MRI for staging of rectal carcinoma

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Ms Skye Newton, Ms Tracy Merlin, Ms Hedyeh Hedayati, Mr Tom Sullivan, Dr Jackie Street and Professor Janet Hiller from Adelaide Health Technology Assessment, Discipline of Public Health, The University of Adelaide. The report was edited by Ms Jo Mason, MasonEdit, South Australia. This recommendation was endorsed by the Minister for Health and Ageing on 28th August 2008.

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Contents

Tables

Boxes

Figures

Executive summary

The procedure

Magnetic resonance imaging (MRI) uses strong magnetic fields and radiofrequency pulses to excite protons within the body. These protons emit radiofrequency signals that are detected by transmitters and converted into an image. MRI is used to determine the depth of tumour invasion in patients with rectal carcinoma. There are several different components to locoregional rectal carcinoma staging, the most important of which is the circumferential resection margin (CRM). The CRM has been found to be highly predictive of the rate of local recurrence (Hermanek & Junginger 2005). MRI is able to visualise the CRM, unlike the comparative form of imaging, endorectal ultrasound (ERUS). MRI is proposed as an *alternative* to ERUS, and an *addition* to multi-slice computed tomography (MSCT), which is currently performed on the patient to identify the presence of distant metastases. Knowledge of the CRM (prior to surgery) of rectal carcinoma in a patient informs the physician's decision to provide targeted neoadjuvant therapy. The Australian NHMRC *Guidelines for the prevention, early detection and management of colorectal cancer* currently have a strong recommendation promoting the use of pre- or postoperative radiotherapy for high-risk rectal cancer, which is defined as tumour stage 3 or 4 or lymph node metastases (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). If high-risk rectal cancer is redefined as an involved or threatened CRM, as is likely, and assuming that treatment guidelines are followed, there should be a *decrease* in the use of neoadjuvant therapy if MRI were introduced for this indication.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from Adelaide Health Technology Assessment was engaged to conduct a systematic review of literature on MRI staging of rectal carcinoma. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of MRI staging of rectal carcinoma

Clinical need

The proposed indications for MRI staging of rectal carcinoma include:

- patients newly diagnosed with rectal carcinoma;

- patients who require restaging after neoadjuvant therapy, to determine whether the tumour has receded from the prostate, sacrum or other adjacent organs; and
- patients who are suspected of having or are diagnosed with tumour recurrence.

In Australia in 2001, 4,301 new cancers of the rectum were identified. Patients at a clinically early or advanced staged disease or with comorbidities may not require locoregional staging. It has therefore been suggested by the Applicant (the Colorectal Surgical Society of Australasia) and the Advisory Panel that an estimated 3,000 newly diagnosed patients per year could use MRI if it were funded for this indication.

The Advisory Panel also estimated that 150 patients per year would require restaging after neoadjuvant therapy. Of these, 100 would receive MRI. An additional 150 patients per year may receive MRI for the diagnosis or staging of local tumour recurrence.

Safety

MRI itself is a very safe procedure if appropriate precautions are taken to ensure that patients with ferromagnetic or electrical implants are not imaged, and that the imaging environment is free from objects that may become projectiles.

Diagnostic or staging tests may be unsafe if they are inaccurate, as patients may receive harmful treatments as a consequence of a false result. However, MRI is as accurate as, or more accurate than, currently available imaging techniques, and is therefore considered to be safe.

Effectiveness

For newly diagnosed patients

No direct evidence was identified that reported on health outcomes associated with the different staging modalities. Two medium-quality studies reported that patients who received MRI, and had their MRI results discussed by a multidisciplinary panel, were much more likely to receive neoadjuvant therapy. Fewer patients subsequently had an involved CRM as determined by histopathology. However, there were confounding factors such as history effects (one study was a historically controlled trial) and differences between the study findings and the expected treatment practices in Australia (where it is expected that MRI would result in a *decrease* in the use of neoadjuvant therapy). Consequently, a linked evidence approach was also required to ascertain whether MRI would be of benefit to patients.

No studies compared MSCT alone to MSCT followed by MRI. One small (n=42) medium-quality study reported that MRI and MSCT had similar accuracy in determining involvement of the CRM. The results of this study were considered clinically irrelevant due to the unusual definition of the CRM used. Six further studies reported that MRI had high accuracy (range 70–100%, median 91%), as verified by histopathology, for determining involvement of the CRM.

One study reported that, compared to ERUS, MRI would result in a decreased use of short-course radiation, and an increased use of long-course radiation and primary surgery. It was deemed that, had treatment decisions been based on MRI alone,

considerably more patients would have been treated correctly than if they had been treated based on ERUS alone. There is currently no evidence assessing whether the addition of MRI would result in a change in patient management compared to staging with MSCT alone. The hypothesis was that MRI would allow patients to be treated according to their CRM status, which should result in patient benefits. Only one study was identified comparing treatments where patients were stratified by CRM status. The Dutch Colorectal Cancer Group reported that neoadjuvant therapy resulted in less local recurrence than primary surgery (with/without adjuvant therapy). Further, those with an involved or threatened CRM benefited more from preoperative therapy, compared to those without a threatened CRM, in regards to an absolute reduction of risk in local recurrence. There was no indication of how quality of life differed between patients who received neoadjuvant therapy compared with those who received primary surgery with/without adjuvant therapy.

Since MRI is highly accurate at determining the surrogate and clinically relevant outcome of CRM status, it is therefore inferred that MRI would allow neoadjuvant therapy to be targeted more appropriately, which should result in patient benefits. While it is possible that, in the future, MSCT may be used to determine CRM status in some patients, it is also likely that MRI technology will improve.

For restaging

No direct evidence was available to report on the health outcomes associated with different restaging techniques. The accuracy of all the staging techniques was reduced after neoadjuvant therapy, as it can be difficult to distinguish between the tumour, residual non-tumorous tissue such as fibrosis, and an inflammatory reaction (Hoffmann et al 2002). MRI was reported to be accurate at determining the CRM involvement in 77–82% of patients even after neoadjuvant therapy. There were no studies identified that compared MRI against other staging modalities at visualising the CRM.

There were no studies identified that linked the accuracy data of MRI for this indication with any impact on patient management. Data on the accuracy of MRI is therefore used to infer diagnostic effectiveness.

For suspected/diagnosed tumour recurrence

Data were not available on the impact of MRI on patient relevant health outcomes for this indication. No studies reported on the ability of MRI to *stage* rectal carcinoma within the population diagnosed as having local tumour recurrence. Three medium- to poor-quality studies reported on the ability of MRI to distinguish between local recurrence and benign postoperative changes (ie *diagnosis*). Only one of these studies compared MRI against an alternative form of imaging, conventional CT, but this technology has now largely been replaced by MSCT and is not in common use. Thus, there were no relevant data available on the comparative accuracy of MRI for diagnosing rectal carcinoma recurrence.

Cost considerations

There were insufficient data on the accuracy of MRI plus MSCT, compared to MSCT alone, to warrant a cost-effectiveness analysis. For newly diagnosed patients, MRI is proposed as an additional imaging test to MSCT in all patients and an alternative to

ERUS in 12% of patients. The financial incidence analysis was based on the costs of staging and subsequent neoadjuvant therapy without incorporating downstream costs associated with differential rates of adjuvant therapy, toxicities or local recurrence. The Applicant and Advisory Panel estimated an expected usage of MRI by 3,000 newly diagnosed patients per year if it were funded for the staging of rectal carcinoma. This would result in an additional cost of $1,162,024 per year to society. Of this total cost, $1,013,174 would be borne by the Australian Government. If, however, it is assumed that the visualisation of the CRM would allow patients staged T3, N0 and CRM– to *not* receive neoadjuvant therapy, it is estimated that 818 fewer patients per year would receive this treatment. If the cost savings resulting from reduced neoadjuvant therapy use are used to offset the costs associated with staging of rectal carcinoma with MRI, there would be an overall cost saving of $499,487 per year to the Australian Government, and an overall saving to society of $5,636,565.

On the assumption that 100 patients would receive MRI in addition to other imaging modalities available (predominantly MSCT) for restaging after neoadjuvant therapy, the cost to the Australian Government of funding MRI for restaging would be $34,275 per year. The cost to society would be $40,575.

The cost to society of diagnosis/staging with MRI of 150 patients suspected of having or diagnosed with tumour recurrence is expected to be $57,981 per year, of which the majority ($50,703) is expected to be borne by the Australian Government.

Recommendation

MSAC has considered the safety, effectiveness and cost-effectiveness of magnetic resonance imaging (MRI) for the initial staging, restaging and diagnosis of recurrence of rectal carcinoma in addition to conventional imaging.

MSAC finds that MRI for the initial staging, restaging and diagnosis of recurrence of rectal carcinoma is safe.

MSAC finds MRI for the initial staging of rectal cancer to be effective because MRI is able to define the circumferential resection margin of rectal carcinoma, which is highly predictive of the rate of local recurrence.

MSAC finds that MRI for the initial staging of rectal carcinoma is likely to be cost-effective.

MSAC recommends that public funding is supported for the initial staging of rectal carcinoma by MRI. There is insufficient evidence to support public funding for the restaging and diagnosis of recurrence of rectal carcinoma by MRI.

The Minister for Health and Ageing noted this advice on 28 August, 2008.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of magnetic resonance imaging (MRI) for the staging of rectal carcinoma. This is a diagnostic procedure for patients with rectal carcinomas that have been confirmed by biopsy. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as surgery, diagnostic imaging, pathology, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for MRI for the staging of rectal carcinoma. This covers the staging of newly diagnosed patients prior to treatment, the restaging of patients after neoadjuvant therapy, and the diagnosis/staging of patients suspected of having or diagnosed with a recurrence of rectal carcinoma.

Rationale for assessment

The Colorectal Surgical Society of Australasia has submitted an application to MSAC to have an assessment undertaken of the safety, effectiveness and cost-effectiveness of MRI for the staging of rectal carcinoma.

Background

Magnetic resonance imaging (MRI)

The procedure

The magnetic resonance (MR) scanner is a tube surrounded by a large magnet (Figure 1). The patient lies on a bed which moves longitudinally inside the gantry of the MR system (MSAC 2001). Sedatives may need to be given to patients who feel uncomfortable with being confined for 30–60 minutes. A standard protocol for MR imaging consists of T2-weighted Turbo Spin Echo (Vliegen & Beets-Tan 2003). Phased surface coils are placed on the pelvis and kept in place with belts, allowing a large field of view combined with high spatial resolution (Klessen et al 2007). A contrast agent may be used, but there is contradictory evidence regarding whether gadolinium (Gd) chelate improves imaging or not (Vliegen & Beets-Tan 2003).

Magnetic resonance images are produced through the interaction between the external magnetic field and hydrogen protons within the body (Braunwald et al 2001b). The body is exposed to a uniform magnetic field, forcing the spinning of atomic nuclei to align in parallel or antiparallel to the magnetic field (Westbrook et al 2005). Radiofrequency (RF) pulses are applied to the body, exciting protons to a high energy state. When the RF pulse is removed, the protons return to their equilibrium state, emitting energy as an RF signal which is detected by a transmitter and converted into an MR image (American Academy of Neurology; MSAC 2001). By varying the sequence of pulses applied and collected, different image forms are collected (American Academy of Neurology). An important factor in image quality is the magnetic field strength, which is measured in Tesla (T) (Kuo et al 2007). For medical purposes, MR systems are usually 0.5–3.0 T (expert opinion of the Advisory Panel).

Magnetic resonance imaging (MRI) may be used in conjunction with an endorectal coil to enhance images of the rectum. The coil consists of a probe, which is inserted into the rectum, with an inflatable balloon that assists with positioning (Ladd et al 2000). While endorectal coils may allow highly accurate differentiation of the layers in the intestinal wall, they have a limited field of view and are not used in Australia (Klessen et al 2007). Studies using endorectal coils have therefore not been included in this review.

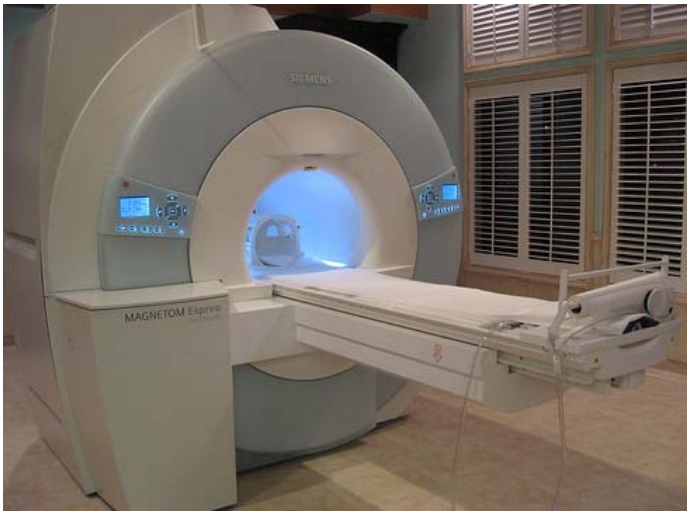


Figure 1 Magnetic resonance scanner

Intended purpose

The optimal treatment for rectal carcinoma depends on the extent of the tumour. It is therefore important to have a reliable way of determining the extent or stage of the tumour prior to treatment.

Importantly, MRI may be used to measure the minimum distance of the tumour from the proposed surgical resection margin (margin of the mesorectal fascia). The distance between the tumour and the circumferential resection margin (CRM) has been found to be the most important predictor of local tumour recurrence (Hermanek & Junginger 2005). Thus, the ability to visualise the CRM is critical in determining patient management. Assessing the CRM prior to surgery allows preoperative therapies to be given based on an individual's risk of local recurrence. Preoperative (chemo)radiotherapy is less toxic and has been found to be more effective at reducing local recurrence than postoperative treatments (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Targeted *neoadjuvant* therapy, which is based on MRI imaging of the CRM, should therefore result in better patient outcomes than targeted *adjuvant* therapy, which is based on the CRM as determined by histopathology.

The global standard in rectal cancer staging is the TNM classification (Table 1), which requires knowledge of the extent of the primary tumour (T); the involvement of regional lymph nodes (N); and distant metastases, such as liver, lung etc (M) (International Union Against Cancer 2004). The International Union Against Cancer (UICC) system incorporates these three elements to describe the stage of the cancer (Table 2) (Klessen et al 2007). MRI may also be used to measure the T stage (the depth of invasion through the perirectal tissue and any invasion of adjacent organs) and the N stage of rectal tumours. This measurement identifies whether the tumour has spread to lymph nodes around the rectum or around blood vessels passing to or from the rectum.

Table 1 TNM classification for colorectal cancer

Type	Description
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour involves submucosa
T2	Tumour involves muscularis propria
T3	Tumour beyond muscularis propria
T4	Tumour reaches peritoneal surface or invades adjacent organ
N0	No involved nodes
N1	Up to three perirectal/colic nodes
N2	Four or more perirectal/colic nodes
M0	No distant metastases
M1	Metastases to distant organs

Source: (Klessen et al 2007); TNM = tumour, nodes, metastases

Table 2 UICC staging of rectal carcinoma

Stage	Description			Approximate 5-year survival
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	>90%
	T2	N0	M0	85%
Stage IIA	T3	N0	M0	70–80%
IIB	T4	N0	M0	
Stage IIIA	T1, T2	N1	M0	35–65%
IIIB	T3, T4	N1	M0	
IIIC	Every T	N2	M0	
Stage IV	Every T	Every N	M1	5%

Source: (Klessen et al 2007; Braunwald et al 2001a); for definitions see Table 1

Indications

The proposed service will be offered to patients with rectal carcinoma (including cancer of the rectosigmoid and the anorectum) requiring further staging of the disease for treatment planning. They will have been referred for staging by the diagnosing clinician (surgeon, gastroenterologist). This will include staging of rectal carcinoma within:

- patients newly diagnosed with rectal carcinoma, prior to treatment;
- patients who have undergone preoperative chemoradiotherapy, restaged prior to surgery; and
- patients who are suspected of having or are diagnosed with recurrent rectal carcinoma.

Patients with certain metallic implants, notably some cardiac pacemakers, intracranial aneurysm clips and cochlear implants, are at risk from the high magnetic fields associated with MRI, and thus are not offered this service (Braunwald et al 2001b).

Incremental or replacement test?

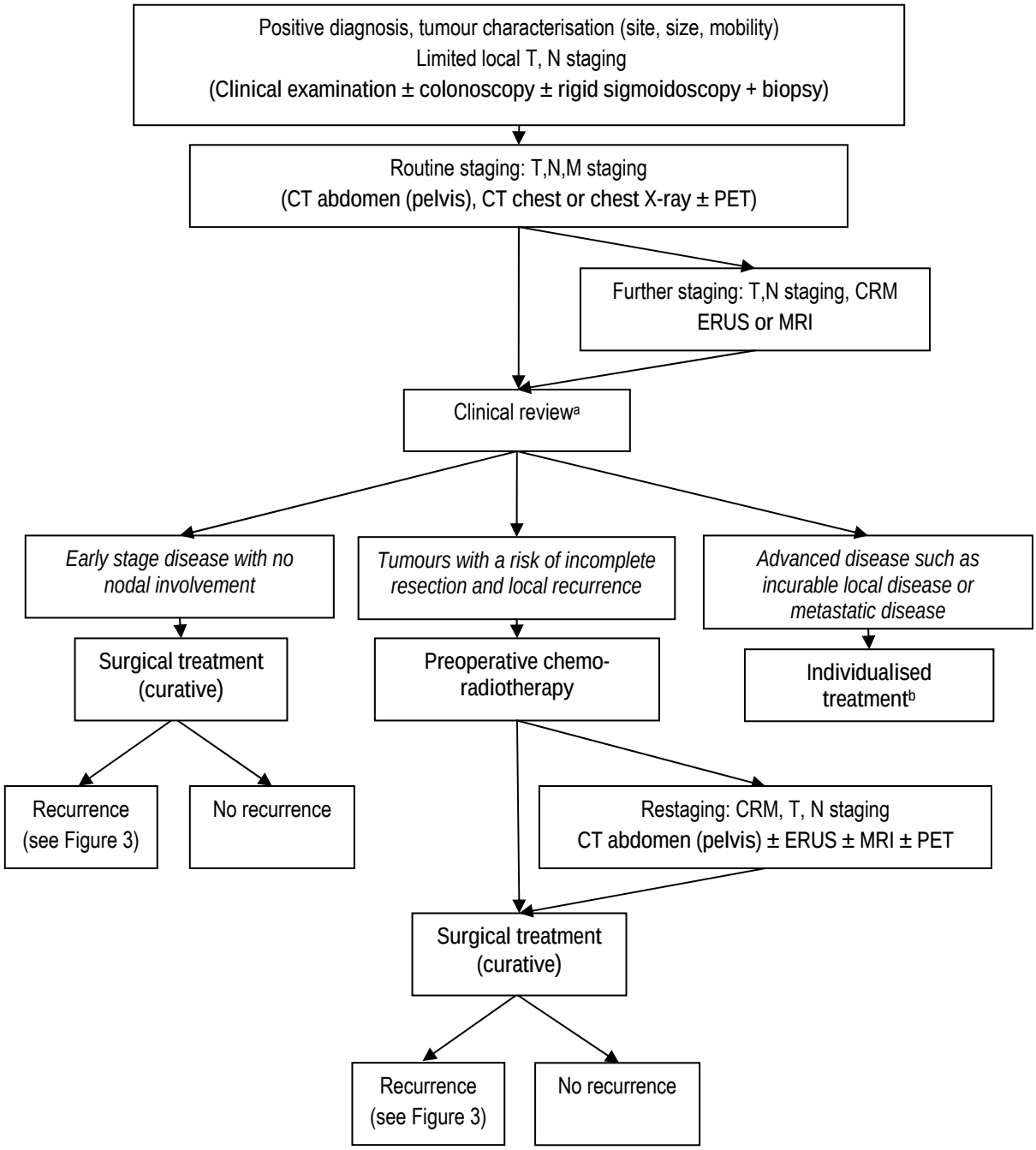
Currently, multi-slice computed tomography (MSCT) and occasionally positron emission tomography (PET) are used to determine whether a rectal carcinoma has metastasised. As MRI is not proposed as a means of assessing distant metastases, it is therefore suggested that it would be used primarily as an incremental test.

The Applicant expects that MRI will largely replace endorectal ultrasound (ERUS) for lesions clinically suspected to be stage T2 or above. Endorectal ultrasound is not a common procedure in Australia due to the cost and lack of access to the procedure, so MRI is likely to be seen as its alternative.

Clinical flowchart

It is acknowledged that patients should participate in the decision-making process regarding their treatment. Treatment options should be presented by the physician, and the pros and cons of each treatment discussed, so that the patient may make an informed decision. The figures below outline common treatment options for rectal carcinoma. Figure 2 is a proposed clinical practice flowchart for newly diagnosed rectal carcinoma patients (showing initial staging and the option for restaging after neoadjuvant therapy). Figure 3 shows possible clinical management options for patients suspected of having or diagnosed with recurrent rectal carcinoma.

Figure 2 Clinical pathway for patients diagnosed with rectal carcinoma



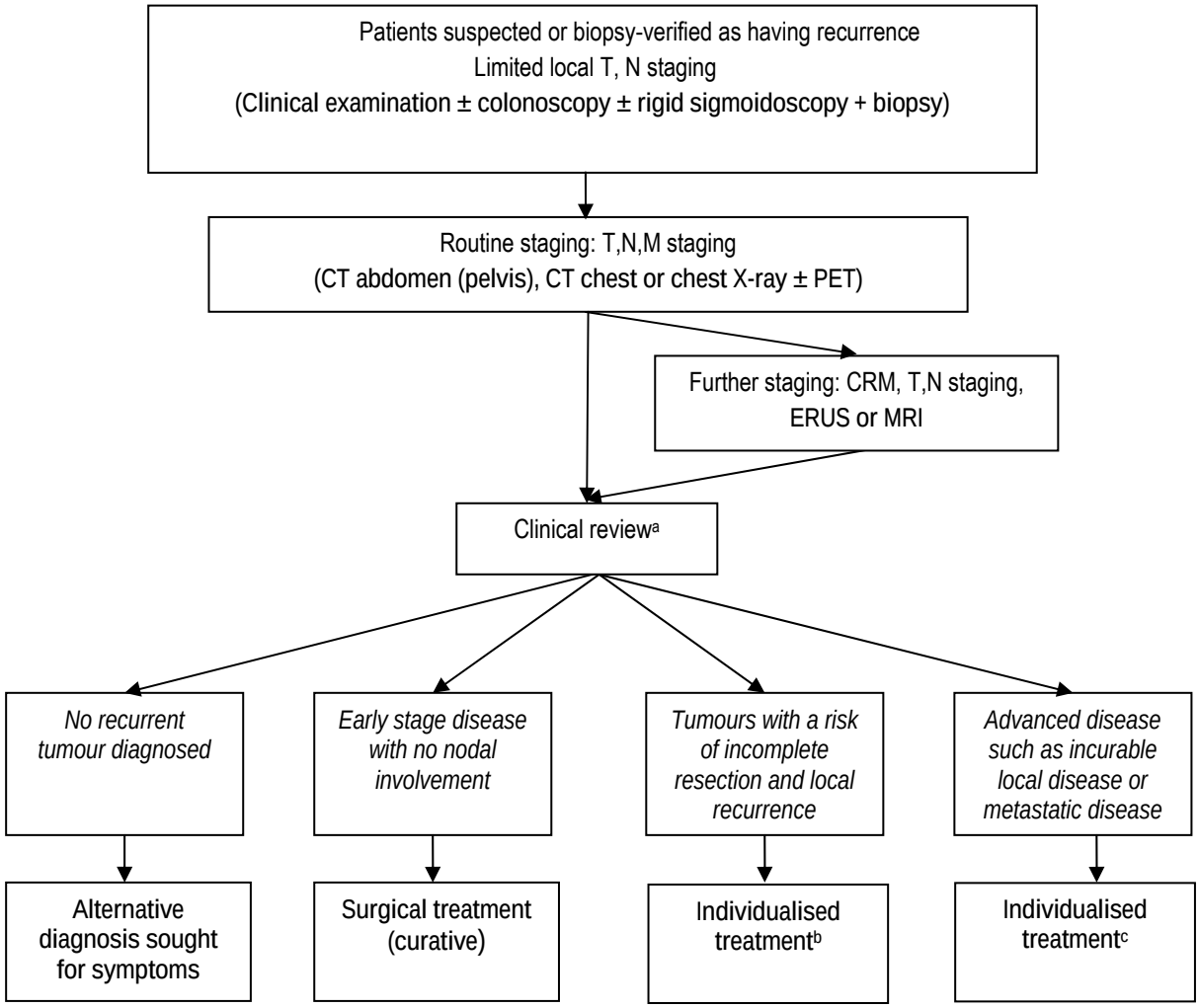
Abbreviations:

T = tumour; N = nodal involvement; M = metastatic disease; CRM = circumferential resection margin; CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; ERUS = endorectal ultrasound

Notes:

[a] Preferentially conducted by a multidisciplinary team; [b] may involve locoregional control ± local surgical treatment ± chemotherapy ± radiotherapy or palliation

Figure 3 Clinical pathway for patients with suspected or diagnosed recurrence of rectal carcinoma



Abbreviations:

T = tumour; N = nodal involvement; M = metastatic disease; CRM = circumferential resection margin; CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; ERUS = endo-rectal ultrasound

Notes:

[a] Preferentially conducted by a multidisciplinary team; [b] depending on previous treatment; [c] may involve locoregional control ± local surgical treatment ± chemotherapy ± radiotherapy or palliation

Reference standard

The gold standard for determining the stage of carcinoma is through the pathology of a resected specimen. As this can only be performed during or after surgery, it is an inadequate means of planning preoperative adjunctive treatment or assessing surgical options. For the purposes of assessing direct evidence, the reference standard is all clinical information available to the clinician (oncologist/gastroenterologist), including histopathology. For assessment of diagnostic accuracy, when using a linked evidence approach (MSAC 2005), the reference standard is histopathology. However, if the patient has already received neoadjuvant therapy, histopathology will no longer provide an accurate standard against which to measure the pretreatment staging of the carcinoma (treatment paradox bias) (MSAC 2005). For this reason, when assessing diagnostic accuracy, studies of initial staging (prior to treatment), where patients received long-course radiation or chemotherapy, were excluded.

Due to the limited amount of evidence available, a reference standard of all available clinical information (which did not include histopathology) was used for three studies in the assessment of the accuracy of MRI for diagnosing recurrent rectal carcinoma.

Existing tests

MRI is being proposed as a method to determine tumour involvement in the mesorectal fascia, regional nodal involvement and tumour depth of the rectal carcinoma. Staging of rectal carcinoma currently involves a physical examination and colonoscopy or rigid sigmoidoscopy to determine the extent of tumour invasion into the surrounding tissue. This is supplemented by computed tomography (CT) and sometimes PET to assess whether the cancer has spread to distant organs or lymph nodes. In some cases this is also supplemented by ERUS for local tumour staging (Colorectal Surgical Society of Australasia 2006).

Computed tomography

Computed tomography (CT) is used in the detection of metastatic disease (liver, lungs and remote lymph nodes). It can also be used to estimate the spread of tumour into the adjacent organs, as well as local lymph node involvement (Bipat et al 2004). Conventional single-slice CT scanning is rarely useful for imaging early primary rectal carcinoma due to its lack of sensitivity in detecting the extent of local disease and local lymphadenopathy (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). However, in patients with large bulky tumours (particularly those than cannot be imaged by ERUS), CT may be a useful means of staging rectal carcinoma (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Conventional CT is not used to predict the CRM as it lacks the sensitivity required (Wolberink et al 2007). However, there are initial reports that newer MSCT may be used to image the CRM (Wolberink et al 2005a). Conventional CT is no longer in common use in Australia, having been replaced by MSCT (at least four slices) (expert opinion of the Advisory Panel).

Endorectal ultrasound

Endorectal ultrasound (ERUS) has been used as a technique for visualising anorectal diseases since 1956 (Klessen et al 2007; Petrovic et al 2002). An endoscopic probe is inserted into the rectum, and a latex balloon is inflated with degassed water for acoustic contact (Petrovic et al 2002). High-frequency sound waves (ultrasound) are generated and an image is formed from the pattern of the sound waves as they echo off the tissue. Endorectal ultrasound is unsuitable for patients who have a carcinoma obstructing the passage of the ultrasound probe (Skandarajah & Tjandra 2006).

Fluorodeoxyglucose-positron emission tomography

Fluorodeoxyglucose-positron emission tomography (FDG-PET) is currently recommended as a staging technique for the follow-up of patients with probable or proven colorectal cancer (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). While not considered a comparator for newly diagnosed patients with rectal carcinoma, it was considered a comparator in patients who may have scar tissue / fibrosis due to prior surgery or adjuvant therapies.

Rectal carcinoma

Clinical features

Symptoms of rectal carcinoma include blood in the stool, tenesmus, constipation, diarrhoea, abdominal cramps, decrease in size or width of stools, weight loss or persistent lethargy (Majumdar et al 1999). The disease and treatments for rectal carcinoma may impact on the patient's sense of wellbeing and health-related quality of life (Le et al 2007). The most common treatment for rectal carcinoma is surgical resection, which is associated with significant morbidity, such as urologic and sexual dysfunction. Patients may feel stigmatised due to rectal carcinoma, particularly those who have a colostomy, and this feeling of stigma is associated with poor physical and emotional health (MacDonald & Anderson 1984). Sphincter-preserving methods of treatment may also be associated with defecation-related symptoms, such as urgency or soiling (Le et al 2007).

Burden of disease

Colorectal cancer is the second most common cancer in men (after prostate cancer) and women (after breast cancer) (AIHW 2005). Each year there are 4,700 deaths from colorectal cancer and 12,600 new cases diagnosed (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Rectal cancer accounts for one-third of all colorectal cancers (Harewood & Wiersema 2002). It rarely occurs in people under 50 years of age, but it becomes one of the most significant diseases later in life in terms of morbidity and mortality (Figure 4) (Folkesson et al 2005). The incidence of rectal carcinoma is expected to increase as the population ages (Le et al 2007). Five-year survival for rectal cancer, between 1992 and 1997, was 57% for males and 61% for females (Australian Bureau of Statistics 2006). Based on the Australian population in 2001, it is estimated that men have a 1-in-44 risk of having rectal cancer (2.3% lifetime prevalence) and women have a 1-in-72 risk (1.4%) (SA Cancer Registry 2005). A cohort

study of 41,528 people aged between 27 and 75 years living in Melbourne found a point prevalence of 0.48% for rectal carcinoma (MacInnis et al 2006).

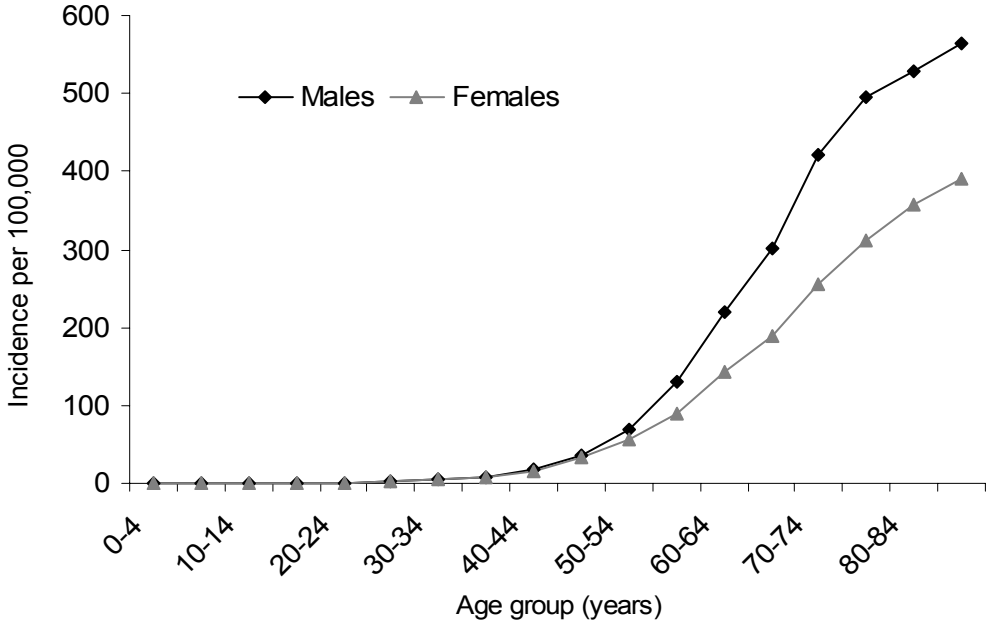


Figure 4 Age-specific incidence of colorectal cancer, Australia, 2000

Source: Australian Institute of Health and Welfare (AIHW) and Australian Association of Cancer Registries (AACR) 2003. *Cancer in Australia 2000*. AIHW cat. no. CAN 18. Canberra: AIHW.

The Australian Institute of Health and Welfare reported 4,301 new cancers of the rectum and rectosigmoid in 2001 (AIHW). Patients at a clinically early stage of disease do not require staging. Others may not be suitable for aggressive treatment as a consequence of having advanced disease or comorbidities. It is therefore estimated that the annual usage of MRI for primary staging of rectal cancer would be approximately 3,000 procedures per year (Colorectal Surgical Society of Australasia 2006). It is proposed that 5% of these patients would require restaging after neoadjuvant therapy (150 patients), and that 100 of these would receive MRI.

Recurrent rectal carcinoma

Rates of rectal carcinoma recurrence vary greatly depending on the disease stage, grade and degree of vessel invasion, and factors such as surgical methods and the use of neoadjuvant therapies. Recurrence rates of between 3% and 50% have been reported in patients who have undergone curative resection (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Salvage surgery would be considered for 50% of patients with isolated local recurrence (Heriot et al 2006). The expert opinion of the Advisory Panel was that approximately 5% of rectal carcinoma patients would be staged with MRI for suspected or diagnosed local recurrence, which would result in an additional 150 procedures per year.

Treatment for rectal carcinoma

Both the disease itself and its treatment may influence the quality of life and longevity of patients with rectal cancer. It is therefore important to determine which treatment will optimise patient-relevant outcomes.

Treatment of rectal neoplasms depends on the stage of cancer, so that the balance between preventing local recurrence and retaining anorectal and genitourinary function can be optimised. Either overtreatment or undertreatment can be detrimental to the patient (Klessen et al 2007). Early stage disease with no nodal involvement and no (or minimal) mesorectal infiltration may be treated with primary surgical excision (Colorectal Surgical Society of Australasia 2006). Rectal carcinoma has a high rate of recurrence and a poor prognosis after traditional blunt dissection due to incomplete removal of the tumour (32–35%) (Wolberink et al 2006). In order to counter this problem, total mesorectal excision (TME), involving a sharp dissection of the rectum and the surrounding mesorectal fat (Wolberink et al 2006), has become the standard surgical technique for treating rectal cancer. This technique reduces the rate of tumour recurrence to between 4% and 9% of cases (Wolberink et al 2006).

Later-stage disease with a higher risk of incomplete resection and local recurrence (if the mesorectal fascia is infiltrated or at risk) is treated with neoadjuvant therapy, then curative surgery (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). The two most common forms of neoadjuvant therapy for rectal carcinoma are short-course radiotherapy and chemoradiation (Bujko, Nowacki et al 2006). Radiotherapy uses ionising radiation to kill carcinoma cells within the treatment beam (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). In short-course radiotherapy, a total of 25 gray (Gy) of radiation are given in five 5 Gy fractions on consecutive days (Morris et al 2007). More advanced disease, with invasion of other organs or metastasis to distant sites, may be treated with aggressive chemotherapy in an attempt to down-stage the cancer, which may then be amenable to resection (Colorectal Surgical Society of Australasia 2006). Chemotherapy is a cytotoxic drug that may kill carcinoma cells circulating in the body, and has a radio-sensitising action when combined with radiotherapy (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Chemoradiation combines long-course radiotherapy (1.8–2 Gy per fraction, total dose 45–50.4 Gy over 5–6 weeks) with chemotherapy (Morris et al 2007; Ngan et al 2005). A systematic review found that the relative risk of local recurrence was reduced by 44% after preoperative radiotherapy and 33% after postoperative radiotherapy (Colorectal Cancer Collaborative Group 2001).

Tumours reaching beyond the mesorectal fascia with nodal involvement are unlikely to benefit from TME, as a resection is unlikely to result in a free circumferential resection margin (CRM) (Wolberink et al 2006). Even if potentially curative resection is not possible, substantial palliation can be achieved in these cases (through relief of pain and symptoms such as nausea, jaundice and constipation) (Colorectal Surgical Society of Australasia 2006; Hobbs 2000). Nodal disease may require aggressive treatment to maximise the chance of an adequate surgical resection (Colorectal Surgical Society of Australasia 2006).

Potential impact of the test

Optimal staging of rectal carcinoma after diagnosis offers the best chance of selection of the most effective treatment, and therefore of long-term cure. Radiologists currently use tools such as MRI, MSCT and ERUS to decide whether radiation and chemotherapy would be helpful. An additional minor use may be to assess whether laparoscopic rather than open resection is possible (Colorectal Surgical Society of Australasia 2006).

It is expected that the decision of whether to refer a patient for ERUS or MRI would depend on clinical indication, modified by the availability of imaging, as well as physician experience and physician/patient preference.

Marketing status of the technology

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). The MRI hardware listed on the ARTG is provided in Table 3.

Table 3 MRI systems listed on the Australian Register of Therapeutic Goods (ARTG)

Product name	ARTG #	Product #	Sponsor
MRI system	98485	170254	Siemens Limited
MRI system	98887	171347	Philips Electronics Australia Ltd
MRI system	108415	187811	GE Medical Systems Australia Pty Ltd
MRT – MRI system	126911	210918	Toshiba Australia Pty Ltd

Source: Australian Register of Therapeutic Goods, available at: http://www.tgasime.health.gov.au [accessed 4/1/07]

Current reimbursement arrangement

There is currently no reimbursement arrangement for the use of MRI to stage rectal carcinoma; however, a limited number of Australian centres are currently using MRI for this indication on an unfunded basis. This assessment is being conducted to determine whether use of MRI for this indication should be listed on the Medicare Benefits Schedule (MBS).

Currently, partial reimbursement is available for the comparative technique endorectal ultrasound (ERUS) by MBS items 55731 (ultrasound of the pelvis or abdomen; female; $98.00) and 55044 (ultrasound of the pelvis or abdomen; male; $111.30) (Medicare Australia 2006). Reimbursement for CT and MSCT is available through MBS item 56807 (CT scan of chest, abdomen and pelvis with/without neck; $560.00).

Approach to assessment

Objective

The objective of this assessment is to determine whether there is sufficient evidence, in relation to clinical need, safety, effectiveness and cost-effectiveness, for MRI staging of rectal carcinoma to be recommended for public funding. This includes the staging of newly diagnosed rectal carcinoma, the restaging of rectal carcinoma after neoadjuvant chemoradiotherapy (prior to surgery) and the staging of recurrent rectal carcinoma.

Methodological approach

The effectiveness of a diagnostic test depends on whether it improves patient outcomes. This can be assessed by studies that directly investigate the impact of the test on health outcomes (direct evidence) or, in some situations, by linking evidence from studies that report on the:

- staging test performance (ie the diagnostic accuracy)
- impact on clinical decision-making
- impact of the treatment on the health of staged patients.

There was limited direct evidence available on the impact of MRI staging of rectal carcinoma on patient outcomes; therefore, a linked approach was also undertaken, using the methods outlined in the MSAC *Guidelines for the assessment of diagnostic technologies* (MSAC 2005).

Research questions

The research questions on the safety, effectiveness (both for a direct and linked evidence approach) and cost-effectiveness of using MRI for the three different indications are listed in the following chapters—Safety, Effectiveness and Economic Considerations.

Diagnostic assessment framework

This assessment of MRI for staging of rectal carcinoma is based on the framework outlined in the MSAC *Guidelines for the assessment of diagnostic technologies* handbook (MSAC 2005).

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies concerning MRI staging of rectal carcinoma for the period spanning 1995 to July 2007. A search alert was set up within PubMed, and any relevant studies published within the search period were also included. Appendix C describes the electronic databases that were used for this search and other sources of evidence that were investigated. Grey literature[1] was included in the search strategy. Unpublished literature, however, was not canvassed as it is difficult to search for this literature exhaustively and systematically, and trials that are difficult to locate are often smaller and of lower methodological quality (Egger et al 2003). It is, however, possible that these unpublished data could impact on the results of this assessment.

The search terms, presented in Appendix C, were used to identify literature from electronic bibliographic databases on the safety, effectiveness and cost-effectiveness of the use of MRI for staging of rectal carcinoma.

Inclusion/exclusion criteria

In general, studies were excluded if they:

- did not address the research question
- did not provide information on the pre-specified target population (eg used MRI to evaluate specimens rather than patients)
- did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes (ie presented results graphically)
- were studies in other languages that were of a lower level of evidence than those available in English
- did not have the appropriate study design
- did not separate between patients with cancer of the colon and those with cancer of the rectum
- used the wrong form of MRI (ie below 1.5 T or used an endorectal coil).

Where two (or more) papers reported on different aspects of the same study, such as the methodology in one and the findings in the other, they were treated as one study. Similarly, if the same data were duplicated in multiple articles, results from the most comprehensive or most recent article only were included.

[1] Literature that is difficult to find including published government reports, theses, technical reports, non-peer reviewed literature etc.

The criteria for including studies in this evaluation are presented in the relevant areas of the Results section. Criteria relevant to determining the *safety* of MRI for staging of rectal carcinoma can be found in Box 1. Criteria for including studies relevant to determining the *effectiveness* of MRI for staging of rectal carcinoma may be found in Box 2 to Box 12. Amendments were made to the inclusion criteria in Box 7 so that the reference standard was suitable for studies which included patients who did not receive curative surgery.

Search results

The process of study selection for this report went through six phases:

1. All reference citations from all literature sources were collated into an Endnote 8.0 database.

2. Duplicate references were removed.

3. Studies were excluded, on the basis of the citation information, if it was obvious that they did not meet the pre-specified inclusion criteria. Citations were conservatively assessed by one reviewer. Where there was doubt about any reference based on the title and/or abstract, the full paper was retrieved.

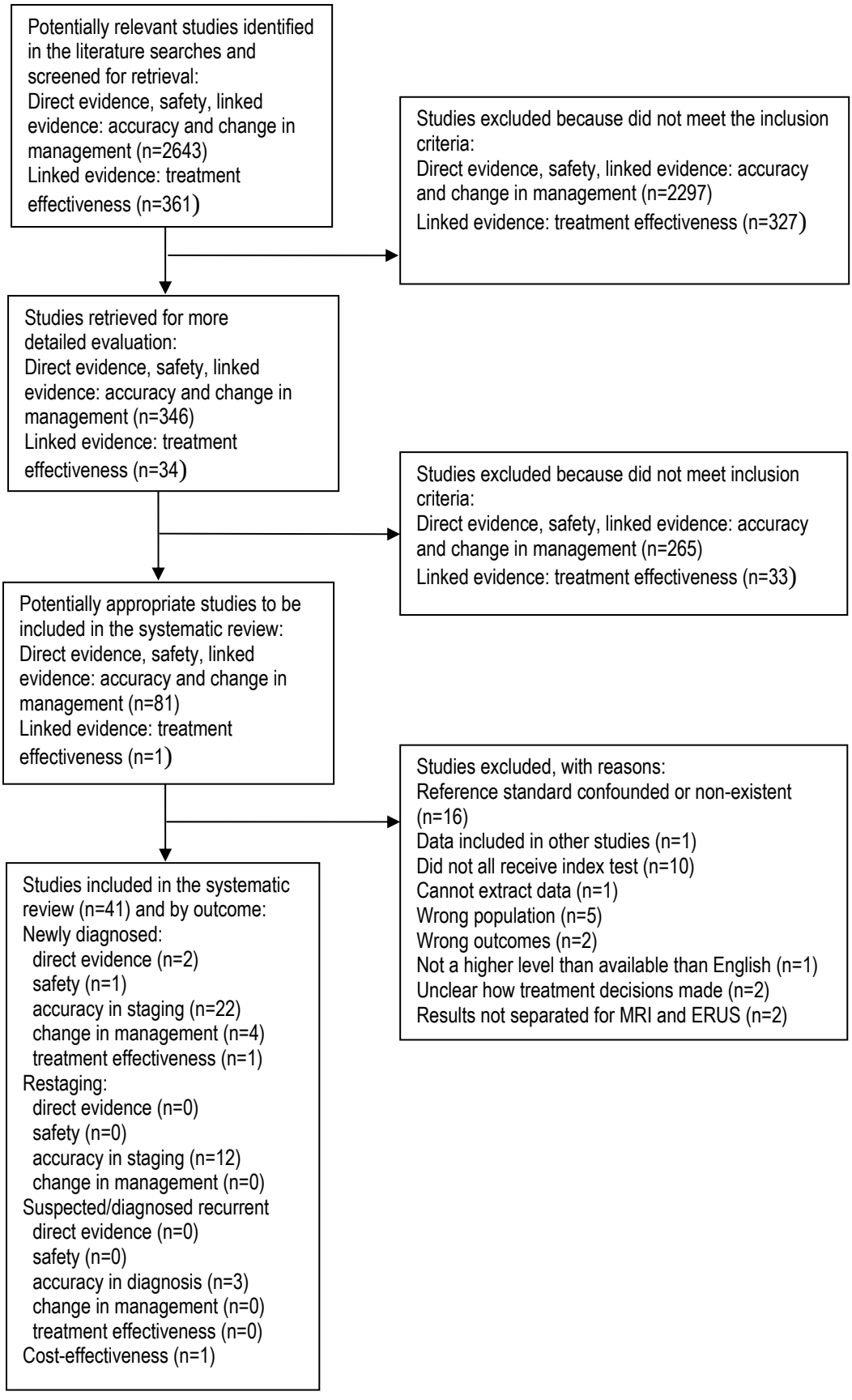
4. Studies were included to address the research questions if they met the pre-specified criteria applied to the full-text articles. Those articles meeting the criteria formed part of the evidence-base. The remainder provided background information.

