Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial

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Summary

Background **MRI might improve diagnosis of breast cancer, reducing rates of reoperation. We assessed the clinical efficacy of contrast-enhanced MRI in women with primary breast cancer.**

Methods **We undertook an open, parallel group trial in 45 UK centres, with 1623 women aged 18 years or older with biopsy-proven primary breast cancer who were scheduled for wide local excision after triple assessment. Patients were randomly assigned to receive either MRI (n=816) or no further imaging (807), with use of a minimisation algorithm incorporating a random element. The primary endpoint was the proportion of patients undergoing a repeat operation or further mastectomy within 6 months of random assignment, or a pathologically avoidable mastectomy at initial operation. Analysis was by intention to treat. This study is registered, ISRCTN number 57474502.**

Findings **816 patients were randomly assigned to MRI and 807 to no MRI. Addition of MRI to conventional triple assessment was not significantly associated with reduced a reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the no MRI group, (odds ratio 0·96, 95% CI 0·75–1·24; p=0·77).**

Interpretation **Our findings are of benefit to the NHS because they show that MRI might be unnecessary in this population of patients to reduce repeat operation rates, and could assist in improved use of NHS services.**

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Introduction

The quality-assurance standard for the UK National Health Service Breast Screening Programme (NHS BSP)[1] has set a target for reoperation rates for incomplete tumour excision of less than 10%. In 2001, when the COMICE protocol was written, the actual rate was 14·2% and has not reduced over time. According to the 2006–07 UK audit of screen-detected breast cancers,[2] 17% of patients with primary breast cancer with a diagnosis of definite malignant disease (C5 or B5) underwent reoperation for positive tumour margins.[2]

In studies of surgery[3,4] without subsequent radiotherapy for treatment of primary breast cancer, researchers reported a 25–40% risk of local tumour recurrence when the initial disease was multifocal or multicentric, compared with 11% for more than one malignant focus. An increased rate of inadequate or indeterminate resection margins in specimens with more than one malignant foci could account for these findings, but detailed sectioning of mastectomy specimens revealed that additional tumour foci were present in 30–63% of women who were mammographically suspected of having unifocal disease.[5] When tumour resection margins are clear and radiotherapy is administered, rates of recurrence for unifocal and multifocal tumours are similar.[6,7]

Malignant lesions are difficult to detect in the mammographically dense breast. Substantial evidence exists for a good relation between MRI and histology of resected specimens, with results exceeding those for X-ray mammography or ultrasound.[8–10] Findings from two observational studies[11,12] of the role of dynamic contrast-enhanced MRI in clinical management of patients scheduled for breast-conservation surgery have shown management to be altered in 14–18% of patients because of detection of disease that was more extensive than was first diagnosed, although neither study reported factors predictive of alteration in outcome.

Cost-effectiveness of MRI in this clinical setting is unknown. In 2001, we started the COmparative effectiveness of MR Imaging in breast CancEr (COMICE) trial to assess the clinical efficacy and cost-effectiveness of contrast-enhanced MRI in women with primary breast cancer who were scheduled for wide local excision. In this trial, we address the uncertainty about preoperative identification of multicentric disease, the effect of MRI on clinical management, quality of life measures, and patient satisfaction, and incorporated a health economic assessment.

Here we report results of the primary endpoint of the trial, the proportion of patients undergoing a repeat operation or further mastectomy within 6 months of randomisation, or a pathologically avoidable mastectomy at initial operation, and provide data about quality of life and health economic assessments.[13]

Methods

Patients

COMICE is a multicentre, randomised, controlled, open-label, parallel group trial, designed to compare the efficacy of MRI and standard triple assessment with triple assessment alone in reduction of reoperation rates.

