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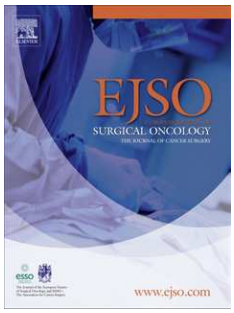

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Magnetic Resonance for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis

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Abstract

Introduction: Current methods of identifying axillary node metastases in breast cancer patients are highly accurate, but are associated with several adverse events. This review evaluates the diagnostic accuracy of Magnetic Resonance Imaging techniques for identification of axillary metastases in early stage newly diagnosed breast cancer patients.

Methods: Comprehensive searches were conducted in April 2009. Study quality was assessed. Sensitivity and specificity were meta-analysed using a bivariate random effects approach, utilising pathological diagnosis via node biopsy as the comparative gold standard.

Results: Based on the highest sensitivity and specificity reported in each of the nine studies evaluating MRI (n=307 patients), mean sensitivity was 90% (95% CI: 78-96%; range 65-100%) and mean specificity 90% (95% CI: 75-96%; range 54-100%). Across five studies evaluating ultrasmall super-paramagnetic iron oxide (USPIO)-enhanced MRI (n=93), mean sensitivity was 98% (95% CI: 61-100%) and mean specificity 96% (95% CI: 72-100%). Across three studies of gadolinium-enhanced MRI (n=187), mean sensitivity was 88% (95% CI: 78-94%) and mean specificity 73% (95% CI: 63-81%). In the single study of in vivo proton MR spectroscopy (n=27), sensitivity was 65% (95% CI: 38-86%) and specificity 100% (95% CI: 69-100%).

Conclusions: USPIO-enhanced MRI showed a trend towards higher sensitivity and specificity and may make a useful addition to the current diagnostic pathway. Additional larger studies with standardised methods and standardised criteria for classifying a node as positive are needed. Current estimates of sensitivity and specificity do not support replacement of SLNB with any current MRI technology in this patient group.

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Introduction

Identification of axillary metastases in early stage newly diagnosed breast cancer is important for staging disease and planning treatment, but current techniques are associated with a number of adverse events. Approximately 40% of women who present with early stage breast cancer also have axillary metastases. The number of metastases present determines the stage of the disease, contributes to the overall prognosis and helps in the planning of adjuvant treatment. In the UK, women usually follow the diagnostic pathway described in the National Institute for Health and Clinical Excellence (NICE) guidelines(1) (Figure 1). If women have a negative ultrasound or ultrasound-guided biopsy of the axilla, they proceed to sentinel lymph node biopsy. Sentinel lymph node biopsy (SLNB) is the excision of the first nodes to receive lymph from the breast (the sentinel nodes). Once removed, the lymph nodes are subject to histological analysis to determine the presence of metastases. If SLNB or the ultrasound-guided biopsy are positive, women proceed to axillary lymph node dissection (ALND), where all lymph nodes are removed to reduce the risk of uncontrolled axillary disease.

SLNB is a highly accurate method of identifying axillary metastases, and whilst it involves the removal of fewer lymph nodes than ALND, it is still associated with both short and long term adverse events. It is estimated that lymphoedema occurs in 21%(2-4) of patients who undergo ALND and 7%(5) of patients who undergo SLNB. Other adverse events include surgical complications such as risk of infection, seroma, insertion of surgical drains and sensitivity to the dyes used in SLNB. Non-invasive alternatives to these diagnostic tests could reduce the incidence of adverse events in women undergoing staging procedures. Any such technique would need to demonstrate acceptable sensitivity to avoid missing metastatic nodes and acceptable specificity to avoid false positive diagnoses, as well as acceptable levels of adverse events.

