# Impact of receptor phenotype on nodal burden in patients with breast cancer who have undergone neoadjuvant chemotherapy

**M. R. Boland[1], T. P. McVeigh[4], N. O'Flaherty[4], G. Gullo[2], M. Keane[5], C. M. Quinn[3], E. W. McDermott[1], A. J. Lowery[4], M. J. Kerin[4] and R. S. Prichard[1]**

Departments of [1]Breast Surgery, [2]Oncology and [3]Pathology, St Vincent's University Hospital, Dublin, and Departments of [4]Breast Surgery and [5]Oncology, University College Hospital Galway, Galway, Ireland
*Correspondence to:* Mr M. R. Boland, Department of Breast Surgery, St Vincent's Hospital, Dublin 4, Ireland (e-mail: michaelboland@rcsi.ie)

**Background:** Optimal evaluation and management of the axilla following neoadjuvant chemotherapy (NAC) in patients with node-positive breast cancer remains controversial. The aim of this study was to examine the impact of receptor phenotype in patients with nodal metastases who undergo NAC to see whether this approach can identify those who may be suitable for conservative axillary management.

**Methods:** Between 2009 and 2014, all patients with breast cancer and biopsy-proven nodal disease who received NAC were identified from prospectively developed databases. Details of patients who had axillary lymph node dissection (ALND) following NAC were recorded and rates of pathological complete response (pCR) were evaluated for receptor phenotype.

**Results:** Some 284 patients with primary breast cancer and nodal metastases underwent NAC and subsequent ALND, including two with bilateral disease. The most common receptor phenotype was luminal A (154 of 286 tumours, 53·8 per cent), with lesser proportions accounted for by the luminal B–Her2 type (64, 22·4 per cent), Her2-overexpressing (38, 13·3 per cent) and basal-like, triple-negative (30, 10·5 per cent) subtypes. Overall pCR rates in the breast and axilla were 19·9 per cent (54 of 271 tumours) and 37·4 per cent (105 of 281) respectively. Axillary pCR rates were highest in the Her2-overexpressing group (27 of 35, 77 per cent) and lowest in the luminal A group (35 of 153, 22·9 per cent) ($P < 0.001$). Nodal burden (median number of positive nodes excised) was lower in the Her2-overexpressing group compared with the luminal A group (0 *versus* 3; $P < 0.001$).

**Conclusion:** Her2 positivity was associated with increased rates of axillary pCR and reduced nodal burden following NAC.

Presented to the Annual Meeting of the Society of Academic and Research Surgery, Dublin, Ireland, January 2017

## Introduction

The past decade has seen a dramatic increase in the use of chemotherapy before primary surgery in patients with newly diagnosed breast cancer[1−4]. Neoadjuvant chemotherapy (NAC) was initially used to downstage large tumours and, if sufficiently successful, to increase rates of breast-conserving surgery[3,5,6]. More recently, NAC has been used with the aim of achieving a complete pathological response (pCR)[7−13], which, if identified correctly, might influence further treatment strategies.

Axillary nodal status remains one of the most important prognostic indicators in newly diagnosed breast cancer.

Decisions regarding the need for axillary lymph node dissection (ALND) and the use of adjuvant treatments for axillary disease are no longer based solely on traditional factors such as tumour stage and lymph node status, but more on a range of characteristics that include receptor phenotype and individualized genomic analysis, which predicts response to such treatments. ALND is currently used primarily to stage the axilla of patients with confirmed nodal disease. The use of ALND to obtain locoregional disease control has been brought into question in the past 10 years with the publication of the American College of Surgeons Oncology Group (ACOSOG) Z011

trial[14] indicating that certain patients with nodal metastatic disease do not benefit from completion ALND. Among patients with node-positive disease diagnosed at the outset, a number of studies[15−18] have attempted to identify individuals who could potentially avoid an ALND after NAC.