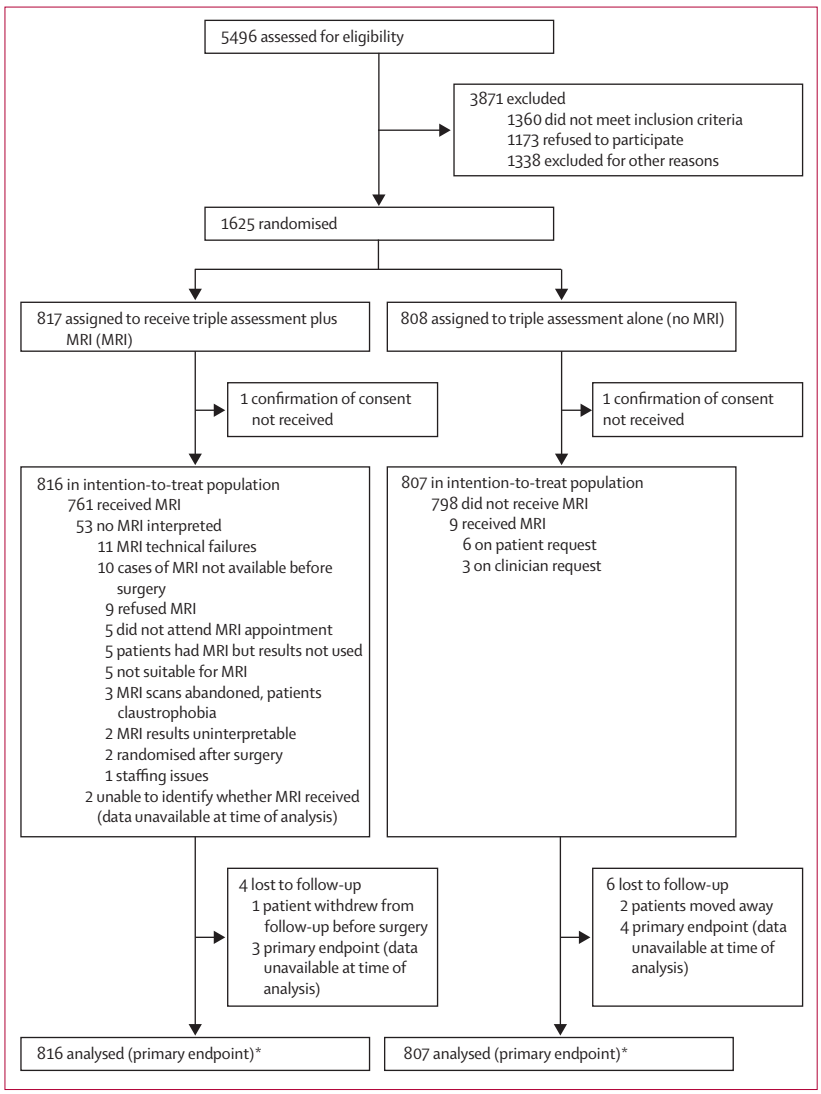

Figure 1: **Trial profile**
*Patients lost to follow-up regarded as not having a primary endpoint event.

Triple assessment was defined as clinical, radiological (X-ray mammography and ultrasound) and pathological (fine-needle aspiration cytology or core biopsy) assessment. The study was undertaken at 45 UK centres. We chose an approach to trial design that would enable results to be generalisable to clinical practice. Women aged 18 years or older with biopsy-proven primary breast cancer who were scheduled for wide local excision after triple assessment were eligible. Exclusion criteria included patients who: were medically unstable; had known contraindications to MRI; had allergic reactions to paramagnetic contrast agent or severe allergic diathesis; were on renal dialysis; had undergone chemotherapy or hormonal therapy for cancer for the contralateral breast in previous 12 months, or had chemotherapy planned to any site before breast surgery; had previous surgery or radiotherapy for cancer to the ipsilateral breast or previous surgery to the ipsilateral breast within the past 4 months for benign breast disease; had a history of serious breast trauma within the past 3 months; were pregnant or breastfeeding; or had a disability preventing MRI in a prone position. Patients scheduled for wide local excision on the basis of triple assessment were invited to participate in the study by the consultant breast surgeons or consultant radiologist during discussions about treatment options. Further information was provided by the research nurse, and, whenever possible, patients were given at least 24 h to consider participation.

All patients provided written informed consent. The trial was approved by multicentre and local research ethics committees. An independent Data Monitoring and Ethics Committee (DMEC) was used to ensure safety issues and ethical considerations were appropriately addressed.

Randomisation and masking

Patients were randomised to receive either MRI or no further imaging (no MRI) on a 1:1 basis, with a minimisation algorithm incorporating a random element. Minimisation factors were the consultant breast surgeon, age (<50 *vs* ≥50 years), and breast density group[1] (American College of Radiology Breast Imaging—Reporting and Data Systems [ACR BI-RADS type 1] *vs* group 2 ACR BI-RADS type 2, 3, or 4). Randomisation was administered by the University of Leeds Clinical Trials Research Unit's automated 24-hour telephone randomisation system, by either the research nurse or the consultant breast surgeon.

Procedures

X-ray mammography and ultrasound were undertaken according to standard local protocol. We used a standard protocol for MRI, which was done on 1.5T systems (GE Healthcare, London UK; Siemens AG, Berlin, Germany; and Philips Healthcare, Amsterdam, the Netherlands) with dedicated bilateral breast-surface coils for signal reception, with a few scans done at 1.0T. Multiple thin-slice (in-plane resolution 1·3×0·8 mm, slice thickness 4 mm) fast-gradient echo sequences (temporal resolution 45 s) were acquired coronally through both breasts for up to 450 s to measure the pattern of contrast uptake. The first two datasets were obtained before and the remainder after an intravenous bolus injection of Gadolinium-based contrast agent was given (0·1 mmol Gd-diethylenetriaminepenta-acetic acid per kg of body-weight). High resolution (0·7 mm×0·4 mm in-plane, slice thickness 2·5 mm) post-contrast, fat-suppressed three dimensional MR images were obtained coronally for morphological information.

We classified lesions according to the pattern of the time-signal intensity curve and morphological appearance.[14–16] Details of the MRI protocol and method of analysis can be obtained from the HTA monologue.[13]

Patients allocated to no MRI were scheduled to undergo wide local excision as planned. If the findings for those undergoing MRI were not equivalent to those of triple assessment, results were reviewed by a multidisciplinary team. MR-guided biopsy sampling (either at locality or regional centre) or, if unavailable, MR-localised, ultrasound-guided fine-needle aspiration cytology or core biopsy was needed for multicentric lesions that were 5 mm or larger, and was recommended for multifocal lesions in cases that were diagnostically difficult.

Surgery was planned as appropriate, with any changes in management recorded. Clear margins were assumed to be free of both ductal carcinoma in situ and invasive tumour. Every participating consultant breast surgeon provided their local definition of a clear margin before starting recruitment. Local definitions were applied to both trial groups, and ranged from 0·5–5·0 mm for invasive disease and 1·0–10·0 mm for ductal carcinoma in situ.

Histopathological assessment of excised specimens was done at every participating centre in accordance with guidelines in the NHS BSP publication—pathology reporting in breast cancer screening.[17] These core guidelines contain the minimum dataset for breast cancer histopathology reports, and were defined by the Royal College of Pathologists.