Magnetic resonance imaging (MRI) is a non-ionising, minimally-invasive in-vivo imaging technique. Unlike x-ray computerised tomography (CT), which uses the attenuation of ionising radiation as the basis of image contrast, standard MRI relies on the magnetic resonance characteristics of hydrogen nuclei (predominantly associated with water and fat) within the body. The technique utilises how these nuclei respond when placed in a magnetic field and are ‘excited’ by radio-waves during the application or switching of magnetic field gradients. The resultant signal is used to build up a set of images in 2 or 3 dimensions and, of particular importance, the contrast between different soft-tissues and pathologies can be highly informative, depending on many factors such as the hydrogen nuclei’s chemical environment. Of importance to axilla imaging, MRI can thus provide information about the size and morphology of lymph nodes. The administration of intravenous contrast media can give

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additional information. The presence of exogenous paramagnetic contrast media perturbs the magnetic field at localities where the media collects, which leads to alterations of local image contrast. This can increase lesion conspicuity (where the media collects) and provide additional information regarding the nature of pathological tissue based on the pattern of uptake. Such information can aid the judgement of whether a node is metastatic or not. As well as MRI of hydrogen nuclei attached to water and fat, the technique of proton MR spectroscopy (^{1}H-MRS) can provide information regarding other molecules, the chemical status of which may be relevant to the presence of pathology. To consider MR imaging and spectroscopy as an alternative to SLNB, its sensitivity and specificity must be estimated. We have conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy and adverse events associated with MRI for assessment of axillary metastases in early stage newly diagnosed breast cancer patients.

[Figure 1.]

Methods

Search strategy

The systematic review followed the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(6;7) statement. Eleven databases were searched in April 2009, namely MEDLINE, Medline in Process, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials, DARE, NHS EED, HTA database, Science Citation Index, and BIOSIS previews. The search strategy included terms for breast cancer, MRI imaging, the axilla or lymph nodes, and diagnostic studies. Searches were also made of the following research registers: National Research Register archive until 2007(www.nrr.nhs.uk), UK NIHR Clinical Research Network post-2007 (www.ukcrn.org.uk), ClinicalTrials.gov (www.clinicaltrials.gov) and Current Controlled Trials (www.controlled-trials.com), and the following relevant conference proceedings: American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO). Additional searching included contact with experts and scrutiny of bibliographies of retrieved papers and reviews. The search was undertaken as part of a broader review on imaging of the axilla for the UK NIHR Health Technology Assessment (HTA) Programme.(8) An additional brief search was performed on MEDLINE for new literature between 2009 to January 2011. Searches were not restricted according to language or publication date.

Study selection strategy

Studies were selected for inclusion by two reviewers (SH and KC) in three stages. Irrelevant titles were excluded by one reviewer and checked by a second. Abstracts of the remaining titles were

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assessed for inclusion by two reviewers, and the full text of potentially includable articles were obtained and scrutinised for inclusion by two reviewers.

Inclusion and exclusion criteria

Cohort studies were included if they assessed the diagnostic accuracy of any MRI technique for assessing axillary metastases in women with early stage newly diagnosed breast cancer, defined as TNM stage I, II or IIIA.(9-11) Patients with carcinoma in situ (ductal or lobular; DCIS or LCIS) were excluded where possible as they do not generally undergo diagnostic axillary surgery. Studies were only included if 80% of patients met the above criteria, or if data could be extracted for a subset of patients where 80% met the above criteria. Studies were included if they compared MRI to an acceptable reference standards test, defined as ALND, SLNB or 4NS. Only studies in which numbers of true negative (TN), true positive (TP), false negative (FN) and false positive (FP) cases were reported or could be calculated were included. Non-English language studies and case-control studies were excluded, though the searches did not identify any case-control studies.

Data extraction and quality assessment

Data was extracted from included studies by one reviewer and checked by a second. Studies were quality assessed by two reviewers using the QUality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist.(12) In accordance with the guidelines for using QUADAS, two items from the published checklist were omitted as they were not relevant to this review (partial verification bias, incorporation bias). The “description of selection criteria” item was also omitted as this was covered by the “patient spectrum” item, where only studies which recruited early-stage newly-diagnosed patients in a prospective, consecutive manner scored positively. The remaining ten items were used to assess study quality.

Data synthesis

A pooled analysis of results was undertaken where study homogeneity allowed. As sensitivity and specificity are inversely linked, a bivariate random effects method was employed, using Stata (copyright StataCorp). This approach assumes a bivariate normal distribution for the logits of sensitivity and specificity, which allows the correlation between them to be accounted for in the meta-regression model; covariates may be used to adjust the (marginal) logits of both sensitivity and specificity.(13;14) Where significant heterogeneity was observed, the random effects method was used in order to account for variation both within and between studies. To explore possible sources of bias, all study quality variables were added as covariates in univariate regression models for sensitivity and specificity to test whether any variables had a significant effect ($p < 0.10$) on

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sensitivity or specificity. Review Manager 5 (copyright Cochrane Collaboration) (15)was used to generate graphical representations.