5. The reference lists of the included articles were pearled for additional relevant studies. These were retrieved and assessed according to phase 4.

6. The evidence-base consisted of articles from phases 4 and 5 that met the inclusion criteria.

Any doubt concerning inclusions at phase 4 was resolved by consensus between the two reviewers, with a third reviewer available (although not required) for adjudication. The results of the process of study selection are provided in Figure 5.

Figure 5 Summary of the process used to identify and select studies for the assessment of MRI for staging of rectal carcinoma



Adapted from (Moher et al 1999)

Data extraction and analysis

A profile of key characteristics was developed for each included study (). These study profiles described the level of evidence, quality assessment, authors, publication year, location, study design, study population characteristics, type of intervention (field strength of MRI machine, single or double image interpreter etc), comparator intervention (where relevant), reference standard, inclusion/exclusion criteria and outcomes assessed for each included study.

Studies that met the inclusion criteria but contained insufficient or inadequate data for inclusion are provided in Appendix E. Definitions of all technical terms and abbreviations are provided in the Glossary on page 165.

Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies.

Assessing diagnostic accuracy

To assess the diagnostic accuracy of each of the tests for dichotomous outcomes, calculations of the following factors were undertaken where possible: sensitivity, specificity, negative and positive predictive values of the tests, false negative and false alarm rates, and 95% confidence intervals. Data were extracted using the classic 2 x 2 table, whereby the results of the index diagnostic test are cross-classified against the results of the reference standard (Armitage et al 2002; Deeks 2001), and Bayes' Theorem is applied:

		Reference standard *Histopathological assessment of CRM involvement*		
		Disease+	*Disease–*	
Index test	*Test+*	True positive	False positive	Total test positive
MRI predicted CRM involvement	*Test–*	False negative	True negative	Total test negative
		Total CRM+	Total CRM–	Total tested

The sensitivity of the index test (MRI for detecting the tumour involvement of the CRM) was calculated as the proportion of people with an involved CRM who have positive confirmation by histopathology:

Sensitivity (true positive rate, %) = number of true positives / total with involved CRM * 100

The specificity of the index test (MRI) was calculated as the proportion of people without an involved CRM confirmed by histopathology:

Specificity (true negative rate, %) = number of true negatives / total CRM negative * 100

When a 95% confidence interval was not provided in the relevant study, this was calculated using exact binomial methods.

In some instances where studies reported enough information to present calculations of sensitivity, specificity, positive predictive value and negative predictive value, dichotomous data were presented in terms of accuracy (percentage correct):

% accuracy = (true positives + true negatives) / (total patients tested) * 100

A simple kappa (κ) statistic was calculated on the dichotomous data to provide a chance-corrected measurement of the absolute agreement between MRI (or the comparator) and histopathology.

For ordinal data (eg T stage and, in some instances, N stage), accuracy was calculated as:

% accuracy = (number of patients correctly classified) / (total number of tested patients) * 100

As MRI is less accurate at staging of early disease than late disease, and the assessment of late disease is more important for the purposes of treatment planning, stages T1 and T2 were combined for the calculation of accuracy.

A weighted κ statistic (using linear weights) was calculated on the ordinal data to provide a chance-corrected measurement of the agreement between MRI and histopathology. The weighted κ statistic is an extension of the simple κ statistic, in which weights are used to quantify the relative difference between categories. For outcomes with more than two categories, a weighted κ statistic is generally preferable to a simple κ statistic.

There are no absolute definitions for the interpretation of the κ statistic (Reznek 2004) but the cut-offs shown in Table 4 were used for this assessment.

Table 4 Interpretation of the κ statistic

κ values	Strength of agreement
<0.20	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Good
0.81–1.00	Very good

Sourced from (Altman 1991; Landis & Koch 1977)

Meta-analyses could not be conducted due to both the heterogenous nature of the available evidence and the lack of availability of raw data. A narrative meta-synthesis of the data was therefore undertaken.

Assessing safety

The number of patients incorrectly staged was considered to be a secondary safety outcome, as incorrectly staged patients are likely to receive inappropriate treatment. For newly diagnosed patients, the false positive rate is the number of patients who are falsely staged as having a threatened or involved CRM, as a proportion of all of those who do not actually have a threatened or involved CRM:

False positive rate (%) = number with false positive CRM /
total number with CRM– (determined by histopathology) * 100

Likewise, the false negative rate is the proportion of patients who are falsely staged as not having a threatened or involved CRM, as a proportion of those who do have a threatened or involved CRM:

False negative rate (%) = number with false negative CRM /

total number with CRM+ (determined by histopathology) * 100

Appraisal of the evidence

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 5) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention; the last two require expert clinical input as part of their determination.

Table 5 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect—it reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 6

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 7. Study quality was assessed using the critical appraisal checklists provided in Table 8.

With respect, specifically, to diagnostic evidence, the individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria (MSAC 2005), as shown in Table 7. Studies of diagnostic accuracy in patients with newly diagnosed rectal carcinoma were at risk of 'treatment paradox bias', whereby systematic error in the assessment of diagnostic accuracy occurs when patients treated prior to undergoing the reference standard are included in the study population (MSAC 2005). In this case, patients who received long-course neoadjuvant therapy were likely to be down-staged, which would increase the number of false negative results identified. These patients were therefore excluded, and only patients who received primary surgery (surgery without any neoadjuvant therapy) or short-course radiation were included. While this was required in order to ensure that histopathology was a suitable reference standard, the samples included in the studies of diagnostic accuracy were not representative of the disease severity that would occur in the population receiving MRI. Studies which excluded patients who received neoadjuvant therapy were therefore classified as P2 (limited applicability of the population).

Studies only including patients who received neoadjuvant therapy were included to determine the accuracy of restaging.

Table 6 Designations of levels of evidence[a] according to type of research question (NHMRC 2005)

Level	Intervention[b]	Diagnostic accuracy[e]
I [a]	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with an independent, blinded comparison with a valid reference standard[f] among consecutive patients with a defined clinical presentation [g]
III-1	A pseudorandomised controlled trial (ie alternate allocation or some other method)	A study of test accuracy with an independent, blinded comparison with a valid reference standard[f] among non-consecutive patients with a defined clinical presentation[g]
III-2	A comparative study with concurrent controls: non-randomised, experimental trial[c] cohort study case-control study interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for level II and level III-1 evidence
III-3	A comparative study without concurrent controls: historical control study two or more single-arm studies[d] interrupted time series without a parallel control group	Diagnostic case-control study[g]
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[h]

Notes

[a] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

[b] Definitions of these study designs are provided in NHMRC 2000 (pp. 7–8).

[c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie using A vs B and B vs C to determine A vs C).

[d] Comparing single-arm studies, ie case series from two studies.

[e] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. (MSAC 2005).

f The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified, and can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

[g] Well-designed population-based case-control studies (eg screening studies where test accuracy is assessed on all cases, with a random sample of controls) capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease, are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

[h] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials. Physical harms and psychological harms may need to be addressed by different study designs. Harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question (eg level II intervention evidence, level IV diagnostic evidence).

Table 7 Grading system used to rank included diagnostic studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Study design: NHMRC level of evidence Study quality (QUADAS checklist): Q1 high quality Q2 medium quality Q3 poor reference standard: - poor quality or - insufficient information

Table 8 Quality checklists

Study type	Checklist
Systematic reviews / HTA reports	NHMRC Checklist Table 1.4 (NHMRC 2000)
Randomised controlled trials	NHMRC Checklist Table 1.4 (NHMRC 2000)
Cohort study	NHMRC Checklist Table 1.4 (NHMRC 2000)
Case-control	NHMRC Checklist Table 1.4 (NHMRC 2000)
Diagnostic test cross-sectional study	QUADAS quality assessment tool (Whiting et al 2003)
Intervention case series	NHS CRD Quality Assessment Scale (Khan et al 2001)

HTA = health technology assessment; NHMRC = National Health and Medical Research Council; NHS CRD = National Health Service Centre for Reviews and Dissemination (UK)

Statistical precision

Statistical precision was determined using standard statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real (NHMRC 2000).

Size of effect in individual studies

It is important to establish whether statistically significant differences are also clinically important. The size of the effect needs to be determined, as well as whether the 95% confidence interval includes only clinically important effects (NHMRC 2000).

Relevance of evidence in individual studies

Similarly, the outcome being measured in the studies should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000).

Assessment of the body of evidence

Once the results of the studies were synthesised, the overall conclusion as derived from the body of evidence (Table 9) was presented to answer each clinical question (see Discussion section).

Table 9 Body of evidence assessment matrix (NHMRC 2005)

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population	population/s studied in the body of evidence are similar to the target population	population/s studied in body of evidence different to target population but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Expert advice

An advisory panel with expertise in consumer issues, colorectal surgery, gastroenterology, oncology and radiology was established to evaluate the evidence from this assessment report and to provide advice to MSAC from a clinical or consumer perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the advisory panel associated with this MSAC assessment is provided at Appendix B.

Safety

Is MRI safe?

As there were limited studies on the safety of using MRI for staging/restaging of rectal carcinoma or diagnosis of recurrent rectal carcinoma, the following research questions were considered together:

Staging of newly diagnosed rectal carcinoma

- What is the safety of MRI staging, versus ERUS, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

- What is the safety of adding MRI staging to CT abdomen (pelvis), with/without PET, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

Restaging of rectal carcinoma

- What is the safety of MRI, with/without other imaging modalities, compared to no imaging, an alternative modality of imaging or a combination of imaging techniques in patients with rectal carcinoma requiring restaging of the disease after neoadjuvant therapy?

Diagnosis/staging of recurrent rectal carcinoma

- What is the safety of MRI versus ERUS in patients suspected of having or diagnosed with rectal carcinoma recurrence, and requiring diagnosis/staging for further treatment planning?

- What is the safety of adding MRI to CT abdomen (pelvis), with/without PET, in patients suspected of having or diagnosed with rectal carcinoma recurrence, and requiring diagnosis/staging for further treatment planning?

Box 1 outlines the inclusion criteria determined a priori for assessment of the safety of using MRI for staging of rectal carcinoma.

Box 1 Inclusion criteria for studies assessing the safety of MRI staging of rectal carcinoma

Characteristic	Criteria	
Publication type	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports or systematic reviews of these study designs. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.	
Population	Patients with suspected or diagnosed primary or recurrent rectal carcinoma requiring further staging of the disease for treatment planning	
Intervention/test[a]	1. Magnetic resonance imaging (MRI)	2. CT abdomen (pelvis) with/without PET plus MRI
Comparators	1. Endorectal ultrasound	2. CT abdomen (pelvis) with/without PET
Outcome	Primary: physical adverse events, eg burns, reactions to contrast agent, pain, discomfort; psychological, eg claustrophobia Secondary: radiation exposure; harms from over- or undertreatment due to incorrect staging	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Note: CT abdomen (pelvis) may refer to multi-slice CT, which is more commonly used in Australia than conventional CT.

Physical adverse events

Only one study was identified that provided comparative data on the safety of MRI relative to multi-slice CT (MSCT). Matsuoka et al (2003) reported that there were no complications from either imaging modality. Although the systematic review did not identify any physical safety concerns regarding MRI for staging of rectal carcinoma, a further narrative review of safety considerations is provided in the 'Other relevant considerations' section, page 86.

Harms from under- and overtreating due to incorrect staging

No studies were identified that reported on the safety implications of patients having been overstaged or understaged. Rates of false positive and false negative staging have been provided in the 'Effectiveness' section of this report, as they are components of the diagnostic accuracy of the staging techniques. Notwithstanding the lack of direct evidence on the impact of incorrect staging from MRI or its comparators, it is clear that if patients are staged incorrectly they will be given inappropriate treatment. This is discussed further on page 88.

Summary

What is the safety of MRI staging, versus ERUS, in patients with rectal carcinoma requiring further staging of the disease for treatment planning? What is the safety of adding MRI staging to CT abdomen (pelvis), with/without PET in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

What is the safety of MRI, with/without other imaging modalities, compared to no imaging, an alternative modality of imaging or a combination of imaging techniques in patients with rectal carcinoma requiring restaging of the disease after neoadjuvant therapy?

What is the safety of MRI, versus ERUS, in patients suspected of having or diagnosed with rectal carcinoma recurrence, and requiring diagnosis/staging for further treatment planning? What is the safety of adding MRI to CT abdomen (pelvis), with/without PET, in patients suspected of having or diagnosed with rectal carcinoma recurrence, and requiring diagnosis/staging for further treatment planning?

No studies reported on any physical complications directly related to MRI for staging of rectal carcinoma (either newly diagnosed or after neoadjuvant therapy) or when used to diagnose recurrent rectal carcinoma.

Harms may result from incorrect disease staging. No studies reported on the safety implications of incorrect staging.

Effectiveness

The effectiveness of MRI for each of the three rectal carcinoma indications was investigated using the following research questions. The type of question depended on the type of evidence available and thus whether a direct evidence or linked evidence approach was appropriate.

Is MRI effective for staging of newly diagnosed patients?

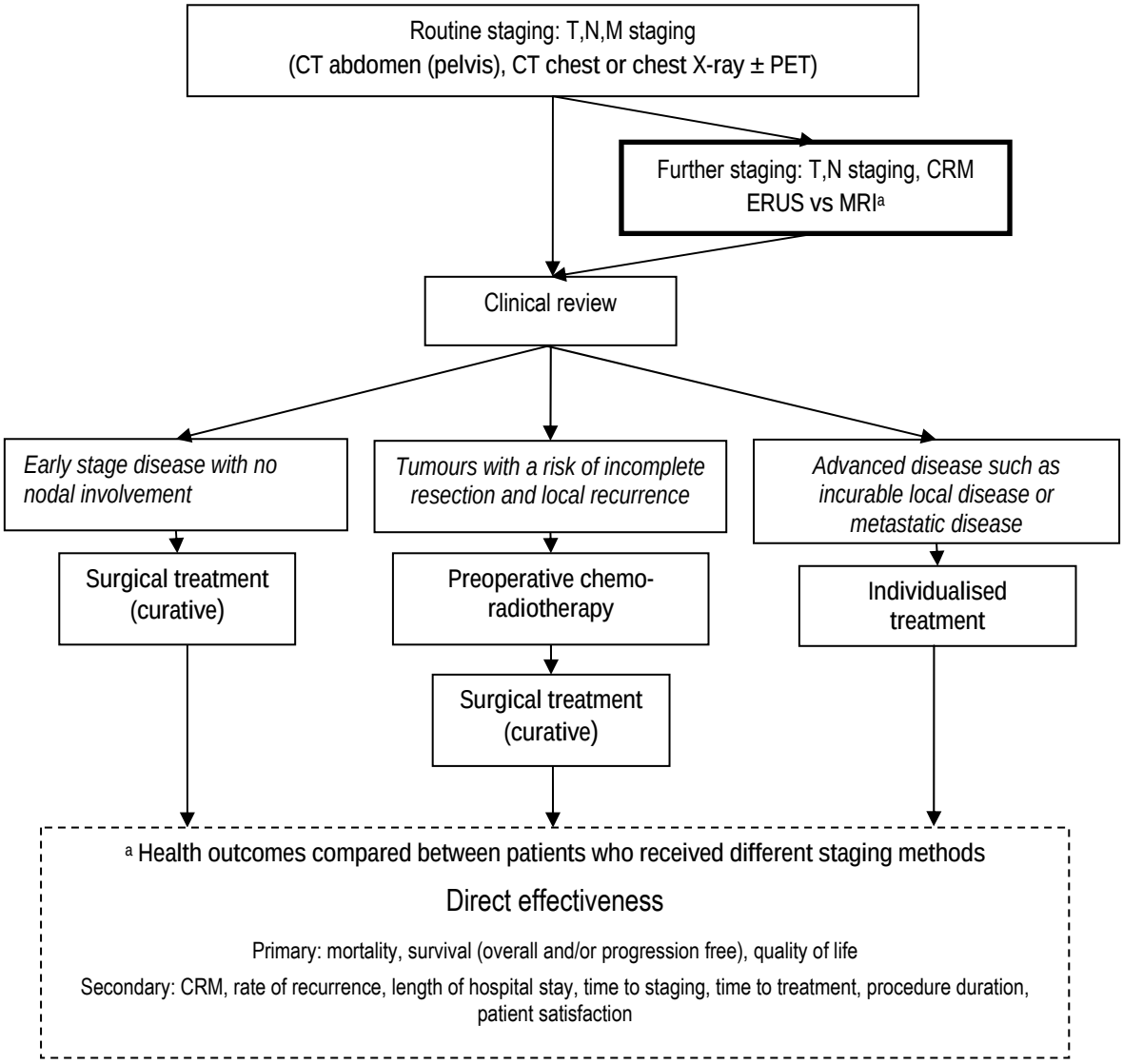
Direct evidence of effectiveness

- What is the clinical effectiveness of MRI staging and subsequent interventions on patient outcomes, compared to ERUS, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

- What is the clinical effectiveness of adding MRI staging to CT abdomen (pelvis), with/without PET, on patient outcomes in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

Figure 6 outlines the components of the clinical pathway for the staging of rectal carcinoma with MRI that are relevant to the research questions posed above.

Figure 6 Assessing direct evidence of effectiveness of staging newly diagnosed rectal carcinoma with MRI



Studies assessing the direct effectiveness of MRI staging at improving health outcomes were included if they met the inclusion criteria outlined a priori in Box 2.

Box 2 Inclusion criteria for studies assessing the effectiveness of MRI staging of newly diagnosed rectal cancer

Characteristic	Criteria	
Publication type	Randomised or non-randomised controlled trials or cohort studies or systematic reviews of these study designs. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.	
Population	Patients with rectal carcinoma requiring further staging of the disease for treatment planning	
Intervention/test[a]	1. MRI for assessment of CRM and/or staging of tumour depth, nodal staging	2. CT abdomen and CT pelvis with/without PET plus MRI
Comparators[a]	1. Endorectal ultrasound	2. CT abdomen and CT pelvis with/without PET
Reference standard	All clinical information, including histopathology findings	
Outcome	Primary: mortality, survival (overall and/or progression free), quality of life Secondary: CRM, rate of recurrence, length of hospital stay, time to staging, time to treatment, procedure duration, patient satisfaction	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Note: CT abdomen (pelvis) may refer to multi-slice CT, which is more commonly used in Australia than conventional CT.

No studies were identified that reported on the patient relevant primary health outcomes listed a priori for assessing the direct effectiveness of MRI for staging of rectal carcinoma. There were, however, two medium-quality retrospective studies that reported on the secondary outcome, circumferential resection margin (CRM) status, with and without usage of MRI staging. Because CRM status has been found to be a strong predictor of disease-free survival after curative surgery for rectal carcinoma, it is used as a surrogate health outcome (Adam et al 1994; Birbeck et al 2002; Mawdsley et al 2005).

The larger study (level III-3 interventional evidence) compared resection rates in patients who underwent MRI for preoperative staging (1998–2002) against a historical control group who did not receive MRI (1993–97) (Beets-Tan et al 2005). Prior to the introduction of MRI, the imaging of rectal carcinoma consisted of preoperative computed tomography (CT) only for the obviously advanced cases. Post-treatment, the group of patients who received MRI staging had fewer involved resection margins than the patients who underwent surgery prior to the introduction of MRI staging (Table 10). However, during this time period the introduction of MRI was not the only change in practice. Total mesorectal excision (TME) was standardised in the mid 1990s, and short-course radiotherapy was introduced in 1996 and became standard in 2001. There are therefore substantial confounding factors that make it difficult to ascertain the effect of MRI staging on patient outcomes.

Burton et al (2006b) (level III-2 interventional evidence) reported on a retrospective audit of rectal carcinoma cases within one healthcare network, consisting of four hospitals and six colorectal surgeons, in the United Kingdom. The policy of the network was for patients to receive pelvic MRI, abdominal CT and either a chest X-ray or CT of the thorax to identify metastatic disease (Burton et al 2006b). An analysis was performed comparing patients whose MRI results had been discussed by a multidisciplinary team (MDT; n=197) with patients who were referred to surgery without an MDT meeting (those who did not undergo MRI (42/62) or whose MRI results were not discussed (20/62)). All 62 patients who did not have MRI staging results discussed by an MDT

proceeded to primary surgery (surgery without prior adjuvant therapy). The discussed group (n=197) received either surgery alone (59%) or chemoradiotherapy followed by surgery (35%), or were deemed irresectable after chemoradiotherapy (6%). Prior to treatment, 30% of patients with MDT discussion of MRI were predicted to have a positive CRM (60/197), which was not significantly different from the histological CRM positivity rate in the non-discussed group (26%). The group who had MDT discussion of MRI and subsequent selective chemoradiotherapy had a 63% reduction in positive CRMs relative to the non-discussed group (Table 10), indicating perhaps that neoadjuvant therapy had been appropriately targeted.

Table 10 Effectiveness of MRI staging at improving health outcomes

Author Location	Study design Quality	Study population	Definition of CRM+	Proportion of patients CRM+ [95%CI]		
(Burton et al 2006b) United Kingdom	Level III-2 interventional evidence Medium quality (NHMRC = 4/6)	n=259 Median age = 67 years (range 28–88) 125 females, 173 males	<1 mm to mesorectal fascia	Without MDT discussion of MRI staging	With MDT discussion of MRI staging	Relative Risk
				25.8% (16/62) [16, 39]	9.6% (19/197) [6, 15]	0.37 [0.21, 0.68]
(Beets-Tan et al 2005) The Netherlands	Level III-3 interventional evidence Medium quality (NHMRC = 4/6)	n=311 Patient characteristics not stated	Tumour extension into mesorectal fascia	Without MRI staging	With MRI staging	Relative Risk
				7.5% (11/147) [4, 13]	3.0% (5/164) [1, 7]	0.41 [0.15, 1.15] p=0.08
			<1 mm to mesorectal fascia	15.6% (23/147) [10, 23]	7.9% (13/164) [4, 13]	0.51 [0.27, 0.96] p=0.03

MDT = multidisciplinary team

Summary

What is the clinical effectiveness of MRI staging and subsequent interventions on patient outcomes, compared to ERUS, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

There were no studies available that provided direct evidence comparing MRI and ERUS with respect to their impact on health outcomes.

What is the clinical effectiveness of adding MRI staging to CT abdomen (pelvis), with/without PET, on patient outcomes in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

One medium-quality study compared the health outcomes of patients who were staged with MRI with those who were not. This was supplemented by another medium-quality study which compared the health outcomes of patients whose MRI results were discussed by a multidisciplinary team (MDT) against those whose results were not discussed (the majority of whom did not receive an MRI). Considerably fewer patients had a positive CRM after they were staged by MRI or discussed by an MDT compared with those who were not staged by MRI or not discussed by an MDT. This was reflected in the choice of management of patients with rectal carcinoma. Those patients receiving MRI staging or MDT discussion of MRI staging received selective neoadjuvant therapy, whereas all those who were not staged by MRI or did not have their MRI results discussed by an MDT received surgery alone.

Linked evidence

As there was limited direct evidence of the health benefits of using MRI to stage rectal carcinoma, it was supplemented with an analysis of linked evidence which was undertaken in a number of stages and discussed below.

Diagnostic accuracy (staging)

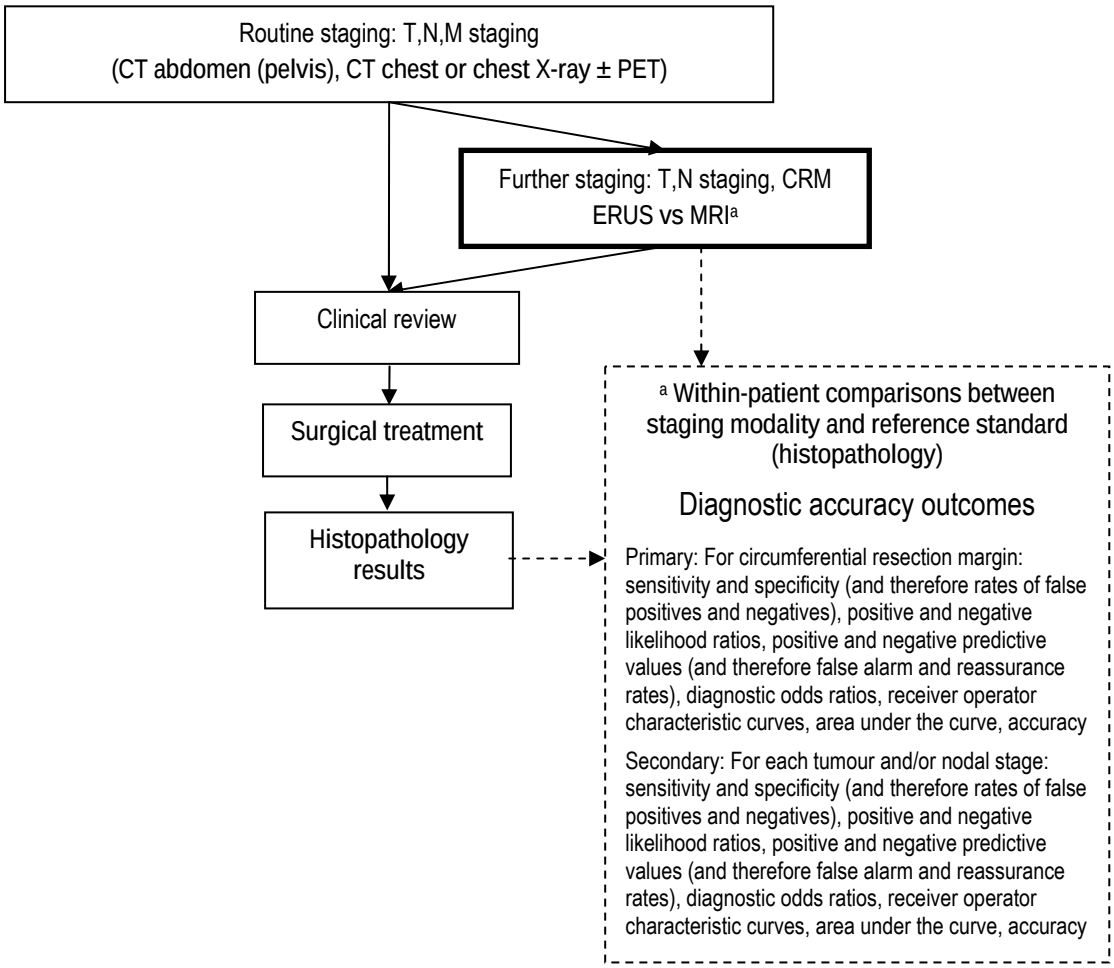
- What is the diagnostic accuracy of MRI staging, compared to ERUS, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

- What is the diagnostic accuracy of adding MRI staging to CT abdomen (pelvis), with/without PET, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

These two research questions were evaluated by assessing evidence using the components of the clinical pathway shown in Figure 7. Studies on the accuracy of MRI for newly diagnosed patients with rectal carcinoma were only included if the patients received primary surgery ± short-course radiotherapy. Patients who do not receive surgery do not provide any data on the reference standard of histopathology, and

patients who undergo long-course radiotherapy, chemotherapy or chemoradiotherapy prior to surgery are likely to show treatment effects in their histopathology (and thus would provide an imperfect reference standard).

Figure 7 Linked evidence approach: assessing the accuracy of MRI and comparators for staging of newly diagnosed rectal carcinoma, versus the reference standard



The inclusion criteria for studies assessing the diagnostic accuracy of MRI staging of rectal carcinoma are shown in Box 3.

Box 3 Inclusion criteria for studies assessing the diagnostic accuracy of MRI staging of rectal carcinoma

Characteristic	Criteria
Publication type	Cross-sectional studies where patients are cross-classified on the test and comparator(s) and/or reference standard; systematic reviews of cross-sectional studies. Case-control diagnostic studies were only acceptable if cross-sectional studies were not available. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.
Population	Patients with rectal carcinoma requiring further staging of the disease for treatment planning
Intervention/test	1. MRI for assessment of the CRM or staging of tumour depth, and/or nodal involvement
	2. CT abdomen (pelvis) with/without PET plus MRI
Comparators	1. Endorectal ultrasound
	2. CT abdomen (pelvis) with/without PET
Reference standard	Histopathology
Outcome	Primary: For circumferential resection margin: sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values (and therefore false alarm and reassurance rates), diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy Secondary: For each tumour and/or nodal stage: sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values (and therefore false alarm and reassurance rates), diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.

Note: CT abdomen (pelvis) may refer to multi-slice CT, which is more commonly used in Australia than conventional CT; studies which included patients who received neoadjunctive therapy, and did not provide a subgroup analysis for patients who proceeded to primary surgery (or short-course radiation), were excluded, due to the risk of treatment paradox bias.

The results are divided into the three main outcome measures—assessment of the CRM (the primary outcome), and assessment of tumour (T) stage and regional lymph node (N) status (secondary outcomes).

There were 21 studies included that assessed the accuracy of MRI compared to the reference standard of histopathology. Four comparative studies were identified that compared MRI against endorectal ultrasound (ERUS) (n=1), and computed tomography (CT, multi-slice CT) (n=3).

Primary outcome

Accuracy of MRI for detecting circumferential resection margin

The distance between the CRM and the rectal tumour has been found to be the most important predictor of local recurrence (Hermanek & Junginger 2005). MRI allows preoperative imaging of the CRM, which determines whether patients would benefit from neoadjuvant therapy (such as radiotherapy, chemotherapy or a combination of both) or not. For more details see the section on 'Change in management', page 46, and the section on the clinical benefit resulting from the change in management expected from MRI, page 50.

Only one study was available that reported on the ability of MRI compared to MSCT for determining whether the CRM is threatened or involved (Table 11). As MRI is proposed as an additional imaging tool, rather than an alternative, to MSCT (as MSCT is the gold

standard for assessing distant metastases), the additional benefit of MRI should be assessed. In the included study MRI was no more accurate at determining whether the CRM was involved than MSCT (Taylor et al 2007). However, the authors believed it likely that MRI is superior to MSCT at imaging very low rectal tumours, due to better tissue contrast with the former imaging technique and its ability to image the coronal plane. This medium-quality study would have been subject to spectrum bias, as patients who received intensive preoperative therapy were excluded. Further bias was possibly introduced through the use of two independent interpreters of the images, as skill levels potentially differed. The utility of this study was further limited as the authors used a cut-off of 5 mm to distinguish between involved and uninvolved CRMs. Based on this definition, they found that both MRI and MSCT were poor predictors of CRM status compared with histopathology (MRI accuracy = 54%; MSCT accuracy = 64%). The authors retrospectively analysed their data and found that a cut-off of 3 mm would have resulted in higher accuracy (Taylor et al 2007). The Advisory Panel's opinion was that the atypical definition of the CRM meant that the results were not clinically meaningful. The usual definition of an involved CRM is a tumour within 1 mm of the mesorectal fascia (Table 12), and no published studies were available that compared MRI with MSCT using this definition.

Table 11 Accuracy of MRI and MSCT at predicting CRM involvement

Author Location	Study design Quality	Study population	Definition of CRM+	MRI						MSCT					
				Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]	FP rate [95%CI]	FN rate [95%CI]	Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]	FP rate [95%CI]	FN rate [95%CI]
Population not representative of full spectrum of disease severity (patients with long-course neoadjuvant therapy excluded)															
(Taylor et al 2007) United Kingdom	Level III-2 diagnostic evidence P2 Q2 Medium quality (QUADAS = 11/14)	n=42 Sex not stated Median age = 74 years (range 47–93) 41 patients received no preoperative therapy 1 patient underwent short-course radiation	≤5 mm to mesorectal fascia (CRM threatened or involved)	56% (5/9) [21, 86]	54% (18/33) [36, 72]	25% (5/20) [09, 49]	82% (18/22) [60, 95]	45% (15/33) [28, 64]	44% (4/9) [14, 79]	56% (5/9) [21, 86]	67% (22/33) [48, 82]	31% (5/16) [11, 59]	85% (22/26) [65, 96]	33% (11/33) [18, 52]	44% (4/9) [14, 79]
			Tumour at surface of mesorectal fascia (CRM involved)	0% (0/2) [0, 94]	100% (40/40) [91, 100]	Un-determined (0/0)	95% (40/42) [84, 99]	0% (0/40) [0, 9]	100% (2/2) [16, 100]	0% (0/2) [0, 94]	98% (39/40) [87, 100]	0% (0/1) [0, 98]	95% (39/41) [83, 99]	3% (1/40) [0, 13]	100% (2/2) [16, 100]

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; MSCT = multi-slice computed tomography; FP = false positive; FN = false negative; CRM = circumferential resection margin

The accuracy of MRI relative to histopathology alone was investigated in six studies (Table 12). Studies are presented in order of their population applicability, level of evidence and quality score. The majority of studies classified a CRM as involved (CRM+) if the tumour was less than 1 mm from the mesorectal fascia. The accuracy of MRI (percentage correct) ranged from 73% to 100% (median 93%). These studies were considered too heterogeneous to combine the results using a meta-analysis. The sensitivity and specificity of MRI at determining CRM status varied substantially between the studies. The accuracy in these studies was, however, higher than in the one comparative study (Taylor et al 2007), which possibly relates to the different definition of an involved CRM.

The largest study (n=311) had 10 patients who were reported to have a negative CRM at the time of staging with MRI, but whose tumours were perforated during surgery (which could not have been predicted by MRI), resulting in poor sensitivity (MERCURY Study Group 2006). When intraoperative perforations were excluded, the sensitivity of MRI in this study increased to 58%.

Sensitivity and specificity are the most stable measures of assessing test accuracy, as they are not affected by prevalence in the test population of the disease being diagnosed. In this instance the test population all have rectal carcinoma and the test is being used to stage the disease. As a consequence, the positive and negative predictive values of the test (measures of test accuracy that vary according to prevalence of the disease in the test population) may be more clinically useful measures. The negative predictive value indicates the proportion of patients who are correctly predicted by the test to have a non-threatened CRM. These patients would be less likely to suffer recurrence. MRI had consistently high negative predictive values (median 98%, range 70–100%) across all the accuracy studies included in Table 12. This means that MRI could be used to accurately select patients suited for primary surgery, rather than neoadjuvant therapy.

The false negative rate is the proportion of patients with an involved CRM that receive a negative test result. False negative rates are a concern, as patients who receive a negative test result (signalling that their CRM is not involved) would not receive the benefits of neoadjunctive therapy prior to surgery. This can result in worse patient outcomes, as *adjuvant* therapy results in higher levels of local recurrence and higher toxicity than *neoadjuvant* therapy (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Up to 59% of those patients who were CRM positive as determined by histopathology were staged as negative by MRI (Table 12).

False positive rates relate to the proportion of patients who do not have a threatened or involved CRM but who receive a staging result suggesting a positive CRM. These patients would likely receive unnecessary neoadjunctive therapy prior to surgery. A discussion of the adverse events that may occur from neoadjunctive therapy is provided in 'Other relevant considerations', page 87. False positive rates in these studies ranged between 0% and 16% (Table 12).

Table 12 Accuracy of MRI at predicting CRM involvement

Author Location	Study design Quality	Study population	Definition of CRM+	Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]	FP rate [95%CI]	FN rate [95%CI]
Disease spectrum representative of those receiving test in clinical setting									
(Akasu et al 2005) Japan	Level III-2 diagnostic evidence P1 Q1 High quality (QUADAS = 13/14)	n=34 9 women, 25 men Median age = 57 years (range 34–82)	Mesorectal fascia involvement	100% (8/8) [63, 100]	100% (26/26) [87, 100]	100% (8/8) [63, 100]	100% (26/26) [87, 100]	0% (0/26) [0, 13]	0% (0/8) [0, 37]
Population not representative of full spectrum of disease severity (patients with neoadjuvant therapy excluded)									
(Ferri et al 2005) Italy	Level II diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=22/33 patients who were staged T3 or T4 10 women, 23 men Mean age = 66±10 years	≤1 mm to CRM	100% (2/2) [15, 100]	90% (18/20) [68, 99]	50% (2/4) [7, 93]	100% (18/18) [81, 100]	10% (2/20) [1, 30]	0% (0/2) [0, 84]
(Burton et al 2006a) United Kingdom	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 13/14)	n=57/75 who received primary surgery (all initially predicted CRM–) 34 women, 41 men Median age = 65 years (range 37–86)	<1 mm to CRM	100% (1/1) [3, 100]	96% (54/56) [88, 100]	33% (1/3) [1, 91]	100% (54/54) [93, 100]	4% (2/56) [0, 12]	0% (0/1) [0, 98]
(Vliegen et al 2005) The Netherlands	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=56/83 without preoperative treatment Mean age = 65 years (range 15–86) 22 women, 61 men	<1 mm to CRM (T2 weighted)	*Ob 1* 85% (11/13) [55, 98] *Ob 2* 77% (10/13) [46, 95]	*Ob 1* 93% (40/43) [81, 99] *Ob 2* 88% (38/43) [75, 96]	*Ob 1* 79% (11/14) [49, 95] *Ob 2* 67% (10/15) [38, 88]	*Ob 1* 95% (40/42) [84, 99] *Ob 2* 93% (38/41) [80, 98]	*Ob 1* 7% (3/43) [1, 19] *Ob 2* 12% (5/43) [4, 25]	*Ob 1* 15% (2/13) [2, 45] *Ob 2* 23% (3/13) [5, 54]
			<1 mm to CRM (CE T1 & T2 weighted)	*Ob 1* 85% (11/13) [55, 98] *Ob 2* 85% (11/13) [55, 98]	*Ob 1* 84% (36/43) [69, 93] *Ob 2* 84% (36/43) [69, 93]	*Ob 1* 61% (11/18) [36, 83] *Ob 2* 61% (11/18) [36, 83]	*Ob 1* 95% (36/38) [82, 99] *Ob 2* 95% (36/38) [82, 99]	*Ob 1* 16% (7/43) [7, 31] *Ob 2* 16% (7/43) [7, 31]	*Ob 1* 15% (2/13) [2, 45] *Ob 2* 15% (2/13) [2, 45]
(Kim et al 2008) South	Level III-2 diagnostic evidence	n=57 24 women, 33 men	≤1 mm to CRM	41% (9/22) [21, 64]	89% (31/35) [73, 97]	69% (9/13) [39, 91]	70% (31/44) [55, 83]	11% (4/35) [3, 26]	59% (13/22) [36, 79]

Author Location	Study design Quality	Study population	Definition of CRM+	Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]	FP rate [95%CI]	FN rate [95%CI]
Korea	P2 Q1 High quality (QUADAS = 12/14)	Median age = 62 years (range 30–81)	≤2 mm to CRM	91%	77%	71%	93%	NR	NR
			≤3 mm to CRM	95%	20%	43%	88%	NR	NR
(MERCURY Study Group 2006) 11 colorectal units in 4 European countries	Level III-2 diagnostic evidence P2 Q2 Medium quality (QUADAS = 11/14)	n=311/408 Median age = 68 years (range 29–92) 161 women, 247 men Some patients received short-course radiotherapy	Tumour or malignant nodes ≤1 mm to mesorectal fascia or intraoperative perforations	42% (15/36) [26, 59]	98% (269/275) [95, 99]	71% (15/21) [48, 89]	93% (269/290) [89, 95]	2% (6/275) [1, 5]	58% (21/36) [a] [41, 75]
			Tumour or malignant nodes ≤1 mm to mesorectal fascia	58% (15/26) [37, 77]	98% (269/275) [95, 99]	71% (15/21) [48, 89]	96% (269/280) [93, 98]	2% (6/275) [1, 5]	42% (11/26) [23, 63]

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; FP = false positive; FN = false negative; CRM = circumferential resection margin; CE = contrast enhanced; Ob 1 = observer 1; Ob 2 = observer 2; NR = not reported; [a]10/21 false negatives were due to intraoperative perforation; primary surgery = surgery without any neoadjuvant therapy

Secondary outcomes

Accuracy of MRI for detecting T stage

Prior the introduction of MRI and the ability to visualise the CRM, staging was performed by an assessment of T and N stages, which are key components of the International Union Against Cancer (UICC) staging system for cancer (for more details see Table 2, page 4).

One poor-quality comparative study was identified that compared the accuracy of MRI against multi-slice CT (MSCT) at determining T stage. Both imaging techniques were highly accurate at assessing tumour depth within the small sample presented, although the authors stated that it was difficult to discriminate rectal wall layers with MSCT imaging (Matsuoka et al 2003b).

Table 13 Accuracy of MRI and MSCT at predicting tumour staging

Author Location	Study design Quality	Study population	Accuracy to predict tumour stage	
			MRI	MSCT
Disease spectrum assumed representative of those receiving test in clinical setting				
(Matsuoka et al 2003b) Japan	Level III-1 diagnostic evidence P1 Q3 Insufficient information (QUADAS = 9/14)	n=21 7 women, 14 men Mean age = 64 years (range 37–83) Neoadjunctive treatments not mentioned	100% (21/21) [84, 100] κ = 1.0 0% understaged	95.6% (20/21) [76, 100] κ not stated % understaged – NR

NR = not reported

Thirteen studies assessed the accuracy of MRI at predicting T stage against the reference standard but without comparing it to alternative staging methods (Table 14). Accuracy

values ranged from 63% to 100% (median 85%). Based on simple and weighted kappa calculations, the agreement between MRI and histopathology ranged from fair (weighted $\kappa = 0.31$) to very good (simple $\kappa = 1.0$), with most studies reporting moderate to good agreement (much higher than the agreement expected by chance). Understaging is considered a more serious problem than overstaging in newly diagnosed patients, as it may result in neoadjuvant therapy being withheld in patients who could potentially benefit. Understaging was generally low, but one study reported understaging as high as 25% (Burton et al 2006a).

It is unclear what caused the heterogeneity in the results between studies. However, the criteria for determining the depth of tumour invasion are controversial (Matsuoka et al 2003a) and misdiagnosis may be due to inflammation around the tumour. Learning curves at interpretation of phased-array MRI may be responsible for poor early results such as Hadfield et al (1997) (Table 14). The large multicentre MERCURY study also included results from two centres which were using 1.0 -T machines.

Table 14 Accuracy of MRI at predicting T stage

Author Location	Study design Quality	Study population	Accuracy of MRI to predict tumour stage [95%CI]
Disease spectrum representative of those receiving test in clinical setting			
(Matsuoka et al 2003a) Japan	Level II diagnostic evidence P1 Q1 High quality (QUADAS = 12/14)	n=19 17 patients with rectal carcinoma, 2 with malignant melanoma of anal canal 4 women, 15 men Mean age = 62 years	84% (16/19) [60, 97] κ not stated % understaged NR
(Hadfield et al 1997) United Kingdom	Level III-1 diagnostic evidence P1 Q3 Insufficient information (QUADAS = 9/14)	n=38 10 women, 28 men Mean age = 69 years (range 38–89)	63% (24/38) [46, 78] weighted κ = 0.31 [0.05, 0.57] 18% understaged
(Akasu et al 2005) Japan	Level III-2 diagnostic evidence P1 Q1 High quality (QUADAS = 13/14)	n=34 9 women, 25 men Median age = 57 years (range 34–82)	85% (29/34) [32, 90] weighted κ = 0.81 [0.67, 0.95] 9% understaged
(Arii et al 2006) Japan	Level III-2 diagnostic evidence P1 Q1 High quality (QUADAS = 12/14)	n=53 14 women, 39 men Mean age = 62 years (range 34–83)	68% (36/53) [54, 80] weighted κ = 0.47 [0.21, 0.73] 9% understaged
(Brown et al 1999) United Kingdom	Level III-2 diagnostic evidence P1 Q1 High quality (QUADAS = 12/14)	n=25 completely excised tumours (from 28 patients) Mean age = 62 years (range 32–88) 8 women, 20 men Patients received short-course radiotherapy	100% (25/25) [86, 100] κ = 1.0 0% understaged
(Low et al 2003) United States of America	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 11/14)	n=21 patients with rectal cancer, from 48 consecutive patients 22 women, 26 men Mean age = 65 years (range 38–90)	95% (20/21) [76, 100] κ not reported 5% understaged
(Kim et al 2000) South Korea	Level III-2 diagnostic evidence P1 Q3 Insufficient information (QUADAS = 9/14)	n=217 Patient characteristics not stated	82% (177/217) [76, 86] weighted κ = 0.57 [0.45, 0.69] 8% understaged
Population not representative of full spectrum of disease severity (patients with neoadjuvant therapy excluded)			
(Ferri et al 2005) Italy	Level II diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=33 10 women, 23 men Mean age = 66 ± 10 years	88%[a] (29/33) [72, 97] κ = 0.75 [0.52, 0.98] 12% understaged
(Burton et al 2006a) United Kingdom	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 13/14)	n=57 who received primary surgery 34 women, 41 men Median age = 65 years (range 37–86)	63% (36/57) [49, 76] weighted κ = 0.48 [0.29, 0.66] 25% understaged
(Kim et al 2008) South Korea	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=57 24 women, 33 men Median age = 62 years (range 30–81)	89% (51/57) [78, 96] κ = 0.74 [54, 93] 4% understaged

Author Location	Study design Quality	Study population	Accuracy of MRI to predict tumour stage [95%CI]
(Kim et al 2006) South Korea	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=35 15 women, 20 men Mean age = 57 years (range 45–74)	*Observer 1* 94% (33/35) [81, 99] weighted κ = 0.88 [0.73, 1.00] 6% understaged *Observer 2* 89% (31/35) [73, 97] weighted κ = 0.77 [0.56, 0.98] 9% understaged *Observer 3* 91% (32/35) [77, 98] weighted κ = 0.82 [0.63, 1.00] 3% understaged
(MERCURY Study Group 2007) 9 United Kingdom centres, and 3 European centres	Level III-2 diagnostic evidence P2 Q2 High quality (QUADAS = 11/14)	n=300/311 who underwent primary surgery Median age = 67 years (range 33–92) 128 women, 183 men 51 patients underwent short-course radiation therapy (5.5 Gy)	63% (190/300) [57, 68] weighted κ = 0.32 [0.22, 0.42] 22% understaged
(Gagliardi et al 2002) United States of America	Level III-2 diagnostic evidence P2 Q3 Insufficient information (QUADAS = 9/14)	n=28 10 women, 18 men Mean age = 63 years (range 26–89)	86%[a] (24/26) [75, 99] κ = 0.69 [0.41, 0.97] 7% understaged

NR = not reported; [a] accuracy of detecting extramural tumour invasion (ie T1 and T2 versus T3 and T4)

Accuracy of MRI for detecting N stage

Lymph node status has been found to be a predictor of overall survival, independent of the resection margin (Arii et al 2006). It is also a component of the TNM staging system (Table 1 and Table 2).