The ACOSOG Z1071 trial demonstrated that axillary pCR rates after NAC differed significantly based on receptor phenotype, with Her2-overexpressing tumours most likely to achieve a pCR[19]. There has been little focus, however, on receptor phenotypes to identify patients receiving NAC who could avoid ALND. Most studies examining such characteristics have looked at pCR as the primary outcome, and few have examined the burden of nodal disease in the axilla after NAC in an attempt to stratify response. It is clear from the ACOSOG Z011 study that a low axillary nodal burden (2 or fewer positive nodes) can signify an excellent prognosis, and using residual nodal burden based on receptor phenotype, and not just pCR, could be important in identifying patients who might avoid ALND after NAC.

The aim of this study was to assess differences in axillary nodal burden, pCR rates and residual lymph node ratio (LNR) found on completion ALND between receptor phenotypes in patients with breast cancer undergoing NAC.

## Methods

A longitudinal cohort study was undertaken, with retrospective analysis of a prospectively developed histopathological database across two specialist tertiary referral centres in Ireland. All patients managed with chemotherapy before definitive primary breast and axillary surgery following a diagnosis of primary breast cancer (T1–T4) between 2009 and 2014 were included. All patients had cytological or histological confirmation of positive ipsilateral nodal metastatic disease by means of fine-needle aspiration cytology (FNAC) or core biopsy of radiologically or clinically suspicious nodes, or sentinel lymph node biopsy (SLNB). All patients then received NAC as guided by the treating medical oncologist, with subsequent therapeutic ALND. Patients who underwent SLNB after NAC were excluded. Demographic data and tumour clinicopathological characteristics were recorded for each patient.

### Assessment of tumour subtype

Four phenotypes were defined. Patients whose tumours predominantly expressed oestrogen receptors (ERs) and did not overexpress Her2/neu receptors were classified in the luminal A group. In clinical practice, expression of the Her2/neu receptor is frequently used as a surrogate marker of the luminal B subtypes[20], and thus patients within the luminal B–Her 2 group demonstrated expression of ERs and Her2/neu receptor overexpression. Patients in the Her2-overexpressing group demonstrated amplification of Her2/neu receptors, but did not have evidence of ER expression. Basal-like 'triple-negative' phenotypes did not express oestrogen or Her2/neu receptors. All breast cancers underwent molecular profiling before commencement of NAC. Her2 amplification was defined by a score of 3 or more on immunohistochemical assessment or by amplification on fluorescence *in situ* hybridization analysis.

### Surgery type and quantification of nodal disease

Definitive breast and axillary surgery was performed within 6 weeks of completion of NAC. All patients had repeat imaging and were assessed clinically before the end of the chemotherapeutic regimen. ALND was defined as an anatomical level I and II dissection. Each level was dissected separately. Histopathological dissection of excised nodes involved routine bisection and haematoxylin and eosin staining. Immunohistochemical staining was used in equivocal cases. The total number of nodes excised during ALND and the total number of positive nodes were recorded for all patients. If a patient had SLNB before ALND, this was recorded and included in the total number of nodes excised (but was discounted from analysis of nodal burden following NAC).

### Response to neoadjuvant chemotherapy

In the breast and axilla, pCR was defined as the absence of either residual, *in situ* or invasive disease on haematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of NAC[21]. Pathological response to chemotherapy was assessed in one unit by the method of Sataloff and co-workers[22] and in the other unit using that described by Ogston and colleagues[23]. For this reason, and for the purposes of this study, pathological response was graded as complete (pCR) or less than complete. pCR within the breast and axillary specimens was recorded separately for each patient when data were complete.

