# Human Epidermal Growth Factor Receptor-2 Positivity Predicts Locoregional Recurrence in Patients with T1-T2 Breast Cancer

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**Abstract.** *Aim: To determine the impact of biological subtypes defined by hormonal receptors and human epidermal growth factor receptor-2 status on risk of recurrence in women with invasive breast cancer treated with breast-conserving therapy. Patients and Methods: Between 2001-2005, we observed 590 women with invasive breast cancer. They underwent conservative surgery, adjuvant radiotherapy and hormonotherapy or chemotherapy. None received adjuvant trastuzumab. The Kaplan-Meier method was applied to calculate for the 36-month and 60-month rates of locoregional recurrence-free survival and overall survival. Results: The overall 36- and 60-month actuarial Kaplan-Meier survival rates were 98.5% and 97.7%, respectively; the locoregional recurrence-free survival rates were 95.2% and 91.2%, respectively. Locoregional recurrence rate was significantly greater in patients with human epidermal growth factor receptor-2 (15.2% vs. 5.3%, p<0.001). Conclusions: Patients with hormone receptor-negative or human epidermal growth factor receptor-2-positive T1-T2 breast cancer seem to have a greater risk of disease recurrence.*

In the past four decades, breast-conserving surgery followed by whole-breast irradiation has become the standard of care for the treatment of early-stage breast carcinoma (1). Adjuvant radiotherapy after modified radical mastectomy and breast-conserving surgery for early-stage invasive breast cancer substantially reduces the risk of locoregional failure and is evidence-based (2). Traditionally, the occurrence of locoregional failure is related to clinical and pathological factors and these are usefully employed to classify patients into subgroups by risk of locoregional recurrence (LRR). Factors such as age, tumor histological grade and type, size, lymph node (LN) involvement, surgical margins, and lymph vascular invasion (LVI) typically provide prognostic information. Some studies observed that young age, positive surgical margins and omission of radiation therapy are independent risk factors for increased LRR (3-4). In other series, age, tumor size, extensive intraductal component, surgical margins and grading were proven prognostic factors for recurrent disease. All these clinical factors can be routinely used with respect to prognosis and prediction of risk of LRR and in decisions regarding locoregional treatment of breast cancer.

Recently, a role for molecular markers has emerged; these may provide sufficient information to allow for accurate individual risk assessment, in order to identify patients who might benefit from irradiation. Despite hundreds of reports on tumor markers, findings are controversial and the number of validated markers for clinical practice is small. During the past decade, genome-wide analyses have revolutionized cancer research. Such studies of invasive breast carcinoma have focused on three biological biomarkers: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2). ER, PR, and HER2 have proved to be important independent prognostic and predictive biomarkers in breast cancer. ER and PR are prognostic and predictive factors commonly used in radiotherapy practice; some reports have correlated their expression with LRR (5-9). HER2 status (positive *versus* negative) has been validated in different patient cohorts and was associated with different outcomes (10-12).

The potential of integration of classifying molecular subtypes of breast cancer into clinical decision-making may contribute to tailoring treatment of locoregional disease. The current treatment decisions for locoregional disease are based on clinicopathological factors and the application of molecular profiling of breast cancer to assess the risk of LRR is not well developed for women newly diagnosed with breast cancer. Recently, several authors have shown that patients with HER2-positive and ER/PR-negative T1a,bN0

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breast cancer had a greater risk of LRR (13,14). The primary purpose of our study was to determine in our experience the impact of biological subtypes of breast cancer defined by hormonal receptor and HER2 status on risk of LRR in newly-diagnosed women treated with breast-conserving therapy (BCT).

## Patients and Methods

*Patient population*. Between 2001 and 2005, we studied 590 women who were diagnosed as having invasive breast carcinomas 5 cm or smaller and presenting with or without nodal involvement. A total of 307 patients were eligible for the study because 283 patients with ductal carcinoma *in situ* and microinvasion, lack of receptor information and recurrent breast cancer at presentation were excluded from the analysis. The patients observed underwent BCT and adjuvant hormonotherapy or chemotherapy. None received adjuvant trastuzumab.