Three studies (level III-1 and III-2 diagnostic evidence) compared the accuracy of MRI for evaluating whether lymph nodes were involved, compared to CT, multi-slice CT (MSCT) and ERUS. MRI is not being proposed as an alternative to staging with CT, as CT will still be used for assessing whether there are metastases in distant organs. However, the results of MRI compared to CT were included to assess whether there would be additional benefit from staging with MRI. No significant differences between MRI and MSCT were found (Matsuoka et al 2003b). When compared to conventional CT, Arii et al (2006) found that MRI was superior to CT for the detection of involved lateral lymph nodes. For regional nodes, MRI was statistically better than CT in regards to positive predictive value ($p<0.001$); for lateral pelvic lymph nodes, MRI was statistically superior to CT in regards to specificity and positive predictive value ($p<0.001$) but worse on negative predictive value ($p<0.001$). A small but high-quality cohort study (level III-2 diagnostic evidence) compared the accuracy of a 3 -T MRI machine with ERUS (Chun et al 2006). While there was no statistically significant difference between the accuracies of MRI and ERUS at detecting lymph node status ($p=0.43$), MRI showed higher values for sensitivity, specificity, positive predictive value and negative predictive value. While the authors concluded that the two methods were comparable, ERUS can only be used to image perirectal lymph nodes, whereas MRI is able to visualise periiliac lymph nodes (Chun et al 2006).

Table 15 Comparative accuracy of MRI at detecting lymph node involvement

Author Location	Study design Quality	Study population	Definition of metastasis	MRI				Comparator			
				Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]	Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]
Disease spectrum representative of those receiving test in clinical setting											
(Matsuoka et al 2003b) Japan	Level III-1 diagnostic evidence P1 Q3 Insufficient information (QUADAS = 9/14)	n=21 7 women, 14 men Mean age = 64 years (range 37–83)	>5 mm	67% (6/9) [30, 93]	75% (9/12) [43, 95]	67% (6/9) [30, 93]	75% (9/12) [43, 95]	MSCT			
								67% (6/9) [30, 93]	58% (7/12) [28, 85]	55% (6/11) [24, 83]	70% (7/10) [35, 93]
(Arii et al 2006) Japan	Level III-2 diagnostic evidence P1 Q1 High quality (QUADAS = 12/14)	n=53 14 women, 39 men Mean age = 62 years (range 34–83)	Regional LN >7 mm	71% (12/17) [44, 90]	61% (22/36) [43, 77]	46% (12/26) [27, 66]	81% (22/27) [62, 94]	CT (pelvis)			
								50% (3/6) [12, 88]	51% (24/47) [36, 66]	12% (3/26) [2, 30]	89% (24/47) [36, 66]
			Lateral pelvic LN >7 mm	56% (10/18) [31, 78]	97% (34/35) [85, 100]	91% (10/11) [59, 100]	81% (34/42) [66, 91]	33% (1/3) [1, 91]	78% (39/50) [64, 85]	8% (1/12) [0, 38]	95% (39/41) [83, 99]
Population not representative of full spectrum of disease severity (patients with neoadjuvant therapy excluded)											
(Chun et al 2006) South Korea	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=24 12 women, 12 men Mean age = 59 years (range 32–79)	Regional LN of any size with an indistinct border or irregular margin or mixed signal intensity	64% (21/33) [45, 80]	92% (36/39) [79, 98]	88% (21/24) [68, 97]	75% (36/48) [60, 86]	ERUS			
								58% (19/33) [39, 75]	82% (32/39) [66, 93]	73% (19/26) [52, 88]	70% (32/46) [54, 82]

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; MSCT = multi-slice computed tomography; ERUS = endorectal ultrasound; LN = lymph node

Thirteen studies were identified that reported on the accuracy of MRI at detecting lymph node metastases (Table 16). Results are provided per patient rather than per individual node, unless otherwise specified. There was little consistency in the criteria used to determine whether or not nodes were malignant. Brown et al (2003) reported that the most accurate predictor of node status was if nodes were classed as suspicious if they had an irregular border or mixed signal intensity (Brown et al 2003). Using the size criterion, MRI resulted in frequent false positives and negatives, as microscopic metastases occurred in small nodes and some uninvolved lymph nodes were swollen (Matsuoka et al 2003b). The ability of MRI to identify metastases in small nodes was suboptimal, and Brown and colleagues suggested that clear nodal status on MRI should not be used to classify patients as being suitable for primary surgery, as microscopic metastases may be missed (Brown et al 2003). The median accuracy of MRI for predicting N stage was 69% (range 59–89%). Negative predictive value ranged from 60% to 96%.

Table 16 Accuracy of MRI at detecting lymph node involvement

Author Location	Study design Quality	Study population	Definition of metastasis	Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]
Disease spectrum representative of those receiving test in clinical setting							
(Matsuoka et al 2003a) Japan	Level II diagnostic evidence P1 Q1 High quality (QUADAS = 12/14)	n=19 17 patients with rectal carcinoma, 2 with malignant melanoma of anal canal 4 women, 15 men Mean age = 62 years	>5 mm	71% (5/7) [29, 96]	100% (12/12) [74, 100]	100% (5/5) [48, 100]	86% (12/14) [57, 98]
(Hadfield et al 1997) United Kingdom	Level III-1 diagnostic evidence P1 Q3 Insufficient information (QUADAS = 9/14)	n=38 10 women, 28 men Mean age = 69 years (range 38–89)	>5 mm	57%	88%	NR	NR
(Brown et al 2003) United Kingdom	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 11/14)	n=42 Patient characteristics not stated 437 lymph nodes harvested	>5 mm	81%	68%	NR	NR
			Mixed signal intensity or border contour irregular	77% (17/22) [55, 92]	80% (16/20) [56, 94]	81% (17/21) [58, 95]	76% (16/21) [53, 92]
			>5 mm (per node)	42% (25/60) [29, 55]	87% (194/224) [81, 91]	45% (25/55) [32, 59]	85% (194/229) [79, 89]
			>10 mm (per node)	3% (2/60) [0, 12]	100% (224/224) [98, 100]	100% (2/2) [19, 100]	79% (224/282) [74, 84]
			>3 mm (per node)	78% (47/60) [66, 88]	59% (132/224) [52, 65]	34% (47/139) 26, 42]	91% (132/145) [85, 95]
			Mixed signal intensity (per node)	48% (29/60) [35, 62]	99% (218/221) [96, 100]	91% (29/32) [75, 98]	88% (218/249) [83, 91]
			Border contour irregular (per node)	77% (46/60) [64, 87]	98% (217/221) [96, 100]	92% (46/50) [81, 98]	94% (217/231) [90, 97]
			Mixed signal intensity or border contour irregular (per node)	85% (51/60) [73, 93]	98% (216/221) [95, 99]	91% (51/56) [80, 97]	96% (216/225) [93, 98]
(Low et al 2003) United States of America	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 11/14)	n=21 patients with rectal cancer, from 48 consecutive patients 22 women, 26 men Mean age = 65 years (range 38–90)	>10 mm or cluster of three or more small nodes	89% (8/9) [52, 100]	NR	NR	NR
(Kim et al 2000) South Korea	Level III-2 diagnostic evidence P1 Q3 Insufficient information	n=217 Patient characteristics not stated	Regional LN	85%	41%	58%	60%

	(QUADAS = 9/14)						
Population not representative of full spectrum of disease severity (patients with neoadjuvant therapy excluded)							
(Ferri et al 2005) Italy	Level II diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=33 10 women, 23 men Mean age = 66±10 years	>5 mm	90% (9/10) [56, 100]	42% (8/19) [20, 67]	45% (9/20) [23, 68]	89% (8/9) [52, 100]
(Burton et al 2006a) United Kingdom	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 13/14)	n=57 who received primary surgery 34 women, 41 men Median age = 65 years (range 37–86)	Not stated	61% (14/23) [39, 80]	68% (23/34) [49, 83]	56% (14/25) [35, 76]	72% (23/32) [53, 86]
(Kim et al 2008) South Korea	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=57 24 women, 33 men Median age = 62 years (range 30–81)	Irregular border characteristics or a mixed signal intensity	50% (16/32) [32, 68]	96% (24/25) [80, 100]	94% (16/17) [71, 100]	60% (24/40) [43, 75]
(Kim et al 2006) South Korea	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 12/14)	n=35 15 women, 20 men Mean age = 57 years (range 45–74)	Regional LN of any size with an indistinct border or irregular margin or mixed signal intensity	80%	98%	86%	96%
(Kim et al 2004) South Korea	Level III-2 diagnostic evidence P2 Q1 High quality (QUADAS = 11/14)	n=62 Patient characteristics not stated	Regional LN >5 mm, or heterogeneous signal intensity or irregular border	*Non-distended* 84 *Distended* 83	*Non-distended* 55 *Distended* 56	NR	NR
(Oh et al 2005) South Korea	Level III-2 diagnostic evidence P2 Q2 High quality (QUADAS = 11/14)	17 patients who proceeded to have local recurrence 8 women, 9 men Mean age = 59 years (range 22–77) 54 patients who did not have local recurrence within 3 years 27 women, 27 men Mean age = 56 years (range not stated)	Regional LN >5 mm, or heterogeneous signal intensity or irregular border	77	35	35	77
(Koh et al 2004) United Kingdom	Level III-2 diagnostic evidence P2 Q2 Medium quality (QUADAS = 11/14)	n=12 5 women, 7 men Mean age = 62 years (range 53–75)	Central low-signal-intensity pattern after USPIO	Not stated	Not stated	67 [47, 87]	NR
(Gagliardi et al 2002) United States of America	Level III-2 diagnostic evidence P2 Q3 Insufficient information (QUADAS = 9/14)	n=26/28 10 women, 18 men Mean age = 63 years (range 26–89) 2 patients had no nodes removed	>5 mm	67 (8/12) [35, 90]	71 (10/14) [42, 92]	67 (8/12) [35, 90]	71 (10/14) [42, 92]

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; LN = lymph node; USPIO = ultrasmall particles of iron oxide; distension = rectum filled with balloon of warm water until patient indicated a sensation of fullness in the rectum; NR = not reported

Summary

What is the diagnostic accuracy of MRI staging, compared to ERUS, in patients with rectal carcinoma requiring further staging of the disease for treatment planning? What is the diagnostic accuracy of adding MRI staging to CT abdomen (pelvis), with/without PET, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

Only one study (level III-2 diagnostic evidence) compared the accuracy of MRI with another form of imaging, multi-slice computed tomography (MSCT), for assessing the most important accuracy outcome, the circumferential resection margin (CRM). This medium-quality study found that both staging methods were equivalent to each other, being poor at predicting CRM involvement. However, clinicians on the Advisory Panel suggest that the definition of CRM involvement used in this study is not clinically relevant. Six further studies reported variable MRI accuracy at predicting CRM involvement, but found consistently high negative predictive values (median 98%). When MRI was used to determine whether a CRM was threatened or involved, the false negative rate ranged from 0% to 59%. Of those who were classified by MRI as having a threatened or involved CRM result (tumour ≤1 mm from the mesorectal fascia), 0–16% did not have the result confirmed by histopathology (false positive rate).

Studies were inconsistent regarding the accuracy of MRI for predicting depth of tumour invasion (T stage). The majority of studies (n=10) reported high accuracy and low numbers of patients who were understaged, but a small number of studies (n=4) reported low to moderate accuracy of MRI. While no clear pattern was identified to explain the heterogeneity, learning curves at interpretation and different types of MRI systems may be partly responsible. Only one small study provided information on MRI accuracy for staging compared to MSCT, and this poor-quality study (level III-1 diagnostic evidence) found that MRI was equivalent to MSCT.

MRI was found to be as good as, or better than, conventional CT, multi-slice CT or ERUS at determining the metastatic status of regional lymph nodes (N stage) (level III-1 and III-2 diagnostic evidence). However, all four imaging modalities showed only moderate accuracy at predicting N stage. There was a large amount of variation between the studies in regard to the methods of defining a metastatic lymph node.

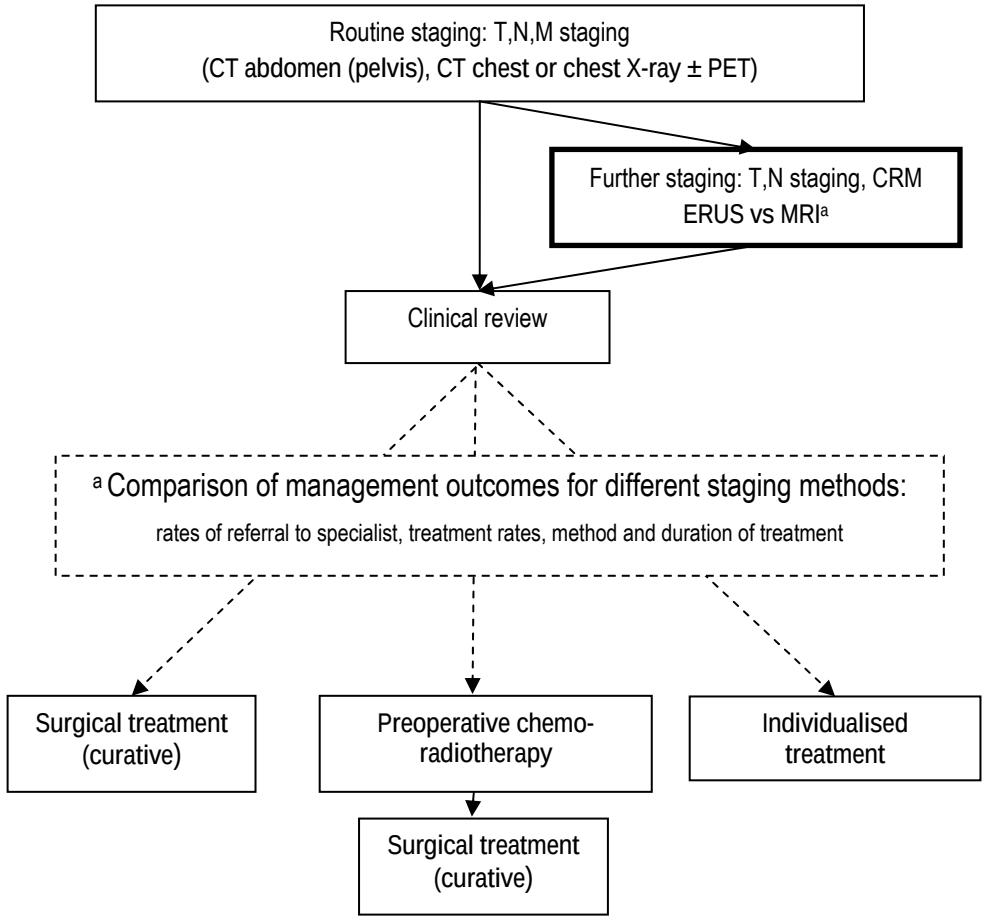
Results of staging with MRI on patient management

- Does using MRI to stage rectal carcinoma, as compared to ERUS, result in a change in clinical management of the patient?

- Does using MRI to stage rectal carcinoma in addition to CT abdomen (pelvis), with/without PET, result in a change in clinical management of the patient?

The ability of MRI to visualise the CRM should allow greater precision in determining treatment strategies. In order to assess whether there is any patient benefit from a change in management resulting from MRI staging, studies were first assessed to see if a change in management occurs (Figure 8). Inclusion criteria for studies assessing the change in management are outlined in Box 4.

Figure 8 Linked evidence approach: assessing whether staging of newly diagnosed rectal carcinoma with MRI would result in a change of clinical management of the patient compared to other staging methods



Box 4 Inclusion criteria for studies assessing the change in management as a consequence of MRI staging of rectal carcinoma

Characteristic	Criteria
Publication type	Randomised or non-randomised controlled trials (including before-and-after studies) or cohort studies or systematic reviews of these study designs; uncontrolled pre-test/post-test case series. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.
Population	Patients with rectal carcinoma
Intervention/test	1. MRI for assessment of the CRM or staging of tumour depth, and/or nodal involvement
	2. CT abdomen (pelvis) with/without PET plus MRI
Comparators	1. Endorectal ultrasound
	2. CT abdomen (pelvis) with/without PET
Outcome	Rates of referral to specialist, treatment rates, method and duration of treatment
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.

Note: CT abdomen (pelvis) may refer to multi-slice CT, which is more commonly used in Australia than conventional CT.

There were no studies that directly compared how MRI and the comparator staging techniques affected the management of patients.

One diagnostic accuracy study reported on what *potential* treatment patients would have received, based on digital rectal examination, ERUS or MRI alone. In the clinical setting, treatment decisions would be based on the results of a combination of tests, so the study does not accurately reflect what would happen in practice (Brown et al 2004). The results are presented below (Table 17). Only 54 patients (55%) were sufficiently staged by ERUS due to: failed bowel preparation (n=5), tumours not accessible by the probe due to bulk or height of tumour (n=28), or patients experiencing severe pain or declining the procedure (n=11). Brown et al (2004) reported that MRI would have selected the appropriate treatment in 88% of cases, compared to only 48% from ERUS staging. Compared to ERUS, MRI would have substantially decreased the proportion of patients (31%) receiving short-course radiotherapy prior to surgery. It would, however, have increased the proportion of patients receiving primary surgery alone (11%), as well as those receiving long-course radiotherapy prior to surgery (20%).

Table 17 Effectiveness of MRI compared to ERUS at changing patient management

Author Location	Study design Quality	Study population	Imaging	Decision-making criteria	Treatment rates
(Brown et al 2004) United Kingdom	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 11/14)	n=98 Age range = 28–89 years	MRI	Favourable = T1N0, T2N0 or T3 <1 mm N0	38 (39%) patients would have received primary surgery
				No favourable features identified = node positive, T3 >1 mm	37 (38%) patients would have received short-course radiotherapy prior to surgery
				Locally advanced = T4 or tumour ≤1 mm from mesorectal fascia	23 (23%) patients would have received long-course radiotherapy prior to surgery
			ERUS	Favourable = T1N0, T2N0 or T3 <1 mm N0	27 (28%) patients would have received primary surgery
				No favourable features identified = node positive, T3 >1 mm Tumour not assessable due to bulk or location beyond the edge of the probe	68 (69%) patients would have received short-course radiotherapy prior to surgery
				Locally advanced = T4	3 (3%) patients would have received long-course radiotherapy prior to surgery

Three further uncontrolled studies supported the suggested change in management by Brown et al (2004) regarding the use of MRI. The majority of patients in each of the studies proceeded to primary surgery alone, ie no neoadjuvant therapy (Table 18).

Table 18 Effectiveness of MRI at influencing patient management

Author Location	Study design Quality	Study population	Decision-making criteria	Treatment rates
(Burton et al 2006a) United Kingdom	Level IV interventional evidence High quality (NHS CRD = 5/6)	n=75 34 women, 41 men Median age = 65 years (range 37–86)	Good prognosis = T1–T2, T3 <5 mm, N0–N1, no EMV, potentially CRM– Bad prognosis = T3 ≥5 mm, T4, N2, EMV present, potentially CRM–	57 (76%) patients underwent primary surgery
			Bad prognosis = T4 invading adjacent organs and/or potentially CRM+	18 (24%) patients underwent preoperative chemoradiotherapy and surgery
(Poon et al 2005) United Kingdom	Level IV interventional evidence High quality (NHS CRD = 5/6)	n=49 For the 42 patients who had resection: 16 women, 26 men Mean age = 64 years	Clinical (tumour fixity, position within the rectum) and radiological features (tumour invading deeply within the mesorectal tissues, encroaching on mesorectal fascia)	36 (73%) patients underwent primary resection
				6 (12%) patients underwent preoperative chemoradiotherapy and surgery
				1 (2%) patient treated by stenting
				6 (12%) patients underwent palliative treatment
(Beets-Tan et al 2000) The Netherlands	Level IV interventional evidence High quality (NHS CRD = 5/6)	n=19 For the 26 patients in the accuracy study: Mean age = 58 years (range 29–85) 11 patients with biopsy-proven primary rectal cancer 15 patients with local recurrence of previously resected tumour	CT and MRI findings discussed with surgeons before surgery or irradiation. Staging done on all available information	12 (63%) patients underwent primary surgery
				7 (37%) patients underwent 6 weeks of preoperative radiotherapy and surgery

T = tumour stage, N = nodal stage, EMV = extramural vascular invasion; CRM = circumferential resection margin; LRT = long-course radiotherapy

Summary

Does using MRI to stage rectal carcinoma, as compared to ERUS, result in a change in clinical management of the patient?

Compared to ERUS, staging with MRI results in more patients being referred for both primary surgery and long-course radiotherapy (rather than the standard short-course radiotherapy) (level III-2 diagnostic evidence).

Does using MRI to stage rectal carcinoma in addition to CT abdomen (pelvis), with/without PET, result in a change in clinical management of the patient?

No studies compared the management after MRI staging in addition to CT abdomen (pelvis).

Is there a clinical benefit resulting from the change in management?

The treatment effectiveness of neoadjuvant radiotherapy (preoperative long-course or short-course radiotherapy) in combination with total mesorectal excision has been established through several large randomised controlled trials (Wong et al 2007). Combination treatment of long-course radiotherapy and chemotherapy provides further local control (Wong et al 2007) and neoadjuvant chemoradiation has now emerged as a standard of care (Kachnic et al 2008). However, there is a concern that patients whose tumour is not threatening the mesorectal fascia may be receiving unnecessary treatment, and that treatment by surgery alone may be sufficient for this subpopulation. The main benefit expected from staging with MRI is the ability to distinguish between those patients with a threatened or involved CRM and those with a clear CRM. This information would allow a multidisciplinary panel to decide whether patients should receive neoadjuvant chemoradiation therapy or go straight to surgery. The Advisory Panel suggested that this would result in patients with clear resection margins not receiving unnecessary neoadjuvant therapy.

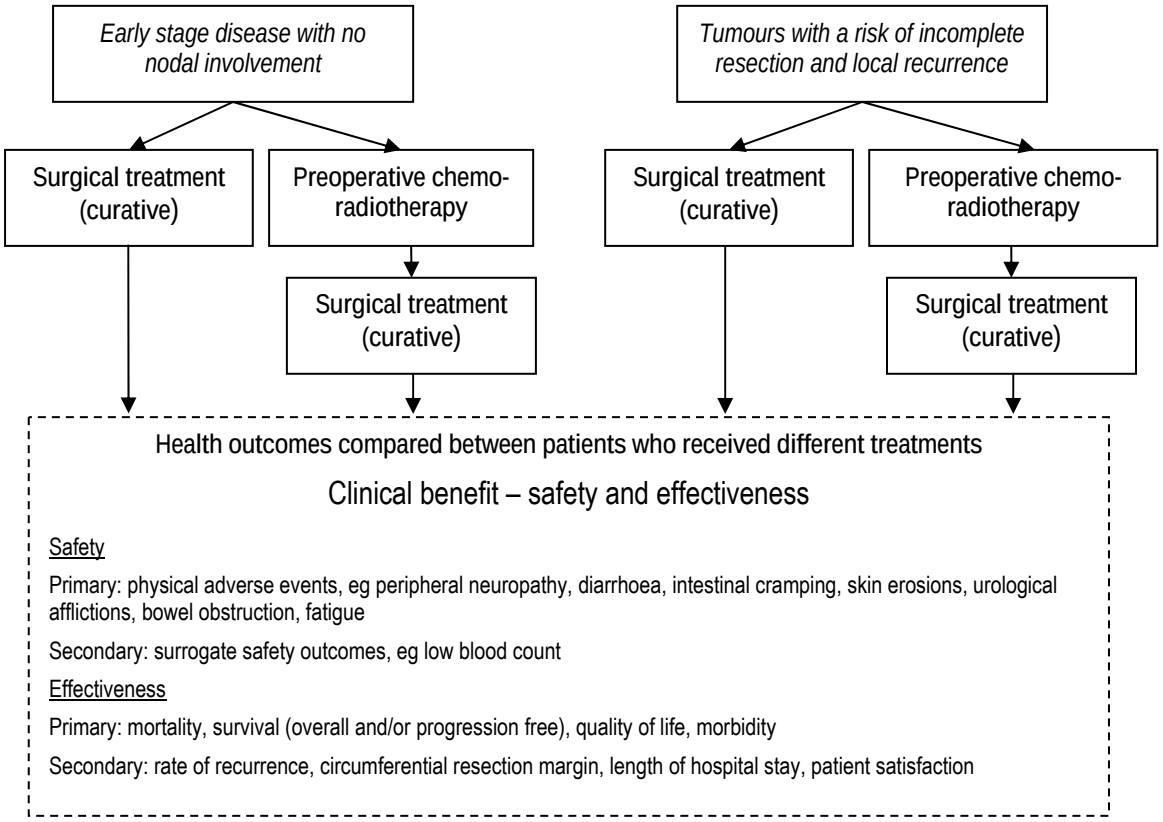
Using the linked evidence approach, the effect of MRI on patient relevant outcomes was therefore assessed by the following questions:

- Is there a clinical benefit in avoiding chemoradiation therapy in patients who do not have a threatened mesorectal fascia?

- Is there a clinical benefit in providing selective chemoradiation therapy to patients whose mesorectal fascia is threatened or involved?

Inclusion criteria for studies assessing the clinical benefit from the anticipated change in management are shown in Box 5 and illustrated in Figure 9.

Figure 9 Linked evidence approach: assessing whether staging of newly diagnosed rectal carcinoma with MRI would impact on patient health outcomes compared to other staging methods



Box 5 Inclusion criteria for studies assessing the safety and effectiveness of selective treatment on the basis of MRI staging

Characteristic	Criteria
Publication type	Randomised or non-randomised controlled trials (including before-and-after studies) or cohort studies or systematic reviews of these study designs. Uncontrolled pre-test/post-test case series, non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.
Population	Patients with rectal carcinoma: a. with a mesorectal fascia not threatened by the tumour b. with a threatened or involved mesorectal fascia
Intervention/test	Preoperative chemoradiation therapy followed by surgery
Comparators	Surgery without preoperative therapy
Outcome	1. Primary: physical adverse events, eg peripheral neuropathy, diarrhoea, intestinal cramping, skin erosions, urological affections, bowel obstruction, fatigue, morbidity Secondary: surrogate safety outcomes, eg low blood count 2. Primary: mortality, survival (overall and/or progression free), quality of life Secondary: rate of recurrence, circumferential resection margin, length of hospital stay, patient satisfaction
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.

No studies that met the inclusion criteria specified in Box 5 were identified that reported on the comparative harms to patients of preoperative chemoradiation and surgery versus primary surgery in the specific populations of interest (studies that provided separated patient results for involved versus non-involved mesorectal fascias). However, it is clear that there are risks associated with every treatment strategy, and they must be weighed up against the potential benefits from the treatment. A discussion of general safety concerns associated with different treatment strategies may be found in 'Other relevant considerations', page 76.

In the absence of evidence related to preoperative chemoradiation (neoadjuvant chemotherapy and long-course radiotherapy combined), evidence on preoperative short-course radiotherapy was accepted.

Rate of recurrence

A large high-quality multicentre randomised controlled trial was organised by the Dutch Colorectal Cancer Group to compare the benefits of adding preoperative radiotherapy to total mesorectal excision (TME) (Table 19) (Marijnen et al 2003). Patients who were randomised to primary surgery but who were found to have a positive CRM or a tumour spillage during surgery received postoperative radiotherapy. Overall, preoperative radiotherapy and TME resulted in significantly less local recurrence after 2 years (2.4%) compared to TME alone, or with TME with postoperative radiotherapy (8.2%; $p<0.0001$). Post hoc subgroup analyses were performed to determine whether there were differential effects of preoperative radiotherapy in patients, stratified by CRM. Of those patients with threatened or involved CRMs (tumours less than 1 mm from the CRM), 13% had local recurrence after 2 years. Patients with over 2 mm between the tumour and the CRM had only a 3% recurrence rate after 2 years. Preoperative radiotherapy substantially reduced the rate of recurrence in all patient groups, but the effect was not statistically significant in patients with a positive CRM (tumour less than 1 mm from the CRM).

These results suggest that among patients with a tumour within 1 mm of the CRM, 15 patients need to be treated with preoperative radiotherapy prior to TME in order to prevent one case of local recurrence within 2 years. If the definition of an involved or threatened CRM is changed to a tumour within 2 mm of the CRM, the number needed to treat (NNT) to prevent one local recurrence is 11 patients. In patients with a tumour over 2 mm from the CRM, the NNT increases to 21 patients. Therefore, while preoperative radiotherapy results in statistically significant benefits in patients with tumours greater than 1 mm from the CRM, providing neoadjuvant treatment to all patients, regardless of CRM status, would result in many people being overtreated and having consequent unnecessary adverse health effects (see page 88).

Table 19 Results of effectiveness of preoperative radiotherapy stratified by CRM status

Author Location	Study design Quality	Study population	CRM involvement	2-year local recurrence rate		
				TME ± postoperative radiotherapy (n=656)	Preoperative Radiotherapy + TME (n=662)	Difference
(Marijnen et al 2003) The Netherlands	Level II interventional evidence High quality (NHS CRD = 3/3)	n=1,318 Dutch patients 482 women, 836 men Mean age = 64 years (range 23–92)	≤1 mm	n=120 16.4%	n=107 9.3%	p=0.08 NNT=15
			1–2 mm	n=53 14.9%	n=47 0%	p=0.02 NNT=7
			>2 mm	n=483 5.8%	n=504 0.9%	p<0.0001 NNT=21
			>10 mm	3.3%	0%	p=0.0002 NNT=31

Note: raw data on local recurrences were not provided, and cannot be determined from the given information.

Is MRI effective for restaging of patients after neoadjuvant therapy?

As there was no direct evidence of the health benefits of using MRI to restage rectal carcinoma, a linked evidence approach was used. Appendix F outlines the criteria used for studies assessing the direct effectiveness of MRI for restaging (page 145).

Diagnostic accuracy (restaging)

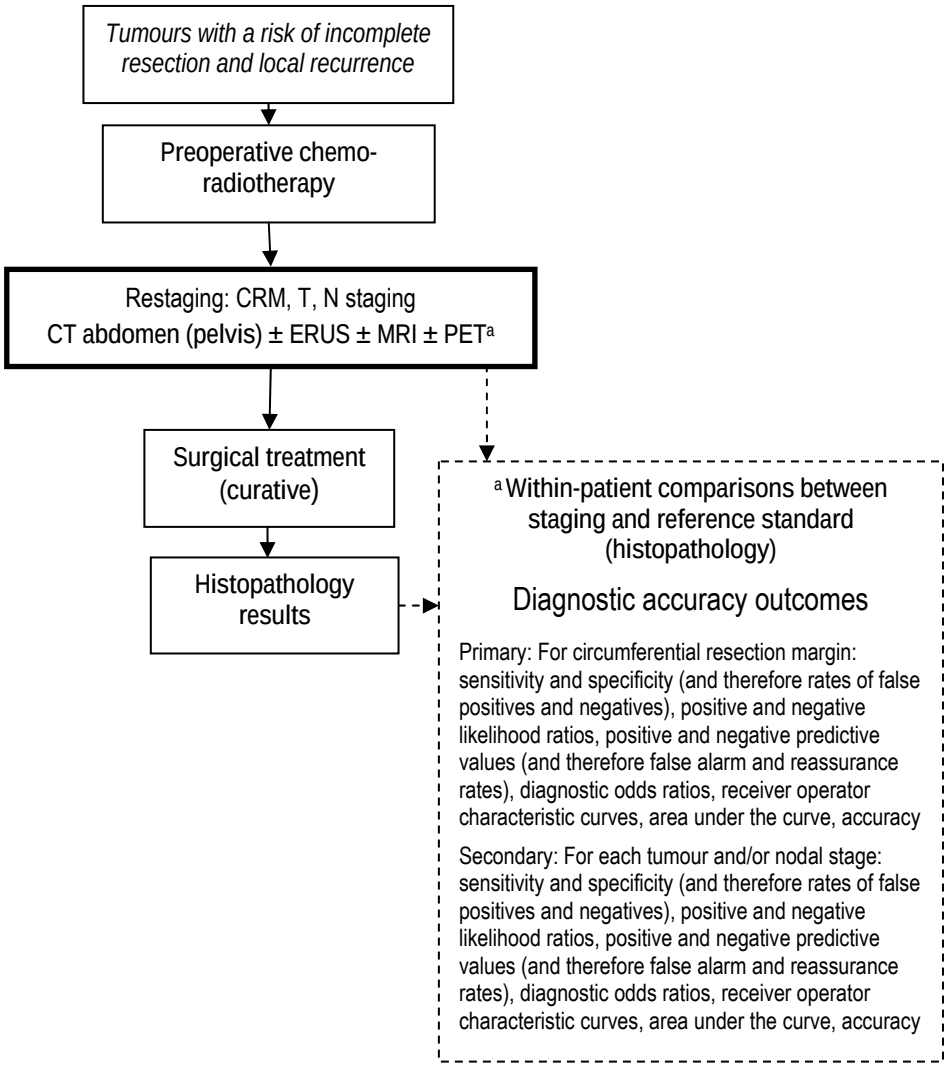
Patients with tumours abutting adjacent organs such as the prostate or sacrum may be restaged after neoadjuvant therapy, in order to determine whether the tumour has regressed. With accurate restaging, the extent of surgery may be planned prior to the initiation of the surgical procedure. Without accuracy restaging, a patient may be subjected to an unnecessarily extensive surgical procedure, such as the surgical removal of the prostate or other organ which may not have been involved. Alternatively, without accurate restaging, the patient may receive the same final procedure but there will be greater uncertainty about the resources required to undergo the surgical procedure (such as surgeons of other specialties being on stand-by in case the tumour has not regressed and more extensive surgery involving other organs is required). There would also not be the qualitative benefit of patients knowing the extensiveness of the procedure they will undergo.

The accuracy of restaging with MRI was used to infer effectiveness, with the following question:

- What is the diagnostic accuracy of MRI, with/without other imaging modalities, compared to no imaging, an alternative modality of imaging or a combination of imaging techniques, in patients with rectal carcinoma, for restaging of the disease after neoadjuvant therapy?

Figure 10 outlines the branch of the clinical pathway required to assess diagnostic accuracy outcomes for the restaging of rectal carcinoma with MRI.

Figure 10 Linked evidence approach: assessing the accuracy of MRI and comparators for restaging rectal carcinoma, compared to the reference standard



The inclusion criteria for studies assessing the diagnostic accuracy of MRI restaging of rectal carcinoma after neoadjuvant therapy are shown in Box 6.

Box 6 Inclusion criteria for studies assessing the diagnostic accuracy of MRI for restaging of rectal carcinoma

Characteristic	Criteria	
Publication type	Cross-sectional studies where patients are cross-classified on the test and comparator(s) and/or reference standard; systematic reviews of cross-sectional studies. Case-control diagnostic studies were only acceptable if cross-sectional studies were not available. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.	
Population	Patients with rectal carcinoma who have undergone neoadjunctive therapy requiring restaging of the disease for treatment planning	
Intervention/test[a]	1. MRI with/without PET, for reassessment of circumferential resection margin and/or staging of tumour depth, nodal staging	2. Other forms of imaging plus MRI
Comparators[a]	1. No imaging 1. Another form of imaging, ie endorectal ultrasound, positron emission tomography or CT abdomen (pelvis) 1. Other forms of imaging in combination	2. Other forms of imaging
Reference standard	Histopathology	
Outcome	Primary: For circumferential resection margin: sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values (and therefore false alarm and reassurance rates), diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy Secondary: For each tumour and/or nodal stage: sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values (and therefore false alarm and reassurance rates), diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Note: CT abdomen (pelvis) may refer to multi-slice CT, which is more commonly used in Australia than conventional CT.

A total of 12 studies reported on the accuracy of MRI for restaging of rectal carcinoma after neoadjuvant therapy. Only one study reported that the interpretation of the reference standard of histopathology was blinded to the stage predictions made by MRI, and was classified as level II diagnostic evidence (Torkzad et al 2007). The remaining 11 studies did not report whether histopathology interpretation was blinded, so therefore were classified as level III-2 diagnostic evidence. Three medium-quality studies provided results of the accuracy of MRI compared to the comparative imaging techniques of CT, MSCT, ERUS or PET (Barbaro et al 1995; Blomqvist et al 2002; Denecke et al 2005). A common source of bias within the included studies was that imaging with MR or the comparative techniques often occurred at least 2 weeks prior to the surgery, and it is possible that further treatment effects due to the neoadjuvant therapy may have occurred during that time.

Patients with tumours abutting adjacent organs such as the prostate or sacrum may be restaged after neoadjuvant therapy, in order to determine whether the tumour has regressed. Contrary to newly diagnosed patients, overstaging within the population who are restaged prior to surgery would be more serious than understaging, as it could result

in the unnecessary removal of organs adjacent to the rectum. Understaging may result in the need for a change in surgical technique during the procedure, but this is considered less of a problem than the unnecessary removal of organs. Overstaging is therefore reported where appropriate.

Primary outcome

Accuracy of MRI at detecting circumferential resection margin

After preoperative chemoradiotherapy, the CRM is still a useful prognostic indicator of local tumour recurrence and disease-free survival (Mawdsley et al 2005). It has been proposed that MRI may be useful for imaging patients who have undergone preoperative therapy, to assess whether a clear resection margin is likely to be achieved during surgery (Allen et al 2007).

Only two average-quality studies (level III-2 diagnostic evidence) reported on the primary outcome measure of accuracy of MRI at predicting CRM status, and neither of these compared MRI against other forms of imaging (Table 20). MRI predicted CRM status correctly in 77–82% of patients (Allen et al 2007; MERCURY Study Group 2006). The larger of the two studies reported moderate accuracy (simple κ=0.47), with 94% sensitivity, 73% specificity, 45% positive predictive value, and 98% negative predictive value (MERCURY Study Group 2006). The study found that tumours were twice as likely to be overstaged after neoadjuvant therapy than understaged when MRI was used (22% compared to 11% of patients) (MERCURY Study Group 2006).

The rate of false positives or false negatives could not be calculated from one of the included studies due to inconsistencies in the reported data (Allen et al 2007). The remaining medium-quality prospective cohort study (level III-2 diagnostic evidence) reported a false positive rate of 27% (21/79) [95%CI 17, 38] and false negative rate of 6% (1/18) [95%CI 1, 27] (MERCURY Study Group 2006).

Table 20 Accuracy of MRI at predicting CRM involvement after neoadjuvant therapy

Author Location	Study design Quality	Study population	Definition of CRM involvement	Accuracy of MRI to predict CRM involvement [95%CI]
(Allen et al 2007) United Kingdom	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 11/14)	n=22/30 (did not include patients who were staged as T2) 10 women, 20 men Mean age = 59 years (range 21–76) All patients received chemoradiotherapy	≤2 mm of mesorectal fascia	82% (18/22) [66, 98] κ not calculable % overstaged NR
(MERCURY Study Group 2006) 11 colorectal units in 4 European countries	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=97/408 (only those that received neoadjuvant therapy) Median age = 68 years (range 29–92) 161 women, 247 men Patients received long-course radiotherapy or chemo-radiotherapy	≤1 mm of mesorectal fascia	77% (75/97) [69, 86] κ = 0.47 [0.31, 0.64] 22% overstaged

NR = not reported

Secondary outcomes

Accuracy of MRI for detecting T stage

Three medium-quality level III-2 diagnostic evidence studies compared the accuracy of MRI at detecting T stage with ERUS, CT or MSCT after neoadjuvant therapy (Barbaro et al 1995; Blomqvist et al 2002; Denecke et al 2005) (Table 21). The largest of these studies compared the accuracy of MRI at restaging of patients, compared to CT or ERUS (Barbaro et al 1995). All patients received CT but MRI was only introduced partway through the study, while ERUS was only used in patients with low rectal cancer. It is unknown whether the MRI used in this study had a field strength of ≥1.5 T or whether phased array coils were used. The results provided for the first 19 patients who underwent MRI within this institution showed poorer accuracy compared to CT and ERUS. Regardless of whether the type of MRI used was consistent with the inclusion criteria for this review (≥1.5 T with phased array coils), MRI was only introduced during the study period, so experience at interpretation of the MR images for this indication would be limited and subject to a learning curve. Both MRI and CT interpretation showed a tendency towards overstaging. The authors stated that it was impossible for MRI to differentiate neoplastic from fibrous tissue, the latter a result of preoperative radiotherapy (Barbaro et al 1995).

Blomqvist et al (2002) reported (level III-2 diagnostic evidence) that MRI was more accurate than conventional CT at predicting T stage. However, due to the small sample size, the confidence intervals surrounding the accuracy rates overlapped considerably, so any conclusions on the comparative accuracy of MRI are tentative. When compared to MSCT, MRI was reported to have a very similar diagnostic accuracy, although with less overstaging (Denecke et al 2005) (level III-2 diagnostic evidence).

Blomqvist et al (2002) and two other studies also provided enough data to compare restaging after neoadjuvant therapy with not restaging, ie using the initial staging data gathered prior to the initiation of radiotherapy or chemoradiotherapy as the comparator (Baatrup et al 2006; Blomqvist et al 2002; Chen et al 2005; Torkzad et al 2007). The primary aim of neoadjuvant therapy is to down-stage tumours. If treatment effects occur as a result of neoadjuvant therapy, and the tumour is successfully down-staged, histopathology would no longer be an accuracy reference standard for pretreatment stage. Pretreatment MRI T stage corresponded to the histopathological stage in 29–69% of patients. Restaging of patients with MRI after neoadjuvant therapy resulted in slightly better accuracy overall in these studies (60–76%). Imaging prior to neoadjuvant therapy resulted in more overstaging (with reference to histopathology) than restaging after neoadjuvant therapy (13–32% versus 15–64%).

Table 21 Accuracy of MRI, CT, ERUS and MSCT at predicting T stage after neoadjuvant therapy

Author Location	Study design Quality	Study population	Accuracy to predict tumour stage	
			MRI	Comparator
MRI restaging compared against another form of restaging				
(Barbaro et al 1995) Italy	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=61 14 women, 47 men Mean age = 58 years (range not stated) Patients received radiotherapy	79% (15/19) [54, 94] weighted κ = 0.41 [–0.01, 0.82] 21% overstaged	CT 84% (51/61) [72, 92] weighted κ = 0.67 [0.49, 0.86] 15% overstaged ERUS 91% (20/22) [71, 99] weighted κ = 0.83 [0.61, 100] 5% overstaged
(Denecke et al 2005) Germany	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=23 7 women, 16 men Mean age = 53±12 years (range 21–69) Patients received chemoradiotherapy with regional hyperthermia	69% (9/13) [38, 91] weighted κ = 0.57 [0.19, 0.94] 23% overstaged	MSCT 65% (15/23) [43, 84] weighted κ = 0.47 [0.19, 0.74] 35% overstaged
(Blomqvist et al 2002) Sweden	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=15/16 6 women, 10 men Median age = 60 years (range 28–76) 15 patients received chemoradiotherapy 1 patient received chemotherapy	67% (10/15) [38, 88] weighted κ = 0.40 [0.00, 0.82] 13% overstaged	CT 46% (6/13) [19, 74] weighted κ = 0.31 [0.00, 0.62] 8% overstaged
MRI restaging compared against no restaging (staging prior to neoadjuvant therapy)				
(Torkzad et al 2007) Sweden	Level II diagnostic evidence P1 Q1 High quality (QUADAS = 13/14)	n=25 8 women, 17 men Mean age = 67 years (range 40–81) Patients received radiotherapy	72% (18/25) [50, 88] weighted κ = 0.54 [0.23, 0.84] 16% overstaged	Pretreatment MRI 64% (16/25) [43, 82] weighted κ = 0.38 [0.06, 0.69] 32% overstaged
(Chen et al 2005) Taiwan	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=50 26 women, 24 men Mean age = 64±14 years (range 39–86) Patients received chemoradiotherapy	60% (30/50) [45, 74] weighted κ = 0.40 [0.19, 0.62] 32% overstaged	Pretreatment MRI 56% (28/50) [41, 70] weighted κ = 0.35 [0.17, 0.54] 42% overstaged

Author Location	Study design Quality	Study population	Accuracy to predict tumour stage	
			MRI	Comparator
(Blomqvist et al 2002) Sweden	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=15/16 6 women, 10 men Median age = 60 years (range 28–76) 15 patients received chemoradiotherapy 1 patient received chemotherapy	67% (10/15) [38, 88] weighted κ = 0.40 [0.00, 0.82] 13% overstaged	Pretreatment MRI 69% (9/13) [39, 91] weighted κ = 0.39 [0.00, 0.81] 15% overstaged Pretreatment CT 44% (4/9) [14, 79] weighted κ = 0.00 [0.00, 0.44] 11% overstaged
(Baatrup et al 2006) Norway & Denmark	Level III-2 diagnostic evidence P1 Q3 Insufficient information (QUADAS = 9/14)	n=17/18 (one patient did not have surgery) 13 women, 5 men Median age = 65 years (range 34–82) Patients treated with chemoradiotherapy	76% (13/17) [50, 93] weighted κ = 0.70 [0.43, 0.97] 18% overstaged	Pretreatment MRI 29% (5/17) [10, 56] weighted κ = 0.22 [0.00, 0.46] 64% overstaged

CT = computed tomography; ERUS = endorectal ultrasound; MSCT = multi-slice CT

Three medium-quality studies and one poor-quality study (level III-2 diagnostic evidence) provided data on the accuracy of MRI (Table 22). MRI prediction of T stage corresponded to histopathology findings in 47–60% of patients.