Results

Number and characteristics of included studies

Searches identified 658 unique titles for the broader review relating to imaging of the axilla. The full text of 138 titles were obtained and examined for inclusion in the broad review. Of these, nine titles(16-24) representing nine studies met the inclusion criteria for this review, and were included. Three studies(18;21;22) reported results for gadolinium enhanced MRI, five(16;17;19;20;23) for ultrasmall super paramagnetic iron oxide (USPIO)-enhanced MRI and one(24) for ^{1}H-MRS.

Study and patient characteristics are reported in Table 1. Where reported, mean age of included participants ranged from 53 to 66. Study size ranged from 10 to 67 patients, though one study only reported the number of axillae (75 axillae). Of the included studies six were prospective, and five of these also stated that consecutive patients were selected. The reference standard was ALND in eight studies, and ALND or SLNB in the other study.

[Insert table 1.]

Quality of included studies

Study quality was generally acceptable (Figure 2) with most items scoring positively. Four items scored poorly or unclear overall: representative patient spectrum, blinding of reference standard to index test results, availability of relevant clinical information and reporting of uninterpretable results.

[insert figure2]

Sensitivity and Specificity of MRI

Across all studies included, sensitivity of MRI ranged from 65%(24) to 100%(16;17;19;22;23) and specificity ranged from 54%(22) to 100%(17;19;20;24) (Figure 3). Several studies used more than one set of criteria for scoring a node as positive, such as size, morphology, contrast uptake or combinations of these. When pooling the data, results for the criteria that gave the best estimates of diagnostic accuracy per study were used. The pooled estimates of sensitivity and specificity were 90% (95% confidence interval (CI) 78% to 96%) and 90% (95% CI 75% to 96%) respectively (Table 2).

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[Insert figure 3]

[Insert Table 2.]

When each MRI modality is considered separately and the estimates of sensitivity and specificity are pooled, USPIO-enhanced MRI gives the highest estimates with a pooled sensitivity of 98% and specificity of 96% (Table 2). These figures are similar to published estimates of sensitivity and specificity of SLNB (sensitivity of approximately 93-95%, and specificity of 100%,(25;26))when compared to ALND and are therefore clinically promising. However, it should be noted that the number of patients is small at 93. Gadolinium-enhanced MRI gave somewhat poorer estimates of 88% and 73% respectively (Table 2), whilst MR spectroscopy estimates are based on one study only, and had sensitivity 65% and specificity 100%.

Subgroup analyses: criteria for positivity

As criteria for positivity varied within and across studies of USPIO enhanced and gadolinium-enhanced MRI, subgroup analyses were performed to assess the effects of these criteria on sensitivity and specificity. Within this analysis, some studies appear more than once. The exact combinations of criteria were often not consistent across studies and the methods of interpreting contrast uptake patterns varied within and between studies.

The most promising diagnostic accuracy in subgroup analyses comes from a pooling of four studies which used USPIO uptake pattern as a criterion for positivity (Table 2). The studies which assessed gadolinium-enhanced MRI used different combinations of criteria for positivity, including uptake pattern, dynamic signal intensity, size, morphology and washout pattern (Table 2). These yielded pairs of estimates lower than those for USPIO-enhanced MRI. Size and morphological criteria for positivity were also considered across the two MRI modalities, though these analyses were mostly based on one study in each category, and none yielded estimates superior to the uptake pattern of USPIO-enhanced MRI.

Sensitivity analyses

Analyses were attempted to assess the effects of study characteristics and study quality on estimates of sensitivity and specificity. Analyses of the effects of size and number of axillary metastases, clinical nodal status, T-stage and reference standard used were not possible due to lack of data or lack

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of variation in data between studies. Studies in which all analysed patients were early-stage newly-diagnosed and did not have a diagnosis of DCIS had a trend towards a higher sensitivity, and a significantly lower specificity, than studies in which not all patients were early-stage, newly-diagnosed and non-DCIS; however, there was wide variation in results between studies. There was no clear correlation between prevalence of axillary metastases within the study and estimates of sensitivity and specificity. There was also no clear correlation between any of the quality assessment items and estimates of diagnostic accuracy, but this analysis is limited by a lack of variation in quality assessment scores between studies.