We gathered clinical follow-up data at 6 and 12 months after surgery, then yearly thereafter, until all patients had been followed up for at least 1 year. We undertook a quality assurance process to ensure that MRI scans were completed in accordance with the technical needs of the trial protocol, and that scan interpretation was consistent between all participating centres. This process was completed by an independent radiologist, who was masked to the original MRI findings. Full details of the quality assurance protocol are in the HTA monologue.[13]

	MRI (n=816)	No MRI (n=807)	Total (n=1623)
Number of patients recruited by surgeon undertaking randomisation			
Fewer than 10	115 (14%)	115 (14%)	230 (14%)
10 or more	701 (86%)	692 (86%)	1393 (86%)
Age at randomisation			
Younger than age 50 years	187 (23%)	187 (23%)	374 (23%)
50 years or older	629 (77%)	620 (77%)	1249 (77%)
Median (IQR)	57 (50–63)	57 (50–64)	57 (50–64)
Breast density at randomisation			
ACR BI-RADS group 1 (type 1)	102 (13%)	106 (13%)	208 (13%)
ACR BI-RADS group 2 (type 2, 3, or 4)	714 (88%)	701 (87%)	1415 (87%)
Menopausal status			
Premenopausal	232 (28%)	234 (29%)	466 (29%)
Postmenopausal	574 (70%)	565 (70%)	1139 (70%)
Missing data	10 (1%)	8 (1%)	18 (1%)
Contraceptive pill or slow-release injection use			
Current (at randomisation)	23 (3%)	28 (4%)	51 (3%)
Previously	458 (56%)	478 (59%)	936 (58%)
Never	327 (40%)	294 (36%)	621 (38%)
Missing data	8 (1%)	7 (<1%)	15 (<1%)
HRT use			
Current (at randomisation)	63 (8%)	46 (6%)	109 (7%)
Previously	232 (28%)	231 (29%)	463 (29%)
Never	514 (63%)	528 (65%)	1042 (64%)
Missing data	7 (<1%)	2 (<1%)	9 (<1%)
Type of surgery			
Wide local excision	750 (92%)	787 (98%)	1537 (94%)
Mastectomy	58 (7%)	10 (1%)	68 (4%)
Quadrantectomy and mini flap	1 (<1%)	0 (0%)	1 (<1%)
Other	2 (<1%)	0 (0%)	2 (<1%)
Did not have surgery	2 (<1%)	2 (<2%)	4 (<2%)
Lost to follow-up	1 (<1%)	1 (<1%)	2 (<1%)
Missing data	2 (<1%)	7 (<1%)	9 (<1%)

Data are n (%) unless otherwise stated. HRT=hormone replacement therapy. ACR BI-RADS=American College of Radiology Breast Imaging Reporting and Data System.

Table 1: **Baseline characteristics**

Outcome measures

The primary clinical outcome was the proportion of patients undergoing a repeat operation—either further wide local excision or mastectomy within 6 months of random assignment, or a pathologically avoidable mastectomy at initial operation (termed reoperation rate). Imaging findings from patients undergoing a mastectomy at initial operation were reviewed every 12 months in conjunction with histopathological findings by the DMEC to identify any false-positive MR findings that could lead to a pathologically avoidable mastectomy. The definition of a pathologically avoidable mastectomy that was specified by the independent DMEC and agreed by the Trial Steering Committee was as follows: MRI-detected multifocal lesions resulting in mastectomy, but histopathology showing only localised malignant disease; or, the size of the index lesion, as measured by MRI, being larger than that detected by triple assessment alone, resulting in mastectomy, but histopathology showing that either the size of the index lesion or the size of the index lesion and ductal carcinoma in situ was 30 mm or less in diameter.

We also undertook an economic assessment according to the NHS cost perspective (ie, actual cost of care delivered to patients) and quantified health-related quality of life, as assessed by the Euro quality of life 5D questionnaire (EQ-5D),[18,19] to investigate the cost-effectiveness of MRI in this setting. This assessment formed the primary health economic endpoint. Secondary endpoints were change in clinical management, quality of life as assessed by the functional assessment of cancer therapy (breast cancer version; FACT-B)[20,21] at 8 weeks after randomisation and 6 and 12 months after initial surgery, local tumour recurrence, and the effectiveness of the imaging techniques.

	MRI (n=816)	No MRI (n=807)	Total (n=1623)
Weight of specimen (g) from wide local excision			
Median (IQR)	54·0 (35·0–90·0)	51·0 (33·0–77·0)	52·8 (34·0–83·4)
Missing data	55/750 (7%)	62/787 (8%)	117/1537 (8%)
Invasive carcinoma			
Total	743 (91%)	723 (90%)	1466 (90%)
Tumour type			
Mucinous carcinoma	20 (3%)	13 (2%)	33 (2%)
Tubular carcinoma	24 (3%)	28 (4%)	52 (4%)
Ductal non-specified tumour	570 (77%)	544 (75%)	1114 (76%)
Lobular carcinoma	63 (9%)	70 (10%)	133 (9%)
Not assessable	2 (<1%)	1 (<1%)	3 (<1%)
Mixed	8 (1%)	15 (2%)	23 (2%)
Other	54 (7%)	52 (7·2%)	106 (7%)
Missing data	2 (<1%)	0 (0%)	2 (<1%)
Grade			
I	177 (24%)	179 (25%)	356 (24%)
II	358 (48%)	331 (46%)	689 (47%)
III	200 (27%)	205 (28%)	405 (28%)
Missing data	8 (1%)	8 (1%)	16 (1%)
Extent of disease			
Localised	613 (83%)	631 (87%)	1244 (85%)
Multifocal	90 (12%)	72 (10%)	162 (11%)
Not assessable	11 (2%)	5 (<1%)	16 (1%)
Multicentric	11 (2%)	6 (<1%)	17 (1%)
Missing data	18 (2%)	9 (1%)	27 (2%)
Size of index lesion (mm)			
Median (IQR)	15·0 (11·0–21·5)	15·0 (11·0–21·0)	15·0 (11·0–21·0)
Missing data	12/743 (2%)	11/723 (2%)	23/1466 (2%)
Size of invasive plus DCIS (mm)			
Median (IQR)	18 (14–26)	18 (13–25)	18 (13–26)
Missing	127/743 (17%)	112/723 (15%)	239/1466 (16%)
Invasive tumour			
Margin status for invasive tumour			
Reaches margin	99 (13%)	106 (15%)	205 (14%)
Uncertain	17 (2%)	26 (4%)	43 (3%)
Does not reach margin	620 (83%)	582 (81%)	1202 (82%)
Missing data	7 (1%)	9 (1%)	16 (1%)
Distance of invasive tumour to margin (mm)			
Median (IQR)	4·0 (1·0–6·0)	4·0 (1·0–6·0)	4·0 (1·0–6·0)
Missing data	53/743 (7%)	57/723 (8%)	110/1466 (8%)
DCIS			
Marginal status for DCIS			
Reaches margin	94 (16%)	83 (15%)	177 (15%)
Uncertain	19 (3%)	18 (3%)	37 (3%)
Does not reach margin	333 (57%)	347 (61%)	680 (9%)
Missing data	140/586 (24%)	120/568 (21%)	260/1154 (23%)
Distance of DCIS to margin (mm)			
Median (IQR)	3·0 (1·0–7·0)	3·0 (1·0–6·0)	3·0 (1·0–6·0)
Missing data	206/586 (35%)	193/568 (34%)	399/1154 (35%)