Hoffman et al (2002) noted that there was no difference in the accuracy of MRI for those patients whose tumour responded to chemoradiotherapy with/without hyperthermia treatment and those whose tumour did not respond ($p>0.05$). However, understaging only occurred in patients whose tumours did not respond to treatment, whereas overstaging occurred exclusively in patients who responded partially or fully to treatment (Hoffmann et al 2002). Overstaging occurred in up to 47% of patients (Kuo et al 2005). Kuo et al (2005) reported that nearly every case of overstaging had fibrotic tissue evident at histopathology as a result of radiation therapy. Fibrosis (a non-viable tumour 'scar') is easily mistaken for a tumour using MRI.

Table 22 Accuracy of MRI at predicting T stage after neoadjuvant therapy

Author Location	Study design Quality	Study population	Accuracy of MRI to predict tumour stage [95%CI]
(Allen et al 2007) United Kingdom	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 11/14)	n=30 10 women, 20 men Mean age = 59 years (range 21–76) Patients received chemoradiotherapy	60% (18/30) [42, 78] weighted κ = 0.40 [0.12, 0.68] 23% overstaged
(Kuo et al 2005) Taiwan	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=36 14 women, 22 men Mean age = 56 years (range 28–79) Patients received chemoradiotherapy	47% (17/36) [30, 66] κ not calculable 47% overstaged
(Hoffmann et al 2002) Germany	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS =10/14)	n=35 12 women, 23 men Mean age = 57 years (range 30–73) All patients received chemoradiotherapy 23 patients (66%) also received regional hyperthermia treatment	54% (19/35) [37, 71] κ not calculable 26% overstaged
(Jonas & Bahr 2006) Germany	Level III-2 diagnostic evidence P1 Q3 Insufficient information (QUADAS = 7/14)	n=28 10 women, 18 men Age ~ 63 years (unclear if median or mean) Patients received chemoradiotherapy	57% (16/28) [37, 76] κ not calculable 38% overstaged

NR = not reported

Accuracy of MRI for detecting N stage

Seven studies reported on the accuracy of MRI at predicting regional lymph node status. Two medium-quality comparative studies (level III-2 diagnostic evidence) compared MRI against MSCT, PET and conventional CT using the reference standard of histopathology (Table 23). The larger of the two studies (n=61) reported that both MRI and conventional CT were poor at predicting nodal status. It is unclear, however, what type of MRI was used in this study. Furthermore, the interpretation of MRI would have likely been subject to a learning curve due to being recently introduced into the institution. Denecke et al (2005) assessed the accuracy of MRI, MSCT and PET after patients underwent chemoradiotherapy and regional hyperthermia. They found that MRI was more accurate than MSCT or PET, with a high sensitivity (100%) and negative predictive value (100%), but low specificity (43%). MSCT was neither as sensitive (91%) nor as specific (33%) as MRI, whereas PET had very low sensitivity (9%) but high specificity (92%).

There is a trade-off between sensitivity and specificity in diagnostic or staging tests. Based on the study that was least likely affected by a learning curve, MRI would result in many more patients receiving more intensive surgery than they require than if they were staged with PET. The downside of staging with PET, however, is that 44% of patients would be understaged. MSCT had similar results to MRI. If a patient is understaged, a change in surgical strategy may occur mid-procedure. As overstaging is thought to be a more serious problem than understaging, PET is more suitable for assessing stage after neoadjuvant therapy than MRI or MSCT, despite the lower overall accuracy.

Table 23 Accuracy of MRI, CT, MSCT and PET at predicting N stage after neoadjuvant therapy (as a dichotomous variable)

Author Location	Study design Quality	Study population	Definition of metastasis	Accuracy to predict lymph node metastases	
				MRI	Comparator
(Barbaro et al 1995) Italy	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=61 (only 19 received MRI) 14 women, 47 men Mean age = 58 years (range not stated) Patients received radiotherapy	Based on size (unclear what size)	58% (11/19) [34, 80] weighted κ = 0.39 [–0.04, 0.81] 16% overstaged	CT 64% (39/61) [51, 76] weighted κ = 0.51 [0.32, 0.70] 26% overstaged
(Denecke et al 2005) Germany	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=23 (only 13 received MRI) 7 women, 16 men Mean age = 53±12 years (range 21–69) Patients received chemoradiotherapy with regional hyperthermia	Diameter >5 mm or irregular border or mottled signal on T2-weighted images (for MRI)	69% (9/13) [39, 91] κ = 0.41 [0.02, 0.80] 31% overstaged	MSCT 61% (14/23) [38, 80] κ = 0.24 [-0.08, 0.55] 35% overstaged PET 52% (12/23) [31, 73] κ = 0.01 [-0.23, 0.25] 4% overstaged

Four medium-quality and one poor-quality study provided information on the accuracy of MRI at predicting the regional lymph node status of patients who have undergone neoadjuvant treatment (Table 24). Accuracy ranged from 54% to 70%.

Hoffman et al (2002) reported that there was no difference in accuracy between those patients who responded to therapy and those who did not ($p>0.05$) (Hoffmann et al 2002). As with T staging, there was a tendency towards overstaging of nodal status in those who responded to treatment, and towards understaging in those who did not respond.

Table 24 Accuracy of MRI at predicting N stage after neoadjuvant therapy

Author Location	Study design Quality	Study population	Definition of metastasis	Accuracy of MRI to predict N stage [95%CI]
(Allen et al 2007) United Kingdom	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 11/14)	n=30 10 women, 20 men Mean age = 59 years (range 21–76) All patients received chemoradiotherapy	>5 mm in diameter	70% (21/30) [54, 86] κ not calculable % overstaged NR
(Chen et al 2005) Taiwan	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=50 26 women, 24 men Mean age = 64±14 years (range 39–86) Patients received chemoradiotherapy	>5 mm in diameter	68% (34/50) [53, 80] κ = 0.29 [0.03, 0.55] 24% overstaged
(Kuo et al 2005) Taiwan	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=36 14 women, 22 men Mean age = 56 years (range 28–79) Patients received chemoradiotherapy	Not stated	64% (23/36) [46, 79] κ not calculable 28% overstaged
(Hoffmann et al 2002) Germany	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=35 12 women, 23 men Mean age = 57 years (range 30–73) All patients received chemoradiotherapy 23 patients (66%) also received regional hyperthermia treatment	Round shaped and sharply delineated	54% (19/35) [37, 71] κ not calculable 17% overstaged
(Jonas & Bahr 2006) Germany	Level III-2 diagnostic evidence P1 Q3 Insufficient information (QUADAS = 7/14)	n=28 10 women, 18 men Age ~ 63 years (unclear if median or mean) Patients received chemoradiotherapy	Not stated	68% (19/28) [48, 84] κ not calculable 18% overstaged

NR = not reported

Summary

What is the diagnostic accuracy of MRI, with/without other imaging modalities, compared to no imaging, an alternative modality of imaging or a combination of imaging techniques, in patients with rectal carcinoma, for restaging of the disease after neoadjuvant therapy?

Two studies (level III-2 diagnostic evidence) reported that MRI was moderately accurate (77–82%), relative to the reference standard, at predicting CRM involvement after neoadjuvant therapy. In the single study that reported on the outcome, overstaging of patients was common (up to 22%). Of those whose tumour no longer threatened or involved the CRM, 27% were falsely reported by MRI as still having a positive CRM after neoadjuvant therapy. There were 6% of patients who were reassured as not having an involved or threatened CRM but were misclassified, and were CRM positive.

Limited data suggest that MRI may be more accurate than CT at predicting T stage and regional lymph node status, and as accurate as MSCT. Comparisons against ERUS were only made in a setting where a learning curve would be expected for the interpretation of MRI but not for the comparative techniques. The majority of studies reported high levels of overstaging of T stage and lymph node status subsequent to neoadjuvant therapy, particularly for those patients whose tumours were down-staged from the neoadjuvant therapy. In contrast, patients who did not respond to neoadjuvant therapy were frequently understaged for both T stage and N stage. This was consistent between imaging modalities. MRI was more accurate at detecting regional lymph node metastases than PET but resulted in far more overstaging (31% versus 4% of patients).

Does restaging with MRI change patient management?

- Does restaging with MRI, with/without other imaging modalities result in a change in clinical management of the patient compared to no restaging, or restaging with an alternative modality of imaging or a combination of imaging techniques?

Restaging of rectal carcinoma after neoadjuvant therapy is only worthwhile if the surgeon is likely to trust the results of the restaging, and consequently to adapt their surgical technique. Box 9 (Appendix F) outlines the criteria for including studies that assessed whether MRI influences treatment methods differently to other forms of restaging imaging. No studies were identified that met the inclusion criteria outlined in Box 9.

Is MRI effective for diagnosis/staging of patients with suspected/diagnosed recurrence of rectal carcinoma?

As there was no direct evidence of the health benefits of using MRI to stage or diagnose recurrent rectal carcinoma, a linked evidence approach was used. Appendix F outlines the criteria used for studies that assessed the direct effectiveness of MRI for diagnosis/staging of recurrence of rectal carcinoma (page 145).

Linked evidence

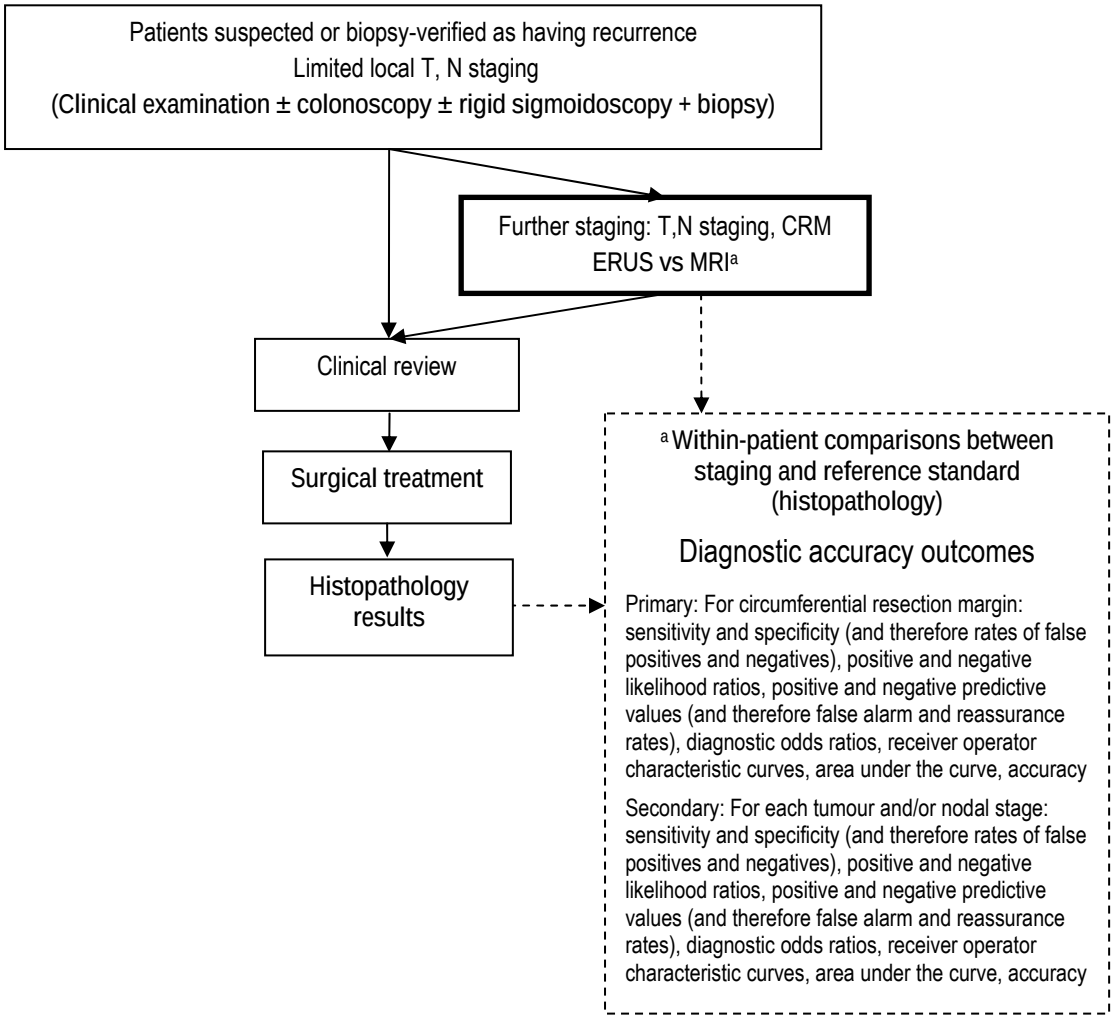
Diagnostic accuracy (diagnosis/staging)

- What is the diagnostic accuracy of MRI diagnosis/staging, compared to ERUS, in patients with suspected or confirmed recurrent rectal carcinoma?

- What is the diagnostic accuracy of adding MRI staging/diagnosis to CT abdomen (pelvis), with/without PET, relative to this imaging combination alone, in patients with suspected or confirmed recurrent rectal carcinoma?

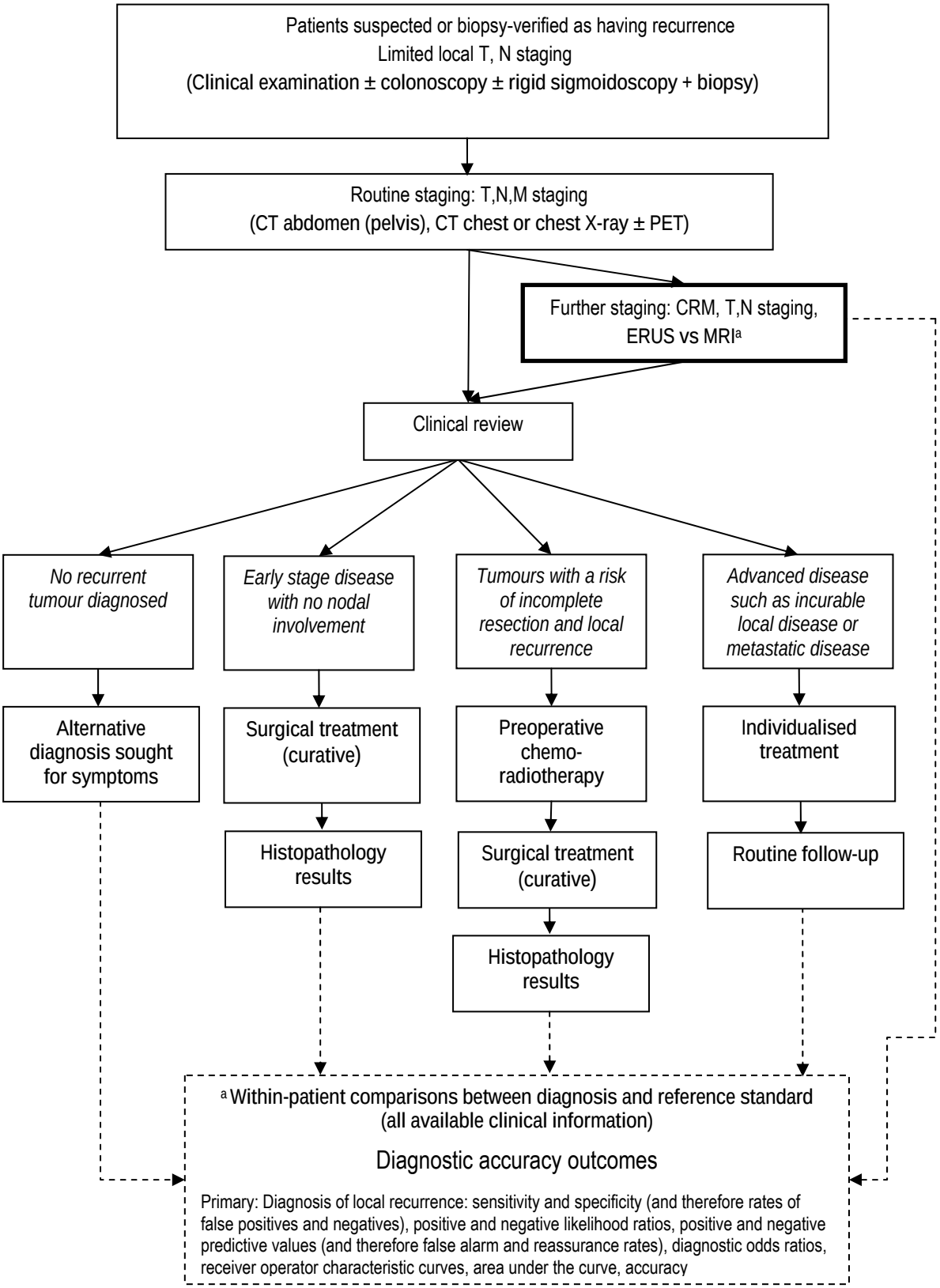
Figure 11 outlines the form of evidence required to assess the diagnostic accuracy of MRI for staging of suspected or recurrent rectal carcinoma.

Figure 11 Linked evidence approach: assessing the accuracy of MRI for staging of suspected recurrent rectal carcinoma



However, no evidence was identified on the effectiveness of using MRI to *stage* recurrent rectal carcinoma. While not strictly meeting the inclusion criteria due to the reference standards (all available clinical information), Figure 12 outlines the types of studies that reported on the diagnostic accuracy of using MRI to *diagnose* recurrent rectal carcinoma.

Figure 12 Linked evidence approach: assessing MRI accuracy for diagnosing recurrent rectal carcinoma



The criteria for including studies assessing the diagnostic accuracy of MRI for identification or staging of recurrent rectal carcinoma are shown in Box 7. Studies were excluded if MRI was used entirely for surveillance (follow-up of patients without clinical suspicion of local recurrence) as they were not the population of interest.

Box 7 Inclusion criteria for studies assessing the diagnostic accuracy of MRI for diagnosis/staging of recurrent rectal carcinoma

Characteristic	Criteria	
Publication type	Cross-sectional studies where patients are cross-classified on the test and comparator(s) and/or reference standard; systematic reviews of cross-sectional studies. Case-control diagnostic studies were only acceptable if cross-sectional studies were not available. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.	
Population	Patients suspected of having or diagnosed with recurrent rectal carcinoma requiring diagnosis/staging for further treatment planning	
Intervention/test[a]	1. MRI for assessment of the circumferential resection margin or staging of tumour depth, and/or nodal involvement	2. CT abdomen (pelvis) with/without PET plus MRI
Comparators[a]	1. Endorectal ultrasound	2. CT abdomen (pelvis) with/without PET
Reference standard	Histopathology	
Outcome	Primary: For circumferential resection margin: sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values (and therefore false alarm and reassurance rates), diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy Secondary: For each tumour and/or nodal stage: sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values (and therefore false alarm and reassurance rates), diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Note: CT abdomen (pelvis) may refer to multi-slice CT, which is more commonly used in Australia than conventional CT.

No studies reported on the accuracy of MRI when used to *stage* recurrent rectal carcinoma. Three studies reported on the use of MRI to distinguish between local recurrence and benign postoperative changes (fibrosis) (ie diagnosis). Two of the three studies included patients undergoing routine follow-up, those who were suspected as having local recurrence and those diagnosed with local recurrence (Blomqvist et al 1998, 2000). While these studies were not ideal, as MRI is not being proposed as a means of standard follow-up, they were included due to the paucity of evidence available. The remaining study was an average-quality study that only included the population of interest, ie patients suspected of having recurrent rectal carcinoma (Torricelli et al 2003).

Only one of the included studies compared MRI with CT (Table 25). This small study was deemed poor quality as the reference standard varied between patients; it was not always assessed independently from MRI results (ie in one patient the tumour was said to be obvious on MRI, so did not need alternative imaging or biopsy to confirm it); and the time period between MRI and the reference standard was not always short enough to be reasonably sure that the recurrence status did not change between the two tests. MRI imaging before and after oral intake of superparamagnetic particles was found to be as specific as contrast-enhanced CT, and slightly more sensitive at diagnosing recurrent

rectal carcinoma, although both techniques had only moderate accuracy overall (75% for MRI versus 69% for CT). Blomqvist et al (2000) found that MRI resulted in the same high number of false diagnoses of local recurrence as CT, but fewer false negatives (Table 25). There were twice as many false negatives with CT relative to MRI. However, the sample size of this study was too small to draw any firm conclusions on whether there are statistically or clinically significant differences between MRI and CT.

Two low- to medium-quality studies reported that MRI had high sensitivity and specificity at diagnosing locally recurrent carcinoma (Table 26). Against a variable reference standard, MRI was reported to accurately diagnose patients correctly in 83–94% of cases. These studies found that the rate of false positives varied between 0% and 17% of those who did not have local recurrence (Table 26). There were slightly more false negatives than false positives reported for MRI, with the false negative rate ranging from 7% to 20% depending on the criteria used to define a local recurrence.

Table 25 Accuracy of MRI and CT for diagnosing locally recurrent rectal carcinoma

Author Location	Study design Quality	Study population	Diagnosis of recurrence	MRI						CT					
				Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]	FP rate [95%CI]	FN rate [95%CI]	Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]	FP rate [95%CI]	FN rate [95%CI]
(Blomqvist et al 2000) Sweden	Level III-2 diagnostic evidence P2 Q3 Poor reference standard, insufficient information (QUADAS = 8/14)	n=16/17 6 women, 11 men Median age = 60 years (range 40–76) 13 patients had previous low anterior resection 4 patients had previous abdominoperineal rectum resection	Unenhanced MRI – criteria NR	91% (10/11) [59, 100]	40% (2/5) [5, 85]	77% (10/13) [46, 95]	67% (2/3) [9, 99]	60% (3/5) [15, 95]	9% (1/11) [0, 41]	82% (9/11) [48, 98]	40% (2/5) [5, 85]	75% (9/12) [43, 95]	50% (2/4) [7, 93]	60% (3/5) [15, 95]	18% (2/11) [2, 52]
			Contrast-enhanced MRI – criteria NR	91% (10/11) [59, 100]	40% (2/5) [5, 85]	77% (10/13) [46, 95]	67% (2/3) [9, 99]	60% (3/5) [15, 95]	9% (1/11) [0, 41]						

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; NR = not reported

Table 26 Accuracy of MRI at diagnosing local recurrence

Author Location	Study design Quality	Study population	Diagnosis of recurrence	Sn [95%CI]	Sp [95%CI]	PPV [95%CI]	NPV [95%CI]	FP rate [95%CI]	FN rate [95%CI]
(Torricelli et al 2003) Italy	Level III-2 diagnostic evidence P1 Q2 Medium quality (QUADAS = 10/14)	n=36 19 women, 17 men Age range = 41–79 years All patients had abdominal-perineal amputation 2 months – 7 years before start of study 11 patients had received adjuvant postoperative radiotherapy to the pelvis 6–36 months before MRI	Morphology and signal intensity on unenhanced MRI – presence of nodular lesions or asymmetric mass with irregular borders and high signal intensity on T2-weighted sequences, or lesions clearly infiltrating the sacrum and coccyx	80% (12/15) [52, 96]	86% (18/21) [64, 97]	80% (12/15) [52, 96]	86% (18/21) [64, 97]	17% (3/18) [4, 41]	20% (3/15) [4, 48]
			Dynamic contrast-enhanced MRI – lesions showing an increase of 50% or greater in signal intensity over the baseline value at the end of the first post-contrast sequence	87% (13/15) [60, 98]	100% (21/21) [84, 100]	100% (13/13) [75, 100]	91% (21/23) [72, 99]	0% (0/21) [0, 16]	13% (2/15) [2, 40]
			Dynamic contrast-enhanced MRI – lesions showing an increase of 40% or greater in signal intensity over the baseline value at the end of the first post-contrast sequence	93% (14/15) [68, 100]	90% (19/21) [70, 99]	93% (14/16) [62, 98]	95% (19/20) [75, 100]	10% (2/21) [2, 30]	7% (1/15) [0, 32]
(Blomqvist et al 1998) Sweden	Level III-2 diagnostic evidence P2 Q3 Poor reference standard, insufficient information (QUADAS = 7/14)	n=30/31 11 women, 20 men Median age = 66 years (range 39–84) 14 patients had previous low anterior resection 16 patients had previous abdomino-perineal excision 14 patients had received irradiation	Non-dynamic contrast-enhanced MRI – criteria NR	88% (15/17) [64, 99]	100% (13/13) [75, 100]	100% (15/15) [78, 100]	87% (13/15) [60, 98]	0% (0/13) [0, 25]	12% (2/17) [1, 36]

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; NR = not reported

Summary

What is the diagnostic accuracy of MRI for diagnosis/staging, compared to ERUS, in patients with suspected or confirmed recurrent rectal carcinoma? What is the diagnostic accuracy of adding MRI for staging/diagnosis to CT abdomen (pelvis), with/without PET, relative to this imaging combination alone, in patients with suspected or confirmed recurrent rectal carcinoma?

Three studies reported on the accuracy of MRI for diagnosing recurrent rectal carcinoma. In one very small study MRI was found to be slightly more accurate than conventional CT. Despite the duration between the MRI and the reference standard (potentially allowing recurrence to develop in the interim), the use of MRI was considered to be moderately to highly accurate at diagnosing carcinoma recurrence (75–94%).

Of those who did not have a local recurrence, the rate of false positive diagnoses from MRI ranged from 0% to 60%. A comparatively lower rate of patients (7–20%) who had local tumour recurrence were misclassified by MRI as not having recurrent rectal carcinoma (false negative rate).

Does diagnosis/staging with MRI change patient management?

No studies were identified that described clinician management of patients after using MRI to diagnose or stage recurrent rectal carcinoma. Appendix F outlines the criteria that were applied to studies to determine their suitability for answering this research question.

Is there a clinical benefit resulting from the change in management?

No evidence was identified assessing the benefit of *selective* neoadjuvant therapy in patients with recurrent rectal carcinoma (see Appendix F).

Economic considerations

Background

The purpose of the economic evaluation is to inform the decision made by MSAC on the additional costs and additional gains (health or other socially relevant outcomes) of the proposed service over the comparator when used in the Australian healthcare system. This is to ensure that society's ultimately scarce resources are allocated to those activities from which it will get the most value. That is, it seeks to enhance economic efficiency.

A cost-effectiveness analysis is only undertaken if there is evidence that the procedure under consideration is more effective than the designated comparator(s). Otherwise, an estimate of the financial incidence of the new procedure is all that is required by MSAC.

Existing literature on cost-effectiveness

The literature was searched for evidence on the cost-effectiveness of MRI as a staging technique for patients with rectal carcinoma. There was no evidence available assessing the cost-effectiveness of MRI for patients who are restaged after neoadjuvant therapy or diagnosed/staged after tumour recurrence. For patients with newly diagnosed rectal carcinoma, one paper was identified but was not applicable to the Australian healthcare system, as it did not incorporate the results of MSCT into treatment decisions. Further details on the cost-effectiveness research questions, the inclusion criteria and the included study are provided in Appendix G.

Evidence of effectiveness and methods

For staging of newly diagnosed patients

There is evidence that MRI is an accurate staging method and is particularly useful at imaging the CRM, which allows preoperative treatments to be targeted to those patients with a high risk of local recurrence. However, as there is no evidence that MRI plus MSCT is more accurate than MSCT alone, or MSCT plus ERUS, a cost-effectiveness analysis has not been undertaken.

One small study suggested that MRI is as accurate as the currently funded comparator, MSCT; however, the results may not be clinically relevant, given the atypical definition of an involved CRM that was used in this study. The accuracy of MRI for visualising the CRM (compared with postoperative histopathology) has become established (Taylor et al 2007). Conversely, the accuracy of MSCT at determining CRM involvement, as defined by a tumour within 1 mm of the CRM, is only in the preliminary stages of investigation.[2] MRI imaging of the CRM is trusted more by physicians than MSCT imaging of the CRM, and it is the opinion of the Advisory Panel that MRI has superior contrast

[2] One peer-reviewed article (Sinha et al 2006) and two conference abstracts (Woberink et al 2005a, 2005b) were located in a non-systematic search of the literature on MSCT compared to histopathology, which determined an involved CRM as a tumour within 1 mm of the mesorectal fascia.

resolution. The addition of MRI to MSCT is therefore expected to change patient management in such a way as to benefit patients. Thus, an analysis of the expenditures associated with MRI relative to the comparators has been provided below.

If MRI were funded for staging of rectal carcinoma, it is likely it would reduce the use of neoadjuvant therapies (reducing the burden on the Pharmaceutical Benefits Schedule). Based on current evidence, it is unknown whether MSCT may also change patient management in this manner in the future. However, potential cost offsets due to a reduction in neoadjuvant therapy use are expected to result from any imaging modality (eg MRI) that accurately identifies the CRM rather than T and N stages.

The assumption is that all patients would receive MSCT for the assessment of distant metastases. For the purposes of the financial incidence analysis, the staging of newly diagnosed patients incorporates the following:

- MRI as an addition to MSCT
- MRI as an addition to MSCT and alternative to ERUS.

The cost components of MSCT are assumed to be the same in both arms of the comparisons, so are not considered in the costing for this indication.

For restaging of patients after neoadjuvant therapy

Neither direct evidence nor linked evidence was available reporting on the health outcomes resulting from restaging of patients with MRI prior to surgery. A cost-effectiveness comparison is therefore unable to be performed, and a simple costing has been presented. The cost implications of MRI for restaging of rectal carcinomas incorporate the following:

- MRI as an addition to MSCT

There is uncertainty about the usage of PET for this indication given that the MSAC decision regarding funding is occurring concurrently with this application. The use of PET has therefore not been taken into consideration for this costing.

For the diagnosis/staging of patients with suspected/diagnosed recurrence of rectal carcinoma

Due to a lack of published research in this area, no evidence of patient benefit resulting from diagnosis or staging of recurrent rectal carcinoma by MRI was identified. A cost-effectiveness comparison is therefore unable to be performed, and a simple costing has been presented. MRI may be seen as an alternative, or an addition, to other forms of imaging for the restaging of patients. The following comparisons are examined:

- MRI as an addition to existing imaging (ie MSCT or ERUS)
- MRI as a replacement for ERUS.

In the first comparison MRI is an additional imaging test, so the costs associated with existing forms of imaging would be common to both arms of the comparison and therefore do not need to be examined.

There is uncertainty regarding the usage of PET for this indication given that the MSAC decision regarding funding is occurring concurrently with this application. The use of PET has therefore not been taken into consideration for this costing.

Unit costs

The cost data will cover all non-trivial health system resources directly used in the staging of rectal carcinoma. Indirect costs, also known as productivity costs, are not considered. All cost data are converted to the single year 2007, and expressed in Australian dollars. The costing exercise conducted is not intended for fee scheduling purposes, and is not a recommendation for funding at these levels.

Table 27 outlines the MBS fees and rebates for the comparative staging modality of ERUS. The staging of cervical cancer with MRI is proposed as a similar procedure, in regards to the time required and complexity, as the staging of rectal carcinoma with MRI, and thus has been used as the basis for estimating these latter MBS costs.

The costs of MSCT have not been considered, as it is expected that MRI would not alter the usage of this mode of staging.

Table 27 MBS cost components for staging of rectal carcinoma

Resource item	MBS fee	MBS rebate	Percentage of patients	Source of data
MRI	$403.20	$342.75	100%	Based on MBS item 63470 for staging of diagnosed cervical cancer
ERUS	$98.00	$83.30	47% who undergo ERUS (female)	MBS item 55731 (female) (% based on gender distribution of colorectal cancer (AIHW 2005))
	$111.00	$94.65	53% who undergo ERUS (male)	MBS item 55044 (male) (% based on gender distribution of colorectal cancer (AIHW 2005))

MRI = magnetic resonance imaging; ERUS = endorectal ultrasound

MBS item 63470 MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where: (a) the patient is referred by a specialist or by a consultant physician and (b) the request for scan identifies that (i) a histological diagnosis of carcinoma of the cervix has been made and (ii) the patient has been diagnosed with cervical cancer at FIGO stage 1B or greater Scan of: - Pelvis for the staging of histologically diagnosed cervical cancer at FIGO stages 1B or greater (R) (Contrast) (Anaes.) Fee: $403.20 Benefit: 75% = $302.40 85% = $342.75

MBS item 55731 PELVIS, FEMALE, ultrasound scan of, by any or all approaches, where: (a) the patient is referred by a medical practitioner; and (b) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies; and (c) the referring practitioner is not a member of a group of practitioners of which the providing practitioner is a member; and (d) the service is not performed with item 55036 or 55038 on the same patient within 24 hours (R) Fee: $98.00 Benefit: 75% = $73.50 85% = $83.30

MBS item 55044 PELVIS, male, ultrasound scan of, by any or all approaches, but not being a service associated with the service described in item 55600 or item 55603, where: (a)the patient is referred by a medical practitioner for ultrasonic examination not being a service associated with a service to which an item in Subgroups 2 or 3 of this Group applies; (b) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member; and (c)the service is not performed with item 55036 or 55038 on the same patient within 24 hours (R) Fee: $111.30 Benefit: 75% = $83.50 85% = $94.65

In contrast to other public outpatient procedures, which are required to be funded by the states and territories and provided to the patient without charge at the point of care (Meikle 2005), the current arrangement through the Australian Health Care Agreements allows Medicare benefits to be paid for private *and public* outpatient MRI procedures (provided the imaging is performed at a Medicare-eligible unit). Both private and public hospitals may have Medicare-eligible MRI units, and there are a range of patient charging practices in place for such units. Units granted Medicare eligibility under rules 36(c) and (d) of the Diagnostic Imaging Services Table (DIST) Regulations are required to bulk-bill for all Medicare-eligible services. If imaging is performed in a non–Medicare-eligible unit,

a private patient will be required to pay the full cost of the MRI (assumed to be equivalent to the cost of the MBS rebate plus the gap). If a patient receives MRI in a non–Medicare-eligible unit as a public outpatient, the costs of imaging will be met by the states and territories (under the Australian Health Care Agreements). The majority of patients (55%[3]) are expected to be eligible for bulk-billing, where the MBS rebate is accepted as full payment for radiology services. The remaining 45% of patients are expected to pay a gap payment (Table 28).

Table 28 Approximate gap between MBS rebate and cost of imaging

Resource item	Gap	Source of data
MRI	$140.00	Advice from Radiology SA
ERUS (female)	$82.00	Expert opinion of the Advisory Panel
ERUS (male)	$69.00	Expert opinion of the Advisory Panel

MRI = magnetic resonance imaging; ERUS = endorectal ultrasound

If an involved or threatened mesorectal fascia (CRM+) is used to define high-risk patients (rather than T3/T4 or N1), it is likely that there would be a reduction in the use of neoadjuvant therapy. If it is decided, contrary to the current very limited evidence available, that MSCT is unable to accurately image the mesorectal fascia, whereas MRI can, then the reduction in neoadjuvant therapy may offset the cost of additional imaging with MRI.

However, if these cost offsets are incorporated, it must be acknowledged that, concomitant with a decrease in neoadjuvant therapy, there may be an increase in the rate of adjuvant therapy used (if patients are staged incorrectly as having an unthreatened CRM) and an increase in local recurrence. Conversely, patients who would otherwise have received neoadjuvant therapy may avoid toxicities that would have occurred as a result of treatment. These downstream costs and cost savings have not been incorporated into the financial incidence analysis as their extent is presently unknown.

Outlined in Table 29 are the relevant professional fees listed on the Medicare Benefits Schedule (MBS). Table 31 outlines the cost of fluorouracil and Table 32 the costs of implanted devices and accommodation for chemotherapy. A summary of these costs is presented in Table 33.

[3] Between July 2007 and March 2008, 57% of patients aged ≥65 years and 51.4% of patients aged 0–64 years were bulk-billed for MBS MRI services (pers. comm., Department of Health and Ageing, 2008). Based on data from the Australian Bureau of Statistics (2000, 2006), it is estimated that 67.5% of patients with rectal carcinoma are aged over 65 years. On the assumption that the proportion of bulk-billing for MRI would be consistent for patients with rectal carcinoma, 55.2% ((67.5% x 57%) + (32.5% x 51.4%)) are therefore estimated to be bulk-billed.

Table 29 MBS cost components for neoadjuvant therapy

Resource item	MBS fee	MBS rebate	Source of data (Table 30)	No. of units used[a]	Total MBS fees	Total MBS rebates
Chemotherapy						
Initial consultation	$136.30	$102.25	MBS item 110	1 initial consultation	$136.30	$102.25
Subsequent consultations	$68.20	$51.15	MBS item 116	2 further consultations	$136.40	$102.30
TIVAS or PICC access	$47.40	$35.55	MBS item 13945	1 per week for 6 weeks	$284.40	$213.30
Administration of chemotherapy	$58.75	$44.10	MBS item 13915	1 per week for 6 weeks	$352.50	$264.60
				Total for chemotherapy	$909.60	$682.45
Long-course radiation						
CT planning	$281.40	$239.20	MBS item 15503	1	$281.40	$239.20
CT dosimetry	$306.95	$260.95	MBS item 15521	1	$306.95	$260.95
First field radiation	$53.90	$45.85	MBS item 15254	1 per day for 30 days	$1,617.00	$1,375.50
Additional fields	$34.25	$29.10	MBS item 15269	2 per day for 30 days	$2,055.00	$1,746.00
Check imaging	$60.90	$51.80	MBS item 57715	6 (approximately 1 per week)	$365.40	$310.80
				Total for long-course radiation	$4,625.75	$3,932.45
				Total for chemotherapy and long-course radiation	$5,535.35	$4,614.90
Short-course radiation						
CT planning	$281.40	$239.20	MBS item 15503	1	$281.40	$239.20
CT dosimetry	$306.95	$260.95	MBS item 15521	1	$306.95	$260.95
First field radiation	$53.90	$45.85	MBS item 15254	1 per day for 5 days	$269.50	$229.25
Additional fields	$34.25	$29.10	MBS item 15269	2 per day for 5 days	$342.50	$291.00
Check imaging	$60.90	$51.80	MBS item 57715	1 per day for 5 days	$304.50	$259.00
				Total for short-course radiation	$1,504.85	$1,279.40

[a] Based on expert opinion of the Advisory Panel

TIVAS = totally implantable venous access system; PICC = peripherally inserted central catheters, MBS = Medicare Benefits Schedule

Table 30 MBS items related to neoadjuvant therapy

MBS item	Description
Chemotherapy	
MBS item 110	CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY), REFERRED CONSULTATION - SURGERY OR HOSPITAL (professional attendance at consulting rooms or hospital by a consultant physician in the practice of his or her specialty (other than in psychiatry) where the patient is referred to him or her by a medical practitioner) - INITIAL attendance in a single course of treatment Fee: $136.30 Benefit: 75% = $102.25 85% = $115.90
MBS item 116	Each attendance (other than a service to which item 119 applies) SUBSEQUENT to the first in a single course of treatment Fee: $68.20 Benefit: 75% = $51.15 85% = $58.00
MBS item 13945	LONG-TERM IMPLANTED DRUG DELIVERY DEVICE FOR CYTOTOXIC CHEMOTHERAPY, accessing of Fee: $47.40 Benefit: 75% = $35.55 85% = $40.30
MBS item 13915	CYTOTOXIC CHEMOTHERAPY, administration of, either by intravenous push technique (directly into a vein, or a butterfly needle, or the side-arm of an infusion) or by intravenous infusion of not more than 1 hours duration - payable once only on the same day, not being a service associated with photodynamic therapy with verteporfin or for the administration of drugs used immediately prior to, or with microwave (UHF radiowave) cancer therapy alone Fee: $58.75 Benefit: 75% = $44.10 85% = $49.95
Radiotherapy	
MBS item 15503	RADIATION FIELD SETTING using a simulator or isocentric xray or megavoltage machine or CT of a single area, where views in more than 1 plane are required for treatment by multiple fields, or of 2 areas (not being a service associated with a service to which item 15512 applies) Fee: $281.40 Benefit: 75% = $211.05 85% = $239.20
MBS item 15521	RADIATION DOSIMETRY by a CT interfacing planning computer for megavoltage or teletherapy radiotherapy to a single area by 3 or more fields, or by a single field or parallel opposed fields to 2 areas, or where wedges are used Fee: $306.95 Benefit: 75% = $230.25 85% = $260.95
MBS item 15254	RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site for diseases and conditions not covered by items 15245, 15248 or 15251 Fee: $53.90 Benefit: 75% = $40.45 85% = $45.85
MBS item 15269	RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 2 or more fields up to a maximum of 5 additional fields (rotational therapy being 3 fields) - treatment delivered to primary site for diseases and conditions not covered by items 15260, 15263 or 15266 The fee for item 15254 plus for each field in excess of 1, an amount of $34.25
MBS item 57715	RADIOGRAPHIC EXAMINATION OF PELVIC GIRDLE (R) Fee: $60.90 Benefit: 75% = $45.70 85% = $51.80

Source: http://www9.health.gov.au/mbs/search.cfm (accessed 21 February 2008)

Table 31 PBS cost components of chemotherapy (pharmaceuticals)

Resource item	Dispensed price for maximum quantity	Non-concession fee	Concession fee	No. of units used[a]	Cost per person		
					Total	Non-concession	Concession
Fluorouracil (5-FU) Injection 500 mg in 10 mL	$49.94	$31.30	$5.00	Once a week for 6 weeks	$299.64	$187.80	$30.00

[a] Based on 200 mL/mg/m^2/day; average person ≈ 1.8 m^2, therefore approx 360 mL of 5-FU/day, once a week for 6 weeks

Table 32 Devices and accommodation costs for chemotherapy

Resource item	Cost per item	Source of data	No. of units used[a]	Cost per person
PICC or TIVAS device	$200.00	Expert opinion of Advisory Panel	1	$200.00
Day case hospitalisation	$800.00	AR-DRG Version 5.0, Round 9 (2004–05) public sector cost estimate for R63Z Chemotherapy, minus Ward Medical fees	1 per week for 6 weeks	$4,800.00

[a] Based on expert opinion of the Advisory Panel
PICC = peripherally inserted central catheter; TIVAS = totally implantable venous access system
AR-DRG data available at
http://www.health.gov.au/internet/wcms/publishing.nsf/Content/88F4E78E15620A80CA2571CB0004DDAA/$File/_R9CWNatEst.pdf (accessed 21 February 2008)

Table 33 Summary of costs for neoadjuvant therapy

Neoadjuvant therapy	Resource item	Total fees
Chemotherapy	MBS costs	$909.60
	PBS costs (fluorouracil)	$299.64
	Devices (PICC or TIVAS)	$200.00
	Accommodation	$4,800.00
	Total for chemotherapy	$6,209.24
Long-course radiation	MBS costs	$4,625.75
	Total for long-course radiation	$4,625.75
	Total for chemotherapy and long-course radiation	$10,834.99
Short-course radiation	MBS costs	$1,504.85
	Total for short-course radiation	$1,504.85

PICC = peripherally inserted central catheter; TIVAS = totally implantable venous access system

Neoadjuvant therapy for a person undergoing 30 days (long-course) of radiotherapy in combination with 6 weeks of chemotherapy is estimated to cost $10,835 per person (MBS fees, cost of hospitalisation, fluorouracil and access to an implanted drug delivery device such as the peripherally inserted central catheter (PICC) or a totally implantable venous access system (TIVAS)). The MBS fees relating to 5 days (short-course) of radiotherapy are $1,505 per person.

Financial implications

For newly diagnosed patients

The potential usage of MRI for staging of newly diagnosed rectal carcinoma depends on the number of patients who may be considered for aggressive treatment (ie not at a clinically early stage of disease, and not with advanced disease or comorbidities that would preclude them from aggressive treatment). Based on the 4,301 new cancers of the rectum and rectosigmoid in 2001 (AIHW), expert opinion of the Applicant and Advisory Panel suggested that approximately 3,000 procedures per year may be performed if MRI was funded for this indication.

In 2000 only 12% of Australian patients with rectal carcinoma received an ERUS (McGrath et al 2004). If it is assumed that 12% of the 3,000 patients likely to receive MRI would otherwise have received ERUS, MRI would be an *additional* test in 2,640 patients, and a *replacement* test in 360 patients, per year. Of these 360 patients, 169 are expected to be managed through the private health system (79 female and 90 males) and

191 through the public health system.[4] Of the 169 patients who would otherwise receive ERUS through the private health system, it is estimated that 35 females and 40 males would have been required to pay the gap between the MBS rebate and the fee charged (see Figure 18 and Table 60 in Appendix G for further details).

