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# Pre-Operative MRI in HER-2 Receptor Positive and Her-2 Receptor Negative Breast Cancer: A Comparison

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## Abstract

**Objectives:** MRI is the most sensitive modality for local staging of breast cancer. Herceptin receptor over-expression is seen in 15% - 30% of breast tumours, and is associated with increased aggression, poorer prognosis, higher grade at diagnosis and increased lymphatic dissemination. This study aimed at evaluating the role of MRI in Herceptin receptor positive vs negative tumours. **Methods:** 193 pre-operative MRIs were performed in 2021 for staging of 162 Her-2 negative and 37 Her-2 positive tumours. Recall rates and further biopsies (ipsilateral/contralateral) were assessed in both groups, and MRI largest size was compared to pathological size of invasive cancer and DCIS. **Results:** 36.4% of Her-2 negative tumours were recalled; further ipsilateral malignancy was identified in 13.6%. Contralateral malignancy was identified in 1.2%. 29.7% of Her-2 positive tumours were recalled; further ipsilateral malignancy was identified in 16.2%. No contralateral malignancy was seen in Her-2 positive tumours. The OR of Her-2 positive tumours having ipsilateral foci of malignancy on MRI is 0.83 (CI 0.3, 2.2). Pathological size concordance with MRI size was seen in 70.3% of Her-2 negative, and 48.6% of Her-2 positive tumours. Discordance in both groups was due to MRI size overestimation (70.8% of Her-2 negative discordance; 89.4% of Her-2 positive discordance). **Conclusions:** Pre-operative MRI did not detect significant increased additional foci in Her-2 positive tumours. Significant concordance with pathological size was not seen in both groups; MRI overestimation was the most frequent cause for discordance in both groups. **Advances in Knowledge:** This study compares MRI features of Her-2 positive and Her-2 negative tumours. It demonstrates that there is no significant increased multifocality or multicentricity of Her-2 positive tumours, but MRI over-estimates size in 30% of Her-2 negative and 51% of Her-2 positive cancers.

**Keywords**

Breast MRI, Herceptin Receptor Positive Breast Cancer, Pathological Size Correlation

## 1. Introduction

MRI is widely used in loco-regional staging of breast cancer. As outlined in the RCR guidelines on symptomatic and screening breast imaging [1], MRI is of particular use in cases where sizing is uncertain on clinical evaluation and conventional imaging (mammography and ultrasound); if breast-conserving surgery is being considered for invasive cancer with a lobular component (invasive lobular carcinoma, or mixed carcinomas with a lobular component); in mammographically occult tumours; and where there is suspicion of multifocal disease unconfirmed on conventional imaging.

The efficacy of MRI in pre-operative staging has been extensively studied; in a systematic review by Maria Nieves plana *et al.* [2], 50 publications were assessed; MRI detected additional disease in 20% of women, and contralateral disease in 5.5% of women. True positive MRI findings prompted conversion from WLE to more extensive surgery in 12.8% of women; in 0.3%, this was considered inappropriate. Few studies have assessed MRI in the context of tumour phenotype.

The Human Epidermal growth factor receptor-2 (Her-2), initially discovered by a group of scientists at Harvard and Massachusetts Institute of Technology [3], Rockefeller Center, plays a significant role in uncontrolled cell growth and tumorigenesis. Her-2-receptor overexpression is seen in 15-30% of breast cancers; and has not only been significantly associated with shorter overall survival and disease-free interval [3], but also with higher grade at diagnosis [4], and increased likelihood of spread to lymph nodes [4].

The aim of this study was to retrospectively review pre-operative MRI performed to stage breast cancer between Jan and Dec 2021, evaluating whether MRI found additional foci of disease in the same/contralateral breast in Her-2 positive and Her-2 negative disease, thereby quantifying any differences in MRI staging between the two groups. In addition, pre-operative maximum documented MRI size was correlated with final pathological size to assess accuracy of MRI in measuring disease.

