

***Magnetic
Resonance
Imaging for staging
cervical and
endometrial cancer***

November 2001

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Assessment report

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The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 107
GPO Box 9848
Canberra ACT 2601

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth 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.

This report was prepared for the Medical Services Advisory Committee by Elizabeth Barr, Research Assistant, Josephine Belcher, Research Assistant and Kirsten Howard, Epidemiologist, from the NHMRC Clinical Trials Centre, with recommendations by the MSAC Supporting Committee for MRI for staging cervical and endometrial cancer. The report was endorsed by the Commonwealth Minister for Health and Ageing on 5 February 2002.

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

Contents

Executive summary	vii
Introduction	1
Background	2
Magnetic Resonance Imaging (MRI)	2
Issues in evaluation of MRI.....	3
Clinical need/burden of disease	6
Existing procedures	7
Comparator.....	7
Marketing status of the device/technology.....	7
Current reimbursement arrangement.....	7
Approach to assessment	8
Review of literature	8
Expert advice.....	12
Results of assessment	13
Is it safe?.....	13
Is it effective?.....	14
What are the economic considerations?.....	47
Conclusions	54
Safety	54
Effectiveness.....	54
Cost-effectiveness.....	56
Recommendations	57
Appendix A MSAC terms of reference and membership	59
Appendix B Supporting committee	61
Appendix C Studies included in the review	63
Appendix D Flow chart – role of MRI	91
Appendix E Cost estimates	92
Abbreviations	95
References	97

Tables

Table 1	Evaluating and applying the results of studies of diagnostic tests	6
Table 2	Measures of disease burden for selected conditions.....	7
Table 3	Search strategy for Medline database for MRI.....	8
Table 4	Search strategy for EMBASE database for MRI.....	9
Table 5	Health Technology Assessment Organisations.....	10
Table 6	Designation of levels of evidence.....	10
Table 7	FIGO staging of cervical cancer.....	17
Table 8	MRI publications regarding cervical cancer.....	18
Table 9	Detection of parametrial invasion using a 1.5T system ^{a,b}	22
Table 10	Detection of vaginal invasion using a 1.5T system ^a	24
Table 11	MRI and response to treatment.....	26
Table 12	MRI detection of residual/recurrent disease ^a	28
Table 13	FIGO staging of endometrial cancer.....	32
Table 14	MRI publications in endometrial cancer.....	35
Table 15	Diagnostic accuracy of MRI compared with conventional procedures to detect myometrial invasion of endometrial cancer.....	39
Table 16	Diagnostic accuracy of MRI compared with conventional imaging to detect cervical invasion of endometrial cancer.....	42
Table 17	Medline search strategy for economic evaluations.....	47
Table 18	EMBASE search strategy for economic evaluations.....	48
Table 19	Descriptive or partial economic evaluations of MRI in gynaecological malignancies.....	49
Table 20	Patient number estimates.....	50
Table 21	Accuracy of diagnostic tests.....	51
Table 22	Number of patients with accurate and inaccurate diagnoses (based on sensitivity and specificity above).....	51
Table 23	Incremental benefit (avoidance of incorrect results) of MRI over CT.....	51
Table 24	Cost of imaging.....	52
Table 25	Healthcare cost for diagnosis and subsequent treatment (cost per 100 patients assessed with MRI and/or CT)	52
Table 26	Cervical cancer (CC) data extraction - detection of parametrial and vaginal invasion.....	63
Table 27	Cervical cancer data extraction – radiotherapy field planning	68
Table 28	Cervical cancer (CC) data extraction - response to treatment and microcirculation assessment.....	69
Table 29	Endometrial cancer (EC) data extraction – diagnostic accuracy of MRI compared with other conventional procedures	72

Table 30	Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion.....	77
Table 31	Endometrial cancer (EC) data extraction - meta-analyses.....	86
Table 32	Endometrial cancer (EC) data extraction - diagnostic accuracy of detecting malignant from benign endometrial lesions.....	87
Table 33	Endometrial cancer (EC) data extraction - diagnostic accuracy of MRI compared with IOGD to detect endometrial cancer invasion.....	89
Table 34	Costs of treatments.....	92
Table 35	Number of patients (based on 692 evaluated with CT or MRI).....	93
Table 36	Total diagnostic and treatment costs for patients assessed by CT.....	93
Table 37	Total diagnostic and treatment costs for patients assessed by MRI (pelvic and abdominal MRI).....	93
Table 38	Total diagnostic and treatment costs for patients assessed by MRI (pelvic MRI only).....	94
Table 39	Total healthcare cost for diagnosis and subsequent treatment of patients (n=692 assessed).....	94

Executive summary

The procedure

Magnetic Resonance Imaging (MRI) is a non-invasive imaging device that uses magnetic resonance as a means of producing anatomical images. Various MRI sequences can be employed, such as T1 and T2-weighted MRI, dynamic MRI and contrast-enhanced MRI, in order to obtain suitable images to represent the anatomical part under investigation.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth 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 the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre, University of Sydney was engaged to conduct a systematic review of literature on MRI from 1997 onwards. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of Magnetic Resonance Imaging for staging cervical and endometrial cancer

MRI is currently used to diagnose a range of clinical conditions in Australia including head and spine, musculoskeletal and cardiovascular conditions. This review evaluates the available evidence for the use of MRI as a diagnostic test to stage cervical and endometrial cancer. Four questions are covered in this report.

What is the value of MRI in:

- assessment of patients with newly diagnosed cervical cancer to determine extent of disease to aid in planning treatment?
- assessment of patients with newly diagnosed cervical cancer where conventional assessment indicates tumour extension past the cervico-paracervical margin to aid in radiotherapy planning?
- assessment of patients with a persistent mass after treatment for cervical cancer to differentiate residual or recurrent disease from benign anatomical or post treatment changes?
- assessment of patients with newly diagnosed endometrial cancer for staging of disease prior to surgery?

Clinical need

In 1997, there were 795 new cases of cervical cancer. This translates into an age-standardised incidence rate of 8.0 cases/100,000 amongst all women. In the same year 291 women died from cervical cancer, representing an age-standardised mortality rate of 2.7 cases/100,000 and 3,693 person-years life lost (PYLL). Peak incidence of cervical cancer occurred between the ages of 35-55 years (Australian Institute of Health and Welfare 2000b).

In 1997, there were 1,394 new cases of endometrial cancer (uterine cancer), representing an age-standardised incidence rate of 13.5 cases/100,000 Australian women. Furthermore, 271 women died from endometrial cancer, representing an age-standardised mortality rate of 2.4 cases/100,000 and 1,605 PYLL. Endometrial cancer was more likely to occur between the ages of 55-65 years (Australian Institute of Health and Welfare 2000b).

Safety

MRI is considered to be a safe non-invasive imaging modality. Patients undergoing MRI examination are exposed to low levels of electromagnetic radiation for short periods of time. The electromagnetic radiation dose emitted by the MRI apparatus is not sufficient enough to result in irreversible or hazardous biological effects in patients undergoing the tests.

Acoustic noise may be a potential hazard to patients undergoing MRI examination. It is therefore recommended that patients wear disposable ear-plugs to prevent temporary hearing loss.

MRI is contraindicated in patients with ferromagnetic and electronic implants such as pacemakers and aneurysm clips. Each patient should be assessed on an individual basis, as the ferromagnetic properties and the anatomical position of the implant will determine whether the patient is a suitable candidate for MRI.

MRI often involves the intravenous administration of a contrast agent, commonly gadopentetate dimeglumine. Clinical trials and extensive clinical use have shown that such contrast agents are safe and generally well tolerated by patients, especially when compared to the contrast agents used to perform computer tomography, which are considered relatively more toxic.

Effectiveness

Cervical cancer

Diagnostic accuracy

It is difficult to evaluate the relative diagnostic accuracy of MRI over other treatment modalities due to a lack of papers directly comparing the different modalities. However, MRI does appear to have a high level of diagnostic accuracy in the detection of parametrial invasion (median sensitivity and specificity of approximately 85%) compared to computed tomography (CT) (accuracy of approximately 70%).

Based on a small number of studies, the overall accuracy of MRI for the detection of vaginal invasion appears to be lower. Sensitivity was moderate, while specificity was higher, generally above 90%.

It was not possible to assess the role of MRI in the assessment of suspected residual or recurrent disease because of methodological limitations and small sample sizes of the available evidence.

Early studies indicate that MRI may be able to monitor individual patient treatment response, although there is insufficient evidence at this time to fully assess this potential role.

Impact on clinical decision making and health outcomes

MRI's ability to detect parametrial invasion could influence the decision as to how a particular patient will be treated. MRI was also shown to alter radiotherapy field planning. However, no studies reported the effect such changes in management had on patient outcomes. Although very early and limited data suggests that MRI may be useful in monitoring an individual patient's treatment response, some of the techniques require complex post-imaging calculations and may not be applicable to the Australian setting.

Endometrial cancer

Diagnostic accuracy

MRI appears to have improved diagnostic accuracy over fractional curettage, cervical cytology, intrauterine sonography, serum markers CA-125 and CA 19-9, and at least comparable diagnostic accuracy compared with transvaginal ultrasonography in the differentiation of extensive endometrial cancer from early disease. The positive predictive value of MRI (67-85%) does not appear to be sufficiently high to suggest that MRI should replace current staging practices. There was insufficient evidence to compare MRI with CT in the differentiation of extensive endometrial cancer from early disease. Furthermore, many of the studies included in this review were case series. When relying on data from case series, comparison across individual studies is difficult owing to the inherent problems that arise, due to the lack of a control group and the potential for bias. Therefore, these limitations may affect the generalisability of any conclusions.

Impact on clinical decision making and health outcomes

Based on very limited evidence, MRI may provide some information on patient prognosis. However, the implications for management of patients with endometrial cancer remain unclear at this stage. Therefore, there is insufficient evidence available to make any conclusions regarding the role of MRI on changing patient management or subsequent health outcomes.

Cost effectiveness

There are few reliable head-to-head comparisons of MRI and CT in the assessment of patients with cervical cancer. Based on available data MRI appears to have improved sensitivity and specificity (both 85%) over CT (both 75%), however there is still uncertainty associated with these estimates.

A modelled cost analysis was conducted based on modest improvements in the diagnostic accuracy of MRI over CT. Based on a number of estimates and assumptions, the cost effectiveness of MRI would be as follows.

For every 100 patients where MRI was used to assess the extent of disease:

- The incremental cost per 100 patients would range from saving \$1,300 to costing an extra \$17,000.
 - These cost estimates incorporate treatment costs and also depend upon the eventual Medicare Benefits Schedule fee for MRI in this indication and whether it is used as a replacement or an incremental test to CT.
- There would be five fewer false positive results (potentially avoiding inappropriate radical chemoradiation) based on improved specificity.
- There would be five fewer false negative results (potentially avoiding inappropriate surgery) based on improved sensitivity.

Recommendations

MSAC recommends on the strength of evidence pertaining to Magnetic Resonance Imaging (MRI) for staging of cervical and endometrial cancer that:

1. Public funding should be supported for MRI staging of histologically proven cervical cancer at FIGO stages IB or greater following assessment by examination under anaesthesia;
 2. At present there is insufficient evidence to support public funding for MRI in patients with recurrent cervical cancer but further studies may require this issue to be reviewed in the future; and
 3. Public funding should not be supported for MRI staging of endometrial cancer at this time.
- The Minister for Health and Ageing accepted these recommendations on 5 February 2002. -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of Magnetic Resonance Imaging as a diagnostic test for staging cervical and endometrial cancer. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme 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 diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

The Supporting Committee members are drawn from the Royal Australian and New Zealand College of Radiologists (RANZCR), RANZCR Faculty of Radiation Oncology, Royal Australian and New Zealand College of Gynaecologists and Obstetricians, and MSAC. Each member is listed in Appendix B.

This report summarises the assessment of current evidence for MRI for the indications of cervical and endometrial cancer.

Background

Magnetic Resonance Imaging (MRI)

MRI is a diagnostic imaging modality that uses magnetic resonance as a means of producing images.

How it works

The MRI system is comprised of a magnet housed inside a gantry. The magnet is the largest and most costly component of the MRI system. There are three different types of magnet; resistive (electromagnetic), permanent and superconductive. Superconductive magnets are currently the most frequently used and contain supercooled metal alloys. The strength of the magnet is measured in Tesla (T) and there are five different magnet strengths available; ultra high-field systems ($>2T$), high-field systems ($1.5-2T$), medium-field magnets ($0.5-1T$), low-field magnets ($0.1-0.5T$) and ultra low-field magnets ($<0.1T$) (Matwiyoff & Brooks 1999; Yochum & Barry 1996). Generally, the signal-to-noise ratio improves with magnet strength thus improving image production. However, the utilisation of surface coils and new computer software systems has enabled weaker magnets to produce images of excellent quality. Surface coils are small coils which are used to image small regions. A smaller field of view provides a greater signal-to-noise ratio, and therefore improved contrast resolution and image production. Numerous coils exist depending on the size and shape of the body part to be examined (Yochum & Barry 1996).

The magnetic resonance image is produced by the complex interaction between hydrogen protons within the body and the external magnetic field. When a person is exposed to the magnetic field produced by the magnet, the randomly assigned precessing protons are forced into alignment (Wood & Wehrli 1999; Yochum & Barry 1996). When a radiofrequency pulse (RF) is generated at the appropriate Larmor frequency, the atoms are excited to a high energy state due to their altered orientation relative to the external magnetic field. When the RF pulse is removed, the proton's reorientation emits a signal which is interpreted by the transmitter and used to produce the MR image (Wood & Wehrli 1999; Yochum & Barry 1996). In spin-echo sequences, the RF pulses are repeated several times (usually at 90° , then at 180° , then again at 90°). The time interval between the two 90° pulses is called the repetition time (TR). The time between the pulse and the detection of MR signal is known as the echo time (TE). The manipulation of TR and TE produces different image characteristics. The effectiveness of a given MR examination is highly dependent on the imaging parameters, or pulse sequences, selected (Wood & Wehrli 1999; Yochum & Barry 1996).

T1-weighted (T1W) MRI (short TR and TE) provides excellent anatomical information where fat tissue is hyperintense (bright) and water is hypointense (dark). T2-weighted (T2W) MRI (long TR and TE) presents water as hyperintense and fat tissue as hypointense. Proton density-weighted images (long TR and short TE) provide characteristics of both T1W and T2W MRI (Yochum & Barry 1996). Furthermore, contrast-enhanced (CE) MRI uses intravenous administration of gadolinium attached to a chelating agent (such as diethylene triamine pentaacetic acid (DTPA)). The contrast agent appears bright on T1W MRI (Runge & Nelson 1999; Yochum & Barry 1996).

Fast spin-echo and gradient-echo sequences acquire images with a reduced scan time, therefore reducing the examination time. Fast spin-echo sequences also increase spatial resolution and thus image quality (Bradley, Jr. et al. 1999; Yochum & Barry 1996). Whereas gradient-echo sequences may have increased susceptibility to artefacts, three-dimensional (3-D) volume acquisitions provide thin-section (slice thickness as small as 1mm or less) evaluations of a region, and are therefore useful in the assessment of small anatomical structures (Yochum & Barry 1996). Fat suppressed MRI is a technique whereby the signal from fat is suppressed, thereby making small areas of pathologic change (which often produce high signal images due to increased fluid content) more visible and improving the overall sensitivity of the examination (Szumowski & Simon 1999; Yochum & Barry 1996).

The procedure

The patient is placed in a supine position on a couch which then moves longitudinally inside the gantry of the MR system. Once the patient is inside the system, the patient and couch remain still during the examination. When surface coils are employed, the patient usually remains outside the gantry unit (Yochum & Barry 1996).

Issues in evaluation of MRI

Intended purpose

MRI is currently used to diagnose a range of clinical conditions in Australia. In October 1997, the Australian Health Technology Advisory Committee (AHTAC) completed a review of MRI use in Australia. The review's results provided a basis for examining the appropriateness of current MRI funding and delivery arrangements. Following this, the Commonwealth Department of Health and Aged Care established a committee to evaluate the AHTAC report, and with further consultation, provided advice to the Minister on the appropriate number and distribution of MRI units needed to best serve Australia's future population. The Committee considered evidence provided by the Medical Technology Assessment Group (M-TAG Pty Ltd), the Royal Australian and New Zealand College of Radiologists (RANZCR) and the Monash Medical Centre literature review, and made 10 recommendations, which were reported in the *Blandford Report*. One of the recommendations outlined a range of new MRI clinical applications to be referred to MSAC for review as an immediate priority. The clinical applications included the use of MRI for; magnetic resonance cholangiopancreatography (MRCP), staging of endometrial and cervical carcinoma, and angiography if radiographic iodine-based CT is contraindicated. Other clinical applications referred to MSAC for further review included the use of MRI to examine breast tissue, stage prostate and rectal cancer, examine cardiac tissue including coronary angiography, examine the liver, and have a role in angiography.

This review will therefore evaluate the available evidence for the use of MRI in staging cervical and endometrial cancer. Extensive additional information about each of these indications is included within the Results of Assessment section of this review.

The research questions

Specific questions addressing the use of MRI for staging endometrial and cervical cancer were formulated from information on current practice (ie common usage of MRI in Australia), and the disease area and purpose of the test (eg evaluation of the extent of disease before surgery or evaluation of recurrent disease). An *a priori* decision was made to evaluate only data published from 1997 onwards. The Supporting Committee was of the opinion that prior to this date, MRI technology was sufficiently different to that currently available as to make comparison inappropriate. Clinical flow charts depicting the diagnosis, staging and subsequent treatment of patients with newly diagnosed endometrial and cervical cancer and assessment of patients with suspected residual or recurrent cervical cancer were developed. These flow charts were used to define the potential role(s) of MRI in the evaluation of these diseases. Based on these flow charts, four questions were developed and are covered in this report.

What is the value of MRI in:

- assessment of patients with newly diagnosed cervical cancer to determine extent of disease to aid in planning treatment?
- assessment of patients with newly diagnosed cervical cancer where conventional assessment indicates tumour extension past the cervico-paracervical margin to aid in radiotherapy planning?
- assessment of patients with a persistent mass after treatment for cervical cancer to differentiate residual or recurrent disease from benign anatomical or post treatment changes?
- assessment of patients with newly diagnosed endometrial cancer for staging of disease prior to surgery?

Principles of diagnostic test evaluation

Evaluation of diagnostic tests

Several authors have discussed the sequence of evaluations that can be done on a diagnostic test (Jaeschke, Guyatt, & Sackett 1994; Masci et al. 1999; National Health and Medical Research Council 2000). These include diagnostic test performance, therapeutic impact and outcome.

Diagnostic test performance ('accuracy') can be measured as sensitivity, specificity, or likelihood ratios. This involves comparing test results against a valid reference or 'gold standard' which represents the 'truth'. Appropriate gold standards can include pathology findings (for example, histopathological confirmation of the presence or absence of disease) or clinical outcome (eg, subsequent disease progression or resolution of symptoms and signs).

Therapeutic impact is measured as the change in treatment decision made by clinicians in response to the information provided by the test.

Outcome: Ideally, it is desirable to know whether people who have a diagnostic test have better outcomes. This can be assessed by examining randomised trials of the test and outcomes of subsequent management resulting from the test. Such information is

usually not available and surrogates have to be used. However, changes in outcome may be reasonably inferred from a combination of evidence of improved diagnostic accuracy, evidence of changes in management and evidence of the effective treatment of a given condition. That is, in conjunction with evidence of improved diagnostic accuracy and changes in management, there should be evidence (ideally from randomised controlled trials) that alternative treatment or management results in improved long term health outcomes for patients. For example, if a diagnostic test allowed earlier diagnosis of a condition, evidence that earlier treatment is more effective than delayed treatment is needed to infer that improved outcomes result from the diagnostic test result.

Methodological constraints may prevent some of these studies being done. For example, if it is not possible to measure a reference standard, tests of diagnostic test performance characteristics are not feasible. Flow diagrams showing the suggested pathway by which testing should improve outcomes are a helpful way of summarising why we expect a test may be valuable (Flynn & Adams 1996). Studies done for each step or for groups of steps can be appraised and the quality of the evidence noted. Flow diagrams can also be helpful in clarifying the specific clinical question of interest. For example, if there are trials showing the effect of testing on the final outcome, studies on the intervening steps are of less interest. Assessing diagnostic accuracy is most relevant when randomised controlled trials suggest that intervention based on that diagnosis is effective.

Study quality

Studies vary in quality, whether they are looking at diagnostic accuracy (for which the ideal is cross-sectional analytic studies of consecutive patients all followed up with a valid reference standard), or effect on outcomes (where the ideal is a randomised trial of alternative tests). The quality of the study influences the reliability and validity of the results. Several checklists of study quality criteria are available, including the NHMRC handbook on how to conduct systematic reviews (National Health and Medical Research Council 2000). Jaeschke et al (1994) indicated that to evaluate whether the results reported in an article about diagnostic tests are valid the issues shown in Table 1 should be considered.

There is potential for verification or 'work-up' bias in the studies conducted on MRI if the result of the test being evaluated influences the decision to perform the reference standard (Begg & Greenes 1983; Choi 1992; Shuchleib et al. 1999). A potential example in the current reviews would be if patients suspected of having a cervical tumour as a result of having a positive test result (such as an MRI scan) are more likely to undergo biopsy of the cervix in order to determine histopathological results (the reference standard) than those with a negative test.

Table 1 Evaluating and applying the results of studies of diagnostic tests

Question	Quality indicator
Are the results of the study valid? – primary guides	Was there an independent, blind comparison with a reference standard? Did the patient sample include an appropriate spectrum of patients to whom the diagnostic test will be applied in clinical practice?
– secondary guides	Did the results of the test being evaluated influence the decision to perform the reference standard? Were the methods for performing the test described in sufficient detail to permit replication?
What were the results?	Are the likelihood ratios for the test results presented or are the data necessary for their calculation provided?
Will the results help me in caring for my patients?	Will the reproducibility of the test result and its interpretation be satisfactory in my setting? Are the results applicable to my patient? Will the results change my management? Will patients be better off as a result of the test?

Source: Jaeschke et al (1994)

Incremental or replacement test?

In clinical practice MRI may be used as an incremental test on top of conventional work-up diagnostic procedures (eg biopsy, clinical examination under anaesthesia etc), or as a replacement test for one or more of these procedures.

Ideally, in the situation where MRI is seen as a replacement for computer tomography (CT) or ultrasound (US), the results of one test should be evaluated blind to the results of the other, to minimise test-review bias. In clinical practice the results of a particular diagnostic test may also be used to provide incremental information over and above that provided by conventional assessment. In this situation, the blinded assessment of test results is not as critical as it will be used in conjunction with, rather than instead of, other tests in clinical practice. In many studies included in this review, blinding of the assessment of MRI was not explicitly reported.

Whether MRI is used as a replacement or as an additional diagnostic procedure will also have implications for the cost. Where MRI is used as an incremental test, any cost offsets resulting from MRI would relate to changes in management, rather than avoiding the use of other tests.

Clinical need/burden of disease

In 1997, there were 795 new cases of cervical cancer. This translates into an age-standardised incidence rate of 8.0 cases/100,000 amongst all women. In the same year 291 women died from cervical cancer, representing an age-standardised mortality rate of 2.7 cases/100,000 and 3,693 person-years life lost (PYLL). Peak incidence of cervical cancer occurred between the ages of 35-55 years (Australian Institute of Health and Welfare 2000b).

In 1997, there were 1,394 new cases of endometrial cancer (uterine cancer), representing an age-standardised incidence rate of 13.5 cases/100,000 Australian women. Furthermore, 271 women died from endometrial cancer, representing an age-standardised mortality rate of 2.4 cases/100,000 and 1,605 PYLL. Endometrial cancer

was more likely to occur between the ages of 55-65 years (Australian Institute of Health and Welfare 2000b). Table 2 summarises these disease burdens.

Table 2 Measures of disease burden for selected conditions

Condition	ICD-9-CM code ^a	Age standardised incidence rate (1997) Per 100,000	Age standardised mortality rate (1997) Per 100,000	Person-years life lost (PYLL)
Cervical cancer	ICD 180	8.0	2.7	3,693
Endometrial cancer	ICD 179 + 182 ^b	13.5	2.4	1,605

^a ICD 10 codes: Cervical cancer C53.9; Endometrial Cancer C54.1

^b The AIHW provide epidemiological information for both endometrial and uterine cancer combined. These two cancers are clinically very similar.

Existing procedures

Cervical cancer is diagnosed by biopsy and clinical examination under general anaesthesia, following onset of vaginal or post-coital bleeding, or positive Papanicolaou (Pap) test. Endometrial cancer is also diagnosed by biopsy and clinical examination under general anaesthesia following onset of symptoms such as dysfunctional vaginal bleeding. The histopathological results of the biopsy are used to grade and classify the tumour. Tumour type and grade are prognostic factors for cervical and endometrial cancer.

Cervical cancer staging is based on clinical examination. Imaging modalities such as US and CT have also been used to evaluate the extent of local invasion and metastatic involvement. Endometrial cancer however, is diagnosed and staged according to the histopathological results following surgery. Chest radiographs are also of value in both groups of patients.

Comparator

In this review MRI is compared to a number of alternative diagnostic procedures that are used to pre-operatively stage endometrial and cervical cancer including CT, US, clinical examination and biopsy.

Marketing status of the device/technology

MRI is currently readily available in Australia.

Current reimbursement arrangement

MRI is currently funded under the Medicare Benefits Scheme (MBS) for a variety of head and spine, musculoskeletal and cardiovascular conditions (item numbers 63000-63946) (Commonwealth Department of Health and Aged Care 2001). MRI is not currently funded under the MBS for assessment of cervical and endometrial cancer.

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period between January 1997 and August 2001. Searches were conducted via the following databases:

- Medline
- Current contents
- EMBASE
- The Cochrane Library
- ISTAHC Online database (International Society for technology Assessment in Health Care)
- NHS Centre for Reviews and Dissemination Databases (DARE, HTA, EED)

Search strategy

The following search strategy (Tables 3 and 4) was used to identify MRI papers in Medline and EMBASE. For all other databases a simple search strategy using terms for MRI and cervical or endometrial cancer was employed.

Table 3 Search Strategy for Medline database for MRI

	Search	Results
1	exp Magnetic Resonance Imaging/ or magnetic resonance imaging.mp.	98274
2	MRI.tw.	34967
3	MR imaging.tw.	14141
4	exp Magnetic Resonance Spectroscopy	87579
5	MR spectroscopy.tw.	970
6	Nuclear magnetic resonance.mp.	15330
7	NMR.tw.	38840
8	or/1-7	194285
9	limit 8 to (human and english language)	97759
10	exp uterine Neoplasms/	55140
11	(endometrial\$ adj (cancer or carcinoma or neoplasm\$ or tumor?r)).mp.	8192
12	(cervi\$ adj (cancer or carcinoma or neoplasm\$ or tumor?r)).mp.	19386
13	or/10-12	59093
14	limit 13 to (human and english language)	40471
15	9 and 14	700
16	limit 15 to yr=1997-2001	317

Table 3 Search strategy for Medline database for MRI (continued)

	Search – Genital Neoplasms	Results
17	exp Genital Neoplasms, Female/	95332
18	17 or 11 or 12	98331
19	limit 18 to (human and english language)	67532
20	9 and 19	1076
21	limit 20 to yr=1997-2001	488
22	limit 21 to yr=1997-2001	488
23	22 not 16	171
24	from 23 keep 1-171	171

Note: 17-24 relate to a search to identify cervical cancer papers that have been incorrectly MeSH coded in Medline

Table 4 Search strategy for EMBASE database for MRI

	Search	Results
1	Magnetic resonance imageing.mp	89085
2	MRI.tw.	32095
3	MR imaging.tw.	12061
4	exp Nuclear Magnetic Resonance Imaging/ or nuclear magnetic resonance imaging.mp.	82807
5	Exp Nuclear Magnetic Resonance/ or nuclear magnetic resonance.mp	175792
6	NMR.tw	39278
7	Magnetic resonance spectroscopy.mp. or exp Nuclear Magnetic Spectroscopy/	16268
8	MR spectroscopy.tw.	875
9	or/1-8	190551
10	limit 9 to (human and english language)	81400
11	Exp uterus tumor/ or exp endometrium tumor/ or exp uterine cervix tumor/ or exp uterus cancer/ or exp endometrium cancer/ or exp uterine cervix cancer/	34892
12	(endometrial\$ adj (cancer or carcinoma or neoplasm\$ or tumor?r)).mp.	10205
13	(cervi\$ adj (cancer or carcinoma or neoplasm\$ or tumor?r)).mp.	20030
14	Or/11-13	37136
15	Limit 14 to (human and english language)	29012
16	10 and 15	744
17	Limit 16 to yr=1997-2001	378

A Broad search using the terms MRI or 'magnetic resonance imaging' was used for the NHS databases.

Electronic searching also included the Internet sites of the following health technology assessment groups and information sources (Table 5).

Table 5 Health Technology Assessment Organisations

Organisation	Website
International Society for Technology Assessment in Health Care (ISTAHC)	www.istahc.org
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohpr.state.or.us/ohrc
Minnesota Department of Health (US)	www.health.state.mn.us
ECRI(US)	www.ecri.org
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (US)	http://text.nlm.nih.gov
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca
National Information Centre of Health Services Research and Health Care Technology (US)	www.nlm.nih.gov/nichsr/nichsr.html
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	www.stakes.fi/finohta/linkit/
Institute Medical Technology Assessment (Netherlands)	www.bmg.eur.nl/imta/
AETS (Spain)	www.isciii.es/unidad/aet/cdoc.htm
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence which is shown in Table 6.

Table 6 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: NHMRC National Health and Medical Research Council, A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: NHMRC, 1999.

Strict inclusion criteria were applied to the studies identified. The criteria were based on those used by existing reviews and are detailed in the sections for each specific clinical question.

Existing reviews of the evidence

Existing reviews or health technology assessments evaluating the role of MRI in pre-surgical staging of cervical or endometrial cancer that were identified include:

- 1990 National Health Technology Advisory Panel (NHTAP)

- *Review of Magnetic Resonance Imaging* - A report of the Australian Health Technology Advisory Committee (AHTAC) – 1997
- *Blandford Report* – MRI Review Committee, Commonwealth Department Health and Aged Care, 2000. This review committee then commissioned the Medical Technology Assessment Group (M-TAG Pty Ltd) to complete a review of the scientific literature about MRI:
 - Literature review of the developments in Magnetic Resonance Imaging since the AHTAC 1997 review prepared by M-TAG Pty Ltd – December 1999
- MRI Review Committee, Commonwealth Department of Health and Aged Care, also called for submissions on the use of MRI. Two literature reviews were received in the public submissions:
 - RANZCR review (1997-1999)
 - Monash Medical Centre literature review (1999)

Eligibility of studies

The search identified 386 non-duplicate abstracts. The abstracts were then evaluated to determine whether they met the following eligibility criteria.

- Patients must have cervical or endometrial carcinoma
- MRI used
- Papers must have more than 10 patients with the condition of interest
 - The exception for this may be in the situation where there are no publications with more than 10 patients. Rather than excluding all papers for a clinical indication on the basis of this criterion, available information was reported, noting limitations.
 - Case studies excluded.
- Review only / editorial / technical papers excluded
- Data available in abstract form only excluded
- Papers which report no clinical results excluded
- All non-English papers excluded
- Animal studies excluded where these could not be determined from abstracts

These criteria were also used to evaluate full papers with the exception of the final criteria regarding animal studies.