If it is assumed that all 3,000 patients are able to access a Medicare-eligible MRI unit, the additional expenditure borne by the Australian Government per year is estimated to be $1,013,174 (Table 34). Patients would contribute another $183,230 per year towards the cost of staging with MRI, while the states and territories are expected to *save* $34,380 if 191 public patients receive MRI rather than ERUS, based on the advice of the Advisory Panel that ERUS costs $180. Overall, the direct cost to society of staging with MRI (without any analysis of the downstream effects of MRI on patient management and health outcomes) is estimated to be $1,162,024 per year.

Table 34 Expenditure in one full year for newly diagnosed patients

Resource item and population	Incremental cost of proposed service[a]	Usage[b]	Expenditure[a]
Costs to the Australian Government			
MBS rebate for MRI	$342.75	2,831	$970,325
MBS rebate for MRI rather than ERUS (male)	$248.40	90	$22,356
MBS rebate for MRI rather than ERUS (female)	$259.40	79	$20,493
Total expenditure borne by the Australian Government			$1,013,174
Cost savings to the states and territories			
Cost of not performing ERUS in a public outpatient clinic	–$180.00	191	–$34,380
Total expenditure borne by the states and territories			–$34,380
Costs to patients			
Gap for MRI	$140.00	1,274	$178,360
Gap for MRI rather than ERUS (male)	$71.00	40	$2,840
Gap for MRI rather than ERUS (female)	$58.00	35	$2,030
Total expenditure borne by patients			$183,230
Total expenditure borne by society			$1,162,024

[a] Negative result indicates a cost saving; [b] see Figure 18 and Table 60 in Appendix G

Potential change in management

It is currently strongly recommended that patients with high-risk rectal carcinoma (T3/T4 or N1) receive (neo)adjuvant therapy (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). If the CRM is able to be visualised accurately by MRI (or possibly, in the future, MSCT), it is suggested that the definition of high-risk rectal cancer may change to a threatened or involved CRM (Adam et al 1994; Birbeck et al 2002; Mawdsley et al 2005). If neoadjuvant therapy is reserved for patients with a threatened or involved CRM, the usage is expected to decrease. It is not expected that patients who are staged T4 or N1 would receive any different treatment (all would

[4] The ratio of public to private separations was based on Diagnostic Code C20 'Malignant neoplasm of the rectum' recorded by the National Admitted Patient Care Collection (Department of Health and Ageing 2007), and the sex ratio was based on data on the stratified incidence of colorectal cancer in Australia AIHW (2005).

receive neoadjuvant therapy). The population in whom treatment is expected to change are those patients who are staged T3 and N0, and are found to be CRM negative.

It is estimated that 4,301 new cases of rectal carcinoma are diagnosed in Australia each year (based on 2001 data; AIHW 2005). No published data were available on the percentage of these cases who were staged T3 and N0, and found to be CRM negative. In the absence of this data, an assumption was therefore made that the disease spectrum of patients reported in the included studies in the systematic review is similar to the Australian population. Table 62 (Appendix G) outlines the studies that reported the T stage distribution of patients imaged with MRI. A median of 63.4% of patients imaged with MRI were staged by histopathology as being T3. The assumption is therefore made that, of the 3,000 newly diagnosed patients potentially suitable for MRI per year in Australia, 1,902 (63.4% of 3,000) are likely to be staged T3.

A Norwegian study by Eriksen et al (2007) described the distribution of patients with T3 tumours according to tumour distance from the CRM and nodal status. Table 35 outlines the percentages provided by Eriksen et al (2007), and provides the consequent numbers expected in Australia according to different categories of distance to the CRM and nodal status.

If the definition of high-risk rectal carcinoma is changed from T3/T4 or N1 to CRM positive (as conservatively defined as a tumour less than or equal to 2 mm from the mesorectal fascia) or N1, it is estimated that 43% of T3 tumours, or approximately 818 patients, are overtreated in Australia per year. If the definition of CRM positive is changed to a tumour within 1 mm of the mesorectal fascia, it is estimated that 47.1% (896) of T3 patients are being overtreated each year.

Table 35 Number of rectal carcinoma patients in Australia potentially being overtreated

Tumour distance from the CRM	Percentage of T3 patients (Eriksen et al 2007)	T3 patients in Australia (total n=1,902)
>3 mm	40.5%	770
>2 mm	43.0%	818
>1 mm	47.1%	896

It is unknown how a reduction in neoadjuvant therapy would influence downstream costs. There would likely be a small increase in the rate of local recurrence, as neoadjuvant therapy has been found to reduce the *relative* risk of local recurrence in all rectal carcinoma patients, irrespective of CRM status, even though the *absolute* risk difference is very small in patients without a threatened or involved CRM (Marijnen et al 2003). However, the small absolute risk increase of local recurrence that may occur from a reduction in neoadjuvant therapy is likely to be offset by a reduced rate of toxicities. Downstream costs or cost savings are therefore not considered.

It is assumed that, of the 818 patients being overtreated each year, 614 (75%) would be receiving chemoradiation and 202 (25%) short-course radiotherapy (percentages based on expert opinion of the Advisory Panel). Figure 19 and Table 61 (Appendix G) outline the proportion and number of patients expected to receive neoadjuvant therapy in the private or public health system, and those who are likely to be eligible for concession. Table 36 provides the cost savings expected if 818 patients per year avoid neoadjuvant therapy. For the sake of simplicity, it has been assumed that the gap for radiotherapy and

chemotherapy is equal to the gap between the Schedule fee and the MBS rebate. It is estimated that if 818 fewer people receive neoadjuvant therapy each year, there would be a cost saving to the Australian Government of $1,512,661 and an overall saving to society of $6,798,589.

Table 36 Annual cost savings expected if 818 fewer patients receive neoadjuvant therapy

Resource item and population	Incremental cost of proposed service[a,b]	Usage[c]	Expenditure[a]
Cost savings to the Australian Government			
MBS rebate for short-course radiotherapy	–$1,279.40	95	–$121,543
MBS rebate for long-course radiotherapy	–$3,932.45	289	–$1,136,478
MBS rebate for chemotherapy	–$682.45	289	–$197,228
Difference between fluorouracil at dispensed price and maximum recordable value	–$111.84	130	–$14,539
Difference between fluorouracil at dispensed price and concession rate	–$269.64	159	–$42,873
Total expenditure borne by the Australian Government			–$1,512,661
Cost savings to the states and territories			
Cost of short-course radiotherapy	–$1,504.85	107	–$161,019
Cost long-course radiotherapy	–$4,625.75	325	–$1,503,369
Cost of chemotherapy	–$909.60	325	–$295,620
Cost of fluorouracil at dispensed price	–$299.64	325	–$97,383
Cost of PICC or TIVAS for chemotherapy	–$200.00	325	–$65,000
Cost of day case hospitalisation for chemotherapy	–$4,800.00	325	–$1,560,000
Total expenditure borne by the states and territories			–$3,682,391
Cost savings to patients or private health insurance			
Gap for short-course radiotherapy	–$225.45	43	–$9,694
Gap for long-course radiotherapy	–$693.30	130	–$90,129
Gap for chemotherapy[d]	–$227.15	130	–$29,530
Fluorouracil at maximum recordable value	–$187.80	130	–$24,414
Fluorouracil at concession rate	–$30.00	159	–$4,770
Cost of PICC or TIVAS for chemotherapy[d]	–$200.00	289	–$57,800
Cost of day case hospitalisation for chemotherapy[d]	–$4,800.00	289	–$1,387,200
Total expenditure borne by patients or private health insurance			–$1,603,537
Total expenditure borne by society			–$6,798,589

[a] Negative result indicates a cost saving; [b] see Table 29, Table 31and Table 32; [c] see Figure 19 and Table 61 (Appendix G); [d] private health insurance likely to cover; PICC = peripherally inserted central catheter; TIVAS = totally implantable venous access system

If the cost savings from reduced neoadjuvant therapy use offset the costs of MRI for the staging of rectal carcinoma, it is estimated there would be an overall cost saving to the Australian Government of $499,487 and an overall cost saving to society of $5,636,565 (Table 37).

Table 37 Financial impact of MRI staging and subsequent changes to neoadjuvant therapy

Funding source	Incremental cost of MRI[a, b]	Incremental cost of reduced neoadjuvant therapy[a, b]	Overall cost saving[a]
Australian Government	$1,013,174	–$1,512,661	–$499,487
States and territories	–$34,380	–$3,682,391	–$3,716,771
Patients and private health insurance	$183,230	–$1,603,537	–$1,420,307
Society	$1,162,024	–$6,798,589	–$5,636,565

[a] Negative result indicates a cost saving; [b] see Table 34; [c] see Table 36

For restaging of patients after neoadjuvant therapy

It is proposed that approximately 150 patients per year would require restaging after neoadjuvant therapy, of which 100 may receive MRI if it is funded for this indication (expert opinion of the Advisory Panel). It is assumed that 55 (55%) of these patients would not be required to pay a gap (see Figure 20 and Table 63 in Appendix G).

If it is assumed that MRI would always be used *in addition* to MSCT, and that all patients are able to access a Medicare-eligible MRI unit, the additional expenditure borne by the MBS due to funding MRI within this population would be $34,275 per year (Table 38). The costs to society would be $40,575.

Table 38 Expenditure in one full year for restaging

Resource item	Incremental cost of proposed service[a]	Usage[b]	Expenditure
Costs to the Australian Government			
MBS rebate for MRI	$342.75	100	$34,275
Total expenditure borne by Australian Government			$34,275
Costs to patients			
Gap between rebate and fee charged for MRI	$140.00	45	$6,300
Total expenditure borne by patients			$6,300
Total expenditure borne by society			$40,575

[a] See Table 27 and Table 28; [b] see Figure 20Error! Reference source not found. and Table 63 in Appendix G.

For the diagnosis/staging of patients with suspected/diagnosed recurrence of rectal carcinoma

The Advisory Panel estimated that a further 5% of cases (150 patients) would undergo MRI for suspected or diagnosed recurrent carcinoma per year if funded for this indication. If it is assumed that MRI would be used in addition to MSCT ± PET in all 150 patients, and as an alternative to ERUS in 18 patients (12%[5] of 150), the cost to the Australian Government is estimated to be $50,703. The cost to society would be $57,981 if funded for this indication. This is based on the same assumptions as outlined for newly diagnosed patients, and is further outlined in Figure 21 and Table 64 in Appendix G.

[5] In 2000 only 12% of Australian patients with rectal carcinoma received an ERUS (McGrath et al 2004).

Table 39 Expenditure in one full year for diagnosis/staging of carcinoma recurrence

Resource item and population	Incremental cost of proposed service[a, b]	Usage[c]	Expenditure[a]
Costs to the Australian Government			
MBS rebate for MRI	$342.75	142	$48,671
MBS rebate for MRI rather than ERUS (male)	$248.40	4	$994
MBS rebate for MRI rather than ERUS (female)	$259.40	4	$1,038
Total expenditure borne by the Australian Government			$50,703
Cost savings to the states and territories			
Cost of not performing ERUS in a public outpatient clinic	–$180.00	10	–$1,800
Total expenditure borne by the states and territories			–$1,800
Costs to patients			
Gap for MRI	$140.00	63	$8,820
Gap for MRI rather than ERUS (male)	$71.00	2	$142
Gap for MRI rather than ERUS (female)	$58.00	2	$116
Total expenditure borne by patients			$9,078
Total expenditure borne by society			$57,981

[a] Negative result indicates a cost saving; [b] see Table 27 and Table 28; [c] see Figure 21and Table 64 in Appendix G

Other relevant considerations

Included in this section are considerations that are worthy of mention, but either were not found in the systematic literature review or were outside the scope of the research questions concerning safety and effectiveness.

Safety considerations of MRI

MRI has been used for approximately 20 years, with over 150 million examinations having been performed. During this time there have been very few serious injuries as a direct result of MRI. The rare fatalities have been due to instances of safety precautions not being followed, or as a consequence of outdated information on biomedical implants or devices being consulted (Shellock & Crues 2004). While MRI is generally considered a safe procedure, suitable precautions must be taken, as there are some safety issues due to: the effects of high magnetic fields and radiofrequency pulses on the body and implanted devices, claustrophobia, hearing loss and side effects of contrast agents (Chung 2002).

Magnetic fields and radiofrequency pulses

There are three types of MRI emissions that may impact on implants: the strong static magnetic field, weaker time-varying gradient magnetic fields and radiofrequency pulses. The static magnetic fields from an MRI machine are present even when it is not imaging. Although field strengths as large as 8.0 T have been found to have no adverse effects, patients may occasionally experience vertigo, nausea and a metallic taste (Chung 2002). Injuries that occur are a result of implanted or foreign metallic objects being introduced into the MR environment (Chung 2002; Shellock & Crues 2004). Patients need to be screened to determine whether they have any ferromagnetic or electronic implants. Objects such as surgical clips, coils or stents may move or dislodge, resulting in tearing of tissues (Chung 2002). Pacemakers are a strict contraindication for MRI, as the electrical systems may be disrupted by the magnetic and gradient fields, causing fibrillation, arrhythmias and burns (Chung 2002).

Exposure to radiofrequency energy when imaging patients may result in tissue heating. While small increases in temperature are able to be regulated by the body, care needs to be taken with metal implants or electrical conductors that are near the body (such as cables on monitoring devices, ferromagnetic or not), as they may heat up more than the body tissue and result in burns (Zhuo & Gullapalli 2006).

The magnetic field created by the time-varying gradient is very small compared to the static magnetic field. It is considered insufficient to cause any biological effects, except for peripheral nerve stimulation and magnetophosphenes, which are believed to be caused by electrical stimulation of the retina (Chung 2002).

Claustrophobia

MRI involves a patient being inserted into a narrow tunnel and remaining still during the procedure. Approximately 2% of people suffer from claustrophobia and find the proximity to the inner wall of the gantry distressing (Eshed et al 2007). For a pelvic MRI, patients may be positioned with their head near the opening of the bore, to reduce

distress. However, a small proportion of patients may benefit from sedation (Chung 2002).

Acoustic noise

Patients may hear loud banging, tapping, knocking or chirping noises during an MRI, resulting from the gradient magnetic current pulsing through the coils (Shellock & Crues 2004; Zhuo & Gullapalli 2006). To prevent potential hearing loss, patients should wear disposable ear plugs or noise-abatement headphones (Shellock & Crues 2004).

Medications

Anti-spasmodic medications such as hyoscine (Buscopan) or glucagon are used in rectal MRI to limit motion artefacts from the gastrointestinal tract. There have been very few reports of cases or suspected adverse events arising from these medications (Tytgat 2007).

Contrast agents

It is common to use contrast agents during MRI examinations. These may cause minor adverse events such as nausea, vomiting, hives, headache or pain at the injection site (Chung 2002). Serious adverse events, ie cardiovascular, gastrointestinal or neurological complications, are rare (Chung 2002). While contrast agents were used in a large proportion of studies included in this systematic review, they are not commonly used for rectal carcinoma patients in Australia.

Safety considerations of endorectal ultrasound

Patients may experience pain during insertion of the rectal probe for the endorectal ultrasound (ERUS), and anaesthesia may be required (Inal et al 2007). It is also possible that infectious diseases may be transmitted by the endorectal probe if strict sterilisation procedures are not followed (Masood et al 2007). It has been suggested that rectal perforation may occur (Colorectal Surgical Society of Australasia 2006). However, evidence of this, or of any other complications linked to ERUS, have not been identified.

Patients who cannot undergo ERUS

The rigid ultrasound probe may be unable to pass bulky tumours or stenoses in the proximal rectum, which would result in inadequate imaging (Skandarajah & Tjandra 2006).

Safety considerations of computed tomography

There are two main safety concerns associated with computed tomography (CT). These are patient reactions to contrast materials and exposure to ionising radiation. Contrast media may be required to enhance visualisation during CT. The patient risks associated with this can include life-threatening reactions such as anaphylaxis, hypotension, cardiovascular events and renal dysfunction (McCullough 2006).

The use of CT involves patient exposure to radiation. The radiation dose and subsequent level of exposure associated with staging of rectal carcinoma varies between the different types of CT (conventional and multi-slice (MSCT)). As a result, there is a wide range in doses. An Australian survey of CT facilities carried out in 1997 identified the average radiation dose from CT examinations to the general population (Thomson & Tingey 1997). As an example, the effective dose for an abdomen examination ranged from about 3 mSv to 75 mSv, while the number of slices ranged from 9 to 60. The overall average effective dose for a CT examination was 6.6 mSv. An updated survey incorporating the impact of new technologies (eg MSCT) and procedures on patient doses in CT is necessary (Thomson & Tingey 1997).

Safety considerations resulting from over- and understaging

Anti-cancer treatment is often associated with significant morbidities that must be outweighed by the health benefits it confers.

Patients who are overstaged are likely to receive unnecessary neoadjuvant treatment (radiotherapy or chemoradiation), resulting in significant costs and morbidity.

While it has been found that neoadjuvant therapy reduces the risk of local recurrence across patients with all levels of circumferential resection margin (CRM) involvement, the absolute risk of recurrence in patients without a threatened or involved CRM is very small, and may be outweighed by the significant morbidity and mortality associated with the additional chemotherapy and/or radiation treatment (Gibbs et al 2004).

Neoadjuvant therapy, as compared to adjuvant therapy, has been found to reduce local recurrence, although overall survival is not affected (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Neoadjuvant therapy has also been found to reduce acute and late toxicities to the patient (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Providing neoadjuvant therapy to all patients at high risk of local recurrence, as determined by stage T3, T4 or N1, has therefore been preferred over administering adjuvant therapy (reserved for those with involved surgical margins). The theory behind staging with MRI is the ability to provide more selective neoadjuvant therapy (based on preoperative prediction of CRM status), thus further reducing the rate of complications and improving patient safety (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005).

Complications from neoadjuvant therapy

Short-term side effects from radiotherapy include lethargy, nausea, diarrhoea, the frequent urge to empty the bowel but difficulty in doing so, urinary frequency, painful inflammation of the skin and shedding of the outer layer of skin (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Most patients experience some of these complications during radiotherapy, but the effects are short lived.

Long-term side effects of radiotherapy include damage to the small bowel and rectum, which is seen in 3–11% of cases (Frykholm et al 1993). Symptoms may be permanent, and include bleeding, stricture, malabsorption, reduced reservoir capacity, frequency and incontinence (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Quality of life measures are reduced after radiotherapy. A Dutch study found that, 2 years after surgery, patients who were sexually active prior to the operation

and were randomised to receive radiotherapy were less likely to still be sexually active after the operation than if they had surgery alone (67% compared with 76% for males and 72% compared with 90% for females) (Marijnen et al 2005). Preoperative radiation also results in impairment in social functioning in 30% of patients due to bowel dysfunction, as compared to only 10% in patients without radiation (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005).

Chemoradiotherapy results in fewer cases of local recurrence of rectal carcinoma than radiotherapy alone (although no benefit in survival has been found). The rate of severe toxicity increases with the addition of chemotherapy (Wong et al 2007). This includes acute and late morbidities, and both haematological and non-haematological toxicities (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). Compared with radiotherapy alone, chemoradiotherapy is associated with increased diarrhoea, leucopoenia, incontinence and urgency, and worse renal function (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005).

No statistically significant differences have been found regarding the number of complications resulting from neoadjuvant therapy between young and elderly rectal carcinoma patients. However, when complications occur, the results are far more serious for the elderly (Rutten et al 2007). For example, Rutten et al (2007) reported that if anastomotic leakage occurs, patients over 75 years of age have a 50% chance of dying as a result, compared to only a 7.1% chance in younger patients ($p<0.001$).

While the adverse events discussed are not specific to the population with false positive results, they may give an indication of the negative effects of overstaging. The transferability of these results, however, is unclear, as it is unknown whether adverse events from neoadjunctive therapy are likely to vary by disease stage.

Patient's viewpoint

Patient preferences regarding staging techniques

While evidence on patient preference regarding MRI for staging rather than other staging techniques has not been identified, patients may prefer to undergo MRI than ERUS, as ERUS requires a full bowel preparation. Bowel preparation involves a liquid diet for a day before the procedure, and usually also involves several enemas. When MR colonography and colonoscopy have been compared, patients prefer MR colonography, due to the limited bowel preparation required (Florie et al 2007). It is hypothesised that MRI for staging of rectal carcinoma would be preferred by patients (who do not suffer from claustrophobia) due to the reduced bowel preparation required compared to ERUS. In comparison to CT, MRI may be preferred due to the lack of radiation.

Delays in treatment

A disadvantage of further staging by MRI or ERUS is that the addition of another investigation before the patient is treated may potentially delay the time between diagnosis and treatment. From a biological perspective, decreasing the time between diagnosis and treatment by 1–2 weeks would have minimal impact on patient outcomes compared to reducing prediagnostic delays (which are over 3 months in 72% of patients). However, the time interval between diagnosis and treatment is the most important influence on patient satisfaction with access to care (Porter et al 2005). While this study

did not assess how the receipt of staging tests influences satisfaction, further information made available by staging may not always result in increased psychological wellbeing of the patient.

Patient preferences regarding treatment

One of the key factors that should be taken into account when choosing whether to stage tumours with MRI or any other staging technique is to determine what treatments the carcinoma patient is willing to undergo. If a patient is unwilling to receive neoadjuvant therapy regardless of the risk of local recurrence, there would be no reason to stage the tumour with MRI. Similarly, if the patient is risk averse, and would prefer any reduction in the risk of local recurrence without consideration of the impact on quality of life, neoadjuvant therapy rather than further staging may be required.

While treatment decisions are usually based on tumour stage, risk of local recurrence, prognosis and quality of life, patient preference is increasingly being recognised as an important factor in treatment selection (Couture et al 2005). When patients have a choice between alternative treatments that have minimal difference in terms of overall survival (as is the case for rectal carcinoma), management decisions are strongly influenced by individual values. For example, symptoms of urgency and incontinence may have very different meaning for an airline pilot compared to a retired person in the privacy of their own home (Couture et al 2005). One Canadian study reported that the majority of colorectal cancer patients interviewed would be willing to accept a higher risk of local recurrence for a better quality of life. These patients would only consider a more toxic therapy if it meant an absolute risk difference of 5% (Couture et al 2005). This was in keeping with a Dutch study that also found that a 5% gain in local control was the average point at which patients would consider preoperative radiotherapy prior to surgery (Pieterse et al 2007). However, there was considerable variability (0–11%) in the point at which patients would be prepared to receive one treatment over another (Pieterse et al 2007). Important variables that impacted on patients' hypothetical decisions were the value placed on bowel functioning and fear of carcinoma recurrence (Couture et al 2005). An Austrian study reported that older patients placed less value on having a complete cure of colorectal cancer than younger patients ($p<0.05$), although all patients placed a high value on avoiding a colostomy (Holzer et al 2006). This intra-individual variability highlights the need to discuss the implications of different treatment strategies with each patient, so that patients' outcome preferences can be incorporated in the decision-making process (Pieterse et al 2007).

Barriers to optimal management of patients with rectal carcinoma

Skills shortage

The required MRI hardware is fairly widely available, but the necessary skills to accurately predict rectal carcinoma stage, based on MRI, are not. The procedure is currently available on an unfunded basis at a few Australian centres, where there is increasing pressure for scanner time to be used for other funded indications. In the continued absence of funding, it is unlikely that the necessary training and skills will be disseminated, nor that scanner time will be made available, outside those few centres (Colorectal Surgical Society of Australasia 2006).

There is currently a shortage of radiographers and radiologists in Australia, and the growth in demand for diagnostic tests is outstripping the available workforce (Smith & Baird 2007).

Equity and access

Even if MRI were to be funded for staging of rectal carcinoma, it is likely that the skills required to use MRI for this indication would be available only in cities and regional centres (Colorectal Surgical Society of Australasia 2006). Access to ERUS is also limited. In 2000 only 12% of Australian patients with rectal carcinoma received an ERUS. Further, those seen by low-volume surgeons (who operated on less than six colorectal cancer patients in a 3-month period) were only half as likely to receive an ERUS as those seen by high-volume surgeons (10.4% versus 20.4%) (McGrath et al 2004). MRI is likely to remain available only to those who live near or are able to travel to MRI equipment. However, it may provide an alternative to ERUS, so that access to one technique or the other would increase compared to ERUS alone. In September 2007 it was announced that there would be funding for 13 further Medicare-eligible MRI units, bringing the number to 126 around Australia (Abbott 2007). A large multicentre trial has shown MRI to be accurate in a range of settings (MERCURY Study Group 2006, 2007). This is an advantage over ERUS, which is highly operator dependent (expert opinion of the Advisory Panel).

It is likely that MSCT with a higher number of slices (16, 40, 64 or 256) would have greater accuracy than 4-slice or 8-slice CT. While the majority of rectal carcinoma patients are able to access some form of MSCT for assessment of distant metastases, access to MSCT with at least 16 slices is currently limited to major centres. The majority of small private practices currently have only 8-slice CT, whereas major institutions, those in highly populated areas and those which compete with other radiology clinics for customers are likely to have at least 16-slice CT (pers. comm., Siemens Pty Ltd, February 2008).

Differential treatment of elderly patients

A study on radiotherapy usage in Western Sydney between 1994 and 2001 found that age was an independent predictor of radiotherapy use. When TNM stage, type of operation and surgeon caseload were controlled for, patients under 70 years of age were significantly more likely to receive radiotherapy than those over 70 (41% versus 23%, adjusted OR = 2.96, 95%CI 1.75, 5.03) (Hegi-Johnson et al 2007). A recent narrative review found 10 population-based studies that supported the Australian data, consistently reporting that increased age is associated with less use of (neo)adjuvant treatment (Martijn & Vulto 2007). While it is hypothesised that elderly patients receive less radiotherapy or chemotherapy due to toxicity concerns, no differences in the rate of complications, by age, have been found when modern radiotherapy and small tissue volumes are used (Martijn & Vulto 2007). From this evidence, it has been suggested that elderly patients with rectal carcinoma are being undertreated (Chang et al 2007). It is unknown whether the differential treatment of elderly patients is due to physician decision-making on behalf of the patient, or whether it is a consequence of patient preference. Possible reasons as to why physicians and/or patients are choosing reduced use of neoadjuvant therapies include both the level of existing patient comorbidities and the perceived reduction in capacity to benefit from neoadjuvant therapy, as a result of a higher general mortality rate from non–cancer-related causes.

It is possible that physicians are currently unclear whether the benefits of reduced local carcinoma recurrence outweigh the risks of providing neoadjuvant therapy. Without information regarding the CRM (and subsequent risk of recurrence), physicians may be more likely to refer patients who are under 70 years of age to chemoradiotherapy in case they have an involved CRM. Patients over 70 years of age may be less likely to be referred to chemoradiotherapy, in case their CRM is clear, in an effort to minimise the ill-effects of neoadjuvant therapy. If this is the case, the use of MRI to stage patients under 70 years of age would result in fewer patients in this age bracket, and more patients over 70 years of age, receiving neoadjuvant therapy.

Expert opinion

The Advisory Panel was of the strong opinion that MRI is superior to MSCT at visualising the mesorectal fascia, due to higher contrast resolution and better tissue characterisation. The findings of Taylor et al (2007) are emphasised within this systematic review, as it is the only study that provides data on the primary accuracy outcome measure–the CRM. However, the accuracy of MRI in the study by Taylor et al (2007) was moderately low, compared to the six other studies that reported CRM as an outcome measure, suggesting that there may be confounding factors. It is possible that, had Taylor and colleagues defined an involved CRM as within 1 mm of the mesorectal fascia, results may have been different. Furthermore, part of the difficulty in determining the comparative accuracy of MRI and MSCT is that a large number of patients were excluded from most studies, due to receiving neoadjuvant therapy. The use of neoadjuvant therapy would result in histopathology no longer being an accurate reference standard.

An important distinction between MRI and MSCT is that MRI has the ability to visualise low rectal tumours. MRI has high tissue resolution from direct coronal and sagittal imaging, which delineates adjacent structures such as the puborectalis muscle, prostate and uterus, all of which can be difficult to visualise with MSCT.

The Advisory Panel strongly feel that MRI is essential in the local staging of rectal carcinoma, which is in keeping with the majority of European and North American centres.

Implications for future research

In regards to assessing the health benefits of staging of rectal carcinoma with MRI, the ideal study design would be a randomised controlled trial where patients are randomised to receive imaging with MSCT ± ERUS or MSCT + MRI. These patients should then be followed, noting the treatments given based on the different types of imaging and the consequent health outcomes. Should MRI be accessible for this indication, physicians may then feel it is unethical to withhold MRI from patients, due to the potential additional information it may provide. Recruitment for a randomised trial in such a situation may therefore be difficult[6].

[6] This was demonstrated recently when the MSAC recommended that vertebroplasty receive interim funding despite a paucity of good quality comparative evidence. This decision has been criticised as an Australian randomised controlled trial that was underway then had difficulty recruiting participants. The

Further evidence comparing the *accuracy* of MSCT ± ERUS versus MSCT + MRI against the reference standard of histopathology would be simpler to produce. In order to determine whether MRI has additional benefit over MSCT, it would be advisable for multidisciplinary panels to ascertain whether the addition of MRI would change the management of patients. In a similar manner to Brown et al (2004), it may be possible to determine whether the correct preoperative treatment (ie neoadjuvant therapy versus no neoadjuvant therapy) was given (Brown et al 2004). However, there will inevitably be treatment effects that interfere with the accuracy of these results.

Simpler still would be production of further evidence on the accuracy of MSCT versus MRI by staging a consecutive group of rectal carcinoma patients with both imaging modalities, and comparing the results against histopathology. Further research comparing the diagnostic accuracy of MRI and MSCT is currently underway (Kim et al 2005; Rudralingam et al 2005). Within the next year or two it is possible that there will be evidence that resolves the uncertainties surrounding the results of Taylor et al (2007) (ie that MSCT has similar accuracy at predicting CRM status as MRI). The problem, of course, with this study design is that the *incremental* benefit of staging with MRI over and above MSCT imaging (as is current Australian practice) cannot be determined. Spectrum bias will also remain an issue, as histopathology is not an accurate reference standard in patients who receive long-course radiation or chemotherapy prior to surgery.

In summary, it is unlikely that any studies will be published that are able to *clearly* show the health benefits of staging with MRI, due to ethical considerations and the systematic bias that is inevitable to occur. However, the literature that has already been published is also subject to these flaws, so future research comparing MRI and MSCT on the outcomes of health benefits, proposed management strategies (and histopathologically determined suitability of these) and CRM involvement would still be informative.

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true effectiveness of vertebroplasty will therefore only be known once international trials are completed (Buchbinder 2006.)

Discussion

Is it safe?

The safety of diagnostic or staging tests relate to any physical or psychological harms that occur from undergoing the test itself, as well as the impact of the staging or diagnostic result and subsequent management of the disease. Physical adverse events associated with MRI were not identified in the systematic review, although it is clear that rare harms can occur.

The impact that a correct staging or diagnostic result has on a patient is beyond the scope of this systematic review. The impact of *inaccurate* staging or diagnosis on patients can be considerable. Patients may be overstaged or understaged, and either of these options would result in less than optimal treatment decisions being made. There were no reports, however, that actually stated the safety implications of inaccuracies from MRI staging. A total of 10 studies were included that reported on the number of patients who were staged incorrectly, or were not correctly diagnosed as having or not having locally recurrent disease. These studies were included in the assessment of diagnostic accuracy within the Effectiveness section of this review.

Is it effective for newly diagnosed patients?

Direct evidence

Two medium-quality retrospective studies were identified that reported on the ability of imaging with MRI to reduce the rate of positive circumferential resection margins (CRMs), a surrogate health outcome or prognostic indicator for disease-free survival.

In both these studies the group of patients who did not undergo imaging with MRI were much more likely to receive surgery alone. It is highly likely that the reduced rate of CRM positivity is due to the neoadjuvant therapy provided to the patients who underwent MRI staging. The applicability of these results to the Australian healthcare context is questionable. The Advisory Panel suggested that without MRI staging, patients would be *more* likely to receive neoadjuvant therapy. Thus, MRI would be used to select people who would be suitable for *surgery alone* rather than patients for neoadjuvant therapy, as implied by the two studies identified.

Without MRI, patients over 70 years of age are less likely to receive neoadjuvant therapy than those under 70 years of age (Hegi-Johnson et al 2007). It is therefore possible that MRI staging may *increase* the usage of chemoradiotherapy prior to surgery in patients over 70 years of age with involved or threatened CRMs (a similar outcome to the study results).

While neoadjuvant therapy may have an impact on the CRM (which has been found to be a useful predictor of disease-free survival after neoadjuvant therapy and surgery), it is unclear whether this outcome has direct relevance to patient quality of life.

Table 40 provides an overview of the direct evidence available assessing MRI staging on patient health outcomes.

Table 40 Body of evidence assessment matrix for direct evidence of effectiveness[a]

Component	Excellent	Good	Satisfactory	Poor
Evidence base				level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent			
Clinical impact			moderate	
Generalisability		population/s studied in the body of evidence are similar to the target population		
Applicability				not applicable to Australian healthcare context

[a] The preferred method of assessing effectiveness

Linked evidence

Accuracy

The accuracy of MRI was determined through assessment of three different staging components: whether the CRM was involved (CRM status), the depth of tumour invasion (T stage) and whether metastases were present in lymph nodes of the mesorectum (N stage). Due to its high prognostic value, accuracy at predicting involvement of the CRM was the primary outcome. One disadvantage of the CRM as an outcome is that if a surgeon unintentionally strays from the mesorectal fascia as the resection margin, the outer border of the resection specimen may not correspond with the mesorectal fascia, and the reference standard would thus be imperfect. Similarly, if the tumour is perforated during surgery, this may be classified as an affected CRM, which could not have been predicted by preoperative imaging (MERCURY Study Group 2006). Where it was clear that this occurred, results were provided excluding patients with intraoperative perforations.

Only one medium-quality study (level III-2 diagnostic evidence) was identified that provided comparative information for the primary outcome of accuracy at detecting CRM involvement. This study found that MRI was similar to multi-slice CT (MSCT) at predicting CRM status. Since MRI is proposed as an addition to CT imaging (most commonly MSCT) rather than an alternative, these results would suggest that there would be no benefit in providing MRI in addition to MSCT. However, the definition of an involved CRM used in this study may have been inappropriate and not clinically relevant. The accuracy of both MRI and MSCT in the one study that compared the two modalities was much lower than the accuracy of MRI reported in the series of studies without the comparison to MSCT. One possible reason for this is the different definition of an involved CRM, ie a tumour within 5 mm of the mesorectal fascia, as opposed to the common definition of within 1 mm of the mesorectal fascia.

If the typical definition of an involved CRM is a tumour within 1 mm of the mesorectal fascia, there is evidence that MRI is accurate (and has high negative predictive value)

when compared with histopathology, whereas there is currently only limited evidence available assessing MSCT using this definition. One peer-reviewed article and two conference abstracts were identified from a non-systematic search of the literature which reported on studies that compared MSCT against histopathology (Sinha et al 2006; Wolberink et al 2005b; Wolberink et al 2005a). Despite 10 of 57 patients receiving preoperative chemoradiation, Sinha et al (2006) reported that 16-slice MSCT predicted an involved CRM with 96.5% accuracy using multiplanar images (sensitivity = 91.7%, specificity = 97.8%), and 91.2% accuracy with axial images (sensitivity = 66.7%, specificity = 97.8%). Evidence directly comparing MRI and MSCT using the clinically relevant definition of an involved CRM is required before the comparative accuracy of the two imaging modalities, or the additional benefit to be derived from imaging with MRI as well as MSCT, may be known.

Spectrum bias is likely to influence the results of all the included studies, as those patients who receive long-course radiotherapy cannot be assessed accurately with the reference standard (histopathology) due to confounding effects of the treatment. If MRI is better at visualising the mesorectal fascia than MSCT, and those patients whose mesorectal fascias are threatened or involved are systematically excluded due to subsequent long-course treatment, the accuracy results of the remaining patients may not be representative of the whole patient spectrum. This is equally likely to occur should MSCT be more accurate than MRI. Thus, the comparative accuracy of the two technologies cannot be definitively determined in those patients identified with an involved CRM who receive neoadjuvant therapy. It can only be assessed in those patients without an involved CRM, or with an involved CRM who do not receive neoadjuvant therapy. Given the known efficacy of neoadjuvant therapy, it would be unethical to withhold neoadjuvant therapy in those patients with an involved or threatened CRM. The ascertainment of accuracy of MRI and MSCT across the whole patient spectrum is therefore unlikely to occur.

While it is unclear from the limited evidence currently available as to how the accuracy of MRI compares to MSCT, MRI is likely to be more accurate than the comparators, conventional CT and endorectal ultrasound (ERUS). ERUS is limited in its ability to distinguish between soft tissues, and, with a limited field of view, is unable to visualise the CRM. While no studies directly compared MRI against conventional CT for assessing CRM status, one study reported that conventional CT lacks the sensitivity required to determine CRM status, and discussed the superiority of MRI for this indication (Wolberink et al 2007). Conventional CT had a sensitivity of only 43.3–46.7% and a specificity of 89.5–92.6% (Wolberink et al 2007). The negative predictive value of CT was 83.8–84.6%. As false positives are thought to be less important than false negatives (ie it is better for patients to be overstaged and receive more treatment than needed, than understaged and not receive enough), the sensitivity of CT was deemed by the authors to be too low for detecting involved CRMs, and thus to be used for this indication.

Treatment decisions may be based on whether the CRM is threatened or involved. Six studies reported on the accuracy of MRI for assessing CRM status in newly diagnosed patients. Only one of these studies included a population likely to be representative of those who would undergo the imaging in clinical practice, and thus was not subject to spectrum bias. Five studies reported on the accuracy of MRI for assessing whether the CRM is threatened or involved, as defined by a tumour or metastatic lymph node within 1 mm of the mesorectal fascia. Within these studies the false positive rate ranged between 0% and 16%. This means that up to 16% of patients who could have received primary surgery alone also underwent neoadjuvant therapy. While neoadjuvant therapy

may reduce the rate of local recurrence in all populations, the absolute rate of local recurrence among patients without a threatened CRM is very small. Therefore, overstaged patients would be risking a reduction in their quality of life for a treatment that may benefit only a small number of patients.

These five studies also reported that up to 59% of patients who had a threatened or involved CRM were not classified as such (false negatives). The implication of this is the increased likelihood that patients would have received primary surgery alone rather than the appropriate treatment of neoadjuvant therapy prior to surgery. As a positive CRM has been found to be a predictor of local recurrence, and neoadjuvant therapy assists in decreasing the rate of recurrence, a false negative staging result may result in patients having a higher risk of recurrence than if they were staged and treated correctly.

Without MRI (or MSCT should future evidence indicate that it is a viable alternative) for determining the involvement of the CRM, the Advisory Panel suggested that patients with stage 3 tumours (which may or may not involve the CRM) would receive neoadjuvant therapy, as it is better to overtreat than undertreat rectal carcinoma. Because all patients with a positive CRM will have T3 or T4 tumours, a false negative CRM means that patients who would otherwise have received neoadjuvant therapy on the basis of tumour stage would now be inappropriately treated. However, this assumption relies on the notion that these patients would otherwise receive neoadjuvant therapy, which is not always the case. A study of two hospitals in Sydney found that surgeons who treat up to four cases of rectal carcinoma per year were far less likely to refer patients for neoadjuvant or adjuvant therapy than surgeons who treated over 20 cases per year (Hegi-Johnson et al 2007). This study found that in 2001, the presence of a positive CRM did not influence radiotherapy usage ($p=0.9$) (Hegi-Johnson et al 2007).

It is unknown whether the proportion of patients (in the literature) who are staged incorrectly from MRI is consistent with current practice in Australia (where the usage of MRI for this indication is limited). ERUS and standard CT are accepted as poor predictors of CRM status, and the accuracy of MSCT is currently unknown, so treatment decisions are likely to be made without information on CRM involvement, and thus on the basis of tumour and nodal stages alone. It is clear that up to 45% of these patients could avoid unnecessary neoadjuvant therapy with the use of MRI for staging.

Assessment of tumour (T) stage has been the traditional method of determining prognosis, but it is limited in that, for patients with stage 3 tumours, there is large variability in prognosis depending on whether the mesorectal fascia is involved or not (MERCURY Study Group 2007). While it does not provide as much clinically useful information as a prediction of the CRM, it was a commonly reported outcome measure for the accuracy of MRI. Fourteen studies provided information on MRI at assessing T stage. One poor-quality study (level III-1 diagnostic evidence) found that MRI was similar to MSCT (accuracy of 100% versus 96%, respectively). Several studies reported much lower rates of accuracy for MRI prediction of T stage. No clear patterns were identified to explain the heterogeneity between studies.

Sixteen studies reported on the ability of MRI to determine regional lymph node status (N stage). MRI showed superior results compared to conventional CT and ERUS, and similar sensitivity and specificity to MSCT. If optimal criteria are established for defining suspicious lymph nodes, the accuracy of MRI should increase further. As with the other accuracy outcomes (CRM status and T stage), the N stage accuracy results were highly variable. Treatment decisions should therefore not be made on N stage prediction alone.

The reported accuracy of MRI varied considerably for all three conventional diagnostic accuracy outcome measures. As the use of phased array systems is still relatively new, it is likely that the accuracy of MRI will improve as the experience levels of radiologists increase. Many different techniques were used within the included studies. The studies were mostly limited to machines of 1.5 T or higher, with the exception of the large multicentre MERCURY study, which included results from two centres that used 1.0 T machines. Other variables included the use of contrast agents (gadolinium-based contrast, ultrasmall particles of iron or nothing), distension with water, different methods of bowel preparation, different numbers of elements within the phased array coil, and the use of antispasmodics. The variation in techniques and experience level of interpreters of MRI is likely to contribute to the heterogenous results.

Furthermore, the vast majority of studies were subject to spectrum bias, which may contribute to poor estimates of accuracy. Spectrum bias is due, in this case, to the treatment paradox. In order to assess the accuracy of MRI in newly diagnosed patients, only studies which reported on patients who received primary surgery or short-course radiotherapy were included, as intensive preoperative therapy such as long-course radiation or chemoradiotherapy would result in histopathology becoming an imperfect reference standard. When patients have received intensive preoperative therapy after MRI, the treatment may down-stage the tumour, and histopathology would no longer reflect the initial staging result.

An overall evaluation of the evidence on the accuracy of MRI within a newly diagnosed population is provided in Table 41.

Table 41 Body of evidence assessment matrix for evidence of diagnostic accuracy in newly diagnosed patients

Component	Excellent	Good	Satisfactory	Poor
Evidence base			level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency			some inconsistency reflecting genuine uncertainty around clinical question	
Clinical impact (N/A)				
Generalisability			population/s studied in body of evidence differ to target population but it is clinically sensible to apply this evidence to target population	
Applicability		applicable to Australian healthcare context with few caveats		

N/A = not applicable; diagnostic accuracy is part of the linked evidence approach; the clinical impact of MRI staging on health outcomes has yet to be determined.

Change in management

Staging of patients with rectal carcinoma by MRI or other methods is only worthwhile if it influences the way patients are managed.

One diagnostic accuracy study (level III-2 diagnostic evidence) reported that if treatment decisions had been based on MRI alone, compared to ERUS alone, MRI would have resulted in more patients being referred for primary surgery or long-course radiotherapy rather than short-course radiotherapy. This study was not ideal, as it was not reporting what treatments were actually received, and did not reflect the clinical setting where treatment decisions would be made based on a combination of MSCT and MRI or MSCT and ERUS. However, it showed that MRI results in more *selective* use of preoperative therapies in a setting where MSCT is not used. Three further uncontrolled studies (level IV interventional evidence) reported on the treatment decisions made subsequent to staging with MRI. The majority of patients in these studies were referred for primary surgery. An overall assessment of the body of evidence is outlined in Table 42.

Although one average-quality study was identified that reported that MSCT was as accurate as MRI at predicting CRM status, this study used a definition of the CRM that was unusual (tumour within 5 mm of the mesorectal fascia). The Advisory Panel therefore suggested that these results would not be clinically relevant. While it is possible that further evidence may be published on the accuracy of MSCT at predicting CRM involvement (where the tumour is within 1 mm of the mesorectal fascia), there is currently only one full-text article of a study addressing this (Sinha et al 2006). The addition of MRI is therefore highly likely to influence patient management, as physicians are unlikely to trust the results obtained from MSCT.

Without the use of MRI to visualise the CRM, a multidisciplinary panel may place higher emphasis on other factors in their decision-making process regarding what treatment a patient should receive. They would balance the likelihood of the patient tolerating preoperative chemoradiation, and how preoperative treatment would affect their quality of life, against the expected risk of local recurrence. Both Australian and international studies have found that patient age is a large predictor of whether a patient is likely to be given (neo)adjuvant treatment (Hegi-Johnson et al 2007; Martijn & Vulto 2007). The reasons for this are unclear (whether it is patient choice or medical concern that they would not tolerate treatment). It is possible that the use of MRI would *decrease* the amount of neoadjuvant therapy used within the younger population, who would have otherwise been more likely to receive neoadjuvant therapy, but may *increase* the use of neoadjuvant therapy in the older population. There is evidence to suggest that the older population may have a similar complications rate to the younger population. Therefore, if it is confirmed that they are at high risk of local recurrence due to CRM involvement, they may be more likely to receive such therapy. However, it is also possible that this change in patient management would not occur, as complications may have more serious consequences in the elderly.