Data are median (IQR), n/N (%), or n (%). DCIS=ductal carcinoma in situ.

Table 2: **First operation pathology details**

Statistical analysis

With an assumption that the addition of MRI would reduce the overall primary-endpoint rate from about 15%[4] to 10%, we needed 1840 patients to detect this reduction with 90% power at a 5% (two-sided) significance level, with a χ^2 test without continuity correction. Conventional minimum 80% power is associated with a widely accepted level of risk for large-scale clinical trials. The COMICE trial was powered at 90% because we believed this power was achievable; however, were 80% power chosen, we would have needed 1372 patients.

We compared the reoperation rate between groups with use of logistic regression, adjusting for the minimisation factors. Patients undergoing a mastectomy at initial operation because of patient decision alone were regarded as having a reoperation. Those who were lost to follow-up were classified as not having a primary-endpoint event. We undertook prespecified exploratory subgroup analyses to assess the interaction of tumour type (lobular carcinoma *vs* all other types) with MRI and ad-hoc exploratory analyses to assess the interaction of age with MRI.

Effectiveness of imaging examined the agreement between predicted patient management established from results of MRI compared with management based on results of histopathological assessement of the excised specimen. Predicted patient management was based on raw data and calculated with special reference to: number and type (benign or malignant) of lesions detected; maximum diameter of all foci of invasive or in-situ carcinoma, or the sum of invasive and in-situ carcinoma present; and location and extent of additional tumours (localised, multifocal, or multicentric). DMEC definitions (pre-established criteria) were used to establish whether a change in surgical management from wide local excision to mastectomy was needed on the basis of results from both MRI and histopathology separately. With an assumption that histopathology was the gold standard, and regarding mastectomy to be a positive outcome and wide local excision to be negative, we calculated sensitivity, specificity, and positive and negative predictive values for the predicted management. In further exploratory analyses, we examined the extent of agreement (linear-weighted κ) in size of tumour between histopathology and the imaging techniques.

We summarised quality of life data with a timeframe of plus or minus 14 days around the expected date of completion of the 8-week questionnaire, plus or minus 28 days for the 6-month questionnaire, and 56 days for the 12-month questionnaire. We calculated health-related quality of life, as measured by the EQ-5D, and resource costs for every patient, and compared the groups with regression analyses, adjusting for age, body-mass index, baseline health-related quality of life, and cancer recurrence. All hypothesis tests were two-sided and undertaken at the 5% significance level. Analysis was by intention to treat. All statistical analyses were undertaken with SAS version 9.1.

Role of the funding source
The sponsors of this study commissioned this research, but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to all study data and were responsible for the decision to submit for publication.

Results

The randomisation phone line was made live in December, 2001, but the first patient was not randomly assigned until Feb 20, 2002. The last patient was randomly assigned on Jan 31, 2007. 1623 patients were randomly assigned (816 in the MRI group and 807 in the no MRI group) to the COMICE trial by 107 consultant breast surgeons and radiologists from 45 UK centres. Although the achieved sample size was smaller than was the sample size of 1840 patients needed for 90% power, this number still provides the study with 86% power to detect a difference of 5% in reoperation rates. 1393 patients (86%) were recruited by consultant breast surgeons who recruited at least ten patients. Figure 1 shows the study protocol.[22]

Table 1 shows the baseline characteristics of patients. Characteristics were well balanced between the groups. Most patients were 50 years or older, had breast density group 2 (2, 3, or 4 on the ACR BI-RADS scale), were postmenopausal, and had been identified through the NHS Breast Screening Programme (n=847, 52%). The proportion of premenopausal to postmenopausal women was consistent with the expected age distribution of breast cancer. Median time from randomisation to MRI for patients assigned to receive MRI was 3 days (IQR 1–6), and from randomisation to initial surgery was 14 days (8–20) in this group and 13 days (8–18) in the group with no further imaging. For those undergoing a mastectomy in the MRI group, the median time from randomisation to surgery was 19 days (12–34), consisting of a median of 22 days (10–47) for those undergoing an additional biopsy before surgery and a median of 17 days (7–25) for those proceeding directly to mastectomy. An interval of 243 days between randomisation and surgery was recorded for one patient who underwent neoadjuvant chemotherapy. The protocol specified that an MRI scan should not delay surgery; therefore, only 2% of patients waited longer than 40 days between random assignment and surgery, and less than 1% more than 50 days.

