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Magnetic resonance imaging (MRI) for assessment of axillary lymph node metastases in breast cancer: systematic review

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INTRODUCTION

Assessment of axillary lymph node status is important in breast cancer staging. UK guidance recommends sentinel lymph node biopsy (SLNB) or 4-node sampling (4-NS) where ultrasound and ultrasound-guided biopsy are negative. Where biopsy, SLNB or 4-NS are positive, axillary lymph node dissection (ALND) is recommended. The surgical procedure ALND, and to a lesser extent SLNB and 4-NS, are associated with adverse effects such as arm lymphoedema. Magnetic resonance imaging (MRI) provides detailed images of the body in any plane and is a non-invasive technique with few adverse events. An MRI scan may provide information on whether a lymph node is suspicious for metastasis, avoiding the need for surgery and its associated adverse effects. However, it is unclear whether MRI can match the excellent diagnostic accuracies of ALND, SLNB and 4-NS.

OBJECTIVE

To assess the diagnostic accuracy and effect on patient outcomes of MRI for assessment of axillary lymph nodes in newly diagnosed early breast cancer.

METHODS

A systematic review was undertaken to identify studies reporting sensitivity and specificity of MRI for the assessment of axillary lymph node metastases in early-stage breast cancer. The following databases were searched in April 2009: 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. Research registers and conference proceedings were also searched. Articles were considered for inclusion by two reviewers and were included in the review if they met the inclusion criteria (Table 1). Data were extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. Discrepancies were resolved by discussion. Study quality was assessed using the QUADAS checklist (QUality Assessment of Diagnostic Accuracy Studies).[1] A bivariate random effects approach was used for the meta-analysis of pairs of sensitivity and specificity to allow for the observed inverse relationship between the two.

Table 1. Inclusion criteria

Population	80% or more newly diagnosed early stage breast cancer (TNM stage I, II or IIIA)
Diagnostic test	Diagnostic tests utilising MRI technology
Reference standard	ALND, SLNB or 4NS
Outcome	Sensitivity and specificity of MRI for assessment of axillary metastases
Study design	Cohort studies from which true positive, false positive, true negative and false negative numbers could be extracted or calculated

Table 2. Study and patient characteristics

Study	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
Kimura 2009[2]	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)
Harada 2007[3]	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)
Memarsadeghi 2006[4]	USPIO-enhanced	100% ALND	Prospective Consecutive	24 22		T1=59%, T2=41%	NR	27%	CNB
Stadnik 2006[5]	USPIO-enhanced	100% ALND	Prospective NR	10 10	56 (41 to 74) Female	Stage not reported. Included pts scheduled for mastectomy	NR	50%	NR
Michel 2002[6]	USPIO-enhanced	100% ALND	Prospective Consecutive	18 18	53 (22-76) Female	T1=56%, T2=39%, T4=6%	NR	61%	Cytology 95%, histology 5%
Murray 2002[7]	Dynamic gadolinium-enhanced	100% ALND	NR NR	47 47	63 (50-87) Female	T1/T2=100%	NR	21%	Histology (no further detail)
Kvistad 2000[8]	Dynamic gadolinium-enhanced	100% ALND	NR NR	67 65	59 (38-79) NR	T1=58%, T2=31%, T3/T4=11% (neoadjuvant chemotherapy)	Positive and negative (% NR)	37%	Histology or FNAC
Mumtaz 1997[9]	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)
Yeung 2002[10]	MR spectroscopy	100% ALND	Prospective Consecutive	32 27	53 (26-82) NR	Stage not reported	52% negative 48% positive	63%	CNB

RESULTS

The search identified 658 citations (646 from the literature search and 12 from other sources such as relevant reviews), of which nine satisfied the inclusion criteria and were included in the review (Table 2). There were five studies of USPIO-enhanced MRI,[2-6] two studies of dynamic gadolinium-enhanced MRI,[7,8] one study of (non-dynamic) gadolinium-enhanced MRI,[9] and one study of in vivo proton MR spectroscopy.[10] Study quality was generally good though there were problems with the representativeness of the patient sample and with the lack of availability of the same clinical information as would be used in practice in around half the papers. No papers gave information regarding blinding of the reference standard.

Several studies reported more than one set of results, according to different criteria for defining whether axillary metastases were present. Criteria were based on size, morphology, contrast media uptake pattern, or a combination of these. The best results from each study were used in meta analysis. Across all nine MRI studies, USPIO-enhanced MRI showed a trend towards higher sensitivity and specificity than gadolinium-enhanced MRI (Table 3).

Table 3. Meta analysis of included studies

Diagnostic test	N studies	N patients	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
All MRI studies				
All MRI studies[2-10]	9	307	90 (78 to 96)	90 (75 to 96)
MRI studies by type of MRI				
USPIO-enhanced MRI[2-6]	5	93	98 (61 to 100)	96 (72 to 100)
Gadolinium-enhanced MRI[7,8,9]	3	187	88 (78 to 94)	73 (63 to 81)
MR spectroscopy[10]	1	27	65 (38 to 86)	100 (69 to 100)

The diagnostic accuracy data was analysed according to the criteria for defining whether axillary metastases were present. The use of contrast uptake pattern as the main criterion for defining a node as metastatic appeared to give better combined sensitivity and specificity than size and morphology, although many studies used criteria based on both uptake and size/morphology, and the methods of interpreting uptake patterns varied within and between studies. Sensitivity analyses were performed where data allowed. A non-significant trend towards higher sensitivity and significantly lower specificity was observed where all patients were newly diagnosed and early stage. Study quality and prevalence of metastases did not affect results, though study quality was largely homogenous making for a limited analysis. Only mild to moderate adverse events were reported, including back pain and claustrophobia whilst in the scanner, and allergic reactions (rash) to the contrast media USPIO.

CONCLUSIONS

Compared to reported values for SLNB and 4-NS (sensitivity approximately 93-95%, specificity 100%[11,12]), USPIO-enhanced MRI showed higher sensitivity but lower specificity, gadolinium-enhanced MRI showed lower sensitivity and specificity, whilst one study of in vivo proton MR spectroscopy showed much lower sensitivity and equal specificity. Therefore, replacing SLNB/4-NS with USPIO-enhanced MRI could lead to fewer false negative women at risk of recurrence, but more false positive women undergoing unnecessary ALND with the associated risk of adverse events. No women would undergo SLNB/4-NS. An option for consideration may be the addition of MRI to the current diagnostic pathway prior to SLNB/4-NS. All these results should be interpreted with caution due to the small number of studies and participants and consequent wide confidence intervals, and the wide variation in sensitivity and specificity between studies. Further large studies of USPIO-enhanced MRI in this setting may be valuable.

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