## 2. Methods

MRIs were performed on a Siemens 1.5 T scanner with intravenous Gadolinium administered at 0.1 mmol/kg body weight. Axial T2WI and T1WI were followed by axial dynamic contrast enhanced images; subtracted enhanced axial images were obtained by computerised subtraction of "mask" T1WI from contrast enhanced T1WI.

Patients were selected for MRI at staging multidisciplinary meeting of biopsy

proven cancers; the commonest indications were dense breast tissue, to accurately delineate tumour mass and assess multifocality, as well as to assess contralateral breast tissue. MRI was also considered important if breast conserving surgery was planned, to exclude additional foci.

MRI was also used as additional radiological investigation in patients less than 50 years of age at diagnosis; and where estimated clinical size exceeded radiological size on standard imaging.

Our centre does not have an MRI biopsy facility; hence patients were recalled from MRI for second look ultrasound if further enhancing foci were evident in ipsilateral or contralateral breast. A careful search for additional foci correlating anatomically with MRI was performed, and corresponding lesions biopsied with marker placement; results were re-discussed at multidisciplinary meeting.

An Excel spreadsheet MRI database was created to document MRI data from 1st Jan 2021 to 31st Dec 2021 retrospectively. Anonymised patient details (age of presentation), Grade of tumour, receptor status including Her-2 receptor status, size on MRI, details of recall biopsies, and final pathology including grade, and final pathological size were documented.

## 3. Results

162 Her-2 Negative tumours and 37 Her-2 positive tumours underwent pre-operative MRI staging. Recalls in both groups were assessed for ipsilaterality/contralaterality; benign/malignant biopsy; grade and Her2 statuses (Table 1 & Table 2).

The maximum dimension of mass-like and non-mass like enhancement on MRI was compared to final pathological size of invasive cancer and associated DCIS. In cases that underwent Neo-adjuvant chemotherapy prior to surgery, pre-operative MRI size was compared to size of tumour bed on pathology.

Of the 162 Her-2 negative tumours, 36.4% of patients were recalled; 22% of these recalls had benign biopsies. Further ipsilateral malignancy was found in 13% of patients; 3% had further B3/B4 biopsies. Contralateral malignancy was discovered in 1.2% of patients.

**Table 1.** Patient demographics for Her2 Neg and Her2 pos tumours.

| Age | Her-2 NEGATIVE = 156 patients (2 multifocal; 2 bilateral) | Her-2 POSITIVE = 37 Patients |
|---|---|---|
| 20 - 30 Y | 2 | 0 |
| 30 - 40 Y | 20 | 9 |
| 40 - 50 Y | 33 | 9 |
| 50 - 60 Y | 61 | 12 |
| 60 - 70 Y | 27 | 5 |
| 70 - 80 Y | 11 | 2 |
| 80+ Y | 2 | 0 |

Table 2. Her2 pos and Her2 neg recalls.

| MALIGNANT RECALLS | | | |
|---|---|---|---|
| HER2 POS | PRIMARY TUMOUR | RECALL | |
| 1 | Grade 2 NST | HG DCIS | Deceased, no op |
| 2 | Grade 3 NST | HG DCIS | ER POS |
| 3 | Grade 2 NST | HG DCIS | ER NEG |
| 4 | Grade 2 ILC | Grade 2 ILC | Her2 neg different from primary |
| 5 | Grade 2 NST | HG DCIS | ER POS |
| 6 | Grade 3 NST | Grade 2 NST | ER POS Her2 POS |