Expert advice

A supporting committee with expertise in MRI and clinical oncology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Is it safe?

MRI is a non-invasive imaging modality that exposes the patient to three different forms of electromagnetic radiation; a static magnetic field, gradient magnetic fields, and radiofrequency (RF) electromagnetic fields. The degree to which electromagnetic radiation significantly affects body tissues is dose related, where higher levels may cause significant bioeffects (Shellock 2000).

Static magnetic fields have been shown to cause changes in body temperature and cardiac waveforms on the electrocardiogram. In theory, electrical impulse conduction in nerve tissue may also be altered in the presence of static magnetic fields, however, there is inconclusive biological evidence to support this claim. Overall, no evidence exists of irreversible or hazardous biological effects related to short-term human exposure to static magnetic fields of up to 2.0T (Shellock 2000).

Gradient magnetic fields can induce electrical fields and currents in conductive media such as biological tissue. During MRI examination the patient is exposed to rapidly changing magnetic fields which may have a thermal effect on human tissue. However, studies have shown that the effect is minimal and not clinically significant. Electrical stimulation of the retina may result in the production of magnetophosphenes, however, this process has been found to be reversible with no associated health effects (Kanal, Shellock, & Talagala 1990).

Radiofrequency magnetic fields generate heat in human tissues and therefore may have a biological effect. However, MRI is not thought to generate sufficient levels to have a clinically significant effect (Shellock, Schaefer, & Crues 1989). Despite this, it has been suggested that further studies are needed to evaluate the effect of radiofrequency magnetic fields in people presenting with thermoregulatory system impairment. This may include: patients who are elderly or obese; patients with diabetes mellitus, cardiovascular disease or fever; and patients taking certain medication that may affect the thermoregulatory system (Shellock 2000).

Acoustic noise may also present as a potential hazard to the patient undergoing MRI. It is therefore recommended that patients wear disposable ear plugs during the procedure in order to prevent temporary hearing loss (Shellock & Kanal 1991).

MRI is contraindicated in patients with ferromagnetic and electronic implants including cardiac pacemakers, aneurysm clips, intraocular metal fragments, cochlear implants, implanted drug infusion devices, and some vascular implants and devices such as prosthetic heart valves. Each patient should be assessed on an individual basis as the ferromagnetic properties and the anatomical position of the implant will determine whether the patient is a suitable candidate for MRI. Furthermore, all ferromagnetic devices and metallic objects need to be removed prior to MRI examination as they may become projectile hazards (Yochum & Barry 1996).

Obese patients may be too large to fit inside the gantry of the MRI unit and may need to be referred to a facility where rectangular or open-architecture magnets are installed. Claustrophobic patients may also prefer examination with open-MRI (Yochum & Barry 1996).

MRI often involves the intravenous administration of a contrast agent, commonly gadopentetate dimeglumine (Gd-DTPA). The gadolinium ion is quite toxic and is therefore chelated to another structure in order to reduce toxicity. Clinical trials and extensive clinical use have shown that such contrast agents are safe and generally well tolerated by patients, especially when compared to the contrast agents used during CT, which are considered relatively more toxic (Runge 2000). However, adverse reactions can occur in approximately 5% of patients. The most common reactions include nausea, emesis, hives and headache. Local injection site symptoms include irritation, focal burning or a cool sensation. Anaphylaxis is rare, but has been reported. Therefore, a prolonged examination period following the MRI contrast-enhanced procedure is advised (Shellock & Kanal 1999). It should be noted that contrast agents used in CT scanning tend to be associated with a higher incidence of adverse reactions, with a larger proportion of the reactions being severe or life-threatening (Hosoya et al. 2000; Swanson et al. 1985).

Is it effective?

The questions pertaining to possible uses for MRI in the staging of endometrial cancer and cervical cancer will be addressed separately.

Cervical carcinoma

The clinical problem

There were three areas of interest within the indication of cervical cancer. The first was the use of MRI in patients where conventional workup indicates large volume disease, but tumour is confined to the cervix. It was felt that in this situation MRI could help to determine the type and extent of treatment. The second area of interest was the use of MRI in patients where disease extended beyond the cervico/paracervical junction on conventional workup. These patients are generally treated with radiotherapy and it was felt that MRI could play a role in improving field planning and identifying disease requiring radiotherapy boosts. The final area of interest was in patients with a persistent mass after treatment (ie suspected residual or recurrent disease). It was felt that MRI may be able to differentiate between benign and malignant abnormalities.

Information on other potential applications of MRI in cervical cancer will also be summarised as appropriate.

Epidemiology and clinical presentation

Cervical cancers usually originate in the transformational zone of the cervix where the squamous epithelial cells of the ectocervix meet the columnar epithelium of the endocervix. In Australian women in 1996, squamous cell carcinomas (SCCs) accounted for 68.6% of all cervical cancers. Adenocarcinomas were the next most common type of cervical cancer (18.6%), followed by adenosquamous carcinomas at 5.2%. Carcinomas of mixed type or unknown histology made up the final 7.6% of cervical cancers (Australian Institute of Health and Welfare 2000b).

Early cervical cancer is often asymptomatic but more advanced cases may present with symptoms of unusual vaginal bleeding or watery vaginal discharge. Research suggests that up to 90% of all cases of the most common forms of cervical cancer can be prevented if women are screened every two years (Commonwealth of Australia 1998; International Agency for Research on Cancer 1986).

In Australia in 1997, there were 795 new cases of cervical cancer. This translates to an age-standardised incidence rate of 8.0 cases/100,000 amongst all Australian women. Cervical cancer was responsible for 291 deaths in Australian women (2.7/100,000 all Australian women). The median age of death was approximately 64 years and the potential life years lost to the disease was 3,693 (Australian Institute of Health and Welfare 2000a).

By 1998 cervical cancer had dropped from the 8th (in 1996) to the 14th most common cause of cancer death in Australian women. There has been a rise in the 5-year survival over the past 20 years, and a corresponding 4.1% drop in the age-standardised incidence rate (Australian Institute of Health and Welfare 2000b).

Infection with human papillomavirus (HPV) is now considered to be a major risk factor for development of cervical cancer (National Cancer Institute 2001a; Moscicki et al. 2001; Yu, Forstner, & Hricak 1997; Schiffman & Brinton 1995). However, the majority of women infected with HPV do not go on to develop invasive cervical cancer and it is thought that other co-factors need to be present to promote the development of the

disease (Commonwealth of Australia 1998). Other risk factors implicated are low socio-economic status, oral contraceptive use, diet, parity and smoking.

Prognosis of the disease is markedly affected by the extent of disease at the time of diagnosis. Among the major factors that influence prognosis are stage, volume and grade of tumour, histologic type, lymphatic spread, and vascular invasion (Burghardt et al. 1992; Stehman et al. 1991; Zaino et al. 1992). Para-aortic and pelvic nodal involvement are strong predictors of progression-free and overall survival. Adequate evaluation of these nodes in locally advanced disease is very important (Stehman et al. 1991).

Conventional staging and treatment

Staging

Cervical cancer can take ten years or longer to develop, but prior to this, pre-cancerous cells may be present. Pre-cancerous cells are divided into two grades; low-grade abnormalities unlikely to progress to cancer and high-grade abnormalities that are more likely to progress to a cancer. These high-grade abnormalities include cervical intra-epithelial neoplasia 2 (CIN 2 or moderate dysplasia) and CIN 3 (severe dysplasia carcinoma *in situ*) (Commonwealth of Australia 1994). Longitudinal studies have shown that 30-70% of untreated patients with *in situ* cervical cancer will develop invasive carcinoma over a period of 10 to 12 years (National Cancer Institute 2001a). However, in about 10% of patients, lesions can progress from *in situ* to invasive in a period of less than one year.

The pattern of spread of invasive cervical cancer is usually predictable. Initially the tumour breaks through the basement membrane and begins to invade the underlying cervical stroma and muscle. It can then go on to involve the vaginal fornices and the inner parametrium. Extension beyond the cervix most commonly follows a lateral path infiltrating the parametrium and then the suspensory ligaments to the pelvic sidewall and pelvic lymph nodes (Hunter 1995).

In addition to local invasion, carcinoma of the cervix can spread via the regional lymphatics or, less commonly, via the bloodstream. Tumour dissemination is generally a function of the extent and invasiveness of the local lesion. While cancer of the cervix generally progresses in an orderly manner, occasionally a small tumour with distant metastasis is seen. For this reason, patients must be carefully evaluated for metastatic disease.

Conventional staging usually consists of an examination under anaesthesia (EUA), which indicates the extent of disease spread and allows a stage to be assigned. In advanced tumours CT scans may also provide valuable information regarding retroperitoneal nodal involvement and spread to other areas.

Stages are defined by the Federation Internationale de Gynecologie et d'Obstetrique (FIGO), the American Joint Committee on Cancer's (AJCC) TNM classification (Shepherd 1996) or Union Internationale Contre le Cancer (UICC) TNM classification 1997 (American Joint Committee on Cancer 1997a; Creasman 1995). All three classification systems are equivalent and interchangeable. The FIGO system is referred to in this report (Table 7).

Table 7 FIGO staging of cervical cancer

Stage	Characteristics
Stage I	<p>Stage I is carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded.</p> <p>Stage IA: Invasive cancer identified only microscopically. All gross lesions even with superficial invasion are stage Ib cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.</p> <p>Stage IA1: Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm diameter.</p> <p>Stage IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.</p> <p>Stage IB: Clinical lesions confined to the cervix or preclinical lesions greater than stage IA.</p> <p>Stage IB1: Clinical lesions no greater than 4 cm in size.</p> <p>Stage IB2: Clinical lesions greater than 4 cm in size.</p>
Stage II	<p>Stage II is carcinoma that extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.</p> <p>Stage IIA: No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina.</p> <p>Stage IIB: Obvious parametrial involvement, but not onto the pelvic sidewall.</p>
Stage III	<p>Stage III is carcinoma that has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina. All cases with a hydronephrosis or non-functioning kidney should be included, unless they are known to be due to other causes.</p> <p>Stage IIIA: No extension onto the pelvic sidewall but involvement of the lower third of the vagina.</p> <p>Stage IIIB: Extension onto the pelvic sidewall or hydronephrosis or non-functioning kidney.</p>
Stage IV	<p>Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.</p> <p>Stage IVA: Spread of the tumour onto adjacent pelvic organs.</p> <p>Stage IVB: Spread to distant organs.</p>

Treatment

The method of treating cervical carcinoma is usually dependent upon the clinical staging (ie the volume and extent) of the tumour. The general condition of the patient, their age and wish to preserve fertility can also affect treatment decisions. In general, surgery is used for pre-cancerous lesions and in FIGO stages I to IIA, although treatment practices may vary between centres. Surgical procedures include cautery excision for carcinoma *in situ*, radical (Wertheim's) hysterectomy for invasive disease and total pelvic exenteration for recurrent or very advanced disease (Hunter 1995).

Radiotherapy is used when the tumour has spread beyond the cervix (ie FIGO stages IIB-IV). It can also be used in patients with large cervical lesions (>4cm). Treatment consists of a combination of external-beam and intracavitary radiation. Chemoradiation is now recommended in all patients for whom radiotherapy is suitable. A recent meta-analysis of 19 randomised controlled trials indicates a significant improvement in both overall and progression free survival in patients treated with chemoradiation compared to radiotherapy alone (Green et al. 2001). As would be expected, it also indicated that patients treated with chemoradiation had a higher incidence of haematological and gastrointestinal toxicity.

Patients who develop loco-regional recurrence after radiotherapy can sometimes be treated with a total pelvic exenteration. Very rarely, women with small recurrences limited to the cervix or upper vagina can be treated with radical hysterectomy and partial vaginectomy. Patients who develop local recurrence after primary surgery can be treated with radical radiotherapy. The survival rate amongst women with local recurrence is 30-

35%. Patients with disseminated disease or those patients in whom radiation and surgery has not been successful can be treated with chemotherapy. However, at this point, the chances of cure are very small and the chemotherapy is often palliative in nature (Hunter 1995).

Potential value of MRI

This review examines the role of MRI in the management of primary cervical cancer and in the detection of recurrent or residual disease.

In patients with large volume disease confined to the cervix on conventional staging, MRI may have a role in determining the optimal type and extent of treatment by more accurately defining whether disease is truly confined to the cervix or not. In these patients the information from MRI may influence the type and extent of treatment (either surgery or radiotherapy) that is recommended as the treatment of choice. By more accurately detecting the size of the primary tumour, it is possible that inappropriate surgical treatment may be avoided in patients who would be better treated with radiotherapy. In patients where MRI detects tumour extension outside the cervix, the extent of radiotherapy (eg field and boost planning) may be influenced.

If MRI is used in a serial manner it may also provide information on prognosis or response of patients during treatment that may, in some cases, lead to alterations in management strategy.

MRI may also have a role in the evaluation of suspected residual or recurrent disease. If MRI is better able to distinguish residual or recurrent disease from fibrotic changes resulting from previous therapy, it may be possible to commence treatment earlier than if recurrence/residual disease was diagnosed on clinical symptoms alone. At this stage, however, it is unclear whether earlier treatment of recurrent disease would lead to improved patient outcomes.

Results

The 20 papers forming the basis of this review are summarised in Table 8 and in more detail in Appendix C.

Table 8 MRI publications regarding cervical cancer

Eligibility	Number
Papers that provide an estimate of the MRI diagnostic accuracy for detection of parametrial or vaginal invasion	9
Papers that provided radiotherapy field-planning information	1
Papers regarding the use of MRI as an indicator of treatment response	3
Papers that provide an estimate of MRI diagnostic accuracy for the detection of recurrence	5
Papers investigating the role of MRI in providing information on tumour microcirculation for prognostic purposes	2
Total	20

Methodological issues in the studies

All the studies included in this review were case series. There are inherent problems in relying on data from case series due to the lack of a control group and the potential for bias. In addition to these problems a number of the studies also had further methodological issues:

- Retrospective rather than prospective data collection (Ng et al. 1998; Yu et al. 1998).
- Recruitment of the cases in a consecutive manner was not explicit (Amano et al. 1998; Boss et al. 2001; Hatano et al. 1999; Hawighorst et al. 1997; Hawighorst et al. 1998b; Hawighorst et al. 1998a; Lam et al. 2000; Mayr et al. 1997; Mayr et al. 1998; Mayr et al. 2000; Ng et al. 1998; Sheu et al. 2001; Thomas et al. 1997).
- Overestimation of the sensitivity and specificity by basing calculations on parametria/hemipelvi rather than patients (Hawighorst et al. 1998a; Lam et al. 2000; Postema et al. 2000; Shiraiwa et al. 1999).
- The potential for verification or work-up bias (ie where the result of the test being evaluated influenced the decision to perform the reference standard) should also be noted, as some studies only performed confirmatory biopsies for patients who were MRI positive (Amano et al. 1998; Hatano et al. 1999; Kinkel et al. 1997; Shuchleib et al. 1999; Sugiyama & Atomi 1999).
- Very small patient numbers in the studies meant that small changes in the classification of patients resulted in large changes in sensitivity and specificity.

Diagnostic accuracy of MRI

Detection of parametrial invasion

Bulky cervical cancer that is confined to the cervix (IB2) can be treated with surgery or radiotherapy. Involvement of the parametria upstages the cancer to IIB. This stage is usually treated with radiotherapy. Therefore, if MRI is able to accurately detect the extent of local disease within the cervix and parametria, the most appropriate treatment modality can be identified.

There are nine papers (Hawighorst et al. 1998a; Kim et al. 1997; Lam et al. 2000; Ng et al. 1998; Postema et al. 2000; Scheidler et al. 1998; Sheu et al. 2001; Shiraiwa et al. 1999; Yu et al. 1998) that describe the ability of MRI to detect parametrial invasion. The data vary according to the type of MRI utilised but accuracies (Acc) range from 40-97%, sensitivities (Sn) range from 20-100% and specificities (Sp) range from 5-97%.

All nine papers compared the imaging results to histopathological specimens obtained at surgery. One paper (Postema et al. 2000) also included nine patients in whom hydronephrosis or positive cystoscopy/urine cytology was accepted as a gold standard. All imaging, with the possible exception of Ng et al. (1998), was performed on a 1.5T system. This paper gave no information on the MRI system. Summaries of each paper can be found in Table 9.

Hawighorst et al (1998a) studied T1-weighted spin-echo (T1W SE) MRI and T2-weighted turbo spin-echo (T2W TSE) MRI in 33 patients. MRI was performed with a circularly polarised phased-array of four surface coils. The left and right parametria of

each patient were assessed independently for invasion and the accuracy, sensitivity and specificity were reported for 66 parametria. Reporting on parametria instead of patients may have led to an overestimation of diagnostic accuracy. T1W SE MRI had a sensitivity of 74%, a specificity of 65% and an accuracy of 71%. In contrast, T2W TSE MRI had a sensitivity of 86%, a specificity of 80% and an accuracy of 84%. Both forms of MRI overstaged one IB patient as IIB.

Kim et al (1997) were interested in comparing the accuracy of T1W fast spin-echo (FSE) MRI using a pelvic phased-array coil to that of T1W FSE MRI using a transrectal surface coil. A gold standard was available in 28 patients who underwent surgery. The sensitivity, specificity and accuracy of MRI with the transrectal surface coil were 100%, 96% and 96%, respectively. MRI with the pelvic phased-array coil had a sensitivity of 100%, specificity of 92% and accuracy of 93%. The difference in parametrial staging accuracy between the two coils was not found to be significant. One IB patient was overstaged as IIB by imaging with the pelvic phased-array coil. Another IB patient was overstaged as IIB by both the transrectal coil and the pelvic coil imaging.

Lam et al (2000) compared T1W TSE, T2W TSE, short tau inversion recovery (STIR) and T1W dynamic Gd-DPTA enhanced SE MRI in 38 patients. All imaging was performed on a 1.5T system but no mention is made as to the type of coil used. The denominator for calculations of the accuracy, sensitivity and specificity of MRI was given in terms of hemipelvi not patients. Reporting on hemipelvi rather than patients may have led to an overestimation of diagnostic accuracy. T1W SE MRI had a sensitivity of 60%, a specificity of 80% and an accuracy of 78%. T2W TSE MRI had a sensitivity of 90%, a specificity of 92% and an accuracy of 92%. STIR MRI had a sensitivity of 90%, a specificity of 94% and an accuracy of 93%. Dynamic MRI had a sensitivity of 90%, a specificity of 80% and an accuracy of 82%. T2W and STIR sequences were significantly better ($p=0.05$) at detecting parametrial invasion than T1W TSE and dynamic T1W MRI. There was no significant difference between the T2W TSE and the STIR sequences.

Ng et al (1998) retrospectively compared computer tomography (CT) in 29 patients to MRI in 25 patients against a reference standard of histopathology. The paper did not give any details as to the system or MRI sequences used in the imaging. The images were compared to histopathological findings in all patients. In the detection of parametrial invasion, MRI had a sensitivity of 100%, a specificity of 88% and accuracy of 92%. CT had a sensitivity of 67%, a specificity of 70% and an accuracy of 69%. Only nine patients of the 54 underwent both CT and MRI and therefore comparisons between the relative accuracies of each technique may be compromised.

Postema et al (2000) compared the combined results of T2W FSE and T1W SE MRI to histopathological results in 91 patients. All imaging used the system's body coil. Two observers independently diagnosed parametrial invasion from the MRI images. The inter-observer agreement was moderate ($\kappa = 0.57$). The sensitivity, specificity and accuracy statistics were based upon 148 parametria, rather than patients, which may have led to an overestimation of diagnostic accuracy. It is unclear why parametrial invasion was not assessed in 182 parametria, as would be expected if the hemipelvi of all 91 patients had been investigated. Observer one's sensitivity was 20%, specificity was 97% and accuracy was 92%. The sensitivity for observer two was 60%, specificity was 73% and accuracy was 72%.

Scheidler et al (1998) studied the ability of six different MRI sequences to detect parametrial invasion. All imaging was performed using a circularly polarised phased-array coil. T1W SE MRI and T2W TSE MRI were performed in 35 patients. Turbo STIR was

performed in 33 patients, T1W fat-suppressed Gd-DPTA enhanced SE MRI in 30 patients, T1W Gd-DPTA SE MRI in 28 patients and T1W fat-suppressed SE MRI in 25 patients. Patient intolerance of the prolonged imaging time and technical difficulties led to this drop in patient numbers and therefore comparisons between the groups may be compromised. Bearing this in mind, T1W SE, T1W Gd-DPTA enhanced SE and T1W fat-suppressed SE MRI were all significantly worse at detecting parametrial invasion than T2W TSE MRI ($p < 0.001$, $p < 0.05$, $p < 0.01$, respectively). The combination of all the results from the different MRIs performed on the same patient did not significantly improve ability to detect parametrial invasion when compared to T2W TSE alone. The results for each type of MRI used in this study can be found in Table 9.

Sheu et al (2001) compared the staging information gained from T2W FSE MRI to that obtained from clinical examination in 31 patients. The gold standard used for comparison was surgical staging. All imaging was performed using a pelvic or a torso phased-array coil. The sensitivity of MRI was 100%, specificity was 96% and accuracy was 97%. Two of the 21 patients surgically staged as IB were overstaged, one patient as IIA and another as IIB. The researchers suspected that MRI was unable to distinguish between peritumoural oedema and true parametrial invasion. Clinical examination overstaged five patients surgically staged as IB.

Shiraiwa et al (1999) investigated axial T2W MRI and thin-section oblique axial T2W MRI in 50 patients. All imaging was done with a body coil. The left and right parametria were assessed independently. By reporting on parametria instead of patients the diagnostic accuracy may have been overestimated. The sensitivity of axial T2W MRI was 46%, specificity was 92% and accuracy was 79%. The sensitivity of thin-section oblique axial MRI was 68%, specificity was 97% and accuracy was 89%. Thin-section oblique axial MRI was significantly better at detecting parametrial invasion than axial T2W MRI.

Yu et al (1998) retrospectively compared 62 patients who underwent T2W SE MRI using a body coil and a separate set of 32 patients who underwent T2W FSE MRI using a pelvic phased-array coil. The gold standard used for comparison was surgical pathology. The sensitivity of T2W SE MRI was 100%, specificity was 95% and accuracy was 95%. The sensitivity of T2W FSE MRI was 100%, specificity was 93% and accuracy was 94%. The differences in sensitivity, specificity and accuracy were not found to be significant. However, it should be noted that as T2W SE MRI and T2W FSE were performed in different groups of patients the ability to compare the relative accuracies of each technique may be compromised.

Summary

Data was evaluated for 1997 onwards. Over this time, there were no studies which evaluated the role of MRI in addition to CT scanning. One small study compared CT and MRI to histopathology, where 25 patients received both MRI and CT. This study suggested that MRI (Sn 100%, Sp 88%, Acc 92%) may be better than CT (Sn 67%, Sp 70%, Acc 68%) at detection of parametrial invasion, however, the number of patients included is small. Data published prior to 1997 for CT indicate diagnostic accuracy comparable to these results (Ho et al. 1992; Kim et al. 1990; Kim et al. 1993; Sironi et al. 1991; Subak et al. 1995). All other studies evaluated one or more types of MRI against a reference standard of histopathology. Overall, these studies suggest that MRI has a median sensitivity and specificity of approximately 85% for detection of parametrial involvement.

Table 9 Detection of parametrial invasion using a 1.5T system^{a,b}

Study	Hawighorst et al 1998 ^c (n=33)			Kim et al 1997 (n=28)			Lam et al 2000 ^d (n=38)			Ng et al 1998 ^e (n MRI=25, CT=29)			Postema et al 2000 ^f (n=91)			Scheidler et al 1998 ^g			Sheu et al 2001 ^h (n=31)			Shiraiwa et al 1999 ⁱ (n=50)			Yu et al 1998 ^j (SE=62, FSE=32)			Averages				
	Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc	n	Sn	Sp	Acc	
CT									67	70	69															29	67	70	69			
Unknown or combination of different techniques									100	88	92	20	97	92	92	82	86										151	68	85	83		
												60	73	72																		
T1W SE MRI	74	65	71				60	80	78						100	5	40										106	78	50	63		
T1W CE SE MRI															85	20	50										28	85	20	50		
T1W fat-suppressed SE MRI															100	21	56										25	100	21	56		
T1W fat-suppressed CE SE MRI															75	78	77										30	75	78	77		
T1W FSE MRI with PCC ⁱ				100	92	93																					28	100	92	93		
T1W FSE MRI with TRC ^j				100	96	96																					28	100	96	96		
Axial T2W MRI																					46	92	79				50	46	92	79		
Thin-section oblique axial T2W MRI																					68	97	89				50	68	97	89		
T2W SE MRI																								100	95	95	62	100	95	95		
T2W TSE MRI	86	80	84				90	92	92						92	73	80										106	89	82	85		
T2W FSE MRI																				100	96	97				100	93	94	63	100	95	96
STIR MRI							90	94	93						85	75	79										71	88	85	86		
Dynamic MRI							90	80	82																		38	90	80	82		

^aSn, Sp & Acc given as percentages ^bYu et al & Ng et al are retrospective studies - all other studies are prospective ^cCircularly polarised phased-array coil ^dNo information on coil type ^eBody coil ^fT1W SE, T2W TSE & combined MRI n=35, STIR MRI n=33, T1W fat-suppressed CE SE MRI n=30, T1W CE SE MRI n=28 & T1W fat-suppressed SE MRI n=25 ^gPelvic/torso phased-array coil ^hT2W SE used body coil, T2W FSE used pelvic phased-array coil ⁱPCC –pelvic phased-array coil, TRC – transrectal surface coil.

Detection of vaginal invasion

Bulky cervical cancer that is confined to the cervix (IB2) is usually treated with surgery. Invasion of the upper two-thirds of the vagina upstages the cancer to IIA. This stage is also usually treated with surgery but additional information from MRI may lead to alterations in surgical planning.

There were three papers (Hawighorst et al. 1998a; Sheu et al. 2001; Yu et al. 1998) that reported on the ability of MRI to detect vaginal invasion. All papers compared the imaging results to histopathological specimens obtained after surgery. All imaging used a 1.5T system. The figures reported varied according to type of MRI utilised but accuracies ranged from 78% to 94%, sensitivities ranged from 33% to 75% and specificities ranged from 81% to 97%. Summaries of each paper can be found in Table 10.

Hawighorst et al (1998a) performed both T1W SE MRI and T2W TSE MRI in 33 patients. MRI was performed with a circularly polarised phased-array of four surface coils. There was no significant difference in the ability to detect vaginal invasion between the two types of MRI. The sensitivity, specificity and accuracy of T1W SE MRI were 67%, 81% and 78%, respectively. The sensitivity, specificity and accuracy of T2W TSE MRI were 67%, 92% and 87%, respectively.

Sheu et al (2001) gathered information on vaginal invasion from T2W FSE MRI in 31 patients. The sensitivity of MRI was 75%, specificity was 88% and accuracy was 87%. One patient was overstaged as IIA. The researchers suggested this false positive was due to the vaginal fornices being stretched by a large bulky cervical carcinoma.

Yu et al (1998) retrospectively compared 62 patients who underwent T2W SE MRI using a body coil and a separate set of 32 patients who underwent T2W FSE MRI using a pelvic phased-array coil. The sensitivity of T2W SE MRI was 33%, specificity was 97% and accuracy was 94%. The sensitivity of T2W FSE MRI was 50%, specificity was 97% and accuracy was 94%. As T2W SE MRI and T2W FSE were performed in different patient groups it is difficult to draw conclusions about the relative accuracies of each technique.

Summary

As with those studies which evaluated MRI for parametrial invasion, there were no studies (published from 1997 onwards) that evaluated MRI in addition to CT, or compared MRI to CT in the detection of vaginal involvement. Based on a small number of studies, the overall accuracy of MRI for this indication appears to be lower than for the detection of parametrial involvement. Sensitivity appeared to be approximately 60-70%, while specificity was higher, generally above 90%. Overall accuracy was approximately 80-90%.

Change in management

Unfortunately none of the papers evaluated for either of the above indications provided any details as to how management of patients was altered by MRI. It might be reasonable to assume that in the assessment of parametrial invasion, some of those patients could have avoided surgical intervention if we were confident in the ability of MRI to diagnose parametrial involvement.

Table 10 Detection of vaginal invasion using a 1.5T system^a

Study	n	Coil	T1W SE MRI			T2W SE MRI			T2W TSE MRI			T2W FSE MRI		
			Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc	Sn	Sp	Acc
(Hawighorst et al. 1998a)	33	Cp phased-array of four surface coils	67	81	78				67	92	87			
(Sheu et al. 2001)	31	Pelvic or torso phased-array coil										75	88	87
(Yu et al. 1998) <i>Retrospective study</i>	T2W SE n=62 T2W FSE n=32	Body coil (T2W SE MRI) & pelvic phased-array coil (T2W FSE MRI)				33	97	94				50	97	94
Average			67	81	78	33	97	94	67	92	87	63	93	91

^aSn, Sp and Acc given as percentages

Other uses of MRI

MRI and radiotherapy field planning

Thomas et al (1997) evaluated T2W TSE MRI in four-field radiation treatment planning of 18 patients. All imaging was performed on a 1.0T system. In one group of 11 patients radiologic simulation was based on clinical examination, CT and standard guidelines. Diagnostic MRI was not available in this group. Diagnostic MRI (using a phased-array coil) was available in the second group of seven patients and radiologic simulation was based on these MRI results, clinical examination, standard guidelines and CT. After radiologic simulation was completed a treatment-planning MRI (using a body coil) was performed in all patients and the adequacy of the simulated variation ports was evaluated by correlation with the MRI defined tumour volume and its potential extension. In the first group, the treatment-planning MRI led to a change in fields for seven patients (63%) with MRI indicating six inadequate margins of lateral fields and one of the anterior and lateral fields. In most cases the adjustments were an increase of 10mm, equally matched between the anterior and posterior borders of the lateral fields. In the second group, the treatment-planning MRI led to a change in fields for five patients (71%). All changes were in the lateral fields with a mean adjustment of 10mm. In two patients the anterior borders were increased. In one, the posterior border was increased and in another both the anterior and posterior borders were increased. In the last patient the posterior border was decreased. In both groups, the modifications allowed both adequate margins around the uterine fundus and adequate coverage of the cervical tumour. Although the addition of MRI information changed field planning it is difficult to assess the impact of these changes on patient outcomes.

The use of MRI as an early indicator of treatment response to radiotherapy

Mayr et al (1997) performed T1W SE MRI and T2W SE MRI on 43 patients. All imaging, except for five early examinations, was performed on a 1.5T system. The early scans were performed on a 0.5T system. No information on coil type is reported for either system. MRI studies and pelvic examinations were performed before radiotherapy, at 2-2.5 weeks/20-24Gy (Examination 2), at 4-5 weeks/40-50Gy (Examination 3) and 1-2 months after completion of radiotherapy. Separate tumour regression rates for MRI and pelvic examination were calculated from the volumes measured at each examination and the regression rates were then categorised as rapid or slow. MRI was found to be significantly better at differentiating between groups likely to have a higher incidence of

local failure (the slow regression group) and groups unlikely to have local failure (the rapid regression group). MRI was also an earlier predictor of recurrence; it was able to predict local failure at Examination 2, Examination 3 and the follow-up examination ($p=0.004$, $p<0.0001$ and $p=0.007$ respectively). Pelvic examination was only able to differentiate between the slow and rapid regression groups at the follow-up examination ($p=0.012$). MRI was also better than pelvic examination at predicting disease-free survival based on initial tumour size.