Table 2 shows pathology results for the initial operation. The median weight of wide local excision specimens, the size and extent of tumour, and the percentage of excision margins associated with either invasive cancer or ductal carcinoma in situ were similar between groups. 153 MRI scans (19%) were reread as part of the quality-assurance process, including all recruiting centres. 12 scans (8%) were technically non-compliant with the scanning protocol, and we regarded five (3%) as misreported (three of which arose from non-compliant scans). 12 of the non-compliant scans were from six centres, all with low recruitment. Combined, these centres accounted for only 43 (5%) of the total number of MRI scans undertaken within the trial. The remaining two misreported scans were from two centres with high recruitment, accounting for 31 (4%) of the total MRI scans. As such, no sensitivity analyses were deemed necessary.

	MRI (n=816)	No MRI (n=807)	Total (n=1623)
Initial operation			
Wide local excision	750 (92%)	787 (98%)	1537 (95%)
Mastectomy	58 (7%)	10 (1%)	68 (4%)
Other	3 (<1%)	0	3 (<1%)
Did not undergo initial surgery	2 (<1%)	2 (<1%)	4 (<1%)
Lost to follow-up or missing data	3 (<1%)	8 (1%)	11 (<1%)
Repeat operations within 6 months			
Further wide local excision	85 (10%)	90 (11%)	175 (11%)
Mastectomy	48 (6%)	61 (8%)	109 (7%)
Other	1 (<1%)	1 (<1%)	2 (<1%)
Pathologically avoidable initial mastectomy or patient choice	19 (2%)	4 (<1%)	23 (1%)
Did not undergo further surgery	659 (81%)	645 (80%)	1304 (80%)
Lost to follow-up	4 (<1%)	6 (<1%)	10 (<1%)

Table 3: **Initial and repeat operations**

	Histopathology		Total
	Wide local excision	Mastectomy	
MRI			
WLE	458 (84%) (true negative)	89 (16%) (false negative)	547
Mastectomy	55 (38%) (false positive)	89 (62%) (true positive)	144
Total	513	178	691

Table 4: **MRI-predicted patient management**

309 patients (19%) underwent either a repeat operation or mastectomy at further operation within 6 months of randomisation, or a pathologically avoidable mastectomy at initial surgery, with a difference between the MRI and no MRI group of 0·58% (95% CI –3·24 to 4·40%). No significant difference in reoperation rates was identified between the groups (odds ratio [OR] 0·96, 0·75 to 1·24, p=0·77). For the minimisation factors, neither breast density (p=0·51) nor surgeon (p=0·34) were identified to be significantly associated with reoperation rates. Patients aged 50 years or older, however, were reported to be less likely to undergo a reoperation (as previously defined) than were those younger than 50 years (OR 0·64, 0·47–0·86, p=0·0029). We undertook multilevel modelling to further investigate surgeon effect, but no such effect was identified (p=0·12) when surgeon was classed as a random effect.

Table 3 shows a breakdown of initial and further surgery. 16 patients in the MRI group (2%) underwent a pathologically avoidable mastectomy at initial surgery, as did two patients in the no MRI group (<1%) who had

