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Multiple foci of invasive breast cancer: Can breast MRI influence surgical management?

Miss L Johnson, Prof S Pinder, Mr M Douek

Department of Research Oncology, Kings College London, 3rd Floor Bermondsey Wing, Guys Hospital, London, SE1 9RT

Tel: 020 7188 4238

Fax: 020 7188 9986

Email: laura.johnson@kcl.ac.uk

Abstract

The use of MRI to assess the extent of breast disease is gaining increasing popularity with the subsequent detection of multiple invasive foci within the breast that had not been identified on previous standard mammography and ultrasonography. What impact this has on subsequent surgical management and ultimately disease free survival remains a controversial topic. Should histologically confirmed multiple foci of invasive disease within a breast steer the surgical management towards mastectomy or is there a role in select patients for breast conserving surgery, even if two or more incisions are required? This review considers the evidence for how MRI affects the mastectomy rate and compares this to surgical outcomes for breast conserving surgery in the presence of multiple invasive foci.

Keywords

Multiple invasive foci, breast cancer, mastectomy, breast conserving surgery. MRI.

Introduction

The primary aim of surgery for breast cancer is complete resection of the tumour with a margin of benign tissue. Breast conserving surgery (BCS), plus adjuvant whole breast radiotherapy, is comparable to mastectomy in terms of overall survival after 20 years [1] and should be offered to patients with breast cancer, in whom a complete surgical excision of the tumour and acceptable cosmetic outcome is anticipated.

Magnetic resonance imaging (MRI) is increasingly being used for the management of breast cancer; for example, to assess the extent of disease in the breast (particularly invasive lobular carcinoma and when other imaging modalities provide incongruent results) and also to assess tumour response to primary medical treatment. Patients at high risk of developing breast cancer including those whom have a genetic pre-disposition are typically young with dense breasts when the sensitivity of mammogram and ultrasound together is low (49% detection). The use of MRI in this situation improves detection to 91% compared with only 25% sensitivity with mammogram alone [2]. However, a recognised drawback of breast MRI is the relatively low specificity and the detection of additional enhancing foci in 16% of patients [3]. Pathological studies have reported that additional foci of tumour are present in 60% of mastectomy specimens, with over 40% of these distant from the index quadrant [4]. Intriguingly, these appear not to impact on patient prognosis, as over 90% of local recurrences occur in the index quadrant, despite an apparent surgical complete resection. A concern, therefore, is that if some, or all of, these tumour foci were detected by breast MRI, its use may lead to unnecessary mastectomy [5]. Subsequent studies have provided conflicting evidence [6,3]. This review considers whether the identification of multiple foci of invasive breast cancer (or *in situ* disease) by MRI, necessarily indicates the need for mastectomy.

The surgical options for multiple invasive foci in breast cancer

The terms *multifocal* and *multicentric* have been used inappropriately and sometimes interchangeably in the literature, causing confusion. *Multifocal* breast cancer is often defined as the presence of different tumour foci at least 5mm apart in the same quadrant of the same breast whilst *multicentric* disease is the presence of tumours at least 5mm apart in different quadrants of the same breast requiring a double incision [7]. To add to the complexity, invasive tumour size is defined histologically by the maximum dimension of the largest tumour focus [8], not the sum of multiple foci, if present. An agreed radiological definition does not exist, however foci within 50mm of one another are usually classified as multifocal whereas those more than 50mm apart are termed multicentric [9]. As a result of this controversy, the UK NHS breast-screening programme pathology guidelines [10] have replaced the terms multifocal and multicentric breast cancer with the more self-explanatory and generic “multiple invasive foci”. Likewise, the American Joint Committee of Cancer (AJCC) 7th Edition, recommends the use of the term “multiple carcinomas” [8].

Traditionally, the presence of multiple invasive foci of breast cancer was considered an indication for mastectomy, irrespective of the size of the lesions [11]. Local failure, disease-free and overall survival in this setting is comparable to those of patients with unifocal breast cancer similarly treated with mastectomy [12]. Early studies challenging the notion those patients with multiple ipsilateral foci of invasive disease required mastectomy, failed to demonstrate that BCS was a viable option for long-term disease control [13-15]. However, with incremental improvements in adjuvant systemic treatments and radiotherapy, statistical equivalence of local failure rate and survival in patients having mastectomy or BCS for the surgical management of multiple invasive foci of the breast has been demonstrated [16-20]. This evidence, albeit based on small series, has paved the way for larger studies including several large cohort studies and randomised clinical trials.

