1-Epidemiology:

The incidence of colorectal cancer is 15 times higher in adults older than 50 years; it is 40% higher in men than in women and the mortality rates are highest in African American men and women [32]. About 72% of cases arise in the colon and about 28% in the rectum. It is uncommon to have CRC before the age of 40, except if there is a predisposing condition.

The incidence and mortality rate of CRC have been declining for the last several decades. This decrease in incidence has been influenced by the improvement of diagnostic techniques, screening programs, the removal of precancerous polyps and patient education [33-34].

2.2-Risk factors:

Many factors increase the risk of CRC; about 75% of colorectal cancers are sporadic and the etiological factors include physical inactivity, high fat and high consumption of red meat such as beef, lamb and processed meats. People who are overweight have a greater chance of developing colorectal cancer, cigarette smoking consider as an important risk.

There is a link between colorectal cancer and heavy alcohol consumption [35,36,37].

The remaining 25% of cases occur in people who have a family history of CRC or adenomatous polyps or a personal history of chronic inflammatory bowel disease.

Other significant risk factors are genetic predispositions such as hereditary non-polyposis colorectal cancer (HNPCC), which is correlated with mutations in genes involved in the

repair pathway of DNA (MLH1 and MSH2) genes; responsible mutations in individuals with HNPCC can also cause Lynch syndrome [38].

Additionally, inflammatory bowel disease (IBD), which includes ulcerative colitis, Crohn's disease increases an individual's overall risk of developing colorectal cancer [39], besides familial adenomatous polyposis (FAP), which is caused by changes (mutations) in the *APC* gene that a person receives from his or her parents.

Families with a history of adenomatous polyps in one or more first-degree relatives are at increased risk [40]. People with FAP are at a higher risk for other cancers, such as cancer of the stomach and small intestines.

People with a history of adenomatous polyps in one or more first-degree relatives are at an increased risk of developing rectal cancer [40].

2.3-Clinical presentation:

- Bleeding from the rectum
- Blood in the stool
- Dark- or black-colored stools
- Cramping
- Discomfort or an urge to have a bowel movement
- Constipation or diarrhea
- Other symptoms such as a change in bowel habits, weight loss, abdominal pain, and anemia [41,42].

The diagnosis is usually made by digital rectal examination to assess the rectal tone and detect penetration of the mass into the external and internal sphincters.

Some blood work (carcinoembryonic antigen measurement) is done, in addition to sigmoidoscopy and colonoscopy, double-contrast enema examination and histologic confirmation.

2.4-Staging:

The TNM staging system by the American Joint Committee (AJCC) is the recommended staging system for colorectal cancer [43].

Staging is the predictor of survival for patients with colorectal cancer [44].

The T refers to the extent of the primary tumors. The N refers to the involvement of regional lymph nodes and the lymphatic system. The M refers to metastatic disease.

Tis carcinoma in situ does not have any metastatic potential. T1 tumors invade the submucosa; without evidence of invasion into the muscularis propria, T2 tumors invade, but do not go through, the muscularis propria. T3 tumors invade the muscularis propria and infiltrate the perirectal fat. T4 tumors invade surrounding organs and structures.

Table 1. Staging rectal cancer:

Primary tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: Intraepithelial or invasion of lamina propria
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades the muscularis propria into pericolorectal tissues
T4a Tumor penetrates to the surface of the visceral peritoneum
T4b Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional nodal metastasis
N1 Metastasis in 1-3 regional lymph nodes
N1a Metastasis in 1 regional lymph node
N1b Metastasis in 2-3 regional lymph nodes
N1c Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2 Metastasis in 4 or more regional lymph nodes
N2a Metastasis in 4-6 regional lymph nodes
N2b Metastasis in 7 or more regional lymph nodes

Distant metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

M1a Metastasis confined to 1 organ or site (i.e., liver, lung, ovary, non-regional node)

M1b Metastases in more than 1 organ/site or the peritoneum

AJCC stage	**TNM stage**
Stage 0	Tis N0 M0
Stage 1	T1 N0 M0
Stage 1	T2 N0 M0
Stage IIA	T3 N0 M0
Stage IIB	T4 N0 M0
Stage IIIA	T1-2 N1 M0
Stage IIIB	T3-4 N1 M0
Stage IIIC	AnyT, N2, M0
Stage IV	Any T, any N, M1

T1:

The tumor invades submucosa without invading the muscularis propria.

Accurate diagnosis of a T1 rectal cancer is essential in determining treatment options, which include either local excision or oncologic resection [45-46].

Local excision by transanal excision or transanal endoscopic microsurgery is performed only in certain patients if the rectal tumor is less than 3 cm, less than 8 cm from the anal verge, well to moderately differentiated and absent of lymphovascular or perineural invasion.

In the presence of lymphovascular invasion or poorly differentiated histology, T1 rectal cancer oncologic resection should still be endorsed [47].

T2:

The tumor invades the muscularis propria. It has always been difficult to stage T2 because the muscularis propria could appear thickened and irregular, which could be attributed to the presence of an inflammatory lymphocytic infiltration at the edge of the tumor.

This may lead to an over-staging problem, 22-24.

Local excision is not recommended in T2 due to a high local recurrence of more than 20% [48-49].

2.5-Surgical options for rectal cancer treatment:

In the early stages, rectal cancer surgery is the standard care for treatment, with the goal of optimizing oncologic control while reducing the effects of treatment on quality of life; therefore, different methods were recommended, including local excision and transanal endoscopic microsurgery (TEM).

Local excision is used to treat stage T1N0 rectal cancers, with strict selection criteria including a freely mobile lesion less than 3 cm in size and less than 30% of the bowel circumference, histology being well-to-moderately differentiated and a lack of involvement of lymphovascular or perineural invasion and negative node. Local excision is associated with a higher recurrence rate (40%), especially if it is used in higher risk stage I rectal cancer (T2) lesions [50].

The transanal endoscopic microsurgery (TEM) procedure was presented in 1984 as a minimally invasive procedure that served as an alternative to radical surgery and that provides better visualization of tumors and allows for the excision of lesions located in the rectum by endoscopic view of the rectum with decreased morbidity and mortality.

The procedure is technically challenging due to the narrow operating field; the patient undergoes general anesthesia and a bowel preparation, then is placed supine or prone on the operating table to keep the lesion close to the 6 o'clock position. The TEM technique includes a laparoscopic camera, an operating proctoscope and modified laparoscopic instruments.

After a dilating digital exam, a proctoscope is inserted through the anus with a length of 20 cm and a 4-cm diameter. After insertion of the proctoscope, the lesion is identified and

the proctoscope is fixed to the operating table. The proctoscope has a port for high-flow carbon dioxide to maintain dilatation of the rectum [51].

The faceplate of the proctoscope has four ports for insertion of instruments, including a camera and three modified laparoscopic instruments to ease the full-thickness excision of rectal lesions; tumor excision is performed by monopolar hook cautery [51].

Several retrospective and prospective studies reported that TEM is highly successful, with the advantage of fast recovery [52], the absence of scars, a rapid return to regular activities [53], a decreased need for colostomies, a short hospital stay with less operating time, only brief use of analgesia, a decreased rate of complication of 2-12% [54,55] and recurrence rates of 0–19% [56,57].

TEM is an oncological procedure that is safe for early-stage rectal carcinomas and that has achieved low local recurrence and high survival rates. Complications after TEM are considerably rare, mainly urinary difficulty.

In case of positive resection margin or unfavorable histology, total mesorectal excision (TME) surgery will be performed [58].

If the pathology revealed a T2/T3 rectal cancer, patients' cases will be presented at tumor board meetings for offering additional radical surgery, including low anterior resection (LAR) or abdominoperineal resection (APR).

LAR involves mobilization of the rectum, sigmoid colon, by performing mobilization of the rectum; a technique called total mesorectal excision (TME) is required.

TME is the therapeutic gold standard in patients as a part of low anterior resection for middle and lower third rectal cancers; it is a procedure defined as the excision of the rectum with the surrounding mesorectum at the level of the pelvic floor.

The patient is positioned in a lithotomy position. A Foley catheter is inserted and the rectum is irrigated with both saline and iodine. Ureteral stents are placed if indicated and a temporary colostomy or ileostomy is performed in case of LAR in addition to intensive postoperative monitoring. Most of the time, TME is performed laparoscopically in bloc resection of the rectal cancer with a complete pararectal lymph node dissection in addition to the resection of radial and circumferential margins, not breeching the fascia propria of the rectum [59]. Postoperative complications of TME include an increased risk of anastomotic bleeding, urinary leakage, urgency and the feeling of incomplete bladder emptying, while the lower anterior reaction side effects include sexual and urinary dysfunction, dehiscence, intestinal obstruction, anastomotic site stenosis, stoma problems and fistula [60].

An abdominal perineal resection (APR) is still done in selected patients with low-lying rectal adenocarcinomas or poor sphincter function.

APR includes the resection of the sigmoid colon, rectum, and anal sphincter using both anterior abdominal and perineal incisions and resulting in a permanent colostomy.

Patients who undergo APR must have one of these criteria: progressive rectal cancer, failure to achieve a negative distal margin by a sphincter-sparing procedure or local recurrent [61].

The importance of accurate staging of rectal cancer is essential for the clinician in helping patients select appropriate management, to identify patients who can undergo sphincter-preserving surgery or new adjuvant treatment and to foresee prognosis.

Many imaging modalities are utilized for staging rectal cancer, but the precision of EUS in the literature has been varied for T1 and T2 diagnosis; therefore, we conducted a

systematic review to summarize the accuracy of EUS and to predict the impact of EUS in the diagnostic workup by under diagnosing T1 or not recognizing it, and then performed a decision analysis to evaluate the added utility of EUS.

2.6-Diagnostic imaging:

Several imaging techniques' modalities are used in the pre-operative staging of colorectal cancers, such as computed tomography (CT), magnetic resonance imaging (MRI), endorectal ultrasound (ERUS) and positron emission tomography (PET) with and without CT fusion.

Each modality has its own benefits and drawbacks; the benefits should be weighed against the drawbacks of using the modality. An important element in choosing an imaging modality for staging is the availability of that imaging modality.

MRI and ERUS are considered the two standard imaging techniques used for the primary staging of rectal cancer [10]

A computed tomography (CT) scan is considered in the staging of rectal cancer for the detection of metastatic disease spread to the liver and/or lungs; the accuracy of CT (T-stage) improves in more locally advanced tumors than in early staging [62].

A CT scan is not useful in evaluating the layers of the rectal wall due to inherent low-contrast resolution presented by CT imaging techniques. It can precisely detect lymph nodes staging in a range from 54 to 70% [19].

High-resolution magnetic resonance imaging (MRI) is considered an important component of rectal cancer staging. MRI is used to measure the extent of a tumor in the adjacent mesorectum and tumor proximity to the mesorectal fascia (MRF) to determine

the risk of local recurrence and identify nodal involvement [20].

If MRF was involved or proximal to the tumor, this would expand the risk of compromised radial, the circumferential resection margin CRM after radical surgery [21].

MRI fails to differentiate between T1 and T2 cancers because the submucosal layer is usually not visualized on MRI [63]; also, MRI cannot differentiate between T2 and T3 cancers because of the desmoplastic reaction seen near tumors [64,65]. A high-resolution MRI image appears to be superior to EUS for locally advanced disease and for the detection of lymph node metastases.

Nodal staging by MRI ranges between 39 and 95% [66,67,68,69]; it allows for visualization of nodes as small as 2 mm in the entire mesorectal part, as well as outside the mesorectum [67].

PET/CT scan with radioactive glucose is useful in displaying whether the cancer has spread to lymph nodes or nearby structures, or in the case of obstructing colorectal cancers; in addition, it will aid in the detection of a suspected recurrence of CRC or tumor response to therapy [69,70].