| HER2 NEG IPSILATERAL | | | |
|---|---|---|---|
| 1 | Grade 2 NST | Grade 2 NST | ER POS Her2 neg |
| 2 | Grade 1 NST | Grade 1 NST | ER 0 HER2 NEG-ER DIFF FROM PRIMARY |
| 3 | Grade 1 with IGDCIS | IG DCIS | ER POS |
| 4 | Grade 2 NST | Grade 2 ILC | ER POS; LOB DIFFERENT |
| 5 | Grade 2 NST | DCIS | ER POS |
| 6 | Grade 2 NST | Grade 3 NST | ER POS |
| 7 | Grade 3 NST (IN NODES) | Grade 2 ILC | ER POS HER2 NEG |
| 8 | Grade 2 NST | Grade 2 NST | ER POS HER2 NEG |
| 9 | Grade 2 NST | Grade 1 NST | ER POS HER2 NEG |
| 10 | Grade 2 NST | Grade 2 NST | ER POS HER2 NEG |
| 11 | Grade 2 ILC | Grade 2 ILC | ER POS HER2 NEG |
| 12 | Grade 1 NST | Grade 1 NST | ER POS HER2 NEG |
| 13 | Grade 2 ILC | Grade 2 NST | ER POS HER2 NEG |
| 14 | Grade 2 NST | Grade 1 tubular | ER POS HER2 NEG |
| 15 | Grade 2 NST | Grade 2 NST | ER POS HER2NEG |
| 16 | Grade 2 NST | Grade 1 NST | ER POS HER2 NEG |
| 17 | Grade 2 ILC | Grade 2 ILC | ER POS |
| 18 | Grade 2 iLC | Grade 2 ILC | ER POS |
| 19 - 22 | | No bx, markers | |

| HER2 NEG CONTRALATERAL | | | |
|---|---|---|---|
| 1 | Grade 3 NST rt | Grade 2 ILC lt | BOTH ER POS |
| 2 | Grade 1, Grade 2 NST rt | Grade 2 NST lt | BOTH ER POS |

Amongst the 37 Her-2 positive patients, 11% of recalled patients had benign biopsies; 16% of recalls had further malignancy in the ipsilateral breast, and 3%

had B3/B4 biopsies. No contralateral malignancy was identified in Her2 positive patients (See Table 3 for summary).

A size difference of 10 mm was used as a cut-off for significant size difference between MRI size and final pathological size. 70% of Her-2 negative tumours showed good correlation between MRI size and final pathological size, in comparison to Her-2 positive tumours, where size correlation was only 48.6%.

19 Her-2 positive cases had MRI-Path size difference of greater than 10 mm; in 17 of these cases, MRI size exceeded pathological size.

48 Her-2 negative cases had MRI-Path size difference of 10 mm or greater; in 34 of these cases, MRI overestimated size.

## 4. Discussion

### 4.1. Additional Foci and Her2 Status

Herceptin receptor over-expression in breast cancer is associated with more aggressive disease, higher recurrence rate and shortened survival [5] [6] [7]. In a study by Tiwari *et al.* [7], 17 of 61 patients had over-amplification of the Her-2 receptor gene; no significant difference was found with non-Her-2 amplification with respect to tumour diameter, hormone receptor status or age; but a significant correlation was found with axillary node metastases. Of only 2 patients who did not have axillary node involvement, one had bone marrow involvement—hence 94% had more aggressive disease at diagnosis.

Does the greater aggressiveness of Her-2 amplified tumours correlate with greater involvement of the breast at diagnosis? This study set about to answer this question with a retrospective review of 189 MRIs performed pre-operatively for local staging.

The most common reason for performing MRI in these patients was to exclude

Table 3. Summary of MRI Characteristics of Her-2 tumours.

| | Her-2 NEGATIVE = 162 | Her-2 POSITIVE = 37 |
|---|---|---|
| Recalled | 59 (36.4%) | 11 (29.7%) |
| Further ipsilateral malignancy | 22 (13.5%) | 6 (16.2%)<br>(OR 0.83, 95% CI 0.3 - 2.2) |
| Contralateral malignancy | 2 (1.2%) | 0 |
| B3/B4 | 5 (3.08%) | 1 (2.7%) |
| MRI/PATH SIZE CONCORDANCE (*WITHIN* 10 *MM)* | 114 (70.3%) (p value > 0.1) | 18 (48.6%) (p value > 0.2) |
| MRI/PATH SIZE DISCORDANCE (>10 *MM DISCORDANCE*) | 48 (29.6%) | 19 (51.3%) |
| MRI > PATH SIZE (10 *MM OR MORE DIFFERENCE*) | 34/48<br>(70.8% OF DISCORDANCE) | 17/19<br>(89.4% OF DISCORDANCE) |

multifocality/multicentricity, particularly in dense breast tissue, where further evaluation using standard imaging techniques was difficult or limited. Herceptin receptor positivity was not considered a baseline reason for investigation. Other reasons for MRI staging included clinical size vs imaging size discrepancy; to exclude contralateral disease; and young age (less than 50 years) at diagnosis.