	MRI				No MRI			
	n	Median (IQR)	Mean (SD)	95% CI	n	Median (IQR)	Mean (SD)	95% CI
Baseline								
FACT-B total	613	114·0 (100·5–123·0)	110·4 (17·6)	109·0–111·8	613	114·0 (100·0–123·8)	110·3 (16·9)	109·0–111·7
FACT-G total	624	88·0 (77·3–95·0)	84·6 (13·6)	83·5–85·6	619	88·0 (75·8–95·0)	84·7 (12·9)	83·6–85·7
FACT-B physical wellbeing	640	25·7 (23·0–27·0)	24·6 (3·5)	24·3–24·8	632	25·8 (23·0–27·0)	24·7 (3·2)	24·4–24·9
FACT-B social and family wellbeing	637	26·0 (24·0–28·0)	24·8 (4·2)	24·4–25·1	631	26·0 (23·0–28·0)	24·5 (4·4)	24·2–24·9
FACT-B emotional wellbeing	635	14·0 (10·0–16·0)	12·9 (4·6)	12·5–13·2	626	14·0 (10·0–17·0)	13·1 (4·6)	12·7–13·4
FACT-B functional wellbeing	640	24·0 (20·0–27·0)	22·3 (5·4)	21·9–22·7	629	24·0 (19·0–27·0)	22·4 (5·1)	22·0–22·8
FACT-B additional concerns	634	26·0 (22·0–30·0)	25·8 (5·7)	25·3–26·2	626	26·0 (22·0–30·0)	25·7 (5·5)	25·2–26·1
Trial outcome index	624	75·0 (66·0–81·9)	72·7 (12·3)	71·7–73·7	619	74·0 (66·0–82·0)	72·7 (11·5)	71·8–73·6
8 weeks after randomisation								
FACT-B total	421	112·0 (93·0–123·0)	107·2 (20·7)	105·3–109·2	412	111·0 (95·6–123·0)	107·4 (20·4)	105·4–109·3
FACT-G total	420	86·0 (71·8–94·1)	82·3 (15·6)	80·8–83·8	412	85·3 (73·0–94·3)	82·2 (15·4)	80·7–83·7
FACT-B physical wellbeing	423	24·0 (20·0–26·0)	22·1 (5·1)	21·6–22·6	417	24·0 (20·0–26·0)	22·4 (4·7)	21·9–22·8
FACT-B social and family wellbeing	426	26·0 (23·3–28·0)	24·6 (4·5)	24·2–25·1	416	26·0 (22·2–28·0)	24·2 (4·7)	23·7–24·7
FACT-B emotional wellbeing	425	16·0 (13·0–18·0)	15·1 (4·0)	14·7–15·5	416	16·0 (13·0–18·0)	15·1 (4·2)	14·6–15·5
FACT-B functional wellbeing	428	22·0 (16·5–25·0)	20·5 (6·0)	19·9–21·1	416	22·0 (17·0–25·0)	20·5 (6·0)	20·0–21·1
FACT-B additional concerns	429	26·0 (21·0–30·0)	24·9 (6·6)	24·3–25·5	418	26·0 (21·0–30·0)	25·2 (6·4)	24·6–25·8
Trial outcome index	422	70·0 (57·5–80·0)	67·5 (15·4)	66·1–69·0	415	71·0 (59·0–80·0)	68·1 (14·9)	66·7–69·5
6 months after initial surgery								
Fact-B total	545	112·0 (92·0–126·0)	107·2 (22·2)	105·3–109·1	533	111·0 (92·3–125·0)	107·2 (21·8)	105·4–109·1
FACT-G total	549	87·0 (71·0–96·0)	82·5 (16·4)	81·1–83·9	535	86·0 (73·0–96·0)	82·4 (16·3)	81·0–83·8
FACT-B physical wellbeing	559	24·0 (19·0–26·0)	22·3 (5·3)	21·9–22·7	541	24·0 (19·8–26·0)	22·1 (5·2)	21·7–22·6
FACT-B social/family wellbeing	559	25·0 (21·0–28·0)	23·7 (4·8)	23·3–24·1	540	25·7 (21·0–28·0)	23·7 (4·9)	23·3–24·2
FACT-B emotional wellbeing	553	16·0 (14·0–18·0)	15·5 (3·9)	15·2–15·9	541	16·3 (13·0–18·0)	15·4 (4·0)	15·1–15·8
FACT-B functional wellbeing	554	23·0 (17·0–26·0)	21·0 (6·2)	20·5–21·5	542	22·0 (17·0–26·0)	21·1 (6·0)	20·6–21·6
FACT-B additional concerns	556	26·0 (20·0–30·0)	24·7 (7·0)	24·1–25·3	543	26·0 (21·0–30·0)	24·8 (6·7)	24·2–25·3
Trial outcome index	547	72·0 (57·0–82·0)	67·9 (16·5)	66·5–69·3	535	71·0 (58·0–81·0)	68·1 (15·8)	66·7–69·4
1 year after initial surgery								
FACT-B total	583	115·8 (96·0–126·0)	109·9 (21·0)	108·2–111·6	569	115·0 (98·0–127·0)	110·6 (20·3)	109·0–112·3
FACT-G total	586	88·9 (75·0–97·0)	84·3 (15·8)	83·0–85·5	575	89·0 (76–98·0)	84·7 (15·8)	83·5–86·0
FACT-B physical wellbeing	601	25·0 (22·0–27·0)	23·5 (4·6)	23·1–23·8	583	25·0 (22·0–27·0)	23·6 (4·3)	23·3–24·0
FACT-B social/family wellbeing	605	25·7 (21·0–28·0)	23·6 (5·1)	23·2–24·0	582	25·7 (21·0–28·0)	23·5 (5·4)	23·0–23·9
FACT-B emotional wellbeing	595	16·0 (13·0–18·0)	15·3 (3·9)	15·0–15·6	583	16·0 (14·0–18·0)	15·5 (3·9)	15·2–15·8
FACT-B functional wellbeing	604	23·6 (18·0–27·0)	21·9 (5·8)	21·4–22·3	587	24·0 (19·0–27·0)	22·1 (5·6)	21·6–22·5
FACT-B additional concerns	609	27·0 (21·4–31·0)	25·7 (6·5)	25·1–26·2	583	27·0 (22·0–30·0)	25·8 (6·0)	25·3–26·3
Trial outcome index	590	75·3 (61·2–82·0)	71·1 (14·9)	69·9–72·3	576	75·0 (63·0–82·0)	71·6 (13·9)	70·4–72·7

FACT-B=functional assessment of cancer therapy-breast. FACT-G=functional assessment of cancer therapy-general

Table 5: **Quality of life summaries for patients who completed questionnaires within set timeframes**

an MRI. 39 patients (5%) in the MRI group correctly underwent a mastectomy as a result of MRI findings, and a further three patients underwent a mastectomy on the basis of patient decision alone. When taking into account only those patients who underwent a repeat operation, the median time from randomisation to this operation was 41 days (32–56 days).

Additionally, 13 patients (2%) underwent previously unplanned surgery to the contralateral breast at initial operation because of additional findings that were identified by MRI (12 patients underwent wide local excision and one chose to have a mastectomy). 27 patients had a biopsy sample taken from the contralateral breast on the basis of MRI findings.

A change in clinical management that was attributable to MRI findings was proposed for 55 patients (7%) in the MRI group, and an additional three patients chose to have a mastectomy. A change in management was made for 50 of 55 patients (91%) because additional disease was identified by MRI. Of these patients,

15 (30%) underwent a pathologically avoidable mastectomy as defined by the DMEC, with the other 35 patients correctly managed. For the remaining five patients, a change in management was proposed because of extensive microcalcifications secondary to ductal carcinoma in situ (identified on review of mammography and ultrasound; three patients), primary lung malignancy detected on MRI (one patient), and the reason was missing for one patient. Of the 58 patients who underwent a mastectomy, 32 had an additional biopsy, 11 did not have a biopsy, and data were unavailable for the remaining 15 patients. Of the 16 patients who underwent an avoidable mastectomy, three did and six did not have a biopsy, and data are missing for the remaining seven patients.