Withdrawal rates and adverse events

Four studies reported that between 3% and 18% of patients withdrew. Reasons for withdrawal included no ALND, inadequate MRI data, and claustrophobia or poor health. No serious adverse effects were reported in any of the MRI studies. Mild-to-moderate adverse effects included mild rash following USPIO administration (recovered without treatment or following antihistamine treatment) and inability to complete the MRI scan due to claustrophobia or back pain as a result of holding the same position for some time. In addition, many of the studies excluded patients with contraindications to MRI, such as strong allergic disposition, allergy to contrast agents, or liver dysfunction.

Discussion

Overall pooled estimates of sensitivity and specificity for MRI were 90% and 90% respectively, with USPIO-enhanced MRI giving the highest overall diagnostic accuracy with sensitivity of 98% and specificity of 96%. Gadolinium-enhanced MRI gave sensitivity of 88% and specificity of 73% and MR spectroscopy gave a sensitivity of 65% and specificity of 100%. Confidence intervals were wide, and there was considerable variation in the criteria used to class a node as positive.

This study uses a bivariate random effects method of meta-analysis to pool estimates of sensitivity and specificity, which takes into account the inverse relationship between the two values. We have also made a thorough review of the literature to April 2009, and the brief update search performed in MEDLINE in January 2011 indicates that no eligible studies have been published subsequently. However, the study is limited by the small amount of available data, both in terms of numbers of participants and numbers of studies.

SLNB is reported to have a sensitivity of approximately 93-95%, and a specificity of 100%.(25;26) Replacing SLNB at a population level with MRI, based on the overall pooled estimates within this

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review (pooled sensitivity 90%, specificity 90%), would result in an increase in missed metastases as MRI has a lower sensitivity than SLNB, leading to more false negative cases. It would result in an increase in unnecessary ALND procedures, as MRI has lower specificity than SLNB, leading to more false positive cases. It would also mean a large number of women would not undergo SLNB and would therefore avoid the risk of adverse events associated with these procedures. However, the associated increase in women with false negative results who would therefore be put at greater risk of cancer recurrence may not be acceptable despite the reduction in adverse events.

Subgroup analyses indicated, however, that USPIO-enhanced MRI had superior sensitivity (98%), but inferior specificity (96%) to SLNB. In addition, subgroup analyses indicate that the criteria used to classify a node as positive may affect diagnostic accuracy, though wide confidence intervals preclude firm conclusions. Whilst these results come from a small number of patients and the criteria for positivity varied between the studies that have been pooled, they are promising and fall within the ranges of sensitivity reported for SLNB. Further technological development, especially of USPIO-enhanced MRI, would seem warranted, and research to identify the optimal criteria for classing a node as positive may lead to improvements in diagnostic accuracy independent of technological advances.

Given current estimates of diagnostic accuracy, an alternative strategy, where MRI is added to the current pathway before ALND/SLNB, could be considered. This way, women at greatest risk (positive for nodal metastases by any of ultrasound, biopsy or USPIO-enhanced MRI) could be triaged for ALND, whilst those who are negative would still receive SLNB and benefit from the high specificity of this procedure. Fewer women would have to undergo two operations, namely SLNB followed by ALND where positive. A cost-effectiveness model considering these two options and based on the results of this review, is reported elsewhere.(8;27)

An alternative technique, the intra-operative analysis of lymph nodes, is in use in some centres. This technique aims to reduce the need for women to undergo two operations as excised nodes are tested for metastases during the initial operation to remove the tumour. Improvements in and more widespread use of this technique may reduce the potential usefulness of adding MRI to the diagnostic pathway prior to ALND/SLNB.

Conclusion

In summary, USPIO-enhanced MRI shows promising diagnostic accuracy for identifying axillary lymph node metastases in patients with early stage newly diagnosed breast cancer. Furthermore, MRI may make a useful addition to the current diagnostic pathway, by enabling more women to be

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correctly triaged for ALND, and avoid the need for two operations. However, there is a need for more and larger studies with standardised methods and standardised criteria for classifying a node as positive before any changes to policy and practice should be considered. Current estimates of sensitivity and specificity do not support replacement of SLNB with the assessed current MRI methodologies and technologies.