Recall rate for second look ultrasound was 29.7% for Her-2 positive and 36.4% for Her-2 negative lesions. At recall, further malignancy (B5A/B5B), or B3/B4, was found in ipsilateral breast in 19% of Her-2 positive lesions and 16% of Her-2 negative lesions.

MRI detected additional foci of malignancy more commonly in the ipsilateral breast, particularly in ER positive disease. The Odds Ratio of Her-2 positive disease having further foci in the same breast is 0.83 (95% CI 0.3 - 2.2). This suggests that there is no strong correlation between Her-2 positivity and increased additional foci of disease on MRI in the ipsilateral breast.

Contralateral disease was seen in 1.2% of cases in Her-2 negative tumours; no contralateral disease was identified in Her-2 positive disease. Plana MN *et al.* [2] detected contralateral malignancy in 5.5% of cases on MRI in a meta-analysis of 50 studies; our rate in current study is lesser.

In a study by L Corke *et al.* of 530 early stage breast cancer patients, divided into 2 groups—186 who underwent MRI prior to neoadjuvant chemotherapy and 330 patients who did not, MRI reported a greater extent of disease in the breast (37.6%), more nodal involvement (18.8%), and multifocal disease (15.1%) [8]. However, there was no significant difference in phenotype and Her2 status in the MRI and non-MRI groups (62.9 vs 63.4% Her2 Neg; 37.1 vs 36.6% Her2 Pos).

Pre-operative MRI has consistently detected mammographically occult cancers in the ipsilateral as well as contralateral breast [9] [10] but a review by SY Kim *et al.* [11] suggested that the reduced re-operation rate and subsequent cancer detection rate is balanced by the trade-off with increased mastectomy rate and false-positive recall rate.

The false positive benign biopsy rate was 22% for Her-2 negative patients and 11% for Her-2 positive patients; once again re-inforcing that while MRI is sensitive, it lacks specificity.

In a large meta-analysis of 19 studies with 2610 patients who underwent MRI by Houssami *et al.* [12], additional foci were found in 16% of patients, similar to the 2 arms in our study, where additional foci were found in 13% of Her2 negative and 16% of Her-2 positive cancers.

But what is the impact of these additional foci in ipsilateral and contralateral breast detected on MRI? The COMICE (Comparative Effectiveness of MRI in Breast Cancer) trial included 1623 patients randomised to MRI and non-MRI groups. Re-operation rate was 19% in both MRI and non-MRI groups; $p = 0.77$; and mastectomy rates were higher in the MRI vs Non-MRI group (7% vs 1%) [13].

The Pre-operative MRI of the Breast (POMB) trial from Sweden established lower re-operation rates for MRI group vs non-MRI group (5% vs 17%), but in this study, a negative excision margin of 10 mm was taken as standard, which would have influenced results [14].

We investigated the effect of additional ipsilateral foci on final surgical outcome by comparing maximum size on MRI with final pathological size of invasive and non-invasive disease.

### 4.2. MRI Size vs Pathological Size

In 48.6% of Her-2 positive cases, MRI size correlated with final pathological size. In 19 of 37 Her-2 positive cases, correlation with final pathological size was lost—in the majority of these (17 of 19 cases), MRI size overestimated tumour size.

MRI overestimation was an issue in 30% of Her-2 negative tumours as well, though to a lesser extent. Even with excluding lesions with 10 mm or greater size difference between MRI and final pathological size, no significant correlation was found between MRI size estimate and final pathological size (Her-2 pos $p > 0.2$; Her-2 neg $p > 0.1$)

Most lesions in the current study were staged as T1-T2, and N0-N1, hence qualifying as Early Breast cancer. Her-2 positivity, while conferring an increased level of aggression with lymphatic/vascular dissemination, did not correlate with significant increased multifocality or multicentricity locally, with comparable rates of recall and additional foci between Her-2 positive and negative lesions.

