MRI in women with primary breast cancer scheduled for wide local excision – the COMICE trial

Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE)

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Executive summary

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Executive summary

Background

In 2001–2 the reoperation rate for positive margins following wide local excision (WLE) averaged 14.2%, whilst in the most recent audit reported in 2006–7 this value had risen to 17.0%. This reoperation rate constitutes a considerable additional burden both to the patient and the UK NHS. The NHS Breast Screening Programme (NHS BSP) quality assurance target reoperation rate is 10%.

Objectives

The main objective of the COMICE trial was to determine whether the addition of magnetic resonance imaging (MRI) of the breast to current patient evaluation by triple assessment (clinical, radiological and pathological) would aid tumour localisation within the breast and hence reduce the reoperation rate in women with primary tumours who were scheduled for WLE. The cost-effectiveness of MRI in this clinical setting was unknown and the economic analysis of this trial attempted to answer the question whether the addition of MRI was worthwhile from the perspective of the NHS.

Methods

Design

COMICE was a multicentre, randomised, controlled, open, parallel group trial with equal randomisation in women with biopsy-proven primary breast cancer who were scheduled for WLE following triple assessment. Patients were randomised to receive MRI or no MRI. A pragmatic approach to trial design was chosen so that results could be generalisable in clinical practice and to reduce unnecessary protocol-driven trial costs.

The main trial design was also supplemented with a qualitative study of 100 patients, in order to assess patients' experiences of the treatment process and the care pathway. This supplemental study included the development and validation of a non-scheduled standardised interview (NSSI) to assess the self-reported psychosocial effects of specific aspects of trial participation.

Setting

This study took place at 45 hospitals throughout the UK.

Participants

Women aged 18 years or over, who had undergone X-ray mammography and ultrasound scanning (USS) during the current episode, had pathologically documented primary breast carcinoma, and were scheduled for WLE and capable of providing written informed consent, were recruited. Patients were excluded if they were medically unstable, had a known contraindication to MR scanning or use of a paramagnetic contrast agent, had renal failure, had undergone chemotherapy/hormonal therapy in the previous 12 months or had undergone previous surgery, radiotherapy or serious trauma to the ipsilateral breast, were pregnant or breastfeeding, or had a disability preventing prone scanning.

Interventions

Patients were randomised to receive MRI or no MRI. Randomisation was performed using minimisation incorporating a random element. The following minimisation factors were incorporated: consultant breast surgeon, patient's age (< 50 years versus ≥ 50 years) and breast density [American College of Radiologists breast imaging reporting and data system (ACR BI-RADS) pattern 1 versus ACR BI-RADS pattern 2, 3 or 4].

All MRI was performed at 1.5 T or 1 T with a dedicated bilateral breast coil. Dynamic contrast-enhanced MRI utilised a T1-weighted, three-dimensional fast spoiled gradient echo (FSPGR) sequence (temporal resolution 45 seconds), acquired following intravenous injection of contrast agent (0.1 mmol Gd-DTPA/kg body weight), and high-resolution (0.7 mm × 0.9 mm in plane) fat-suppressed T1-weighted three-dimensional SPGR images were acquired for lesion morphology. Data

analysis included evaluation of the signal–intensity time curves and lesion morphology.

Main outcome measures

The primary end point of the COMICE trial was the reoperation rate. This was defined as the number of patients in each arm experiencing a repeat operation or mastectomy further to initial surgery, within 6 months of randomisation, plus the number of patients who had undergone a pathologically avoidable mastectomy at initial operation in each arm divided by the total number of patients in each arm.

Secondary outcome measures included: factors associated with discrepancy between imaging findings and histopathology; the effectiveness of imaging in terms of agreement with histopathology; change in clinical management following MRI; the rate of chemotherapy, radiotherapy and additional adjuvant therapy interventions; the clinical significance of MR-only-detected lesions; the ipsilateral tumour recurrence rate; patient quality of life (QoL); and cost-effectiveness.

The economic evaluation considered costs from the perspective of the NHS and assessed outcomes in terms of health-related quality of life (HRQoL), based on the EQ-5D, and clinical outcomes. It was planned that if differences in clinical outcome (particularly survival and cancer recurrence) emerged during the trial follow-up period, extrapolation modelling would be undertaken to express these differences in terms of quality-adjusted life-years (QALYs) and costs.

Results

In total, 1623 patients were consented and randomised between December 2001 and January 2007 (816 MRI, 807 no MRI). No differences in the reoperation rate were found between the two groups of patients [MRI patients 18.75%, no-MRI patients 19.33%, difference = 0.58%, 95% confidence interval (CI) –3.24 to 4.40], and the addition of MRI to conventional triple assessment alone was not found to be statistically significantly associated with a reduced reoperation rate (odds ratio = 0.96, 95% CI 0.75 to 1.24, $p = 0.7691$).