Few studies have suggested that preoperative PET combined with CT scan improves the staging of rectal cancer [71] and plays a role in changing preoperative management in about 17% of patients [72]. However, PET/CT is not used routinely for the staging of primary rectal cancer, as no specific evidence supports the routine clinical use of PET/CT.

CHAPTER 3:

Research Objective

3.1-Aim of the study review:

This study aims to perform a systematic review that analyzes studies to evaluate the diagnostic imaging accuracy of ERUS (endorectal ultrasound) in adult patients with local-stage rectal cancer as well as to summarize the diagnostic test accuracy (e.g., sensitivity, specificity) in comparison to the histopathology findings of the subsequent surgical specimen, thus highlighting the impact of EUS value in staging CRC. This study will also provide future practice recommendation.

3.2-Review question(s):

- What is the diagnostic accuracy of imaging techniques (ERUS)? (Measuring sensitivity and specificity)
- What is the impact of imaging techniques on the clinical outcome?

3.3-Primary objective:

The primary objective of this study is to systematically review the currently published articles that evaluate the diagnostic test accuracy of using endorectal ultrasound for the staging of primary rectal cancer. The review compares ERUS and histopathological findings for staging early rectal cancer patients.

3.4-Specific objectives:

To extract information about imaging diagnostic tests for the investigation of rectal cancer.

To identify all studies in the existing literature related to the diagnostic accuracy of ERUS used to detect early stages of rectal cancer.

To extract data on sensitivity and specificity for (T1, T2) rectal cancer.

To synthesize and compare extracted data to pathology staging.

CHAPTER 4:

Methodology

4.1-Methods:

We will perform a literature search that inspects the studies identified and choose those that meet the eligibility criteria. The description of methods in this chapter will match the diagnostic test accuracy methods at Cochrane Collaboration [73]. Next, the data will be extracted from the selected studies for an evaluation of their methodological quality.

In this chapter, we follow the Preferred Reporting Items for Systematic Review Protocols (PRISMA-P) recommendations [74] Appendix C.

4.2-PICO frameworks

Participants/Presentation

Inclusion: All adult patients ≥18 years, undergoing pre-operative ERUS staging and diagnosed with primary rectal cancer stage 1 (T1/T2) will be eligible for inclusion.

Exclusion: People under 18 years, studies focusing on patients with advanced-stage rectal cancer, recurrent cancer, or metastasis and patients who received neoadjuvant treatment.

Studies that did not meet all the inclusion criteria, Case reports, crossover studies and abstract material were not included in determining the accuracy of the study. Studies performing EUS after treatment, restaging imaging for follow-up or investigating local recurrence rates or responses to treatment were all excluded. So were studies not reporting an endoscopic ultrasound as a diagnostic measure, studies in which the restaging findings were not compared with pathological results, duplicate studies and other types of cancer.

Index test

The index test is endorectal ultrasound (ERUS)/endoscopic ultrasound (EUS).

All studies that evaluated the accuracy of ERUS as diagnostic imaging in primary colorectal cancer were included.

All studies involving humans were included. Studies performing this investigation after treatment or investigating recurrence rates or responses to treatment were excluded.

Patients who were staged preoperatively by other imaging modality (MRI or CT) were excluded.

Comparator (reference standards)

The reference test is the "gold standard" test to which physicians use the results from the index test (ERUS) to reach a stage compared to the one founded by the reference standard. In this review, we included studies that used the histopathology of surgically resected specimens as a reference standard for the pretreatment staging of CRC.

We pursued comparative studies of ERUS test accuracy that evaluated the (ERUS) index test versus histopathology following either surgery or biopsy in staging early rectal cancer.

These comparisons will advise how many patients were staged correctly and allow us to calculate the test performance of sensitivity, specificity, and accuracy.

Outcome(s):

Primary outcome

- Diagnostic accuracy (sensitivity, specificity) of tumor staging by ERUS
- Test performance (understaging, overstaging) against a reference standard test (pathology examination)
- Changes in therapeutic management
- Impact of survival

Secondary outcomes

None

Time frame studies:

A well-defined period of time will be considered for research, starting form

2009- September 2016.

4.3. Criteria for study inclusion and exclusion:

Condition or domain being studied:

The target conditions were colorectal cancer patients.

Study types include:

Diagnostic studies were included with any study design that evaluated test accuracy of EURS diagnosis, and compared with histopathology.

Findings:

Diagnostic case-control studies were excluded because clinically relevant estimates of specificity and sensitivity can be derived only from the clinical population and not healthy controls.

Exclusion:

Case reports because they lack sufficient diagnostic test accuracy data.

Case-control studies because they are prone to bias and estimates of specificity and sensitivity, which can be derived only from the clinical population and not healthy controls [75].

Conference abstracts because they do not include adequate details about experimental methods to permit an evaluation of study design and conduct.

Cross-over studies.

Setting:

Studies from the clinic or hospital were included.

Full-length articles:

The articles had to be published as full-length, peer-reviewed studies.

Prospective study:

A prospective study collects data in the process, assesses outcomes, and is a good choice for rare exposure. The study usually involves taking a cohort of subjects and monitoring them over an extended period of time. Prospective studies usually have fewer potential sources of bias and confusion than do retrospective studies. The weaknesses of prospective studies include loss of follow up and difficulty selecting and maintaining a non-exposed group.

Retrospective study:

A retrospective study is one that collects data from the past; it looks backwards and examines exposures to investigate risk or protection factors in relation to an outcome, making this type of study appropriate for studying multiple outcomes. Most sources of error due to confusion and bias are more common in retrospective studies than in prospective studies, but timeframes for completion are usually short in retrospective studies. With respect to weaknesses, retrospective studies cannot demonstrate temporality; an investigator has no control over exposure and requires a large sample for rare exposure.

In the assessment of the diagnostic test, both retrospective and prospective studies are used to assess and compare accuracy. A retrospective study is usually recruited based on whether patients have the disease. In contrast, for a prospective study patients are selected based on their symptoms [75].

Observational study designs are admissible in our study; they include retrospective and prospective cohorts. Diagnostic study designs division of observational studies which evaluate the accuracy of diagnostic procedures and tests as compared to other diagnostic

measures, including diagnostic accuracy designs and diagnostic cohort designs [76].

The crossover study design was excluded from our study because a crossover design is a repeated measurements design in which patients receive different treatments during different time periods; it is a controlled trial in which each participant receives both therapies in a random order and is relevant only if the outcome, such as symptoms, is reversible with time.

The main disadvantage of the crossover study is the carryover effects, defined as the effects of the treatment from the previous time period on the current time period's response; these effects cannot be estimated separately [77].

4.4-Search strategy:

Early scoping research:

An initial systematic review of the literature was performed for articles published in the last 16 years about the diagnostic accuracy of ERUS in the staging of CRC by searching the databases:

1-PubMed

2-EMBASE

3-Ovid

4-Cochrane Library, which includes Cochrane Reviews, DARE and the Central Register of Controlled Clinical Trials

All articles were in the English language.

Search strategy:

In consultation with a librarian specialist in electronic bibliographic databases, information was identified for scoping the research. The guidelines for building a search strategy in each database were consulted. The search strategy used text words to identify articles discussing the accuracy of endorectal ultrasound in staging patients diagnosed with early rectal cancer.

The following electronic databases were used: MEDLIN (Ovid, PubMed), EMBASE and Cochrane Database; with modifications to search terms as necessary (see appendix A,B)

A limitation with respect to the publication year (2009 to 2016) was applied.

The search strategy used text words and relevant indexing to identify articles discussing the diagnostic accuracy of endorectal sonography for early detection of rectal. Results were limited to articles published in English between 2009 and 2016 in a peer-reviewed journal, terms relating to the intervention, text in the English language and text applying only to humans. Conference abstracts, comments, case reports, editorials, and letters were excluded.

Relevant studies of the diagnostic accuracy of ERUS in the staging of rectal cancer were identified.

4.5-The key search term:

To guarantee an efficient search, medical subject headings (Mesh) words, were used to define relevant articles for our study. For each database, keywords and index terms were used to identify other index terms to determine the relevance of each term.

Subsequently, while categorizing the keywords, we added “OR” and “And” to make our

search more precise.

The full MEDLINE strategy was applied to all databases, with modifications to search terms as necessary.

The MEDLINE database was searched using these keywords: (a)

"rectal neoplasm" (medical subject heading, or Mesh), (b) "EUS" (Mesh) or "ultrasonography" (Mesh) and (c) "specificity", "sensitivity" or "accuracy".

The EMBASE, Cochrane databases were also checked for significant articles by applying (a) "rectal cancer" and (b) "ultrasonography", "accuracy" or "histopathology".

We used terms such as "sensitivity and specificity" or "accuracy", called methodological search filters; the search terms used are described in detail in the Appendix A-B.

4.6-Study selection:

Initially, one reviewer screened titles and abstracts for relevant studies. At this stage, studies were excluded if the condition was not early rectal cancer, if the study performed on patients received neoadjuvant treatment, if the study included recurrent cancer or metastases, or if the study did not use ERUS. Full texts of identified articles were then obtained and assessed for study eligibility using the full set of inclusion and exclusion criteria. The study selection process was illustrated using a PRISMA (**P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses) flow diagram. See Appendix E.

4.7-Search methods for identification of studies:

Systematic electronic searches were customized to each of the following databases:

MEDLINE via Ovid SP (2009 to September 2016; Appendix A.1)

Medline via PUBMED (2009 to September 2016; Appendix A.2)

EMBASE via Ovid SP (2009 to September 2016; Appendix A.3)

The Cochrane Library (2009 to September 2016; Appendix A.4)

In addition, reference lists for all included papers were searched for relevant studies.

All results were collected and duplicate studies removed and exported to EndNote version 7.0.

The selection of qualified studies was performed in a stepwise approach (titles and abstracts, then full texts).

Research Ethics Board review was not required for this systematic review.

Studies eligible for our systematic reviews were required to compare ERUS assessment of T stage with histopathology T stage for early rectal cancer.

4.8-Data source:

Studies were classified by searching a range of electronic databases and reference lists of relevant studies.

We looked in the systematic review at the diagnostic accuracy of ERUS and compared it with the pathology result after the surgery.

ERUS studies were selected based on surgical histology. Standard criteria were used to determine the T stage:

T1: Hypoechoic mass in the lamina propria or submucosa, without evidence of invasion into the muscularis propria.

T2: Hypoechoic mass invading the muscularis propria.

Definitions:

Accuracy: the percentage of patients in whom the diagnostic imaging ERUS for staging rectal cancer matched the pathological stage.

Under-staging: the percentage of patients in whom the ERUS stage was less than the pathological stage.

Over-staging: the percentage of patients in whom the ERUS stage was greater than the pathological stage.

4.9-Data extraction:

Data was collected according to the PICO framework, as explained above. One reviewer extracted data using the search strategy to identify studies that potentially met the inclusion criteria outlined above. This data was then verified by a second reviewer; both these reviewers, worked independently. All studies that met inclusion criteria were selected for full-text review. Relevant findings were summarized and presented in an evidence table.

Data extraction will include the following variables:

Study characteristics

Title

First author

Year of publication

Study design

Confirmatory procedure

Population characteristics: inclusion/exclusion criteria for individual studies

Setting

Intervention test

Outcome measures

2x2 table for diagnostic studies presenting the sensitivity and specificity of T1-T2 rectal cancer

4.10-Assessment of methodological quality (risk of bias):

Each full paper was assessed for risk of bias by one reviewer and proven for accuracy with respect to all the assessed studies by another.

This checklist is a modified version of the quality assessment of the diagnostic accuracy studies' (QUADAS-2) assessment tool [78, 79], which will be used to assess the quality of the included diagnostic accuracy studies.

QUADAS-2 consists of 4 key domains:

These domains include patient selection, index test, reference standard, and flow of patients through the study and timing of the index test(s) and a reference standard to evaluate each article. The items were rated as yes, no or unclear.