### Evaluation of lymph node ratios

The LNR following NAC was defined as the ratio of positive nodes to the total number of nodes excised for each receptor phenotype. LNRs were divided into three

**Table 1** Patient and tumour characteristics

| | All patients (n = 284) | Receptor phenotype | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | | Luminal A | Luminal B–Her2 | Her2-overexpressing | Basal-like | P† |
| No. of tumours | 286 | 154 (53·8) | 64 (22·4) | 38 (13·3) | 30 (10·5) | |
| Age at diagnosis (years)* | 50·3(10·8) | 50·1(10·5) | 49·3(10·6) | 51·1(11·8) | 52·3(11·2) | 0·617‡ |
| Histological type | | | | | | 0·060 |
| Invasive ductal | 242 (84·6) | 119 (77·3) | 59 (92) | 37 (97) | 27 (90) | |
| Invasive lobular | 25 (8·7) | 21 (13·6) | 2 (3) | 0 (0) | 2 (7) | |
| Mixed ductolobular | 12 (4·2) | 8 (5·2) | 3 (5) | 1 (3) | 0 (0) | |
| Other | 3 (1·0) | 3 (1·9) | 0 (0) | 0 (0) | 0 (0) | |
| Missing | 4 (1·4) | 3 (1·9) | 0 (0) | 0 (0) | 1 (3) | |
| Surgery type | | | | | | 0·005 |
| Breast-conserving | 94 (32·9) | 42 (27·3) | 18 (28) | 17 (45) | 17 (57) | |
| Mastectomy | 192 (67·1) | 112 (72·7) | 46 (72) | 21 (55) | 13 (43) | |
| AJCC grade | | | | | | 0·001 |
| I | 10 (3·5) | 9 (5·8) | 0 (0) | 1 (3) | 0 (0) | |
| II | 152 (53·1) | 94 (61·0) | 34 (53) | 12 (32) | 12 (40) | |
| III | 116 (40·6) | 45 (29·2) | 30 (47) | 24 (63) | 17 (57) | |
| Missing | 8 (2·8) | 6 (3·9) | 0 (0) | 1 (3) | 1 (3) | |

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †χ² test, except ‡ANOVA.

**Table 2** Rates of complete pathological response and nodal burden following neoadjuvant chemotherapy

| | All patients (n = 284) | Receptor phenotype | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | | Luminal A | Luminal B–Her2 | Her2-overexpressing | Basal-like | P† |
| No. of tumours | 286 | 154 (53·8) | 64 (22·4) | 38 (13·3) | 30 (10·5) | |
| Axillary response | | | | | | |
| No. of nodes excised after NAC* | 19 (5–58) | 19 (5–58) | 19·5 (6–55) | 19 (8–39) | 18 (6–41) | 0·761‡ |
| No. of positive residual nodes at ALND after NAC* | 1 (0–27) | 3 (0–27) | 1 (0–20) | 0 (0–4) | 0 (0–26) | <0·001‡ |
| 0 | 105 | 35 | 28 | 27 | 15 | <0·001 |
| 1 | 41 | 23 | 13 | 3 | 2 | |
| 2–4 | 63 | 41 | 12 | 5 | 5 | |
| 5–10 | 43 | 32 | 8 | 0 | 3 | |
| > 10 | 29 | 22 | 3 | 0 | 4 | |
| Missing | 5 | 1 | 0 | 3 | 1 | |
| LNR after NAC* | 0·08 (0–1) | 0·14 (0–1) | 0·04 (0–1) | 0 (0–0·27) | 0 (0–1) | <0·001‡ |
| Tumour response | | | | | | |
| pCR – breast | 54 of 271 (19·9) | 9 of 147 (6·1) | 17 of 62 (27) | 20 of 35 (57) | 8 of 27 (30) | <0·001 |
| Final T status | | | | | | <0·001 |
| ypT0 | 54 | 9 | 17 | 20 | 8 | |
| ypT1 | 68 | 35 | 20 | 8 | 5 | |
| ypT2 | 98 | 61 | 20 | 6 | 11 | |
| ypT3 | 45 | 40 | 2 | 1 | 2 | |
| ypT4 | 6 | 2 | 3 | 0 | 1 | |
| Missing | 15 | 7 | 2 | 3 | 3 | |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). NAC, neoadjuvant chemotherapy; ALND, axillary lymph node dissection; LNR, lymph node ratio; pCR, complete pathological response. †χ² test, except ‡Kruskal–Wallis test.

categories (0·20 or less, low; 0·21–0·65, intermediate; more than 0·65, high) to identify those likely to have poorer outcomes, as described previously[24,25].