This project was funded by the NIHR Health Technology Assessment Programme (project number 08/35/01) and will be published in full in the monograph series Health Technology Assessment. See the HTA programme website for further project information. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

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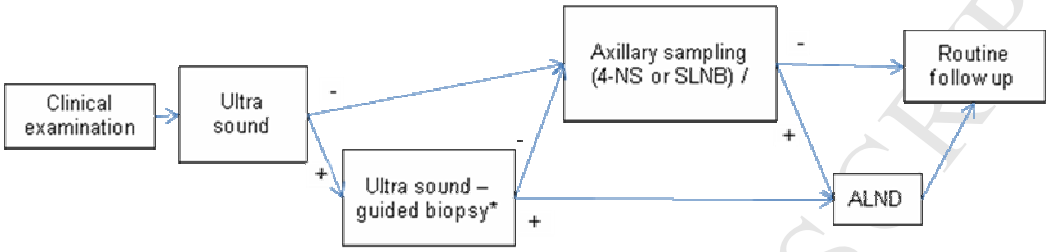
Figure 1: Diagnostic pathway for axillary metastases as recommended in NICE 2009 breast cancer guidelines (1)



*Either fine needle aspiration cytology (FNAC) or core biopsy.

Figure 2. Quality of included studies scored against the QUADAS criteria.