Each domain was assessed in terms of risk of bias; each of these domains also summarizes the review question, tailors the tool, produces review-specific guidance, constructs a flow diagram for the primary study and judges risk of bias and concern

regarding applicability [78].

The results of the quality assessment will be presented later to provide an evaluation of the quality of the selected papers.

For the systematic reviews, methodological quality will be assessed using the AMSTAR tool [80], it's an 11-item questionnaire that can be used to assess the methodological quality of systematic reviews by assessing the presence of:

An a priori design; duplicate study selection and data extraction; a complete literature search; and the use of status of publication as an inclusion criteria; a list of included/excluded studies; characteristics of included studies; documented assessment of the scientific quality of included studies; appropriate use of the scientific quality in forming conclusions; the appropriate use of methods to combine findings of studies; assessment of the likelihood of publication bias; and documentation of conflict of interest.

4.11-Strategy for data synthesis:

Developing a philosophy of how, why and for whom the intervention works, we will create an initial synthesis of findings of included studies and explore the relationships within and between studies. Results of the evaluation of the accuracy of ERUS will be analyzed according to the diagnostic measures of sensitivities and specificities calculated for each study. We will produce the 2 X 2 contingency table for each study, so as to be able to determine the pooled estimates' of sensitivity and specificity.

4.12-Graphic representation

Results of diagnostic test accuracy systematic reviews can be represented as Forrest plots graph, one for sensitivity, and the other for specificity for each of the selected primary studies.

Table 2. Inclusion and exclusion criteria of selected papers

	Inclusion criteria	Exclusion criteria
Population	Adult patients with early rectal cancer	-Children with rectal cancer -Adult patients with recurrent rectal cancer, metastasis or another type of cancer -Neoadjuvant/adjuvant therapy
Intervention	Endoscopic ultrasound (EUS)	
Comparator	Endoscopic ultrasound with pathological staging	No endoscopic ultrasound, no histopathology
Outcomes	-Diagnostic accuracy -Survival - Changes in therapeutic management	
Study design	- Diagnostic studies with any study design.	-Crossover -Case report
Publication type	-Original research manuscripts published in a peer-reviewed journal	-Conference abstract -Abstract
Language	All studies published in the English language	Languages other than English

Chapter 5:

Result

5.1-Result analysis:

Two systematic reviews published 2008-2009 were identified [81-82]; a second search looking for other articles was then conducted using the same databases from 2009 to September 2016. The terms used for search were endoscopic ultrasound, EUS, rectal cancer, histopathology, and staging.

Our search strategy identified 323 relevant articles of which 173 were excluded as titles articles and 118 as abstracts. Thirty-two studies were satisfied the eligibility criteria and retrieved for full-texts reviewed. After full-text review, 22 articles were excluded for various reasons. Thus, 10 articles published in peer reviews Journal as full text and met the inclusion criteria's were included in this systematic review [Table 3]. Details of the selected papers are outlined in APPENDIX E in accordance with PRISMA guidelines for reporting of systematic reviews [93] figure 2.

All patients in the 10 studies were assessed clinically and then underwent pre-operative ERUS examination, then they compared the result to asses the staging accuracy with the histopathology reports, which were obtained for all patients. The results of each included study and the author's conclusion were described in [Table 4]. The methodological quality (QUADAS-2) presents the percentage of included studies for which the item was rated "low," "high" or "unclear," for each quality assessment domain. (QUADAS-2) for each article are described in APPENDEX F.

Table 3. Characteristics of studies included in this analysis

	Year	First author	Study design & confirmatory procedure	Intervention & setting	Population characteristics	Outcome measure
1	2011 [83]	Gloria Fernandez Esparrach	Prospective Cohort Surgery	EUS and MRI Tertiary Center	Mean age = 68 Gender = 54 males, 36 females	Overstage Understage Sensitivity Specificity
2	2010 [84]	Jimmy C.M. Li	Prospective Cohort Surgery	ERUS Hospital	Mean age = 67 Gender = 36 males, 31 females	Overstage Understage Sensitivity Specificity
3	2011 [85]	Shiyong Lin	Retrospective Surgery	ERUS Hospital	Mean age = 59 (23-83)	Overstage Understage Sensitivity Specificity
4	2014 [86]	D.Mondel	Prospective Surgery	ERUS Hospital	Mean age = 66 Gender = 30 males, 23 females	Overstage Understage Sensitivity Specificity
5	2014 [87]	Rikesh Kumar	Retrospective Analysis	ERUS Tertiary	Mean age = 58 52 patients	Overstage Understage

		Patel	Surgery	Colorectal Center		Sensitivity Specificity
6	2011 [88]	Davide Ravizza	Retrospective Observational Study Surgery	ERUS Division of Endoscopy Clinic	Mean age = 63 Gender = 56 males, 36 females	Sensitivity Specificity
7	2014 [89]	Alessandra Surace	Retrospective Surgery	ERUS Hospital	Mean age =63	Sensitivity Specificity Overstage Understage
8	2010 [90]	Belk›s ÜNSAL 1	Retrospective Study Surgery	ERUS Hospital	Mean age = 63 Gender = 22 males, 9 females	Sensitivity Specificity
9	2012 [91]	J. Yimei	Prospective Study Surgery	ERUS and MRI Hospital	Mean age = 62 Gender = 77 males, 52 females	Sensitivity Specificity Overstage Understage
10	2009 [92]	Luigi Zorcolo	Retrospective Analysis Surgery	ERUS Hospital	Mean age = 66 Gender = 46 males, 35 females	Overstage Understage Sensitivity Specificity

Table 4: The results of each included study and the author's conclusion.

	Year	First author	Follow up	Result	Conclusion
1	2011 [83]	Gloria Fernandez Esparrach	2 years	No significant differences between EUS and MRI in terms of sensitivity, specificity, positive and negative predictive value, and accuracy in T staging of rectal tumors	EUS is good techniques for T and N staging of rectal cancer.
2	2010 [84]	Jimmy C.M Li	2 years	The overall accuracy rates of uT and uN staging were 86 and 66%. High accuracy rate for uT staging.	ERUS was accurate in preoperative staging of rectal cancer.
3	2011 [85]	Shiyong Lin	6 years	The overall accuracy of ERUS T staging was 86.5%. When counted separately, the accuracy rates were 86.7% for sonographic stage T1, 94.0% for T2, 86.2%	Endoscopic sonography is safe and effective for preoperative staging of rectal cancer and should be a routine

					examination before surgery
4	2014 [86]	D.Mondel	2 years	Our study showed that in our institution, ERUS staging of early rectal tumours correlated with histopathological staging in 90 % of patients	ERUS has a high accuracy in predicting the Tstage of early rectal cancers.
5	2014 [87]	Rikesh Kumar Patel	25 months	ERUS. T-staging was accurate in 73.1% with identification of T1 lesions having a sensitivity of 70.8% and a specificity 100 %	ERUS has 100% specificity in determining that a lesion is limited to the mucosa or submucosa, useful in determining suitability for local excision.
6	2011 [88]	Davide Ravizza	9 years	The sensitivity, specificity, overall accuracy rate, PPV , and NPV of ERUS for pT0–1 were 86%, 95.6%, 91.3%, 94.9% and 88.7%.	ERUS has proved to be a reliable tool to identify rectal neoplasia suitable for local treatment

7	2014 [89]	Alessandra Surace	4 years	Specificity for T1 88.2% . Sensitivity and specificity for pT2 stage are respectively 83% and 91%.	ERU represents very important radiological staging methods to evaluate T1 and T2 rectal cancer
8	2010 [90]	Belk›s ÜNSAL1	1 year	Endoscopic rectal ultrasonography had 80.6% accuracy, 93.4% sensitivity, and 96.5% specificity in T stage.	ERUS is an effective and reliable method in the detection of the (T staging)
9	2012 [91]	J. YIMEI	1 year	EUS had higher sensitivity in T1 and specificity in T2 than MRI. Reference values for surgery EUS was. 76. 7%, The T Accuracy of ERUS was 83 %.	ERUS is good for early-stage patients Combined TN staging
10	2009 [92]	Luigi Zorcolo	12 years	ERUS enabled distinction between early and advanced rectal lesion with 96% sensitivity and 85% specificity, giving accuracy of 94%	ERUS is useful to predict depth of mural invasion in early rectal cancer.

Results for the accuracy of ERUS analyzed and presented in a table according to the diagnostic measures of sensitivities and specificities that were calculated for each study [Table 6], then, we performed a Forrest plot (random-effects model) for sensitivity and specificity for each of the selected primary studies. These measures provide a clear indication of the diagnostic value of a test.

Table 6: Diagnostic accuracy of EUS for T staging

T1

	Sensitivity	**Specificity**
Glòria Fernández	89%	96%
Jimmy C. M	50%	50%
Shiyong Lin	86%	87%
D.Mondel	90%	89%
Rikesh Kumar Patel,	71%	100%
Davide Ravizza	86%	95%
Alessandra Surace	77%	88%
Belk›s ÜNSAL	100%	96%
J. YIMEI	87%	97%
Luigi Zorcolo	96%	94%

T2

	Sensitivity	**Specificity**
Glòria Fernández	50%	83%
Jimmy C. M	70%	100%
Shiyong Lin	95%	78%
D.Mondel	90%	75%
Rikesh Kumar Patel	76%	100%
Davide Ravizza	87.5%	95.9%
Alessandra Surace	83%	90%
Belk›s ÜNSAL	72%	100%
J. YIMEI	77%	97%
Luigi Zorcolo	81	85%

In these diagnostic test accuracy reviews, two Forrest plots are presented side by side: one for sensitivity and the other for specificity. These graphs thus show 95% of confidence intervals for each individual selected primary study. [Figures 3 and 4].

Figure 3: T1 Forrest plot

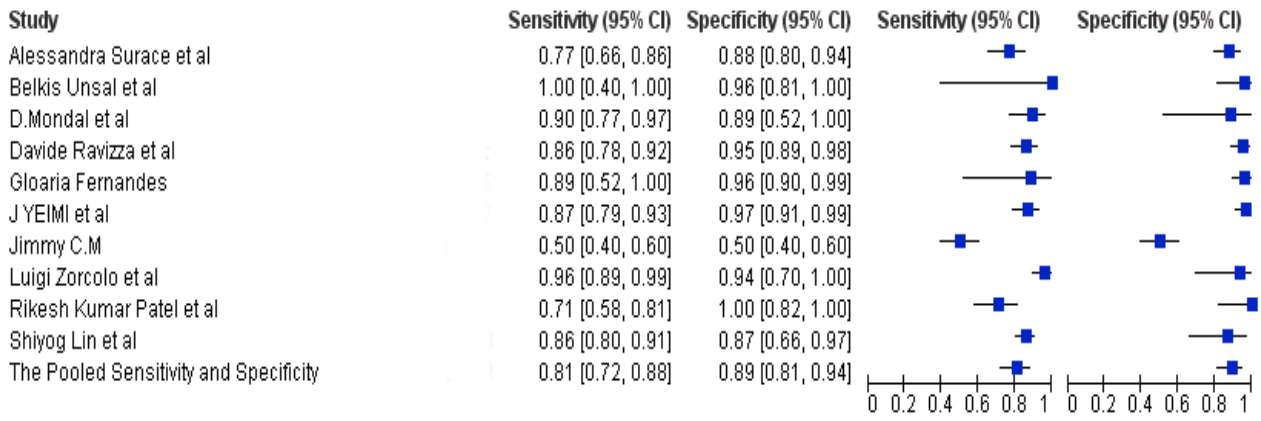
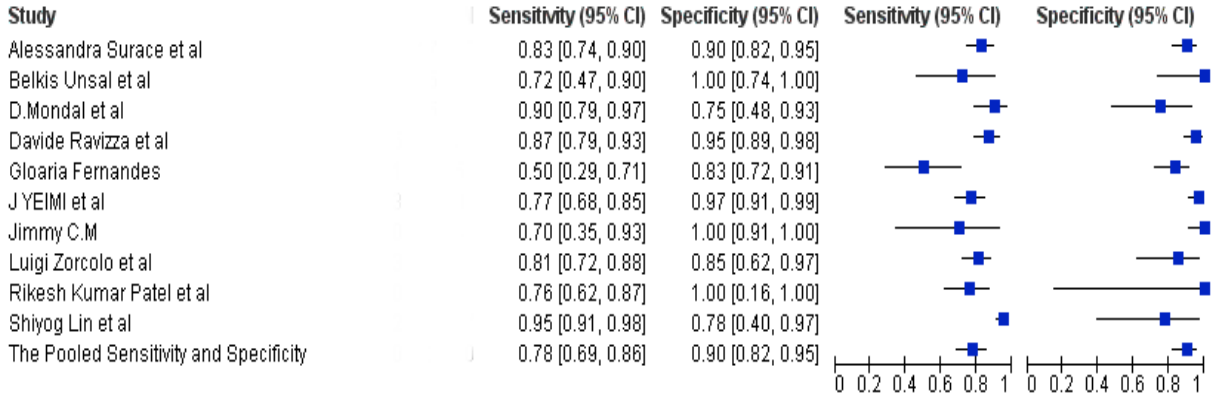


Figure 4: T2 Forrest plot



The result of the accuracy of EUS for T1 rectal cancer, showed that the pooled sensitivity was 0.81 (95% CI 0.72– 0.8) and the pooled specificity was 0.89 (95% CI 0.81–0.94). However for T2 disease the pooled sensitivity was 0.78 (95% CI 0. 69–0.86) and the pooled specificity was 0.90 (95% CI 0.82–0.95).