The standard radiotherapy approach for BCT during the study period was to treat the whole breast to 50 Gy in 25 fractions using medial and lateral tangent fields, followed by a boost to the tumor bed with 10 Gy in five fractions.

*Pathology methods*. A dedicated breast pathologist performed immunohistochemical (IHC) analysis or fluorescence *in situ* hybridization (FISH) to determine hormone receptor and HER2 status.

Nuclear staining 10% of either ER or PR was considered a positive result. HER2 positivity was defined as 3+ receptor overexpression on IHC staining or as gene amplification found on FISH.

*Statistical methods*. All qualitative variables were summarized as frequencies and percentages and all quantitative variables as means and standard deviations. The Kaplan Meier method was used to calculate the 36-month and 60-month rates of LRR-free survival and overall survival. The follow-up was defined as the time interval between surgery and death due to disease or, for LRR-free survival, as the time between surgery and the locoregional event. In patients in which no such event occurred, the observational time interval was defined as the period from surgery to the last follow-up visit. The Kaplan Meier method was also used to estimate LRR rate and the 95% confidence interval (95% CI) at 60 months of follow-up, after stratifying patients for ER, PR, and HER2 status and all other factors. Statistical significance of the difference between survival curves was evaluated using the log-rank test.

A $p$-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using SPSS® software 11.0 (SPSS Inc., Chicago, IL, USA).

## Results

Patients' characteristics are summarized in Table I. Out of the 307 patients, 30.9% had HER2-positive, 72.0% had ER-positive and 55.4% had PR-positive disease. All patients had undergone BCT and received adjuvant hormonal therapy (48.2%), chemotherapy (33.9%), or hormono-chemotherapy (15.3%). No patient had received adjuvant trastuzumab therapy.

The median follow-up was of 37 months (range=8-78 months). In this period, a total of 15 LRR events occurred, corresponding to a rate of 4.9%.

Out of all patients, 13 (4.2%) experienced distant metastasis and four (1.3%) died due to causes related to breast cancer.

The overall 36- and 60-month actuarial Kaplan Meier survival rates were 98.5% and 97.7%, respectively; the LRR-free survival rate was 95.2% and 97.7%, respectively (Table II).

LRR by ER, PR, and HER2 status are shown by the Kaplan-Meier curves in Figures 1-3.

The 60-month LRR rate was greater in patients with PR-negative disease (12.9% *vs*. 4.0%, $p=0.051$), and HER2-positive disease (15.2% *vs*. 5.3%, $p<0.001$); in patients with ER-negative disease, a greater tendency for LRR was observed although this did not reach statistical significance (13.1% *vs*. 6.1%, $p=0.131$) (Table III).

In the univariate analysis, we also analyzed additional factors that adversely affected the LRR rates; factors significantly related to the LRR were: histological type ($p=0.032$); great N stage ($p<0.001$) and grading (G2 *vs*. G1 $p=0.023$ and G3 *vs*. G1 $p<0.001$).

ER, PR and HER2 status were subsequently combined to assess the prognostic power of four possible subtypes. Tumors that were ER- or PR-positive were categorized as hormone receptor (HR)-positive, while they were HR-negative if negative for both ER and PR. The Kaplan-Meier analysis was repeated based on these tumor subtypes: $HR^+$ $HER2^-$, $HR^+$ $HER2^+$, $HR^-$ $HER2^+$, HR- $HER2^-$ (Figure 4). Among these groups, a statistically significant difference ($p<0.001$) was observed in LRR, with the $HR^-$ $HER2^+$ group experiencing the greatest LRR.

## Discussion

In the present study, we have shown that patients with T1-T2 stage breast cancer $HR^-$ $HER2^+$ have a greater risk of LRR. This result seems to confirm the suggestion that these tumor subtypes are more clinically aggressive, even if small in size.