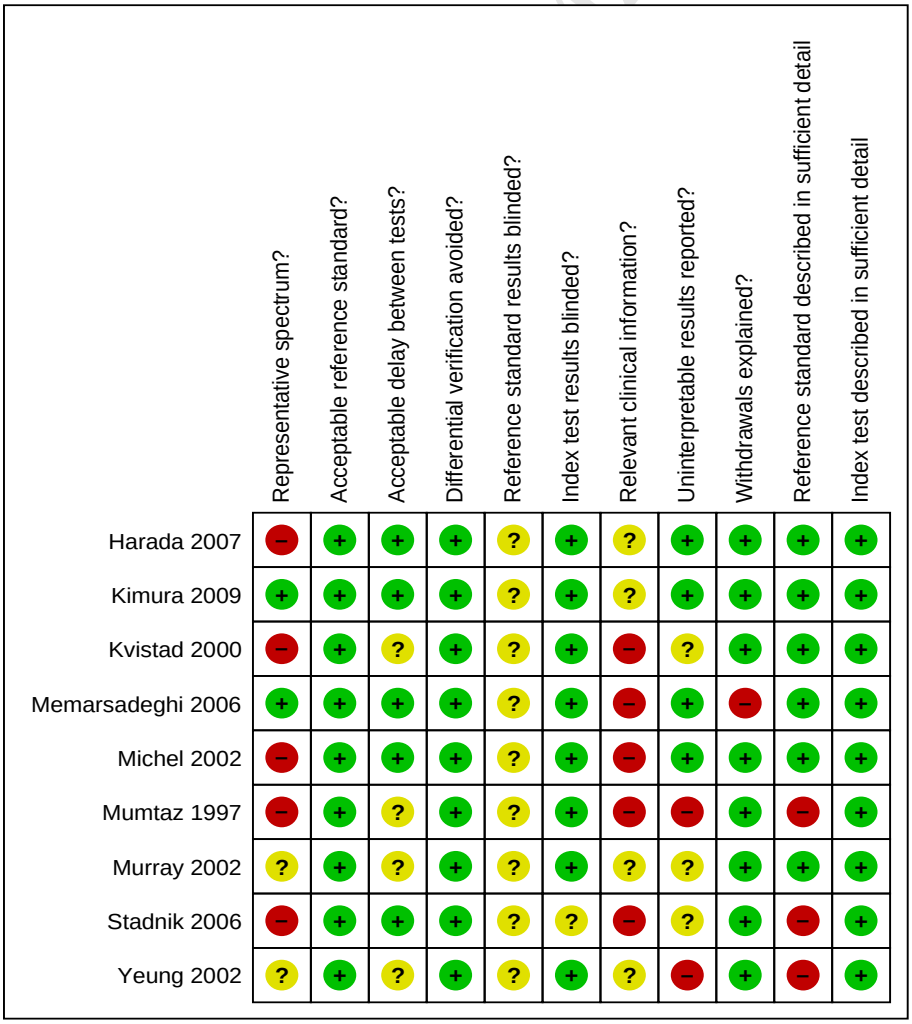


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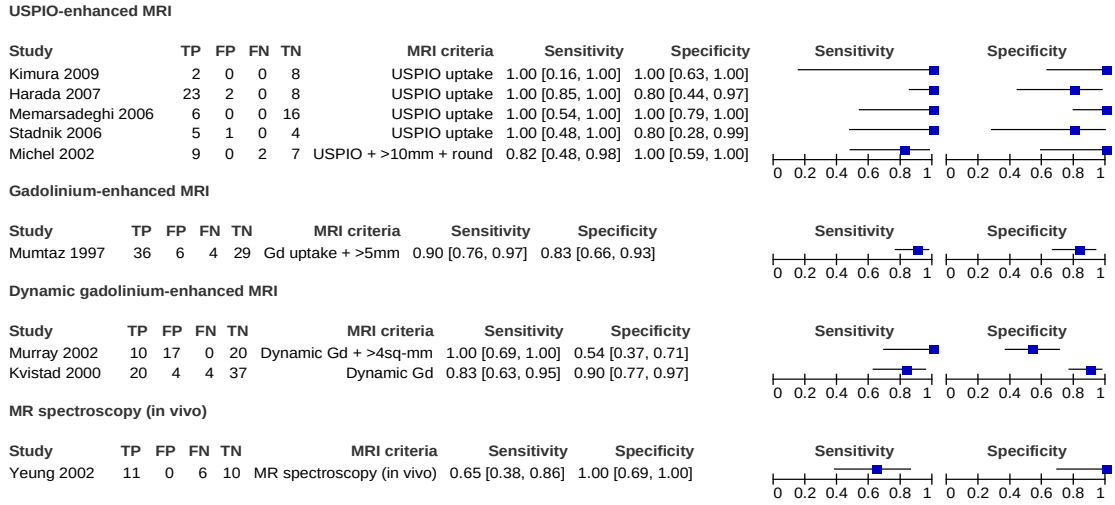
Figure 3. Forest plot of all MRI studies*



TP=true positive, FP=false positive, FN=false negative, TN=true negative. Brackets show 95% confidence intervals. The figure shows the sensitivity and specificity for each study (squares) and 95% confidence intervals (horizontal lines). *Where studies report results using more than one set of criteria for positivity, these analyses use data corresponding to the criteria with the highest reported estimates of diagnostic accuracy per study. The criteria used for each study are shown on the plot.

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Table 1. Characteristics of included MRI studies

Study	Country	Index test	Reference standard	Prospective/ retrospective? Consecutive?	N met criteria† N analysed	Age Gender	Cancer stage	Clinical nodal status	Prevalence of axillary metastases	Confirmation of breast cancer	Other inclusion and exc criteria
Kimura 2009(17)	Japan	USPIO-enhanced	ALND and/or SLNB	Prospective Consecutive	10 10	66 (35 to 79) Female	100% clinically T2 N0 M0 (stage IIA)	100% negative	20%	Pathology (no further detail)	Exclusion: strong allergic disposition, liver dysfunct
Harada 2007(16)	Japan	USPIO-enhanced	100% ALND	Prospective Consecutive	33 33	58 (36-77) 97% female	Stage II=73% Stage IIIA=24% Stage IIIB=3%	NR	70%	Pathology (no further detail)	Exclusion: stage I, strong disposition, liver dysfunct
Memarsadeghi 2006(19)	Austria	USPIO-enhanced	100% ALND	Prospective Consecutive	24 22	60 (40-79) Female	T1=59%, T2=41%	NR	27%	CNB	Exclusion: contraindicatio MRI, allergy to dextran o salts, chemotherapy or radiotherapy, no ALND, pregnancy, lactation, unab cooperate, other trial, und of guardian
Stadnik 2006(23)	Belgium	USPIO-enhanced	100% ALND	Prospective NR	10 10	56 (41 to 74) Female	Stage not reported.§ Included pts scheduled for mastectomy	NR	50%	NR	Exclusion: not scheduled mastectomy, contraindica MRI, strong allergic dispo to gadolinium, dextrans o salts, unable to obtain PE technical or accessibility
Michel 2002(20)	Switzerland	USPIO-enhanced	100% ALND	Prospective Consecutive	18 18	53 (22-76) Female	T1=56%, T2=39%, T4=6%	NR	61%	Cytology 95%, histology 5%	Exclusion: strong allergic disposition, contraindicati MRI