The accuracy of EUS with Confidence interval to T-Stage Rectal cancer from the systematic review and a meta-analysis by Puli et al [81] between 1986 and 2008 showed the pooled sensitivity and specificity of EUS for T1 88% (95% CI 85.–90.0%) and 98.3% (95% CI 98-99%), and for T2 stage cancer, EUS had a pooled sensitivity of 80% (95% CI 78–83%) and specificity of 96% (95% CI 95–96%).

The p value for all the pooled accuracy assessments was > 0.10.

Their conclusion was over the past two years, the sensitivity, and specificity of EUS to early stage rectal cancers has continued to be elevated, therefore EUS believed to be the most accurate investigative choice in staging early rectal cancer.

The second met analysis and systematic reviews by Puli et al [82] had 11 studies that met the inclusion criteria and also printed in peer-review journals as full articles. They looked mainly on T0 staging rectal cancer.

The Pooled sensitivity of EUS was 97.3% (95% CI: 93.7–99.1) and a pooled specificity of 96.3% (95% CI: 95.3–97.2). All the pooled are calculated by the fixed-effect model.

We did not use the second systematic reviews [82] because it's only looked at T0 rectal cancer.

Next we added the pooled sensitivities, specificities, and the 95% confidence intervals for the articles included in the systematic reviews to the pooled analysis of sensitivity and specificity from the met analysis study [81] and we present the combined data in a Forrest plot figure [figures 5-6].

Figure 5: Forrest plot showing sensitivity and specificity for T1 of our Systematic review combined with the meta-analysis study:

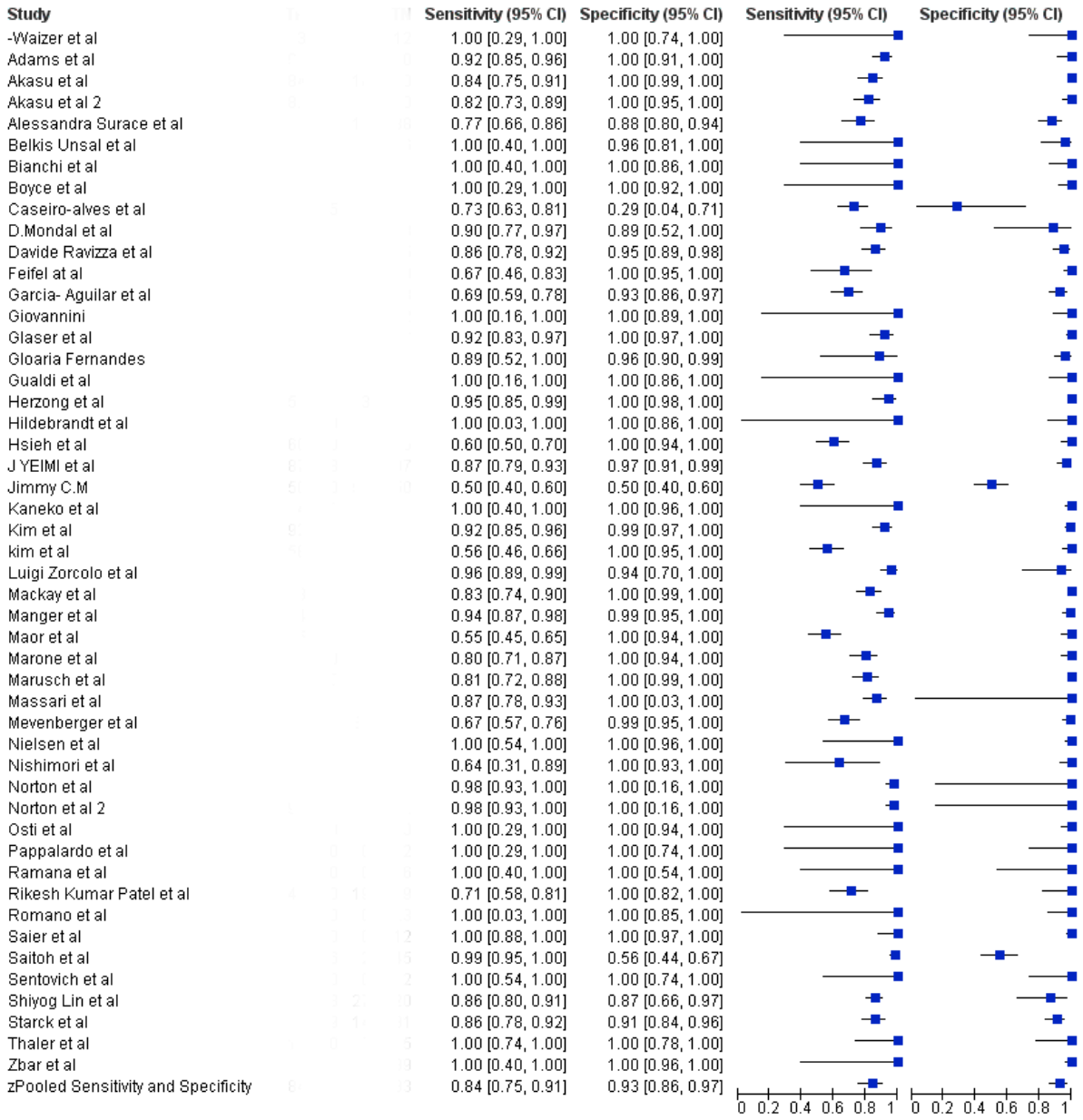


Figure 6: Forrest plot showing sensitivity and specificity for T2 of our Systematic review combined with the meta-analysis study:

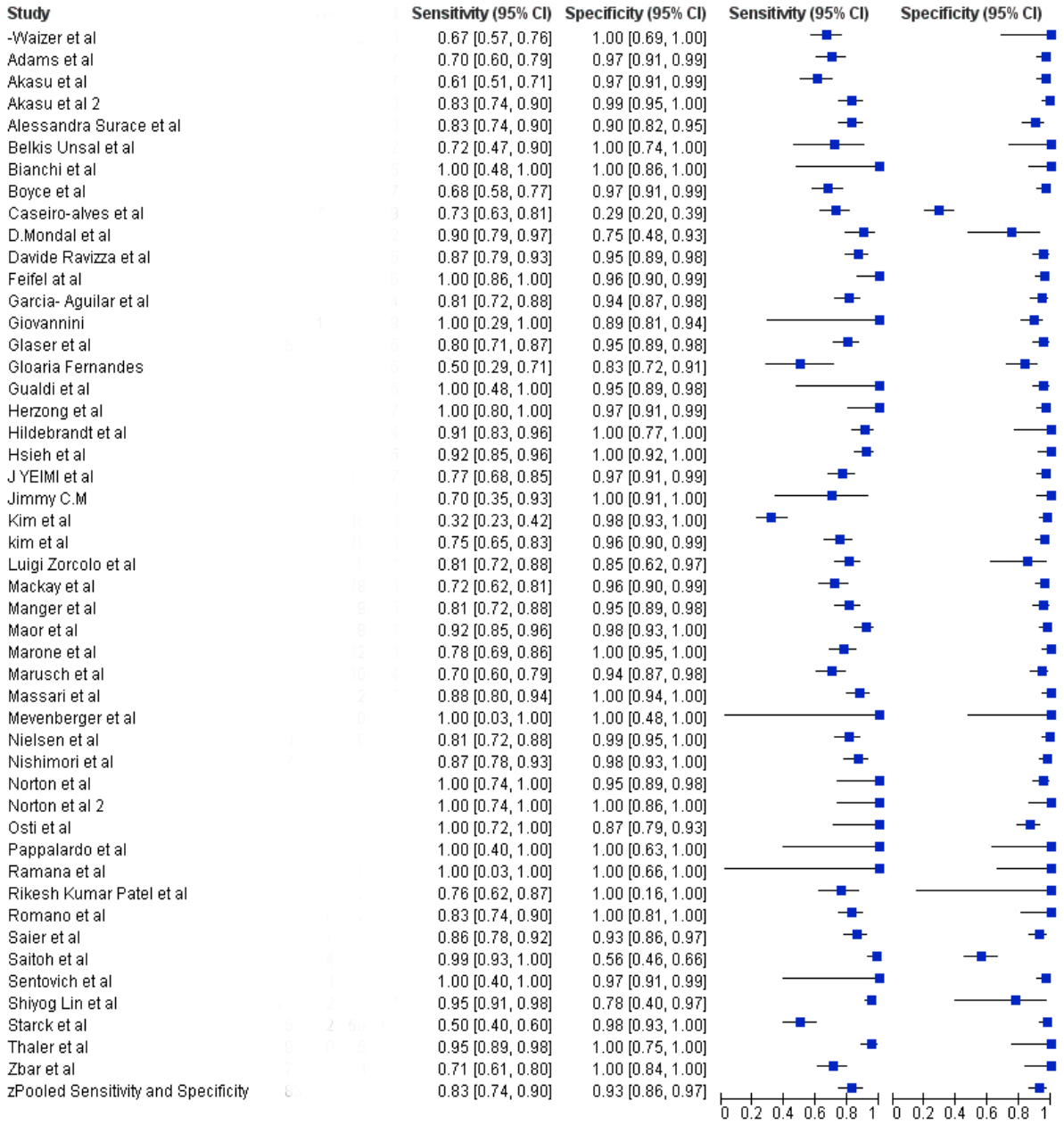


Table 7: Sensitivity analysis including rectal cancer, results from 10-pooled studies

	T1	T2
Sensitivity	81%	78%
CI	72–88	69-86
Specificity	89%	90%
CI	81-94	82-95

Table 8: Pooled analysis from Pauli [81] systematic review for T-stage

	T1	T2
Sensitivity	88%	80%
CI	85-90	78-83
Specificity	98%	96%
CI	78-83%	95-96%

Table 9: The accuracy of EUS with Confidence interval from the combined analysis

	T1	T2
Sensitivity	84%	83%
CI	75–91.%	74-90%
Specificity	93%	93%
CI	86 –97%	86-97%

5.2-Methodological quality

This section includes a narrative summary of the overall methodological quality of the included studies, which will be presented in a table showing the results of the critical appraisal, which shows individual Y/N scores per study. The overall study quality that found in articles was moderate to good quality.