MRI is only useful as a staging tool if the results are used to influence further treatment. If a patient is unlikely to receive neoadjuvant therapy, regardless of CRM status, due to comorbidities or a preference to avoid irradiation, then MRI should not be performed.

Table 42 Body of evidence assessment matrix for change in management

Component	Excellent	Good	Satisfactory	Poor
Evidence base				level IV studies
Consistency	all studies consistent			
Clinical impact (N/A)				
Generalisability		population/s studied in the body of evidence are similar to the target population		
Applicability				not applicable to Australian healthcare context

N/A = not applicable; change in management is part of the linked evidence approach; the clinical impact of MRI staging on health outcomes has yet to be determined.

Clinical benefit from change in management

A Cochrane systematic review reported that neoadjuvant therapy has been found to significantly reduce the rate of local carcinoma recurrence and allow a modest improvement in overall survival, but is also associated with decreased rectal and sexual functioning compared to surgery alone (Wong et al 2007). In order to assess whether MRI results in better patient outcomes, the *selective* use of neoadjuvant therapy was evaluated to determine if it had patient benefits. The Advisory Panel suggested that the use of MRI would result in patients with a threatened or involved CRM receiving preoperative therapy, and patients without a threatened CRM receiving primary surgery.

One study (Marijnen et al 2003) was identified that assessed the ability of preoperative radiotherapy to reduce local recurrence for patients of different CRM status. When the benefits of preoperative radiotherapy were stratified to compare the different effects in patients with involved versus uninvolved CRMs (measured by histopathology), preoperative radiotherapy was found to significantly reduce local recurrence within 2 years across all patient groups. Unfortunately, the pretreatment CRM status of patients is unknown, and it is possible that a small proportion of patients treated with neoadjuvant therapy may have had their tumour down-staged prior to their histopathology being analysed. The different treatment effects shown in this study for patients of varying CRM status may therefore vary slightly from actual CRM status determined preoperatively by MRI. In this study it is assumed that short-course radiation did not down-stage tumours in the 10 days between the initiation of irradiation and surgical resection. Based on the results of this study, 15 patients with a tumour or metastasised node less than 1 mm from the mesorectal fascia would need to be treated in order to prevent one case of local tumour recurrence. In comparison, 21 patients with more than 2 mm between the tumour or metastasised node and the mesorectal fascia would need to be treated by preoperative radiotherapy in order to prevent one case of local carcinoma recurrence.

If neoadjuvant therapy were without harms, treatment of *all* patients regardless of CRM status would be worthwhile, and there would be no patient benefit to staging with MRI. However, all treatments for carcinoma are associated with significant morbidities, which must be balanced against the benefits of treatment at reducing cancer persistence or recurrence (Australian Cancer Network Colorectal Cancer Guidelines Revision

Committee 2005). Unfortunately, no quality of life data were presented in the one included study on treatment effectiveness. From this study alone, it is impossible to determine the overall patient benefit of staging with MRI. As MRI is able to visualise the CRM, it can distinguish between patients who are at a higher risk of recurrence. Among patients with a high risk of local recurrence, neoadjuvant therapy may be of clinical benefit. However, in a population with less risk of recurrence, the side effects of neoadjuvant therapy may outweigh the benefits. Targeting the treatment to the individual's situation is therefore important.

An assessment of the one included study on the clinical benefit of selective neoadjuvant therapy is provided in Table 43.

Table 43 Body of evidence assessment matrix for clinical benefit from altered management

Component	Excellent	Good	Satisfactory	Poor
Evidence base		one level II study with low risk of bias		
Consistency (N/A)				
Clinical impact		substantial		
Generalisability		population/s studied in the body of evidence are similar to the target population		
Applicability		applicable to Australian healthcare context with few caveats		

N/A = not applicable

Is it effective for restaging of patients after neoadjuvant therapy?

Direct evidence

There was no direct evidence available for assessing health outcomes after patients were restaged with MRI compared with not being restaged, or restaged by another method. Diagnostic accuracy was therefore used to infer effectiveness.

MRI after neoadjuvant therapy may be used to assess where surgical dissection may be difficult, and identify patients who may benefit from further therapy (Allen et al 2007).

Linked evidence

Accuracy

With any diagnostic test, the implications of overstaging and understaging must be considered. After neoadjuvant therapy, overstaging of the CRM, T stage and N stage was common, due to the difficulty in distinguishing between tumour, residual non-tumorous tissue (such as fibrotic or necrotic tissue) and an inflammatory reaction (Hoffmann et al 2002).

For the small population of patients who undergo neoadjuvant therapy and are restaged in order to determine the appropriate surgical technique, the safety implications of an inaccurate staging result are different to those of newly diagnosed patients prior to any treatment. Overstaging may result in the removal of an organ that could have been retained had a correct restaging result been available. The alternative to restaging is to use an educated guess, based on the initial staging, with the potential to alter the surgical technique during surgery. Unfortunately, there was no direct evidence comparing patient outcomes when restaged with MRI (with the large potential for being overstaged due to the difficulty in distinguishing between tumorous tissue and fibrotic tissue) or if treatment is planned without restaging. If surgery after neoadjuvant therapy is planned based on initial staging results, an even greater proportion of patients would be overstaged.

Understaging is likely to result in the surgical margins being changed during the surgery. The impact this has on the patient is unclear, but would likely result in more psychological trauma than if they have had a chance to mentally prepare themselves for a particular procedure. The impact for the hospital would be that extra unplanned resources would be needed.

No studies were identified that compared the accuracy of MRI against the alternative or complementary techniques, ERUS or MSCT (with/without PET), in patients who have undergone neoadjuvant therapy. Nor were there any studies that assessed the safety of restaging with MRI compared to no restaging.

Only two studies (level III-2 diagnostic evidence) were identified that reported the accuracy of MRI for predicting CRM involvement after neoadjuvant therapy. In these studies 77–82% of patients were accurately staged. Overstaging occurred twice as frequently as understaging in one study. Only one study (level III-2 diagnostic evidence) reported on the rates of false positives and negatives from MRI prediction of CRM involvement in patients who were restaged after neoadjuvant therapy. This large multicentre study found that 27% of patients who had a clear CRM were predicted by MRI as having an involved or threatened CRM. Conversely, 6% of patients who had a threatened or involved CRM were misclassified as having a clear CRM.

The accuracy of restaging with MRI after neoadjuvant therapy was also compared with the accuracy of staging prior to neoadjuvant therapy (against the reference standard of histopathology) in three studies. All three studies found that MRI was less likely to overstage patients, in terms of tumour restaging, than at the initial MRI staging. However, two of the studies reported slightly higher overall accuracy from initial staging than at restaging.

Overstaging was also a common problem when assessing T stage and N stage within this population, particularly among those patients who responded to the neoadjuvant therapy. Despite these limitations, MRI was as accurate as, or more accurate than, the comparative restaging techniques. One small study found that MRI and MSCT had similar results for T and N staging. MRI was more accurate overall than PET at N staging, but overstaging was far more common with MRI than with PET (31% versus 4%). One average-quality study reported results from initial experience with MRI. It was found to be less accurate at predicting T stage than ERUS or conventional CT, and less accurate at predicting N stage than CT. However, it is unclear what type of MRI was used for this study, and results would likely have been affected by a radiologist learning curve.

Table 44 provides an overview of the evidence on the accuracy of using MRI for restaging of patients after neoadjuvant therapy.

Table 44 Body of evidence assessment matrix for diagnostic accuracy of restaging of patients after neoadjuvant therapy

Component	Excellent	Good	Satisfactory	Poor
Evidence base			level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency		most studies consistent and inconsistency may be explained		
Clinical impact (N/A)				
Generalisability		population/s studied in the body of evidence are similar to the target population		
Applicability		applicable to Australian healthcare context with few caveats		

N/A = not applicable; diagnostic accuracy is part of the linked evidence approach; the clinical impact of MRI staging on health outcomes has yet to be determined

Change in management

No studies reported on the impact of MRI restaging on the management of patients who had neoadjuvant therapy. The assumption is that patients whose tumours are down-staged from chemoradiotherapy would be treated differently to those who do not respond to neoadjuvant therapy.

Bujko, Kepka et al (2006) performed a systematic review to determine whether rectal tumour shrinkage from neoadjuvant therapy increased the likelihood of anterior resection. They did this by assessing randomised trials that compared different preoperative treatments against a control group, resulting in smaller tumours in the experimental group. They then assessed whether patients were more likely to receive sphincter-preserving anterior resection if they had undergone neoadjuvant therapy. It was not specified how the tumour size was determined (hence, the study did not meet the inclusion criteria for the current systematic review). The differences in anterior resection rates varied between 19% in favour of the experimental group and 12% in favour of the control. Overall, tumour shrinkage by neoadjuvant therapy was not associated with a statistically significantly higher rate of anterior resections (Bujko, Kepka et al 2006). The authors suggested that if preoperative therapy was not able to reduce the rate of permanent stomas required, it may result in worse outcomes due to the side-effects of radiation. However, several of the included studies were performed prior to 1995, and the applicability of these results to current practice is unknown. In order to ascertain whether restaging with MRI after neoadjuvant therapy results in better health

outcomes for the patient, further research is needed to determine the validity of this assumption.

As many of the studies of diagnostic accuracy of MRI after neoadjuvant therapy report that MRI is unable to differentiate between fibrotic tissue and tumour, several authors have suggested that surgery be performed according to pretreatment staging due to the inaccuracy of MRI after chemoradiotherapy (Chen et al 2005; Kuo et al 2005; Torkzad et al 2007; Hoffmann et al 2002).

Is it effective for patients with recurrent rectal carcinoma?

Direct evidence

There was no direct evidence reporting on whether patients have better health outcomes if local recurrence is diagnosed or ruled out by MRI, or if staging of locally recurrent carcinoma with MRI results in better health outcomes than staging by other methods.

Accuracy

Local recurrence occurs in 30–50% of patients who undergo abdominal–perineal resection for rectal carcinoma (Torricelli et al 2003). While surveillance with MRI for recurrent rectal carcinoma is not recommended (Berman et al 2000; Titu et al 2006), MRI may be used in patients suspected of having recurrence. Detection of recurrence at an early stage may be difficult due to scarring from previous surgery, or inflammation or fibrosis resulting from adjuvant chemotherapy or radiotherapy (Torricelli et al 2003).

One very small low-quality study reported that MRI was slightly more accurate than conventional CT at diagnosing recurrence. However, the small sample size precludes any definitive conclusions. In two further poor- to average-quality diagnostic accuracy studies, MRI was moderately to highly accurate at diagnosing recurrent carcinoma (83–94% accuracy). These studies reported that MRI resulted in 7–20% of patients who had local recurrence being misdiagnosed as being carcinoma free. Meanwhile, 0–60% of patients who were disease free were classified as having a local recurrence.

The NHMRC *Guidelines for the prevention, early detection and management of colorectal cancer* suggest that PET is probably the best available method for distinguishing recurrence of rectal carcinoma from fibrosis (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005), but no evidence was available comparing MRI against PET for this indication. The MSAC decision regarding funding for recurrent colorectal cancer is occurring concurrently with this application.

Table 45 Body of evidence assessment matrix for evidence of diagnostic accuracy in patients suspected of having local recurrence

Component	Excellent	Good	Satisfactory	Poor
Evidence base				level IV studies, or level I to III studies with high risk of bias
Consistency			some inconsistency reflecting genuine uncertainty around clinical question	
Clinical impact (N/A)				
Generalisability			population/s studied in body of evidence different to target population but it is clinically sensible to apply this evidence to target population	
Applicability			probably applicable to Australian healthcare context with some caveats	

N/A = not applicable; diagnostic accuracy is part of the linked evidence approach; the clinical impact of MRI staging on health outcomes has yet to be determined

Change in management and clinical benefit from change in management

It is unclear how the management of patients suspected of having local recurrence may change if MRI were funded for this indication. No studies were identified reporting on the ability of MRI to influence management in this patient population. While it is hypothesised that accurate diagnosis may assist in allowing the patient to be treated more effectively, the vast majority of cases of local recurrence are inoperable and incurable (Australian Cancer Network Colorectal Cancer Guidelines Revision Committee 2005). If diagnosis of recurrence does not result in a change in management, patient benefits are likely to be limited to psychological outcomes rather than physical health outcomes.

What are the economic considerations?

One cost-effectiveness analysis compared the resource effects of staging with MRI versus ERUS (Brown et al 2004). It is expected that, in Australia, the vast majority of patients would receive MSCT prior to MRI or ERUS (see Figure 2, page 6). In addition, as the current limited evidence does not rule out a role for MSCT in predicting CRM involvement (the primary outcome), the appropriate comparison would be MSCT plus MRI versus MSCT with/without ERUS. The study by Brown and colleagues therefore does not reflect clinical practice in Australia.

Studies comparing the accuracy of MSCT plus MRI against MSCT alone were not available, so it is unknown whether the addition of MRI would result in increased accuracy for staging of rectal carcinoma. It is also unknown whether this potential increased accuracy would be worth the additional cost. However, MRI is currently the only imaging modality that is established as accurate for predicting CRM involvement.

Hence, it is expected that if MRI were funded, it would result in a change in management that would assist treatment decisions to be made based on CRM status, which is expected to improve health outcomes. If evidence is produced that MSCT is as accurate as MRI at visualising the CRM, and if it is found that MSCT plus MRI is no more effective than MSCT alone, treatment decisions could potentially be made based on imaging with MSCT without a requirement for MRI. However, even if this were the case, there would be patients in whom MSCT would be unlikely to be able to evaluate the CRM (eg those with low or anterior tumours). Therefore, MRI would still be a useful additional staging tool.

In the absence of evidence that MRI plus MSCT is more accurate than MSCT alone, a cost-effectiveness analysis could not be undertaken and a financial incidence analysis was all that was required. It is assumed that, for the majority of patients, MRI would be used as an additional locoregional staging technique. If 3,000 people are estimated to receive MRI per year for newly diagnosed rectal carcinoma, the expenditure borne by the Australian Government is predicted to be $1,013,174. However, if 12% of patients would otherwise have received ERUS, and 53% of those would be expected to receive ERUS as a public patient in a public hospital, the reduction in ERUS procedures would result in a cost saving of $34,380 to the states and territories. This is due to the unusual situation that the Australian Government funds MRI procedures that occur both in the private *and public* hospital systems.

If the definition of high-risk rectal carcinoma is changed from T3/T4 or N1 to CRM positive or N1, it is expected that there would be 818 patients per year in Australia who would have received neoadjuvant therapy previously but would no longer be recommended for it. This reduction in neoadjuvant therapy is estimated to save the Australian Government $1,512,661 and society $6,798,589. If these cost savings are used to offset the costs of MRI for newly diagnosed rectal carcinoma, there would be an overall cost saving of $499,487 to the Australian Government and of $5,636,565 to society. The downstream costs or savings that may result from any change in the rate of adjuvant therapy, toxicities or impact on rates of recurrence are unknown at this time.

Restaging with MRI is estimated to cost the MBS $34,275 per year and society $40,575. These costs may potentially be offset by the benefits of being able to more accurately plan the resources required when undertaking subsequent surgery.

MRI is not proposed as a means of surveillance for patients who have been treated for rectal carcinoma; however, it may be used as a means of investigating cases suspected as having local tumour recurrence. If 150 patients are investigated per year with MRI for tumour recurrence, there would be an incremental expenditure of $50,703 borne by the Australian Government.

Conclusions

Safety

No physical harms were reported as resulting directly from the MRI staging procedure or the comparative staging techniques. Harms are very rare provided suitable precautions are taken. However, patients must be screened for ferromagnetic or electrical implants prior to a MRI, as they may dislodge or become disrupted by the strong magnetic fields. A small proportion of patients will suffer from claustrophobia and so find the MRI procedure distressing.

Harms may arise as a result of incorrect staging, so safety is linked to the accuracy of the staging techniques.

Effectiveness

Two retrospective studies reported that staging of newly diagnosed patients with MRI results in better health outcomes than without MRI (using circumferential resection margin (CRM) involvement as a surrogate outcome). However, there were too many confounding factors to attribute the improved health outcomes to the staging alone rather than the different management techniques used between the populations.

A linked evidence approach was therefore used to determine whether MRI improves health outcomes.

MRI is currently the only locoregional staging modality that has established accuracy for predicting the outcome most useful for influencing patient management—the CRM. There was very little evidence comparing the accuracy of MRI against other forms of preoperative imaging. One small study reported that multi-slice computed tomography (MSCT) had similar results to MRI for predicting the CRM, but these results were deemed clinically irrelevant due to the atypical definition of CRM used. On the basis of one study per comparison, MRI and MSCT appear to have similar accuracy for predicting T stage and N stage, while MRI was more accurate at predicting N stage than either conventional CT alone or endorectal ultrasound (ERUS). The expert opinion of the Advisory Panel is that MRI provides superior contrast resolution to MSCT and is more effective at defining the CRM.

Use of MRI to determine whether patients should receive neoadjuvant therapy or proceed to primary surgery is likely to result in an increased number of patients being recommended for primary surgery when compared to patients staged by conventional CT or ERUS. However, this depends on the assumption that patients would otherwise have received neoadjuvant therapy, which is not always the case, particularly in the elderly. While decreasing the use of neoadjuvant therapy will result in slightly higher rates of local recurrence, it is likely that quality of life will be improved for those who are not at high risk of recurrence. Conversely, for the elderly population, an increase in the use of neoadjuvant therapy may result in a decrease in local recurrence but also a decrease in quality of life. The evidence is still contradictory on whether neoadjuvant therapy improves overall survival in this population. These factors would need to be balanced before any treatment decisions are made. Unfortunately, this systematic review did not

identify any studies that reported on patient quality of life or overall survival, so the true impact of MRI is unknown. Furthermore, from the current evidence, it is unknown whether MSCT would result in a similar change in management as that expected with MRI, should evidence of the accuracy of MSCT at visualising the CRM become established.

There was no evidence relating to whether patients who are restaged with MRI after receiving neoadjuvant therapy have better health outcomes than those restaged by any other method or not restaged. Because MRI was often unable to distinguish between tumorous tissue and fibrous or necrotic tissue resulting from neoadjuvant therapy, large proportions of patients were overstaged. While the diagnostic accuracy of MRI was less than optimal within this patient group, comparative staging techniques such as MSCT were also only moderately accurate. Although the overall accuracy of restaging using positron emission tomography (PET) was low, few patients were overstaged using this method.

MRI was found to be moderately to highly accurate at diagnosing local recurrence but the impact of this on patient outcomes is also unclear.

Cost considerations

It is estimated that funding MRI for newly diagnosed patients would cost $1,162,024 to society, of which $1,103,174 would be borne by the Australian Government. It is possible that the additional costs would be counteracted by less use of neoadjuvant therapy. The cost offset to the Australian Government of reduced neoadjuvant therapy is estimated to be $1,512,661 per year. If the cost savings from reduced neoadjuvant therapy use are used to offset the costs of MRI, there would be an overall cost saving of $499,487 to the Australian Government and $5,636,565 to society.

If, prior to surgery, 100 patients undergo MRI after receiving neoadjuvant therapy, the cost to the Australian Government will be $34,275 per year.

If MRI were funded for the diagnosis/staging of patients with suspected or diagnosed local tumour recurrence, it is estimated that MRI would cost the Australian Government $50,703 per year.

Recommendation

MSAC has considered the safety, effectiveness and cost-effectiveness of magnetic resonance imaging (MRI) for the initial staging, restaging and diagnosis of recurrence of rectal carcinoma in addition to conventional imaging.

MSAC finds that MRI for the initial staging, restaging and diagnosis of recurrence of rectal carcinoma is safe.

MSAC finds MRI for the initial staging of rectal cancer to be effective because MRI is able to define the circumferential resection margin of rectal carcinoma, which is highly predictive of the rate of local recurrence.

MSAC finds that MRI for the initial staging of rectal carcinoma is likely to be cost-effective.

MSAC recommends that public funding is supported for the initial staging of rectal carcinoma by MRI. There is insufficient evidence to support public funding for the restaging and diagnosis of recurrence of rectal carcinoma by MRI.

The Minister for Health and Ageing noted this advice on 28 August, 2008.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumer health, and health administration and planning:

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	General surgery
Professor Brendon Kearney (Deputy Chair)	Health administration and planning
Dr William Glasson (Second Deputy Chair)	Ophthalmology
Associate Professor John Atherton	Cardiology
Associate Professor Michael Cleary	Emergency medicine
Associate Professor Paul Craft	Clinical epidemiology and oncology
Professor Geoff Farrell	Gastroenterology
Dr Kwun Fong	Thoracic medicine
Professor Richard Fox	Oncology
Professor Jane Hall	Health economics
Professor John Horvath	Department of Health and Ageing Chief Medical Officer
Associate Professor Terri Jackson	Health economics
Associate Professor Frederick Khafagi	Nuclear medicine
Dr Ray Kirk	Health research
Dr Ewa Piejko	General practice
Dr Ian Prosser	Haematology

Ms Sheila Rimmer	Consumer health issues
Dr Judy Soper	Radiology
Professor Ken Thomson	Radiology
Dr David Wood	Orthopaedics
Mr Peter Woodley	Department of Health and Ageing representative

Appendix B Advisory Panel and Evaluators

Advisory panel application 1110 - MRI staging of rectal carcinoma

Advisory panel	
Associate Professor Michael Cleary (Chair)	Member of MSAC Emergency Medicine
Dr K Chip Farmer	Royal Australasian College of Surgeons nominee Colorectal surgery
Dr David Gillespie	Former member of MSAC Gastroenterology
Dr Jeremy Sharr	Royal Australian and New Zealand College of Radiologists nominee Radiology
Mr Brian Stafford	Consumer Health Forum nominee Consumer health issues
Dr Niall Tebbutt	Medical Oncology Group of Australia nominee Oncology
Evaluators	
Ms Skye Newton, Research Officer Ms Hedyeh Hedayati, Research Officer Dr Shuhong Wang, Health Economist Mr Thomas Sullivan, Research Officer Ms Tracy Merlin, Manager Prof Janet Hiller, Director	Adelaide Health Technology Assessment (AHTA), School of Population Health and Clinical Practice, University of Adelaide
Dr Jackie Street, Lecturer and Consultant	Discipline of Public Health, School of Population Health and Clinical Practice, University of Adelaide

Appendix C Search strategies

Literature sources

Electronic bibliographic databases were searched to find relevant studies (those meeting the inclusion criteria) addressing each of the research questions developed for this MSAC assessment. These databases are described in Table 46. MRI machines of 1.5 T field strength have been used in clinical practice since the late 1990s. Therefore, the search period was restricted to between 1995 and June 2007.

Table 46 Bibliographic databases

Electronic database	Time period
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1995 – 6/2007
Current Contents	1995 – 6/2007
Embase.com (including Embase and Medline)	1995 – 6/2007
Pre-Medline	6/2007
ProceedingsFirst	1995 – 6/2007
Web of Science – Science Citation Index Expanded	1995 – 6/2007
EconLit	1995 – 6/2007

Search terms for identifying literature within these bibliographic databases are given below. Table 47 describes the search terms used to identify studies of direct evidence, diagnostic accuracy and change in management (for all three indications). Table 48 describes the search terms used to identify treatment effectiveness studies (for newly diagnosed patients and those suspected of having or diagnosed as having recurrent rectal carcinoma). Studies addressing one research question may have been identified within the evidence-base collated to address a different research question.

Table 47 Search terms for MRI rectal carcinoma staging

Element of clinical question	Search terms
Population	((rectal OR rectum OR "rectum"[MeSH]) AND (cancer OR cancerous OR cancers OR malignan* OR neoplas* OR "neoplasms"[MeSH] OR carcinoma OR "carcinoma"[MeSH] OR adenocarcinoma OR tumour* OR tumor)) OR "rectal neoplasms"[MeSH]
Intervention/test	magnetic resonance imag* OR MRI OR "magnetic resonance imaging"[MeSH]
Comparators (if applicable)	N/A
Outcomes (if applicable)	N/A
Limits	Human; 1995–2007

MeSH = Medical Subject Heading, based on a Medline/PubMed platform

Table 48 Search terms to identify treatment effectiveness studies (based on primary staging of newly diagnosed or recurrent rectal carcinoma)

Element of clinical question	Search terms
Target population	(((rectal OR rectum OR "rectum"[MeSH]) AND (cancer OR cancerous OR cancers OR malignan* OR neoplas* OR "neoplasms"[MeSH] OR carcinoma OR "carcinoma"[MeSH] OR adenocarcinoma OR tumour* OR tumor* OR tumorous)) OR "rectal neoplasms"[MeSH]) AND ("mesorectal fascia" OR "resection margin" OR CRM OR "fascia propria")
Intervention/test	(preoperative OR adjunctive OR neoadjuvant OR adjuvant) AND (radiation OR radiotherapy OR chemoradiation OR chemoradiotherapy) OR "radiotherapy, adjuvant"[MeSH] OR "chemotherapy, adjuvant"[MeSH]
Comparator (if applicable)	N/A
Outcomes	N/A
Limits	Human; 1995– 2007

MeSH = Medical Subject Heading, based on a Medline/PubMed platform

Additional sources of literature—peer-reviewed or grey literature—were sought from the sources outlined in Table 49 and from the health technology assessment agency websites provided in Table 51. Websites of specialty organisations were also searched for any potentially relevant information (Table 50).

Table 49 Additional sources of literature

Source	Location
Internet	
NHMRC- National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	http://www.update-software.com/National/
Google Scholar	http://scholar.google.com/
Hand searching (journals 2006–07)	
Diseases of Colon and Rectum	Library or electronic access
Colorectal Disease	Library or electronic access
Journal of Magnetic Resonance Imaging	Library or electronic access
Imaging Decisions MRI	Library or electronic access
Expert clinicians	
Studies other than those found in regular searches	MSAC Advisory Panel
Pearling	
All included articles had their reference lists searched for additional relevant source material	

Specialty websites

Table 50 Specialty organisation websites

RECTAL CANCER	
The Cancer Council of Australia	http://www.cancer.org.au
The American Cancer Society	http://www.cancer.org
Bowel Cancer UK	http://www.bowelcanceruk.org.uk
Cancer Research UK	http://www.cancerhelp.org.uk
Colorectal Cancer Coalition	http://www.c-three.org
RADIOLOGY	
The Royal Australian and New Zealand College of Radiologists	http://www.ranzcr.edu.au
SURGICAL	
The Colorectal Surgical Society of Australia and New Zealand	http://www.cssa.org.au
The Royal Australasian College of Surgeons	http://www.surgeons.org
The American Gastroenterological Association	http://www.gastro.org
The American Society of Colon and Rectal Surgeons	http://www.fascrs.org

Table 51 Health Technology Assessment Agency websites

AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/open/asernip-s.htm
Centre for Clinical Effectiveness, Monash University	http://www.mihsr.monash.org/cce
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/che/
AUSTRIA	
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita/e1-3.htm
CANADA	
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.php/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Institute of Health Economics	http://www.ihe.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/engelsk.html
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://www.stakes.fi/EN/index.htm

FRANCE	
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gr.nl/index.php
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
NORWAY	
Norwegian Knowledge Centre for Health Services	http://kunnskapssenteret.no
SPAIN	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS)	http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/salud/orgdep/AETSA/default.asp?V=EN
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.aatrm.net/html/en/Du8/index.html
SWEDEN	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/english/publications
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/www/index.asp
SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.hta.nhsweb.nhs.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry	http://www.tufts-nemc.org/cearegistry/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/consumertec/index.html
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.va.gov/resdev

Table 52 Study profiles of included studies of direct evidence of MRI in newly diagnosed patients

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Health outcomes	Comments
(Beets-Tan et al 2005) The Netherlands University Hospital of Maastricht 1993–97 compared with 1998–2000	Level III-3 interventional evidence Historical control study Medium quality (NHS CRD = 4/6)	n=311	Inclusion Patients with primary rectal cancer between 1993–97 and 1998–2002 Exclusion Patients with palliative resection because of incurable metastatic disease Patient characteristics 1993–97 n=147 1998–2002 n=165	Index test Routine use of preoperative MRI Comparator Restricted use of preoperative CT for obvious advanced cases of rectal cancer	Proportion of complete resections	Confounded by other changes that occurred over the time period that MRI was introduced (in mid 1990s TME principles were standardised, and short-course 5x5 Gy^2 radiotherapy became standardised in 2001)
(Burton et al 2006b) United Kingdom Royal Marsden Hospital Jan 1999 – Dec 2002	Level III-2 interventional evidence Retrospective cohort study Medium quality (NHS CRD = 4/6)	n=259/ 298	Inclusion Patients with biopsy-proven primary rectal cancer who were categorised non-palliative by preoperative MRI Exclusion Refused surgery Patient characteristics Median age = 67 years (range 28–88) 125 females, 173 males	Index test 1.5 T pelvic MRI with PPA coil and abdominal CT with either chest X ray or CT thorax with multidisciplinary discussion of MRI Comparator No multidisciplinary discussion of MRI	Proportion of complete resections	Not strictly MRI compared to no MRI, as some of the patients whose results were not discussed received MRI

TME = total mesorectal excision; PPA = pelvic phased array

Table 53 Study profiles of included studies for accuracy of MRI in newly diagnosed patients

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
(Akasu et al 2005) Japan National Cancer Center Hospital, Tokyo June 2001 – April 2002	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients Q1 High quality (QUADAS = 13/14) CX, P1	n=34	Inclusion Patients with primary rectal cancer proven by biopsy Exclusion Not stated Patient characteristics 9 women, 25 men Median age = 57 years (range 34–82) No preoperative radiation therapy	Index test 1.5 T whole-body system MRI with wraparound quadrature PPA coil, supine position, intramuscular antispasmodic administered T2-weighted sequences 1 radiologist and 1 colorectal surgeon interpreted images in consensus Reference standard Histology, fixated with formalin, embedded in paraffin, slice thickness not stated	CRM Sn, Sp, PPV, NPV, FP rate, FN rate T stage Accuracy	
(Arii et al 2006) Japan Wakayama Medical University May 1999 – Dec 2003	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients Q1 High quality (QUADAS = 12/14) CX, P1	n=53	Inclusion Patients with lower rectal cancer undergoing curative resections Exclusion Not stated Patient characteristics 14 women, 39 men Mean age = 62 years (range 34–83) No radiotherapy or chemotherapy given	Index test 1.5 T MRI with PPA coil (Magnetom Vision Plus; Siemens), no bowel preparation, no mention of contrast agent 2 independent radiologists assessed images, used consensus Comparator CT (pelvis) (Aquilon; Toshiba Medical Systems), spiral single CT with 10 mm intervals, before and after contrast medium (Iopromide) 2 independent radiologists assessed images, used consensus Reference standard Histology fixated with formalin, section thickness not stated	T stage Accuracy N stage (regional, lateral) Sn, Sp, PPV, NPV	Data on accuracy of CT were available for N stage, but not T stage

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
(Brown et al 2003) United Kingdom University Hospital of Wales, Llandough Hospital NHS Trust Time period not stated	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P1	n=42	Inclusion Biopsy determined rectal carcinoma patients who underwent TME Exclusion Not stated Patient characteristics Not stated 22 patients with nodal metastases 437 lymph nodes harvested Unclear if patients received neoadjunctive therapies	Index test 1.5 T MRI with PPA coil (Horizon Advantage, version 5.62; GE Medical Systems), no contrast agent or antiperistaltic agents, supine position T2-weighted sequences 2 radiologists assessed images independently Reference standard Histology, fixation and slice thickness not stated	N stage Sn, Sp, PPV, NPV	Likely overlap with (Brown et al 2004)
(Burton et al 2006a) United Kingdom Mayday University Hospital, Royal Marsden Hospital Jan 1999 – Dec 2002	Level III-2 diagnostic evidence Retrospective cohort study, blinding not stated, consecutive patients Q1 High quality (QUADAS = 13/14) CX, P2	n=75	Inclusion Patients with upper rectal, rectosigmoid, and distal sigmoid cancer referred for MRI Exclusion Not stated Patients characteristics 34 women, 41 men Median age = 65 years (range 37–86) 57/75 went to primary surgery	Index test 1.5 T MRI (Siemens) with a PPA coil, supine position, no intravenous antiperistaltic agents or contrast agents T2-weighted sequences Single radiologist Reference standard Histopathology, fixation and thickness not stated	CRM Sn, Sp, PPV, NPV, FP rate, FN rate T stage Accuracy N stage Sn, Sp, PPV, NPV	Overlap with (Burton et al 2006b)
(Chun et al 2006) South Korea Sunkyunkwan University School of Medicine	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients Q1 High quality (QUADAS = 12/14)	n=24	Inclusion Patients with histopathologically proven primary rectal cancer who underwent preoperative MRI and endorectal ultrasound and had surgical resection Exclusion Patients who received preoperative radiation or	Index test 3.0 T MRI (Intera Achieva 3T, Philips Medical Systems) using a 6-element PPA coil (SENSE), no antiperistaltic agents, rectal cleansing using suppository pills, distension with water T1- & T2-weighted sequences 3 experienced observers blinded to each other and	N stage Accuracy	Patients overlap with (Kim et al 2006)

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
Nov 2004 – June 2005	CX, P2		chemotherapy, refused surgery, inoperable, anal fistula or endometriosis in the rectum Patient characteristics 12 women, 12 men Mean age = 59 years (range 32–79)	histopathology Comparator Endorectal ultrasound Reference standard Histology, fixated with formalin, sliced at 3-mm intervals		
(Ferri et al 2005) Italy University of Rome – 'La Sapienza' Dec 1999 – June 2003	Level II diagnostic evidence Cohort study (unclear if retrospective or prospective), blinded, consecutive patients Q1 High quality (QUADAS = 12/14) CX, P2	n=33	Inclusion Patients with biopsy proven tumours localised within 15 cm of anal verge Exclusion Did not undergo MRI, had a cardiac pacemaker or an intraocular lens implant, incomplete MRI due to claustrophobia, not operated on due to disseminated disease, or had locally recurrent tumour, or had received preoperative chemoradiotherapy Patient characteristics 10 women, 23 men Mean age = 66±10 years	Index test 1.5 T MRI (Magnetom Vision plus; Siemens) with a PPA body coil, supine position, no rectal lumen distension or contrast medium used T2-weighted sequences Image evaluation by consensus of 2 radiologists blinded to clinical data Reference standard Histopathology, fixed in formalin, slice thickness not stated	CRM Sn, Sp, PPV, NPV, FP rate, FN rate T stage Accuracy N stage Sn, Sp, PPV, NPV	
(Gagliardi et al 2002) United States of America Yale University School of Medicine Time not stated	Level III-2 diagnostic evidence Cohort study (unclear if retrospective or prospective), blinding not stated, consecutive patients Q3 Insufficient information (QUADAS = 9/14) CX, P2	n=28	Inclusion Patients with biopsy proven rectal cancers Exclusion Patients who received neoadjuvant therapy Patient characteristics 10 women, 18 men Mean age = 63 years (range 26–89)	Index test 1.5 T MRI (Signa; GE Medical Systems) with a PPA surface coil, prone position following air insufflation, no bowel preparation used T1- & T2-weighted sequences Single radiologist Reference standard Histopathology, fixation and thickness not stated	T stage Accuracy N stage Sn, Sp, PPV, NPV	

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
(Hadfield et al 1997) United Kingdom Royal Hull Hospitals, Castle Hill Hospital Time not stated	Level III-1 diagnostic evidence Prospective cohort study, blinded, not stated if consecutive Q3 Insufficient information (QUADAS = 9/14) CX, P1	n=38	Inclusion Patients with biopsy proven rectal carcinoma Exclusion Not stated Patient characteristics 10 women, 28 men Mean age = 69 years (range 38–89) Not stated if patients had neoadjuvant therapy	Index test 1.5 T MRI (Signa Advantage; IGE Medical Systems) with a PPA coil (IGE Medical Systems). Supine position after intravenous injection of hyoscine butylbromide T1- & T2-weighted sequences Staged by a single radiologist Reference standard Histopathology	T stage Accuracy N stage Sn, Sp, PPV, NPV	
(Kim et al 2008) South Korea Yonsei University College of Medicine Dec 2005 – Sept 2006	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients Q1 High quality (QUADAS = 12/14) CX, P2	n=57	Inclusion Patients with biopsy proven primary rectal cancer Exclusion Upper rectal tumour located above 10 cm from anal verge or above the peritoneal reflection, or lower rectal tumour located less than 5 cm from the anal verge or a T4 lesion according to TNM classification. Patients with a history of previous pelvic irradiation Patient characteristics 24 women, 33 men Median age = 62 years (range 30–81) Stage T1 – 7 patients Stage T2 – 10 patients Stage T3 – 40 patients	Index test 1.5 T whole-body system MRI with 4-channel SENSE body coil (Philips Medical Systems), no bowel preparation, air insufflation, or antispasmodic agents used T1- & T2-weighted sequences Single radiologist Reference standard Histology, fixed with formalin, sections at 5 mm	CRM Sn, Sp, PPV, NPV, FP rate, FN rate T stage Accuracy N stage % agreement	Population restricted to stages T1–T3

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
(Kim et al 2000) South Korea Yonsei University College of Medicine Feb 1997 – Dec 1999	Level III-2 diagnostic evidence Cohort study (not stated if retrospective or prospective), blinding not stated, consecutive patients Q3 Insufficient information (QUADAS = 9/14) CX, P1	n=217	Inclusion Patients with histopathologically proven primary rectal cancer Exclusion Not stated Patient characteristics Not stated Neoadjunctive treatments not mentioned	Index test 1.5 T MRI, (Horizon, General Electric Medical Systems) coil type not stated, contrast (gododiamide) administered intravenously T1- weighted sequences 2 radiologists interpreted images Reference standard Histology	T stage Accuracy N stage Sn, Sp, PPV, NPV	Possible overlap in patients with (Oh et al 2005)
(Kim et al 2004) South Korea Yonsei University College of Medicine Jan 2002 – Aug 2002	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P2	n=62	Inclusion Presumed diagnosis of rectal carcinoma Exclusion Preoperative chemoradiotherapy before surgery, finally diagnosed with conditions other than rectal carcinoma, or no surgery performed Patient characteristics Not stated No neoadjunctive treatments given	Index test 1.5 T MRI (Signa Horizon, General Electric Medical Systems) with PPA coil, no bowel preparation, scopolamine butylbromide used if not contraindicated, with or without water distension T1- & T2-weighted sequences 2 independent radiologists Reference standard Histology, slice thickness and fixation not stated	N stage Sn, Sp	Study comparing MRI when rectum is non-distended and distended
(Kim et al 2006) South Korea Sunkyunkwan University School of Medicine Nov 2004 – July 2005	Level III-2 diagnostic evidence Retrospective cohort study, blinding not stated, consecutive patients Q1 High quality (QUADAS = 12/14) CX, P2	n=35	Inclusion Patients with histopathologically proven primary rectal cancer who underwent preoperative MRI and had surgical resection Exclusion Patients who received preoperative radiation or chemotherapy, refused surgery, inoperable, anal fistula or endometriosis in the rectum Patient characteristics 15 women, 20 men Mean age = 57 years (range 45–74)	Index test 3.0 T MRI (Intera Achieva 3T, Philips Medical Systems) using a 6-element PPA coil (SENSE), no antiperistaltic agents, rectal cleansing using suppository pills, distension with water T1- & T2-weighted sequences 3 experienced observers blinded to each other and histopathology Reference standard Histology, fixated with formalin, sliced at 3 mm intervals	T stage Accuracy N stage Sn, Sp, PPV, NPV	Results for N stage are the mean of 3 observers Patients overlap with (Chun et al 2006)

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
(Koh et al 2004) United Kingdom Royal Marsden Hospital, Epsom General Hospital, St Helier's General Hospital Time period not stated	Level III-2 diagnostic evidence Prospective cohort study, not blinded, consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P2	n=12	Inclusion Newly diagnosed rectal cancer, candidates for primary TME and who had nodes visible within the mesorectum but were judged to be node negative or to have N1 (TNM classification) at T2-weighted MR staging Exclusion Prior neoadjuvant treatment Patient characteristics 5 women, 7 men Mean age = 62 years (range 53–75)	Index test 1.5 T MRI with PPA coil (Magnetom Vision; Siemens), contrast—ultrasmall particles of iron oxide (USPIO), supine position T2-weighted sequences 2 radiologists assessed images independently and in consensus Reference standard Histology section 3 mm Fixated with formalin	N stage PPV	Population for this study is very specific—the 14 patients who fitted the criteria came from a total of 140 patients referred for MRI This study assesses MRI with USPIO, which is not standard practice in Australia
(Low et al 2003) United States of America Sharp Memorial Hospital 1997–2002	Level III-2 diagnostic evidence Retrospective cohort study, blinding not stated, consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P1	n=21	Inclusion Patients referred for presurgical MRI of the abdomen and pelvis Exclusion Not stated Patient characteristics 21 patients with rectal cancer, from 48 consecutive patients (47 with colon cancer) 22 women, 26 men Mean age = 65 years (range 38–90) Unclear if patients received neoadjuvant therapy	Index test 1.5 T MRI (Signa, GE Medical Systems), with oral contrast material, body coil used in 27 patients, combined body coil for abdomen and PPA coil for pelvis (n=19), dynamic gadolinium-enhanced imaging after intravenous contrast injection T1- & T2-weighted sequences One of 2 radiologists Reference standard Surgical reports, interviews of the surgeon immediately after laparotomy, or histopathology	T stage Accuracy N stage Accuracy	
(Matsuoka et al 2003a) Japan Kyorin University	Level II diagnostic evidence Prospective cohort study, blinded, consecutive patients	n=19	Inclusion Consecutive patients with rectal or anal tumour Exclusion Not stated Patient characteristics	Index test 1.5 T MRI with PPA coil (Magentom Vision; Siemens), gadolinium enhanced, scopolamine butylbromide to reduce motion artefacts, position not stated T1- & T2-weighted sequences	T stage Accuracy N stage Sn, Sp, PPV, NPV	Article compared endorectal coil with phased array coil. Only the phased array results have been

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
Dec 1999 – Sept 2001	Q1 High quality (QUADAS = 12/14) CX, P1		17 patients with rectal carcinoma, 2 with malignant melanoma of anal canal 4 women, 15 men Mean age = 62 years No radiotherapy or chemotherapy	Specialist radiologist blinded to colonoscopy or barium enema results Reference standard Histology evaluated without knowing of MRI findings, fixation not stated, slice thickness not stated		included in this review Possible overlap with (Matsuoka et al 2003b) and (Matsuoka et al 2004)
(Matsuoka et al 2003b) Japan Kyorin University Jan 2000 – July 2001	Level III-1 diagnostic evidence Prospective, blinded, not stated if consecutive Q3 Insufficient information (QUADAS = 9/14) CX, P1	n=21	Inclusion Patients with rectal carcinoma who underwent both MRI and MDCT before surgical and endoscopic treatment Exclusion Not stated Patient characteristics 7 women, 14 men Mean age = 64 years (range 37–83) Neoadjunctive treatments not mentioned Stage Tis – 1 patient Stage T1 – 1 patient Stage T2 – 2 patients Stage T3 – 15 patients Stage T4 – 2 patients	Index test 1.5 T MRI, no mention of coil (Magentom Vision; Siemens), gadolinium enhanced, scopolamine butylbromide to reduce motion artefacts, position not stated T1- & T2-weighted sequences Image interpretation personnel not stated Comparator Multi-slice helical CT (MSCT; Aquilon; Toshiba Medical Systems), contrast medium used (Iopromide), scopolamine butylbromide to reduce motion artefacts Reference standard Histology, fixation not stated, slice thickness not stated	T stage Accuracy N stage Sn, Sp, PPV, NPV Safety Complications	Coil type not stated. Possible overlap in patients with (Matsuoka et al 2003a) and (Matsuoka et al 2004)
(MERCURY Study Group 2006) 11 colorectal units in 4 European	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients	n=408 total	Inclusion Patients with biopsy proven rectal adenocarcinoma, over 18 years of age, able to give informed consent Exclusion	Index test 1.0–1.5 T MRI with PPA coil, no contrast agent or antiperistaltic agents, position not stated T2-weighted sequences Interpreted by specialist gastrointestinal radiologist	CRM Sn, Sp, PPV, NPV, FP rate, FN rate	Some centres use 1.0 T machines Overlap in population with (MERCURY Study Group 2007)

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
countries Jan 2002 – Oct 2003	Q2 Medium quality (QUADAS = 10/14) CX, P2		Pregnancy or history of pelvic malignancy, pelvic radiotherapy, or pelvic floor surgery for faecal incontinence or rectal prolapse Unable to undergo MRI because of metal fragments or implanted metal devices in the body Patient characteristics Median age = 68 years (range 29–92) 161 women, 247 men 311 received primary surgery (short-course radiotherapy / surgery alone) 97 received surgery after chemoradiotherapy / long-course radiotherapy (results not included)	(unclear if single or double reading) CRM classified potentially affected if tumour ≤1 mm from mesorectal fascia Reference standard Histopathology, section thickness not stated Fixation not stated Clear margin defined as ≥1 mm between tumour and CRM		
(MERCURY Study Group 2007) 9 United Kingdom centres, and 3 European centres	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P2	n=311	Inclusion Patients with adenocarcinoma of the rectum (distal 15 cm region of the large bowel) who underwent primary surgery Exclusion Pregnancy or previous history of pelvic malignancy, pelvic radiation therapy, or pelvic floor surgery for faecal incontinence or rectal prolapse Unable to undergo MRI owing to claustrophobia or metal fragments or implanted metal devices in the body Patients who were referred for palliative care only or who received treatment outside of study centres Patients who had or were scheduled to undergo local excision of the primary tumour Patients who had or were scheduled to undergo combined chemotherapy–radiation therapy or long-course radiation therapy (but not short-course therapy) before the planned surgery	Index test 1.0–1.5 T MRI with PPA coil, no contrast agent or antiperistaltic agents, supine position T2-weighted sequences Images assessed by single specialist gastrointestinal radiologist Reference standard Maximal extramural depth defined at histopathology as the distance from the outer edge of the longitudinal muscularis propria to the outer edge of the tumour Histology section 1 mm Fixation not stated	T stage Accuracy	Appendix E2 of (MERCURY Study Group 2007) states that 2/12 centres used 1.0 T machines Overlap in population with (MERCURY Study Group 2006)