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Study	Country	Index test	Reference standard	Prospective/ retrospective? Consecutive?	N met criteria† N analysed	Age Gender	Cancer stage	Clinical nodal status	Prevalence of axillary metastases	Confirmation of breast cancer	Other inclusion and excl criteria
Murray 2002(22)	UK	Dynamic gadolinium-enhanced	100% ALND	NR NR	47 47	63 (50-87) Female	T1/T2=100%	NR	21%	Histology (no further detail)	Exclusion: primary tumou <0.5cm or >3.1cm.
Kvistad 2000(18)	Norway	Dynamic gadolinium-enhanced	100% ALND	NR NR	67 65	59 (38-79) NR	T1=58%, T2=31%, T3/T4=11% (neoadj chemotherapy)	Positive and negative (% NR)	37%	Histology or FNAC	NR
Mumtaz 1997(21)	UK	Gadolinium-enhanced	100% ALND	NR NR	92 axilla 75 axilla	49‡ (29-80) NR	T1=11%, T2=72%, T3=3%, T4=3%, Tx=11%, DCIS=4%	NR	53%	FNAC 90%, CNB 10% (if equivocal)	NR
Yeung 2002(24)	Hong Kong	MR spectroscopy	100% ALND	Prospective Consecutive	32 27	53 (26-82) NR	Stage not reported∫	52% negative 48% positive	63%	CNB	Exclusion: receiving chemotherapy

†Number meeting criteria for this review. § Stage was not reported, but tumours were 1-3cm indicating all participants were early stage. ∫ Stage was not reported, but only data relating to patients with tumours ≤5cm (early stage) were used in analysis. Ages are mean (range) unless marked ‡which indicates median (range). ALND=axillary lymph node dissection; CNB=core needle biopsy; FNAC=fine needle aspiration cytology; MRI=magnetic resonance imaging; NR=not reported; SLNB=sentinel lymph node biopsy; USPIO= ultrasmall super-paramagnetic iron oxide.

Table 2. Summary of pooled sensitivities and specificities for MRI studies* overall and according to criteria for positivity.

Diagnostic test	N studies	N patients	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
All MRI studies				
All MRI studies	9	307	90 (78 to 96)	90 (75 to 96)
MRI studies by type of MRI				
USPIO-enhanced MRI	5	93	98 (61 to 100)	96 (72 to 100)

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Diagnostic test	N studies	N patients	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Gadolinium-enhanced MRI	3	187	88 (78 to 94)	73 (63 to 81)
MR spectroscopy	1	27	65 (38 to 86)	100 (69 to 100)
Criteria for positivity	**N studies**	**N patients**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**
USPIO-based criteria				
USPIO uptake	4	75	98 (63 to 100)	94 (69 to 99)
USPIO uptake, size >10mm, round shape (not clear if "and" or "or")	1	18	82 (48 to 98)	100 (59 to 100)
Gadolinium-based criteria				
Gd uptake, size >5mm(21) (not clear if "and" or "or")	1	75	90 (76 to 97)	83 (66 to 93)
Dynamic Gd signal intensity increase	2	112	86 (68 to 94)	59 (45 to 72)
Dynamic Gd + positive washout	1	65	71 (49 to 87)	90 (77 to 97)
Dynamic Gd + size >4sq-mm	1	47	100 (69 to 100)	54 (37 to 71)
Dynamic Gd + size >5mm + abnormal morphology	1	65	63 (41 to 81)	93 (80 to 98)
Size and/or morphological criteria				
Size >4sq-mm	1	47	100 (69 to 100)	19 (08 to 35)
Size >5mm	1	33	100 (85 to 100)	10 (0 to 45)
Size >10mm	1	33	43 (23 to 66)	80 (44 to 97)
Abnormal morphology	1	33	96 (78 to 100)	20 (03 to 56)
Size >5m + abnormal morphology	1	65	63 (41 to 81)	80 (65 to 91)
Size >10mm and/or round shape	1	22	83 (36 to 100)	31 (11 to 59)

*Where studies report results using more than one set of criteria for positivity, these analyses use data corresponding to the criteria with the highest reported estimates of diagnostic accuracy per study. Gd = Gadolinium

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