Table 5: Critical appraisal results for included studies using the JBI critical appraisal checklist

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Author	Gloria Fernandez Esparrach	Jimmy C.M. Li	Shiyong Lin	D. Mondel	Rikesh Kumar Patel	Davide Ravizza	Alessandra Surace	Belkıs ÜNSAL1	J. Yimei	Luigi Zorcolo
Y/N/U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y - Yes, N - No, U – Unclear

The methodological quality for the systematic reviews was assessed using the AMSTAR tool Appendix G, regarding (How Good is Endoscopic Ultrasound in Differentiating Various T Stages of Rectal Cancer? Meta-Analysis and Systematic Review) article [81] the AMSTAR score was 9/11, while for the other article (Can Endoscopic Ultrasound Predict Early Rectal Cancers That Can Be Resected Endoscopically? A Meta-Analysis and Systematic Review) [82] the AMSTAR score was 8/11.

Chapter 6:

Discussion

6.1-Main findings

Determining the management of rectal cancer and its early detection during curable stages improves the prognosis for any malignant neoplasia and predicts the chances of survival.

The five-year survival rate for patients with stage I rectal cancer is 87%, and for stage IIA it is about 80%. For stage IIB cancer the five-year survival rate is about 49%, for stage IIIA rectal cancers it is about 84%, for stage IIIB cancers it is about 71%, and for stage IIIC cancers it is about 58%.

Several choices exist for staging primary rectal cancer. Nevertheless, endorectal ultrasonography (ERUS) remains the most attractive modality. In this systematic review we look at the diagnostic accuracy of the ERUS imaging techniques and compare them with the histopathological findings. We identified ten studies for which the sensitivity and specificity were measured, and then we compared the data of our analysis with the meta-analysis data in the literature for ERUS [81]. Next, we combined our data with the met analysis data that found in the literature, and then pooling was conducted (using random-effects model).

A random-effects model estimates the mean of a distribution of effects. We assume that each study estimates a unique effect, and we want to ensure that all these effect sizes are represented in the summary estimate. Study weights are more balanced under the random-effects model than under the fixed-effect model. Large studies are assigned less relative weight and smaller studies are assigned more relative weight as compared with

the fixed-effect model. Moreover under the random effects model there are two levels of sampling and two levels of error [95].

It is recommended in the meta-analysis of the diagnostic test accuracy that the results of the individual studies graph using the Receiver Operating Characteristic (ROC) show pairs of sensitivity and specificity values for the included studies, which are plotted as points in an ROC space that highlights the co-variation between sensitivity and specificity [94].

The ROC method is a complicated statistical approach and we preferred to present the data in the same manner as many published papers. Therefore in our systematic reviews we used Forrest plots that include the previous studies, which contained in the original systematic review plus the new studies that were found in our search.

We obtained the sensitivity and specificity values for T1 and T2 for all the included articles; ERUS shows a sensitivity of (81%) and a specificity of (89%) for pT1, with a higher risk of over-staging than under-staging. For T2 the sensitivity was (78%) and a good specificity of (90%). With regard to the values of sensitivity and specificity, our analysis shows lower values than the Puli analysis [81] for stages T1 and T2.

Forrest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The accuracy of ERUS from the combined analysis showed the pooled estimates of sensitivity for T1 were 84% (95% confidence interval (CI) 0.75 to 0.91) and for the specificity they were 93 % (95% CI 0.86 to 0.97), whereas for T2 the sensitivity was 83% (95% confidence interval (CI) 0.74 to 0.90) and the specificity was 93% (95% CI 0.86 to 0.97).

Our analysis shows that ERUS has very good diagnostic performance in staging early

rectal cancer (T) stage.

If we look at each result of the included articles in our studies, we notice that the study by Fernandez showed that ERUS has a better resolution in early rectal cancer diagnosis, which is a potential advantage in supporting the use of TEM.

For T1 the sensitivity of ERUS was 89% and the specificity 96%, while for T2 the sensitivity was 50% and the specificity 83% with regard to lymph node (N) staging. The accuracy of MRI was greater than ERUS, while its distinction was not statistically significant. Over-staging in T1 was found by ERUS in one patient and no under-staging, although in T2 rectal cancer there was over-staging in seven patients and under-staging in two patients [83].

In addition, ERUS has been found to provide significant information. Yimei et al. [84] reported that ERUS had 87% greater sensitivity in T1 and 97% higher specificity in T2; with an accuracy of 83% for over-staging and 8.3% for under-staging. The majority of the studies included in this analysis were either retrospective or perspective and consecutive, and they recommend that T1 patients undergo ERUS to prevent unnecessary TME, additionally, the overall QUADA2 assessment for all the included studies were good.

Another analysis by Mondel [86] indicates that ERUS is highly accurate in diagnosing the T-stage of early rectal cancer; it can differentiate between T1 tumors and T2 tumors that are invading the muscularis propria, with accuracy of between 69 and 97%, and a sensitivity of 90%. ERUS is the only imaging technique that has the ability to distinguish all five layers of the bowel wall, which allows the selection of patients for TEM.

Patel et al. [87] evaluated patients by ERUS during two time periods. The sensitivity and

specificity for recognizing whether a lesion was confined to the mucosa or submucosa were 70.8% and 100%, respectively. He also documented an increase in accuracy (73.1% to 78.3%) and a reduction in over-staging (26.9% to 21.7%). The sensitivity varied from (70.8% to 77.3%) for the initial period and after two years, while the specificity remained at 100% for both the initial period and after two years.

The results obtained by J. Li [91] sowed that accuracy rate by ERUS for detecting the depth of a rectal tumor's invasion is 86 to 92%. ERUS is an easy procedure to learn, with no radiation exposure and negligible discomfort for patients, as well as practically zero morbidity. Over-staging by REUS happens more commonly than under-staging at a rate of 10% vs. 4%. The first reason is inflammation around a tumor, which cannot be differentiated from malignant tissue by ERUS due to hypoechoic presentation, and second, performing a biopsy before ERUS can lead to over-staging. Li stated that the accuracy of nodal staging by ERUS was 66%, with a sensitivity of 73.9% and a specificity of 59.3%.

Accordingly, it is worth doing ERUS in order to have better utility with fewer complications and recurrence rates. It also plays a role in accurately staging early rectal cancer. Shiyong Lin et al. [85] concluded that ERUS is safe and effective for preoperative staging of rectal cancer and should be a routine examination before surgery. The overall accuracy of ERUS T-staging was 86.5%, and the accuracy rates for T1 and T2 were 86.7% and 94.0 %, respectively. No over-staging was found in T1, while T2 had over-staging in two patients.

Over staging occurs due to a peritumoral inflammatory reaction that results from preoperative biopsies, which cannot be distinguished by ERUS from the tumor itself,

while understaging occurs mainly from a failure to detect microscopic cancer infiltration. A longer period between the ERUS and the histopathology will lead to a change in the disease status and decrease in the biased power of the diagnostic test.

Over staging by ERUS may lead to over treating of rectal cancer, which would typically need endoscopic resection, and as a result of this it will increase the rate of complications and affect the outcome**.**

Zorcolo et al. [92] assessed the accuracy of ERUS for early-stage rectal cancer and determined that it is useful in anticipating the depth of invasion. The results revealed that small lesions limited to the submucosa have a small chance of nodal metastases and can be treated locally with an ERUS sensitivity of 96 %, a specificity of 85%, and 94% accuracy. Seven patients (36.8%) were over-staged preoperatively.

ERUS is an effective and reliable method in detecting the depth of invasion of rectal tumors (T-staging), and if ERUS could diagnose T1 stage rectal cancers, 95% of which were later confirmed pathologically, this would assist physicians in proposing treatments with their confidence based on the ERUS staging of rectal cancer. The sensitivity, specificity, overall accuracy rate, PPV, and NPV of ERUS for pT1 were 86%, 95.6%, 91.3%, 94.9%, and 88.7%, respectively. A specificity of 88.2% for T1, was observed by David Ravizza [88].

ÜNSAL et al. [90] showed that endoscopic rectal ultrasonography had 80.6% accuracy, 93.4% sensitivity, and 96.5% specificity in T-stage. It is a really effective and reliable method in detecting the depth of invasion of rectal tumors (T-staging).

In a study by Surace et al. [84] endoscopic rectal ultrasonography had 93.4% sensitivity and 96.5% specificity in T-stage, with a high risk of over-staging (47%) and a low risk of

under-staging for T2 (11%). The sensitivity and specificity for pT2 stage are 83% and 91%, respectively.

For the diagnostic accuracy reviews we used the modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [78,79]. This assesses the quality of included studies in terms of risk of bias and concerns regarding applicability over four domains. Most of the studies in the literature evaluating the T-staging of rectal cancers had similar scores, and the majority of the included studies had a high quality score.

The use of ERUS for T-staging was an easy procedure to acquire for accurate tumor staging, but identifying lymph nodes by ERUS is frequently challenging. Lymph node is important in staging but ERUS has lower accuracy in evaluating nodal metastases because it requires extensive skill and experience to achieve accuracy in nodal staging [90]. The accuracy of ERUS in predicting lymph nodes in the literature ranges from 70-75% [83] .

Puli et al. [81] looked at the accuracy of ERUS for the nodal involvement in the meta analysis, and showed that more than 2000 patients underwent ERUS for the diagnosis of nodal metastasis in rectal cancer with a sensitivity of 73 % and a specificity of 75.8%.

In summary, this review of the diagnostic accuracy of ERUS techniques in early rectal cancer staging provides an example where there is some convincing evidence of the benefits of intervention. The good quality of the ERUS resolution in early rectal cancer is consistent with the findings of other studies.

We have learned that ERUS is very useful in clinical assessment and is considered one of the most used methods for identifying appropriate T stage (T1-T2) in early rectal cancer.

This is deemed an advantage as it will help clinicians determine whether rectal tumors can be resected by endoscopic resection (TEM), rather than open surgery, and therefore, result in fewer complications.

As a further step, this could be done in future research, to use patients' level data from the Centre hospitalier de l'Université de Montréal (CHUM), and combine clinical and administrative databases in order to evaluate the utility of ERUS. We could also carry out an economic evaluation to determine whether ERUS is cost-effective.

6.2-Strengths and limitations

It is more challenging to perform diagnostic test accuracy reviews, because they are limited by the availability of test accuracy studies that address important and relevant questions. Moreover, further improvements are needed in terms of interpreting and presenting the results of diagnostic test accuracy reviews [Mariska M.G. Leeflang] [94].

This review has several strengths; we used a wide-ranging search strategy on numerous databases, and identified studies that compare ERUS diagnostic tests with histopathology. Two review author's evaluated selected full studies for their inclusion.

Several trials included consecutive patients to avoid selection bias. In another study the cohort of patients was a carefully selected group because the indication for ERUS was to assess their lesions' suitability for local excision.

Furthermore, in several studies ultrasound scans were performed by only two operators, which helped minimize any bias due to a combination of reports written by different operators**.**

Nevertheless, numerous limitations should be expected in this review.

Some studies have a small number of pT1, which reflects the high incidence of T2 stages at diagnosis.

The learning curve for orientation, interpretation, and precise probe positioning by an experienced operator can yield good results, however in this review there was an article

That showed the responsible for ERUS could only estimate his accuracy in ERUS staging after surgical resection and reevaluate the ERUS images retrospectively to improve his accuracy rate, which limited the chance of achieving a rapid learning curve of the procedure, and subsequently limiting the results of this study.

The ERUS we used were from various manufacturers and had different MHz frequencies.

The procedure is highly operator dependent and cannot be performed on stenotic tumors due to the limited depth of the ERUS diffusion; to avoid this we could use catheter probe ERUS with a standard endoscope, which helps obtain accurate tumor staging in cases of malignant stenosis.

An additional limitation of ERUS in one trial was the difficulty distinguishing between a malignant and inflammatory process. Both are monitored as irregular bordered and hypo echoic, which affects the precision of ERUS [90].

