Institution: University of Hull

Unit of Assessment: A3: Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Optimising the pre-operative utilisation of magnetic resonance mammography for enhancing primary breast cancer treatment

1. Summary of the impact (indicative maximum 100 words)

Breast cancer affects 1/9 women accounting for significant healthcare resources. The Centre for Magnetic Resonance Investigations in Hull have demonstrated that the addition of MRI to conventional triple assessment does not reduce the re-operation rate for most patients, but instead exposes them to unnecessary investigations. These studies have underpinned the formulation of British, European and American Guidelines on optimal utilisation of MRI in women with early breast cancer scheduled for local excision. The knowledge is widely available on Cancer Help web-sites, helping patients to understand their treatment better. The resulting changes in clinical practice have reduced delays in surgery improving patient treatment whilst saving healthcare resources.

2. Underpinning research (indicative maximum 500 words)

A patient's best chance of a successful outcome following breast cancer relies on accurate identification of all tumour foci. Failure to detect additional tumour may under-stage disease and deny the patient appropriate surgery and opportunity for adjuvant therapies. Invasive lobular cancer accounts for 10-15% of all breast cancers and is biologically distinct from other sub-types. In 2010, almost 50,000 women in the UK were diagnosed with invasive breast cancer of whom approximately 7,700 had the invasive lobular sub-type. Its growth pattern causes difficulties in determining the extent of tumour spread. Consequently magnetic resonance imaging (MRI) has been examined with the objective of improving tumour delineation and tissue characterisation. The CMRI in Hull has contributed significantly to clinical studies and technical developments in this field.

Neovascularisation is a functional target for detecting malignancy and monitoring response to therapy using dynamic contrast-enhanced (DCE)-MRI. The CMRI has demonstrated that: DCE-MRI derived pharmacokinetic (PK) parameters determine invasive tumour size with an excellent correlation between histological and MR measurements compared with X-ray mammography; DCE-MRI can differentiate benign from malignant disease with good accuracy, even for small lesions; can predict response to neoadjuvant chemotherapy in advanced breast cancer; and MRI measurement of tumour size correlates better with histopathology than other commonly used techniques (Turnbull, 2010 & 2010).

DCE-MRI acquisition schemes and PK models have been developed using arterial input functions and inclusion of water exchange parameters (Lowry, 2009). To aid clinical tissue discrimination, the group has published extensively on imaging and data analysis methods. These techniques were used in loco-regional staging of lobular carcinoma (Kneeshaw, 2003) and to investigate suspicious mammographic micro-calcifications (Kneeshaw, 2006). They resulted in superior accuracy compared with empirical data and lesion morphology in lobular carcinoma, reducing re-operation rate for residual tumour to 5%, compared to management by triple assessment (Kneeshaw, 2003). Results showed a strong association between pre-treatment tumour morphology and treatment outcome / survival (Pickles, 2009).

On the basis of the above work (funded through a £6.7M capital endowment from Yorkshire Cancer Research) a multi-centre NIHR HTA funded RCT (**COMICE**, led by Prof Turnbull, Award £1.01M) was established to compare, in women with primary breast cancer scheduled for wide local excision (WLE), the effectiveness of MRI relative to triple assessment alone, to reduce the rate of re-operation or mastectomy following unsuccessful WLE (reported in 2010). The addition of MRI did not reduce the re-operation rate (MRI 18.75%, No MRI 19.33%, p=0.77). Pre-specified exploratory analyses identified tumour type as a significant variable associated with re-operation rate (Test statistic=7.20, p=0.0073). Patients with lobular carcinoma were more likely

to undergo re-operation (p=0.0242) at 5% significance level (Turnbull, 2010; Turnbull, 2010). These results have prompted development of new techniques to improve surgical precision and are in use at the CMRI.

Work undertaken at University of Hull from 1999 to 2010. Key researchers: Prof Lindsay Turnbull (Scientific Director to date), Dr Martin Lowry (Research Associate, 1998 to date), Dr Peter Gibbs (Lecturer, 1999 to date); Dr Martin Pickles (Research Associate, 2006 to date), Dr David Manton (Research Associate, 1994-2010), Dr Clara Tan (PhD student, 2002-2005), Dr Stavros Mussurakis (Lecturer, 1997-2000), Mr Philip Drew (Surgery, 1997-2009), Mr Peter Kneeshaw (Surgery, 2002-2005).

3. References to the research (indicative maximum of six references)

1) Kneeshaw, PJ; Lowry, M; Manton, D; Hubbard, A; Drew, PJ; Turnbull, LW Differentiation of benign from malignant breast disease associated with screening detected micro-calcifications using dynamic contrast enhanced magnetic resonance imaging, 2006, BREAST, 15 (1): 29-38 doi:10.1016/j.breast.2005.05.002

2) Kneeshaw PJ, Turnbull LW, Smith A, Drew PJ. Dynamic contrast enhanced magnetic resonance imaging aids the surgical management of invasive lobular breast cancer, 2003, European Journal of Surgical Oncology, 29: 32-37. doi: 10.1053/ejso.2002.1391

3) Lowry M, Zelhof B, Liney G, Gibbs P, Pickles M, Turnbull LW Analysis of Prostate DCE-MRI Comparison of Fast Exchange Limit and Fast Exchange Regiment Pharmacokinetic Models in the Discrimination of Malignant from Normal Tissue, 2009, Investigative Radiology, 44, 9, 577-584. doi: 10.1097/RLI.0b013e3181b4c1fe

4) Pickles M, Manton D, Lowry M, Turnbull LW Prognostic value of pre-treatment DCE-MRI parameters in predicting disease free and overall survival of breast cancer patients undergoing neoadjuvant chemotherapy, 2009, European Journal of Radiology, 71, 498-505. doi: 10.1016/j.ejrad.2008.05.007