Several recent studies have assessed the risk of LRR for breast cancer after both conservative surgery and mastectomy in relation to the molecular characteristics of tumors and to subgroups deriving from the combination of HER2 and ER/PR. One of the first studies examining this issue was a small case-control analysis that compared the rate of HER2 expression in 16 patients who developed LRR after BCT with that of matched controls who had not developed recurrence, showing that 56% of recurrent tumors overexpressed HER2 compared with only three matched controls (18%) (15). Harris and co-workers, examining HER2 overexpression in 352 patients with stage I-II breast cancer treated with BCT, did not find differences in LRR

Table I. *Histological and clinical characteristics of 307 patients with breast cancer.*

| Characteristic | Number of patients (%) | | Number of patients (%) |
|---|---|---|---|
| Age, mean±SD | 55.7±10.9 | HER2 status | |
| ≤50 years | 101 (32.9) | Positive | 95 (30.9) |
| >50 years | 206 (67.1) | Negative | 212 (69.1) |
| Histological features | | ER status | |
| Ductal | 245 (79.9) | Positive | 221 (72.0) |
| Lobular | 36 (11.7) | Negative | 76 (24.7) |
| Other | 26 (8.4) | Unknown | 10 (3.3) |
| T Stage | | PR status | |
| T1 | 250 (81.4) | Positive | 170 (55.4) |
| T2 | 57 (18.6) | Negative | 126 (41.0) |
| N Stage | | Unknown | 11 (3.6) |
| N0 | 300 (97.8) | Margin status | |
| N+ | 7 (2.2) | Free ( ≥10 mm) | 191 (62.2) |
| Grading | | Close (<2 mm) | 10 (3.3) |
| G1 | 117 (38.1) | Unknown | 106 (34.5) |
| G2 | 85 (27.7) | Adjuvant therapy | |
| G3 | 52 (16.9) | Chemotherapy | 104 (33.9) |
| Unknown | 53 (17.3) | Hormonal therapy | 148 (48.2) |
| Menopausal status | | Chemo+hormonal therapy | 47 (15.3) |
| No | 65 (21.2) | No | 8 (2.6) |
| Yes | 144 (46.9) | | |
| Unknown | 98 (31.9) | | |

ER, Estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2.

rates between those with the $HER2^+$ and HER2- tumors, with a very low LRR rate in both groups (16). Some reports have correlated ER negativity with increased LRR making it a predictive factor for LRR (17, 18).

More recently, some authors correlated LRR risk with both HER2 and HR status, by their four possible combinations. Nguyen and colleagues analyzed data from 793 consecutive patients treated with BCT and correlated breast cancer subtype, in relation to ER/PR/HER2 receptor status, with LRR and distant metastasis. They observed a 5-year LRR rate of 1.8% overall, with higher rates being obtained for the $HR^-$ $HER2^-$ (7.1%) and $HR^-$ $HER2^+$ (8.4%) subgroups (19).

Albert and co-workers reviewed data from 911 patients with stage T1a,bN0 breast cancer who had received definitive treatment, both BCT and radical mastectomy, and prospectively analyzed ER/PR/HER2 expression from the archival tissue blocks of 756 patients. After a median follow-up of 6.0 years, they recorded 5- and 8-year LRR rates of 1.6% and 5.9%, respectively, without a statistically significant difference between BCT and mastectomy groups ($p$=0.347). The 8-year LRR rates were greater in patients with $ER^-$, $PR^-$ or $HER2^+$ tumors. On multivariate analysis, $ER^-$ and $PR^-$ disease and $HER2^+$ disease independently predicted for LRR (13).

Table II. *Outcomes at follow-up in 307 patients.*

| | |
|---|---|
| Media Follow-up, months, (range) | 37 (8-78) |
| LRR, n (%) | 15 (4.9) |
| Death due to breast cancer, n (%) | 4 (1.3) |
| Distant metastases, n (%) | 13 (4.2) |
| LRR-free survival rate, % | |
| 36 Month | 95.2±1.5 |
| 60 Month | 91.2±2.4 |
| Overall survival rate, % | |
| 36 Month | 98.5±0.9 |
| 360 Months | 97.7±1.2 |

LRR, Locoregional recurrence.