Mayr et al (1998) performed T1W FSE, T2W FSE and dynamic CE MRI on 20 patients before radiotherapy (pre-therapy) and after two weeks/20-22Gy (early therapy) of radiotherapy. Imaging was performed on a 1.5T system with a body coil. Local tumour recurrence was correlated with the dynamic enhancement pattern shown on dynamic CE MRI and tumour volume individually, and with the combination of both parameters. Initial tumour size alone (small, intermediate or large) was not a significant predictor of recurrence. The pre-therapy enhancement pattern alone, or in combination with tumour size, was not a significant predictor of recurrence. The early therapy dynamic enhancement patterns alone were able to distinguish between high and low recurrence risk groups ($p=0.005$). The best predictor of recurrence was the combination of tumour volume and early therapy enhancement patterns in intermediate and large sized tumours where the prediction rates were 80% and 75%, respectively. The combined analysis was not able to predict recurrence rates in small tumours. The combined analysis in intermediate tumours allowed significant differentiation between patients with a high risk of recurrence and patients with a low risk of recurrence ($p=0.01$).

Mayr et al (2000) performed dynamic CE MRI on 16 patients after two weeks of radiotherapy. Imaging was performed on a 1.5T system with a body coil. They then analysed the images pixel by pixel and generated a relative signal intensity (RSI) for each pixel based on the ratio of the post-contrast signal intensity to the baseline (pre-contrast) signal intensity. The RSI values for each patient were tabulated in an RSI pixel histogram and a number of parameters were correlated with the endpoint of tumour recurrence/control using analysis of variance. The most significant predictor of tumour recurrence was the 10th percentile RSI ($p=0.00001$). The authors found that patients with a 10th percentile RSI value of >2.5 had a recurrence rate of 0%. Patients with a 10th percentile RSI value of <2.5 had a recurrence rate of 88% ($p=0.0004$). The next most significant predictors of recurrence were median RSI and mean RSI, both with a p -value = 0.0001. Pixel number (which was a reflection of tumour size) was also a significant predictor of recurrence ($p=0.05$) with the rate of recurrence increasing with larger pixel numbers. The combination of the pixel number and 10th percentile RSI parameters enabled 100% correct prediction of subsequent tumour control or recurrence. It should be noted that this kind of post-scan analysis is quite complex and that the software necessary is not widely available. It should also be noted that these 16 patients may be a subset of the 20 patients from the 1998 study. This was not clear in the paper. However, as this paper had a median follow-up of 4.6 years and the 1998 study had a median follow-up of 25 months it was felt that the information from each paper was sufficiently different to warrant separate reporting.

Hatano et al (1999) performed T1W SE MRI and T2W SE MRI on 42 patients before radiotherapy, at 30Gy of external radiotherapy and at the completion of radiotherapy. Imaging was performed on a 1.5T system but the paper gives no details as to what type of coil was used. Six patients were shown to have residual disease on multiple punch biopsies and cytology of the cervix. Initial tumour volumes were found to have been reduced to less than 30% at 30Gy in 36 patients. Correlation of reduction in tumour

volume at 30Gy and local tumour control indicated that all patients with tumour volumes under 30% of initial tumour volume achieved local control during follow-up. The six patients who had tumours larger than 30% of the initial tumour volume at 30Gy had residual disease.

Results from these studies are summarised in Table 11.

Summary

There is some limited evidence that MRI may be useful in the planning of radiotherapy. There is also some limited evidence that suggests MRI may be of value as an early detector of response to radiotherapy. Given the extent of information available, and the methodological limitations (such as overlapping or duplicate patient groups) with such information, the true value of MRI in this setting remains unclear.

Table 11 MRI and response to treatment

Study	n	Predictor of Recurrence/Failure of Local Control	p-value
(Mayr et al. 1997) <i>5 early scans used 0.5T system All others used 1.5T system</i>	43	Initial tumour volume (based on small, intermediate & large tumours) ^a Tumour regression rate (rapid vs slow) ^b - Exam 2 - Exam 3 - Follow-up	0.018 0.004 <0.0001 0.007
(Mayr et al. 1998) <i>Body coil – 1.5T system</i>	20	Initial tumour volume (based on small, intermediate & large tumours) ^a Dynamic enhancement pattern (low vs high) ^c – Pretherapy - Early Therapy Combination of small tumour volume & enhancement pattern Combination of intermediate volume & enhancement pattern Combination of large tumour volume & enhancement pattern	NS NS 0.005 NS 0.010 NS
(Mayr et al. 2000) <i>Body coil – 1.5T system</i>	16	10 th percentile relative signal intensity (RSI) 10 th percentile RSI using threshold value of 2.5 Mean RSI Median RSI Pixel number Combination of 10 th percentile RSI & pixel number gave 100% accuracy	0.00001 0.0004 0.0001 0.0001 0.05 -
(Hatano et al. 1999) <i>1.5T system</i>	42	Patients with tumour volumes under 30% of initial tumour volume at 30Gy achieved local control	-

^aTumour sizes classified as follows; small – volume <40cm³/diameter <4cm, intermediate – volume 40-99cm³/diameter 4-6cm, large – volume ≥ 100cm³/diameter ≥6cm

^bRapid vs slow regression rate defined as percentage residual volume of <50% vs ≥50% in Exam 2; <20% vs ≥20% in Exam 3; and 0% vs ≥0% in follow-up exam.

^cLow dynamic enhancement pattern defined as an RSI < 2.8. High dynamic enhancement pattern defined as an RSI ≥ 2.8.

MRI in patients with suspected recurrence

Kinkel et al (1997) studied 34 women in whom CT scans had indicated the presence of at least one abnormal pelvic structure after primary treatment. Fifteen of these women had been treated for cervical carcinomas; the other 19 had been treated for other gynaecological cancers. T2W SE MRI and dynamic CE MRI were performed using a 1.5T system and a body coil. The study found that T2W SE MRI appeared to be better at identifying any abnormality and detected 100% of the lesions. Dynamic CE MRI was only able to detect 96% of the lesions. However, dynamic CE MRI appeared to be better than T2W SE MRI at differentiating malignant lesions from benign lesions. Dynamic CE MRI had a sensitivity of 91%, a specificity of 71%, and accuracy of 85%, while T2W SE MRI had a sensitivity of 91%, specificity of 22% and accuracy of 68%. The differences in specificity and accuracy were reported as being mainly attributable to the tendency of T2W SE MRI to incorrectly classify benign lesions as malignant. It should be noted that there were three different reference standards used in this study: histopathological

results; CT-guided biopsy; and clinical follow-up. The use of CT-guided biopsy, in particular, may have lead to verification/workup bias as MRI positive lesions were more likely to have been histologically confirmed.

Manfredi et al (1998) performed T2W SE MRI on 18 patients before, and four weeks after, concurrent chemotherapy and radiotherapy. Imaging used a 0.5T system and a body coil. Areas of hyperintensity or disruption of the cervical stromal ring in the post-treatment images were interpreted as indicating residual disease. Two weeks later all patients underwent surgery. The histopathological results indicated that 12 patients had complete response to treatment, three patients had a partial response and one patient had no response. The two remaining patients were found to have microscopic neoplastic foci that the authors chose to classify as complete responses on the basis that such foci 'do not change surgical treatment planning and probably do not influence prognosis'. The post-therapy MRIs were then compared to the histopathological results. On the basis of these results (and on the assumption that patients with foci had a complete response to treatment) MRI had a sensitivity of 50%, a specificity of 64% and an accuracy of 50% when hyperintensity was used as the indicator for residual disease. If disruption of the cervical stromal ring was used as an indicator of residual disease MRI had a sensitivity of 25%, a specificity of 93% and an accuracy of 78%. However, if patients with microscopic foci were considered to have residual disease, and hyperintensity was used as the indicator of residual disease, MRI had a sensitivity of 33%, specificity of 58% and an accuracy of 50%. If disruption of the cervical stromal ring was used as an indicator of residual disease MRI had a sensitivity of 17%, a specificity of 92% and an accuracy of 67%. MRI was also 92% accurate in detecting post-treatment parametrial invasion, 93% accurate in detecting post-treatment vaginal invasion, 97% accurate in detecting post-treatment enlarged lymph nodes and 100% accurate in detecting bladder or rectal wall invasion.

Amano et al (1998) used T2W SE MRI in 41 patients after chemotherapy. Imaging used a 1.5T system and a body coil. All patients then underwent a gynaecological examination. On the basis of this examination 10 patients were referred for surgery. Another 30 patients received radiotherapy and one patient died after chemotherapy. After surgery a blinded gynaecologist analysed the histological findings and these findings were correlated with the MR images taken after the last course of chemotherapy. MRI was 100% accurate in its detection of residual disease within the 10 surgical patients. Tumour size estimates made on MRI were found to be within 5mm of the histological specimens. MRI was also able to detect the post-treatment parametrial invasion found in the histological specimen of one patient. It should be noted, however, that it is unclear whether the MRI results were incorporated into the gynaecological examinations. If this was the case then the accuracy of MRI in detection of residual disease may have been overestimated as MRI positive sites may have been more likely to have histological confirmation.

Hatano et al (1999) performed T1W SE MRI and T2W SE MRI on 42 patients before radiotherapy, at the completion of radiotherapy and at one, three and six months after radiotherapy. Imaging was performed on a 1.5T system but the paper gave no information on the type of coil utilised. Six of the patients were shown to have residual disease on multiple punch biopsies and cytology of the cervix. The MRI studies had a sensitivity of 100%, a specificity of 78% and an accuracy of 81% upon completion of radiotherapy, and one month after radiotherapy. At three and six months after radiotherapy the accuracy, sensitivity and specificity of the MRI studies were 100%. The accuracy of MRI in detection of residual or recurrent disease improved three months

after radiotherapy. The accuracy of MRI was affected by eight false positive readings immediately after, and one month after, therapy. Three patients who had shown a complete response to treatment both histologically and on MRI developed distant metastases and died. It should be noted that multiple punch biopsies and cytology of the cervix were obtained at the same time as the MRI. The MRI results were used to direct the site of biopsy and this may have led to an overestimation of the accuracy of MRI in detection of residual disease due to verification/workup bias. This can result when the outcome of the diagnostic test being evaluated is used to influence the decision to perform the gold standard, in this case where biopsies are taken from areas on MRI with a high signal intensity.

Boss et al (2001) investigated fast dynamic CE MRI in 10 patients before radiotherapy and 6-8 weeks after radiotherapy. Imaging was performed on a 1.5T system with a body phased-array coil. Of these 10 patients, five had residual or recurrent disease. Four of these patients subsequently died from the disease. The researchers reported that non-survivors showed an early onset of enhancement after radiotherapy. Survivors had a later onset of enhancement.

The results of these studies are summarised in Table 12.

Table 12 MRI detection of residual/recurrent disease^a

Study	System	n	Sn	Sp	PPV	NPV	Acc	
(Kinkel et al. 1997)	1.5T and body coil	34 ^b						
		Dynamic SE MRI	34	91	71	86	80	85
		T2-weighted SE MRI	34	91	22	70	57	68
(Manfredi et al. 1998)	0.5T & body coil	18						
		Residual disease indicated by hyperintensity & foci classed as complete response		50	64	29	82	50
		& foci classed as residual disease		33	58	29	64	50
		Residual disease indicated by stromal ring disruption						
		& foci classed as complete response		25	93	50	81	78
		& foci classed as residual disease		17	92	50	69	67
		Post-treatment parametrial invasion						92
		Post-treatment vaginal invasion						93
		Post-treatment enlarged lymph nodes						97
		Post-treatment bladder wall invasion						100
Post-treatment rectal wall invasion						100		
(Amano et al. 1998)	1.5T and body coil	10 ^c					100	
(Hatano et al. 1999) ^d	1.5T	42						
		Upon completion of RT	42	100	78	43	100	81
		One month after RT	42	100	78	43	100	81
		Three months after RT	39 ^e	100	100	100	100	100
		Six months after RT	35 ^f	100	100	100	100	100

^aSn, Sp and Acc given in percentages

^bCombined gynaecological cancers – 15 cervical cancer patients

^cPatients were selected from initial group of 41 by gynaecological examination after chemotherapy. It is unclear whether post-treatment MRI results were used in this examination thereby contributing to the selection of patients.

^dPossible verification bias as MRI was used to determine biopsy sites.

^eThree patients excluded due to surgical extirpation.

^fFour deaths, two of which were patients who had shown a complete response to treatment on both histology and MRI, but who then developed distant metastases. One other patient with complete response developed metastases but was still alive at six months.

Summary

There is currently only very limited information available on the usefulness of MRI in the detection of residual or recurrent cervical cancer. Studies in this indication are small and

fraught with potential bias. Sensitivities ranged from 17% to 100%, while specificities ranged from 22% to 100%. The diversity of results makes valid interpretation difficult.

Microcirculation assessment

Tumour microcirculation and oxygenation have an important role in the success of cancer therapy for most tumours. This is related to the importance of blood and oxygen in tumour response to therapy. Radiotherapy destroys tumours by utilising oxygen-derived free radicals that damage the tumour's DNA (Deschner & Gray 1959). Chemotherapy relies on an adequate blood flow within a tumour to deliver the chemotherapeutic in sufficient concentrations. Additionally, many chemotherapeutics depend on the presence of free radicals for their cytotoxic effect (Tannock 1982).

There are numerous reports of a correlation between poor blood supply and radiotherapy failure in treatment of cervical cancer (Dische et al. 1983; Hockel et al. 1993; Mendenhall et al. 1984). It is thought that this is due to the tendency of cervical cancer to be bulky and centrally necrotic. This means that within the tumour there will be regions of radioresistant hypoxic cells found at the interphase of the necrotic and well-perfused tissue (Thomlinson & Gray 1955). Therefore, a method of assessing tumour microcirculation and oxygenation that could detect these areas may improve prognostic stratification of patients and aid in predicting likely outcomes of therapy. The use of dynamic MRI for this purpose is currently being investigated.

Hawighorst et al (1997) correlated dynamic MRI parameters and histological microvessel density (HMVD) counts in an attempt to identify prognostic indicators. The MRI parameters of interest were amplitude (A) and the kinetic parameter k_{21} . Dynamic imaging was performed on 55 patients using a 1.5T system. Tumours with lymphatic system involvement had a significantly higher mean HMVD count than those without lymphatic system involvement ($p < 0.05$). Significantly higher ($p < 0.001$) mean k_{21} values were found in patients with lymphatic involvement than in patients without lymphatic involvement. No significant difference was found in the mean values of A .

Hawighorst et al (1998b) looked for associations between functional dynamic MRI parameters and histomorphological markers of tumour angiogenesis in an attempt to identify prognostic indicators. These markers were HMVD and vascular endothelial growth factors (VEGF) expression. The MRI parameters of interest were amplitude (A) and the kinetic parameter k_{21} . Dynamic imaging was performed on 57 patients using a 1.5T system. An inverse association was found between VEGF expression and HMVD ($p < 0.01$). Significant associations were also found between HMVD and A ($p < 0.001$) and between HMVD and k_{21} ($p < 0.05$). No significant associations were found between VEGF expression and A or k_{21} . A univariate analysis of survival indicated that stratification of k_{21} into low ($k_{21} < 5.4 \text{ min}^{-1}$) and high ($k_{21} > 5.4 \text{ min}^{-1}$) median groups was the only significant predictor of patient survival ($p < 0.05$). HMVD, VEGF and A were not able to predict patient survival.

The studies by Mayr et al (1999) and Mayr et al (2000) (previously discussed) showed that local recurrence was common in patients with tumours of low dynamic enhancement. Low dynamic enhancement is indicative of poor vascular supply and hypoxia. In contrast, patients with tumours with high dynamic enhancement were less likely to suffer from recurrence.

Research into this area is still in an early stage and as yet, studies have not demonstrated consistent results. It is too soon to determine whether the assessment of tumour microcirculation by MRI may have a clinical role.

Conclusions

- MRI appears to have a high level of diagnostic accuracy in patients with cervical cancer (median sensitivity and specificity of approximately 85%).
- Based on small numbers of patients, MRI appears to have moderate sensitivity, but relatively high specificity (generally >90%) for the detection of vaginal invasion.
- Due to methodological limitations and small sample sizes, the role of MRI in the detection of residual or recurrent disease remains unclear at this stage.
- There is some evidence that MRI can alter radiotherapy field planning but it is unclear whether this leads to improvements in patient outcomes.
- There is some very limited evidence that suggests MRI may be useful in the assessment of individual patient treatment response, but the applicability of these analyses to the Australian setting is uncertain.
- MRI has been used to assess tumour microcirculation. There is no consistent evidence to suggest that MRI may be of value in this area. The clinical usefulness of such assessment remains unclear at this stage.
- It is difficult to draw substantive conclusions on the relative diagnostic accuracy of MRI to other imaging modalities (CT or US) as only one study (post-1997) provided a comparison of MRI to CT.
- Based on this one study, and on data prior to 1997, the accuracy of CT appears to be approximately 70% for the detection of parametrial invasion.

Endometrial carcinoma

The clinical problem

Currently the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) recommend surgical staging of endometrial cancer in order to accurately classify the disease and implement appropriate management strategies. Endometrial cancer can present as early disease requiring surgery confined to the uterus, or as more advanced disease requiring more extensive surgery including lymphadenectomy. Imaging modalities such as MRI, computer tomography (CT) and ultrasound (US) have been used more recently to detect various characteristics of endometrial cancer in order to differentiate early and advanced stages of disease prior to surgery. Therefore, the primary area of interest within the indication of endometrial cancer is the use of MRI for the pre-surgical staging of newly diagnosed disease, compared with conventional procedures such as CT and/or US. Additional information from studies comparing the ability of different MRI sequences to detect myometrial and/or cervical invasion of endometrial cancer will also be evaluated.

Epidemiology and clinical presentation

Endometrial cancer is the most common gynaecological malignancy and accounts for approximately six per cent of all cancers in women. Peak incidence occurs between the ages of 55 and 65 years (Frei & Kinkel 2001). In 1997, there were 1,394 newly diagnosed endometrial carcinomas, representing an age-standardised incidence rate of 13.5 cases/100,000 Australian women. In the same year there were 271 associated deaths, which translated into an age-standardised mortality rate of 2.4 cases/100,000 women (Australian Institute of Health and Welfare 2000b). Endometrial cancer is a highly curable tumour, as symptoms often appear early during the course of the disease, thereby enabling early intervention (Ascher, Takahama, & Jha 2001).

Risk factors associated with endometrial cancer include obesity, diabetes mellitus, nulliparity, unopposed oestrogen intake, ovulatory syndromes and tamoxifen use for breast cancer (Ascher, Takahama, & Jha 2001; Frei & Kinkel 2001).

The most common endometrial cancer cell type is endometrial adenocarcinoma which accounts for approximately 75-80% of endometrial cancers. These cancers are further classified according to the glandular pattern, ranging from well differentiated (grade 1) to anaplastic (grade 3). Other histologic types include adenocarcinoma with squamous differentiation, adenosquamous carcinoma, papillary serous carcinoma and clear cell carcinoma (Ascher, Takahama, & Jha 2001; National Cancer Institute 2001b).

The prognosis of women with endometrial cancer is dependent upon the stage of disease at initial diagnosis. Prognostic factors include depth of myometrial and/or cervical invasion, nodal status, and histological type and grade (Boronow et al. 1984; Morrow et al. 1991). Furthermore, capillary-lymphatic space penetration on histological examination increases the likelihood of pelvic and extrapelvic tumour recurrence independent of the depth of myometrial invasion and tumour histologic grade (Hanson et al. 1985). Metastatic spread occurs in a characteristic pattern. Spread to the pelvic and para-aortic

nodes is uncommon, but can occur. Distant metastases can occur and most commonly involve the lungs, inguinal and supraclavicular nodes, liver, bones, brain and vagina.

Postmenopausal women with endometrial carcinoma tend to present with postmenopausal uterine bleeding. In some cases a watery vaginal discharge may be the only symptom. While endometrial cancer is uncommon in younger women, they tend to present with abnormal or heavy bleeding (Carter 1999).

Conventional staging and treatment

Staging

Diagnosis is generally confirmed on endometrial biopsy or curettage. Chest x-ray and CT can provide information regarding nodal involvement and distant spread. In response to poor concordance between pre-operative clinical staging and post-operative histopathological results, surgical staging criteria was adopted by the FIGO or the American Joint Committee on Cancer (AJCC) in 1988 (American Joint Committee on Cancer 1997b; Erratum 1992; Shepherd 1989; UICC 1997) (Table 13).

Table 13 FIGO staging of endometrial cancer

Stage	Characteristics
Stage I	Stage I endometrial cancer is carcinoma confined to the corpus uteri. Stage IA: tumour limited to endometrium Stage IB: invasion to less than one half of the myometrium Stage IC: invasion to greater than one half of the myometrium
Stage II	Stage II endometrial cancer involves the corpus and the cervix, but has not extended outside the uterus. Stage IIA: endocervical glandular involvement only Stage IIB: cervical stromal invasion
Stage III	Stage III endometrial cancer extends outside of the uterus but is confined to the true pelvis. Stage IIIA: tumour invades serosa and/or adnexa and/or positive peritoneal cytology Stage IIIB: vaginal metastases Stage IIIC: metastases to pelvic and/or para-aortic lymph nodes
Stage IV	Stage IV endometrial cancer involves the bladder or bowel mucosa or has metastasised to distant sites. Stage IVA: tumour invasion of bladder and/or bowel mucosa Stage IVB: distant metastases, including intra-abdominal and/or inguinal lymph nodes

Endometrial cancer can also be graded (G) with regard to the degree of differentiation of the adenocarcinoma, as follows:

- G1: 5% or less of a nonsquamous or nonmorular solid growth pattern
- G2: 6% to 50% of a nonsquamous or nonmorular solid growth pattern
- G3: more than 50% of a nonsquamous or nonmorular solid growth pattern

Treatment

Hysterectomy and bilateral salpingo-oophorectomy in conjunction with selective lymphadenectomy is the mainstay of the treatment for endometrial cancer. Varying

combinations of adjuvant radiotherapy are also used in the management of this disease, however, the current literature does not provide clear evidence on the appropriate use of radiotherapy to treat endometrial cancer. Usually radiotherapy is given in selective cases depending on the pathological extent of disease at surgery. When a patient presents with advanced disease or is deemed medically unfit to undergo a surgical procedure as a result of other comorbidities and/or obesity, management with radiotherapy alone is considered. However, as a consequence these patients usually have reduced survival rates. Hormonal therapy and chemotherapy are generally reserved for treatment of advanced and recurrent disease.

Management of women presenting with FIGO stage I disease is dependent on the degree of tumour differentiation and confinement of the tumour to the endometrial corpus. If the tumour is well differentiated and confined to the upper two thirds of the corpus, has less than 50% myometrial invasion, negative peritoneal cytology and without vascular space invasion, a total abdominal hysterectomy and bilateral salpingo-oophorectomy with selective lymphadenectomy is recommended. If nodes are found to be negative, no post-operative treatment is indicated (National Cancer Institute 2001b). Post-operative intravaginal brachytherapy is also advocated by some in order to reduce vaginal reoccurrence, however improvement in 5-year survival has not been shown (Eltabbakh et al. 1997). In patients where the tumour is not well differentiated and/or there is greater than 50% myometrial invasion, there is an increased probability of more distant disease (Boronow et al. 1984) and therefore lymphadenectomy is recommended in order to appropriately stage the disease (Larson et al. 1996). However, there appears to be some debate as to whether extensive lymphadenectomy confers a significant increase in patient mortality and morbidity due to more extensive surgery and potential increase in blood loss. Extensive surgery may also require longer operating times and the presence of a specialist gynaecologist oncologist (Homesley et al. 1992; Orr, Jr., Orr, & Taylor 1996). The decision to proceed with lymphadenectomy and the potential risk of conducting the surgery may need to be balanced with the risk of understaging the true extent of disease. Post-surgical radiotherapy is suggested as some studies have found that it reduces the incidence of pelvic recurrence, however, the evidence is equivocal as to whether survival rates are improved (Creutzberg et al. 2000; Marchetti et al. 1990; Morrow et al. 1991). If both pelvic and periaortic nodes are positive, management with an extended external radiation field and provision of hormonal therapy and chemotherapy may be considered. Determination of treatment will depend on the individual patient, and may not always be feasible in obese and medically unfit women, as the risk of radiotherapy complications increase in this group of patients (Greven et al. 1991; Homesley 1996). Radiation treatment is recommended for women who are unable to undergo surgery due to medical complications, however cure rates are lower compared with women treated with surgery (Grigsby et al. 1987).

Patients presenting with FIGO stage II may be treated with surgery and post-operative radiation therapy (National Cancer Institute 2001b). Post-operative radiation is recommended for patients presenting with cervical stromal involvement. Pelvic recurrence may be reduced by adjuvant external radiotherapy with brachytherapy or radical hysterectomy, however definitive improvement in survival rates has not been shown (Eltabbakh & Moore 1999). Furthermore, Boente et al (1993) advocate that radical hysterectomy without adjuvant radiotherapy may improve survival for women presenting with gross cervical involvement.

Tumours may be inoperable in patients with FIGO stage III disease. It is recommended that patients who are medically fit and present with operable tumours should undergo

total abdominal hysterectomy with bilateral salpingo-oophorectomy or Wertheim's hysterectomy (Gallagher 1995). External beam radiotherapy in conjunction with intrauterine and intravaginal brachytherapy is recommended for women who are unable to proceed with surgery due to extension of the tumour to the pelvic wall. However, relapse is seen more frequently and the prognosis is generally worse for this group of women (Gallagher 1995; National Cancer Institute 2001b).

Women presenting with FIGO stage IV endometrial cancer will rarely undergo surgical management due to the high potential for distant metastatic spread. Curative radiotherapy is infrequently offered, management generally being palliative in nature. External-beam radiotherapy or intracavity brachytherapy may relieve vaginal bleeding and provide pain relief in the presence of pelvic bone tissue metastasis. Hormonal therapy and chemotherapy may be instituted when distant metastases are present. Progesterone therapy has been shown to produce response rates which vary from 15–30%, however, long term survival rates have not been substantially altered (Lentz 1994). Differing response rates of the tumour to treatment appear to be associated with the presence of hormone receptors (Kauppila 1989). There are no chemotherapy treatment recommendations for the treatment of metastatic disease in endometrial cancer. Doxorubicin containing regimes (Hancock et al. 1986) or paclitaxel (Ball et al. 1996) may be of benefit. It is recommended that all patients with advanced disease be considered for clinical trials that evaluate single-agent or combination therapy for this disease (National Cancer Institute 2001b).

For pelvis and para-aortic lymph node recurrences and some selected distant recurrences, irradiation may offer effective palliative therapy. Patients with disease that is hormone receptor positive may respond to progestogen therapy (Kauppila 1989) and there is some evidence that tamoxifen may be of use in patients who do not respond to progestogen therapy (Quinn & Campbell 1989). Doxorubicin-containing regimes may be of benefit, however, improvement in survival has not yet been shown (Hancock et al. 1986; Thigpen et al. 1994). Paclitaxel has been shown to have a significant impact on disease processes (Ball et al. 1996).

Potential value of MRI

This review examines the potential role of MRI in pre-surgical staging of newly diagnosed endometrial carcinoma compared with other modalities such as computer tomography and/or ultrasonography.

Deep myometrial invasion and cervical stromal involvement of endometrial carcinoma are reported to be predictors of lymph node disease (Boronow et al. 1984). Accurate pre-surgical diagnosis of these factors by MRI may potentially optimise surgical and non-surgical management of women with endometrial carcinoma (Frei & Kinkel 2001). If MRI is able to accurately stage early disease then this imaging modality may prevent unnecessary extensive surgery currently required by the FIGO to appropriately stage endometrial cancer. Extensive lymph node dissection or sampling requires specialist oncologist gynaecologist attendance and longer operating times, which may be associated with potential increases in patient morbidity and economic costs. Furthermore, if MRI were able to detect extensive disease that is more likely to benefit from surgical debulking prior to radiation, it would enable the appropriate allocation of women to such treatment prior to surgical intervention.

Results

The 21 papers which form the basis of this review are summarised in Table 14 and appear in more detail in Appendix C.

Table 14 MRI publications in endometrial cancer

Eligibility	Number
Papers which provided an estimate of the MRI diagnostic accuracy for staging of endometrial cancer compared to other conventional pre-surgical staging procedures	7
Papers which provided an estimate of the diagnostic accuracy for staging of primary endometrial cancer with comparison across different MRI sequences	8
Papers which conducted a meta-analysis on the use of MRI in the pre-surgical assessment of endometrial cancer	2
Papers which provided an estimate of the MRI diagnostic accuracy for the differentiation of malignant lesions from benign lesions compared to post-operative histopathology	2
Papers which provided an estimate of MRI diagnostic accuracy for the staging of endometrial cancer compared to intraoperative gross visualisation	2
Total	21

The primary area of interest within the indication of endometrial cancer was the use of MRI in the staging of newly diagnosed endometrial cancer compared with other conventional imaging modalities. Additional information has also been provided from studies that compared the ability of different MRI sequences to detect prognostic factors. One of two prognostic factors, myometrial and cervical invasion, was investigated by each study included in the review. Only one study investigated both factors within the same group of patients. Therefore, subsections reporting the results of studies which investigated the ability of each procedure to detect: (i) myometrial invasion; and (ii) cervical invasion, have been developed to facilitate comparison among studies.

Results of diagnostic studies

Seven studies compared MRI with other conventional pre-operative staging procedures in order to assess their ability to detect myometrial and/or cervical invasion of endometrial cancer. The comparators included; serum CA-125 and CA 19-9 determinations, hysteroscopy, intrauterine sonography, transvaginal ultrasound (TVUS), fractional curettage and endocervical and endometrial curettage, and cervical cytology. Of these studies, five investigated detection of only myometrial invasion, and two studies investigated the detection of only cervical invasion.

Eight studies compared different MRI sequences to assess their ability to detect myometrial and/or cervical invasion of endometrial cancer. Five studies investigated detection of only myometrial invasion, one study investigated both myometrial invasion and cervical invasion, and two studies investigated only cervical invasion of endometrial cancer.

Two studies investigated the ability of MRI to distinguish malignant from benign lesions of the endometrium.

Two meta-analyses were retrieved. One paper compared the usefulness of CT, US and MRI to stage endometrial cancer. The other paper investigated whether, in addition to knowledge of tumour grade, MRI findings were better able to detect myometrial invasion compared to knowledge of tumour grade alone.

Furthermore, two other studies investigating the accuracy of MRI in the detection of myometrial invasion in endometrial cancer compared with intraoperative gross dissection were retrieved and are included in Appendix C. However, these will not be reported in the results section as these papers do not directly relate to the question of interest.

All studies reported staging accuracy of MRI compared to a gold standard (post-operative histopathology). No studies assessed the impact of MRI on patient management and one study attempted to investigate health outcomes as a result of MRI staging.