5) 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), 2010, Health Technology Assessment ; 14 (1) 1 – 182. doi: 10.3310/hta14014

6) Turnbull LW, Brown S, Harvey I, Olivier C, Drew P, Napp V, Hanby A, Brown J. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial, 2010, The Lancet, 375, 1-9. doi: 10.1016/s0140-6736(09)62070-5

4. Details of the impact (indicative maximum 750 words)

The numerous studies carried out by the CMRI, including COMICE, have contributed to the world literature on the routine clinical use of breast MRI from a patient burden aspect and on the appropriate utilisation of health service resources. Data has been presented nationally and internationally including at International Society for MR in Medicine, the European Society for MR in Medicine and Biology, the British Association of Surgical Oncology, Royal College of Radiologists Breast Group and International Congress on MR Mammography. It has lead to an international collaboration with Australia, USA and Canada concerning an IPD analysis of pre-operative MRI from the most influential international groups (Houssami et al., submitted).

Data from the CMRI at the University of Hull has contributed considerably to the evidence used to draft a number of important guidelines, e.g. The NICE Clinical Guideline No. 80 developed by the National Collaborating Centre for Cancer on “Early and locally advanced breast cancer: Diagnosis and treatment” (February 2009) recommends the pre-operative MR assessment of patients with biopsy-proven invasive ductal breast cancer or ductal carcinoma in situ (DCIS) when there is a discrepancy in the extent of disease determined by clinical examination, mammography and ultrasound. Similarly if breast density precludes accurate mammographic assessment; or if breast

conserving surgery is being considered for invasive lobular cancer again MR assessment is recommended, however in the majority of uncomplicated patients breast MRI is not required (Source 1). Similarly, the American National Comprehensive Cancer Network (2009) included the COMICE trial results and did not recommend breast MRI for all breast cancer patients, but did recommend pre-operative MRI for a similar cohort of patients to the NICE guidelines (Source 2). Guidelines from the European Society of Breast Imaging (2008) extensively quoted publications from the CMRI (Kneeshaw, 2003, Pickles, 2006 and others) and recommended pre-operative breast MRI in the case of dense breasts and in patients with histological evidence of invasive lobular carcinoma (Source 3). The European Society of Medical Oncology (ESMO) in their Clinical Practice Guidelines for diagnosis, treatment and follow-up of breast cancer (2011) stipulated that breast MRI is not needed as a routine procedure, but may be considered in problematic cases and more specifically where multiple tumour foci are suspected, in particular with invasive lobular breast cancer (Source 4). In the UK the Association of Breast Surgery at the British Association of Surgical Oncology (BASO) emphasise that accurate pre-operative assessment of the size and extent of the tumour is essential for deciding whether breast conservation surgery is an alternative option to mastectomy. They also advocate the selective use of breast MRI in planning surgical treatment including if the diagnostic core biopsy suggests an invasive lobular cancer (Source 5).

It is crucial that patients are also aware of best clinical practice. Macmillan Cancer Support includes the indications for breast MRI as does Cancer Research UK's CancerHelp and Medline Plus (NIHR) both of these sites specifically cite the results of COMICE and the use of MRI in patients with invasive lobular cancer to inform patients and their relatives (Source 6).

In the UK around 55,000 women per annum are diagnosed with breast cancer, of whom about 10% have the lobular sub-type. Early indications (Cain, *et al.* 2010, Source 7) are that the UK guidelines for preoperative MRI scanning in lobular cancer alter the surgical management in approximately 20% of this subgroup and that an additional 20% of patients will undergo further imaging and biopsies that do not alter management. The health economic results from the COMICE trial are important for the clinical management of all types of breast cancer. Prior to the changes in the guidelines above, the addition of MRI to conventional triple assessment resulted in extra resource being used during the initial treatment phase with few or no benefits in terms of health outcomes. At a tariff value of £250 per MR examination and assuming a 60% WLE rate, if all patients suitable for WLE (excluding those with invasive lobular cancer) were offered MRI this would cost £7.4M / year for the entire NHS, assuming no follow-up investigations were required. Consequently the omission of MRI from this diagnostic pathway not only improves the patient experience but also allow more appropriate utilisation of health service resources (Turnbull, 2010).

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. NICE clinical guideline 80 Developed by the National Collaborating Centre for Cancer, Issue date: February 2009
2. Indications for Breast MRI in the Patient with Newly Diagnosed Breast Cancer. Lehman C, De Martini W, Anderson BO, Edge SB. Indications for Breast MRI in the Patient with Newly Diagnosed Breast Cancer J Natl Compr Canc Netw 2009;7:193-201
3. Breast MRI: guidelines from the European Society of Breast Imaging. European Radiology, 2008, 18: 1307-1318.
4. Clinical practice guidelines. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. S. Aebi, T. Davidson, G. Gruber & F. Cardoso, 2011 Annals of Oncology 22 (Supplement 6): vi12–vi24, doi:10.1093/annonc/mdr371
5. Surgical guidelines for the management of breast cancer. Association of Breast Surgery at BASO, 2009, EJSO Volume: 35 Supplement: 1 Pages: S1-S22 (DOI: 10.1016/j.ejso.2009.01.008)
6. Cancer Research UK's CancerHelp (http://www.cancerresearchuk.org/cancer-help/type/breast-cancer/diagnosis/further-tests-for-breast-cancer#mri)
7. Effect of the introduction of preoperative MRI scans for lobular cancer in an individual breast unit. Cain H, Sinclair J, Martin A, Fasih T, Browell D, Clark K, Lunt L, Redman, A, 2010, *Breast Cancer Research* 2010, 12(Suppl 3):P27 (doi: 10.1186/bcr2680).