In a meta-analysis involving the COMICE, MONET and POMB trials, as well as 16 other comparable studies including 15,274 patients, Houssami *et al.* [15] found that MRI was associated with increased rates of mastectomy, but with no significant association with re-operation, re-excision or positive margins.

However, this was countered by Kuhl *et al.* [16] who suggested that over-treatment by MRI can be avoided if additional cancers found on ultrasound or MRI are treated by additional lumpectomy rather than mastectomy.

But did pre-operative MRI, by detecting additional ipsilateral or contralateral disease, lead to reduced recurrence? In a meta-analysis by Houssami *et al.* [17] of 3169 patients from 4 studies—COMICE [13], Hwang *et al.* [18], Solin *et al.* [19] and Miller *et al.* [20], the 8-year recurrence free survival between MRI and non-MRI groups did not differ significantly (97% vs 95%; $p = 0.87$).

This was also borne out by studies at the University of Pennsylvania in 756 patients with similar rates of ipsilateral recurrence and contralateral breast cancer rates between MRI and non-MRI groups [19] [21].

In a review of 84 cancers treated surgically, comparison was made with pre-operative Mammogram, US and MRI measurements—univariate analysis showed that MRI with non-masslike enhancement or mass with non-mass enhancement were more likely to show discordance with final pathological size, and although MRI showed the highest level of concordance in comparison to other modalities, there was 80% proportionate over-estimation of tumour size by

MRI (30% mammogram; 20% US) [22].

Several studies have shown the discordance between MRI size estimation and pathological size—Onesti *et al.* [23] had a concordance rate of 57.1%; Grimsby *et al.* found a concordance rate of 53% within 0.5 cm [24] and an overestimation rate of 33%.

In a study of 163 patients, concordance rate of MRI size and final pathological size was 91.2% in patients with mass only; presence of non mass enhancement reduced concordance to 72.5%; the association of NME was stronger in Her2 positive patients in this group with IDC [25].

Our study has shown that concordance rate was higher for Her2 Negative patients than Her2 positive patients; but the results of the two groups did not reach significance ($p > 0.05$).

## 5. Limitations

There are limitations to this study—the cohort of Her-2 positive lesions is small compared to Her-2 negative lesions. Further studies with greater numbers, particularly of Her2 positive patients, and more advanced local tumours are recommended.

While additional foci were sought by second look ultrasound in all cases recalled, and marked or biopsied for confirmation, pursuing these with MRI guided biopsy, particularly large volume, might yield more accurate results with greater concordance.

In patients who underwent neo-adjuvant treatment prior to surgery, the pre-operative tumour size on MRI was compared to tumour bed on pathology—this likely shrinks with chemotherapy, and hence concordance is likely to be poor.

## 6. Conclusions

Magnetic resonance imaging plays a significant role in pre-operative detection of additional foci in both Her2 positive and Her2 negative tumours—while invariably associated with false positive recalls and benign biopsies, additional malignant foci were detected in 16% of Her2 positive and 13% of Her2 negative patients. Herceptin receptor positivity did not confer significantly increased locally aggressive features in the breast.

Despite confirmation by second look ultrasound with biopsies or markers, magnetic resonance imaging overestimated disease in relation to final pathological size in 29.6% of Her2 negative and 51.3% of Her2 positive tumours. It is hopeful that with the advent of radiomics, including quantitative analysis and feature extraction, more accurate mapping of tumour and peri-tumoural involvement might allow greater concordance with pathology.

## Ethics Approval

This was a retrospective observational study, personal details of patients were

not utilised, and outcomes did not impact directly on patient treatment. Hence, ethics approval was waived by the South East Scotland Ethics Committee. The study conformed to the principles of the Declaration of Helsinki (2013).

## Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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