Lim et al retrospectively reviewed the outcome of 478 patients who underwent BCS, plus radiotherapy as appropriate, compared to mastectomy for multifocal breast cancer. After a mean of 5 years follow up, there was no statistical difference in local relapse or disease free survival between the groups. In addition, the local failure rate in the BCS group did not differ from that of a control group of 930 patients with unifocal breast cancer treated by BCS. Similarly, Gentilini et al [21] published a series of 476 patients having BCS for multiple invasive foci and, despite the absence of a control group, demonstrated that the 5-year cumulative incidence of local relapse was low (5.1%). They also reported that there was no difference in the recurrence rates of ductal (no special type) and lobular carcinomas, providing the disease was adequately excised. Oestrogen receptor negativity however worsened local disease free survival, as did over expression of HER2. It is important to note, however, that BCS for patients with multiple invasive foci of breast cancer was only regarded as appropriate when the anticipated cosmetic outcome was likely to be acceptable.

The margins of ductal carcinoma in situ (DCIS) are more difficult to assess and the lesion is typically impalpable, raising the question as to whether comparable outcomes can be achieved with BCS and mastectomy in the rare situation of multiple foci of DCIS. Rakovitch et al [22], demonstrated that there was no difference in the 10 year local recurrence and disease free survival rate between patients in either group, provided that radiotherapy was administered to the BCS group post-operatively. Significantly, the omission of adjuvant radiotherapy was a significant predictor of local recurrence in patients with either multifocal or unifocal disease treated with BCS [23].

Breast conservation remains possible even with large single tumours (>4cms) when combined with a reconstructive technique with or without contralateral symmetrisation [24]. In the presence of multiple invasive foci the use of a double incision maybe required when the tumours exist within different quadrants. Individually, each tumour focus may be small however in order to maintain oncological safety the total sum of the volume of tissue excised may exceed cosmetic acceptability. Several onco-plastic techniques are available comprising of volume displacement and volume replacement. Volume replacement is preferentially undertaken for large defects using autologous tissue transfer usually in the form of a flap. The use of an implant for volume replacement is not advocated in BCS due to the requirement for post-operative radiotherapy. either without the use of an implant in lieu of the requirement for post-operative radiotherapy[25]

Imaging modalities to detect multiple invasive foci in breast cancer

The routine radiological assessment of women presenting with suspicious breast symptoms includes mammography and ultrasound (US) imaging. Significantly, both of these imaging modalities have a low sensitivity for the detection of multiple foci of invasive disease (45% and 52% respectively)[4] although the use of both imaging modalities in conjunction overcomes the drawbacks of either method used alone [26].

The limitations of mammography in the detection of multiple invasive foci were demonstrated by Bozzini *et al* (22) who showed that, even with the knowledge of the presence of multiple invasive foci, re-review of mammograms identified only 3 of 165 additional foci seen on histological examination of the resected specimen. Bilateral whole breast US, when added to mammography, identified multiple invasive disease in one third of patients, i.e. more commonly than mammography with targeted ipsilateral breast US (23). On the findings of bilateral whole breast US, 8% of patients underwent a change in surgical management; half of these underwent mastectomy as opposed to BCS.

MRI identifies multiple invasive foci more commonly that mammography and US [3]. A concern is that, with increasing availability, and use, of breast MRI, practice could revert to the days when mastectomy was the standard of care for the surgical management of breast cancer, because of the increased pre-operative identification of such additional malignant foci. Another issue is that positive predictive value of breast MRI for the detection of multiple invasive foci is relatively low (66%). As all identified MRI abnormalities require biopsy for corroboration, there is a financial implication and also potential cost to the patients well-being [3]. However, there is an increasing body of data on the effect of MRI on surgical procedure.

Lim et al retrospectively analysed the use of MRI when added to the standard of mammography and breast ultrasound [27] There was no statistical increase in mastectomy rate, however pre-operative MRI alone identified 66/535 (12.3%) of patients with multiple invasive foci, 15 of whom underwent mastectomy instead of the initially planned BCS. Of 25 patients who were offered mastectomy based on MRI findings alone (multiple invasive foci or a more extensive unifocal lesion), 84% histologically correlated with the breast MRI however 4 patients were regarded as over-treated because histologically the additional identified foci were proliferative disease without atypia which could have been appropriately managed with BCS.

In a similar study, patients whose conventional imaging was considered suspicious or highly suspicious for breast cancer underwent contrast-enhanced MRI (CE MRI) to further delineate the suspected malignancy. MRI identified 47 additional malignant lesions in 21% of patients that were not identified using conventional US and mammography. Multiple invasive foci identified on MRI alone accounted for 11/34 cases, all of whom underwent more extensive surgery, including five patients having mastectomy. The false positive rate of CE MRI of 7.3% was offset against the additional malignancies identified and against 4 lesions that were

considered malignant on conventional imaging but which were correctly identified as benign or non-existent on CE MRI [28]. Nevertheless, this additional 7.3% of patients underwent either additional preoperative core biopsy or more extensive surgery.