Methodological issues in the studies

All the studies included in this review were from case series except one case control study (Grasel et al. 2000). There are inherent problems in relying on data from case series due to the lack of a control group and the potential for bias. In addition to these problems, a number of the studies also had further methodological issues, listed below.

- Retrospective rather than prospective data collection (Hardesty et al. 2000; Imaoka et al. 1999; Lee et al. 1999; Saez et al. 2000; Toki et al. 1998).
- The paper was not explicit in describing whether the study was conducted in a prospective or retrospective manner (Kietlinska et al. 1998; Schneider et al. 1999; Seki, Kimura, & Sakai 1997; Takahashi et al. 1998; Tsuda et al. 1997; Zarbo et al. 2000).
- Recruitment of the case series in a consecutive manner was not explicit, and no further information was provided on the selection criteria of participants, therefore increasing the likelihood of selection bias (Kietlinska et al. 1998; La Fianza et al. 2000; Saez et al. 2000; Seki, Kimura, & Sakai 1997; Seki, Takano, & Sakai 2000; Shen et al. 1999; Tsuda et al. 1997; Zarbo et al. 2000).
- Overestimation of the sensitivity and specificity by basing calculations on number of observations/imaging sites rather than patients (Grasel et al. 2000; Takahashi et al. 1998).
- Inconsistencies between information reported in text and information displayed in table (Hardesty et al. 2000; Imaoka et al. 1999; Saez et al. 2000).
- Selection bias may have resulted in overestimation of the sensitivity and specificity in studies where different subsets of participants from the same sample underwent different diagnostic procedures. The diagnostic accuracy was then compared among the various procedures (Kietlinska et al. 1998; Toki et al. 1998).

Accuracy of detecting myometrial invasion with MRI compared with other conventional modalities in patients with newly diagnosed endometrial cancer

LaFianza et al (2000) (n=80) aimed to investigate the prognosis of stage I endometrial adenocarcinoma by allocating patients to either a low risk group (n=26) or a high risk

group (n=54). Group allocation was based on pre-operative assessment of tumour histology and grade with biopsy, and depth of myometrial invasion with MRI. The low risk group patients were diagnosed as having grade 1-2 pure adenocarcinoma confined to the endometrium or involving the inner portion of the myometrium. The high risk group were diagnosed as having grade 3 pure adenocarcinoma and/or deep myometrial invasion, and/or clear cell, serous papillary adenosquamous carcinomas. The low risk group underwent Piver I hysterectomy, bilateral salpingo-oophorectomy, superior colpectomy and peritoneal washing, whereas the high risk group underwent Piver I hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, superior colpectomy and pelvic and lumboaortic systematic lymphadenectomy. All patients were then followed-up for a minimum of 36 months (median 61 months). After the period of follow-up, 24 of the 26 low risk patients had no evidence of disease (2 patients died from breast cancer), whereas among the high risk patients 36 of the 54 patients had no evidence of disease, (6 patients died from endometrial cancer, and 12 died from other disease). The paper reports the 'grade of myometrial infiltration as assessed at MRI had pathological confirmation in 72 of 80 cases'. Unfortunately, this paper was particularly difficult to interpret, and it is therefore unclear whether this means MRI was concordant in 72 of 80 patients, or whether only 72 of 80 patients underwent pathological confirmation. Given these limitations, this study suggests that MRI assessment of myometrial invasion, in conjunction with other histological and clinical information, may have some value in predicting the prognosis of patients with endometrial cancer.

Schneider et al (1999) (n=100) found that in the detection of deep myometrial invasion from superficial or no invasion, MRI was concordant with histopathological results in 82 of the 100 patients, whereas serum CA-125 and CA 19-9 markers were concordant in 74 of the 100 patients. Twelve false negatives were reported whereby myometrial invasion was underestimated. In detecting FIGO stage IC or higher, MRI was calculated as having a sensitivity of 73%, specificity of 89%, positive predictive value of 85% and negative predictive value of 82%. However, serum tumour markers were calculated as having a sensitivity of 58%, specificity of 87%, positive predictive value of 79%, and negative predictive value of 72%.

Shen et al (1999) (n=73) found that in the differentiation of any myometrial invasion (superficial or deep) from no myometrial invasion, MRI results were concordant with post-operative histopathological examination in 64 out of 73 patients, whereas hysteroscopy results were concordant in 62 out of 73 patients. Nine false negatives were reported for MRI in which myometrial invasion was underestimated. The reasons cited by the authors were a lack of abnormal findings due to histologically minimal invasion of the myometrium, difficulty in interpretation because of an absent or indistinct junctional zone, tumour located at the tube opening and presence of polypoid tumour type. This allowed the calculation of sensitivity (82%), specificity (100%), positive predictive value (100%) and negative predictive value (72%) for MRI. Hysteroscopy was reported to have a sensitivity of 80%, specificity of 96%, positive predictive value 98% and negative predictive value 69%. The sensitivity and specificity results for MRI and hysteroscopy were not found to be significantly different ($p>.05$). There was also sufficient information to allow the calculation of diagnostic accuracy for MRI in the differentiation of deep myometrial invasion compared to superficial or no myometrial invasion. MRI was concordant with post-operative histopathology in 67 out of 73 patients. Sensitivity was 96%, specificity was 90%, positive predictive value was 81% and negative predictive value was 98%. There was insufficient data to calculate similar results for hysteroscopy.

Tsuda et al (1997) (n=20) presented enough raw data to enable the calculation of the diagnostic accuracy of MRI compared with intrauterine sonography (IUS). In the detection of deep myometrial invasion from superficial or no invasion, MRI results were concordant with post-operative histopathological examination in 19 out of 20 patients, whereas IUS was concordant in 18 out of 20 patients. MRI was calculated as having a sensitivity of 100%, specificity of 94%, positive predictive value of 67% and negative predictive value of 100%. IUS was calculated as having a sensitivity of 50%, specificity of 94%, positive predictive value of 50% and negative predictive value of 94%.

Zarbo et al (2000) presented enough raw data to enable the calculation of the diagnostic accuracy for MRI compared with transvaginal ultrasonography (TVUS) in the detection of deep myometrial invasion from superficial or no myometrial invasion. MRI was found to be concordant with histopathology in 24 of 30 (80%) patients, whereas TVUS was found to be concordant in 30 of 33 (91%) patients. MRI was calculated as having a sensitivity of 67%, a specificity of 86%, positive predictive value of 67% and negative predictive value of 86%. TVUS was calculated as having a sensitivity of 91%, specificity of 91%, positive predictive value of 83% and negative predictive value of 95%. No statistical tests were reported to compare the MRI and TVUS results. As not all patients had both MRI and TVUS, these results should be interpreted with caution.

In summary, in the differentiation of deep myometrial invasion from superficial or no invasion, MRI appeared to be better than serum CA-125 and CA 19-9 levels (Schneider et al. 1999) and IUS. In contrast, it appeared to have lower diagnostic accuracy than TVUS (Zarbo et al. 2000). It is difficult to compare the results by Shen et al (1999) with the above papers as the authors do not provide enough information to calculate the diagnostic accuracy of hysteroscopy in the detection of deep myometrial invasion from superficial or no invasion. It is therefore not possible to comment on the diagnostic accuracy of MRI compared to hysteroscopy in the differentiation of deep from superficial or no myometrial invasion. Previously discussed limitations of studies should be borne in mind when interpreting these results. True comparison across studies is further complicated as the studies used different combinations of MRI sequences and some studies did not clearly define MRI application techniques.

Summary

Based on somewhat limited evidence published since 1997, MRI appeared to have higher sensitivity (67-100%) and approximately comparable specificity (86-94%) to cervical cytology, intrauterine sonography, and serum tumour markers CA-125 and CA 19-9 for the detection of extensive disease. MRI appeared to have comparable sensitivity and specificity to TVUS and hysteroscopy in this indication, however, results varied across individual studies. Table 15 summarises the results of these studies.

Table 15 Diagnostic accuracy of MRI compared with conventional procedures to detect myometrial invasion of endometrial cancer

Procedure		Study				Average
		(Schneider et al. 1999)	(Shen et al. 1999)	(Tsuda et al. 1997)	(Zarbo et al. 2000)	
	n	100	73	20	33 ^a	
Accuracy (%) of differentiation of deep myometrial invasion from superficial or no myometrial invasion						
MRI	Sn	73	96	100	67	84
	Sp	89	90	94	86	90
	PPV	85	81	67	67	75
	NPV	82	98	100	86	92
	Acc	82	92	95	80 (24/30) ^a	97
Markers (CA-125, CA 19-9)	Sn	58				58
	Sp	87				87
	PPV	79				79
	NPV	72				72
	Acc	74				74
IUS	Sn			50		50
	Sp			94		94
	PPV			50		50
	NPV			94		94
	Acc			90		90
TVUS	Sn				91	91
	Sp				91	91
	PPV				83	83
	NPV				95	95
	Acc				91 (30/33) ^a	91
Accuracy (%) of differentiation of any (deep or superficial) myometrial invasion from no myometrial invasion						
MRI	Sn		82			82
	Sp		100			100
	PPV		100			100
	NPV		72			72
	Acc		88			88
Hysteroscopy	Sn		80			80
	Sp		96			96
	PPV		98			98
	NPV		69			69
	Acc		85			85

Notes: Table does not include LaFianza et al (2000) as no data was available

^a Overall sample size (n=33): only 30 patients evaluated with MRI, 33 patients were evaluated with TVUS

Missing values indicate that the study did not evaluate these modalities

Accuracy of detecting cervical invasion with MRI compared with other conventional modalities in patients with newly diagnosed endometrial cancer

Kietlinska et al (1998) (n=117) compared the ability of MRI, fractional curettage, hysteroscopy, TVUS and CT with post-operative histopathology to detect cervical invasion of endometrial cancer from no cervical invasion. However, CT was excluded from the final analysis due to difficulties arising in using this test to detect cervical involvement. Not all patients in this case series underwent each of the four procedures. The authors report that patients underwent examination with MRI (n=25), fractional

curettage (n=112), hysteroscopy (n=38), and TUVS (n=45). MRI was concordant with histopathological results in 21 of the 25 patients, fractional curettage was concordant in 66 of the 112 patients, hysteroscopy was concordant in 25 of the 38 patients, and TUVS was concordant in 35 of the 45 patients. One false negative was reported for MRI whereby cervical infiltration was underestimated. This allowed the calculation of sensitivity (75%), specificity (86%), positive predictive value (50%) and negative predictive value (95%). Fractional curettage underestimated cervical involvement in one instance, and overestimated involvement in 45 instances. Therefore sensitivity (88%), specificity (56%), positive predictive value (15%) and negative predictive value (98%) were calculated. Hysteroscopy underestimated cervical involvement in two instances, and overestimated involvement in 11 instances resulting in sensitivity of 33%, specificity of 69%, positive predictive value of 8.3% and negative predictive value of 92%. TUVS underestimated cervical involvement in one instance and overestimated cervical involvement in nine instances resulting in sensitivity of 75%, specificity of 78%, positive predictive value of 25% and negative predictive value of 97%. The paper reported results of statistical analysis to determine whether the differences among the four procedures were significant. However, the results are questionable due to the inappropriate application of multiple t-tests. It is also difficult to compare the diagnostic accuracy of the different modalities, as not all patients had all four assessments, giving vastly different patient numbers in each group. It is unclear which patients had which test, calling into question the comparability of the four patient groups.

Toki et al (1998) (n=64) compared the ability of MRI, cervical cytology, endocervical and endometrial curettage, TUVS, hysteroscopy and serum levels of CA-125 with post-operative histopathology to detect cervical invasion of endometrial cancer from no cervical invasion. Although the authors report on a consecutive case series of 64 women, only 38 of these patients underwent all six procedures. The number of patients evaluated by each of the modalities were; MRI (n=61), cervical cytology (n=64), endocervical curettage (n=46), TUVS (n=56), hysteroscopy (n=60) and CA-125 (n=64). Therefore, the results reported do not necessarily compare each modality for the same patient. However, the authors report, 'The results using 38 cases with complete data for all six procedures were comparable with those using all the cases'. Unfortunately, the data on the 38 patients is not presented separately so the accuracy of this statement cannot be assessed. Post-operative histopathology confirmed cervical invasion in 12 of the total 64 patients. Concordance with histopathological results for MRI occurred in 55 of the 61 patients, in 50 of the 64 patients for cervical cytology, in 33 of the 46 patients for endocervical curettage, in 48 of the 56 patients for TVUS, in 53 of the 60 patients for hysteroscopy and in 43 of the 64 patients for CA-125. Three false negatives were reported for MRI whereby cervical invasion was underestimated due to two mucosal cell infiltrations and one microinvasion. This allowed the calculations of sensitivity (75%), specificity (94%), positive predictive value (75%) and negative predictive value (94%) for MRI. The following values were calculated for: cervical cytology - sensitivity (83%), specificity (77%), positive predictive value (45%) and negative predictive value (95%); endocervical curettage - sensitivity (91%), specificity (66%), positive predictive value (45%) and negative predictive value (96%); TUVS - sensitivity (50%), specificity (93%), positive predictive value (63%) and negative predictive value (90%); hysteroscopy - sensitivity (82%), specificity (90%), positive predictive value (64%) and negative predictive value (96%); and CA-125 - sensitivity (42%), specificity (73%), positive predictive value (26%) and negative predictive value (84%).

Summary

In summary, in the differentiation of cervical invasion from no cervical invasion, MRI was reported to be generally more concordant with histopathology than was fractional curettage (Kietlinska et al. 1998; Toki et al. 1998), hysteroscopy (Kietlinska et al. 1998; Toki et al. 1998), TVUS (Kietlinska et al. 1998; Toki et al. 1998), cervical cytology, and CA-125 marker (Toki et al. 1998) (Table 16). However, true comparison across studies is difficult as the studies used different combinations of MRI sequences, and some studies did not clearly define MRI application techniques. Furthermore, as not all patients had all diagnostic tests, it is difficult to assess the relative diagnostic accuracy of the methods, both within and between studies.

Table 16 Diagnostic accuracy of MRI compared with conventional imaging to detect cervical invasion of endometrial cancer

Procedure		Study		Average
		Kielinska et al (1998) Total sample size: (n=117)	Toki et al (1998) Total sample size: (n=64)	
		Sample size of each modality: MRI (n=25) FC (n=112) HS (n=38) TVUS (n=45)	Sample size of each modality: MRI (n=61) FC (n=46) HS (n=60) TVUS (n=56) CC (n=64) CA-125 (n=64)	
Diagnostic accuracy (%) of each modality to detect cervical invasion of endometrial cancer from no invasion				
MRI	Sn	75	75	75
	Sp	86	94	90
	PPV	50	75	63
	NPV	95	94	95
	Acc	84 (21/25)	90 (55/61)	87
Fractional curettage	Sn	88	91	90
	Sp	56	66	61
	PPV	15	45	30
	NPV	98	96	97
	Acc	59 (66/112)	72 (33/46)	66
Hysteroscopy	Sn	33	82	58
	Sp	69	90	80
	PPV	8.3	64	36
	NPV	92	96	94
	Acc	66 (25/38)	88 (53/60)	77
Transvaginal ultrasonography (TVUS)	Sn	75	50	63
	Sp	78	93	86
	PPV	25	63	44
	NPV	97	90	94
	Acc	78 (35/45)	86 (48/56)	87
Cervical Cytology	Sn		83	83
	Sp		77	77
	PPV		45	45
	NPV		95	95
	Acc		78 (50/64)	78
Serum marker CA-125	Sn		42	42
	Sp		73	73
	PPV		26	26
	NPV		84	84
	Acc		67 (43/64)	67

Note: Missing values indicate that the study did not assess the accuracy of these modalities.

Accuracy of detecting myometrial invasion among various different MRI sequences in patients with newly diagnosed endometrial cancer

The search identified six papers that compared the ability of different MRI sequences to detect myometrial invasion of endometrial cancer.

Joja et al (1999) (n=28) provided enough information to calculate the diagnostic accuracy of detecting deep myometrial invasion from superficial or no myometrial invasion when comparing dynamic MRI (with 3D fast low angle shot (FLASH) technique) with spin-echo (SE) or turbo T1W MRI and CE-T1W MRI. Dynamic MRI was concordant with histopathological results in 27 of the 28 (96%) patients, SE-T2W MRI was concordant in 23 of the 28 (82%) patients and CE-T1W MRI was concordant in 23 of the 28 (82%) patients.

Lee et al (1999) (n=46) provided enough information to enable the calculation of the diagnostic accuracy of T2W MRI compared with CE-T1W MRI in the detection of deep myometrial invasion from superficial and no myometrial invasion. CE-T1W MRI was concordant in 41 of 46 (89%) patients, whereas T2W MRI was concordant with histopathology in 36 of the 46 (78%) patients.

Saez et al (2000) compared plain (T1W and T2W MRI) to whole series (T1W, T2W and CE-T1W MRI) and found that contrast-enhanced images improved the accuracy of staging the extent of myometrial invasion of endometrial cancer. The paper does not provide clear details on the raw data, therefore making it difficult to calculate specific results.

Savci et al (1998) (n=20) found that for the detection of deep myometrial invasion from superficial or no myometrial invasion, both CE-T1W and T2W MRI were concordant with histopathological results in 18 of the 20 (90%) patients.

Seki et al (1997) (n=40) found that in the detection of deep myometrial invasion from superficial or no myometrial invasion, dynamic MRI and CE-T1W MRI were both concordant with histopathological results in 37 of the 40 (93%) patients, whereas T2W MRI was concordant in 33 of the 40 (83%) patients.

Takahashi et al (1998) (n=28) calculated the accuracy (defined by the number of correct sites, rather than patients) of MRI to detect deep myometrial invasion from superficial or no myometrial invasion. T2W MRI was concordant in 59 of the 67 (88%) uterine sites, dynamic sequences were concordant in 56 of the 67 (84%) uterine sites and CE-T1W MRI was concordant in 49 of the 67 (73%) sites.

Accuracy of detecting cervical invasion among various different MRI sequences in patients with newly diagnosed endometrial cancer

The search identified three papers that compared the ability of different MRI sequences to detect cervical invasion of endometrial cancer.

Takahashi et al (1998) (n=28) found that for the detection of cervical invasion from no cervical invasion, T2W MRI was concordant with histopathological results in 23 of the 28 (82%) patients, CE-T1W MRI was concordant in 20 of the 28 (71%) patients and dynamic MRI was concordant in 19 of the 28 (68%) of the patients.

Seki et al (2000) (n=39) found that for the detection of cervical invasion from no cervical invasion, dynamic MRI (fast low angle shot (FLASH) techniques without breath holding)

was concordant with histopathological results in 37 of the 39 (95%) patients, spin-echo CE-T1W MRI was concordant in 35 of the 39 (90%) patients, and T2W MRI (rapid acquisition with relaxation enhancement) was concordant in 33 of the 39 (85%) patients.

Shibutani et al (1999) (n=67) compared thin section oblique and parasagittal CE-T1W MRI with thin section and parasagittal spin-echo or turbo spin-echo T2W MRI. The paper provides enough information to calculate the accuracy of detecting cervical invasion from no cervical invasion. Thin section oblique CE-T1W MRI was concordant with histopathological results in 65 of the 67 (97%) patients and thin section oblique T2W MRI was concordant in 62 of the 67 (93%) patients. However, parasagittal CE-T1W MRI was concordant in 62 of the 67 (93%) patients and parasagittal T2W MRI was concordant in 60 of the 67 (90%) patients.

Meta-analyses reporting the ability of MRI to detect myometrial invasion in endometrial cancer

Two recent meta-analyses have reported on the use of MRI in the assessment of endometrial carcinoma.

The paper by Kinkel et al (1999) compared contrast enhanced MRI (CE-MRI) with plain MRI, CT and US. Six studies met the inclusion criteria for CT, 16 for US, and 25 for MRI. Summary receiver operating characteristics analysis showed no significant differences in the ability of CT, US and MRI to detect overall (myometrial and cervical) involvement of endometrial cancer. However, for the detection of deep myometrial invasion of endometrial carcinoma, CE-MRI performed significantly better than non-enhanced MRI ($p<.001$) and US ($p<.002$) and demonstrated a trend towards better results compared with CT ($p=.002$). The authors report that there was insufficient data on the use of CT and US to detect cervical invasion and therefore, the MRI results on cervical invasion could not be compared with these modalities.

The paper by Frei et al (2000) was aimed at determining whether MRI findings in addition to tumour grade contributed to treatment stratification and specialist referral. The authors conducted a meta-analysis of seven papers (1,875 patients) to determine the mean pre-test probabilities of surgically proven deep myometrial invasion in patients diagnosed with grades 1, 2 and 3 endometrial cancer. They then determined the post-test probability for CE-MRI used in addition to knowledge of tumour grade using Bayesian analysis. Likelihood ratios were based on data from nine studies (742 patients) and were obtained through summary receiver operating characteristics. A positive likelihood ratio of 10.11 was reported and indicated that CE-MRI is clinically useful at diagnosing deep myometrial invasion. A negative likelihood ratio of 0.1 was reported, indicating that CE-MRI was clinically useful in excluding deep myometrial invasion. The results suggest that in patients with grade 1 or 2 endometrial cancer, a lack of deep myometrial invasion at pre-operative CE-MRI can reliably be used to exclude deep invasion. The authors provide a theoretical discussion of the possible implications this may have for treatment, however, no data is provided on whether actual changes in patient management may have occurred as a result of MRI information. They conclude that, compared to tumour grade alone, CE-MRI findings 'significantly affect the post-test probability of deep myometrial invasion'. As a result, it is suggested that CE-MRI should be considered as the preferred diagnostic adjunct for clinical treatment planning and for specialist referral. The clinical applicability of these results to the Australian treatment setting remains unclear.

Accuracy of MRI in distinguishing malignant from benign endometrial lesions

The search identified two papers that investigated the ability of MRI to detect malignant from benign endometrial conditions.

Grasel et al (2000) (n=35) investigated whether MRI compared with histopathology could distinguish between endometrial polyps and endometrial cancers of similar small size. The paper provided enough information to calculate that MRI was concordant with histopathology in 26 of the 35 (74%) patients.

Imaoka et al (1999) (n=55) compared CE-T1W MRI with T2W to distinguish between malignant and benign uterine conditions. CE-T1W MRI was found to be concordant with histopathological results in 49 of the 55 (89%) patients and T2W MRI was concordant in 45 of the 55 (82%) patients.

Staging accuracy of MRI in endometrial cancer

Based on somewhat limited evidence published since 1997, MRI appeared to have higher sensitivity (67-100%) and approximately comparable specificity (86-94%) to cervical cytology, intrauterine sonography, and serum tumour markers CA-125 and CA 19-9 for the detection of extensive disease. MRI appeared to have comparable diagnostic accuracy to TVUS and hysteroscopy, however, results varied across individual studies.

In the detection of more extensive disease from early disease, dynamic and contrast-enhanced MRI appeared to have improved diagnostic accuracy compared with T2W MRI, however again, results varied across individual studies.

Comparison across individual studies is difficult due to previously discussed methodological limitations and differences in the application of MRI scanning study design.

The impact of MRI on clinical management

No studies reported on how MRI changed the clinical management of patients with endometrial cancer. If MRI were able to accurately detect disease confined to the endometrium, it is possible that lymphadenectomy may be avoided in selected patients. Furthermore, if MRI were able to accurately detect prognostic factors suggestive of advanced disease, patients could be appropriately referred to a specialist gynaecologist oncologist for more extensive surgical staging. However, due to the lack of data on changes in management of patients with endometrial cancer it is unclear at this stage whether MRI has a true role in this area.

The impact of MRI on patient outcomes

One study (La Fianza et al. 2000) attempted to investigate the combined impact of MRI and pre-surgical biopsy on the health outcomes of women diagnosed with primary endometrial cancer. The 80 patients in the study sample were classified into low or high risk groups according to the tumour histopathology and extent of myometrial invasion detected by MRI. Subsequent surgical management was tailored according to the patient's risk status. All women were then followed-up for a minimum of 36 months (median 61 months). The authors concluded that women allocated to the low risk group tended to have improved health outcomes compared with the women allocated to the

high risk group, suggesting that MRI may have a prognostic role. No other studies reported on the impact of MRI on patient outcomes.

Conclusions

- In the differentiation of extensive endometrial cancer from early disease, MRI appeared to have improved diagnostic accuracy compared with fractional curettage, cervical cytology, intrauterine sonography, and serum markers CA-125 and CA 19-9. MRI appeared to have comparable diagnostic accuracy with TVUS.
- The positive predictive value (67- 85%) of MRI did not appear to be sufficiently high to allow MRI to replace current conventional surgical staging practices.
- There was insufficient evidence comparing MRI with CT in the detection of extensive endometrial cancer from early disease.
- In the differentiation of more extensive disease from early disease, dynamic and contrast-enhanced MRI appeared to have improved diagnostic accuracy compared with T2-weighted MRI.
- Based on very limited evidence, MRI may provide some information on patient prognosis.
- The implications for management of patients with endometrial cancer remain unclear at this stage.
- The methodological limitations of currently available data should be considered. These limitations may affect the generalisability of any conclusions.

What are the economic considerations?

The data in this report suggests that MRI may be a useful diagnostic tool in the staging of cervical cancer. Despite this, it is difficult to estimate the likely changes in patient management and subsequent patient outcomes that might result as few papers provide such data. Consequently, it is difficult to estimate the long term benefit realised (for example in life years saved or quality adjusted life years saved) as a result of possible improvements in diagnostic accuracy.

Instead, a summary and critical appraisal of published economic evaluations (or more accurately, costing studies) has been conducted. In addition, a modelled analysis of the likely health care cost implications of using MRI to assess disease stage has been conducted.

Published economic evaluations

A search was conducted in Medline, EMBASE and the NHS Centre for Reviews and Dissemination (CRD) Economic Evaluation Database. Search strategies are shown in Tables 17 and 18.

Table 17 Medline search strategy for economic evaluations

	Search Terms	Results
1	exp Magnetic Resonance Imaging/ or magnetic resonance imaging.mp.	100263
2	MRI.mp.	35747
3	MR imaging.mp.	14286
4	exp Magnetic Resonance Spectroscopy/ or magnetic resonance spectroscopy.mp.	88667
5	nuclear magnetic resonance.mp.	985
6	MR spectroscopy.mp.	15423
7	NMR.mp.	39411
8	or/1-7	197539
9	exp ECONOMICS/ or exp "costs and cost analysis"/ or cost-benefit analysis/	315644
10	cost effectiveness.mp.	11021
11	economic evaluation.mp.	1359
12	or/9-11	318744
13	8 and 12	1042
14	exp Genital neoplasms, female/	96066
15	14 and 13	16

Table 18 EMBASE search strategy for economic evaluations

	Search Terms	Results
1	exp Magnetic Resonance Imaging/ or magnetic resonance imaging.mp.	92617
2	MRI.mp.	33319
3	MR imaging.mp.	12464
4	exp nuclear magnetic resonance/ or nuclear magnetic resonance.mp.	180792
5	NMR.mp.	40305
6	MR spectroscopy.mp.	912
7	or/1-6	195627
8	exp female genital tract tumor/ or exp female genital tract cancer/ or exp gynecologic cancer/ or exp ovary cancer/ or exp uterus cancer/ or exp ovary tumor/ or exp uterus tumor/	61857
9	exp COST/ or exp COST BENEFIT ANALYSIS/ or exp COST CONTROL/ or exp COST EFFECTIVENESS ANALYSIS/ or exp COST MINIMIZATION ANALYSIS/ or exp COST UTILITY ANALYSIS/	87719
10	exp Economics/ or exp Economic Aspect/ or exp Cost Effectiveness Analysis/ or exp Cost Benefit Analysis/ or exp Health Economics/ or exp Health Care Cost/	174051
11	9 or 10	174051
12	7 and 11	1331
13	12 and 8	27

The NHS CRD Economic Evaluation Database was also searched using the terms “magnetic resonance imaging or MRI” and “endometr\$ or cerv\$”. Five references were found.

Of the 48 references identified by these searches, six were duplicate citations retrieved from multiple databases. Of the 42 non-duplicate references identified, six papers were identified as possible descriptive or partial economic evaluations. After examination of the full papers, only two were partial or descriptive economic evaluations, and the remaining four papers simply mentioned costs. Neither of these studies were conducted in Australia, therefore costings and results are not directly applicable to the Australian healthcare environment. Pertinent results of these two studies are presented in Table 19.

Table 19 Descriptive or partial economic evaluations of MRI in gynaecological malignancies

Citation	N	Country Indication	Type of study	Methods / Conclusions / Comments
(Hardesty et al. 2000)	25	United States Pre-operative assessment of endometrial cancer	Costing only MRI vs surgical staging to predict lymph node (LN) dissection	<p>Methods: Retrospective comparison of pre-op MRI scans with uterine dissection and histopathology</p> <p>MRI scenario: necessity for LN dissection directed based on MRI + histologic findings at biopsy</p> <p>Actual scenario: LN dissection at surgeon's discretion on basis of dissection of uterus and histologic findings at biopsy; Medicare reimbursements for each scenario for each patient calculated</p> <p>Results: Cost of MRI scenario US\$147,235 (for 25 patients); cost of actual scenario US\$148,500; for 25 patients MRI scenario cost US\$1265 less than actual scenario: US\$51 per patient</p> <p>Authors' conclusions: Costs and accuracy are similar for MRI staging and surgical staging, but MRI may decrease the number of unnecessary LN dissections</p> <p>Comments: It is unclear whether the LN dissections avoided are truly unnecessary as there is no indication of likely patient outcomes following the MRI scenario</p> <p>Costs are not directly applicable to Australia</p>
(Hricak et al. 1996)	246	United states Cervical cancer	Cost effectiveness Efficacy and cost of MRI as the initial diagnostic strategy in patients with cervical cancer	<p>Retrospective</p> <p>Methods: Patients divided into 2 groups: where MRI was initial test in pre-treatment work-up (n=105) and those where MRI was not (n=141). 1995 Medicare (US) global payments used to measure cost, and likelihood ratios calculated for bladder, rectal, parametrial and nodal involvement in stage IB disease.</p> <p>Results: Authors found that significantly fewer procedures and fewer invasive studies were performed in the MRI group. MRI resulted in mean cost savings of \$US401 (for all patients) and \$US449 for the subset of IB patients, compared to the non-MRI group.</p> <p>The increase in predictive values for parametrial and nodal disease was highest for MR imaging when tumour size was at least 2cm.</p> <p>Authors' conclusions: Pretreatment workup in clinical stage IB cervical cancer should be revised, MRI should be used as an adjunct to clinical examination and in treatment planning for IB patients; and although MRI is expensive it resulted in net cost savings because it replaced a number of less expensive procedures</p> <p>Comments: Cost differences are based on differences in the need for diagnostic tests between the two groups of patients. Cost or outcome implications of MRI directed changes in management strategy have not been assessed.</p>

These data are not directly applicable to either the Australian healthcare setting or the specific roles of MRI assessed in the current evaluation. As such, a modelled estimate of

likely healthcare costs and cost offsets attributable to the use of MRI for detection of parametrial invasion is presented below. Cost calculations are presented in more detail in Appendix E.

Modelled costings

It is difficult to provide an estimate of the likely additional cost to government that may be incurred if MRI is listed on the Medicare Benefits Schedule for the pre-treatment evaluation of cervical cancer.