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
			Patient characteristics Median age = 67 years (range 33–92) 128 women, 183 men 51 patients underwent short-course radiation therapy (5.5 Gy)			
(Oh et al 2005) South Korea Yonsei University College of Medicine Oct 1996 – Dec 2000	Level III-2 diagnostic evidence Retrospective cohort study, blinding not stated, non-consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P2	n=71	Inclusion Rectal cancer patients who had undergone preoperative MRI and a curative resection using TME, with local recurrence and/or distant metastasis Exclusion Patients who received preoperative therapy between MRI and surgery Patient characteristics 17 patients who had local recurrence 8 women, 9 men Mean age = 59 years (range 22–77) Inclusion Non-recurrent rectal cancer patients who underwent preoperative MRI following curative surgery within 2 weeks without neoadjuvant therapy, a postoperative pathological stage higher than T1 regardless of the N stage based on the TNM system, and medical records with a pathological stage higher than T1 Exclusion Radiological or clinical evidence of a local recurrence or distant metastasis for at least 3 years	Index test 1.5 T MRI (Horizon, GE Medical Systems), PPA coil, distended with water, use of scopolamine butylbromide if not contraindicated T2-weighted sequences 3 gastrointestinal radiologists independently imaged hard copy images without clinical or pathological data Reference standard Histology, slice thickness and fixation not stated	N stage Sn, Sp, PPV, NPV	Possible overlap in patients with (Kim et al 2000) Study was a case-control, comparing the initial MRI staging of patients who had recurrence with those who did not, but the N stage results were combined

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
			Patient characteristics 54 patients who did not have local recurrence within 3 years 27 women, 27 men Mean age = 56 years (range not stated)			
(Taylor et al 2007) United Kingdom Royal Lancaster Infirmary Time period not stated	Level III-2 diagnostic evidence Retrospective cohort study, blinding not stated, consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P2	n=42	Inclusion Patients with histopathological diagnosis of rectal cancer Exclusion Patients who did not undergo surgery (eg due to comorbidities) or did not undergo both MRI and MSCT, or who received long-course preoperative radiotherapy Patient characteristics Median age = 74 years (range 47–93) Sex not stated 41 patients without preoperative therapy 1 patient with short-course radiotherapy 30 with long-course radiotherapy (results not included)	Index test 1.5 T MRI (Philips Intera, Philips Medical) with flexible PPA coil (Synergy coil, Philips Medical), no intravenous contrast administered, no bowel preparation or rectal distension T2-weighted sequences Interpreted by single radiologist (unaware of MSCT results) Comparator 4-slice CT (MSCT; Lightspeed, General Electric Medical Systems), intravenous contrast used Interpreted by single radiologist (unaware of MRI results) Reference standard Histopathology Fixation and slice thickness not stated	CRM Sn, Sp, PPV, NPV, FP rate, FN rate	
(Vliegen et al 2005) The Netherlands University Hospital of Maastricht July 1997 – April 2001	Level III-2 diagnostic evidence Retrospective cohort study, blinding not stated, consecutive patients Q1 High quality (QUADAS = 12/14) CX, P2	n=83	Inclusion Patients with primary operable rectal cancer who underwent surgery following standard preoperative MRI that included gadolinium-enhanced sequences Exclusion Not stated Patient characteristics Mean age = 65 years (range 15–86)	Index test 1.5 T MRI (Gyroscan, Philips Medical System) with quadrature PPA coil (Synergy spine coil; Philips Medical Systems), gadolinium-enhanced T1 weighted sequences no antiperistaltic agents, supine position T1- & T2-weighted sequences Reading by 2 radiologists blinded to each other and histologic results Reference standard	CRM Sn, Sp, PPV, NPV, FP rate, FN rate	

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
			22 women, 61 men 56 patients without preoperative radiotherapy 27 with preoperative radiotherapy (results not included)	Histopathology, evaluated according to protocol of Quirke et al (1986), 5 mm sections Fixated with formalin		

PPA = pelvic phased array; Sn = sensitivity; Sp = specificity; FP = false positive; FN = false negative; PPV = positive predictive value; NPV = negative predictive value; Acc = accuracy; OS = overstaging; US = understaging; CR = chemoradiation; DRE = digital rectal examination; CRM = circumferential resection margin; NS = not stated; TME = total mesorectal excision; USPIO = ultrasmall particles of iron oxide; TEM = transanal endoscopic microsurgery; MSCT = multi-slice CT; ERUS = endorectal ultrasound

Table 54 Study profiles of included studies on the change in management in newly diagnosed patients

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Management outcomes	Comments
(Beets-Tan et al 2000) The Netherlands University Hospital of Maastricht Dec 1997 – April 1999	Level IV interventional evidence Prospective case series, consecutive patients High quality (NHS CRD = 5/6)	n=19/26	Inclusion Patients with locally advanced primary or recurrent rectal cancer (rectal tumour fixed to surrounding structures on physical examination or on a pelvic CT scan), suitable for curative resection Exclusion Patients with distant metastases Patient characteristics For the 26 patients in the accuracy study: Mean age = 58 years (range 29–85) 11 patients with biopsy proven primary rectal cancer 15 patients with local recurrence of previously resection tumour	Index test All available information, including: 1.5 T MRI (Gyroscan, Powertrak 6000, Philips Medical Systems), with PPA spine coil, supine position, gadolinium enhanced T1- & T2-weighted sequences 2 radiologists in consensus, blinded to CT results Conventional CT scans (Siemens Somatom Plus CT, or Philips Tomoscan CX-S 500, Philips Medical Systems), oral and intravenous contrast 2 radiologists in consensus, blinded to MRI results Comparator Not applicable	Treatment rates / method of treatment	7 patients referred during or after preoperative radiotherapy (therefore staging methods unclear)
(Brown et al 2004) United Kingdom University Hospital of Wales, Velindre Hospital, Llandough Hospital 3-year period	Level III-3 diagnostic evidence Prospective cohort, Blinding not stated, Consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P1	n=98	Inclusion Patients with biopsy diagnosed rectal carcinoma Exclusion Not stated Patient characteristics 26 women, 72 men Age range = 28–89 years	Index test High resolution MRI T2-weighted sequences Comparator Endoluminal ultrasound Single observer, using 7.5/10 mHz radial scanning transducer with water-filled probe cover	Prescribed treatment rates	Unclear how treatment decisions were actually made (if combination of ERUS, MRI and DRE)
(Burton et al 2006a) United Kingdom Mayday	Level IV interventional evidence Retrospective case series, consecutive	n=75	Inclusion Patients with upper rectal, rectosigmoid and distal sigmoid cancer referred for MRI Exclusion	Index test 1.5 T MRI (Siemens) with a PPA coil, supine position, no intravenous antiperistaltic agents or contrast agents	Treatment rates / method of treatment	

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Management outcomes	Comments
University Hospital, Royal Marsden Hospital Jan 1999 – Dec 2002	patients High quality (NHS CRD = 5/6)		Not stated Patients characteristics 34 women, 41 men Median age = 65 years (range 37–86) 18/75 received chemoradiotherapy	T2-weighted sequences Single radiologist Comparator Not applicable		
(Poon et al 2005) United Kingdom Royal Infirmary, Glasgow May 2000 – May 2002	Level IV interventional evidence Retrospective case series, consecutive patients High quality (NHS CRD = 5/6)	n=49/61	Inclusion Patients with rectal carcinoma Exclusion Not stated Patients characteristics For the 42 patients who had resection: 16 women, 26 men Mean age = 64 years	Index test 1.5 T MRI (Gyroscan ACS-NT scanner, Philips Medical Systems), with PPA coil, no air insufflation, no bowel preparation or intravenous contrast, spine position T2-weighted sequences Single radiologist Comparator Not applicable	Treatment rates / method of treatment	12 lost to follow-up (not clear what treatment they received)

PPA = pelvic phased array; ERUS = endorectal ultrasound; DRE = digital rectal examination

Table 55 Study profiles of included studies on the health benefits of the change in management from MRI staging of newly diagnosed patients

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Intervention	Health outcomes	Comments
(Marijnen et al 2003) The Netherlands Mutlicentre study	Level II interventional evidence Randomised controlled trial, unblinded to patients, objective outcomes High quality (NHS CRD = 3/3)	n=1318 Dutch patients	Inclusion Histologically confirmed adenocarcinoma of the rectum, without evidence of distant metastases, and the inferior margin of the tumour had to be located not further than 15 cm from anal verge and below S1-2. Exclusion Patients with fixed tumours or tumours that were treated by local (transanal) resection. Patients with previous or coexisting cancer and those who had previously undergone large bowel surgery, chemotherapy or radiotherapy of the pelvis Patient characteristics 482 women, 836 men Mean age= 64 years (range 23–92)	Intervention Total mesorectal excision (TME), followed by postoperative radiotherapy for those CRM+ Comparator Preoperative short-course radiotherapy (5 Gy x 5 days) and TME	Local recurrence rates	

Table 56 Study profiles of included studies on the cost effectiveness of MRI for staging of rectal carcinoma

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Outcomes	Comments
(Brown et al 2004) United Kingdom University Hospital of Wales, Velindre Hospital, Llandough Hospital 3-year period	Internal validity moderate, generalisability high Medium quality (NHMRC = 12.5/16)	n=98	Inclusion Patients with biopsy diagnosed rectal carcinoma Exclusion Not stated Patient characteristics 26 women, 72 men Age range = 28–89 years	Index test High-resolution MRI T2-weighted sequences Comparator Endoluminal ultrasound Single observer, using 7.5/10 mHz radial scanning transducer with water-filled probe cover	Incremental cost per correctly staged patient	Compares costs of staging, and treatments for incorrectly staged patients. Does not incorporate costs of correctly staged patient

Table 57 Study profiles of included studies on the accuracy of MRI for restaging of rectal carcinoma after neoadjuvant therapy

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
(Allen et al 2007) United Kingdom Royal Marsden Hospital, Surrey Aug 2000 – Sept 2004	Level III-2 diagnostic evidence Retrospective cohort, blinding not stated, non-consecutive patients Q2 Medium quality (QUADAS = 11/14) CX, P1	n=30	Inclusion Biopsy-proven locally advanced rectal cancer who received 5 weeks pre-op CR, due to tumour fixity at DRE or initial MRI staging predicting high likelihood of CRM involvement and incomplete resection Exclusion No MRI assessment before or after CR or inadequate surgical records Patient characteristics 10 women, 20 men Mean age = 59 years (range 21–76) All patients received chemoradiotherapy	Index test 1.5 T MRI with PPA coil (Symphony, Siemens Medical Solutions), with bowel relaxant (hyoscine-*N*-butyl bromide or glucagon), contrast NS, position NS T1- & T2-weighted sequences 2 radiologists assessed films independently and in consensus Reference standard Histology section 3 mm Fixated with formalin	CRM Accuracy T stage Accuracy N stage Accuracy	Retrospective study, where a total of 66/96 patients were excluded due to incomplete data MRI performed prior to and post long-course chemoradiotherapy Patients possibly included in MERCURY studies
(Baatrup et al 2006) Norway & Denmark Haukeland University Hospital, Bergen & Odense University Hospital, Odense May 2002 – Sept 2004	Level III-2 diagnostic evidence Prospective cohort, consecutive, blinding not stated Q3 Insufficient information (QUADAS = 9/14) CX, P1	n=18	Inclusion Patients with fixed rectal adenocarcinomas Exclusion Patients not fit for surgery and patients with non-curable metastatic disease Patient characteristics 13 women, 5 men Median age = 65 years (range 34–82) Patients treated with chemoradiotherapy	Index test MRI of the lower abdomen and pelvis Reference standard Histopathology, evaluated as described by (Quirke 2003)	T stage Accuracy	Unclear what strength MRI machine or what coils were used
(Barbaro et al 1995) Italy Universita Cattolica del S. Cuore,	Level III-2 diagnostic evidence Cohort (unclear if retrospective or prospective), blinding not stated,	n=19 for MRI n=61 for CT	Inclusion Patients shown to be affected by locally advanced (T3-T4, N+ with any T) tumours on combined modality screening, who underwent preoperative radiotherapy and restaging Exclusion	Index test MRI Interpreted by operator unaware of results of other imaging Comparator 1	T stage Accuracy N stage Accuracy	Unclear what strength MRI machine or what coils were used

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
Rome April 1990 – Dec 1994 (MRI from Oct 1992 – Dec 1994)	consecutive patients Q2 Medium quality (QUADAS = 10/14) CX, P1		NS Patient characteristics 14 women, 47 men Mean age = 58 years (range not stated)	ERUS Interpreted by operator unaware of results of other imaging Comparator 2 CT Interpreted by operator unaware of results of other imaging Reference standard Histopathology		
(Blomqvist et al 2002) Sweden Karolinska Hospital/ Karolinska Institute, Stockholm 3-year time period	Level III-2 diagnostic evidence Retrospective cohort, blinding not stated, consecutive patients (QUADAS = 10/14) CX, P1	n=16	Inclusion Patients who, after treatment with chemoradiotherapy, had surgery for locally biopsy-proven rectal cancer with tumours regarded as infiltrating neighbouring organs (T4) Exclusion Patients with tumours clinically regarded as confined to the rectum and perirectal fat (T1–T3) were not included Patient characteristics 6 women, 10 men Median age = 60 years (range 28–76) 15 patients received chemoradiotherapy 1 patient received chemotherapy	Index test 1.5 T MRI (Signa Advantage, GE Medical Systems), with PPA, supine position, injected with glucagon, intravenous gadolinium T1- & T2-weighted sequences Independently evaluated by 4 radiologists, unaware of surgical or histopathological findings Comparator CT (Toshiba TCT 600S; Toshiba Medical Systems, or Siemens Somatom HiQ CT system; Siemens), oral contrast medium, repeat CT with bolus injection of contrast medium if required Independently evaluated by 4 radiologists, unaware of surgical or histopathological findings Reference standard Histopathology, according to current routines	T stage Accuracy	Possible overlap with (Torkzad et al 2007)
(Brown et al 1999) United Kingdom University	Level III-2 diagnostic evidence Prospective cohort, blinding not stated, consecutive patients	n=28	Inclusion Patients with biopsy diagnosed rectal carcinoma Exclusion NS	Index test 1.5 T MRI with PPA coil (Horizon Advantage, version 5.62; GE Medical Systems), no contrast agent or antiperistaltic agents, supine position T2-weighted sequences	T stage Accuracy	Accuracy was based on the 25 patients for whom reliable reference standard results were available (3 patients had

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
Hospital of Wales	Q1 High quality (QUADAS = 12/14) CX, P1		Patient characteristics 8 women, 20 men Mean age = 62 years (range 32–88) All patients received short-course radiation 1 week before surgery	2 radiologists assessed images independently Reference standard Histology section 3 mm Fixated with formalin		incomplete excision)
(Chen et al 2005) Taiwan Taipei Veterans General Hospital & Sun Yat-Sen Cancer Center, Taipei Aug 2000 - June 2003	Level III-2 diagnostic evidence Prospective cohort, blinding not stated, consecutive patients Q2 Medium quality (QUADAS = 10/14) CX, P1	n=50	Inclusion Patients with biopsy-proven middle and lower rectal adenocarcinoma, with initial stage T3-T4 or N+, M0 Exclusion NS Patient characteristics 26 women, 24 men Mean age = 64±14 years (range 39–86) All patients received chemoradiotherapy Stage T2 – 9 patients Stage T3 – 37 patients Stage T4 – 4 patients	Index test 1.5 T MRI (Vision, Siemens Medical Systems) with a torso PA coil, supine position, air inflation T1- & T2-weighted sequences Interpreted by single radiologist Reference standard Histopathology Fixation and slice thickness not stated	T stage Accuracy N stage Accuracy	
(Denecke et al 2005) Germany Amthauer Klinik fuer Strahlenheil-kunde und PET-Zentrum Berline Campus Virchow Klinikum, Charite-Universitaets	Level III-2 diagnostic evidence Prospective cohort, blinding not stated, consecutive Q2 Medium quality (QUADAS = 10/14) CX, P1	n=23	Inclusion Patients with locally advanced (T3/T4) rectal cancer as determined by ERUS Exclusion NS Patient characteristics 7 women, 16 men Mean age = 53±12 years (range 21–69) Patients received chemoradiotherapy with regional hyperthermia	Index test 1.5 T MRI (SP 2000 Symphony, Siemens AG) with a posterior surface coil, patient's lower abdomen strapped to bench, contrast medium instilled rectally T1-weighted sequences Interpretation by 1 radiologist, blinded to other results Comparator 1 4-slice CT (MSCT, Somatom Plus 4, Siemens) Interpretation by 1 radiologist, blinded to other results	T stage Accuracy N stage Sn, Sp, PPV, NPV	

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
medizin, Berlin Time period not stated				Comparator 2 FDG-PET after 8-hour fast, whole-body PET scans in 2-dimensional mode after intravenous injection of F-FDG Interpreted by 2 nuclear medicine investigators blinded to other results Reference standard Histopathology		
(Jonas & Bahr 2006) Germany Municipal Hospital Karlsruhe July 2004 – Aug 2005	Level III-2 diagnostic evidence Cohort study (not stated if prospective or retrospective), blinding not stated, consecutive patients Q3 Insufficient information (QUADAS = 7/14) CX, P1	n=28	Inclusion Patients with advanced adenocarcinoma of the middle and distal third of the rectum (T3/T4 or N+) who underwent neoadjuvant chemoradiotherapy Exclusion NS Patient characteristics 10 women, 18 men Age ~ 63 years (unclear if median or mean)	Index test High spatial resolution MRI with intraluminary contrast Reference standard Histology Fixation and section thickness not stated	T stage Accuracy N stage Accuracy	
(Hoffmann et al 2002) Germany Robert-Roessle Hospital and Tumor Institute, Humboldt University,	Level III-2 diagnostic evidence Prospective cohort, blinding not stated, not stated if consecutive, Q2 Medium quality (QUADAS = 10/14) CX, P1	n=35	Inclusion Patients with biopsy-diagnosed primary adenocarcinoma of the rectum, T3 or T4 Exclusion NS Patient characteristics 12 women, 23 men Mean age = 57 years (range 30–73)	Index test 1.5 T MRI (SP 4000 and Symphony, Siemens AG) using a dorsally located rectangular vertebral surface coil, rectal administration of contrast agent, intravenous contrast T1- & T2-weighted sequences Interpreted by 2 readers in consensus, blinded to other results Reference standard	T stage Accuracy N stage Accuracy	

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
Berlin			All patients received chemoradiotherapy 23 patients (66%) also received regional hyperthermia treatment	Histopathology Fixation and slice thickness not stated		
(Kuo et al 2005) Taiwan Koo Foundation Sun Yat-Sen Cancer Center, Taipei Time period not stated	Level III-2 diagnostic evidence Prospective cohort, blinding not stated, consecutive patients Q2 Medium quality (QUADAS = 10/14) CX, P1	n=36	Inclusion Patients with biopsy-proven primary rectal cancer, adenocarcinoma, T3/T4 or N+, aged between 18 and 75 years, Eastern Cooperative Oncology Group performance score ≤2 Exclusion Prior history of chemotherapy or radiation therapy to the pelvis Patient characteristics 14 women, 22 men Mean age = 56 years (range 28–79) Patients received chemoradiotherapy Stage T2 – 1 patient Stage T3 – 21 patients Stage T4 – 15 patients	Index test 1.5 T MRI (Signa Horizon; GE Medical System) with a 2-element PPA surface coil, bolus dose of gadolinium administered intravenously T1- & T2-weighted sequences Interpreted by single radiologist Reference standard Histology Examined by pathologists according to 1997 American Joint Committee on Cancer TNM system	T stage Accuracy N stage Accuracy	
(MERCURY Study Group 2006) 11 colorectal units in 4 European countries Jan 2002 – Oct 2003	Level III-2 diagnostic evidence Prospective cohort study, blinding not stated, consecutive patients Q2 Medium quality (QUADAS = 10/14) CX, P2	n=408 total	Inclusion Patients with biopsy-proven rectal adenocarcinoma, over 18 years of age, able to give informed consent Exclusion Pregnancy or history of pelvic malignancy, pelvic radiotherapy, or pelvic floor surgery for faecal incontinence or rectal prolapse Unable to undergo MRI because of metal fragments or implanted metal devices in the body	Index test 1.0–1.5 T MRI with PPA coil, no contrast agent or antiperistaltic agents, position not stated T2-weighted sequences Interpreted by specialist gastrointestinal radiologist Reference standard Histopathology, section thickness not stated	CRM Accuracy, FP rate, FN rate	Some centres use 1.0 T machines Overlap in population with (MERCURY Study Group 2007)

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
			Patient characteristics Median age = 68 years (range 29–92) 161 women, 247 men 311 received primary surgery (short-course radiotherapy / surgery alone) (results not included) 97 received surgery after chemoradiotherapy / long-course radiotherapy	Fixation not stated		
(Torkzad et al 2007) Sweden Karolinska University Hospital/ Karolinska Institute, Stockholm Time period not stated	Level II diagnostic evidence Prospective cohort, blinded, consecutive patients Q1 High quality (QUADAS = 13/14) CX, P1	n=25	Inclusion Patients with primary resectable rectal cancer who undergo preoperative radiotherapy Exclusion NS Patient characteristics 8 women, 17 men Mean age = 67 years (range 40–81) Patients received radiotherapy	Index test 1.5 T MRI (Philips Intera, and Signa Advantage, GE Medical Systems) with a 4-channel body PA coil or 5-channel cardiac PA surface coil T1- & T2-weighted sequences Interpretation by 2 independent radiologists Reference standard Histopathology	T stage Accuracy	Possible overlap with (Blomqvist et al 2002)

CR = chemoradiation; DRE = digital rectal examination; CRM = circumferential resection margin; PA = phased array; PPA = pelvic phased array; NS = not stated; FDG = F-2-deoxy-D-glucose; PET = positron emission tomography; Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; FP = false positive; FN = false negative

Table 58 Study profiles of included studies on the accuracy of MRI for diagnosis/staging of suspected/diagnosed recurrent rectal carcinoma

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
(Blomqvist et al 1998) Sweden Karolinska Institute, Stockholm Nov 1994 – Jan 1996	Level III-2 diagnostic evidence Prospective cohort, blinding not stated, consecutive Q3 Poor reference standard, insufficient information (QUADAS = 7/14) CX, P2	n=31	Inclusion Patients with previous surgery for rectal cancer, having routine follow-up after surgery for advanced/recurrent rectal cancer or with suspected/biopsy-verified local recurrence Exclusion NS Patient characteristics 11 women, 20 men Median age = 66 years (range 39–84) Imaging was a mean of 22 months after primary surgery (range 1 month – 5 years) 14 patients previously underwent low anterior resection 16 patients previously underwent abdomino-perineal excision 14 patients had received irradiation	Index test 1.5 T MRI (Signa Advantage, General Electric) with PPA coil, supine position, injection of glucagon, with fast dynamic gadolinium contrast-enhanced T1-weighted gradient-echo protocol T1- & T2-weighted sequences Reference standard *Those diagnosed:* Biopsy guided by rectoscopy, palpation or CT (n=8) Surgery prior to study (n=3) Surgery following the study (n=2) Verified by increase in size of recurrence after 4, 8, 17 months on follow-up MRI (n=3) *Those not diagnosed:* Clinical follow-up between 6 and 22 months (n=5) Follow-up MRI between 6 and 9 months (n=7) Follow-up CT after 8 months (n=1)	Diagnosis of local recurrence Sn, Sp, PPV, NPV, FP rate, FN rate	Possible overlap in patients with (Blomqvist et al 2000) Aim of study was to compare between contrast
(Blomqvist et al 2000) Sweden Karolinska Institute, Stockholm Jan 1995 – April 1997	Level III-2 diagnostic evidence Prospective, blinding not stated, consecutive Q3 Poor reference standard, insufficient information (QUADAS = 8/14) CX, P2	n=17	Inclusion Patients with previous surgery for rectal cancer Clinical suspicion of local tumour recurrence in the pelvis (n=11) Evaluation of treatment with radio- and chemotherapy for local tumour recurrence (n=5) 1-year postoperative follow-up after surgical treatment of locally advanced and recurrent rectal cancer (n=1) Exclusion NS Patient characteristics	Index test 1.5 T MRI (Signa, General Electric) with PPA, glucagon, oral contrast medium T1- & T2-weighted sequences Interpreted by 3 radiologists, one was aware of clinical history, all blinded to follow-up diagnosis Comparator CT (Toshiba TCT 600 S scanner), oral contrast medium, intravenous contrast medium Interpreted by 3 radiologists, one was aware of	Diagnosis of local recurrence Sn, Sp, PPV, NPV, FP rate, FN rate	Possible overlap in patients with (Blomqvist et al 1998)

Study Setting	Study design Quality	Population	Inclusion/exclusion criteria	Staging tests	Accuracy outcomes	Comments
			6 women, 11 men Median age = 60 years (range 40–76) 13 patients had undergone low anterior resection 4 patients had undergone an abdominoperineal rectum resection	clinical history, all blinded to follow-up diagnosis Reference standard Biopsy verified within 1 month (n=3) Surgery within 3 months (n=6) Clinical follow-up at 5, 6 and 9 months (n=3) Obvious clinical manifestation of locally recurrent tumour, clinical follow-up after 2 months and obvious sacral tumour growth on MRI (n=1) Follow-up with MR or CT performed 8–11 months later (n=3) One death prior to verification		
(Torricelli et al 2003) Italy University of Modena and Reggio Emilia, Modena Sept 1997 – Jan 2000	Level III-2 diagnostic evidence Prospective cohort, blinding not stated, not stated if consecutive Q2 Medium quality (QUADAS = 10/14) CX, P1	n=36	Inclusion Patients suspected of having pelvic recurrence of rectal cancer Exclusion NS Patient characteristics 19 women, 17 men Age range = 41–79 years All patients had undergone abdominal-perineal amputation 2 months – 7 years before start of study 11 patients had received adjuvant postoperative radiotherapy to the pelvis 6–36 months before the test Suspicion of recurrence based on: CT results (n=23) or Clinical and laboratory findings (n=13)	Index test 1.5 T MRI (Signa, General Electric) with a body coil, injection of contrast agent T1- & T2-weighted sequences Interpretation personnel not stated Reference standard Diagnosis confirmed with: CT-guided needle biopsy (n=12) Surgery (n=4) Clinical and imaging follow-up (n=20) (diagnosis of recurrence made if lesion was larger on follow-up CT or MRI at 3 and 6 months, or ruled out when lesions were stationary or shrinking at 3 and 6 months without therapy)	Diagnosis of local recurrence Sn, Sp, PPV, NPV, FP rate, FN rate	Study comparing the accuracy of unenhanced versus dynamic contrast-enhanced MRI

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; FP = false positive; FN = false negative; NS = not stated

Appendix E Excluded studies

Studies that met the inclusion criteria but contained insufficient or inadequate data for inclusion for diagnostic accuracy are listed below.

Diagnostic accuracy of MRI staging of newly diagnosed patients

Patients received preoperative chemoradiotherapy, so histopathology results likely to be confounded due to downstaging effects

Beets-Tan, R.G., Beets, G.L. et al (2000). 'Preoperative assessment of local tumor extent in advanced rectal cancer: CT or high-resolution MRI?' *Abdominal Imaging,* 25 (5), 533–541.

Beets-Tan, R.G., Beets, G.L. et al (2001). 'Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery', *Lancet,* 357 (9255), 497–504.

Kim, J.H., Beets, G.L. et al (2004). 'High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size?' *European Journal of Radiology,* 52 (1), 78–83.

Bissett, I.P., Fernando, C.C. et al (2001). 'Identification of the fascia propria by magnetic resonance imaging and its relevance to preoperative assessment of rectal cancer', *Diseases of the Colon and Rectum,* 44 (2), 259–265.

Boyle, K.M., Petty, D. et al (2005). 'MRI assessment of the bony pelvis may help predict resectability of rectal cancer', *Colorectal Disease,* 7 (3), 232–240.

Brown, G., Radcliffe, A.G. et al (2003). 'Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging', *British Journal of Surgery,* 90 (3), 355–364.

Chau, I., Brown, G. et al (2006). 'Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer', *Journal of Clinical Oncology,* 24 (4), 668–674.

Jonas, J. & Bahr, R. (2006). 'Neoadjuvant chemoradiation treatment impairs accuracy of MRI staging in rectal carcinoma [13]', *Gut,* 55 (8), 1214–1215.

Jonas, J., Moroni, E. et al (2007). 'T-level down-staging and complete pathologic response after preoperative long-term chemoradiotherapy for locally advanced rectal cancer', *Il Giornale di Chirurgia,* 28 (3), 65–71.

Martling, A., Holm, T. et al (2003). 'Prognostic value of preoperative magnetic resonance imaging of the pelvis in rectal cancer', *British Journal of Surgery,* 90 (11), 1422–1428.

Panzironi, G., De Vargas Macciucca, M. et al (2004). 'Preoperative locoregional staging of rectal carcinoma: comparison of MR, TRUS and Multislice CT. Personal experience', *Radiologia Medica,* 107 (4), 344–355.

Peschaud, F., Cuenod, C.A. et al (2005). 'Accuracy of magnetic resonance imaging in rectal cancer depends on location of the tumor', *Diseases of the Colon and Rectum,* 48 (8), 1603–1609.

Poon, F.W., McDonald, A. et al (2005). 'Accuracy of thin section magnetic resonance using phased-array pelvic coil in predicting the T-staging of rectal cancer', *European Journal of Radiology,* 53 (2), 256–262.

Strassburg, J., Lewin, A. et al (2007). 'Optimised surgery (so-called TME surgery) and high-resolution MRI in the planning of treatment of rectal carcinoma', *Langenbeck's Archives of Surgery,* 392 (2), 179–188.

Wieder, H.A., Rosenberg, R. et al (2007). 'Rectal cancer: MR imaging before neoadjuvant chemotherapy and radiation therapy for prediction of tumor-free circumferential resection margins and long-term survival', *Radiology,* 243 (3), 744–751.

Only provided preliminary results (included in other studies)

Strassburg, J. (2004). 'Magnetic resonance imaging in rectal cancer: the MERCURY experience', *Techniques in Coloproctology,* 8 (suppl. 1), S16–S18.

Did not all receive index test

(Only 15/32 had MRI with phased-array coil).

Okizuka, H., Sugimura, K. et al (1996). 'Rectal carcinoma: prospective comparison of conventional and gadopentetate dimeglumine enhanced fat-suppressed MR imaging', *Journal of Magnetic Resonance Imaging*, 6 (3), 465–471.

Phased array unlikely (mentioned endorectal coil and air enema technique). This is prior to this particular study group comparing endorectal coil and phased array coil MRI, where they discuss the recent development of phased array. Patients recruited 1997–99. Air enema technique performs worse than endorectal coil.

Matsuoka, H., Masaki, T. et al (2004). 'Gadolinium enhanced endorectal coil and air enema magnetic resonance imaging as a useful tool in the preoperative examination of patients with rectal carcinoma', *Hepato-Gastroenterology*, 51 (1), 131–135.

Mixed results for 1.0T and 1.5T (no mention how many received each)

Zerhouni, E.A., Rutter, C. et al (1996). 'CT and MR imaging in the staging of colorectal carcinoma: report of the Radiology Diagnostic Oncology Group II', *Radiology,* 200 (2), 443–451.

Fuchsjager, M.H., Maier, A.G. et al (2003). 'Comparison of transrectal sonography and double-contrast MR imaging when staging rectal cancer', *American Journal of Roentgenology,* 181 (2), 421–427.

Did not separate results for 1.0T and 1.5T and those with PA coils or body coils

Maier, A.G., Kersting-Sommerhoff, B. et al (2000). 'Staging of rectal cancer by double-contrast MR imaging using the rectally administered superparamagnetic iron oxide

contrast agent ferristene and IV gadodiamide injection: results of a multicenter phase II trial', *Journal of Magnetic Resonance Imaging,* 12 (5), 651–660.

Did not separate results for patients who were investigated with endorectal coil and those with phased array coil

Blomqvist, L., Holm, T. et al (1997). 'Rectal tumours: MR imaging with endorectal and/or phased-array coils, and histopathological staging on giant sections. A comparative study', *Acta Radiologica,* 38 (3), 437–444.

Cannot extract data

Results presented graphically

Matsuoka, H., Nakamura, A. et al (2004). 'MRI diagnosis of mesorectal lymph node metastasis in patients with rectal carcinoma. What is the optimal criterion?' *Anticancer Research*, 24 (6), 4097–4101.

Wrong population (specimens)

Stollfuss, J.C., Becker, K. et al (2006). 'Rectal carcinoma: high spatial-resolution MR imaging and T2 quantification in rectal cancer specimens', *Radiology,* 241 (1), 132–141.

Blomqvist, L., Rubio, C. et al (1999). 'Rectal adenocarcinoma: assessment of tumour involvement of the lateral resection margin by MRI of resected specimen', *British Journal of Radiology,* 72, 18–23.

Not prespecified outcomes

Brown, G., Davies, S. et al (2004). 'Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging?' *British Journal of Cancer,* 91 (1), 23–29.

Change in management in newly diagnosed patients

Not stated how treatment decisions were made

Jonas, J., Moroni, E. et al (2007). 'T-level down-staging and complete pathologic response after preoperative long-term chemoradiotherapy for locally advanced rectal cancer', *Il Giornale di Chirurgia,* 28 (3), 65–71.

Panzironi, G., De Vargas Macciucca, M. et al (2004). 'Preoperative locoregional staging of rectal carcinoma: comparison of MR, TRUS and Multislice CT. Personal experience', *Radiologia Medica,* 107 (4), 344–355.

Treatment decisions made on the basis of MRI and ERUS

Strassburg, J., Lewin, A. et al (2007). 'Optimised surgery (so-called TME surgery) and high-resolution MRI in the planning of treatment of rectal carcinoma', *Langenbeck's Archives of Surgery,* 392 (2), 179–188.

Brown, G., Davies, S. et al (2004). 'Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging?' *British Journal of Cancer,* 91 (1), 23–29.

Diagnostic accuracy of MRI restaging of patients who received neoadjuvant therapy

Study combined patients who received preoperative chemoradiotherapy with those who did not without separating results

Brown, G., Radcliffe, A.G. et al (2003). 'Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging', *British Journal of Surgery,* 90 (3), 355–364.

No reference standard

Hein, P.A., Kremser, C. et al (2001). 'Feasibility of diffusion-weighted MRI in clinical radiation oncology. Monitoring the effects of combined chemoradiation in primary advanced carcinoma of the rectum', In: Kogelnik, H.D., Lukas, P. & Sedlmayer, F. (eds), *'Progress In Radio-Oncology VII, Proceedings',* Monduzzi Editore, 40128 Bologna, pp. 757–762.

No outcomes of interest

DeVries, A.F., Griebel, J. et al (2001). 'Tumor microcirculation evaluated by dynamic magnetic resonance imaging predicts therapy outcome for primary rectal carcinoma', *Cancer Research,* 61 (6), 2513–2516.

Diagnostic accuracy of MRI staging of patients with suspected/diagnosed recurrent rectal carcinoma

Did not receive index test

Field strength too low

Botterill, I.D., Blunt, D.M. et al (2001). 'Evaluation of the role of pre-operative magnetic resonance imaging in the management of rectal cancer', *Colorectal Disease,* 3 (5), 295–303.

Using MRI guided treatment (not staging or diagnosis)

Gellermann, J., Wlodarczyk, W. et al (2005). 'Noninvasive magnetic resonance thermography of recurrent rectal carcinoma in a 1.5 Tesla hybrid system', *Cancer Research,* 65 (13), 5872–5880.

MRI for surveillance not diagnosis or staging

Titu, L.V., Breen, D.J. et al (2006a). 'Is routine magnetic resonance imaging justified for the early detection of resectable liver metastases from colorectal cancer?' *Diseases of the Colon and Rectum,* 49 (6), 810–815.

Titu, L.V., Nicholson, A.A. et al (2006b). 'Routine follow-up by magnetic resonance imaging does not improve detection of resectable local recurrences from colorectal cancer', *Annals of Surgery,* 243 (3), 348–352.

Not a higher level of evidence than English

Meyenberger, C., Wildi, S. et al (1996). 'Tumor staging and follow-up care in rectosigmoid carcinoma: colonoscopic endosonography compared to CT, MRI and endorectal MRI', *Schweizerische Rundschau fur Medizin Praxis = Revue Suisse de Medecine Praxis,* 85 (19), 622–631.

Not correct population

Not specific to rectal carcinoma

Huch Boni, R.A., Meyenberger, C. et al (1996). 'Value of endorectal coil versus body coil MRI for diagnosis of recurrent pelvic malignancies', *Abdominal Imaging,* 21 (4), 345–352.

Not prespecified outcomes

Syk, E., Torkzad, M.R. et al (2006). 'Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer', *British Journal of Surgery,* 93 (1), 113–119.

Economic considerations

Wrong intervention (MRI without phased array coils)

Harewood, G.C. & Wiersema, M.J. (2002). 'Cost-effectiveness of endoscopic ultrasonography in the evaluation of proximal rectal cancer', *American Journal of Gastroenterology,* 97 (4), 874–882.

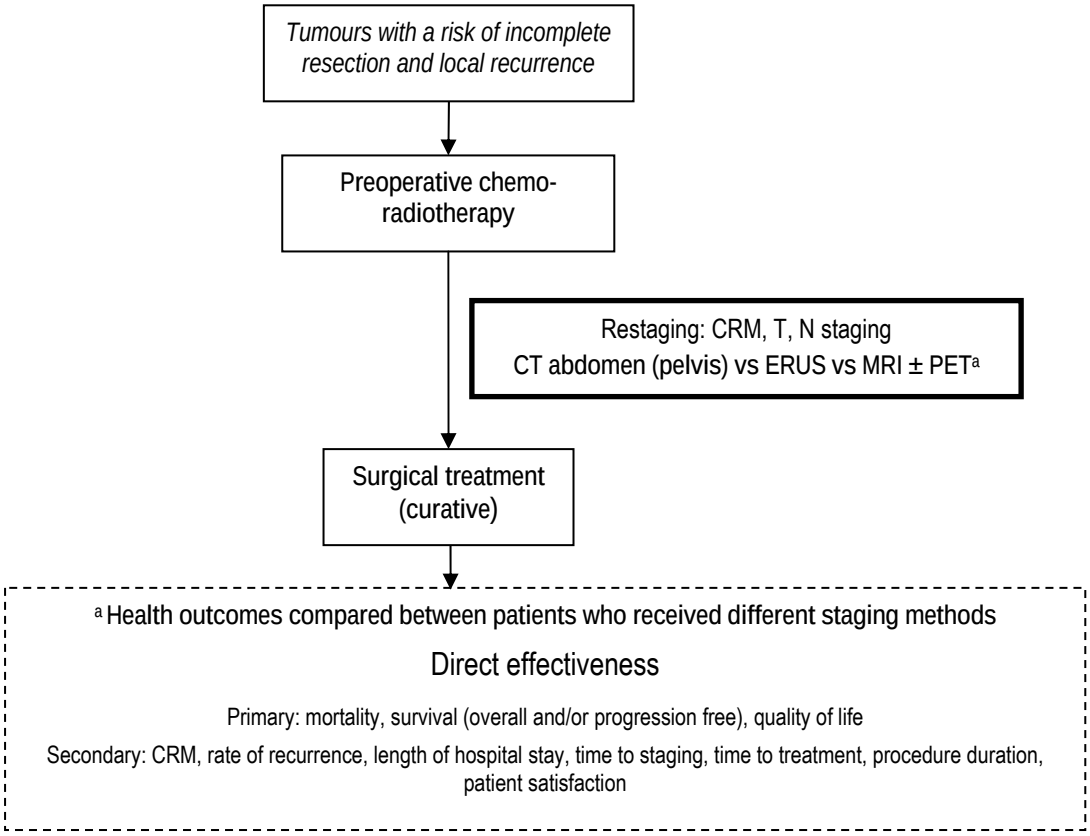
Appendix F Inclusion criteria for research questions without evidence

Direct evidence of effectiveness of MRI for restaging of rectal carcinoma

- What is the clinical effectiveness of MRI, with/without other imaging modalities, compared to no imaging, an alternative modality of imaging or a combination of imaging techniques, in patients with rectal carcinoma requiring restaging of the disease after neoadjuvant therapy?

Figure 13 outlines the components of the clinical pathway relevant to answering the above question.

Figure 13 Assessing direct evidence of effectiveness of restaging of rectal carcinoma with MRI



Studies assessing the effectiveness of MRI restaging at improving health outcomes would have been included if they met the inclusion criteria outlined a priori in Box 8.

Box 8 Inclusion criteria for studies assessing the effectiveness and cost-effectiveness of MRI restaging of rectal cancer

Characteristic	Criteria	
Publication type	Effectiveness: Randomised or non-randomised controlled trials or cohort studies or systematic reviews of these study designs. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded. Cost-effectiveness: Economic studies, decision analytic modelling studies, economic analyses	
Population	Patients with rectal carcinoma, who have undergone neoadjunctive therapy, requiring restaging of the disease for treatment planning	
Intervention/test[a]	1. MRI, with/without PET, for reassessment of circumferential resection margin and/or staging of tumour depth, nodal staging	2. Other forms of imaging plus MRI
Comparators	1. No imaging 1. Another form of imaging, ie endorectal ultrasound, positron emission tomography or CT abdomen (pelvis) 1. Other forms of imaging in combination	2. Other forms of imaging
Reference standard	All clinical information, including histopathology findings	
Outcome	Direct effectiveness: Primary: mortality, survival (overall and/or progression free), quality of life Secondary: CRM, rate of recurrence, length of hospital stay, time to staging, time to treatment, procedure duration, patient satisfaction Cost-effectiveness Cost, cost per event avoided, cost per life year gained, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

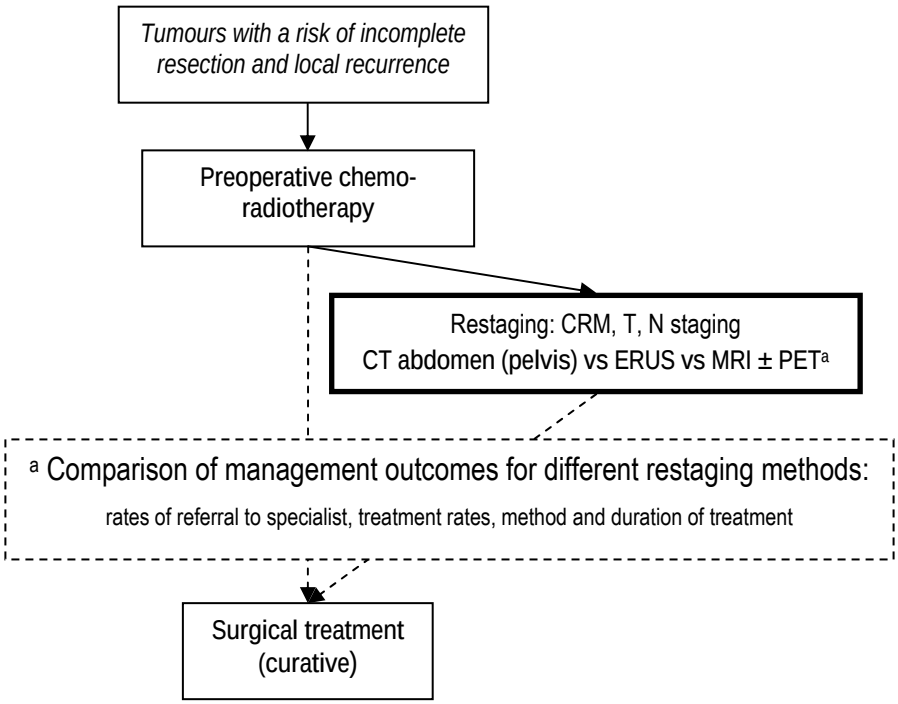
[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Does restaging with MRI change patient management?

- Does restaging with MRI, with/without other imaging modalities, result in a change in clinical management of the patient compared to no restaging, or restaging with an alternative modality of imaging or a combination of imaging techniques?

Restaging of rectal carcinoma after neoadjuvant therapy is only worthwhile if the surgeon is likely to trust the results of the restaging, and consequently to adapt their surgical technique (Figure 14). Box 9 outlines the criteria for including studies that assessed whether MRI influences treatment methods differently to other forms of restaging imaging. No studies were identified that met these criteria.