The heterogeneity depends on the clinical and methodological differences within the trials, and the studies included in the systematic review will certainly be different.

6.3- Sources of bias

When conducting systematic reviews, several sources of bias should be identified and investigated in terms of how they effect the assessments of diagnostic test accuracy. These biases include: publication bias; heterogeneity; spectrum bias, information and verification bias.

We performed a comprehensive literature search of several databases providing a complete systematic review of the current evidence on this subject to minimize the possibility of publication bias.

There was no spectrum bias as all the patients included were representative of the intended segment of the target condition, nor was there any information bias as the reference standard in all the included trials was interpreted without knowing the index test results.

Verification bias was prevented as the reference standard correctly classified the patients with the target condition.

However, there was some heterogeneity bias because the procedure was highly operator dependent and due to the different frequencies of the ultrasound probes from various manufacturers that were used in the included trials.

The time interval between performance of diagnostic tests and the reference test should be short. The time elapsed between test and surgery was not described in some studies, which may lead to Potential bias.

Chapter 7:

Conclusion

Implications for practice

We evaluated 49 studies that compared endorectal ultrasonography (ERUS) with postoperative histology staging. Our results indicate that ERUS has good sensitivity and specificity, and provides more accurate staging for T1 and T2 lesions, which assists physicians in proposing simple operations, and leads to less pain for early stage rectal cancer.

The reliability of the preoperative T-staging and postoperative pathological results was significantly consistent, therefore ERUS is recommended to be used as a tool to determine T-stage by directly imaging the layers of the rectal wall and the contiguous organs, and selecting the appropriate CRC treatment.

Correct diagnosis and appropriate treatment is expected to improve clinical outcomes and to prevent patients from undergoing further invasive surgical procedures such as trans-abdominal resection.

We can conclude that ERUS is a practical, available, and accurate tool that can be used in the local staging of rectal cancers. However, in order to achieve the accuracy required an appropriate learning curve is needed for the orientation and identification of images, as well as significant experience to achieve accuracy for T and nodal staging.

Implications for research

This review shows that the question of the diagnostic accuracy of ERUS in staging early rectal cancer in the patients included in these selected trials should now be considered answered.

Further advancement in this technology will lead to improved diagnosis, staging, and clinical decision-making, and will reduce the drawback of over-staging.

This review highlights the need for more trials to allow for a solitary test in order to provide complete and accurate staging information in people diagnosed with early rectal cancer.

Further analyses will be required to address the cost-effectiveness of these tests, as well as their impact on patients' overall outcome.

Future research is needed in the analysis and presentation of the results of diagnostic test accuracy reviews.

Conflicts of interest

The author declares that this research was conducted without any conflicts of interest.

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APPENDICES

Appendix A-Legends

A.1. Ovid Medline

1 Rectal Neoplasms/ (37408)

2 exp early diagnosis/ (34745)

3 Neoplasm Staging/ (143903)

4 Neoplasm Grading/ (11479)

5 or/2-4 (183508)

6 1 and 5 (5109)

7 Rectal Neoplasms/di, us (4966)

8 (early and (rectal adj3 (cancer or neoplasm* or tumo?r*))).tw,kf. (1923)

9 or/6-8 (10544)

10 Endosonography/ (10436)

11 (EUS or ERUS).tw,kf. (7140)

12 ((endoscop* or endorectal or endo-rectal) adj3 (ultraso* or ultra-so*)).tw,kf. (10586)

13 or/10-12 (18131)

14 9 and 13 (752)

15 Rectal Neoplasms/pa (12533)

16 "Sensitivity and Specificity"/ (312149)

17 "Predictive Value of Tests"/ (169556)

18 validation studies/ (81552)

19 (histolog* or histopatholog* or patholog*).tw,kf. (1236891)

20 or/15-19 (1707171)

21 14 and 20 (604)

22 limit 21 to (case reports or comment or editorial or letter) (75)

23 21 not 22 (529)

24 limit 23 to english language (424)

25 limit 24 to yr="2009 -Current" (170)

26 remove duplicates from 25 (165)

A.2.Medline via PubMed

Search	Query	Items found
#9	Search (#7) AND #8	0
#8	Search publisher[sb] NOT pmcbook	506095
#7	Search (#5) AND #6	108
#6	Search (histolog*[Text Word] OR histopatholog*[Text Word] OR patholog*[Text Word])	3447213
#5	Search (#1) AND #4	150
#4	Search (#2) OR #3	22872
#3	Search ((endoscop*[Text Word] OR endorectal[Text Word] OR endo-rectal[Text Word])) AND (ultraso*[Text Word] OR ultra-so*[Text Word])	20998
#2	Search (EUS[Text Word] OR ERUS[Text Word])	6817
#1	Search ((rectal-cancer[Text Word] OR rectal-neoplasm*[Text Word] OR rectal-tumor*[Text Word] OR rectal-tumour*[Text Word])) AND early[Text Word]	3160
Search	Query	Items found

A.3. Ovid Embase

1 rectum cancer/ (28976)

2 rectum carcinoma/ (12929)

3 1 or 2 (38756)

4 early diagnosis/ (108905)

5 early cancer diagnosis/ (538)

6 early cancer/ (14798)

7 cancer staging/ (214683)

8 cancer grading/ (52660)

9 or/4-8 (365114)

10 3 and 9 (7146)

11 rectum cancer/di [Diagnosis] (2534)

12 rectum carcinoma/di (1633)

13 (early and (rectal adj3 (cancer or neoplasm* or tumo?r*))).tw,kw. (3256)

14 or/10-13 (11900)

15 endoscopic echography/ (23645)

16 echography/ (280964)

17 ultrasound/ (205490)

18 16 or 17 (442305)

19 (endorectal or endo-rectal).tw. (3086)

20 18 and 19 (919)

21 ((endoscop* or endorectal or endo-rectal) adj3 (ultraso* or ultra-so*)).tw,kw. (17223)

22 (EUS or ERUS).tw,kw. (14488)

23 15 or 20 or 21 or 22 (34006)

24 14 and 23 (923)

25 "sensitivity and specificity"/ (265198)

26 validation study/ (62003)

27 diagnostic accuracy/ (210753)

28 histopathology/ (439961)

29 (histolog* or histopatholog* or pathology*).tw,kw. (1716855)

30 or/25-29 (2293426)

31 24 and 30 (628)

32 limit 31 to (editorial or letter or note or report) (23)

33 31 not 32 (605)

34 limit 33 to english language (527)

35 limit 34 to yr="2009 -current" (260)

36 remove duplicates from 35 (254)

A.4. The Cochrane Library

ID	SEARCH	HITS
#1	(early and (rectal near/3 (cancer or neoplasm* or tumor* or tumour*))):ti,ab,kw	167
#2	(EUS or ERUS):ti,ab,kw	402
#3	((endoscop* or endorectal or endo-rectal) near/3 (ultraso* or ultra-so*)):ti,ab,kw	496
#4	#2 or #3	638
#5	#5 #1 and #4 Publication Year from 2009 to 2016	1

- DARE (to issue 2 of 4, April 2015): 1

Appendix B -Legends

B.1. Ovid Medline

Search fields	.mp.	Search as keyword, in different fields including title, abstract and subject headings
	.pt.	Search in publication type
	.jw.	Words searched appear in the journal title
	.ab.	Search in abstract
	.ti.	Search in title
	/ or .sh.	Search in subject heading (MeSH)
Operators	* before a subject heading	The subject heading considered as a major point of the article (focus)
	"exp" before a subject heading	Results retrieved include the selected term and all its more specific terms (explode)
	ADJn	Retrieves records that contain search terms within a specified number (n) of words from each other, in any order
	* after a term	Unlimited truncation: retrieves all possible suffix variations
	$n	Limited truncation: retrieves possible suffix variation with a maximum number (n) of characters
Subheadings	ae	Adverse effects
	di	Diagnosis
	ge	Genetics
	po	Poisoning
	to	Toxicity

Subheadings are qualifiers added to a subject heading to refine the meaning.
A complete list of subheadings is available at:

http://ovidsupport.custhelp.com/app/answers/detail/a_id/2078/~/list-of-medline-subheadings-and-their-codes

B.2.PubMed Medline

Search fields	[TW]	Search as keyword, in different fields including title, abstract and subject headings
	[PT]	Search in publication type
	[TA]	Words searched appear in the journal title
	[TIAB]	Search in title and abstract
	[TI]	Search in title
	[MH]	Search in subject heading (MeSH). Results retrieved include the selected term and all its more specific terms.
Operators	[MAJR]	The subject heading considered as a major point of the article (focus)
	[NoExp]	Results retrieved include only the selected MeSH, without the more specific terms.
	* after a term	Unlimited truncation: retrieves all possible suffix variations
Subheadings	ae	Adverse effects
	di	Diagnosis
	ge	Genetics
	po	Poisoning
	to	Toxicity

A complete list of subheadings is available at:
http://ovidsupport.custhelp.com/app/answers/detail/a_id/2078/~/list-of-medline-subheadings-and-their-codes

B.3. Ovid Embase

Search fields	.mp.	Search as keyword, in different fields including title, abstract and subject headings
	.pt.	Search in publication type
	.jx.	Words searched appear in the journal title
	.ab.	Search in abstract
	.ti.	Search in title
	/ or .sh.	Search in subject heading (EMTREE thesaurus)
Operators	* before a subject heading	The subject heading considered as a major point of the article (focus)
	"exp" before a subject heading	Results retrieved include the selected term and all its more specific terms (explode)
	ADJn	Retrieves records that contain search terms within a specified number (n) of words from each other, in any order
	* after a term	Unlimited truncation: retrieves all possible suffix variations
	$n	Limited truncation: retrieves possible suffix variation with a maximum number (n) of characters
Subheadings	ae	Adverse drug reaction
	di	Diagnosis
	si	Side effects
	th	Therapy
	to	Drug toxicity

Subheadings are qualifiers added to a subject heading to refine the meaning.
A complete list of subheadings is available in the database field guide through Ovid.

B.4 The Cochrane Library

Search fields	ti,ab,kw	Search as keyword, in different fields including title, abstract and subject headings
Operators	Near/n	Retrieves records that contain search terms within a specified number (n) of words from each other, in any order