For predicted patient management, agreement of results from histopathology with imaging findings was considered for patients assigned to have an MR scan on the basis of the definitions used by DMEC for the appropriateness of the chosen surgical procedure. According to histopathological findings, predicted management for 561 patients (69%) in the MRI group was wide local excision, for 196 patients (24%) was mastectomy, and predicted management was not established for 59 patients (7%). Of the 757 patients for whom histopathologically predicted management was established, predicted management according to MRI could not be established for 66 patients (9%), resulting in 691 with predicted management assessable via both modalities.

Table 4 shows MRI-predicted patient management. MRI correctly predicted wide local excision for 458 of 547 patients (84%). For 89 of 547 patients (16%), MRI predicted a need for wide local excision, although histopathology findings suggested that they should have undergone a mastectomy. 89 of 144 (62%) who were predicted by MRI to need a mastectomy were also identified to need such management from results of histopathology, and 55 (38%) were identified by histopathology as needing only wide local excision. Sensitivity was 50·0% (95% CI 42·7–57·4) and specificity 89·3% (86·6–92·0%).

Agreement in the staging of tumours between MRI and histopathology showed that all imaging modalities offer, at most, only some agreement with pathology, when taking into account the size of index lesion alone (κ values; ultrasound 0·46, 95% CI 0·41–0.50, X-ray mammography 0·45, 0·41–0·49], MRI 0·45, 0·39–0·50). However, when incorporating data from patients with ductal carcinoma in situ, agreement with ultrasound was poorer, with the 95% CIs around the weighted κ statistic almost entirely excluding those for MRI (κ values; ultrasound 0·38, 0·34–0·42, X-ray mammography 0·41, 0·37–0·46, MRI 0·48, 0·42–0·53).

We undertook multilevel modelling to investigate whether there was a radiologist effect on the size of lesion and the extent of disease as identified by MRI, compared with histopathological results. We identified that a significant radiologist effect (p=0·0186) was related to the size of lesion; however, the variation in data was attributable to differences between patients rather than to radiologists. No radiologist effect was reported to be associated with differences in extent of disease.

In relation to reoperation rate, we identified no statistically significant interaction between tumour type (lobular carcinoma *vs* all other types) and the addition of MRI to triple assessment (χ^2 0·13, p=0·72), or age and the addition of MRI to triple assessment (χ^2 0·16, p=0·69). Patients with lobular carcinoma were more likely to undergo reoperation (OR 0·52, 0·30–0·92, p=0·0242), compared with patients who did not have lobular carcinoma. However, we interpreted our results with caution because of the low number of patients with lobular carcinoma (9%).

Table 5 shows the quality-of-life results at every time point for patients who completed their quality-of-life questionnaire within the relevant timeframes. Overall, quality-of-life scores were similar between the two treatment groups, decreasing slightly between baseline and 8 weeks after randomisation, then recovering between 6 and 12 months after initial surgery.

In our economic assessment at 12 months after surgery, we identified no statistically significant difference in health-related quality of life, as measured by the EQ-5D, between the two groups (p=0·075). Results of this assessment suggested that a cost difference between the two trial groups might exist, with the MRI strategy having a larger mean resource cost per patient than the no MRI strategy (£5508·40 [US$8877·36] *vs* £5213·50 [$8402·10]), although the difference was not significant (p=0·075). Full details of this assessment are provided elsewhere.[13]

Discussion

Our results show that addition of MRI to conventional triple assessment has no benefit on reduction of reoperation rate. Of 1623 patients, about 11% of all patients underwent a further wide local excision, 7% underwent a mastectomy at further operation, and 1% underwent a pathologically avoidable mastectomy or a mastectomy by choice at initial operation. The overall reoperation rate (19%) was slightly higher than the NHS Breast Screening Programme rate of 10% in 2006–07, although our findings are within the 13–21% range quoted in 2006–07 for the UK.[2]

We incorporated the rate of pathologically avoidable mastectomy at initial operation into the primary endpoint because MRI might have overestimated the size and extent of disease, thus resulting in an avoidable recommendation for mastectomy. In the MRI group, 7% of patients underwent a mastectomy at initial operation, and of these, 16 patients (2% of all MRI patients) had a pathologically avoidable mastectomy, and less than 1% of all MRI patients chose to have a mastectomy. Because we analysed only data for women who were identified via

triple assessment and already scheduled to receive wide local excision, we cannot compare the rate of pathologically avoidable mastectomy as a consequence of triple assessment alone with that for MRI.

These results emphasise the need to take biopsy samples of all lesions that might result in an alteration to the planned surgical procedure. However, we emphasise that 5% of patients correctly underwent a mastectomy at initial operation and 2% underwent contralateral breast surgery for undetected malignancy as a result of MRI findings. Nonetheless, MRI did not result in a significant reduction in the rate of repeat operation or mastectomy at further operation in the MRI group.