For this reason, it should be noted that the information below provides only a crude estimate of costs. The costings below are based on the improved diagnostic accuracy of MRI in detecting parametrial involvement, and the treatment consequences that stem from this information. It is based on a number of assumptions regarding treatment of patients.

Assumptions

- All patients with parametrial invasion on imaging will be treated with chemoradiation.
- All patients with no parametrial involvement on imaging will be treated with surgery.
- 25% of patients treated with surgery will have adjuvant radiotherapy or chemoradiation (Prof. B. Ward, personal communication).
- Patients with negative imaging, but parametrial invasion (false negative on imaging) will be treated with chemoradiation after less aggressive surgery.
- Patients who are false positive for parametrial invasion will be treated as per imaging, as there is no way of knowing whether these patients are true or false positives.

Estimates of patient numbers

An estimate of the number of patients undergoing MRI is based on data from a surgical staging series (Cosin et al. 1998) and incidence data from the AIHW (2000a) (Table 20).

Table 20 Patient number estimates

Description	Estimate	Source
New cases of cervical cancer in 1997	795 patients	(Australian Institute of Health and Welfare 2000a)
Proportion of patients with parametrial invasion (stage IIB) (based on surgical staging series)	40%	(Cosin et al. 1998)
Proportion of patients with early disease (IB or IIA) (based on surgical staging series)	47%	(Cosin et al. 1998)
Number of patients undergoing MRI ^a	692 patients	calculation

^a Assuming patients with clinical stage IA and III/IV disease on CT do not undergo MRI

The accuracy of CT scanning is based on a combination of evidence from the one comparative trial assessed in this evaluation (Ng et al. 1998), and papers that assessed CT and were published prior to 1997 (Ho et al. 1992; Kim et al. 1990; Kim et al. 1993; Sironi et al. 1991; Subak et al. 1995) (Tables 21, 22 & 23). Accuracy of MRI is based on the data in Table 9. Table 23 shows that, based on the improved diagnostic accuracy of MRI over CT, there would be five fewer false positive results (potentially avoiding inappropriate radical chemoradiation) and five fewer false negative results (potentially avoiding inappropriate surgery).

Table 21 Accuracy of diagnostic tests

Detection of parametrial involvement	Sn	Sp	Source
CT	75%	75%	(Ho et al. 1992; Kim et al. 1990; Kim et al. 1993; Ng et al. 1998; Sironi et al. 1991; Subak et al. 1995)
MRI	85%	85%	Median from Table 9, MSAC review

Table 22 Number of patients with accurate and inaccurate diagnoses (based on sensitivity and specificity above)

Detection of parametrial involvement	True positives	False negatives	True negatives	False positives
CT	238.5	79.5	280.2375	93.4125
MRI	270.3	47.7	317.6025	56.0475

Table 23 Incremental benefit (avoidance of incorrect results) of MRI over CT

	Benefit (n=692 assessed with MRI)	Benefit per 100 patients assessed
Fewer false positive results	37	5
Fewer false negative results	32	5

Costs of treatments are documented in Appendix E. Diagnostic imaging costs are detailed below (Tables 24 & 25). A number of assumptions have been made:

Assumptions

- CT cost is based on the current Medicare Benefits Schedule for contrast-enhanced CT of upper abdomen and pelvis.
- In the scenario where MRI is done in addition to CT, the cost of MRI is for scanning of the pelvis only and is based on the Medicare Benefits Schedule for current MRI indications.
- Where MRI is done instead of CT, an estimated additional cost component has been added to reflect the fact that scanning of the upper abdomen will also be done. This additional cost is similar to the cost for conducting a CT scan of the upper abdomen alone (S. Goergen, personal communication).
- This additional component is based on the assumption that some efficiencies may exist when using MRI for both pelvic and abdominal scanning.

- The costing exercise conducted is not intended for fee scheduling purposes and is not a recommendation for funding at these levels.

Table 24 Cost of imaging

MBS item number	Description	Cost
56507	CT upper abdomen/pelvis with contrast	\$ 487.40
AA	MRI pelvis only	\$ 475.00
AA + BB	MRI pelvis + abdomen	\$ 775.00
56407	CT scan of upper abdomen only	\$ 362.90
BB	Extra fee component for MRI of upper abdomen (see above)	\$ 300.00

Table 25 Health care cost for diagnosis and subsequent treatment (cost per 100 patients assessed with MRI and/or CT)

	CT alone (per 100pts)	MRI alone* (per 100pts)	MRI + CT** (per 100pts)	MRI + CT*** (per 100pts)
Patients where imaging indicates parametrial invasion	\$ 310,385	\$ 318,751	\$ 327,593	\$ 321,719
Patients where imaging indicates no parametrial invasion	\$ 168,615	\$ 186,414	\$ 196,311	\$ 189,736
Patients with negative imaging but parametrial invasion (FN) who will require chemoradiation after less aggressive surgery (FN)	\$ 68,741	\$ 41,245	\$ 41,245	\$ 41,245
Total cost per 100 patients assessed by MRI	\$ 547,742	\$ 546,409	\$ 565,149	\$ 552,699
Incremental cost per 100 patients of MRI over CT		-\$ 1,332 (saving)	\$ 17,405	\$ 4,958
Cost per patient		-\$ 13 (saving)	\$ 174	\$ 49

* MRI cost = \$775 (pelvis and abdomen)

** MRI cost = \$475 (pelvis only), CT cost = \$487.40 (pelvis plus abdomen)

*** MRI cost = \$475 (pelvis only), CT cost = \$362.90 (upper abdomen only)

Taking into account estimates of downstream treatment costs that result from the staging of patients, the incremental cost of MRI over CT staging alone range from being cost saving of \$1,300 (when MRI of pelvis and abdomen replaces CT assessment) to an increase of approximately \$17,000 in the situation where MRI is performed in addition to a CT of the pelvis and abdomen. A large component of the above costs is comprised of estimates of downstream treatment costs (surgery, chemoradiation, radiotherapy). In reality, the incremental cost of MRI over CT will depend not only on these treatment costs but also on the eventual MBS fee for MRI in this indication and whether it is utilised as a replacement test for CT or as an incremental assessment over and above CT scanning.

Conclusions

There are few reliable head-to-head comparisons of MRI and CT in the assessment of patients with cervical cancer. Based on available data MRI appears to have improved sensitivity and specificity (85%) over CT (75%), however, there is still uncertainty associated with these estimates.

A modelled cost analysis was conducted based on modest improvements in the diagnostic accuracy of MRI over CT. Based on a number of estimates and assumptions, the cost effectiveness of MRI would be as follows.

For every 100 patients where MRI was used to assess the extent of disease:

- The incremental cost per 100 patients would range from saving \$1,300 to costing an extra \$17,000.
 - These cost estimates incorporate treatment costs and also depend upon the eventual Medicare Benefits Schedule fee for MRI in this indication and whether it is used as a replacement or an incremental test to CT.
- There would be five fewer false positive results (potentially avoiding inappropriate radical chemoradiation) based on improved specificity.
- There would be five fewer false negative results (potentially avoiding inappropriate surgery) based on improved sensitivity.

Conclusions

Safety

MRI is considered to be a safe non-invasive imaging modality. Patients undergoing MRI examination are exposed to low levels of electromagnetic radiation for short periods of time. The electromagnetic radiation dose emitted by the MRI apparatus is not sufficient enough to result in irreversible or hazardous biological effects in patients undergoing the tests.

Acoustic noise may be a potential hazard to patients undergoing MRI examination. It is therefore recommended that patients wear disposable ear-plugs to prevent temporary hearing loss.

MRI is contraindicated in patients with ferromagnetic and electronic implants such as pacemakers and aneurysm clips. Each patient should be assessed on an individual basis, as the ferromagnetic properties and the anatomical position of the implant will determine whether the patient is a suitable candidate for MRI.

MRI often involves the intravenous administration of a contrast agent, commonly gadopentetate dimeglumine (Gd-DTPA). Clinical trials and extensive clinical use have shown that such contrast agents are safe and generally well tolerated by patients, especially when compared to the contrast agents used during CT, which are considered relatively more toxic.

Effectiveness

Cervical Cancer

The specific research questions in relation to this review were as follows.

What is the value of MRI in:

- Assessment of patients with newly diagnosed cervical cancer to determine extent of disease to aid in planning treatment?
- Assessment of patients with newly diagnosed cervical cancer where conventional assessment indicates tumour extension past the cervico-paracervical margin to aid in radiotherapy planning?
- Assessment of patients with a persistent mass after treatment for cervical cancer to differentiate residual or recurrent disease from benign anatomical or post treatment changes?

It was concluded that:

- It is difficult to draw substantive conclusions on the relative diagnostic accuracy of MRI to other imaging modalities (CT or US) as only one study (post 1997) provided a comparison of MRI to CT.
- Based on this one study, and on data prior to 1997, the accuracy of CT appears to be approximately 70% for the detection of parametrial invasion.
- MRI appears to have a high level of diagnostic accuracy in patients with cervical cancer (median sensitivity and specificity of approximately 85%).
- Based on small numbers of patients, MRI appears to have moderate sensitivity, but relatively high specificity (generally >90%), for the detection of vaginal invasion.
- Due to methodological limitations including small population samples, it is not possible to assess the role of MRI in the detection of residual or recurrent disease at this stage.
- There is some evidence that MRI can alter radiotherapy field planning but at this stage it is unclear whether this leads to improvements in patient outcomes.
- There is some very limited evidence that suggests MRI may be useful in the assessment of individual patient treatment response, but the applicability of these analyses to the Australian setting is uncertain.
- MRI has been used to assess tumour microcirculation. There is no consistent evidence to suggest that MRI may be of value in this area. The clinical usefulness of such assessments remains unclear at this stage.

Endometrial Cancer

The specific research question in relation to this review was:

- What is the value of MRI in assessment of patients with newly diagnosed endometrial cancer for staging of disease prior to surgery?

It was concluded that:

- In the differentiation of extensive endometrial cancer from early disease, MRI appears to have improved diagnostic accuracy compared with fractional curettage, cervical cytology, intrauterine sonography and serum markers CA-125 and CA 19-9. MRI appears to have comparable diagnostic accuracy compared with TVUS.
- The positive predictive value of MRI (67–85%) does not appear to be sufficiently high to allow MRI to replace current conventional surgical staging practices.
- There was insufficient evidence to compare MRI with CT in the detection of extensive endometrial cancer from early disease.

- In the differentiation of more extensive disease from early disease, dynamic and contrast-enhanced MRI appear to have improved diagnostic accuracy compared with T2-weighted MRI.
- Based on very limited evidence, MRI may provide some information on patient prognosis.
- The implications for management of patients with endometrial cancer remain unclear at this stage.
- The methodological limitations of currently available data, such as the use of case series lacking a control group, should be considered when interpreting this review. These limitations may affect the generalisability of any conclusions.

Cost-effectiveness

There are few reliable head-to-head comparisons of MRI and CT in the assessment of patients with cervical cancer. Based on available data MRI appears to have improved sensitivity and specificity (85%) over CT (75%), however there is still uncertainty associated with these estimates.

A modelled cost analysis was conducted based on modest improvements in the diagnostic accuracy of MRI over CT. Based on a number of estimates and assumptions, the cost effectiveness of MRI would be as follows.

For every 100 patients where MRI was used to assess the extent of disease:

- The incremental cost per 100 patients would range from saving \$1,300 to costing an extra \$17,000.
 - These cost estimates incorporate treatment costs and also depend upon the eventual Medicare Benefits Schedule fee for MRI in this indication and whether it is used as a replacement or an incremental test to CT.
- There would be five fewer false positive results (potentially avoiding inappropriate radical chemoradiation) based on improved specificity.
- There would be five fewer false negative results (potentially avoiding inappropriate surgery) based on improved sensitivity.

Recommendations

MSAC recommends on the strength of evidence pertaining to Magnetic Resonance Imaging (MRI) for staging of cervical and endometrial cancer that:

1. Public funding should be supported for MRI staging of histologically proven cervical cancer at FIGO stages IB or greater following assessment by examination under anaesthesia.
2. At present there is insufficient evidence to support public funding for MRI in patients with recurrent cervical cancer but further studies may require this issue to be reviewed in the future.
3. Public funding should not be supported for MRI staging of endometrial cancer at this time.

- The Minister for Health and Ageing accepted these recommendations on 5 February 2002. -

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Commonwealth 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 Commonwealth 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 Commonwealth Minister for Health and Ageing on references related either to new 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, consumers, and health administration and planning:

Member	Expertise or Affiliation
Mr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Ian Fraser	reproductive medicine
Associate Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Emeritus Professor Peter Phelan	paediatrics

Dr Ewa Piejko	general practice
Dr David Robinson	plastic surgery
Professor John Simes	clinical epidemiology and clinical trials
Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council
Associate Professor Ken Thomson	radiology
Dr Douglas Travis	urology
Professor David Weedon	pathology (Chair until 24/08/01)
Ms Hilda Bastian	consumer health issues (Member until 24/08/01)
Dr Ross Blair	vascular surgery (New Zealand) (Member until 24/08/01)
Dr Paul Hemming	general practice (Member until 24/08/01)

Appendix B Supporting committee

Supporting committee for MSAC reference 7B, Magnetic Resonance Imaging.

Professor Brendon Kearney (Chair) MBBS, FRANCP, FRACMA Executive Director, Statewide Department of Human Service South Australia State Government	Member of MSAC
Mr Stephen Blamey BSc, MBBS, FRACS Consultant General and Gastrointestinal Surgeon, Monash Medical Centre, Melbourne	Member of MSAC
Dr David Brazier MBBS (Hons), FRACR Staff Specialist Radiologist Royal North Shore Hospital Sydney	Nominated by the Royal Australian and New Zealand College of Radiologists
Dr Graeme Dickie MBBS, MBA, FRACP, FRACR Clinical Associate Professor University of Queensland; Director, Division of Oncology Royal Brisbane Hospital	Nominated by the Royal Australian and New Zealand College of Radiologists – Faculty of Radiation Oncology
Dr Stacy Goergen MBBS (Hons), FRACR, FMGEMS Director of Magnetic Resonance Imaging Monash Medical Centre Melbourne	Nominated by the Royal Australian and New Zealand College of Radiologists
Mr Alan Keith Assistant Secretary Diagnostics and Technology Branch Department of Health and Ageing Canberra	Member of MSAC
Mr Leo Pomery BA Consumer Representative	Nominated by the Consumers' Health Forum of Australia
Professor Bruce Ward MBBS, PhD, FRCOG, FRACOG, CGO Professor of Gynaecological Oncology University of Queensland	Nominated by the Royal Australian and New Zealand College of Gynaecologists and Obstetricians

Table 26 Cervical cancer (CC) data extraction - detection of parametrial and vaginal invasion

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments																																																																					
(Hawighorst et al. 1998a)	33	Pts with biopsy-proven untreated primary cervical cancer of FIGO stage IB or higher.	To stage invasive cervical cancer and pelvic lymph nodes by high resolution MRI with a circularly polarised body phased-array coil in correlation with whole-mount specimen and histopathological findings.	Prospective, pts with histological diagnosis of FIGO stage IB or higher presenting between May 1996 and May 1997.	Mean age 55 yrs (range 20-68).	Pre- and post-contrast T1W spin-echo MRI and high-resolution T2W turbo spin-echo MRI. Images used circularly polarised body phased-array coil – 1.5T.	All high resolution MRIs were evaluated independently by 3 authors blinded to clinical and pathological staging. Agreement was by consensus.	<p>Staging accuracy of T2W TSE MRI vs post-contrast T1W SE MRI</p> <table border="1"> <thead> <tr> <th></th> <th>IB</th> <th>IIB</th> <th>IVA</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>T2W</td> <td>80%</td> <td>81%</td> <td>75%</td> <td>79%</td> </tr> <tr> <td>T1W</td> <td>80%</td> <td>75%</td> <td>75%</td> <td>76%</td> </tr> </tbody> </table> <p>Detect^a of parametrial invasion by T2W TSE MRI vs post-contrast T1W SE MRI (based on 66 parametria)</p> <table border="1"> <thead> <tr> <th></th> <th>Sn</th> <th>Sp</th> <th>PPV</th> <th>NPV</th> <th>Acc</th> </tr> </thead> <tbody> <tr> <td>T2W</td> <td>86%</td> <td>80%</td> <td>90%</td> <td>72%</td> <td>84%</td> </tr> <tr> <td>T1W</td> <td>74%</td> <td>65%</td> <td>83%</td> <td>52%</td> <td>71%</td> </tr> </tbody> </table> <p>Detect^a of vaginal Involvement by T2W TSE MRI vs post-contrast T1W SE MRI (33pts)</p> <table border="1"> <thead> <tr> <th></th> <th>Sn</th> <th>Sp</th> <th>PPV</th> <th>NPV</th> <th>Acc</th> </tr> </thead> <tbody> <tr> <td>T2W</td> <td>67%</td> <td>92%</td> <td>67%</td> <td>92%</td> <td>87%</td> </tr> <tr> <td>T1W</td> <td>67%</td> <td>81%</td> <td>44%</td> <td>91%</td> <td>78%</td> </tr> </tbody> </table> <p>Detect^a of bladder/rectal involvement by T2W TSE MRI vs post-contrast T1W SE MRI (33pts)</p> <table border="1"> <thead> <tr> <th></th> <th>Sn</th> <th>Sp</th> <th>PPV</th> <th>NPV</th> <th>Acc</th> </tr> </thead> <tbody> <tr> <td>T2W</td> <td>88%</td> <td>86%</td> <td>68%</td> <td>96%</td> <td>87%</td> </tr> <tr> <td>T1W</td> <td>88%</td> <td>86%</td> <td>68%</td> <td>96%</td> <td>87%</td> </tr> </tbody> </table> <p>Lymphadenopathy (results for both types of MRI combined)</p> <p>Sn – 68%, Sp – 78%, PPV – 81%, NPV – 65%, Acc – 72%</p>		IB	IIB	IVA	Total	T2W	80%	81%	75%	79%	T1W	80%	75%	75%	76%		Sn	Sp	PPV	NPV	Acc	T2W	86%	80%	90%	72%	84%	T1W	74%	65%	83%	52%	71%		Sn	Sp	PPV	NPV	Acc	T2W	67%	92%	67%	92%	87%	T1W	67%	81%	44%	91%	78%		Sn	Sp	PPV	NPV	Acc	T2W	88%	86%	68%	96%	87%	T1W	88%	86%	68%	96%	87%		<p>Histopathologic al staging obtained from surgery.</p> <p>IB – 5pts IIB – 16pts IVA – 12pts</p> <p>46/66 parametria with tumour involv^e.</p> <p>6pts with vaginal tumour involvem^t, 12 with bladder involvem^t and 5 with rectal involvem^t. 19 pts were positive for pelvic lymph node metastases</p>	<p>Error in results of lymphadenopathy – hist results show 14 true negatives but later in paper this has been written as 19 true negatives.</p> <p><i>Values in italics calculated to facilitate comparison across studies</i></p>
	IB	IIB	IVA	Total																																																																												
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Table 26 Cervical cancer (CC) data extraction - detection of parametrial and vaginal invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments																														
(Kim et al. 1997)	62	Pts with pathologically confirmed invasive CC. Diagnosed in previous month by pap smear or biopsy.	To compare the pre-operative staging accuracy of fast spin-echo (FSE) MRI used in conjunction with a transrectal surface coil with FSE MRI used in conjunction with a pelvic phased-array coil in cervical cancer pts.	Retrospective, consecutive patients.	28 pts had surgery. Mean age 44ys (Range 27-61). 34 pts had chemotherapy or radiotherapy. No age info available. 9 pts excluded as transrectal coil could not be inserted or optimally localised. Pts previously treated with conisation excluded. FIGO stages IB - 27pts IIA - 1pt	FSE MRI with transrectal (TRC) surface coil and FSE MRI with pelvic phased-array coil (PCC). 1.5T.	FSE-pelvic phased-array coil MRI performed on each case followed by FSE transrectal coil MRI. Images from each scan allocated into one of two sets of images. Each set of images was evaluated in random order by 3 authors who determined the stage of disease. The other set was evaluated 1 week later. A consensus decision was reached for all images without comparison with the other set. Authors were blinded to pathological stage and stage obtained from pelvic examinations.	<p><u>Surgical group</u></p> <p>TRC - 50 (88%) tumours detected. PCC - 44 (77%) tumours detected. <i>(P<0.05)</i></p> <p>Parametrial invasion -</p> <table border="1"> <thead> <tr> <th></th> <th>Sn</th> <th>Sp</th> <th>Acc</th> </tr> </thead> <tbody> <tr> <td>TRC</td> <td>100</td> <td>96</td> <td>96</td> </tr> <tr> <td>PCC</td> <td>100</td> <td>92</td> <td>93</td> </tr> <tr> <td>FIGO</td> <td>0</td> <td>100</td> <td>86</td> </tr> </tbody> </table>		Sn	Sp	Acc	TRC	100	96	96	PCC	100	92	93	FIGO	0	100	86		Pathological staging based on path report. 28pts - 57 tumours found.	Info on staging of non-surgical pts given but no 'gold standard'. Paper reports overall staging accuracies but it is unclear how these were calculated. Designation of stage to images where no lesion could be seen is not epidemiologically sound.														
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PCC	100	92	93																																						
FIGO	0	100	86																																						
(Lam et al. 2000)	38	Pts with disease confined to the cervix clinically (FIGO stage I)	To investigate the role of short tau inversion recovery (STIR) MRI in the detection of parametrial invasion.	Prospective, pts recruited between Dec 1995 and Jan 1998.	Mean age 46.4yrs (range 21-72). SCC - 27pts Adenocarc-11pts IB- 30pts IIA - 3pts IIB - 5pts	T1W TSE MRI, TSE T2 MRI, STIR MRI & T1W dynamic MRI. Imaging used 1.5T.	Images interpreted by 2 radiologists blinded to clinical staging, operative findings and histology results. Disagreement resolved by opinion of third reader.	<p>Detection of parametrial invasion -</p> <table border="1"> <thead> <tr> <th></th> <th>Sn</th> <th>Sp</th> <th>PPV</th> <th>NPV</th> <th>Acc</th> </tr> </thead> <tbody> <tr> <td>STIR</td> <td>90%</td> <td>94%</td> <td>69%</td> <td>98%</td> <td>93%</td> </tr> <tr> <td>T1WSE</td> <td>60%</td> <td>80%</td> <td>32%</td> <td>93%</td> <td>78%</td> </tr> <tr> <td>T2WTSE</td> <td>90%</td> <td>92%</td> <td>64%</td> <td>98%</td> <td>92%</td> </tr> <tr> <td>Dyn.</td> <td>90%</td> <td>80%</td> <td>41%</td> <td>98%</td> <td>82%</td> </tr> </tbody> </table>		Sn	Sp	PPV	NPV	Acc	STIR	90%	94%	69%	98%	93%	T1WSE	60%	80%	32%	93%	78%	T2WTSE	90%	92%	64%	98%	92%	Dyn.	90%	80%	41%	98%	82%		Histological findings from 76 hemipelvi. Parametrial invasion found in 10pts.	Hemipelvi not pts.
	Sn	Sp	PPV	NPV	Acc																																				
STIR	90%	94%	69%	98%	93%																																				
T1WSE	60%	80%	32%	93%	78%																																				
T2WTSE	90%	92%	64%	98%	92%																																				
Dyn.	90%	80%	41%	98%	82%																																				

Table 26 Cervical cancer (CC) data extraction - detection of parametrial and vaginal invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Ng et al. 1998)	54	Pts with biopsy proven CC.	To compare CT, MRI and histopathological findings in regard to parametrium and lymph node involvement.	Retrospective, between Jan 1995 and Dec 1997.	No ages given. FIGO stages – IB – 43pts IIA – 4pts IIB – 6pts ??? – 1pt	Type of MRI not given.	All scans interpreted prior to surgery. Surgeon aware of the results before proceeding with the operation. No further information given.	MRI only (25pts) <i>Evaluation of lymph nodes</i> Sn – 75% Sp – 82% PPV – 67% NPV – 88% Acc – 80% <i>Evaluation of parametrium</i> Sn – 100% Sp – 88% PPV – 82% NPV – 100% Acc – 92%	CT only (29pts) <i>Evaluation of lymph nodes</i> Sn – 33% Sp – 80% PPV – 43% NPV – 73% Acc – 66% <i>Evaluation of parametrium</i> Sn – 67% Sp – 70% PPV – 36% NPV – 89% Acc – 69%	Histopathological findings for all pts obtained during surgery.	Combined CT & MRI results are reported – PPV and NPV of 100% for parametrial invasion. 67% predictive rate for pelvic lymph nodes. Very little information on methods. Unsure of 1pt. <i>Values in italics calculated to facilitate comparison across studies</i>
(Postema et al. 2000)	103	Pts referred to hospital for treatment of primary invasive CC.	To compare MRI with pelvic examination (PE)(including general anaesthesia in selected patients) with regard to treatment planning to invasive cervical cancer. Also, to assess the accuracy and reproducibility of MRI for parametrial extension and involvement of the bladder.	Prospective, consecutive pts.	Mean age 49.5ys (range 26-79)	T2-weighted fast spin echo (FSE) MRI and T1-weighted MRI. Imaging used body coil & 1.5T.	All pts underwent pelvic examination by an experienced gynaecological oncologist during the initial outpatient visit. In 78 pts this was extended to EUA (performed with radiation oncologist). Treatment decisions were based on these examinations. MRIs read independently by two radiologists, blinded to pt identity, results of physical examination and surgico-pathological findings. MRI findings were not used to assign treatment.	MRI for extracervical tumour spread (ie RT) Obs 1; Sn – 89% Sp – 82% PPV – 55% NPV – 97% Acc – 84% Obs 2; Sn – 89% Sp – 64% PPV – 38 NPV – 96% Acc – 69% Bladder involvement – Obs 1; Sn-78%, Sp-97%, Acc – 95% Obs 2; Sn-67%, Sp-93%, Acc – 90% Parametrial invasion – Obs 1; Sn-20%,Sp-97%, Acc-92% Obs 2; Sn-60%, Sp-73%, Acc-72%	PE for extracervical tumour spread (ie RT) Sn – 44% Sp – 100% PPV – 100% NPV – 88% Acc – 89%	Surgico-pathological data obtained from 82 surgical pts & 9 RT pts (hydronephrosis and positive cystoscopy/urine cytology accepted as gold standard). 18 should have been assigned RT & 73 surgery.	Inter-observer variability in reading MRI was moderately high (kappa = 0.48). Authors report bias in that MRI interpretation was blinded while PEs were performed unblinded. This could lead underestimate the MRIs performance relative to PE. Parametrial invasion figures. – pts have disappeared??