Appendix C: PRISMA-P

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

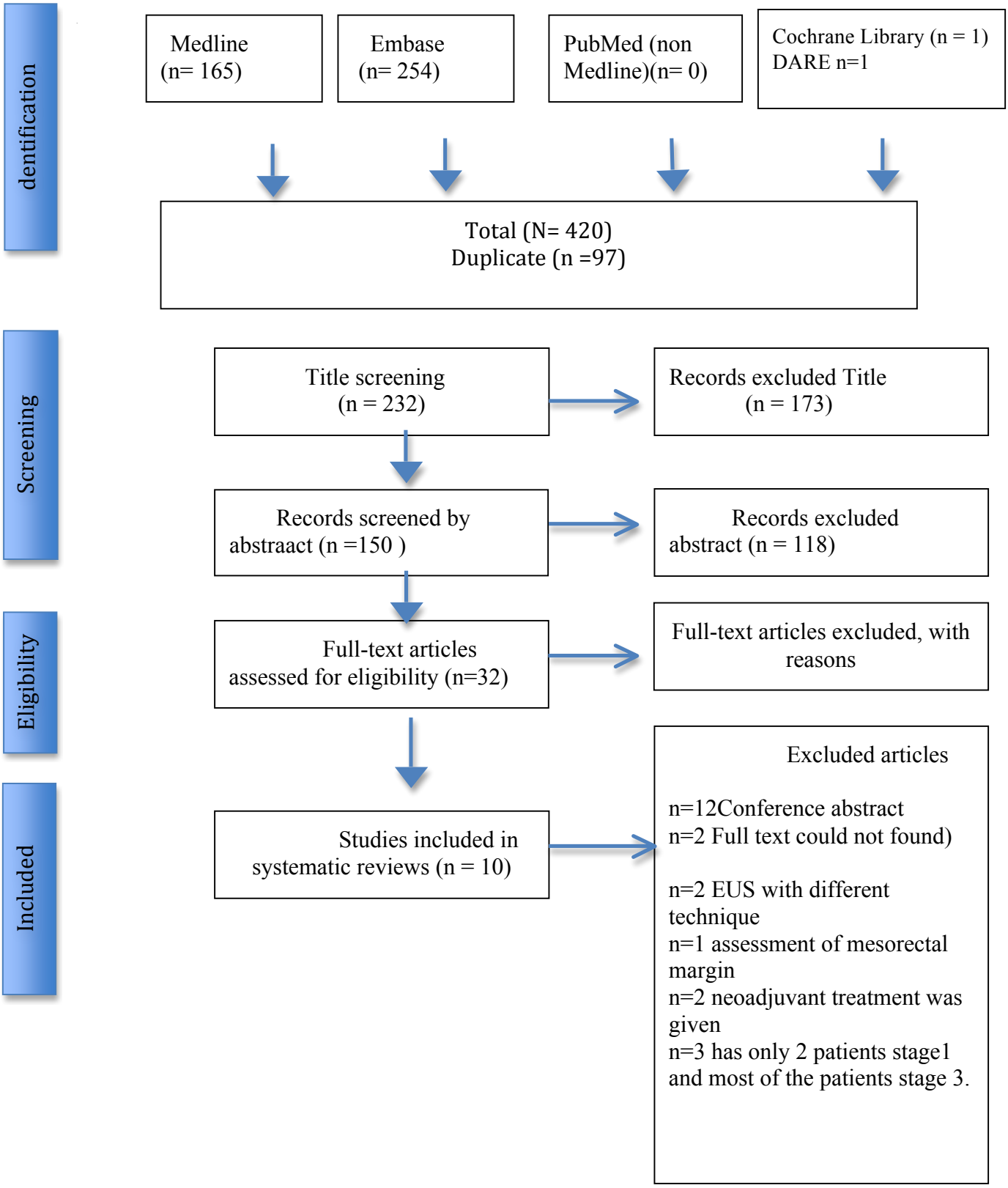
Appendix D – Data extraction

Study characteristic table

Title, Author	
Year of Publication	
Study design	
Confirmatory procedure	
Population characteristics	
Intervention exposure	
Setting (practice, hospital)	
Outcome	

Appendix E

Figure 2:PRISMA flow diagram



Appendix F - Quality Assessment Tool QUADAS-2

Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

- ❖ Was a consecutive or random sample of patients enrolled? Yes/No/Unclear
- ❖ Was a case-control design avoided? Yes/No/Unclear
- ❖ Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias? **RISK: LOW/HIGH/UNCLEAR**

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question? **CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:

- ❖ Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear
- ❖ If a threshold was used, was it pre-specified? Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? **CONCERN: LOW /HIGH/UNCLEAR**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:

- ❖ Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear
- ❖ Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW /HIGH/UNCLEAR**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):
Describe the time interval and any interventions between index test(s) and reference standard:

- ❖ Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
- ❖ Did all patients receive a reference standard? Yes/No/Unclear
- ❖ Did patients receive the same reference standard? Yes/No/Unclear
- ❖ Were all patients included in the analysis? Yes/No/Unclear

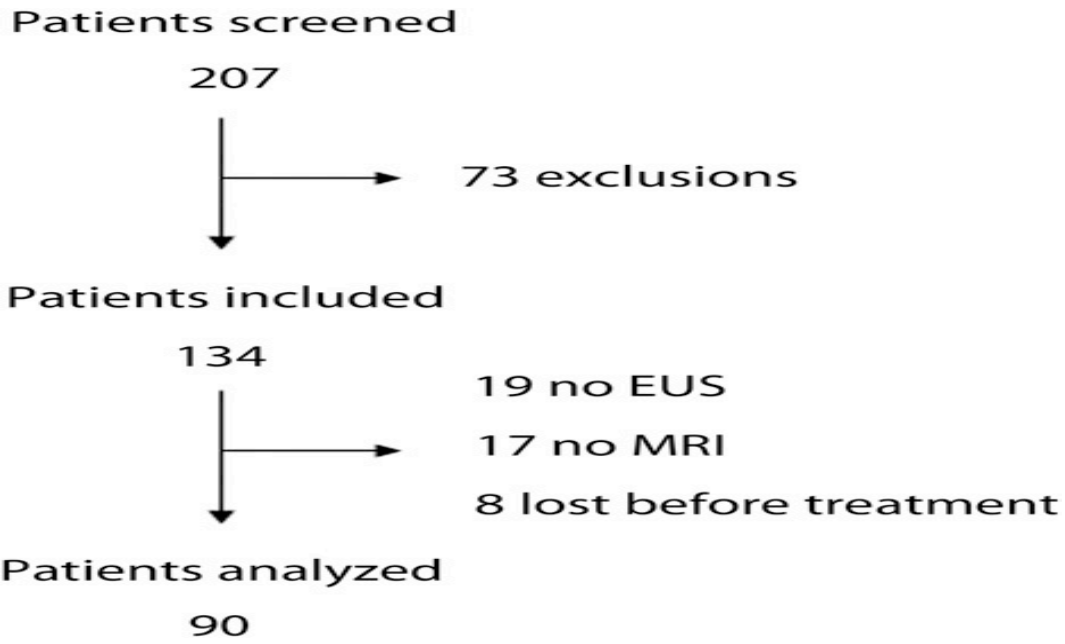
Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

QUADAS-2 tool: Risk of bias and applicability judgments :Glòria Fernández-Esparrach

Domain 1: Patient selection	
A. Risk of bias	
Describe methods of patient selection: All consecutive patients evaluated in the Departments of Gastroenterology and Surgery were asked to participate in this prospective investigation if they met one of the following inclusion criteria: (1) histologically proven rectal cancer and (2 written informed consent	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Patients with histology proven rectal cancer, with written consent.	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
A. Risk of bias	
Describe the index test and how it was conducted and interpreted: EUS and MRI were performed in all patients	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
A. Risk of bias	
Describe the reference standard and how it was conducted and interpreted:	

Pathological examination was done without knowledge of the results of EUS and MRI, preventing an overestimation of the tests' accuracy. The surgical specimen was staged (TNM) according to the guidelines of the American Joint Committee on Cancer

• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
A. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):	



Describe the time interval and any interventions between index test(s) and reference standard:

• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear

• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

QUADAS-2 tool: **The learning curve for endorectal ultrasonography in rectal cancer staging**
Jimmy C. M. Li

Domain 1: Patient selection	
C. Risk of bias	
Describe methods of patient selection: Preoperative ERUS was performed on consecutive patients with rectal cancer to evaluate local tumor and nodal staging in our uni	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
D. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Patients with histology proven rectal cancer, with written consent.	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
C. Risk of bias	
Describe the index test and how it was conducted and interpreted: All ERUS examinations were conducted as a day-case procedure either concurrently with diagnostic colonoscopy or separately after rectal cancer had been diagnosed by prior colonoscopy	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
D. Concerns regarding applicability	
Is there concern that the index test, its conduct, or	CONCERN:

interpretation differ from the review question?	LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
C. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: After ERUS and other relevant preoperative evaluation, all rectal resections were performed within 3 weeks of ERUS.Histopathological examination was then conducted in all resected specimens. The 6th American Joint Committee on Cancer (AJCC) classification was adopted as the histopathological staging system used in this study (pTNM)	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
D. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
B. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): In the 26-month study period, 92 patients with primary rectal carcinoma underwent preoperative ERUS staging. Forty-two patients were excluded from the study due to use of neoadjuvant chemoradiation (n = 18), no subsequent surgery performed (n = 21), or failed examination(n = 3). Reasons for failed examination included stenotic tumors in two patients and balloon failure in one patient.All three of these patients underwent curative resection, and their respective pathological stages were either T3N0 or T2N0. Fifty patients who had surgery without neoadjuvant chemoradiation were included for final analysis. **Describe the time interval and any interventions between index test(s) and reference standard:** **at least 3 weeks of ERUS**	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK:

	LOW/HIGH/UNCLEAR

QUADAS-2 tool: **Application of Endoscopic Sonography in Preoperative Staging of Rectal Cancer**
Shiyong Lin, PhD,

Domain 1: Patient selection	
E. Risk of bias	
Describe methods of patient selection: rectal cancer confirmed by histopathologic evaluation of endoscopic biopsy samples were included in the study retrospectively	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
F. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Patients with histology proven rectal cancer, with written consent.	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
E. Risk of bias	
Describe the index test and how it was conducted and interpreted: the endoscopic sonographic examination was performed 1 to 3 weeks before surgery. The endoscopic sonography system had 4 ultrasonic frequency choices (5, 7.5, 12, and 20 MHz) for detecting different lesion	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
F. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	

E. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: All patients in this study underwent surgical resection for rectal lesions, and the resected specimens were totally subjected to histopathologic evaluation. The specimens were prepared conventionally at the Department of Pathology in our hospital. Both gross inspection and microscopic evaluation were carefully done by certified pathologists. All lesions were staged according to the guidelines of the Union for International Cancer Contro	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
F. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
C. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): **unclear** **Describe the time interval and any interventions between index test(s) and reference standard:** performed 1 to 3 weeks before surgery.	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

QUADAS-2 tool:

How useful is endorectal ultrasound in the management of early rectal carcinoma?

D. Mondal

Domain 1: Patient selection	
G. Risk of bias	
Describe methods of patient selection: Patients with adenomas/early rectal carcinoma being considered for TEM were prospectively studied	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
H. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Patients with adenomas or early rectal carcinoma, who were being considered for TEM at a tertiary referral centre in Oxford, were prospectively studied during a 2-year period (mid-July 2011 to mid-July 2013)	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
G. Risk of bias	
Describe the index test and how it was conducted and interpreted: Each patient underwent an endorectal ultrasound investigation as part of their normal care performed by one of two consultant GI radiologists with 7 years experience in endorectal sonography. The images were reviewed by both radiologists, and the report was a consensus opinion	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
H. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	

G. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: Comparison was also made between the ultrasound stage and the final pathological stage	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
H. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
D. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Ninety-six patients were referred for staging of rectal neoplasiaover 2 years. Nine were out of reach of the rigid probe andwere excluded. Of the remainder, proformas were completedon 53.. Forty-eight patients had a final pathological report on a surgical specimen to compare with the T stage of the ultrasound. Ultrasound agreed with the pathological T staging in 43 patients. **Describe the time interval and any interventions between index test(s) and reference standard:** **unclear**	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

QUADAS-2 tool:

The Role of Endorectal Ultrasound and Magnetic Resonance Imaging in the Management of Early Rectal Lesions in a Tertiary Center

Rikesh Kumar Patel,

Domain 1: Patient selection	
I. Risk of bias	
Describe methods of patient selection: Data collection and analysis was performed by 2 colorectal research fellows . They reviewed the : macroscopic appearance at colonoscopy, histopathological examination of biopsies, depth of invasion determined using MRI and ERUS, surgical procedure undertaken, and final histopathological examination of the excised lesion	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
J. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Retrospective analysis of a prospectively maintained database of patients who underwent ERUS was carried out over an initial 25-month period at a tertiary colorectal center.	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
I. Risk of bias	
Describe the index test and how it was conducted and interpreted: Patients investigated with ERUS and MRI before local excision or formal resection were identified from a prospectively maintained database at a UK tertiary colorectal center over a 25-month period .	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
J. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	

I. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: Local excision should be considered. Salvage surgery can be carried out if the subsequent histopathology reveals the lesion to have adverse oncological features.	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
J. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
E. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): A 65 patients underwent ERUS. Patients were excluded for the following reasons: received 0 neoadjuvant therapy (n . 7); managed with endoluminal contact radiotherapy (n . 4); and treated at other institutions (n . 2). In total, 52 were identified as having undergone assessment of a rectallesion with ERUS who had not received neoadjuvant therapy for whom histology after resection was available. Over the subsequent 12-month period, 27 patients underwent ERUS with 4 patients excluded for the following reasons: managed with endoluminal contact radiotherapy (n . 1); and treated at other institutions (n . 3). The median age of the included patients was 69 (range, 39-83) years over the 2 Study	
Describe the time interval and any interventions between index test(s) and reference standard: **unclear**	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

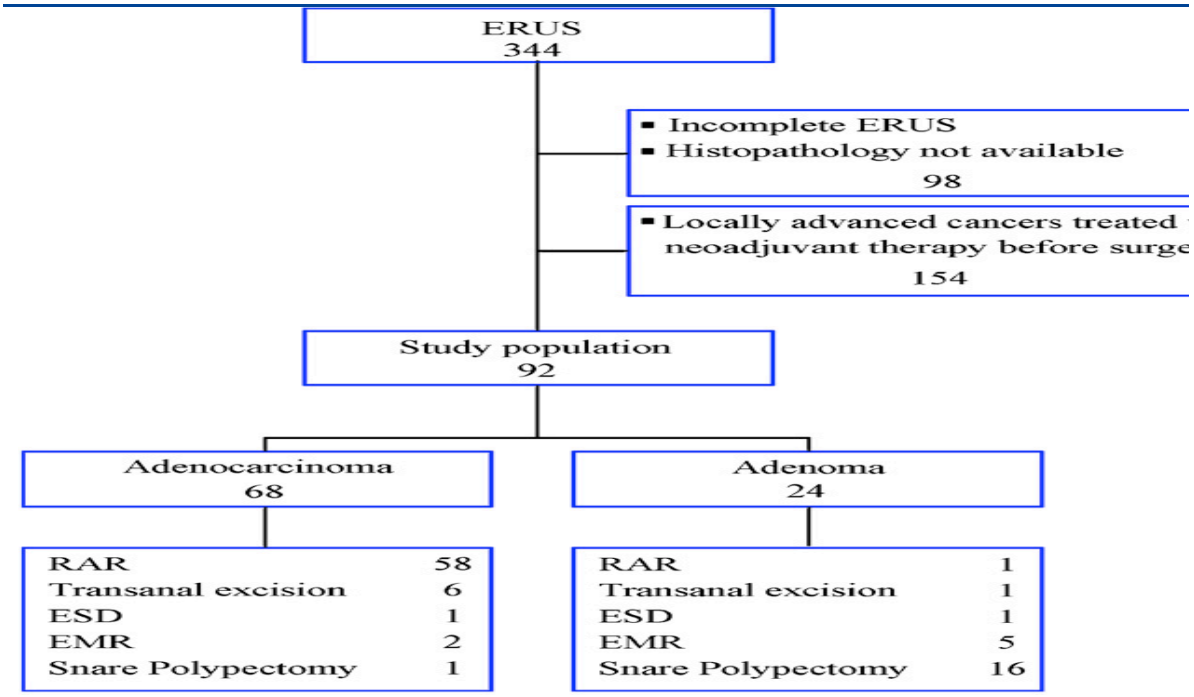
QUADAS-2 tool:

Linear array ultrasonography to stage rectal neoplasias suitable for local treatment

Davide Ravizza*,

Domain 1: Patient selection	
K. Risk of bias	
Describe methods of patient selection: The study population consisted of 92 patients with 92 neoplasias (68 adenocarcinomas and 24 adenomas). A 5 and 7.5 MHz linear array echoendoscope was used. The postoperative histopathologic result was compared with the preoperative staging defined by endorectal ultrasonography. Adenomas and cancers limited to the submucosa were considered together (pT0–1).	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
L. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): The population of this retrospective observational study was obtained by considering all the patients with rectal neoplasia (adenomas and primary adenocarcinomas located within 15 cm from the anal verge) who were staged by ERUS from January 2001 to March 2010 at the Division of Endoscopy of the European Institute of Oncology of Milan.	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
K. Risk of bias	
Describe the index test and how it was conducted and interpreted: All the ERUSs, in all cases preceded by an endoscopic evaluation were performed by two operators.	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR

L. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
K. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: ERUS stages were compared with the histopathological examination (pT and pN), the reference gold standard. Concerning the T parameter, only patients with both ERUS and histopathological examinations were enrolled.	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
L. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
F. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):	



Describe the time interval and any interventions between index test(s) and reference standard:

Unclear

• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

QUADAS-2 tool:

Endorectal ultrasound in the diagnosis of rectal cancer: Accuracy and criticies

Alessandra Surace

Domain 1: Patient selection	
M. Risk of bias	
Describe methods of patient selection: 77 reports ultrasound with the final diagnosis of rectal cancer from the period 2008e2012 were examined. The echographies were performed by two experienced operators, using two ultrasound device with the same technical characteristics.	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
N. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): The population of this retrospective observational study was obtained by considering all the patients with rectal neoplasia (adenomas and primary adenocarcinomas located within 15 cm from the anal verge) who were staged by ERUS from January 2001 to March 2010 at the Division of Endoscopy of the European Institute of Oncology of Milan.	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
M. Risk of bias	
Describe the index test and how it was conducted and interpreted: The echographies were performed by two experienced operators as defined in the literature coming from the same school and with identity setting and reporting: they collaborated for five years and for one year compared to blind their reports. The ultrasound used in the two centers are identical and use a radial probe at a frequency of 10e13 MHz.	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
N. Concerns regarding applicability	

Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
M. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: Characteristics of ERU accuracy were estimated by comparing ultrasound report with the pathological findings, considered the gold standard; for staging TNM classification was used	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
N. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
G. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): On 130 patients operated, 117 are staged with the ERU. Only exclusion criteria was the treatment with neoadjuvant therapy; applying this limit, the patients included in the study were 77	
Describe the time interval and any interventions between index test(s) and reference standard: Unclear	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

QUADAS-2 tool:

The efficacy of endoscopic ultrasonography in local staging of rectal tumors

Belk›s ÜNSAL

Domain 1: Patient selection	
O. Risk of bias	
Describe methods of patient selection: This retrospective study was carried out by the Department of Gastroenterology, ‹zmir Atatürk Training and Research Hospital, which is tertiary level. Thirty-one patients with adenocarcinoma were included in the study. The patients found operable according to computed tomography underwent preoperative local staging by endoscopic ultrasonography. Radial endoscopic ultrasonography and T and N stages were evaluated	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
P. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Thirty-one consecutive patients with resectable rectal carcinoma were recorded from June 2009 to November 2010 Rectal carcinoma was confirmed by histologic analysis of endoscopic biopsy samples, and it was considered that the rectal site extended from the anal verge to the rectosigmoid junction. The patients who previously underwent emergency surgery, chemotherapy or radiotherapy were excluded.	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
O. Risk of bias	
Describe the index test and how it was conducted and interpreted: EUS examinations were performed using a Hitachi EUB-7000 Ultrasonography plus Pentax radial 360° probe (7.5-10 MHz) (Pentax FG36UX ultrasound ultrasoundscanner; Pentax Precision Instruments, NewYork, NY). The examinations were conducted on the patient in a left lateral decubitus position	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have	RISK:

introduced bias?	LOW/HIGH/UNCLEAR
P. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
O. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: The surgical specimen was subjected to full pathologic examination and staged (TNM) in accordance with the guidelines of the American Joint Committee on Cancer. Histological evaluations were carried out by two pathologists	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
P. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
H. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): **42 patients included,** 11 patients were inoperable, and these patients were not included in the study. histological parameters obtained from the surgical materials of the other 31 patients were compared **Describe the time interval and any interventions between index test(s) and reference standard:** **14-17 days**	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

QUADAS-2 tool:

A comparison between the reference values of MRI and EUS and their usefulness to surgeons in rectal cancer

J. YIMEI, Z.

Domain 1: Patient selection	
Q. Risk of bias	
Describe methods of patient selection: From January to December 2011, patients with proven histological primary rectal cancer and evaluated in the Departments of Surgery, Gastroenterology,or Radiology were considered for enrollment in the study, all consecutive patients	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
R. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Patients Underwent colonoscopy and biopsy that proved rectal cancer; 2) no evidence of metastasis from CT; (3) underwent MRI or EUS staging; (4) first time being diagnosed;(5) resectable and had surgery in our Hospital; (6) written informed consent. Also, they must not have met and of the exclusion criteria	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
Q. Risk of bias	
Describe the index test and how it was conducted and interpreted: EUS was performed with a 360-degree radial echo-endoscope (Fujinon EG400, Fujinon Corp., Tokyo, Japan) and a 15MHz high-frequency ultrasound probe (SP-701, SP-702). The operators were senior gastroenterology physicians that facilitated in diagnosis and staging of rectal cancer.	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
R. Concerns regarding applicability	
Is there concern that the index test, its conduct, or	CONCERN:

interpretation differ from the review question?	LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
Q. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: Results for T, N, and TN staging at both MRI and EUS were compared with histopathological staging of the surgical specimen, which was the reference standard (refer to AJCC Cancer Staging Manual H201020	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
R. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
I. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): 202 met the inclusion criteria. Of these, 63 were excluded because of one or more exclusion criteria. The final study population consisted of 129 consecutive patients	
Describe the time interval and any interventions between index test(s) and reference standard: **14-17 days**	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

QUADAS-2 tool: **Preoperative staging of patients with rectal tumors suitable for transanal endoscopic microsurgery (TEM): comparison of endorectal ultrasound and histopathologic findings**

Luigi Zorcolo

Domain 1: Patient selection	
S. Risk of bias	
Describe methods of patient selection: Demographics, preoperative, operative, and postoperative data were prospectively collected into an electronic database. Preoperative evaluation was always carried out by the surgeon deemed to perform the operation and included clinical history, digital examination, complete colonoscopy with tumor biopsies, and rigid sigmoidoscopy to determine the exact distance from the anal verge and the position in the rectal wall.	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
T. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Patients with histology proven rectal cancer, with written consent.	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
S. Risk of bias	
Describe the index test and how it was conducted and interpreted: Local staging of the neoplasm was achieved by endorectal ultrasound (ERUS) with a 10-MHz rotating probe(anorectal probe type 1850; BK Medical).	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
T. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR

Domain 3: Reference standard	
S. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: Histopathologic stage (pT) was then compared with preoperative stage (uT) in order to determine the accuracy of ERUS.	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
T. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
J. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Eighty-eight patients underwent TEM , Seven of them in whom ERUS was not performed and were excluded from this study. Of the remaining, there were 46 men and 35 women were included. **7 patients excluded out of 81 patients**	
Describe the time interval and any interventions between index test(s) and reference standard: **Unclear**	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

□ Yes
□ No
□ Can't answer
□ Not applicable

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2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

□ Yes
□ No
□ Can't answer
□ Not applicable

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3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

□ Yes
□ No
□ Can't answer
□ Not applicable

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4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

□ Yes
□ No
□ Can't answer
□ Not applicable

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5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

□ Yes
□ No
□ Can't answer
□ Not applicable

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6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

□ Yes
□ No
□ Can't answer
□ Not applicable

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7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

- ▫ Yes
- ▫ No
- ▫ Can't answer
- ▫ Not applicable

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8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

- ▫ Yes
- ▫ No
- ▫ Can't answer
- ▫ Not applicable

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9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

- ▫ Yes
- ▫ No
- ▫ Can't answer
- ▫ Not applicable

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10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

- ▫ Yes
- ▫ No
- ▫ Can't answer
- ▫ Not applicable

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11. Was the conflict of interest included?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

- ▫ Yes
- ▫ No
- ▫ Can't answer
- ▫ Not applicable

Shea *et al. BMC Medical Research Methodology* 2007 **7**:10 doi:10.1186/1471-2288-7-10

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.