Gonzales-Angulo and colleagues reviewed 965 cases of T1a,bN0M0 breast cancer. At a median follow-up of 74 months, they recorded a total of 72 recurrences. The 5-year recurrence-free survival rates were 77.1% and 93.7% in patients with $HER2^+$ and $HER2^-$ tumors, respectively ($p$=0.001). In multivariate analysis, patients with $HER2^+$ tumors had higher risk of recurrence (hazard ratio=2.68, 95% CI=1.44 to 5.0; $p$=0.002) than those with $HER2^-$ tumors (14).

Our data demonstrate that patients with ER/PR-negative and $HER2^+$, T1-T2 breast cancer have a greater risk of LRR. At a median follow-up of 37 months, a total of 15 LRR events occurred, corresponding to a rate of 4.9%.

After 36- and 60-month we recorded a rate of overall survival of 98.5% and 97.7%, respectively, and a rate of LRR-free survival of 95.2% and 91.2%, respectively. LRR by ER, PR, and HER2 status showed that the 60-month LRR rate was greater in patients with $PR^-$ disease, and $HER2^+$ disease; in patients with $ER^-$ disease, a greater tendency for LRR was observed although not statistically significant. When ER, PR and HER2 status were combined to assess the prognostic power of the four possible subtypes, the Kaplan-Meier analysis based on the tumor subtypes shows there to be a statistically significant difference ($p$=0.014) in LRR among these groups, with the greater tendency for relapse to be experienced by patients with $HR^-$ $HER2^+$ tumors.

In the univariate analysis, factors that typically adversely affect the LRR were also evaluated: tumor grade and nodal involvement where the only two factors related to recurrence. Age and surgical margins, proven to be prognostic factors for LRR in several studies, were not significant in the present series. The small number of recurrences, the large number of cases with "undefined margins", in addition to the limitations of a retrospective analysis, may have had an impact on determining this result. However, based on the results, patients with $HR^-$ $HER2^+$ breast cancer and stage T1-T2 disease seem to have a higher risk of LRR.

The mechanism explaining how HER2 positivity predicts for LRR is unknown, although some studies have analyzed this (20, 21). Several studies showed the correlation

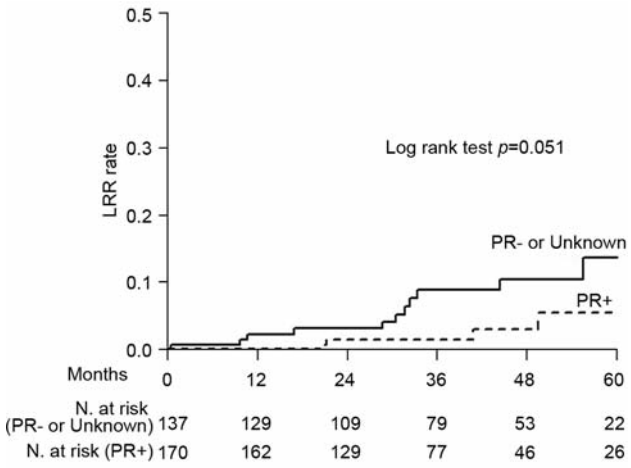


Figure 1. *Kaplan-Meier curves for locoregional recurrence (LRR) stratified by progesterone receptor (PR).*

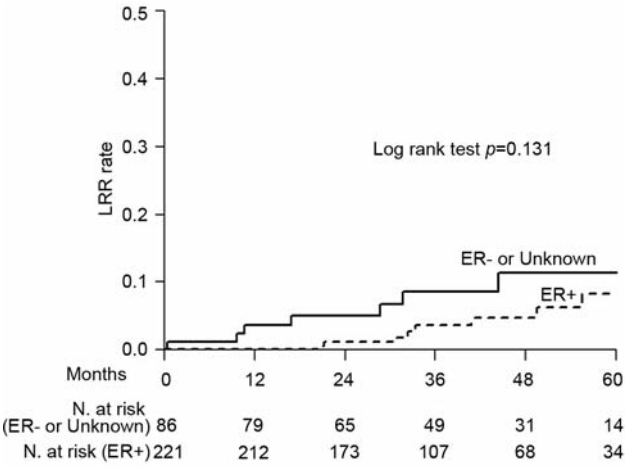


Figure 2. *Kaplan-Meier curves for locoregional recurrence (LRR) stratified by estrogen receptor (ER).*