Table 26 Cervical cancer (CC) data extraction - detection of parametrial and vaginal invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments																																																								
(Scheidler et al. 1998)	35	Pts with biopsy proven primary cervical cancer and a high likelihood that they would be treated by surgery.	To evaluate detection of parametrial invasion at MRI with fat suppression.	Prospective, consecutive pts recruited between Oct 1994 & March 1996.	Mean age 47.6yrs (range 26-71) Exclusions were contraindications to MRI & use of intravenous gadolinium chelates.	T1W SE(1), T1W gadolinium enhanced SE(2), T1W fat suppressed SE(3), T1W fat-suppressed gadolinium-enhanced SE(4), turbo STIR(5), T2W TSE(6) and combined readings (7). Imaging used pelvic phased-array coil & 1.5T.	Images interpreted by 2 radiologists unaware that pts had biopsy proven cervical cancer and blinded to clinical stage of disease. Discrepancies were resolved in conference with a third reader. All images were interpreted by a consensus of 2 radiologists in a second session.	Detection of parametrial invasion (based on the consensus reading) <table border="1"> <thead> <tr> <th></th> <th>n</th> <th>Sn</th> <th>Sp</th> <th>PPV</th> <th>NPV</th> <th>Acc</th> </tr> </thead> <tbody> <tr> <td>1*</td> <td>35</td> <td>100</td> <td>5</td> <td>38</td> <td>100</td> <td>40</td> </tr> <tr> <td>2*</td> <td>28</td> <td>85</td> <td>20</td> <td>48</td> <td>60</td> <td>50</td> </tr> <tr> <td>3*</td> <td>25</td> <td>100</td> <td>21</td> <td>50</td> <td>100</td> <td>56</td> </tr> <tr> <td>4</td> <td>30</td> <td>75</td> <td>78</td> <td>69</td> <td>82</td> <td>77</td> </tr> <tr> <td>5</td> <td>33</td> <td>85</td> <td>75</td> <td>69</td> <td>88</td> <td>79</td> </tr> <tr> <td>6</td> <td>35</td> <td>92</td> <td>73</td> <td>67</td> <td>94</td> <td>80</td> </tr> <tr> <td>7</td> <td>35</td> <td>92</td> <td>82</td> <td>75</td> <td>95</td> <td>86</td> </tr> </tbody> </table> NB. All readings are shown in percentage terms. *Significantly worse when compared to # 6 T2W turbo SE		n	Sn	Sp	PPV	NPV	Acc	1*	35	100	5	38	100	40	2*	28	85	20	48	60	50	3*	25	100	21	50	100	56	4	30	75	78	69	82	77	5	33	85	75	69	88	79	6	35	92	73	67	94	80	7	35	92	82	75	95	86		Histopathologic findings in all 35 pts. IA2 – 2pts IB1 – 11pts IB2 – 5pts IIA – 4pts IIB – 9pts IIIB – 2pts IV – 2pts Parametrial invasion in 13pts	
	n	Sn	Sp	PPV	NPV	Acc																																																													
1*	35	100	5	38	100	40																																																													
2*	28	85	20	48	60	50																																																													
3*	25	100	21	50	100	56																																																													
4	30	75	78	69	82	77																																																													
5	33	85	75	69	88	79																																																													
6	35	92	73	67	94	80																																																													
7	35	92	82	75	95	86																																																													
(Sheu et al. 2001)	31	Pts undergoing radical hysterectomy for CC.	To evaluate the diagnostic efficacy and pitfalls of MRI in pre-operative staging of cancer.	Prospective, pts recruited between Apr 1995 and Apr 1999.	Mean age 53.3yrs (range 32-72). Squamous cell carcinoma – 25pts Adenocarc – 6pts Clinical staging IA – 2pts IB – 18pts IIA – 11pts	Re- & post-contrast T1-weighted spin-echo (SE) MRI and T2-weighted fast spin-echo (FSE) MRI. Pelvic or torso phased-array coil & 1.5T.	MRIs reviewed independently by 2 radiologists without detailed clinical information other than diagnosis of cervical cancer. Decisions reached by consensus.	<u>MRI staging accuracy</u> Ia – 0% all overstaged Ib – 90% 2 overstaged IIa – 100%, IIb – 100% IVa – 100% Total acc – 83.8% Different ⁿ operable & non-operable disease Sn- 100%, Sp – 96% PPV – 86%, NPV – 100% Acc – 96.7 Parametrial Invasion- Sn – 100%, Sp – 96% PPV – 86%, NPV – 100%, Acc – 97% Vaginal invasion Sn – 75%, Sp – 88% PPV – 50%, NPV – 96% Acc – 87% Lymph adenopathy Sn – 71%, Sp – 92% PPV – 71%, NPV – 92% Acc – 87%	<u>Clinical staging acc</u> Ia – 66%, 1 overstaged Ib – 76%, 5 overstaged IIa – 100% IIb – 0% all understaged IVa – 0% all understaged Total acc – 61.3% Different ⁿ operable & non-operable disease Acc – 80.6%	Histopathologic findings. IA – 3pts IB – 21pts IIA – 1pt IIB – 5pts IVA – 1pt	<i>Values in italics calculated to facilitate comparison across studies</i>																																																								

Table 26 Cervical cancer (CC) data extraction - detection of parametrial and vaginal invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Shiraiwa et al. 1999)	50	Pts with invasive CC treated with surgery.	To investigate the efficacy of thin-section oblique axial T2-weighted MRI in assessment of parametrial invasion by CC.	Prospective, consecutive pts between Sept 1992 and Sept 1996.	Mean age 51.4yrs (range 25-81). IB – 17pts IIA – 2pts IIB – 31pts SCC – 35pts Adenocarcinoma – 14pts Adenosquamous cell carcinoma – 1pt	Axial T2W MRI and thin-section oblique axial T2W MRI. Imaging used body coil & 1.5T.	MRI findings analysed independently by 2 radiologists blinded to histological results. Kappa statistics were used to measure inter-observer variability. Determination of parametrial invasion was based on microscopic evaluation by pathologist.	Thin section oblique axial T2W MRI Sn – 67.9%, Sp – 97.2%, PPV – 90.5%, NPV – 88.6%, Acc – 89% Axial T2W MRI Sn – 46.4%, Sp – 91.7%, PPV – 68.4%, NPV – 81.5%, Acc – 79% There is a significant difference b/n Sn, Sp and Acc of axial T2W MRI and thin-section oblique T2W MRI.		Histological results on 100 parametria from 50pts.	
(Yu et al. 1998)	94	Histologically confirmed CC pts, prior to treatment.	To compare fast spin echo (FSE) T2-weighted MRI and pelvic phased-array coil to conventional spin echo (SE) T2-weighted MRI and body coil in the pre-treatment assessment of invasive CC.	Retrospective, consecutive pts between Jan 1989 and May 1996. Conventional T2 MRI was used Jan 1989 – Jan 1993 (62pts) and the FSE TR MRI was used Jan 1993 – May 1996(32 pts). Imaging used 1.5T.	Mean age 43yrs (Range 22-68) Pts at high risk of parametrial invasion after pre-treatment staging were excluded. First group -Squamous cell carcinoma : 42pts -Adenocarcinoma : 15pts -Adenosquamous cell carcinoma : 5pts Second group -Squamous cell carcinoma : 20pts -Adenocarcinoma : 10pts -Adenosquamous cell carcinoma : 2pts	FSE T2-weighted MRI used in conjunction with a pelvic phased-array coil & conventional SE T2-weighted MRI used in conjunction with a body coil. Imaging used 1.5T.	Results for MRI were summarized from official reports of all patients. Tumour size, presence of parametrial or vaginal invasion, presence of enlarged lymph nodes and stage all recorded. Missing data was collected by re-evaluation of the MRI by the attending radiologist who was blinded to the histological results.	FSE T2-weighted MRI (32pts) Staging Acc – 91% <u>Parametrial invasion</u> Sn – 100% (2/2pts) Sp – 93% (28/30pts) PPV – 50% (2/4pts) NPV – 100% (28/28pts) Acc – 94% <u>Vaginal Invasion</u> Sn – 50% (1/2pts) Sp – 97% (29/30pts) PPV – 50% (1/2pts) NPV – 97% (29/30pts) Acc – 94% <u>Lymph node metastasis</u> Sn – 67% (2/3pts) Sp – 93% (27/29pts) PPV – 50% (2/4pts) NPV – 96% (27/28pts) Acc – 91% <u>Tumour size</u> Acc – 93% (27/29pts)	CSE T2-weighted MRI (62pts) Staging Acc – 89% <u>Parametrial invasion</u> Sn – 100% (6/6pts) Sp – 95% (53/56pts) PPV – 67% (6/9pts) NPV – 100%(53/53pts) Acc – 95% <u>Vaginal Invasion</u> Sn – 33% (1/3pts) Sp – 97% (57/59pts) PPV – 33% (1/3pts) NPV – 97% (57/59pts) Acc – 94% <u>Lymph node metastasis</u> Sn – 64% (7/11ts) Sp – 90% (46/51pts) PPV – 58% (7/12pts) NPV – 92% (46/50pts) Acc – 85% <u>Tumour size</u> Acc – 92% (57/62pts)	Histopathological results obtained from official pathology reports of 94 pts, without knowledge of the MRI results. Incomplete data was collected by re-evaluation of slides by the attending pathologist	Statistical difference in tumour size between the two groups with FSE T2 size being 0.97±1.0cm and CSE T2 size being 1.93±1.1cm. No other statistical differences. Authors concluded that both methods gave similar diagnostic information and that although FSE improved image resolution and reduced imaging time it didn't improve staging.

Table 27 Cervical cancer data extraction – radiotherapy field planning

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Thomas et al. 1997) Radiotherapy (RT) planning.	18	Pts with invasive cervical carcinoma prior to treatment, no clinical involvement of the uterosacral ligaments and a tumour for which RT has been decided as the treatment option.	To evaluate MRI in the RT treatment planning of tumours of the cervix treated with a four-field technique.	Prospective pts b/n May 1994 & Feb 1995.	Group 1 (11pts) mean age 54yrs (range 35-82). Group 2 (7pts) mean age 45yrs (range 30-67). -Squamous cell carcinoma : 13pts -Adenocarcinoma : 4pts -Undifferentiated carcinoma : 1pt	Diagnostic MRI – T1W & T2W MRI with phased-array coil. Treatment planning – T2W TSE MRI with a body coil. Imaging used 1.0T.	Adequacy of the simulated variation ports was evaluated by correlation of radiologic simulation data to the treatment planning MRI. The evaluation was performed by two radiation oncologists.	Group 1 – treatment planning MRI led to adjustments in the radiation fields in 7/11 pts (63%). Lateral field <u>Anterior field</u> Anterior border Posterior border ↑25mm ↑10mm ↑7.5mm ↑10mm ↑21mm ↑10mm ↑10mm ↓15mm ↑15mm ↑10mm Group 2 – treatment-planning MRI led to adjustments in the radiation fields in 5/7 pts (71%). <u>Anterior border</u> Posterior border ↑10mm ↑10mm ↑10mm ↑10mm ↑10mm ↓5mm	Standard radiologic simulation.	No pt follow-up.	

Table 28 Cervical cancer (CC) data extraction - response to treatment and microcirculation assessment

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Mayr et al. 1997)	43	Pts treated with radiotherapy (RT) for cervical cancer (CC).	To compare the accuracy of MRI and PE in predicting outcome in CC treated with primary RT and to correlate MRI-derived tumour size measurements with those obtained by PE using the same pt population.	Prospective, pts between 1992 and 1995.	Mean age 52yrs (range 25-89). SCC – 38pts Adenocarcinoma – 5pts FIGO stages – IB – 4pts IB2 – 4pts IIB – 9pts IIIA – 1pt IIIB – 19pts IVA – 3pts IVB – 1pts Recurrent – 2pts	T1 & T2-weighted MRI. Imaging used 1.5T.	MRIs performed at the beginning of radiotherapy, at 20-24 Gy, at 40-50 Gy and at follow-up 1-2 months after radiotherapy. Pelvic examinations (PE) were performed in the same sequence.	Correlation of MRI volumes & PE volumes was low ($r=0.58$) Prediction of local failure based on initial tumour volume measurement was significant ($p=0.018$) Incidence of local failure based on regression rate (rapid vs slow) during and after radiotherapy was significant. 20-24 Gy – $p=0.004$ 40-50 Gy – $p<0.0001$ 1-2 months follow-up – $p=0.007$ Prediction of disease free survival (DFS) was significant ($p=0.0015$). Prediction of DFS based on tumour regression rate at follow-up was significant ($p=0.007$).	<u>Pelvic examination</u> Prediction of local failure based on initial tumour size measurement was not significant in any PE criterion (volume, average diameter, maximum diameter). Incidence of local failure based on regression rate (rapid vs slow) during and after radiotherapy was not significant at 20-24 Gy or 40-50 Gy. It was significant at 1-2 months follow-up ($p=0.012$). Predict [†] of DFS was not significant. Predict [†] of DFS based on tumour regression rate at follow-up was significant ($p=0.015$)	Clinical follow-up ranging from 12 to 60 months. Endpoint was DFS.	Paper does not give the numbers of pts who died or had recurrence within the clinical follow-up period.

Table 28 Cervical cancer (CC) data extraction - response to treatment and microcirculation assessment (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Mayr et al. 1998)	20	Pts with bulky carcinomas of the cervix	To assess the effectiveness of combining morphologic and microcirculatory MRI derived information to predict tumour control in pts treated with conventional radiotherapy.	Prospective.	Mean age 52yrs (range 25-89) IB – 2 IIB – 6 IIIA – 1 IIIB – 9 IVA – 1 Recurrent – 1 Squamous cell carcinoma – 12pts Adenocarcinoma – 3pts	T1-weighted fast spin echo (FSE) MRI & +T2-weighted FSE MRI and dynamic T1-weighted FSE MRI Imaging used body coil & 1.5T.	MRIs taken immediately before RT and at 20-22 Gy.	Incidence of TLR* as function of tumour volume & TDEP† <u>Pre-therapy</u> Low TDEP High TDEP S 0% 0% I 80% 0% L 50% 100% <u>Early Therapy</u> Low TDEP High TDEP S 0% 0% I 80%† 0%† L 75% 0% †P = 0.10 (b/n low & high TDEP groups)	Incidence of TLR as function of tumour volume Small – 0% Intermediate – 33% Large – 60% Mean – 35% Incidence of TLR as function of TDEP <u>Pre-therapy</u> Low TDEP – 55% High TDEP – 11% <u>Early therapy</u> Low TDEP – 64% High TDEP – 0% P=0.005)	Clinical follow-up for an average 25 months (range 11-35months). 7 pts had local tumour recurrence (1° endpoint).	Small tumour (S) < 40cm ³ Intermediate tumour (I) = 40-99 cm ³ Large tumour (L) ≥ 100 cm ³ *TLR - tumour local recurrence †TDEP - tumour dynamic enhancement pattern
(Mayr et al. 2000)	19	Pts with advanced cervical cancer.	To assess the heterogeneity of dynamic enhancement patterns in cervical cancer pts at the time of therapy and its prognostic value for ultimate treatment outcome using pixel-by-pixel analysis of the enhancement pattern.	Prospective, between Nov 1993 & Nov 1995.	Mean age 53yrs (range 25-85). Pts who died within 2 years of treatment completion excluded from analysis. IB2 – 2pts IIB – 5pts IIIB – 7pts IVA/recurrent – 2pts	Dynamic contrast enhanced imaging.	Pixel-by-pixel statistical analysis of the ratio of post- to pre-contrast relative signal intensity (RSI). Pixel histogram analysed in terms of number of pixels, mean RSI, median RSI, variance, standard deviation, kurtosis of distribution of RSI values & RSI percentiles in increments of 10% to quantitate the degree & proportion of lowest enhancement within the tumour region.	The 10 th percentile RSI value was most significant imaging predictor of recurrence (p=0.00001). Recurrence rate amongst pts with a 10 th percentile RSI of <2.5 was 88%. It was 0% in pts with 10 th percentile RSI value of >2.5 (p=0.0004). Mean RSI was a significant predictor of recurrence (p = 0.0001) Median RSI was a significant predictor of recurrence (p=0.0001) Pixel number was a significant indicator of recurrence (p=0.05) Combination of 10 th percentile RSI and pixel number improved prediction rate. This combination correctly classified all pts into groups with and without recurrence.	Clinical followup for a median period of 4.6yrs (range 3.8-5.2 yrs). 7 pts had recurrence.		

Table 28 Cervical cancer (CC) data extraction - response to treatment and microcirculation assessment (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	MRI type(s)	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Hawighorst et al. 1997)	55	Pts with histopathologically proven primary or recurrent CC	To examine the relationship between contrast-enhanced dynamic MRI characteristics and histological microvessel (MVD) density counts (angiogenesis surrogate) in cervical cancer & to correlate these parameters with lymphatic involvement to characterise tumour aggressiveness in terms of lymphatic spread.	Prospective, pts recruited between Dec 1993 and Nov 1996	Mean age 50yrs (range 25-72) 42 pts with primary cervical cancer & 13 with recurrent cervical cancer. Exclusions were claustrophobia, extensive pelvic sidewall infiltration, and artefacts caused by patient movement, which precluded data analysis.	FLASH (fast low angle shot) MRI, T2-weighted TSE MRI, T1-weighted SE MRI & SRTF MRI. Imaging used a body coil (16pts), a pelvic surface coil (24 pts) or a four-element body phased-array coil (15pts) & 1.5T.	Pharmokinetic parameters were calculated from a contrast-enhanced dynamic MRI series. A & k_{21} were determined by least-squares fitting of the measured data and a colour coding scheme was applied to aid visual interpretation. No information as to who or how many people interpreted MRIs and whether interpretation was blinded.	<u>Mean histological microvessel density</u> No lymphatic system involve ^d – 19±10 vessels Lymphatic system involve ^d – 28±9 vessels ($P<0.05$) <u>Mean exchange rate constant k_{21}</u> No lymphatic system involve ^d – 2.1±1.0min ⁻¹ Lymphatic system involve ^d – 6.9±7.0min ⁻¹ ($P<0.001$) <u>Amplitude A</u> No lymphatic system involve ^d – 1.5±0.4 Lymphatic system involve ^d – 1.7±0.5 ($P=0.12$) <u>Detect^d lymphatic involve^d</u> With threshold microvessel density of 27 Sn – 55%, Sp – 85%, PPV – 92%, NPV – 37%, Acc – 62% With k_{21} threshold of 2.4min ⁻¹ Sn – 76%, Sp – 77%, PPV – 91%, NPV – 50%, Acc – 76% <i>Difference b/n Sn & Acc of each method is significant ($P<0.05$)</i>	Histopathological & immunohistochemical specimens.	Discrepancy between my addition of raw data & MVD taken from Sn & Sp analyses. <i>Values in italics calculated to facilitate comparison across studies.</i>	
(Hawighorst et al. 1998b)	57	Pts with biopsy proven primary or recurrent cervical cancer.	To examine the relationship between functional MRI-based parameters with recognised histomorphological markers of tumour angiogenesis (HMVD [†] & VEGF [‡]) & to determine the ultimate value of both approaches to assess functional angiogenic active hotspots as markers of disease outcome in pts.		Mean age 49yrs 45 pts with primary cervical cancer & 12 with recurrent cervical cancer.	T2-weighted FSE MRI, T1-weighted SRTF MRI, pre- & post-contrast T1-weighted SE MRI. Imaging used 1.5T.	Pharmokinetic parameters were calculated from a contrast-enhanced dynamic MRI series. A & k_{21} were determined by least-squares fitting of the measured data and a colour coding scheme was applied to aid visual interpretation. No information as to who or how many people interpreted MRIs and whether interpretation was blinded.	There was an inverse association b/n VEGF expression & HMVD, ie areas of high VEGF expression were associated with low HMVD, and those with low VEGF expression had a high HMVD. ($P<0.01$) A significant association was found between HMVD and amplitude A ($P<0.001$) and between HMVD and k_{21} ($P<0.05$). No significant association was found between A or k_{21} and VEGF. When k_{21} was stratified into low & high median groups, median k_{21} values > 5.4min ⁻¹ was the only significant predictor of poor pt survival ($P < 0.05$). HMVD & VEGF expression were not significant predictors of poor pt survival.	Histopathological & immunohistochemical specimens. Follow-up for a median 24months (range 3-39months). 23 pts died from relapsed disease.	† Histological microvessel density ‡ Vascular endothelial growth factor expression	

Table 29 Endometrial cancer (EC) data extraction – Diagnostic accuracy of MRI compared with other conventional procedures

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(La Fianza et al. 2000)	80	Pts with clinical stage I endometrial adenocarcinoma confirmed with histopathology from curettage or endometrial sampling.	To investigate whether pre-operative prognostic factors such as tumour histotype and grading and grade of myometrial invasion compare with post-operative histopathology, and whether the utilisation of these pre-operative prognostic factors to allocate pts to different treatment groups affects outcomes	<p>Prospective Case-series, ?consecutive</p> <p>Inclusion and exclusion criteria was not explicit.</p> <p>Pts were recruited March 1992- Dec 1996</p> <p>According to the results of pre-operative tests pts. were allocated into either:</p> <p>-group A (n=26): low risk G1-G2, pure adenocarcinoma, MO-M1</p> <p>-group B (n=54): high risk all G3 pure adenocarcinoma and/or M2 and /or clear cell, serous papillary, adenosquamous carcinomas</p> <p>-each group received different surgery, and group B received adjuvant chemotherapy/ irradiation</p> <p>Followed for 36 months (median: 61 months). No. of loss to follow-up were reported, incl. reason</p> <p>MRI TYPE 1.5T magnet</p> <p>T1W MRI T2W MRI CE-T1W with IV .2mL/kg of Gd-DTPA</p> <p>The paper implies that a combination of sequences were used</p>	<p>No info on age or menopausal status of pt.</p> <p>Post operative path staging FIGO: IA : 4 IB : 38 IC : 26 IIB : 4 IIIC : 8</p>	<p>No information is provided as to how the scans were interpreted, who by, or whether blinding to other pre/post-op information occurred.</p> <p>The paper reports that established MRI criteria were used to assess myometrial invasion of EC.</p> <p>Myometrial classification: (This is very unclear)</p> <p>MO: no myometrial invasion</p> <p>M1:<50% myometrial invasion</p> <p>M2:>50% myometrial invasion</p>	<p>MRI accuracy 72/80 = 90% reported (Unsure if this is MRI accuracy, or paper is reported 72/80 had pathological confirmation).</p> <p>Results of follow-up:</p> <p>Low risk group: -24/26 had no evidence of disease (2 died from breast cancer).</p> <p>High risk group: -36/54 no evidence of disease, 12 died from other disease, 6 died from EC.</p>	<p>Tumour histotype Acc. 100% reported</p> <p>Tumour grading Acc: 72/80 = 90% reported (Again, unsure if this is the correct interpretation).</p>	<p>Post-operative histopathological evaluation: macroscopic and confirmed microscopically</p> <p>No information on how this was done, who by, or whether blinding occurred</p>	<p>Difficult to tease out data on each prognostic factor (Tumour grade, tumour histotype, myometrial invasion, to calc. Sn, Sp, etc)</p> <p>Paper generally difficult to interpret</p> <p>General summary reported:</p> <p>Prognostic factors for EC clinical stage 1 can be reliable assessed pre-operatively.</p>

Table 29 Endometrial cancer (EC) data extraction – Diagnostic accuracy of MRI compared with other conventional procedures (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Schneider et al. 1999)	100	Pts with endometrial carcinoma.	To compare CA-125, CA 19-9 and MRI alone and then combined to detect myometrial invasion of EC	Prospective is implied Consecutive Case-series b/w Jan 1992-Dec 1996 All pts underwent surgical staging, although only 18 underwent lymphadenectomy NMR and cytology assessments were reported to be conducted at the same time Does not report the time b/w pre-op assessments and surgery Does not report type of MRI sequence	FIGO post-surgical classification: IA : 13 IB : 42 IC : 31 IIA : 6 IIB : 3 IIIA : 3 IIIC : 2 Presurgical histologic diagnosis: -93 endometrioid adenocarcinoma -3 papillary serous -3 adenosquamous carcinoma -1 clear cell carcinoma	One radiologist performed the scans and interpreted them. ?blinded to other clinical findings Assume that the radiologist was blinded to the post-op results b/c MRI interpretation undertaken prior to surgery. Scan interpretation criteria not given MRI and cytology classification: -positive (stage IC or greater) -negative (stage IA or IB)	MRI results for detecting stage IC or higher: Sn: 73% Sp: 89% PPV:85% NPV: 80% Acc: (82/100) 82% (results checked) Combined results were also reported	Cytology results for detecting stage IC or higher: Sn: 58% Sp: 87% PPV:79% NPV: 72% Acc: (74/100) 74% (results checked)	Post-op histopathology by hospital's institutional laboratory according to uniform standards ? no. of pathologists, ?blinded.	Main summary: The authors report that the predictive value is not sufficiently high enough (alone or combined) to use these pre-op procedures for staging of EC. <i>Results in italics calculated to facilitate comparison across</i>
(Shen et al. 1999)	73	Untreated pts with pathologically confirmed diagnosis of endometrial carcinoma Referred from other hospitals to Ryukyu University Hospital, Okinawa, Japan	To compare MRI and hysteroscopy to detect myometrial invasion.	Prospective Case-series ?consecutive No inclusion or exclusion criteria PT recruited Jan 1994- Dec 1997 All pts underwent hysteroscopy as well as endometrial and endocervical biopsies. MRI performed 2 weeks before surgery MRI TYPES: 1994-1996 (n=45) 0.5 T SE-T1W Fast SE-T2W CE T1W (with 0.1 mmol/kg IV meglumin gadopentetate) From 1997 (n=28) 1.5T T1W T2W CE-T1W	Mean age 56yrs (range: 24-81yrs) 25 premenopausal 48 postmenopausal Post-surgical FIGO stages: IA : 21 IB : 20 IC : 5 II : 7 III : 18 IV : 2 Histological findings: 67 endometrioid adenocarcinoma 3 adenosquamous carcinoma 2 serous adenocarcinoma 1 clear cell adenocarcinoma Tumour grade: 56 - G1 10 - G2 7 - G3	Scans interpreted (?independently, ?in consensus) pre-operatively (assume readers were blinded to post-op results) ? Blinding to hysteroscopy or other results MRI classification criteria reported. Classified: -negative or positive -if positive: superficial (=50%) deep (>50) The paper reports the hysteroscopy procedure, and diagnostic criteria according to image presentation. -? No. of readers, ?blinding not reported	MRI results to detect no myometrial invasion from any (superficial or deep) invasion: (n=73) Sn: 82%# Sp: 100%# PPV: 100% NPV: 72% Acc: (64/73) 88%* #not significantly different to hysteroscopy (p<0.05) (Checked results) <i>Overall accuracy to detect extent of myometrial invasion</i> Acc: (59/67) 81% <i>MRI results to detect deep myometrial invasion from superficial or deep (n=73)</i> Sn:96% Sp: 90% PPV: 81% NPV: 98% Acc: (67/73) 92%	Hysteroscopy results to detect no myometrial invasion from any (superficial or deep) invasion: (n=73) Sn: 80% Sp: 96% PPV: 98% NPV: 69% Acc: (62/73) 85%* (Checked results) <i>Hysteroscopy results to detect deep myometrial invasion from superficial or deep (n=73)</i> <i>Insufficient data to calculate</i>	Post-op histopathology. ?no. of pathologist, ?blinding to previous reports	The paper also looked at MRI combined with hysteroscopy to detect presence of myometrial invasion. Combined tests were statistically more Sn (p=0.025, p=0.014) compared with individual MRI and hysteroscopy respectively. Main summary: Hysteroscopy better at detecting minimal invasion, MRI better at assessing depth Sp was not significantly different among the three groups. <i>data in italics calculated to facilitate comparison among studies</i>

Table 29 Endometrial cancer (EC) data extraction – Diagnostic accuracy of MRI compared with other conventional procedures (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Tsuda et al. 1997)	20	Pts with endometrial disorders	To compare intrauterine sonography (IUS) with MRI to detect depth of myometrial invasion by EC	? direction not explicit ? possible prospective case-series (?consecutive) inclusion/exclusion criteria not reported MRI and IUS performed 4 days prior to surgery Types of surgery are described for all 20 pts MRI TYPE: 1.0-T system SE-T1W SE-T2W It is not clear if all pts underwent all MRI sequences, assume best MRI sequence used to diagnose.	Mean age: 57.9 (range: 37-81) FIGO staging: (n=17 EC) 4 IA 9 IB 2 IC 2 IIIC (n=3) atypical hyperplasia	Experienced radiologists: -? interpretation in consensus or independently -blinding to the IUS results only Myometrial invasion was graded according to previously published MRI criteria Classification myometrial invasion: -No invasion -superficial (50%) -deep (>50%) IUS was performed by a gynaecologist who was blinded to MRI findings	MRI accuracy to detect extent of myometrial invasion. (17/20) 85%. (checked result) <i>MRI detecting deep myometrial invasion from superficial and no invasion</i> Sn: 100% Sp: 94% PPV: 67% NPV: 100% Acc: (19/20) 95%	IUS accuracy to detect extent of myometrial invasion. (17/20) 85%* *authors reported (18/20) 90% <i>calculation from raw data provided within the paper was not concordant with authors' report.</i> <i>IUS detecting deep myometrial invasion from superficial and no invasion</i> Sn: 50% Sp: 94% PPV: 50% NPV: 94% Acc: (18/20) 90%	Post-op histopathology Paper reports that the pathologist was blinded to the MRI and IUS results	Main summary: MRI and IUS imaging may be complimentary. Need further studies <i>Results in italics calculated to facilitate comparison across studies</i>

Table 29 Endometrial cancer (EC) data extraction – Diagnostic accuracy of MRI compared with other conventional procedures (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments																																																
(Zarbo et al. 2000)	33	Pts. with endometrial carcinoma diagnosed by histopathological examination of tissue removed by hysteroscopically controlled biopsy or curettage of uterine cavity	To compare MRI with transvaginal ultrasonography (TVUS) to detect myometrial invasion.	<p>Direction not reported Case-series,?consecutive Pts recruited b/w Jan 1996- Dec 1998</p> <p>Enrolled (n=33) but only examined with MRI and TVUS (n=30) -3 were reported to decline from MRI due to claustrophobia -Therefore MRI results calculated for n=30, and TVUS results are calculated for n=33</p> <p>TVUS and MRI took place a few days before surgery All pts underwent surgery</p> <p>MRI TYPES: T1W and T2W MRI after gadolinium administration</p>	<p>Mean age 65 yrs (range: 48-88 yrs)</p> <p>FIGO staging: IA : 4 IB : 14 IC : 10 IIA : 2 IIIA : 1 IIIC : 2</p> <p>Histotypes: 24 endometrioid 4 adenoacanthoma 4 papillary serous 1 adenosquamous</p> <p>Grading: 3 - G1 28 - G2 2 - G3</p>	<p>Report provides no info on who evaluated the MRI and TVUS results, whether one or more persons,?blinded.</p> <p>Criteria is described for the classification of myometrial invasion with regards to the TVUS and MRI techniques.</p> <p>Pts were divided into 3 groups: -M0 absence of infiltration -M1 infiltration <50% -M2 infiltration >50%</p>	<p>MRI results for detection of extent of myometrial invasion: (%) from paper Authors reported values</p> <table border="1"> <thead> <tr> <th></th> <th>M0</th> <th>M1</th> <th>M2</th> </tr> </thead> <tbody> <tr> <td>Sn</td> <td>50</td> <td>77</td> <td>67</td> </tr> <tr> <td>Sp</td> <td>96</td> <td>62</td> <td>86</td> </tr> <tr> <td>PPV</td> <td>60</td> <td>73</td> <td>67</td> </tr> <tr> <td>NPV</td> <td>94</td> <td>64</td> <td>86</td> </tr> <tr> <td>Acc#</td> <td colspan="3">70</td> </tr> </tbody> </table> <p># acc (21/30) is for overall concordance of MRI with histopathology</p> <p>Checked results – some discrepancies with my calculations for M1 & M2.</p> <p>Discrepancy b/w tables 5a & 6a and values reported in body of text for the number of overestimates/ underestimates for both MRI and TVUS.</p> <p><i>MRI accuracy for detecting deep myometrial invasion from superficial or no invasion.</i></p> <p><i>Acc: (24/30) 80%</i></p>		M0	M1	M2	Sn	50	77	67	Sp	96	62	86	PPV	60	73	67	NPV	94	64	86	Acc#	70			<p>TVUS results for detection of extent of myometrial invasion: (%) from paper Authors reported values</p> <table border="1"> <thead> <tr> <th></th> <th>M0</th> <th>M1</th> <th>M2</th> </tr> </thead> <tbody> <tr> <td>Sn</td> <td>75</td> <td>83</td> <td>91</td> </tr> <tr> <td>Sp</td> <td>97</td> <td>87</td> <td>91</td> </tr> <tr> <td>PPV</td> <td>75</td> <td>88</td> <td>85</td> </tr> <tr> <td>NPV</td> <td>97</td> <td>83</td> <td>95</td> </tr> <tr> <td>Acc#</td> <td colspan="3">85</td> </tr> </tbody> </table> <p># acc (28/33) is for overall concordance of TVUS with histopathology</p> <p>Checked results based on raw data presented in the paper – some discrepancies</p> <p><i>TVUS results to detect deep myometrial invasion from superficial or none:</i> <i>Sn: 91%</i> <i>Sp:91%</i> <i>PPV: 83%</i> <i>NPV: 95%</i> <i>Acc: (30/33) 91%</i></p>		M0	M1	M2	Sn	75	83	91	Sp	97	87	91	PPV	75	88	85	NPV	97	83	95	Acc#	85			<p>Post-surgery, histopathology. ? no. pathologists, ?blinding</p>	<p>Main outcome reported: MRI lower sensitivity and specificity index ; it is a valid method if the cervical canal is involved and/or myometrial invasion is >50% and if lymphatic invasion has to be investigated.</p> <p>*M0: results to detect no myometrial invasion from any myometrial invasion (superficial or deep).</p> <p>M1: results to detect superficial myometrial invasion from none or deep.</p> <p>M2: results to detect deep myometrial invasion from superficial or none.</p>
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Table 29 Endometrial cancer (EC) data extraction – Diagnostic accuracy of MRI compared with other conventional procedures (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Kietlinska et al. 1998)	117	Pts with EC who were operated on in the department of Obstetrics and Gynaecology, Warsaw Scholl of Medicine, Warsaw, Poland.	To evaluate the accuracy of pre-operative diagnostic methods (fractional curettage (FS), hysteroscopy (HS), transvaginal ultrasonography (TVUS), MRI and computer tomography (CT)) used to identify cervical involvement in cases with endometrial carcinoma (EC)	Assume retrospective Case-series, 2consecutive Pts recruited b/w Jan 1991 – Dec 1997 ?inclusion/exclusion criteria Of the 117 surgical pts (i.e. all pts underwent surgery) recruited into the study, diff. proportions of these cases underwent one or more of the tests. FC: n=112 HS: n=38 TVUS: n=45 MRI: n=25 CT: n=10 The paper doesn't report the case mix within each diagnostic test. The paper does not report the time b/w the diagnostic tests and the surgery MRI TYPE 1.5-T magnet T1W-& T2W related with Gd-DTPA contrast	Mean age not provided (n=53) abdominal hysterectomy and bilateral salpingo-oophorectomy (n=64) abdominal hysterectomy and bilateral salpingo-oophorectomy and pelvic lymphadenectomy No info provided on FIGO, histopathologic or grade of EC	No info is provided as to who and how the tests were conducted or interpreted, ?independently, ?blinded to other results Each test aimed to detect cervical invasion of the EC	Results for detecting cervical invasion from no cervical invasion of EC: <u>MRI:</u> Sn: 75% Sp:86% PPV:50% NPV:95% Acc:(21/25) 84% (checked results) Multiple student t tests with statistical significance level at $p<0.05$, were used to compare the Sn, Sp, PPV, NPV and acc results b/w pairs of the diagnostic tests. NB: MRI was reported to have similar or higher Sn, Sp, PPV, NPV, & Acc. scores compared with TVS however the difference. was not reported to be statistically significant.	<u>Fractional curettage:</u> Sn:88% Sp:44% (authors result) Sp:56%* PPV:15% NPV:98% Acc: (66/112) 59% <i>inconsistent calculations, my calculation included</i> <u>Hysteroscopy:</u> Sn:33% Sp:69% PPV:8.3% NPV:92% Acc:(25/38) 66% (checked results) <u>Transvaginal Ultrasound:</u> Sn:75% Sp:78% PPV:25% NPV:97% Acc:(35/45) 78% (checked results) Note: CT scan results were excluded from the final result b/c of difficulty using the test to detect cervical invasion.	Post-operative histopathological examination ? no. of pathologists, ? blinded to other test results.	Main summary reported: (i) High NPV for all test allows exclusion of cervical invasion by EC when a negative result occurs. (ii) PPV values were generally low, therefore none of the tests are reliable enough to recognise cervical invasion by EC (iii) Recommends TVS to assess cervical invasion by EC b/c of its high diagnostic value and cost effectiveness <i>Statistical analysis is questionable</i>

Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Toki et al. 1998)	64 38	Pts with primary endometrial carcinoma (EC) treated by surgery at the department of Gynecology, Shinshu Hospital, Matsumoto, Japan.	To compare the accuracy of different diagnostic procedures to detect cervical involvement of EC. Techniques compared: - cytology - endocervical curettage - transvaginal ultra-sonography - hysteroscopy - MRI - serum CA-125 levels	Retrospective consecutive case series Pts recruited b/w: Jan 1991- August 1996 n=38 pts who underwent all procedures sample size for each pre-op procedure is listed with results Order of pre-op procedures: -cervical cytology & TVUS -MRI (2 weeks before surgery) -hysteroscopy -endocervical and endometrial curettage -serum CA-125 levels within 2 weeks hysteroscopy MRI TYPE: "MRI usually without gadolinium enhancement" (This is all the information provided by the paper).	Mean age 56yrs (Range 29-79yrs) 25 premenopausal 39 postmenopausal FIGO staging post-op: stage I : 42 stage II : 6 stage III : 13 stage IV : 3 Histological diagnosis: 61 endometrioid adenocarcinoma, incl. those with the squamous component - grade 1 : 40 - grade 2 : 12 - grade 3 : 9 2 clear cell carcinoma 1 serous adenocarcinoma	? who interpreted the results, ?independent assessment -? blinded to the outcome of the hysterectomy/ other diagnostic tests Reports diagnostic criteria of each test for cervical invasion. Results using 38 cases with complete data of all six tests were reported to be compatible with those using all the cases, although results for n=38 not provided.	Results for detecting cervical invasion from no cervical invasion of EC: <u>MRI (n=61)</u> Sn 75% Sp: 94% PPV: 75% NPV: 94% Acc: (55/61) 90%* Frank stromal invasion was diagnosed correctly in all 8 pts (All results checked for MRI and comparators)	<u>Cytology: (n=64)</u> Sn: 83% Sp: 77% PPV: 45% NPV: 95% Acc: (50/64) 78% <u>ECC: (n=46)</u> Sn: 91% Sp: 66% PPV: 44% (authors result) PPV: 45% NPV: 96% Acc: (33/46) 71% <u>TVUS (n=56)</u> Sn: 50% Sp: 93% PPV: 63% NPV: 90% Acc: (48/56) 86% <u>HS (n=69)</u> Sensitivity: 82% specificity: 90% PPV: 64% NPV: 96% Acc: (53/60) 88% <u>CA-125 (n=64)</u> Sensitivity: 42% specificity: 73% PPV: 26% NPV: 84% Acc: (43/64) 67%	Post-operative histopathology In 64 pts, 12 confirmed cervical invasion	Endocervical curettage and hysteroscopy are better diagnostic procedures for excluding cervical involvement by EC. MRI and hysteroscopy are better procedures for making a positive diagnosis of cervical involvement. <i>Value in italics calculated from raw data provided in the paper</i>

Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Joja et al. 1999)	28	Pts. with primary untreated EC who were referred for MR imaging following histologic diagnosis of EC	To compare multisection dynamic MRI using a 3D FLASH technique during breath holding with T2W and CE-T1W MRI to detect myometrial invasion of EC.	Prospective Consecutive case-series No time frame reported for recruitment of participants MRI conducted within 7 days prior to surgery All pts underwent surgery: hysterectomy and pelvic lymph node sampling or resection MRI TYPE: 1.5-T magnet with a body coil -SE or turbo SE-T2W -Dynamic MR using 3D-FLASH technique with breath holding -CE SE-T1WI (0.1 mmol/kg IV Gd-DTPA)	Mean age 56.7 years (range: 33-77 yrs) 6 premenopausal 22 postmenopausal Post-op FIGO criteria: 6 IA 6 IB 2 IC 2 IIA 1 IIB 9 IIIA 2 IIIC Pathologic diagnosis: Adenocarcinoma, endometrial -9 grade 1 -10 grade 2 -5 grade 3 2 adenosquamous carcinoma 1 adenoacanthoma 1 clear cell carcinoma	Scans read independently by 2 radiologist, any discrepancies resolved by discussion, blinded to the histologic results, ?blinded to other clinical findings Previously published criteria used to evaluate MRI scans. The paper also reports the criteria for invasion used for the dynamic sequence. Myometrial invasion was classified as: -absent (limited to the endometrium) -superficial (<50% of the myometrium) -deep (>50% of myometrium) Cochran's Q-test was used to compare accuracy rates in the evaluation of myometrial invasion of the 3 sequences	Overall accuracy results to detect extent of myometrial invasion: <u>Dynamic:</u> Acc: (24/28) 86% Overestimated (1/28) Underestimated (3/28) Significant differences b/w: - T2W1 and dynamic ($p=0.014$) - Dynamic and CE T1W1 ($p=0.025$) - Not T2W1 and CE-T1W1 <i>Results to detect deep myometrial invasion from superficial and none:</i> <u>Dynamic:</u> Sn: 100% Sp: 96% PPV: 83% NPV: 100% Acc: (27/28) 96%	Overall accuracy results to detect extent of myometrial invasion: <u>T2W:</u> Acc: (18/28) 64% Overestimated (2/28) Underestimated (8/28) <u>CE-T1W:</u> Acc: (19/28) 68% Overestimated (1/28) Underestimated (8/28) <i>Results to detect deep myometrial invasion from superficial and none:</i> <u>T2W:</u> Sn: 100% Sp: 78% PPV: 100% NPV: 78% Acc: (23/28) 82% <u>CE-T1W:</u> Sn: 100% Sp: 78% PPV: 50% NPV: 100% Acc: (23/28) 82%	Post-op histopathology ?No. of pathologist, ?blinding	Main summary: Multi-section dynamic MRI using the 3D FLASH tech. during breath holding is useful for the evaluation of myometrial invasion by endometrial carcinoma with polypoid growth or unclear junctional zone on T2W. <i>Calculations in italics to facilitate comparison across studies</i>

Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Lee et al. 1999)	46	Pts with primary (FIGO stage I) untreated carcinoma after histologic diagnosis on the basis of fractional dilation and curettage Hospital based	(i) To compare T2W MRI and gadolinium-enhanced T1W MRI in the detection of depth of myometrial invasion of EC. (ii) Evaluate the usefulness of T2W and CE-T1W MRI correlated with pts menopausal status in detecting depth of myometrial invasion of EC	Retrospective Consecutive case-series Pts recruited: May1993-June1997 MRI conducted av. 10day (range:1-25) after curettage Surgery conducted within one week of MRI MRI TYPE: 1.5-T magnet body coil T2W (n=22, T2W) (n=24, fast SE T2W) 0.1 mmol/kg IV gadolinium-enhanced T1W	Mean age: 46 yrs (range: 26-74 yrs) FIGO classification: Premenopausal (n=25) IA: 10 IB: 14 IC: 1 Postmenopausal (n=21) IA: 3 IB: 11 IC: 7	Scans read by two readers in consensus retrospectively Blinded to histopathologic results and menopausal status of pts. MRI sequences were interpreted independent of the other sequence MRI criteria used to determine EC invasion of myometrium cited Classification: -absent Stage IA -superficial stage IB (<50% myometrium) -deep IC (>50% myometrium) The results of staging with the MRI sequences were correlated to the post-op findings in the: (i) combined group (ii) premenopausal (iii) postmenopausal by using Kendall τ b test Staging accuracy was calculated for three groups and compared for stat. sig. differences with either Fischer exact test or Chi-square test.	Paper reports accuracy to detect extent of myometrial invasion: <u>T2W</u> Without respect to menopausal status (n=46): Acc: (27/46) 59% Premenopausal (n=25): Acc: (20/25) 80% Postmenopausal (n=21) Acc: (7/21) 33% Staging became more accurate when MRI sequence was used preferentially for menopausal status ($p < 0.001$, Fisher Exact test) <i>Diagnostic values in detecting deep myometrial invasion from superficial and no invasion:</i> <u>T2W:</u> (n=46) Sn: 50% Sp: 84% PPV: 40% NPV: 89% Acc: (36/46) 78% Premenopausal (n=25) Sn: 100% Sp: 100% PPV: 100% NPV: 100% Acc: (25/25) 100% Postmenopausal (n=21) Sn: 43% Sp: 57% PPV 33% NPV: 67% Acc: (11/21) 52%	Paper reports accuracy to detect extent of myometrial invasion: <u>CE-T1W</u> Without respect to menopausal status (n=46): Acc: (28/46) 61% Premenopausal (n=25) Acc: (11/25) 44% Postmenopausal (n=21) Acc: (17/21) 81% <i>Diagnostic values in detecting deep myometrial invasion from superficial and no invasion:</i> <u>CE-T1W:</u> (n=46) Sn: 88% Sp: 89% PPV: 64% NPV: 97% Acc: (41/46) 89% Premenopausal (n=25) Sn: 100% Sp: 92% PPV 33% NPV 100% Acc: (23/25) 92% Postmenopausal (n=21) Sn: 86% Sp: 86% PPV: 75% NPV: 92% Acc: (18/21) 86%	Post-op histopathologic staging ? no. of pathologists ? blinding previous results	Main summary: T2W MRI is more accurate when used to stage premenopausal women CE-T1W MRI is more accurate when used in postmenopausal women; menopausal status should be considered when choosing MRI sequence Limitation reported: Only one premenopausal stage IC Overall accuracy of MRI when menopausal status was taken into consideration was 80%# (37/46) – where 37 = the no. of accurate staging outcomes for T2W in the premenopausal group, and CE-T1W in the postmenopausal group. #stat.sig. different ($p < .05$, chi-square) compared to accuracy without respect to menopausal status <i>values in italics calculated to facilitate comparison across studies</i>

Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments																																				
(Saez et al. 2000)	85	Pts with histologic diagnosis of EC with fractional dilation and curettage.	To evaluate the usefulness of CE-T1W to detect myometrial invasion of EC.	<p>Retrospective Case-series, ?consecutive</p> <p>Pts recruited b/w Jan 1992-Dec 1996</p> <p>All 85 pts were imaged within 2 weeks prior to surgery.</p> <p>MRI TYPE: 0.5-T magnet</p> <p>Plain vs Whole series</p> <p>Where whole series includes plain & contrast enhanced</p> <p>Plain MRI (T1W and fast SE-T2W)</p> <p>Contrast enhanced: SE T1W (intravenous gadolinium diethylene triamine pentaacetic acid (Gd-DTPA))</p> <p>n=59 dynamic sagittal fast gradient-echo T1W</p>	<p>Mean age 66 yrs (Range 49-84 yrs)</p> <p>FIGO classification: 46 Stages 1A-B 39 Stage 1C</p>	<p>Scans retrospectively evaluated by 2 groups of radiologists (2 people in each group), blinded to pathology reports.</p> <p>The paper alludes that the two groups read scans independently (calculated kappa statistics to test inter-tester reliability) - although this is not clearly mentioned.</p> <p>The paper also suggests consensus reading was done within each group, although this is not clearly stated.</p> <p>Scan criteria was defined prior to study commencement after a consensus reading session with a non-defined group of radiologists using 'trial cases' (population not defined).</p> <p>MRI classification: -None and superficial (< 50% myometrial invasion) -Deep (>50% myometrial invasion).</p>	<p>Results for MRI to detect the depth of myometrial invasion. Assume OB 1 = group 1, OB 2 = group 2.</p> <p><u>Plain MRI</u></p> <table border="1"> <thead> <tr> <th></th> <th>OB 1</th> <th>OB 2</th> </tr> </thead> <tbody> <tr> <td>Sn</td> <td>64%</td> <td>64%</td> </tr> <tr> <td>Sp</td> <td>94%</td> <td>100%</td> </tr> <tr> <td>PPV</td> <td>90%</td> <td>100%</td> </tr> <tr> <td>NPV</td> <td>75%</td> <td>77%</td> </tr> <tr> <td>Acc</td> <td>?</td> <td>?</td> </tr> </tbody> </table> <p>? The paper does not provide enough info to calc. accuracy scores.</p> <p>The information in the body of the paper is insufficient to replicate Table 3 - so results can not be checked</p> <p>Data in Tables 1 and 3 do not match</p> <p>Authors reported <i>p</i>-values for a series of comparisons and report that for pts in FIGO 1C sensitivity and NPV increased significantly when comparing plain and whole MRI, and for pts. in FIGO 1A-B specificity and PPV didn't change. (See full paper for details). (These <i>p</i>-values do not seem to equate with Table 3).</p>		OB 1	OB 2	Sn	64%	64%	Sp	94%	100%	PPV	90%	100%	NPV	75%	77%	Acc	?	?	<p>Whole Series</p> <table border="1"> <thead> <tr> <th></th> <th>OB 1</th> <th>OB 2</th> </tr> </thead> <tbody> <tr> <td>Sn</td> <td>90%</td> <td>87%</td> </tr> <tr> <td>Sp</td> <td>87%</td> <td>96%</td> </tr> <tr> <td>PPV</td> <td>86%</td> <td>95%</td> </tr> <tr> <td>NPV</td> <td>90%</td> <td>90%</td> </tr> <tr> <td>Acc</td> <td>?</td> <td>?</td> </tr> </tbody> </table> <p>?The paper does not provide enough information to calculate accuracy scores.</p> <p>Degree of inter-observer agreement b/w the two groups was assessed with kappa stat. $\kappa=0.644$ for only plain MRI series, $\kappa=0.752$ for whole series</p>		OB 1	OB 2	Sn	90%	87%	Sp	87%	96%	PPV	86%	95%	NPV	90%	90%	Acc	?	?	<p>Post-op histopathology</p> <p>No. of pathologist, ?blinded to the MRI readings or pre-surgical clinical reports</p>	<p>(i) Radiologist groups are not well described</p> <p>(ii) Paper compares plain vs whole sequence MRI which includes plain and contrast-enhanced MRI. Therefore not comparing plain vs contrast-enhanced MRI.</p> <p>(iii) Data b/w Table 1 and 3 does not match</p> <p>Main summary reported: Therefore contrast enhanced MRI improves the assessment of deep myometrial invasion of EC.</p>
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Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Savci et al. 1998)	20	Pts with endometrial carcinoma (EC) according to biopsy under hysteroscopy or dilatation and curettage Uludag University Medical Facility, Gorukle Campus, Bursa, Turkey.	To compare and correlate the findings obtained from both spin-echo T2W MRI and contrast-enhanced dynamic gradient echo (GRE) MRI sequences in distinguishing deep myometrial invasion from lower stages produced by endometrial carcinoma.	Prospective, consecutive case-series All pts underwent surgery 7-10 days following MRI examinations Type of surgery: simple hysterectomy with or without extensive pelvic and para-aortic lymph node dissection MRI TYPE: 1.0 magnet Body coil -SE-T2W -CE-gradient-echo dynamic (0.1mmol/kg IV Gadopentate dimeglumine)	Mean age: 54.6 SD: +/- 2.6 yrs Range: 28-66yrs FIGO post-op staging: 2 IA 9 IB 9 IC histopathologic subtypes: 11 endometrioid adenocarcinoma 2 serous adenocarcinoma 1 mucinous adenocarcinoma 2 endometrial stromal sarcoma	Scans interpreted independently by 2 radiologists, -blinded all other clinical information except the diagnosis of EC. -assume blinding to final post-op results if prospective study design Paper report clear detailed criteria on MRI interpretation. Pts classified into two groups: -Lower stages of myometrial invasion (stages IA & IB) -Deep myometrial invasion (stage IC)	Results to detect deep myometrial invasion from superficial invasion: <u>CE-dynamic (GRE):</u> Sn: 78% Sp: 100% PPV: 100% NPV: 85% Acc: (18/20) 90% (Checked calculations) Paper reports that McNemar's test revealed no significant differences in the Sn of the two MRI sequences ($\chi=0.25$, $p=0.6171$).	<u>SE-T2W:</u> Sn: 89% Sp: 91% PPV: 89% NPV: 91% Acc: (18/20) 90%	Post-op pathological examination performed by the same experienced pathologist. -depth was ascertained by microscopic evaluation of the specimen	Main summary reported: - MRI reliable method for assessing myometrial depth of myometrial invasion - contrast-enhanced GRE MRI performed with appropriate techniques and in the right plan will improve Sp, and PPV. Limitation reported: -small sample size - used a body coil, a pelvic phased-array coil apparently produces a better contrast-to-noise ratio. Report that further studies coupled with pelvic phased-array multi-coils are imperative to confirm results.

Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments																																																																											
(Seki, Kimura, & Sakai 1997)	40	Patients with endometrial cancer Paper doesn't define EC with reference to diagnostic tests	Compare dynamic MRI with T2W MRI and CE-T1W MRI to: (i) Evaluate enhancement patterns of the myometrium and EC (ii) Detect depth of myometrial invasion	Assume prospective Case-series ? Consecutive ? Inclusion/ exclusion criteria Time frame of pt selection not reported All pts had surgery (hysterectomy with lymph node sampling): -34 total abdominal hysterectomy - 6 radical hysterectomy Time b/w MRI assessment and surgery not stated MRI type(s) 1.5T magnet SE T1W SE T2W IV 0.1mmol kg gadopentate dimeglumine Dynamic MRI (during IV CE) -26 pts FLASH -14 pts SE CE-T1W	Mean age 55.7 Range (32-76yrs) 24 pre-menopausal 16 post-menopausal ("no menstruation for several yrs") none on hormone replacement therapy FIGO post-op criteria IA : 9 1B : 11 1C : 5 IIB : 4 IIIA : 6 IIIC : 5 Tumour type post-op: - 35 adenocarcinoma - 2 adenoacanthoma - 2 squamous cell carcinoma - 1 adenosquamous cell carcinoma	1 radiologist -prospective assessment -blinded to reference standard -? blinding to pre-MRI reports Classification of findings: (E) confined to the endometrium (S) superficial myometrial invasion (less than 50% of myometrium depth) (D) deep myometrial invasion (more than 50% of myometrium depth) (TM) transmyometrial invasion (tumour extends to the serosa of the uterus) Reasons for misinterpretation of myometrial invasion were analysed and presented in Table 5	Table representing MRI results (%) for extent of myometrial invasion E: Detecting invasion confined to the endometrium from myometrial invasion. S: Detecting superficial myometrial invasion from endometrial or transmyometrial or deep myometrial invasion. D: Detecting deep myometrial invasion from endometrial or transmyometrial or superficial myometrial invasion. TM: Detecting transmyometrial invasion from endometrial or superficial or deep myometrial invasion. Dynamic MRI <table border="1"> <thead> <tr> <th></th> <th>Sn</th> <th>Sp</th> <th>PPV</th> <th>NNV</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>100</td> <td>90</td> <td>75</td> <td>100</td> </tr> <tr> <td>S</td> <td>82</td> <td>87</td> <td>82</td> <td>87</td> </tr> <tr> <td>D</td> <td>77</td> <td>100</td> <td>100</td> <td>90</td> </tr> <tr> <td>TM</td> <td>100</td> <td>100</td> <td>100</td> <td>100</td> </tr> </tbody> </table> Overall acc. Of detecting extent of myometrial invasion (n=40): -Dynamic: (34/40) 85%# -T2W: (23/40) 58% -CE T1W: (27/40) 68% #stat. sig. higher compared with T2W (X^2 , $p<0.01$) <i>Acc. Of detecting deep myometrial invasion from the other levels of invasion:</i> - dynamic: (37/40) 93% - T2W: (33/40) 83% - CE-T1W: (37/40) 93%		Sn	Sp	PPV	NNV	E	100	90	75	100	S	82	87	82	87	D	77	100	100	90	TM	100	100	100	100	Table representing MRI results (%) for extent of myometrial invasion T2W <table border="1"> <thead> <tr> <th></th> <th>Sn</th> <th>Sp</th> <th>PPV</th> <th>NPV</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>67</td> <td>77</td> <td>46</td> <td>89</td> </tr> <tr> <td>S</td> <td>41</td> <td>74</td> <td>54</td> <td>63</td> </tr> <tr> <td>D</td> <td>69</td> <td>89</td> <td>75</td> <td>86</td> </tr> <tr> <td>TM</td> <td>100</td> <td>97</td> <td>50</td> <td>100</td> </tr> </tbody> </table> CE T1W <table border="1"> <thead> <tr> <th></th> <th>Sn</th> <th>Sp</th> <th>PPV</th> <th>NPV</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>89</td> <td>71</td> <td>47</td> <td>96</td> </tr> <tr> <td>S</td> <td>47</td> <td>83</td> <td>67</td> <td>68</td> </tr> <tr> <td>D</td> <td>77</td> <td>100</td> <td>100</td> <td>90</td> </tr> <tr> <td>TM</td> <td>100</td> <td>100</td> <td>100</td> <td>100</td> </tr> </tbody> </table>		Sn	Sp	PPV	NPV	E	67	77	46	89	S	41	74	54	63	D	69	89	75	86	TM	100	97	50	100		Sn	Sp	PPV	NPV	E	89	71	47	96	S	47	83	67	68	D	77	100	100	90	TM	100	100	100	100	Histopathological (macroscopically & confirmed microscopically) The hysterectomy specimens were sectioned in the corresponding sagittal plane of MR images ? no of pathologist who interpreted the findings ? blinding to previous results	Results are given for different enhancement patterns of the myometrium and EC compared across the sequences Paper reports that dynamic MRI was better able to differentiate important imaging landmarks compared to the other MRI sequences. Paper concludes that dynamic MRI is a more reliable method for assessment of myometrial invasion <i>authors did not calculate acc. for detecting deep myometrial invasion, values in italics calculated to facilitate comparison across studies</i>
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Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments																																																																								
(Takahashi et al. 1998)	35 28	Pts with histopathologically proved EC, diagnosed by endometrial curettage. Pts recruited b/w Sept 1993-Nov 1995	To compare fast SE T2W MRI with a multiple-surface coil and a 512x256 matrix to dynamic fast SE-T1W MRI and fast SE CE-T1W MRI, for the detection of myometrial and cervical invasion of EC.	Direction not explicit Consecutive case-series 35 consecutive women were selected – 7 women were excluded b/c couldn't use contrast medium MRIs performed on all 28 pts prior to surgery. Pts underwent hysterectomy 2-29 days (mean 14.7 days) after MRI. MRI TYPE: 1.5-T magnet pelvic phased-array coil -fast SE-T2W with 512x256 matrix -fast SE-T1W -Serial dynamic fast SE-T1W -CE-T1W (0.1 mmol/kg IV gadopentetate dimeglumine) Note: Did not use 512x256 matrix for dynamic or CE imaging	Mean age 57.5 yrs (Range 29-75yrs) 12 premenopausal 16 postmenopausal Paper doesn't report any other characteristics	Scans interpreted independently by 3 radiologists, blinded to "histopathologic findings" (assume this refers to the reference standard) -? blinding to pre-MRI reports They knew age and whether pre/post-menopausal Sequences were assessed separately at intervals of 2 weeks Intra-observer reliability for each MRI sequence - (?) statistic. Classification of EC invasion, according to clear criteria: (S) superficial myometrial invasion (D) deep myometrial invasion (C) cervical invasion Confidence levels applied to each observation (1-5) 3-5 =positive 1-2 =negative If deep myometrial invasion was assessed as 4 (positive), then superficial myometrial invasion deemed 5 (definitely positive).	Inter-observer reliability: -T2W ($\kappa >0.64$) -dynamic studies ($\kappa >0.67$) -CE T1W ($\kappa >0.57$). Results (%) reported in the paper. Consensus readings only (n=67 regions*) Detect superficial myometrial invasion from none or deep myometrial invasion <table border="1"> <thead> <tr> <th></th> <th>T2</th> <th>Dy</th> <th>CET1</th> </tr> </thead> <tbody> <tr> <td>Sn</td> <td>94</td> <td>94</td> <td>92</td> </tr> <tr> <td>Sp</td> <td>74</td> <td>68</td> <td>79</td> </tr> <tr> <td>Acc</td> <td>88</td> <td>87</td> <td>88</td> </tr> <tr> <td>PPV</td> <td>90</td> <td>88</td> <td>92</td> </tr> <tr> <td>NPV</td> <td>82</td> <td>81</td> <td>79</td> </tr> </tbody> </table> (Checked results) Detect deep myometrial invasion from superficial or no myometrial invasion <table border="1"> <thead> <tr> <th></th> <th>T2</th> <th>Dy</th> <th>CET1</th> </tr> </thead> <tbody> <tr> <td>Sn</td> <td>75</td> <td>63</td> <td>44</td> </tr> <tr> <td>Sp</td> <td>92</td> <td>90</td> <td>82</td> </tr> <tr> <td>Acc</td> <td>88</td> <td>84</td> <td>73</td> </tr> <tr> <td>PPV</td> <td>75</td> <td>67</td> <td>44</td> </tr> <tr> <td>NPV</td> <td>92</td> <td>88</td> <td>82</td> </tr> </tbody> </table> (Checked results) Detect cervical invasion from no cervical invasion(n=28 pts) <table border="1"> <thead> <tr> <th></th> <th>T2</th> <th>Dy</th> <th>CET1</th> </tr> </thead> <tbody> <tr> <td>Sn</td> <td>70</td> <td>40</td> <td>50</td> </tr> <tr> <td>Sp</td> <td>89</td> <td>83</td> <td>83</td> </tr> <tr> <td>Acc</td> <td>82</td> <td>68</td> <td>71</td> </tr> <tr> <td>PPV</td> <td>78</td> <td>57</td> <td>63</td> </tr> <tr> <td>NPV</td> <td>84</td> <td>71</td> <td>75</td> </tr> </tbody> </table> (Checked results) Az (area under ROC curve) values of CE-T1W was stat. sig. <i>lower</i> ($p=0.031$) then T2-W and dynamic.		T2	Dy	CET1	Sn	94	94	92	Sp	74	68	79	Acc	88	87	88	PPV	90	88	92	NPV	82	81	79		T2	Dy	CET1	Sn	75	63	44	Sp	92	90	82	Acc	88	84	73	PPV	75	67	44	NPV	92	88	82		T2	Dy	CET1	Sn	70	40	50	Sp	89	83	83	Acc	82	68	71	PPV	78	57	63	NPV	84	71	75	RESULTS: S: No substantial differences were observed among the MRI sequences D: The specificity of CE-T1W was significantly <i>lower</i> compared to the T2W ($p=0.008$) or dynamic ($p=0.006$). C: No significant differences were observed with Sp and Acc among the MRI sequences. (Sensitivity of T2W was <i>higher</i> than dynamic imaging ($p=0.065$)). Az values b/w T2W and CE-T1W significantly different ($p=0.031$).	Post-op histopathological staging A pathologist, blinded to the MRI findings Classified as: (i) absent (ii) superficial (<50% of the myometrium) (iii) deep (>50% of myometrium)	Main outcome: T2W MRI is reliable for the pre-operative staging of endometrial carcinoma, although gadolinium-enhanced studies may help improve the evaluation of tumour invasion. T2W MRI is as accurate as Dynamic and CE-T1W MRI in assessing EC. <i>*Study design: divided the myometrium into four sections and then assessed the degree of myometrium invasion in each section, not the uterus as a whole – therefore difficult to compare this study's results directly with other studies.</i> <i>Value in italics calculated from material in paper</i> Diagnoses were made by means of <i>consensus</i> , and consensus staging accuracy was calc McNemar test to compare the staging capabilities of each MR sequence. Where superficial or deep myometrial invasion and cervical invasion were assessed as correct or incorrect
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Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Seki, Takano, & Sakai 2000)	39	Pts with untreated endometrial carcinoma after histologic diagnosis made by endometrial curettage	To compare dynamic MRI with T2W and CE-T1W: (i) evaluate enhancement patterns of the cervical epithelium, stroma, and tumour (ii) to detect cervical involvement of EC	Prospective Case-series ? Consecutive ? Inclusion/ exclusion criteria (n=42) pts enrolled in the case-series (n=39) had surgery (n=3) classified FIGO IA and underwent chemotherapy – excluded Final sample n=39 MRI TYPE: 1.5T magnet phased-array coil 20mg IM butylscopolamine bromide T2W with RARE (rapid acquisition with relaxation enhancement) CE-T1W images spin-echo MR 0.1 mmol/kg gadopentetate dimeglumine Dynamic MRI FLASH tech, without breath holding with phase1, phase 2 & phase 3	Mean age 57 yrs (range 30-75 yrs) (n=42) FIGO classification: 5 IA 14 IB 7 IC 4 IIB 4 IIIA 7 IIIC 1 IVA Histological type: Adenocarcinoma (n=38) adenosquamous carcinoma (n=2) clear cell adenocarcinoma (n=2) Pts recruited April 1996- May 1999 39 of the 42 pts underwent surgery 4-19 days (mean 9.5 days) after MRI scans	Scans interpreted independently by 2 readers, blinded to histologic results. Inter-tester reliability: -Dynamic: $\kappa = 1.00$ -T2 (RARE): $\kappa = 0.82$ -CE-T1W: $\kappa = 0.94$ NOTE: Paper mentions that discrepancies in interpretation were resolved by, even though results were interpreted independently.	The diagnostic values for assessing presence of cervical invasion from no cervical invasion: <u>Dynamic MRI:</u> Sn: 90% Sp: 97% PPV:90% NPV:97% Acc: (37/39) 95% (Calculations checked) Differences b/w the three sequences reported not to be statistically significant (no <i>p</i> -value reported).	The diagnostic values for assessing presence of cervical invasion from no cervical invasion: <u>T2W:</u> Sn: 80% Sp: 86% PPV: 67% NPV: 93% Acc: (33/39) 85% (Calculations checked) <u>CE-T1W:</u> Sn: 90% Sp: 90% PPV: 75% NPV: 96% Acc: (35/39) 90% (Calculations checked)	Post-op histopathological findings. Evaluated macroscopically and confirmed microscopically ? no. pathologists ? blinding	Main summary reported: In combination with T2W MRI, dynamic MRI is useful in assessing endometrial carcinoma involvement of the cervix. Enhancement of the cervical epithelium on dynamic MR imaging is a reliable reference in assessing cervical involvement. Contrast noise ratio b/w tumour and cervical epithelium; dynamic MRI showed the greatest contrast compared to T2W, ($p < 0.0001$) and CE-T1W, ($p < 0.001$) Contrast noise ratio b/w tumour and cervical stroma; T2W greatest contrast compared to Dynamic ($p < 0.01$), and CE-T1W ($p < 0.000001$).