Overall, the best agreement between all imaging modalities and histopathology with respect to tumour size and extent of disease was found in patients who were over 50, had ductal tumours NST (no specific type) and who were node negative. Considering the effectiveness of imaging, the sensitivity and positive predictive values of MRI (with regard to determining patient management) were 50.0% (95% CI 42.65 to 57.35) and 61.8% (95% CI 53.87 to 69.74), respectively, and, of the 58 patients undergoing a mastectomy, in the MRI arm 16 (27.6%) were classed as being pathologically avoidable. Weighted kappa statistics ranged from 0.3803 for USS to 0.4767 for MRI when assessing agreement between imaging methods and pathology.

No significant differences were identified in the proportion of patients receiving chemotherapy, radiotherapy or additional adjuvant therapies between the groups ($p = 0.3699$, $p = 0.7439$, $p = 0.5591$). None of the 25 patients with MR-only-detected < 5-mm lesions had a clinically significant lesion evident at their 12-month repeat MR scan. Of the 66 patients with MR-only-detected ≥5-mm biopsy-negative lesions, only three had potentially clinically significant lesions at their 12-month repeat MR scan; however, this was based on overall lesion score as these lesions were not biopsied.

Kaplan–Meier estimates of the local recurrence-free interval rate at 1 year were 99.87% (95% CI 99.05 to 99.98) for patients randomised to MRI, compared with 99.73% (95% CI 98.93 to 99.93), for patients randomised to no MRI. No differences in QoL were seen between the two groups of patients [as measured by Functional Assessment of Cancer Therapy-Breast (FACT-B)].

It proved possible to develop a reliable and acceptable NSSI for use in this population of patients. There were high levels of satisfaction and reassurance in patients randomised to receive MRI, despite reported levels of distress secondary to the procedure.

The economic analysis was consistent with the clinical findings that there was no difference in outcomes between the trial arms. Data analysis at 12 months post initial surgery showed no statistically significant difference in HRQoL between the arms, as measured by the EQ-5D. Thus the addition of MRI to the conventional triple assessment is likely to result in extra resource use with few or no benefits in terms of resource saving or HRQoL.

Conclusions

The COMICE study was the first large pragmatic trial evaluating the effectiveness of MRI of small breast lesions, suitable for WLE. The results have shown that although MRI does improve localisation of the tumour, the addition of MRI to triple assessment in women with small breast tumours, does not result in a reduction in reoperation rates.

These results are important from both a health economic aspect, and also from a patient burden aspect. MRI is an expensive procedure. The findings of this trial are of benefit to the NHS and this population of patients by demonstrating that this additional procedure is not necessary, thereby allowing time and resources to be more effectively used elsewhere.

Implications for practice

The addition of MRI to triple assessment in women with small breast tumours, does not result in a reduction in reoperation rates.

Preoperative biopsy of MR-detected lesions only, prior to surgery, is likely to minimise the incidence of inappropriate mastectomy.

Research recommendations

Acceptance of 'close' surgical margins The cosmetic outcome of breast-conserving surgery is often suboptimal, and it is now recognised that more extensive surgery may have little long-term clinical benefit, as residual disease may be adequately treated with standard adjuvant therapy. Future trials need to consider the adequacy of accepting 'close' surgical margins followed by adjuvant therapy on the local recurrence-free interval.

Improved specificity of MRI To improve specificity, consideration needs to be given to: alternative MR sequences, improvement in signal–noise ratio and uniformity of fat suppression. Imaging at 3.0 T may potentially improve specificity, reducing the necessity for biopsy of equivocal lesions and aid the evaluation of ductal carcinoma in situ (DCIS).

Transfer of imaging data Mechanisms for utilisation of two- and three-dimensional MRI data for preoperative tumour mark-up and surgical management need further evaluation.

Alternative treatment options Technological advances have fuelled interest in the use of minimally invasive, image-guided tumour ablation techniques for small tumours, but successful ablation of the entire tumour will require accurate tumour volume delineation.

Trial registration

This trial is registered as ISRCTN57474502.

Publication

Turnbull LW, Brown SR, Olivier C, Harvey I, Brown J, Drew P, *et al*. Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE). *Health Technol Assess* 2010;**14**(1).

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 99/27/05. The contractual start date was in June 2001. The draft report began editorial review in October 2008 and was accepted for publication in June 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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