Table III. *60-Month locoregional recurrence rate (LRR%) estimates.*

| Characteristic | LRR (95% CI) | *p*-Value | Characteristic | LRR (95% CI) | *p*-Value |
|---|---|---|---|---|---|
| All patients | 8.1 (5.0-13.1) | | HER2 status | | 0.001 |
| Age | | 0.580 | Positive | 15.2 (7.9-28.2) | |
| ≤50 years | 6.3 (2.4-15.9) | | Negative | 5.3 (2.5-10.8) | |
| >50 years | 9.0 (5.1-15.7) | | ER status | | 0.131 |
| Histological features | | 0.032 | Positive | 6.1 (3.1-11.8) | |
| Ductal | 7.4 (4.2-13.0) | | Negative | 13.1 (6.5-25.5) | |
| Lobular | - | | PR status | | 0.050 |
| Other | 21.6 (8.7-47.8) | | Positive | 4.0 (1.5-10.3) | |
| T Stage | | 0.484 | Negative | 12.9 (7.4-22.1) | |
| T1 | 8.7 (5.2-14.5) | | Margin status | | 0.805 |
| T2 | 5.6 (1.4-20.7) | | Free (≥10 mm) | 7.4 (3.8-14.3) | |
| N Stage | | <0.001 | Close (<2 mm) | 16.7 (2.5-62.7) | |
| N0 | 6.2 (3.5-10.9) | | Adjuvant therapy | | 0.490 |
| N+ | 22.7 (13.6-36.5) | | Chemotherapy | 6.5 (2.5-16.4) | |
| Grading | | <0.001 | Hormonal therapy | 7.1 (3.2-15.0) | |
| G1 | 0.0 | | Chemo+ hormonal | 12.9 (5.0-30.8) | |
| G2 | 11.4 (5.3-23.7) | | No | 18.2 (2.8-56.0) | |
| G3 | 22.8 (12.1-40.5) | | | | |
| Menopausal status | | 0.857 | | | |
| No | 7.5 (2.5-21.5) | | | | |
| Yes | 9.4 (4.8-17.8) | | | | |

CI, Confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

between LRR and HER2 HR status, but were mostly retrospective experiences and it is possible to identify several limitations (*i.e.* small tumors, inter-laboratory variability in biomarker assessment, small number of recurrences). Our study is also retrospective, and consequently has several limitations including those related to the retrospective evaluation.

However, our data confirm findings reported in the literature and suggest that patients with ER/PR-negative and $HER2^+$ disease have a greater risk of LRR. On this basis, for this subtype, as therapeutic options, it would seem reasonable to consider chemotherapy, anti-HER2 therapy, or more aggressive locoregional therapies (*e.g.* to irradiate the clavicular lymph nodes even fewer than four lymph nodes