The COMICE trial is the largest randomised clinical trial available to date that has assessed the effectiveness of MRI in the assessment of small breast cancers considered suitable for BCS (5). Although the focus of the trial was not to identify the incidence of multiple invasive foci, but to assess whether pre-operative MRI reduced the requirement for re-excision of margins following BCS, important data can be extrapolated. Multiple invasive foci were identified in the excision specimens of 179/1623 (12%) of patients. Fifty-five of 816 patients were recommended to change their planned surgical procedure based on the MRI finding of 'additional disease' and 50 proceeded with the recommendation; 15 (30%) underwent mastectomy that, following histological examination of their surgical specimen, was interpreted as avoidable. Only three of these 15 women underwent pre-operative biopsy before the surgical plan was altered, highlighting the importance of biopsy of lesions identified on MRI if these are to alter the surgical management. There was no evidence in the COMICE trial to suggest any benefit in reducing re-operation rate for involved margins following BCS by using pre-operative MRI. [6]

Fischer *et al* also examined the addition of MRI to US and mammography to improve the detection of multiple invasive foci in breast cancer (25). In a cohort of 405 patients with breast cancer, 92 (22.7%) had multiple foci on histological assessment. Mammogram and US scan was successful in identifying multiple invasive foci in 41.3% of patients, with the remaining 54 only diagnosed by MRI. Of these 54 patients, 32 underwent mastectomy instead of BCS based on the MRI findings.

A large systematic review and meta-analysis [3] demonstrated that MRI detected additional ipsilateral disease in 16% of women (417/2601), with a positive predicted value of 66%. This altered surgical treatment in 7.8-33.3% of cases. Conversion from BCS to mastectomy occurred in 8.1% with the identification of multiple invasive foci on MRI. However, 1.1% of patients underwent mastectomy for MRI findings that did not correlate with subsequent histology and, in hindsight, could have satisfactorily been treated with BCS. This, as in the COMICE trial, reinforces the requirement to undertake pre-operative biopsy and histological collaboration prior to a change in recommended surgical procedure.

Solin [29] offers a counter argument to the use of MRI in patients with newly diagnosed early breast cancer, highlighting the role of radiotherapy. Additional, sub-clinical, occult disease, which may now be identified by MRI, has been treated successfully over the decades with whole breast irradiation, with equivalent rates of local failure and overall survival to mastectomy. This questions the need for MRI examination in the first instance, with an even stronger argument against subsequent alteration to more extensive surgery based on MRI results, for no perceived additional benefit [30].

Importantly, despite the potential drawbacks of MRI in the setting described, there are sub-groups of patients for whom MRI infers obvious benefit. These include screening of high-risk patients and those with a breast implant, investigation of those with axillary lymph node metastases without a primary breast tumour on mammography or ultrasonography, and for monitoring response to chemotherapy. [29]

Summary

In an era where breast MRI is readily available, the patient should be treated by a multidisciplinary team that includes clinicians with specific expertise of breast MRI. Lesions detected by breast MRI can thus be considered for MR-guided biopsy prior to any proposed change in surgical management, if second-look ultrasound fails to reveal the lesion. In addition, treatment by a specialist breast multidisciplinary team should ensure that appropriate patients are selected for BCS and that overtreatment resulting from the addition of breast MRI to conventional imaging is minimised.

The association between the increasing use of MRI and the increased detection of multiple invasive foci of breast cancer is clear. What remains controversial is what effect, if any, should this have on surgical practice. Indications for mastectomy over BCS include a predicted unacceptable cosmetic outcome particularly in small breasts with tumours in different quadrants, sub-optimal oncological resection and patient choice.

Breast MRI has its place, yet overuse could lead to an increased rate of mastectomy, especially when institutions have fixed practice in offering mastectomy as the only choice of surgical treatment in cases of multiple invasive cancers. The data indicate that BCS is an appropriate choice for selected patients with multiple invasive foci of breast cancer. Such surgery may require more than one incision, but the anticipated cosmetic outcome must be acceptable. Where BCS is feasible, the requirement for post-operative radiotherapy remains, and the patient should be counselled as appropriate pre-operatively. Mastectomy is not the only appropriate surgical treatment for the management of patients with multiple foci of invasive breast cancer.

Conflict of interests
The authors declare no conflict of interest

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