## Statistical analysis

Data were analysed using SPSS® version 24 (IBM, Armonk, New York, USA). Continuous data were assessed for normality using Kolmogorov–Smirnov tests, with parametric and non-parametric tests applied as appropriate. Normally distributed data are described as mean(s.d.) and non-normally distributed data as median (range) values. Univariable analyses of parametric continuous data were performed using the $t$ test for comparisons of two sets of data, and ANOVA for comparisons between more than two groups. Categorical data were compared with the $\chi^2$

**Table 3** Lymph node ratio risk categories for each biological subtype

| LNR risk category | Receptor phenotype | | | | |
|---|---|---|---|---|---|
| | Luminal A | Luminal B−Her2 | Her2-overexpressing | Basal-like | Total |
| No. of positive residual nodes | 35 (22·9) | 28 (44) | 27 (77) | 15 (52) | 105 (37·4) |
| Low risk (≤ 0·20) | 60 (39·2) | 23 (36) | 7 (20) | 9 (31) | 99 (35·2) |
| Intermediate risk (0·21−0·65) | 36 (23·5) | 8 (13) | 1 (3) | 2 (7) | 47 (16·7) |
| High risk (> 0·65) | 22 (14·4) | 5 (8) | 0 (0) | 3 (10) | 30 (10·7) |
| Total | 153 | 64 | 35 | 29 | 281 |

Values in parentheses are percentages. LNR, lymph node ratio.

test. Multivariable analyses were performed using binary logistic regression. All traditional prognostic factors were included in the multivariable analysis to try to account for confounders. Stepwise regression was not applied. For all tests, $P < 0.050$ was considered statistically significant.

## Results

A total of 284 patients with a new diagnosis of primary breast cancer and confirmed ipsilateral axillary metastatic disease received NAC followed by ALND during the study interval. Two patients had bilateral disease, and in these each ALND performed was assessed separately, accounting for a total of 286 cancers. Of the 286 tumours, 241 had a positive finding on ultrasound-guided FNAC before NAC, and 45 had a positive SLNB result.

### Clinicopathological characteristics

The most common pathological tumour subtype was invasive ductal carcinoma (242 tumours, 84·6 per cent), followed by lobular (25, 8·7 per cent) and then mixed/missing/other data (19, 6·6 per cent). With regard to receptor phenotype, 154 tumours (53·8 per cent) were classified luminal A, 64 (22·4 per cent) as luminal B−Her2, 38 (13·3 per cent) as Her2-overexpressing and 30 (10·5 per cent) as basal-like. Mean age at diagnosis did not differ significantly between the groups ($P = 0.617$) (*Table 1*).

Following NAC, breast-conserving surgery was performed for 94 tumours (32·9 per cent), with mastectomy for the remaining 192 (67·1 per cent). The proportion undergoing mastectomy compared with breast-conserving surgery was significantly different across receptor phenotypes, with 72·7 per cent in the luminal A group undergoing mastectomy compared with 72, 55 and 43 per cent in luminal B−Her2, Her2-overexpressing and basal-like cohorts respectively ($P = 0.005$). Wide variation in AJCC tumour grade across receptor phenotype was also appreciated, with luminal A tumours having the lowest proportion of grade III activity (29·2 per cent),

compared with rates in the luminal B−Her2 (47 per cent; $P = 0.010$), Her2-overexpressing (63 per cent; $P < 0.001$) and basal-like (57 per cent; $P < 0.001$) groups (*Table 1*).

### Response to neoadjuvant chemotherapy

A pCR was noted in 54 of 271 cancers (19·9 per cent) in the breast, compared with 217 (80·1 per cent) with a partial or minimal response (*Table 2*). The lowest proportion of patients achieving a pCR in the breast was noted in the luminal A group (9 of 147, 6·1 per cent) compared with other phenotypes ($P < 0.001$). The best response was noted in the Her2-overexpressing cohort (20 of 35, 57 per cent). The number of patients with a high tumour stage (ypT3−4) was higher in the luminal A group than in the other groups ($P = 0.010$) (*Table 2*).