The COMICE study is the first large pragmatic prospective, multicentre trial to investigate the effectiveness of MRI for detection of small breast lesions that are suitable for wide local excision. The 95% CI and p value associated with the OR for undergoing reoperation in the MRI group was highly non-significant, showing that the results would be highly unlikely to differ had the target sample size of 1840 patients been attained.[23]

Our results are similar to those of a systematic review and meta-analysis[24] of non-randomised studies of MRI in preoperative breast assessment. In this meta-analysis, researchers emphasised that MRI investigation of the affected breast in women newly diagnosed with breast cancer could increase the rate of potentially unnecessary surgery. They showed that MRI detected additional multifocal and multicentric disease in the affected breast in 16% of cases. The summary estimate of the positive predictive value was 66·0% (95% CI, 52–77) and the conversion rate from wide local excision to mastectomy was 8·1% (5·9–11·3). 1% of patients underwent a pathologically avoidable mastectomy secondary to MRI. Our results lend support to these findings, thus reiterating that outcomes of the COMICE trial can be generalised to clinical practice. Houssami and Hayes[25] undertook a meta-analysis of 12 observational studies that examined the detection capability and effect of preoperative MRI on newly diagnosed, early breast cancer treatment. They reported that MRI changed surgical management, generally from breast conservation to more radical surgery, but identified no evidence that MRI improved surgical treatment or outcomes. This finding could be a consequence of the mode of presentation of imaging data to the surgeon. Complete excision of tumour depends on the ability of the surgeon to palpate the lesion in its entirety. This procedure is very demanding because: all imaging modalities acquire information with the patient in a different position to that assumed during surgery; palpation of tumour might be difficult, dependent on the composition of the breast and the characteristics of the cancer; and, if wire localisation is used, in which typically only one wire is inserted, the tumour margin could be inadequately delineated. Techniques to ensure surgical precision is at an optimum need further examination.

Extent of experience of the radiologists is acknowledged as a potential limitation of our study, but this issue will always exist in real practice. Although analysis of our data showed a significant radiologist effect, the variation in data was probably attributable to differences between patients rather than between radiologists. Notwithstanding, efforts continue in protocol development to improve the specificity of breast MRI.

Our economic analysis was consistent with the clinical findings. In the analysis, we identified no difference in health-related quality of life between groups 12 months after initial surgery. However, in terms of total costs, results suggested a difference between the two trial groups, with the MRI group costing more than the no MRI group, although the difference was not statistically significant. In view of the similar clinical and health-related quality-of-life outcomes of patients in both groups, we conclude that the addition of MRI to the conventional triple assessment might result in extra use of resources at the initial surgery period, with few or no benefits to saving resources or health outcomes, and the additional burden on patients to attend extra hospital visits.

Our results have important implications in routine clinical practice for the appropriate use of health-service resources and patient burden on health services. MRI is an expensive procedure. Because surgical use of MR data to direct wide local excision is similar worldwide, we believe that our findings are generalisable to all health-care providers, and show that MRI might not be necessary in this population of patients in terms of reduction of reoperation rates.

Contributors

LWT, PD, VN, JB, and AH contributed to trial design and protocol development; VN, CO, and IH set up the trial; IH and VH contributed to centre enrolment; JB and SB undertook statistical analysis; SB, IH, CO, PD, VN, AH, and JB contributed to data monitoring; IH and LWT undertook quality assurance review; CO, PD, VN, and AH collected and verified all data; LWT, SB, CO, JB, PD, AH, and VN analysed and interpreted results; and LWT, SB, CO, IH, JB, PD, AH, and VN drafted the report and approved the final version of the article.

Trial participants

The following UK institutions, centres, and principal investigators contributed patients to the trial: *Barnet Hospital, Barnet, UK* G Kaplan; *Blackpool Victoria Hospital, Blackpool* G Hoadley; *Bristol Royal Infirmary, Bristol* A Jones; *Castle Hill Hospital, Hull* L Turnbull; *Conquest Hospital, Hastings* E Shah; *Crosshouse Hospital, Ayrshire* M Dean; *Darent Valley Hospital, Kent* B Al-Murrani; *Derriford Hospital, Plymouth* K Paisley; *Diana Princess of Wales Hospital, Grimsby* L A Donaldson; *Frenchay Hospital, Bristol* S Cawthorn; *George Eliot Hospital, Nuneaton,* R Nangalia; *Grantham and District Hospital, Grantham* D Valerio; *Hairmyres Hospital, East Kilbride* D Edwards; *Hillingdon, Uxbridge* K Raza; *Hinchingbrooke Hospital, Huntingdon* C Hubbard; *Hope Hospital, Salford* S Datta; *King's College Hospital, London* D Evans; *Leeds General Infirmary, Leeds, UK* B Dall; *Leighton Hospital, Chester, UK* S Evans; *Luton and Dunstable Hospital, Luton* D Wright; *Maidstone Hospital, Maidstone* A Sever; *Mid Yorkshire Hospitals NHS Trust (Clayton Hospital, Dewsbury and District Hospital, Pinderfields General Hospital, Pontefract General Infirmary) Pontefract* F Roberts; *Northwick Park, Harrow* W Teh; *Nottingham City Hospital, Nottingham* J James; *Prince Philip Hospital, Carmarthenshire* A Richards; *Princess of Wales, Bridgend* N Al-Mokhtar; *Rotherham General Hospital, Rotherham* S Varkey; *Royal Bolton Hospital, Farnworth* JHR Winstanley; *Royal Hallamshire Hospital, Sheffield*

C Ingram; *Royal Lancaster Infirmary, Lancaster* J Lavelle; *Royal Sussex County Hospital, Brighton* G Rubin; *Russells Hall Hospital, Dudley* H Renny; *Scarborough Hospital, Scarborough* J Macfie; *St Bartholomew's Hospital, London* S Vinnicombe; *St James's University Hospital, Leeds* M Lansdown; *St Mary's Hospital, London* W Gedroyc; *University Hospital of North Durham, Durham* J Cox; *University Hospital of North Tees Hospital, Stockton-on-Tees* C Hennessy; *Victoria Infirmary, Glasgow* S Stallard; *Walsgrave Hospital, Coventry* M Wallis; *Western General Hospital, Edinburgh* J Rainey; *Western Infirmary, Glasgow* L Wilkinson; *Whiston Hospital, Prescot* R Audisio; *York Hospital, York* S Reaney; *Ysbyty Gwynedd, Bangor* N S A Stuart.

Conflicts of interest

We declare that we have no conflicts of interest.

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