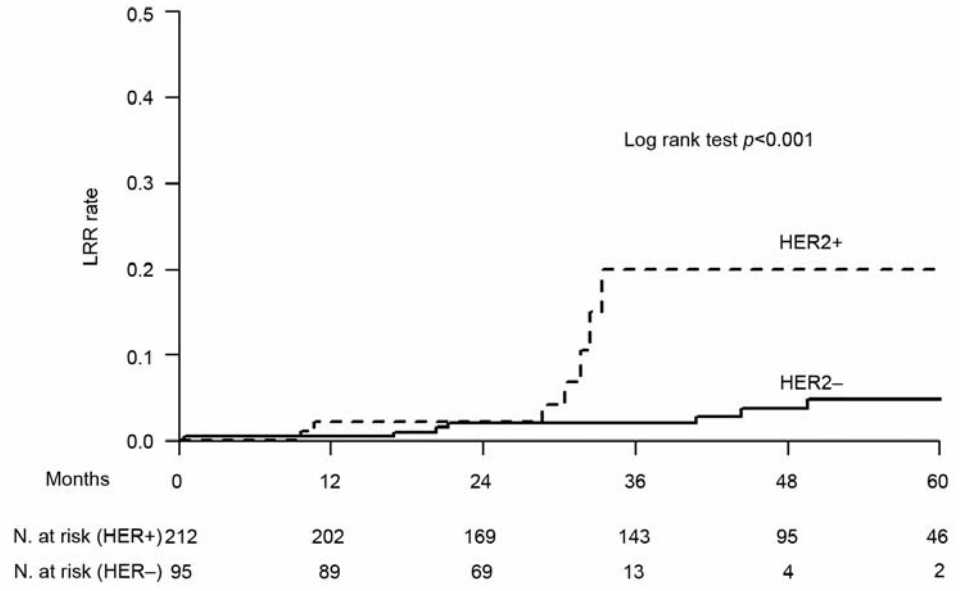


Figure 3. *Kaplan-Meier curves for locoregional recurrence (LRR) stratified by human epidermal growth factor receptor-2 (HER2).*

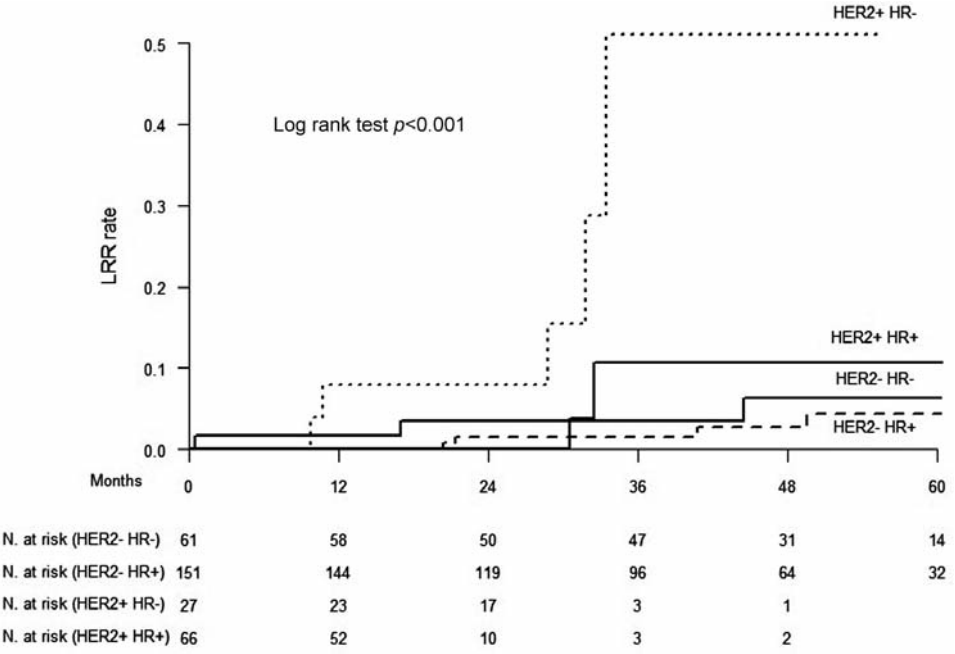


Figure 4. *Kaplan-Meier curves for locoregional recurrence (LRR) stratified by combination of HER2 and hormone receptor (HR) status. $HR^+$, positive for estrogen receptor or progesterone receptor; $HR^-$, negative for estrogen receptor or progesterone receptor.*

are involved, to administer a higher dose to the tumor bed *etc*.) even in those with very early-stage disease. Kiess and colleagues using an institutional database, identified 197 women who had lymph node-negative, $HER2^+$ breast cancer measuring <5 cm and who received BCT, including whole-breast irradiation. They showed that even among women with lower-risk breast cancer, it was possible to reduce the relatively high locoregional failure rates associated with positive HER2 status with adjuvant trastuzumab chemotherapy (22). Future prospective studies are necessary to define the utility of these biomarkers in guiding treatment options in this patient population.

## Conclusion

Patients with ER/PR-negative and HER2$^+$ T1-T2 breast cancer had a greater risk of LRR.

Future prospective studies are required to confirm these findings, to define the utility of these biomarkers in guiding therapeutic decision and to find the optimal and targeted therapeutic strategies, such as the use of chemotherapy, anti-HER2 therapies and more aggressive locoregional treatment for these patients.

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