Figure 14 Linked evidence approach: assessing the change in clinical management of the patient restaged with MRI or comparators (including no restaging)



Box 9 Inclusion criteria for studies assessing the change in patient management as a consequence of MRI restaging of rectal carcinoma

Characteristic	Criteria	
Publication type	Randomised or non-randomised controlled trials (including before-and-after studies) or cohort studies or systematic reviews of these study designs; uncontrolled pre-test/post-test case series. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.	
Population	Patients with rectal carcinoma who have undergone neoadjunctive therapy	
Intervention/test[a]	1. MRI with/without PET, for reassessment of circumferential resection margin and/or staging of tumour depth, nodal staging	2. Other forms of imaging plus MRI
Comparators[a]	1. No imaging 1. Another form of imaging, ie endorectal ultrasound, positron emission tomography or CT abdomen (pelvis) 1. Other forms of imaging in combination	2. Other forms of imaging
Outcome	Rates of referral to specialist, treatment rates and method and duration of treatment	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Direct evidence of effectiveness of MRI for diagnosis/staging of recurrent rectal carcinoma

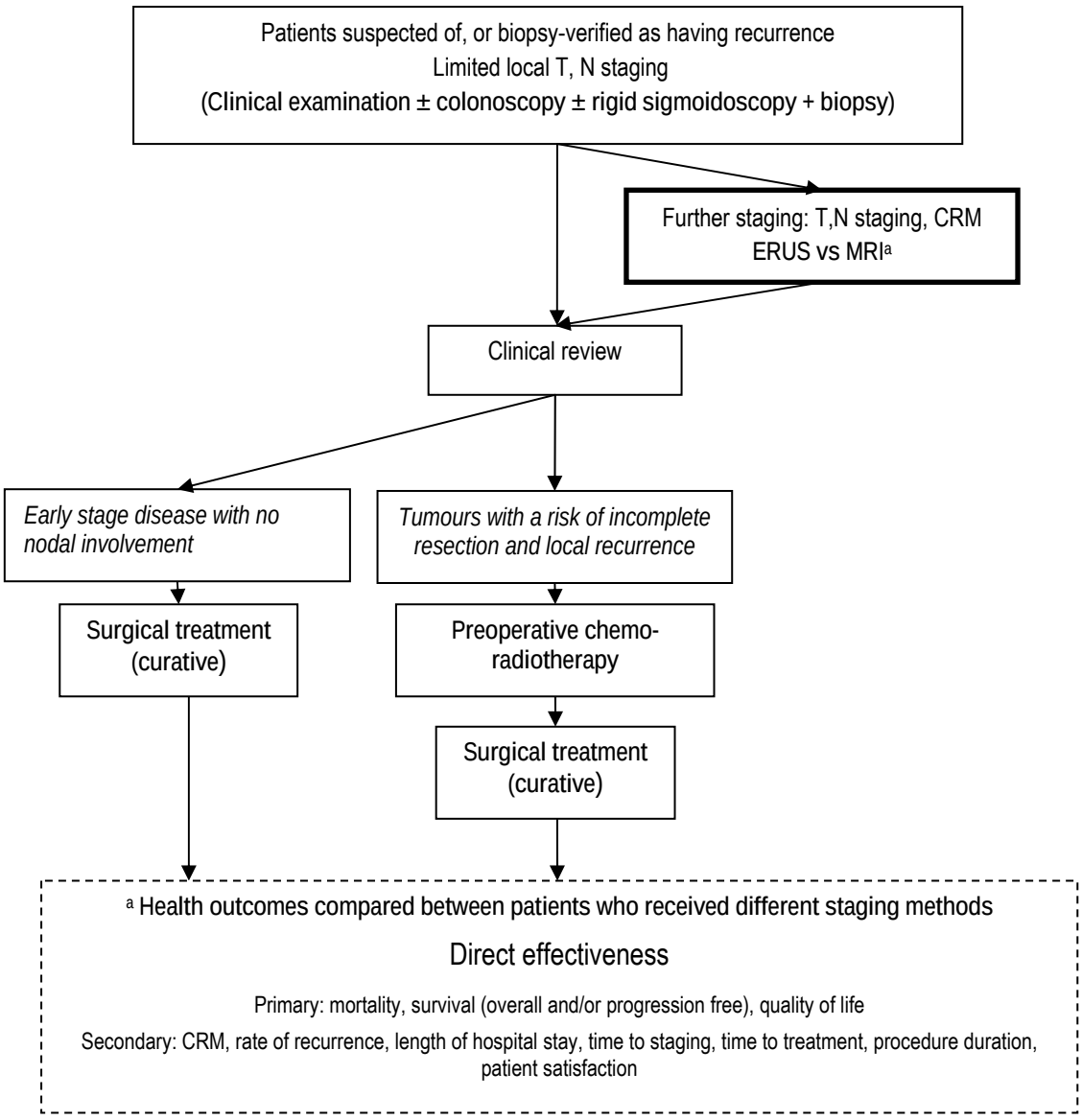
- What is the clinical effectiveness of MRI and subsequent interventions on patient outcomes, compared to ERUS, in patients suspected of having or diagnosed with

rectal carcinoma recurrence, and requiring diagnosis/staging for further treatment planning?

- What is the clinical effectiveness of adding MRI staging to CT abdomen (pelvis), with/without PET, on health outcomes of patients suspected of having or diagnosed with rectal carcinoma recurrence, and requiring diagnosis/staging for further treatment planning?

Figure 15 outlines the components of the clinical pathway relevant to answer the above questions. It is not expected that there would be a change in patient management by the clinician, or any subsequent change in health outcomes, for those with advanced disease such as incurable local disease or metastatic disease.

Figure 15 **Assessing direct evidence of effectiveness of diagnosing/staging of suspected or diagnosed recurrent rectal carcinoma with MRI**



Studies assessing the effectiveness of MRI staging at improving health outcomes would have been included if they met the criteria outlined a priori in Box 10.

Box 10 Inclusion criteria for studies assessing the effectiveness and cost-effectiveness of MRI diagnosis/staging of recurrent rectal cancer

Characteristic	Criteria	
Publication type	Effectiveness: Randomised or non-randomised controlled trials or cohort studies or systematic reviews of these study designs. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded. Cost-effectiveness: Economic studies, decision analytic modelling studies, economic analyses	
Population	Patients suspected of having or diagnosed with recurrent rectal carcinoma requiring diagnosis/staging for further treatment planning	
Intervention/test	1. MRI for assessment of circumferential resection margin and/or staging of tumour depth, nodal staging	2. CT abdomen and CT pelvis with/without PET plus MRI
Comparators	1. Endorectal ultrasound	2. CT abdomen and CT pelvis with/without PET
Reference standard	All clinical information, including histopathology findings	
Outcome	Direct effectiveness: Primary: mortality, survival (overall and/or progression free), quality of life Secondary: CRM, rate of recurrence, length of hospital stay, time to staging, time to treatment, procedure duration, patient satisfaction Cost-effectiveness Cost, cost per event avoided, cost per life year gained, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

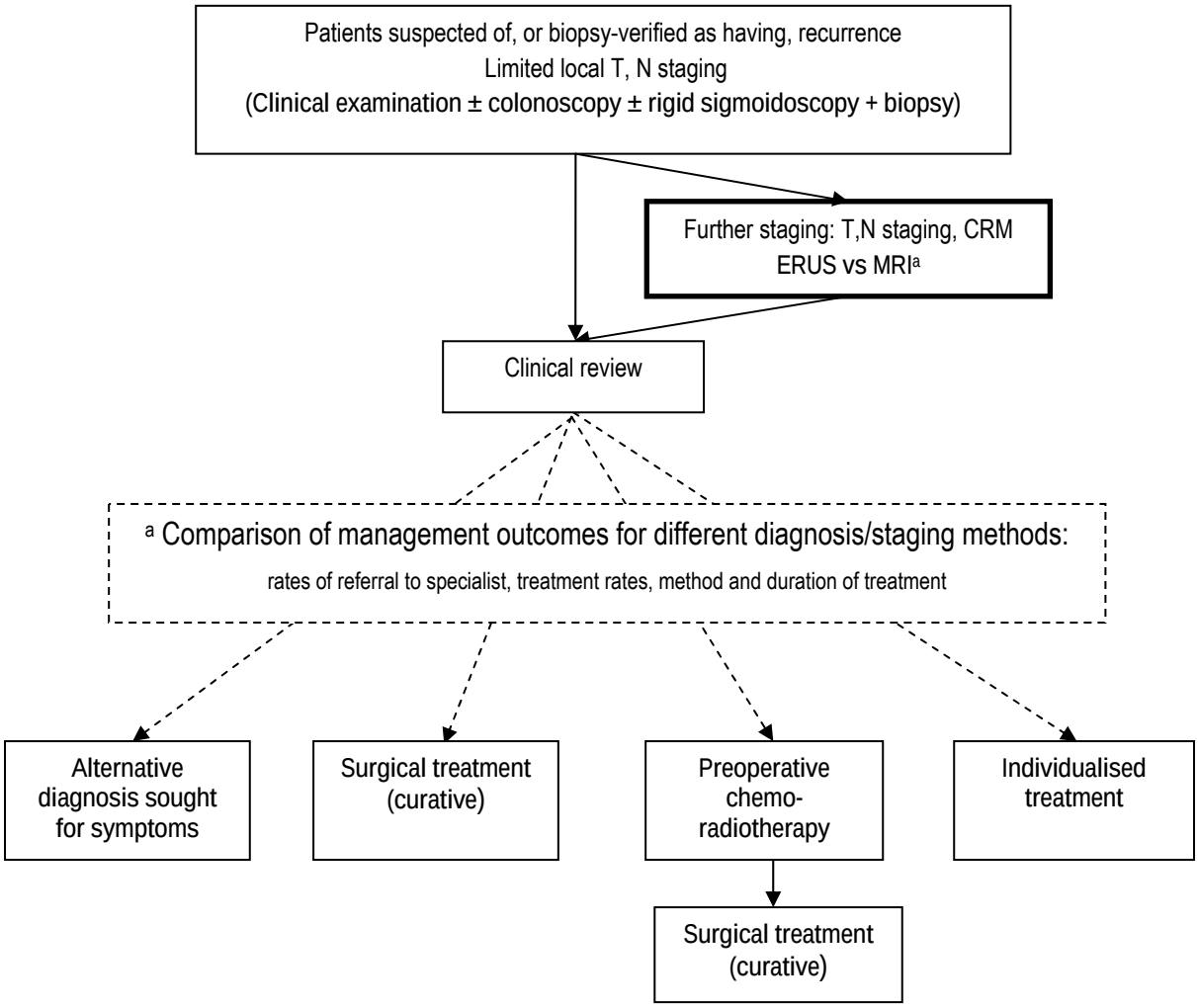
Does staging with MRI change patient management?

- Does using MRI to diagnose/stage recurrent rectal carcinoma, as compared to ERUS, result in a change in clinical management of the patient?

- Does using MRI to diagnose/stage recurrent rectal carcinoma in addition to CT abdomen (pelvis), with/without PET, result in a change in clinical management of the patient?

Figure 16 outlines the components of the clinical pathway that are relevant to the assessment of whether staging with MRI would change clinical management of the patient with suspected/diagnosed recurrent rectal carcinoma.

Figure 16 Linked evidence approach: assessing whether diagnosis/staging of suspected or confirmed recurrent rectal carcinoma with MRI would result in a change of patient management compared to other staging methods



Studies were assessed to see if they met the inclusion criteria listed a priori in Box 11, in order to provide evidence on the effect of MRI for diagnosis/staging on subsequent patient management. No studies were identified that described clinician management of patients after using MRI to diagnose or stage recurrent rectal carcinoma.

Box 11 Inclusion criteria for studies assessing the change in management as a consequence of MRI staging of recurrent rectal carcinoma

Characteristic	Criteria	
Publication type	Randomised or non-randomised controlled trials (including before-and-after studies) or cohort studies or systematic reviews of these study designs; uncontrolled pre-test/post-test case series. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.	
Population	Patients suspected of having or diagnosed with recurrent rectal carcinoma requiring diagnosis/staging for further treatment planning	
Intervention/test[a]	1. MRI for assessment of the circumferential resection margin or staging of tumour depth, and/or nodal involvement	2. MRI plus CT abdomen (pelvis) with/without PET
Comparators[a]	1. Endorectal ultrasound	2. CT abdomen (pelvis) with/without PET
Outcome	Rates of referral to specialist, treatment rates, method and duration of treatment	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

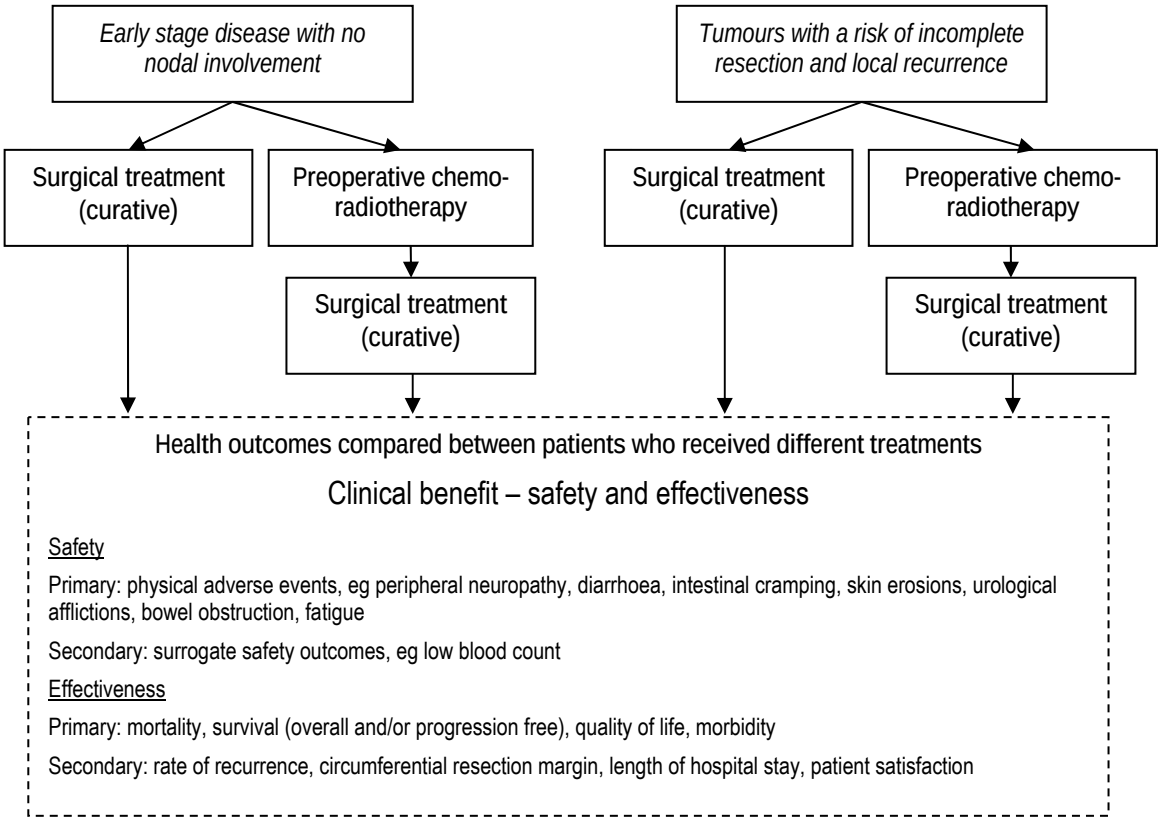
Is there a clinical benefit resulting from the change in management?

- Is there a clinical benefit in avoiding chemoradiation therapy in patients with recurrent rectal carcinoma who do not have a threatened mesorectal fascia?

- Is there a clinical benefit in providing selective chemoradiation therapy to patients with recurrent rectal carcinoma whose mesorectal fascia is threatened or involved?

Studies were assessed to see whether they met the inclusion criteria outlined a priori in Box 12. Figure 17 outlines the form that the ideal studies would have taken to evaluate the benefit of the expected change in clinical management of the patient. No studies were identified that assessed the benefit of *selective* neoadjuvant therapy in patients with recurrent rectal carcinoma.

Figure 17 Linked evidence approach: Assessing whether diagnosis/staging of recurrent rectal carcinoma with MRI would benefit patient health outcomes versus other diagnosis/staging methods



Box 12 Inclusion criteria for studies assessing the safety and effectiveness of selective treatment on the basis of MRI diagnosis/staging for recurrent rectal carcinoma

Characteristic	Criteria	
Publication type	Randomised or non-randomised controlled trials (including before-and-after studies) or cohort studies or systematic reviews of these study designs. Uncontrolled pre-test/post-test case series were assessed if comparative studies are not available. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies were excluded.	
Population	Patients with rectal carcinoma:	
	1. With a mesorectal fascia not threatened by the tumour	2. With a threatened or involved mesorectal fascia
Intervention/test[a]	1. Surgery without preoperative therapy	2. Preoperative chemoradiation therapy followed by surgery
Comparators[a]	1. Preoperative chemoradiation therapy followed by surgery	2. Surgery without preoperative therapy
Outcome	Safety Primary: physical adverse events, eg peripheral neuropathy, diarrhoea, intestinal cramping, skin erosions, urological affections, bowel obstruction, fatigue Secondary: surrogate safety outcomes, eg low blood count Effectiveness Primary: mortality, survival (overall and/or progression free), quality of life, morbidity Secondary: rate of recurrence, circumferential resection margin, length of hospital stay, patient satisfaction	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Appendix G Economic considerations

Existing literature on cost-effectiveness of MRI for staging of newly diagnosed patients

- What is the cost-effectiveness of MRI, compared to ERUS, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

- What is the cost-effectiveness of adding MRI staging to CT abdomen (pelvis), with/without PET, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

The inclusion criteria determined a priori for assessing economic analysis of MRI are outlined in Box 13.

Box 13 Inclusion criteria for studies assessing the cost-effectiveness of MRI staging of rectal cancer

Characteristic	Criteria
Publication type	Economic studies, decision analytic modelling studies, economic analysis
Population	Patients with rectal carcinoma requiring further staging of the disease for treatment planning
Intervention/test[a]	1. MRI for assessment of circumferential resection margin and/or staging of tumour depth, nodal staging
	2. MRI + CT abdomen (pelvis) with/without PET
Comparators[a]	1. Endorectal ultrasound
	2. CT abdomen (pelvis) with/without PET
Reference standard	All clinical information, including histopathology findings
Outcome	Cost, cost per event avoided, cost per life year gained, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Note: CT abdomen (pelvis) may refer to multi-slice CT, which is more commonly used in Australia than conventional CT.

Two studies were identified as potentially relevant based on the inclusion criteria outlined in Box 13. However, one of the studies included data on the accuracy of MRI systems without phased array coils, so was therefore excluded (Harewood & Wiersema 2002). One remaining cost-effectiveness study was included, which compared the costs of staging with MRI versus endorectal ultrasound (ERUS) (Brown et al 2004) (Table 59). The accuracy of MRI was found to be 86/98 (88%), and of ERUS 51/98 (52%; 44/98 were unassessable by ERUS as a consequence of failed bowel preparation, tumour beyond the scope of the probe or patients that experienced pain or refused the procedure). A comparison based purely on the cost of the imaging per patient would mean that ERUS is less costly than MRI. However, when the comparative intention-to-stage diagnostic accuracy is incorporated into the cost calculations, MRI is less costly per patient successfully and correctly staged than ERUS. Using a trial-based analysis of 98 patients in the UK, staging with MRI would result in an additional 39 patients correctly staged at an additional cost of £5,880. Thus, the cost per additional correctly staged patient, relative to ERUS, is £151 (A$351; Table 46).

Table 59 Comparative costs of MRI and ERUS

Author Location	Quality	Resource item	MRI		ERUS	
			Costs (£)	Costs (AU$)	Costs (£)	Costs (AU$)
(Brown et al 2004) United Kingdom	Moderate internal validity High generalisability Medium quality (NHMRC = 12.5/16)	Procedure costs per patient (n=98)	130	302	78	181
		Cost per accurately staged patient	157 (n=86)	365	163 (n=51)	379
		Cost per additional accurately staged patient	151 (additional compared to ERUS) (n=35)	351	N/A	

N/A = not applicable
Note: conversions from United Kingdom pounds to Australian dollars performed based on rate of 0.429 pounds to the dollar, as at 23/9/07.

However, in evaluating the costs of different staging procedures, the implications of correct and incorrect staging should be taken into account. Brown et al (2004) assumed that the probability of recurrence for an understaged patient is 30%, and that the cost of treating one case of local recurrence is £8,460 (A$19,743). Based on the cost of staging the 98 patients with MRI and ERUS, and the costs associated with understaging, Brown et al (2004) reported that the total cost per staged patient was £1,273 (A$2,978) for ERUS and £332 (A$775) for MRI. However, this calculation did not take into account the costs of neoadjuvant therapy, or the probability of local recurrence that occurs in patients who receive accurate staging.

Furthermore, as there is evidence that MSCT may be as accurate as MRI for visualising the CRM, the appropriate comparison is MRI plus MSCT versus MSCT plus or minus ERUS. This was not the comparison discussed in Brown et al (2004).

Existing literature on cost-effectiveness of restaging after neoadjuvant therapy

13. What is the cost-effectiveness of MRI, with/without other imaging modalities, compared to no imaging, an alternative modality of imaging or a combination of imaging techniques, in patients with rectal carcinoma requiring restaging of the disease after neoadjuvant therapy?

The inclusion criteria determined a priori for studies of cost-effectiveness of MRI staging in patients who have undergone neoadjuvant therapy is listed in Box 14. No studies met the inclusion criteria for assessing the cost-effectiveness of MRI within this population.

Box 14 Inclusion criteria for studies assessing the cost-effectiveness of MRI restaging of rectal cancer

Characteristic	Criteria	
Publication type	Economic studies, decision analytic modelling studies, economic analysis	
Population	Patients with rectal carcinoma, who have undergone neoadjunctive therapy, requiring restaging of the disease for treatment planning.	
Intervention/test[a]	1. MRI, with/without PET, for reassessment of circumferential resection margin and/or staging of tumour depth, nodal staging	2. Other forms of imaging plus MRI
Comparators[a]	1. No imaging 1. Another form of imaging, ie endorectal ultrasound, positron emission tomography or CT abdomen (pelvis) 1. Other forms of imaging in combination	2. Other forms of imaging
Reference standard	All clinical information, including histopathology findings	
Outcome	Cost, cost per event avoided, cost per life year gained, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Existing literature on cost-effectiveness of diagnosis/staging of recurrent rectal carcinoma

- What is the cost-effectiveness of MRI, compared to ERUS, in patients suspected of having or diagnosed with rectal carcinoma recurrence, and requiring diagnosis/staging for further treatment planning?

- What is the cost-effectiveness of adding MRI staging to CT abdomen (pelvis), with/without PET, in patients suspected of having or diagnosed with rectal carcinoma recurrence, and requiring diagnosis/staging for further treatment planning?

Box 15 outlines the inclusion criteria determined a priori for assessing the cost-effectiveness of using MRI to diagnose patients suspected of having local recurrence of rectal carcinoma, or staging of patients who are diagnosed as having local recurrence. No studies were identified that met the inclusion criteria.

Box 15 Inclusion criteria for studies assessing the cost-effectiveness of MRI diagnosis/staging of recurrent rectal cancer

Characteristic	Criteria	
Publication type	Economic studies, decision analytic modelling studies, economic analysis	
Population	Patients suspected of having or diagnosed with recurrent rectal carcinoma, and requiring diagnosis/staging for further treatment planning.	
Intervention/test[a]	1. MRI for assessment of circumferential resection margin and/or staging of tumour depth, nodal staging	2. CT abdomen and CT pelvis with/without PET plus MRI
Comparators[a]	1. Endorectal ultrasound	2. CT abdomen and CT pelvis with/without PET
Reference standard	All clinical information, including histopathology findings	
Outcome	Cost, cost per event avoided, cost per life year gained, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio	
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles would have significantly increased the timeframe of the review.	

[a] 1. MRI as an alternative or replacement test
2. MRI as an additional test

Summary

What is the cost-effectiveness of MRI, compared to ERUS, in patients with rectal carcinoma requiring further staging of the disease for treatment planning? What is the cost-effectiveness of adding MRI staging to CT abdomen (pelvis), with/without PET, in patients with rectal carcinoma requiring further staging of the disease for treatment planning?

One study was identified that provided cost estimates for MRI compared with ERUS. Due to limitations in the study results, further analysis will be required.

What is the cost-effectiveness of MRI, with/without other imaging modalities, compared to no imaging, an alternative modality of imaging or a combination of imaging techniques, in patients with rectal carcinoma requiring restaging of the disease after neoadjuvant therapy?

No studies were identified that assessed the cost-effectiveness of MRI for restaging of patients after neoadjuvant therapy.

What is the cost-effectiveness of MRI, compared to ERUS, in patients suspected of having or diagnosed with recurrent rectal carcinoma, and requiring diagnosis/staging for further treatment planning? What is the cost-effectiveness of adding MRI staging to CT abdomen (pelvis), with/without PET, in patients suspected of having or diagnosed with recurrent rectal carcinoma, and requiring diagnosis/staging for further treatment planning?

No studies reported on the cost-effectiveness of using MRI to diagnose/stage recurrent rectal carcinoma.

Population assumptions

In order to estimate the economic impact that staging with MRI would have, a series of assumptions were made in regards to:

- the number of patients who would receive staging with MRI as an *alternative* to another form of staging, and the number of patients would receive MRI as an *addition* to other forms of staging;

- the number of patients who likely receive MRI within the *public* health system and *private* health system; and

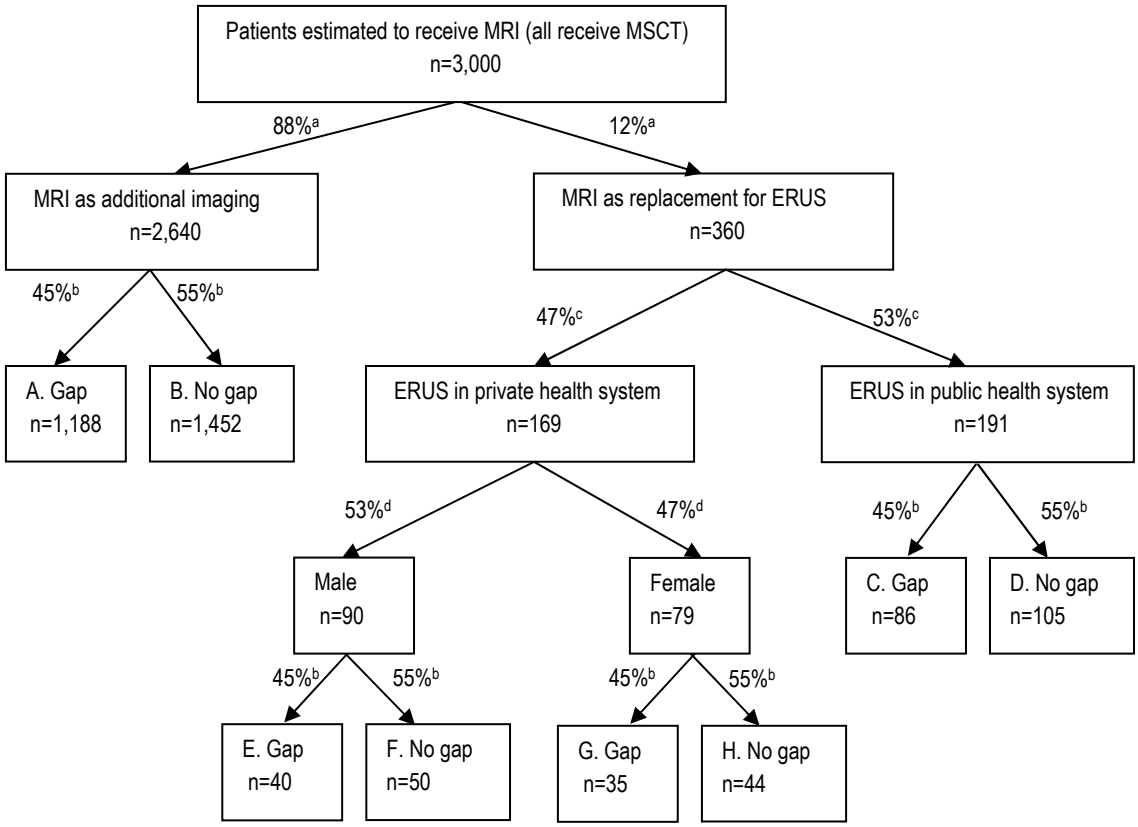
- the number of patients who would likely be eligible for concession.

Figures 18, 20 and 21 outline the proportion and number of patients assumed to be in each of these categories, and Tables 47, 50 and 51 detail the cost components for the different patient groups according to the funding source.

It is possible that staging with MRI would reduce the amount of neoadjuvant therapy used in Australia. Table 62 outlines the studies that reported the T stage distribution of patients imaged with MRI. Figure 19 and Table 61 outline the proportion and number of patients expected to receive neoadjuvant therapy in the private or public health system, and those who are likely to be eligible for concession.

Newly diagnosed patients

Figure 18 Diagram to assist costing of MRI for newly diagnosed patients



[a] On the assumption that 12% of patients with rectal carcinoma would otherwise receive ERUS, based on an Australian clinical practice survey in 2000 (McGrath et al 2004)

[b] Bulk-billing of MBS MRI services occurs in 57% of patients aged 65 years and over, and 51.4% of patients aged 0–64 years (pers. comm., Department of Health and Ageing, 2008). Based on data from the Australian Bureau of Statistics (2000, 2006), it is estimated that 67.5% of patients with rectal carcinoma are aged over 65 years. It is therefore assumed that 55% of rectal carcinoma patients would be bulk-billed and 45% would be required to pay a gap.

[c] The ratio of public to private separations was based on Diagnostic Code C20 'Malignant neoplasm of the rectum', recorded by the National Admitted Patient Care Collection (Department of Health and Ageing 2007).

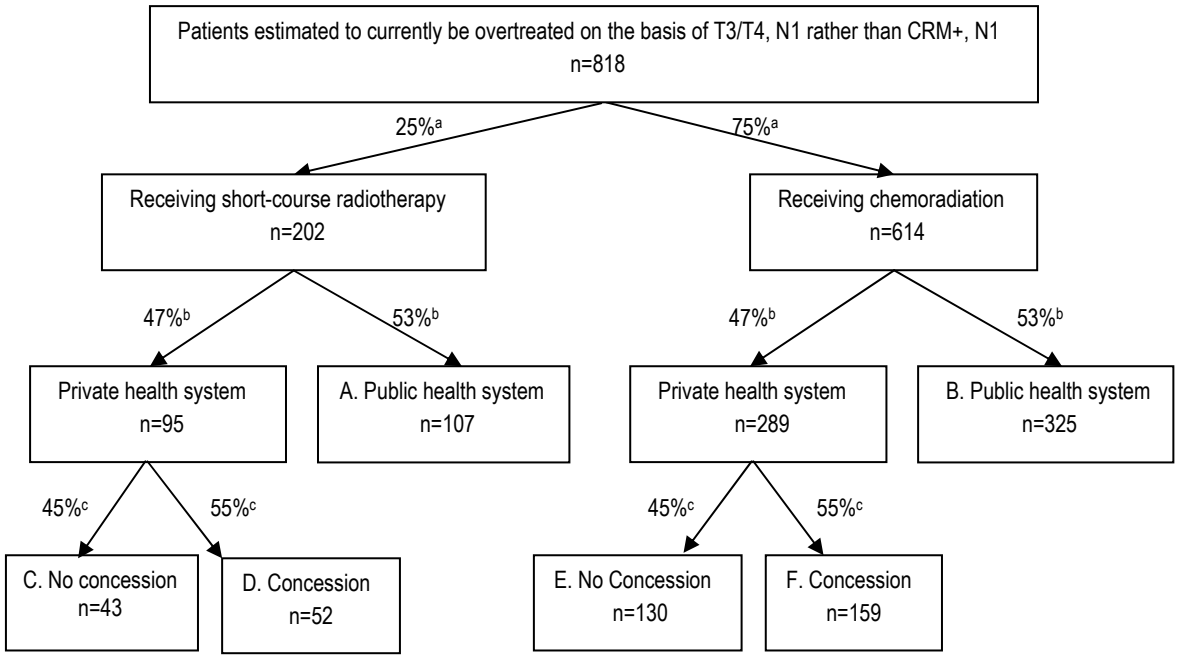
[d] The sex ratio was based on data on the stratified incidence of colorectal cancer in Australia (AIHW 2005).

Table 60 Cost items per population and funding source for MRI in newly diagnosed patients

Population	Cost to Australian Government	Cost to states and territories	Cost to patients
A. n=1,188	MBS rebate for MRI	N/A	Gap for MRI
B. n=1,452	MBS rebate for MRI	N/A	N/A
C. n=86	MBS rebate for MRI	Cost saving of cost of ERUS	Gap for MRI
D. n=105	MBS rebate for MRI	Cost saving of cost of ERUS	N/A
E. n=40	MBS rebate for MRI rather than MBS rebate for ERUS (male)	N/A	Gap for MRI rather than ERUS (male)
F. n=50	MBS rebate for MRI rather than MBS rebate for ERUS (male)	N/A	N/A
G. n=35	MBS rebate for MRI rather than MBS rebate for ERUS (female)	N/A	Gap for MRI rather than ERUS (female)
H. n=44	MBS rebate for MRI rather than MBS rebate for ERUS (female)	N/A	N/A

N/A = not applicable

Figure 19 Diagram to determine cost offsets from accurate determination of CRM status



[a] Based on expert opinion of the Advisory Panel

[b] The ratio of public to private separations was based on Diagnostic Code C20 'Malignant neoplasm of the rectum', recorded by the National Admitted Patient Care Collection (Department of Health and Ageing 2007).

[c] Bulk-billing of MBS MRI services occurs in 57% of patients aged 65 years and over and 51.4% of patients aged 0–64 years (pers. comm., Department of Health and Ageing, 2008). Based on data from the Australian Bureau of Statistics (2000, 2006), it is estimated that 67.5% of patients with rectal carcinoma are aged over 65 years. It is therefore assumed that 55% of rectal carcinoma patients would be bulk-billed and 45% would be required to pay a gap.

Table 61 Cost offset items per population and funding source for neoadjuvant therapy in newly diagnosed patients

Population	Cost to Australian Government	Cost to states and territories	Cost to patients or health insurance[a]
A. n=107	N/A	Cost of short-course radiotherapy	N/A
B. n=325	N/A	Cost of long-course radiotherapy Cost of chemotherapy Cost of fluorouracil at dispensed price Cost of PICC or TIVAS Day case hospitalisation for chemotherapy	N/A
C. n=43	MBS rebate for short-course radiotherapy (85%)	N/A	Gap for short-course radiotherapy (15%)
D. n=52	MBS rebate for short-course radiotherapy (85%)	N/A	N/A
E. n=130	MBS rebate for long-course radiotherapy (85%) MBS rebate for chemotherapy (75%) Difference between fluorouracil at dispensed price and maximum recordable value	N/A	Gap for long-course radiotherapy (15%) Gap for chemotherapy (25%) Fluorouracil at maximum recordable value Cost of PICC or TIVAS Day case hospitalisation for chemotherapy
F. n=159	MBS rebate for long-course radiotherapy (85%) MBS rebate for chemotherapy (75%) Difference between fluorouracil at dispensed price and concession rate	N/A	Fluorouracil at concession rate Cost of PICC or TIVAS Day case hospitalisation for chemotherapy

N/A = not applicable; [a] health insurance may cover the cost of hospitalisation for chemotherapy and PICC or TIVAS; PICC = peripherally inserted central catheter; TIVAS = totally implantable venous access system

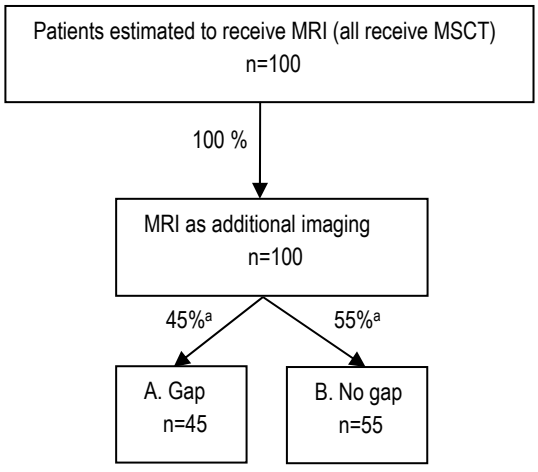
Table 62 Percentage of rectal carcinoma patients presenting with T3 tumours

Study	Criteria	n	Tis/T0/ T1	T2	T3	T4	%T3
(Akasu et al 2005)	Consecutive patients with biopsy-proven rectal carcinoma	34	4	9	15	6	44.1
(Arii et al 2006)	Consecutive patients with lower rectal carcinoma who underwent rectal resection	53	3	13	34	3	64.2
(Brown et al 1999)	Evaluated for surgery	25/28	0	5	18	2	51.4
(Ferri et al 2005)	Patients with invasive carcinomas, suitable for imaging with MRI	29	4	3	20	2	69.0
(Hadfield et al 1997)	Biopsy-proven rectal carcinoma	38	7	4	26	1	68.4
(Kim et al 2006)	Primary rectal cancer, who underwent MRI, and had surgical resection	35	8	7	20	0	57.1
(Kim et al 2000)	Consecutive patients with biopsy-proven rectal carcinoma	217	4	37	162	14	74.7
(Kim et al 2007)	Consecutive patients with biopsy-proven rectal carcinoma, excluding T4	57	7	10	40	–	70.2
(Matsuoka et al 2003b)	Patients with rectal carcinoma, who underwent surgical and endoscopic treatment	21	4		15	2	62.5
(MERCURY Study Group 2006)	Consecutive patients with biopsy-proven rectal carcinoma who received either primary surgery or neoadjuvant therapy followed by surgery	408	43	93	234	38	57.4

T = tumour stage; is = (carcinoma) in situ, see Table 1

Restaging after neoadjuvant therapy

Figure 20 Diagram to assist costing of MRI for restaging after neoadjuvant therapy



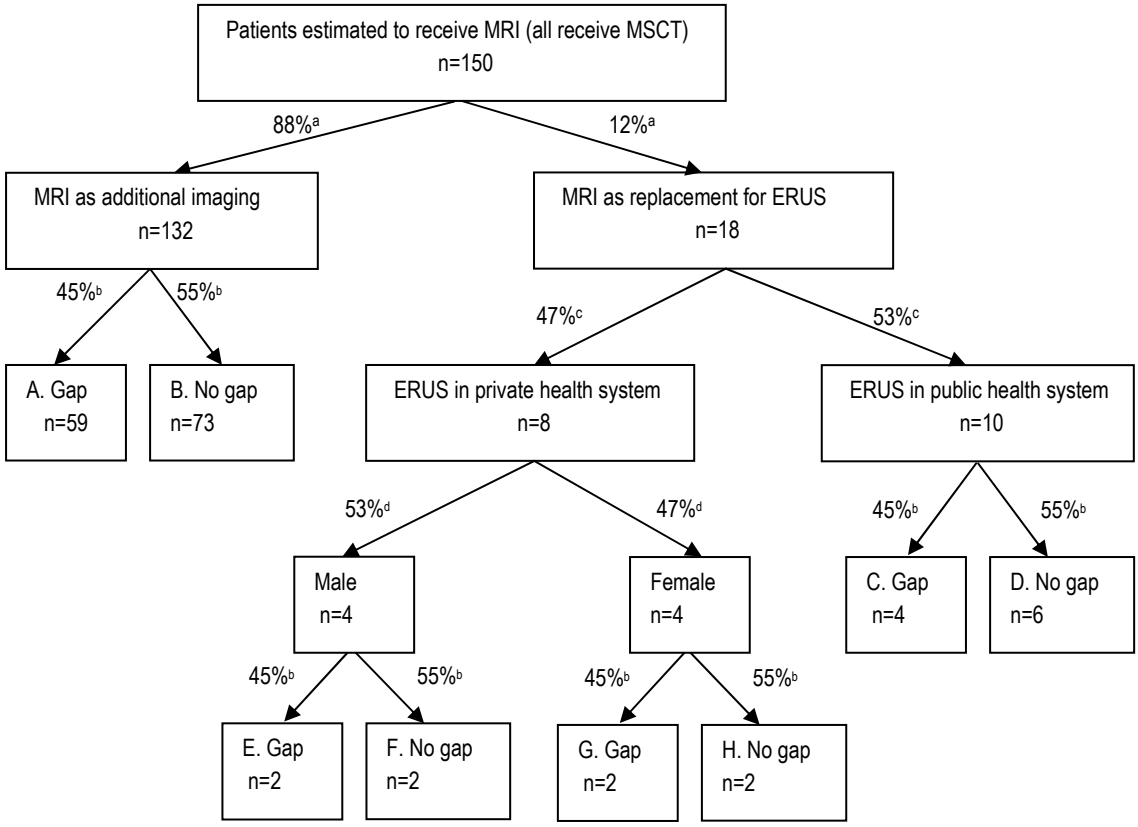
[a] Bulk-billing of MBS MRI services occurs in 57% of patients aged 65 years and over and 51.4% of patients aged 0–64 years (pers. comm., Department of Health and Ageing, 2008). Based on data from the Australian Bureau of Statistics (2000, 2006), it is estimated that 67.5% of patients with rectal carcinoma are aged over 65 years. It is therefore assumed that 55% of rectal carcinoma patients would be bulk-billed and 45% would be required to pay a gap.

Table 63 Cost items per population and funding source for MRI in patients requiring restaging

Population	Cost to Australian Government	Cost to states and territories	Cost to patients
A. n=45	MBS rebate for MRI	N/A	Gap for MRI
B. n=55	MBS rebate for MRI	N/A	N/A

N/A = not applicable

Figure 21 Diagram to assist costing of MRI for diagnosis/staging of local carcinoma recurrence



[a] Assumption that 12% of patients with rectal carcinoma would otherwise receive ERUS, based on an Australian clinical practice survey in 2000 (McGrath et al 2004)

[b] Bulk-billing of MBS MRI services occurs in 57% of patients aged 65 years and over and 51.4% of patients aged 0–64 years (pers. comm., Department of Health and Ageing, 2008). Based on data from the Australian Bureau of Statistics (2000, 2006), it is estimated that 67.5% of patients with rectal carcinoma are aged over 65 years. It is therefore assumed that 55% of rectal carcinoma patients would be bulk-billed and 45% would be required to pay a gap.

[c] The ratio of public to private separations was based on Diagnostic Code C20 'Malignant neoplasm of the rectum', recorded by the National Admitted Patient Care Collection (Department of Health and Ageing 2007).

[d] The sex ratio was based on data on the stratified incidence of colorectal cancer in Australia (AIHW 2005).

Table 64 Cost items per population and funding source for MRI in patients diagnosed with or suspected of having carcinoma recurrence

Population	Cost to Australian Government	Cost to states and territories	Cost to patients
A. n=59	MBS rebate for MRI	N/A	Gap for MRI
B. n=73	MBS rebate for MRI	N/A	N/A
C. n=4	MBS rebate for MRI	Cost saving of cost of ERUS	Gap for MRI
D. n=6	MBS rebate for MRI	Cost saving of cost of ERUS	N/A
E. n=2	MBS rebate for MRI rather than MBS rebate for ERUS (male)	N/A	Gap for MRI rather than ERUS (male)
F. n=2	MBS rebate for MRI rather than MBS rebate for ERUS (male)	N/A	N/A
G. n=2	MBS rebate for MRI rather than MBS rebate for ERUS (female)	N/A	Gap for MRI rather than ERUS (female)
H. n=2	MBS rebate for MRI rather than MBS rebate for ERUS (female)	N/A	N/A

N/A = not applicable

Glossary

AIHW	Australian Institute of Health and Welfare
Area under the curve (AUC)	Calculated as the area under a receiver operator characteristic curve, the AUC provides a numerical description of the accuracy of a diagnostic test; a test with no diagnostic value has an AUC of 0.5, while a perfect test has an AUC of 1.0
ARTG	Australian Register of Therapeutic Goods
CRM	Circumferential resection margin
CT	Computed tomography
DRE	Digital rectal examination
Enema	The injection of liquid into the rectum for the purpose of cleansing
ERUS	Endorectal ultrasound
FA	False alarm
False alarm rate	The proportion of false positive tests among people receiving a positive test
False negative	A negative test result when disease status is positive
False negative rate	The proportion of negative tests among people with the disease
False positive	A positive test result when disease status is negative
False positive rate	The proportion of positive tests among people without the disease or condition
False reassurance rate	The proportion of false negative tests among people without the disease or condition
Heterogeneity	In meta-analysis, refers to variability in the statistical estimates of studies
Inter-quartile range (IQR)	A measure of dispersion calculated as the difference between the 75th and 25th percentiles of a distribution
ITT	Intention-to-treat
LYG	Life years gained
M	Metastases
Magnetophosphenes	The sensation of flashes of light, caused by electrical current stimulating the retina
MBS	Medicare Benefits Schedule
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
MSCT	Multi-slice computed tomography
N	Nodal involvement

Negative predictive value (NPV)	Proportion of patients with negative test results who are correctly diagnosed
NHMRC	National Health and Medical Research Council
NNT	Number needed to treat
Positive predictive value (PPV)	Proportion of patients with positive test results who are correctly diagnosed
Power	Refers to the ability of a statistical test to reject a false null hypothesis
Publication bias	Occurs when studies reporting statistically significant effects are more likely to be published and cited
QALY	Quality-adjusted life year
PET	Positron emission tomography
Relative risk (RR)	A measure of how much a particular risk factor influences the likelihood of an outcome—calculated as the incidence of an outcome in the experimental group divided by the incidence in the control group
Risk difference	The difference in the incidence of an outcome between the experimental group and the control group
Sensitivity (Sn)	Refers to the proportion of people with a disease who report a positive test result
Specificity (Sp)	Refers to the proportion of people without a disease who report a negative test result
T	Tesla or tumour
TME	Total mesorectal excision
UICC	International Union Against Cancer

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