The median total number of nodes excised during ALND was 19 (range 5−58) across the whole cohort and was not significantly different between receptor phenotypes ($P = 0.761$). A total of 105 of 281 patients (37·4 per cent) had a pCR in the axilla following NAC, compared with 176 (62·6 per cent) that had at least one lymph node involved with metastatic disease. Data relating to number of residual nodes were missing for five cancers (*Table 2*). Seventy-seven per cent (27 of 35) of patients with Her2-overexpressing tumours had an axillary pCR compared with 22·9 per cent (35 of 153) of those with luminal A ($P < 0.001$), 44 per cent of those with luminal B−Her2 (28 of 64; $P = 0.007$) and 52 per cent of those with basal-like (15 of 29; $P = 0.070$) subtypes. The median number of positive nodes excised across the entire cohort was 1 (range 0−27). Patients in the luminal A group had a median of 3 (0−27) positive nodes, compared with 1 (0−20) for luminal B−Her2 ($P = 0.010$), 0 (0−4) for Her2-overexpressing ($P < 0.001$) and 0 (0−26) for basal-like ($P < 0.001$) subtypes (*Table 2*).

LNRs following NAC were also significantly different amongst the groups. The lowest LNR (median 0 (range 0−0·27)) was found in the Her2-overexpressing group, and this was significantly different compared with ratios in the luminal A (0·14 (0−1); $P < 0.001$) and luminal

**Table 4** Multivariable logistic regression for prediction of factors associated with complete pathological response in the breast and axilla after neoadjuvant chemotherapy

| | Breast pCR | | Axillary pCR | |
|---|---|---|---|---|
| | Odds ratio | P | Odds ratio | P |
| Age | 0·99 (0·96, 1·02) | 0·490 | 0·97 (0·94, 0·99) | 0·014 |
| Molecular subtype* | | < 0·001 | | < 0·001 |
| Luminal B–Her2* | 6·81 (2·29, 20·24) | 0·001 | 2·38 (1·24, 4·57) | 0·009 |
| Her2-overexpressing* | 31·93 (10·09, 101·03) | < 0·001 | 7·17 (3·10, 16·58) | < 0·001 |
| Basal-like* | 9·45 (2·80, 31·87) | < 0·001 | 3·15 (1·30, 7·60) | 0·011 |
| AJCC grade† | | 0·110 | | 0·040 |
| II† | > 10 000 | 0·999 | 0·67 (0·15, 2·93) | 0·590 |
| III† | > 10 000 | 0·999 | 1·36 (0·30, 6·07) | 0·690 |

Values in parentheses are 95 per cent confidence intervals. pCT, complete pathological response. *Compared with luminal A; †compared with grade I.

B–Her2 (0·04 (0–1); $P = 0.030$) groups. Of eight patients in the Her2-overexpressing group who had residual positive nodes after ALND, seven were found to have low-risk LNRs with the other patient having an intermediate-risk LNR. In the luminal A group, of 118 patients found to have a residual burden after NAC, 60 (50·8 per cent) had a low-risk LNR and 22 (18·6 per cent) had a high-risk LNR. No patient in the Her2-overexpressing group had a high-risk LNR following NAC (*Table 3*).

Univariable and multivariable analyses identified factors that had an independently significant effect on pCR in the breast and axilla. Univariable analysis identified age, tumour grade and receptor subtype as predictors of pCR after NAC in both breast and axilla. In multivariable analysis, when age and grade were accounted for, receptor phenotype was still a significant predictor of pCR in the breast. All three factors were significant in predicting axillary pCR (*Table 4*).

## Discussion

This study has shown that patients with breast cancer and histologically confirmed axillary nodal metastatic disease treated with NAC demonstrate differing axillary response rates according to receptor phenotype. In quantifying the numbers of lymph nodes, the study demonstrated that patients with Her2-overexpressing tumours have a significantly reduced nodal burden after NAC. SLNB after NAC may be considered in this cohort, avoiding the requirement for completion ALND and its associated morbidity.