Table 30 Endometrial cancer (EC) data extraction - comparing diagnostic accuracy of different MRI sequences to detect endometrial cancer invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Shibutani et al. 1999)	67	Pts with primary untreated EC, confirmed by fractional dilatation and curettage who were referred for MRI imaging	To compare thin-section oblique axial MRI with parasagittal MRI to detect cervical invasion by EC.	Prospective Consecutive case-series All pts underwent simple or radical hysterectomy with pelvic lymph node sampling or resection All pts evaluated by MRI within 7 days of surgery Time of recruitment not reported MRI TYPE: 1.5 T magnet Body coil T2W -SE or TURBO SE -parasagittal -thin section oblique CE T1W -using 0.1mmol/kg GD-DTPA IV -parasagittal -thin section oblique	Mean age: 56yrs (range: 26-81yrs) Post-op FIGO staging: 13 IA 15 IB 8 IC 3 IIA 2 IIB 18 IIIA 6 IIIC 2 IVB Histopathologic results: adenocarcinoma endometrial type -grade 1 (n=21) -grade 2 (n=27) -grade 3 (n=11) adenosquamous carcinoma (n=6) adenoacanthoma (n=1) clear cell carcinoma (n=1)	Scans read independently by 2 readers blinded to the post-op. results. Discrepancies resolved by discussion MRI classification criteria based on previously published criteria. Cervical invasion was classified as: Co: no cervical invasion Ca: endocervical glandular involvement only Cb: cervical stromal invasion	Results to detect extent of cervical invasion of EC Thin-section oblique: <u>T2W:</u> Acc: (60/67) 90%# <u>CE-T1W:</u> Acc:(64/67) 96%† #sig. different compared to parasagittal T2W (p=0.002). †sig. different compared to parasagittal CE-T1W (p=0.003). <i>Diagnostic values for detecting cervical invasion from no cervical invasion</i> <u>T2W:</u> Sn: 91% Sp: 98% PPV: 91% NPV: 98% Acc: (65/67) 97% <u>CE-T1W:</u> Sn: 100% Sp: 98% PPV: 92% NPV: 100% Acc: (66/67) 99%	Results to detect extent of cervical invasion of EC Parasagittal <u>T2W:</u> Acc: (50/67) 75% <u>CE-T1W:</u> Acc:(55/67) 82% <i>Diagnostic values for detecting cervical invasion from no cervical invasion</i> <u>T2W:</u> Sn: 36% Sp: 91% PPV: 44% NPV: 88% Acc: (55/67) 82% <u>CE-T1W:</u> Sn: 55% Sp: 93% PPV: 60% NPV: 91% Acc: (58/67): 87%	Post-op histopathology macroscopic confirmed by microscopic results ? no. of pathologists ? blinding to previous reports	Main summary reported: Thin-section oblique axial MRI are considered to be useful for the assessment of cervical invasion by endometrial carcinoma. *authors did not calculate Sn, Sp etc, values in italics calculated to facilitate comparison across studies

Table 31 Endometrial cancer (EC) data extraction - meta-analyses

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Kinkel et al. 1999)		6 studies met inclusion criteria for CT, 16 US, 25 MRI Conducted searches from Jan 1980- Sept 1997 for US and CT Jan 1985- Sept 1997 for MRI	To apply a meta-analysis to compare the utility of CT, US and MRI in staging EC.	Meta-analysis Subgroup analysis was used to compare CE MRI with non-enhanced MRI, US, and CT.			ROC analysis showed no significant difference in the overall performance of CT, US and MRI. CE-MRI performed better than non-enhanced MRI, US when assessing myometrial invasion ($p<0.002$) CE-MRI showed a trend towards better results compared with CT (no significant). Lack of data on cervical invasion determined by CT or US.			CE MRI offers superior pre-treatment evaluation of EC compared with US, CT or non-enhanced MRI.
(Frei et al. 2000)		Mean pre-test probabilities of deep myometrial invasion: -1875 pts from 7 articles and from 125 institutional pathology reports LR for the prediction myometrial invasion with CE MRI: -742 pts from 9 studies.	To determine if, in a pt with an endometrial cancer, in addition to the knowledge of tumour grade, pre-operative MRI findings contribute to treatment stratification and specialist referral.	Meta-analysis Pre-test probabilities for myometrial invasion were correlated with tumour grade. Likelihood ratios were obtained through summary receiver operating characteristics.			Mean weighted pre-test probabilities for deep myometrial invasion in pts with tumour grade 1, 2, 3, were 13%, 35%, or 54% respectively. Post-test probabilities for deep myometrial invasion for grades 1, 2, or 3 were increased to 60%, 84% or 92% respectively, for positive and decreased to 1%, 5% or 10% respectively for negative MRI findings. Positive and negative LR's were 10.11 and 0.1 respectively. Therefore MRI is clinically useful at predicting myometrial invasion.			Main summary reported: The use on CE MRI significantly affects the post-test probability of deep myometrial invasion in pts with all grades of EC and could be used to select pts for specialist referral.

Table 32 Endometrial cancer (EC) data extraction - diagnostic accuracy of detecting malignant from benign endometrial lesions

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Grasel et al. 2000)	35	Women diagnosed with endometrial polyps or endometrial cancer (EC) Cases and controls were obtained from two hospitals MRI reports Jan 1992-Jan 1998	To determine: (i) the MRI characteristics of endometrial polyps (ii) the accuracy of MRI in distinguishing endometrial polyps from similar-sized ECs.	Case-control Cases and controls were matched for tumour size Original sample n=42 pts: 7 exclusions: -inappropriate tumour size -inappropriate endometrial width Final n=35 22 polyps 13 carcinoma MRI TYPES: 1.0T magnet 1mg glucagon IM before imaging (n=35) SE-T2W MRI in sagittal (n=30) SE-T2W in coronal (n=35) Transverse SE-T1W (n=19) CE-T1W, with 0.1mmol/kg IV gadopentetate dimeglumine	Mean age (range): -57 yrs (30-86) polyps -64 yrs (53-79) cancer The paper reports no stat. sig. difference b/w: -age -endometrial width -uterine length -uterine width	Read independently by three radiologists Blinded to histopathologic diagnoses and clinical data Each reader scored the MR images according to a variety of morphological findings as well as their diagnosis on whether polyp or EC was present. They graded their degree of confidence on a scale of 1-5	Paper reports: Overall diagnosis of EC using mean (no. of observations across three readers) values of three readers: Sn: (31/39) 79% Sp: (59/66) 89% PPV: (31/38) 82% NPV: (59/67) 88% Acc: (90/105) 86% k=0.67 for diagnosis of EC Mean ROC (receiver operator curve) diagnosis of EC: 0.87 <i>Results to detect EC from endometrial polyps based on patients (n=35):</i> <i>Sn: (8/13) 62%</i> <i>Sp: (18/22) 82%</i> <i>PPV: (8/12) 67%</i> <i>NPV: (18/23) 78%</i> <i>Acc: (26/35) 74%</i>		Pathology records from: -hysterectomy (n=21) -endometrial biopsy (n=10) -resection (n=4) ? no. pathologists ? blinded to MRI or other previous reports	Main summary: MRI can help to distinguish polyps and EC on the basis of morphologic features, however accuracy doesn't appear to be sufficient to obviate surgery Limitations reported: -unable to generalise to a wider population of different sized tumours -small n <i>*The paper overestimates accuracy of MRI for differentiating b/w polyps or carcinoma b/c their values are calculated using 105 observations rather than using 35 pts</i> <i>Calculations in italics indicate accuracy rates based on 35 patients</i>

Table 32 Endometrial cancer (EC) data extraction - diagnostic accuracy of detecting malignant from benign endometrial lesions (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Imaoka et al. 1999)	54	Pts. suspected of having an abnormal uterine cavity based on MRI findings of a thickened endometrium mass, or a submucosal mass.	To assess the ability of T2W and CE-T1W to distinguish malignant from benign conditions in pts. with an abnormal uterine cavity.	Retrospective case series ? consecutive This sample was drawn from 397 female pts suspected of having gynaecological disease who underwent MRI from Oct 1994- Aug 1997 74 pts were drawn from this sample if they met inclusion criteria defining abnormal uterine cavity 20 pts were excluded b/c MRI could not be correlated with pathology records final sample 54 All pts underwent a surgical procedure: 44 hysterectomy 7 dilatation and curettage 3 endometrial biopsy MRI TYPE: -1.5T magnet phased-array or TORSO multicoil -SE-T1W -SE-T2W -CE-T1W with gadopentetate dimeglumine	Mean age 50/2yrs (range: 35-80yrs) Histopathological findings post-op: -15 endometrial carcinomas -3 malignant mixed mesodermal tumours (MMMT) -1 endometrial stromal metaplasia -1 endometrial atypical hyperplasia -2 endometrial simple hyperplasia -8 endometrial polyps -1 degenerated villi -14 submucosal leiomyomas -10 normal endometrium -1 both submucosal leiomyoma and stage IA EC	MR images were interpreted independently by two radiologists, disagreements were resolved by consensus Blinded to transvaginal ultrasonography and pathologic findings κ statistics used to compare inter-observer reliability The paper describes criteria for MRI to differentiate: (i) submucosal leiomyoma and endometrial abnormalities (ii) benign and malignant endometrial abnormalities	Results to detect malignant lesions from benign: <u>T2W:</u> (both readers in consensus) Sn: 50% Sp: 97% PPV: 90% NPV: 80% Acc: (45/55) 82% (Calculations checked) The two sequences were then compared using McNemar test. Trend towards higher Sn with CE-T1W, the paper reports no significant differences b/w the two sequences in terms of overall Sn, Sp, and acc. $\kappa=0.89$ for inter-observer reliability Results for distinguishing benign submucosal lesions from benign endometrial abnormalities: (? both sequences) Sn: 71% Sp: 100% PPV: 100% NPV: 91% Acc: (51/55) 93% (calculation checked) $\kappa=0.73$ inter-observer reliability	<u>CE-T1W:</u> (both readers in consensus) Sn: 83% Sp: 92% PPV: 83% NPV: 92% Acc: (49/55) 89% (calculations checked) $\kappa=0.67$ inter-observer reliability	Surgical procedure: (i) hysterectomy (ii) curettage (iii) endometrial biopsy to confirm histopathologic findings	Main summary reported: Initial differentiation of submucosal lesions from endometrial lesions provided by T2W MRI. Then CE-T1W MRI may further distinguish malignant from benign endometrial lesions. MRI might be useful when dilatation and curettage is not possible

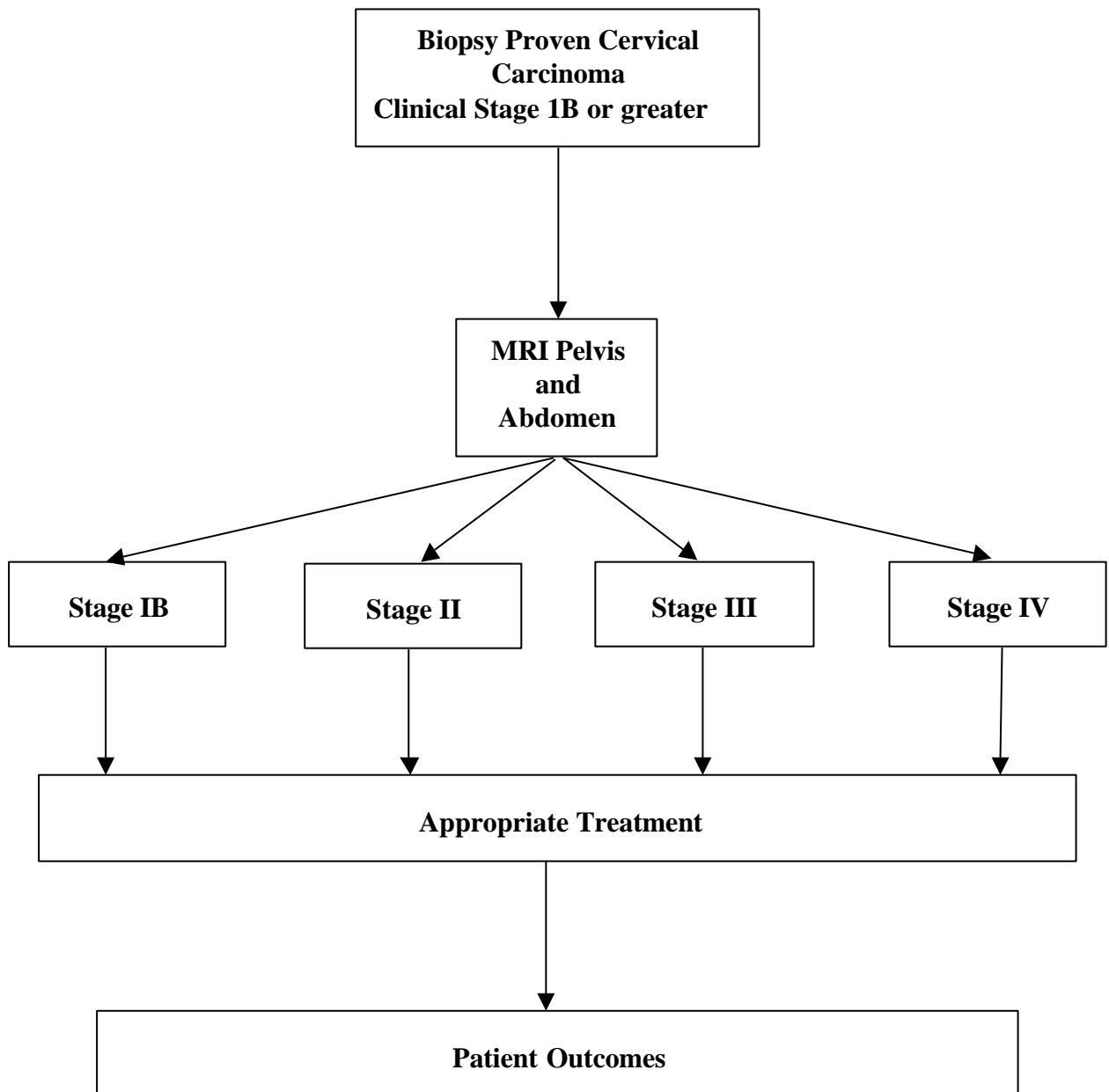
Table 33 Endometrial cancer (EC) data extraction - diagnostic accuracy of MRI compared with IOGD to detect endometrial cancer invasion

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Cunha, Fe, & Cabral 1901)	40	Pts with endometrial carcinoma Hospital based Pts recruited: July 1998- August 1999	Evaluate the accuracy of MRI and GVI (Gross visual inspection) in the detection of myometrial and cervical invasion of endometrial carcinoma.	Prospective Case-series ? consecutive (Paper reports a cohort of pts) All pts that underwent MRI scans underwent surgery, but only 33 were evaluated for the GVI staging The paper does not report the exclusion criteria for GVI MRI TYPE: 1.0-T magnet, using a body coil T1W T2W Dynamic MRI 0.1mmol/kg IV manual administration of gadopentetate dimeglumine An option for those images where invasion was more clearly demonstrated or deeper was used for staging.	Mean age 63.2 yrs (range 45-83 yrs) 6 premenopausal (1 OC) 34 postmenopausal (3 HRT, 1 tamoxifen for breast ca) FIGO stages post-op: I : 26 II : 8 III : 5 IV : 1 See Table 1 for comparisons of histologic diagnosis and tumour grade (mainly endometrioid adenocarcinoma, tumor grade 1 & 2)	One radiologist, MRI findings were interpreted prospectively prior to the surgery Paper does not provide info on whether the radiologist was blinded to pts. clinical status Paper discusses the criteria used to determine EC invasion of myometrium and cervix. Invasion of the myometrium was classified as: -superficial (<50% of the myometrium) -deep (>50% of the myometrium)	MRI results for comparing to the ref. standard, to detect deep myometrial invasion Sn: 80% Sp: 100% PPV: 100% NPV: 89% Acc: 93% MRI results for comparing to the ref. standard, to detect cervical invasion.(checked results) Sn: 33% Sp: 100% PPV: 100% NPV: 78% Acc: 80% kappa scores were reported to evaluate the amount of agreement b/w the MRI and histologic findings: -deep myometrial invasion ($\kappa = 0.8333$) -cervical invasion.($\kappa = 0.4118$)	Gross Visual Inspection (GVI) Surgical specimen was examined immediately after surgery by an experienced senior pathologist who was blinded to MRI result -does not report whether blinded to other clinical factors Paper reports the way in which the uterus was assessed GVI results for comparing to the ref standard, to detect deep myometrial invasion: Sn: 77% Sp: 100% PPV: 100% NPV: 87% Acc: 91% GVI results for comparing to the ref standard, to detect cervical invasion: Sn: 36% Sp: 100% PPV: 100% NPV: 76% Acc: 79% kappa scores were reported to evaluate the amount of agreement b/w the GVI and histologic findings ($\kappa = 0.8016$ deep myo. invasion, $\kappa = 0.4324$ for cervical invasion.	Microscopic Study Conducted by a pathologist -reported to be blinded to the MRI report -it is not clear whether a different pathologist interpreted the macroscopic and microscopic findings, or if it was the same pathologist whether blinding to the GVI results occurred	The paper reports that T2WMRI were used in the majority of cases. Dynamic sequence after admin. of contrast agent was extremely helpful where junctional zone was not clearly visualized. In summary: Accuracy levels for MRI and GVI were very similar, and therefore the two techniques can be used interchangeably.

Table 33 Endometrial cancer (EC) data extraction - diagnostic accuracy of MRI compared with IOGD to detect endometrial cancer invasion (continued)

Study	N	Patient Source	Study Question	Study Design	Patient Characteristics	Scan Interpretation	MRI results	Comparator Results	Reference Standard	Comments
(Hardesty et al. 2000)	25	All pts with primary untreated endometrial carcinoma who underwent pre-operative MRI The histological diagnosis of EC was determined by endometrial biopsy Hospital based Jan 1995- March 1998	To compare the accuracy of pre-operative MRI in the direction of the appropriate use of lymph node dissection with that of conventional intra-operative gross evaluation of the uterus. The study evaluated: 1.The ability of MRI compared with Intraoperative gross dissection (IOGD) to detect the degree of myometrial invasion 2. The ability of MRI staging and surgeon ("actual scenario") to appropriately sample/ dissect lymph nodes in pts with EC.	Retrospective Consecutive case series -34 in this series who were referred for pre-operative MRI; -9 pts were excluded from this series --6 b/c underwent pre-surgical radiation or chemotherapy --3 had mixed mullerian tumours at final histopathologic examination Average time b/w MRI and surgery 7.6 days (range: 1-34 days) MRI TYPE: 1.5 T magnet T1W with body coil Pelvic phased-array coil used for the following sequences SE-T1W Fast SE-T2W Then admin: contrast – 0.1mmol/kg IV gadopentetate dimeglumine Contrast enhanced Dynamic T1 spoiled gradient CE SE-T1W Note: The first 5 pts did not undergo contrast enhanced imaging due to hospital protocol during the time they underwent MR	Mean age: 59yrs (Range: 35-83 yrs) Histopathology: - 22 endometrioid adenocarcinoma - 2 serous carcinoma - 1 clear cell carcinoma FIGO staging: -IA : 1 -IB : 16 -IC : 5 -IIA : 2 -IIB : 1 pts at higher stages were not included b/c they underwent pre-surgical radiotherapy/ chemotherapy Paper reports that the pts in the study's sample were representative of the epidemiological data for endometrial carcinoma	1. Detection of deep myometrial invasion (MRI compared with IOGD) <u>MRI interpretation:</u> 3 experienced radiologists independently retrospectively reviewed images, blinded (except pts had EC) Final MRI interpretations determined on consensus The depth of myometrial invasion classified as: -superficial (<50%) -deep (>50%) -note presence of cervical involvement <u>(IOGD)</u> obtained from the written pathology report provided at the time of surgery 2. Appropriateness of lymph node dissection: (Lymph node dissected in both cases if serous clear cell or grade 3 endometrioid histotype) Compared MRI Staging scenario with IOGD staging to determine appropriateness of lymph dissection	1.Detection of myometrial invasion: Table 3 reports raw data <u>MRI interpretation:</u> Sn: 100% Sp: 84% PPV: 67%* NPV: 100%* Acc: 88% *Checked results and added PPV, NPV 2. Appropriateness of lymph node dissection Table 4 reports raw data (However the data in the table is not consistent with the information provided in the body of the text). <u>MRI staging scenario:</u> Sn: 100% Sp: 86% The paper reports: -Staging at MRI imaging and initial histologic evaluation would have indicated lymph node dissection in 13 of the 25 pts -However, final histologic reports found that 11 of the 25 pts actually exhibited lymph disease requiring dissection -In 2 pts carcinoma was <i>overstaged</i> by MRI, who would have undergone unnecessary lymph node dissections. -In one pt MRI <i>overstaged</i> , however b/c of histological type (serous) they would have required lymph node dissection anyway.	1.Detection of myometrial invasion: <u>IOGD results:</u> Sn: 100% Sp: 86% PPV: 85%* NPV: 100%* Acc: 92% *Checked results and added PPV, NPV 2.Appropriateness of lymph node dissection: <u>Actual scenario:</u> Sn: 92% Sp: 31% The paper reports: -That 20 of the 25 pts. actually underwent lymph node dissection. However, the lymph node dissections were only appropriate in 11 of the 25 pts according to the final histologic findings. -9 of the 25 pts underwent unnecessary lymph node surgery Note: Lymph node sampling was performed at the discretion of the surgeon, the decision was directed by: - pre-operative histologic results from suction endometrial biopsy - intra operator gross dissection of the uterus - the surgeon was reported to be aware of the MRI findings - multiple surgeons performed the operations	Final written pathology report - blinding to other clinical, and MRI information is not explicit	The paper also reports the cost associated with two different practice scenarios (MRI vs IOGD) Main summary: The findings suggest that pre-operative MRI may eventually replace IOGD of the uterus in the selection of pts with EC for lymph node dissection. Limitations reported: -retrospective -selection of pts for pre-operative MRI is unclear -surgeons were not blinded to the MRI results -5 early MRI examination were performed without contrast enhancement. Cases of cervical invasion minimum.

Appendix D Flow chart – role of MRI



Appendix E Cost estimates

Table 34 Costs of treatments

a) Adjuvant Radiotherapy

MBS Item	Description	Cost per item	Quantity	Total
15203 or 15207	Radiation oncology treatment (SPLA or DMLA) (First field)	\$ 45.90	1	\$ 45.90
15204 or 15208	Radiation oncology treatment (SPLA or DMLA) (subsequent fields)	\$ 29.20	3	\$ 87.60
Total MBS/treatment				\$ 133.50
Total cost adjuvant RT			Number of treatments/fractions	25
				\$ 3,337.50

b) Radical Radiotherapy

MBS Item	Description	Cost per item	Total
As above	Adjuvant radiotherapy as above	\$ 3,337.50	\$ 3,337.50
15324	Combined intrauterine/intravaginal brachytherapy	\$ 555.40	\$ 555.40
17706	Administration of anaesthetic	\$ 87.60	\$ 87.60
Total cost (adjuvant + brachytherapy)			\$ 3,980.50
Chemotherapy (as part of chemoradiation)			\$ 2,000.00

c) Surgery

MBS Item	Description	Cost per item	Total
35664	Radical hysterectomy with radical excision of PLN	\$ 1,117.15	
17721	Anaesthetic for 35664	\$ 306.60	\$ 1,423.75
35667	Radical hysterectomy w/o PLN excision	\$ 949.50	
17720	Anaesthetic for 35667	\$ 292.00	\$ 1,241.50
35723	Retro-peritoneal lymph node biopsies	\$ 371.65	
17719	Anaesthetic for 35723	\$ 277.40	\$ 649.05
Assume:			
Proportion treated with radical hysterectomy + PLN excision			70%
			\$ 996.63
Proportion treated with radical hysterectomy w/o PLN excision			30%
			\$ 372.45
Proportion who have retroperitoneal LN biopsies (half done at time of hysterectomy, half at a later date)			10%
			\$ 51.04
Total average cost for surgery			\$ 1,420.11

Note: Total cost of surgery does not include bed days or other inpatient costs, only the MBS reimbursement for procedures

Table 35 Number of patients (based on 692 evaluated with CT or MRI)

Total n= 692	Number true positives	Number false negatives	Number true negative	Number false positives
CT	238.5	79.5	280.2375	93.4125
MRI	270.3	47.7	317.6025	56.0475

Table 36 Total diagnostic and treatment costs for patients assessed by CT

Assessment	N	Cost per CT	Total CT costs	Treatment	Cost of treatment (per patient)	Total treatment cost	Total cost
Total number with parametrial invasion on CT (TP + FP)	331.9125	\$487.40	\$ 161,774.15	Radiotherapy	\$ 3,980.50	\$ 1,321,177.71	\$ 1,482,951.86
				Chemoradiation	\$ 5,980.50	\$ 1,985,002.71	\$ 2,146,776.86
Total number with no parametrial invasion on CT (TN + FN)	359.7375	\$487.40	\$ 175,336.06	Surgery	\$ 1,420.11	\$ 510,866.82	\$ 686,202.88
				Surgery + chemoradiation	\$ 6,757.61	\$ 2,430,965.73	\$ 2,606,301.78
pts with -ve CT but parametrial invasion (FN) who will require CRT or RT after less aggressive surgery	79.5	-	-	Radiotherapy	\$ 3,980.50	\$ 316,449.75	\$ 316,449.75
				Chemoradiation	\$ 5,980.50	\$ 475,449.75	\$ 475,449.75

Table 37 Total diagnostic and treatment costs for patients assessed by MRI (pelvic and abdominal MRI)

Assessment	N	Cost per MRI	Total MRI costs	Treatment	Cost of treatment (per patient)	Total treatment cost	Total cost
Total number with parametrial invasion on MRI (TP + FP)	326.3475	\$ 775.00	\$ 252,919.31	Radiotherapy	\$ 3,980.50	\$ 1,299,026.22	\$ 1,551,945.54
				Chemoradiation	\$ 5,980.50	\$ 1,951,721.22	\$ 2,204,640.54
Total number with no parametrial invasion on MRI (TN + FN)	365.3025	\$ 775.00	\$ 283,109.44	Surgery	\$ 1,420.11	\$ 518,769.73	\$ 801,879.17
				Surgery + chemoradiation	\$ 6,757.61	\$ 2,468,571.83	\$ 2,751,681.26
pts with -ve MRI but parametrial invasion (FN) who will require CRT or RT after less aggressive surgery	47.7	-	-	Radiotherapy	\$ 3,980.50	\$ 189,869.85	\$ 189,869.85
				Chemoradiation	\$ 5,980.50	\$ 285,269.85	\$ 285,269.85

Table 38 Total diagnostic and treatment costs for patients assessed by MRI (pelvic MRI only)

Assessment	N	Cost per MRI (pelvic)	Total MRI costs	Cost per CT (abdominal)	Total CT costs	Treatment	Cost of treatment (per patient)	Total treatment cost	Total cost MRI + CT ^a	Total cost MRI + CT ^b
Total number with parametrial invasion on MRI	326.3475	\$ 475.00	\$ 155,015.06	\$ 362.90	\$ 118,431.51	Radiotherapy	\$ 3,980.50	\$ 1,299,026.22	\$ 1,572,472.79	\$ 1,613,103.06
						Chemoradiation	\$ 5,980.50	\$ 1,951,721.22	\$ 2,225,167.79	\$ 2,265,798.06
Total number with no parametrial invasion on MRI	365.3025	\$ 475.00	\$ 173,518.69	\$ 362.90	\$ 132,568.28	Surgery	\$ 1,420.11	\$ 518,769.73	\$ 824,856.70	\$ 870,336.86
						Surgery + chemoradiation	\$ 6,757.61	\$ 2,468,571.83	\$ 2,774,658.79	\$ 2,820,138.95
pts with -ve MRI, but parametrial invasion (FN) who will require CRT or RT treatment after less aggressive surgery	47.7	-	-	-	-	Radiotherapy	\$ 3,980.50	\$ 189,869.85	\$ 189,869.85	\$ 189,869.85
						Chemoradiation	\$ 5,980.50	\$ 285,269.85	\$ 285,269.85	\$ 285,269.85

^a based on CT: abdominal only scan cost \$362.90

^b based on CT: pelvic and abdominal scan cost \$487.40

Table 39 Total healthcare cost for diagnosis and subsequent treatment of patients (n=692 assessed)

Assessment	CT alone	MRI alone*	MRI + CT**	MRI + CT***
Patients where imaging Indicates parametrial invasion (TP + FP)	\$ 2,146,777	\$ 2,204,641	\$ 2,265,798	\$ 2,225,168
Patients where imaging Indicates no parametrial invasion (TN + FN)	\$ 1,166,228	\$ 1,289,330	\$ 1,357,787	\$ 1,312,307
Patients with negative imaging but parametrial invasion (FN) who will require chemoradiation after less aggressive surgery (FN)	\$ 475,450	\$ 285,270	\$ 285,270	\$ 285,270
Total	\$ 3,788,455	\$ 3,779,241	\$ 3,908,855	\$ 3,822,745
Incremental cost		-\$ 9,214 (saving)	\$ 120,400	\$ 34,290
Cost per patient		-\$ 13 (saving)	\$ 174	\$ 49

* MRI cost = \$775 (pelvis and abdomen)

** MRI cost = \$475 (pelvis only), CT cost = \$487.40 (pelvis plus abdomen)

*** MRI cost = \$475 (pelvis only), CT cost = \$362.90 (upper abdomen only)

Based on assumptions outlined on page 50-52

Abbreviations

The following abbreviations were used:

Acc	accuracy
ASC	adenosquamous carcinoma
b/w	between
CC	cervical cancer
CE	contrast enhanced
CRT	chemoradiotherapy
CT	computer tomography
EC	endometrial cancer
EUA	examination under anaesthesia
FC	fractional curettage
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
FLASH	fast low angle shot
FSE	fast spin-echo
GRE	gradient echo
GVI	gross visual inspection
HMVD	histological microvessel density
HPV	human papilloma virus
HS	hysteroscopy
LN	lymph node
MP-RAGE	magnetisation-prepared rapid acquisition gradient echo
MRI	magnetic resonance imaging
NE	nodal enlargement
NPV	negative predictive value
PPC	pelvic phased-array coil
PE	pelvic examination
PP/PPV	positive predictive value
pt	patient
PYLL	person-years life lost
RF	radiofrequency
ROC	receiver operator curve
RSI	relative signal intensity
RT	radiotherapy
SCC	squamous cell carcinoma
SE	spin-echo
Sn	sensitivity
Sp	specificity
STIR	short tau inversion recovery
T	Tesla
T1W	T1-weighted
T2W	T2-weighted
TDEP	tumour dynamic enhancement pattern
TE	echo time
TLR	tumour local recurrence
TR	repetition time

TRC	transrectal coil
TSE	turbo spin-echo
TVUS	transvaginal ultrasound
US	ultrasound
VEGF	vascular endothelial growth factors

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