The ACOSOG Z11 study[14] questioned the need for ALND in patients with low-volume axillary metastatic disease. Significant focus has been placed recently on identifying certain patients with more aggressive disease undergoing NAC, who might also avoid ALND. Therefore, the use of SLNB after NAC as a means of reassessing the axilla has been examined. The difficulty with such a diagnostic

approach is that previous studies[15,26] evaluating the use of SLNB after NAC have documented a false-negative rate (FNR) greater than 10 per cent. In the SENTINA study[15], the FNR was 14·2 per cent in arm C of the trial (patients with clinically node-positive disease that converted to clinically node-negative disease after NAC). Similarly, in the ACOSOG Z1071 study[26], the FNR was 12·6 per cent in patients with cN1 disease with two or more nodes removed. In that study, the FNR improved to 10·1 per cent when immunohistochemical staining was used to assess the SLNB, and was also influenced by the use of dual tracer techniques and the number of nodes removed. The present study has demonstrated that the majority of patients in the Her2-overexpressing group with biopsy-proven axillary disease who subsequently received NAC have two or fewer positive axillary nodes on completion ALND. It seems unlikely likely that, with such a low burden of residual disease in this specific cohort, the FNR would exceed 10 per cent. Trials (ALLIANCE 11202, NSABP-B51) are currently underway to identify patients with and without residual nodal burden, who may be spared ALND after NAC.

The proportion of patients in the present study with no residual metastatic disease in the axilla was 37·4 per cent, compared with 41 per cent in the ACOSOG Z1071 trial[16]. Eighty-six per cent (30 of 35) of patients in the Her2-overexpressing group had either none or only one extra positive node after NAC. It seems reasonable to propose that SLNB following NAC is attempted in order to avoid ALND where a pCR has been obtained. The CTNeoBC pooled analysis[27] demonstrated that achieving a pCR correlated with improved survival, with prognostic value being most favourable in the Her2-overexpressing and basal-like subtypes, supporting the use of less invasive surgical intervention for patients with these subtypes. Conversely, genomic characterization of Her2-overexpressing breast cancers can identify somatic events in patients unlikely to achieve a pCR[28]. These patients are more likely

to require more aggressive axillary surgery, similar to those in the luminal A group, in whom response to NAC is less favourable.

The present study also showed that the LNR can be used to demonstrate significant differences in response to NAC based on receptor phenotype. Her2-overexpressing and basal-like patient groups had a median LNR of 0, indicating the high proportions in both groups that achieved axillary pCR. Providing LNR values for different receptor phenotypes should add to the evidence that certain patients may benefit from a more conservative approach to the axilla after NAC. These results are similar to those of a recent study[29] that showed strong associations between low LNRs and improved outcomes in the luminal A, luminal B–Her2 and basal-like groups. Although that study was unable to identify a correlation in the Her2-overexpressing group, this was probably due to the inclusion of only 33 patients with this phenotype.

In the present study, 19·9 per cent of patients achieved a pCR in the breast with marked differences between the subtypes (57 per cent of the Her2-overexpressing group, 6·1 per cent in the luminal A group). Patients with Her2 overexpression should be considered for less invasive surgery to both the breast and axilla. Breast-conserving surgery and SLNB should be considered in patients overexpressing Her2 who have received NAC.

This study has a number of limitations. Although the databases were set up prospectively, they were not created specifically for this study. Some differences in the databases existed between the two centres, which account for certain characteristics not being examined between phenotypes. Data were not recorded with respect to locoregional recurrence or overall survival. Details on patients with a partial response in the axilla might also have proved useful to estimate prognosis. Variations in results between this study and other publications probably reflect a lack of standardized pathological reporting of response rates[21], although this and other parameters should lend themselves to more reliable comparison following the publication of recent guidelines[30].

## Acknowledgements

*Disclosure:* The authors declare no conflict of interest.

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