Correlation between response to neoadjuvant chemotherapy and survival in locally advanced breast cancer patients

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Background: Measurement of residual disease following neoadjuvant chemotherapy that accurately predicts long-term survival in locally advanced breast cancer (LABC) is an essential requirement for clinical trials development. Several methods to assess tumor response have been described. However, the agreement between methods and correlation with survival in independent cohorts has not been reported.

Patients and methods: We report survival and tumor response according to the measurement of residual breast cancer burden (RCB), the Miller and Payne classification and the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, in 151 LABC patients. Kappa Cohen’s coefficient (Κ) was used to test the agreement between methods. We assessed the correlation between the treatment outcome and overall survival (OS) and relapse-free survival (RFS) by calculating Harrell’s C-statistic (c).

Results: The agreement between Miller and Payne classification and RCB classes was very high (Κ = 0.82). In contrast, we found a moderate-to-fair agreement between the Miller and Payne classification and RECIST criteria (Κ = 0.52) and RCB classes and RECIST criteria (Κ = 0.38). The adjusted C-statistic to predict OS for RCB index (0.77) and RCB classes (0.75) was superior to that of RECIST criteria (0.69) (P = 0.007 and P = 0.035, respectively). Also, RCB index (c = 0.71), RCB classes (c = 0.71) and Miller and Payne classification (c = 0.67) predicted better RFS than RECIST criteria (c = 0.61) (P = 0.005, P = 0.006 and P = 0.028, respectively).

Conclusions: The pathological assessment of tumor response might provide stronger prognostic information in LABC patients.

Key words: breast cancer, neoadjuvant chemotherapy response

introduction

Neoadjuvant chemotherapy is commonly used in locally advanced breast cancer (LABC) patients to facilitate breast-conserving surgery [1–6]. In addition, neoadjuvant treatment can serve as an in vivo model to study the effects of chemotherapy on breast tumors, therefore being an interesting research tool that allows the investigators to test new drugs and/or new schedules. Scientific and clinical information obtained from clinical trials depends on the assessment of tumor response, as a surrogate end-point. Hence, the measurement of tumor response, after neoadjuvant treatment, which accurately predicts long-term patient survival, is an essential requirement for clinical trials development. To address this issue, several methods have been developed. The Response Evaluation Criteria in Solid Tumors (RECIST) measures tumor response using X-ray, computerized tomography and MRI (magnetic resonance imaging) and stratifies tumor response in four categories, namely CR (complete response), PR (partial response), SD (stable disease) and PD (progressive disease) [7, 8]. Conversely, there are other methodologies to assess tumor response based on different approaches. In this way, Miller and Payne classification estimates tumor response to primary chemotherapy according to the decrease of cancer cellularity after treatment, in patients with large and LABC [9]. On the other hand, more recently, Symmans et al. developed a methodology to measure the residual breast cancer burden (RCB) as a continuous variable (RCB index) based on the primary tumor dimensions, tumor cellularity and axillary nodal status after neoadjuvant...
treatment. According to RCB-index categories of RCB-0 (CR) to RCB-III (chemotherapy resistance) can be defined [10]. To our knowledge, the agreement between these methods and correlation with survival in independent prospective cohorts has not been reported.

In this paper, we report the neoadjuvant chemotherapy tumor response and survival in 151 consecutive LABC patients, included in a neoadjuvant clinical trial and we study the agreement among the mentioned methodologies to assess tumor response as well as the correlation with long-term survival.

**materials and methods**

**study population**

In this study, we report the treatment outcome and survival of 151 LABC patients; these patients were enrolled in a neoadjuvant clinical trial (registered at the following website: [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov); identifier NCT00123929) as described previously [11–13]. The study was approved by the institutional review board of the Hospital Clínico San Carlos, Madrid, Spain. All patients were requested to sign a specific informed consent. Briefly, the eligibility criteria included the following: women aged between 18 and 77 years; clinical stage IIB, IIIA or IIIB breast cancer and palpable breast tumors not amenable to breast-preserving surgery. Patients were randomly assigned to either neoadjuvant docetaxel (Taxotere) 100 mg/m² every 21 days or neoadjuvant doxorubicin (Adriamycin) 75 mg/m², every 21 days, for four cycles.

**IHC, FISH and tumor grading**

Paraffin-embedded tumor samples from core biopsy specimens were evaluated by immunohistochemical staining analysis for estrogen receptor (ER) (clone 1D5, 1:35; Dako Cytomation, Glostrup, Denmark), progesterone receptor (PgR) (clone PgR 636, 1:50; Dako Cytomation), ki-67 (clone MIB-1, 1:75; Dako Cytomation) and E-cadherin (clone NCH-38). After incubation with the primary antibodies, immunohistochemical studies were carried out using the Autostainer link 48 (DakoCytomation, Carpinteria, CA). The ki-67 positivity was defined as ≥20% of stained cells, because the staining in our normal control breast tissue (from the tissue bank of Hospital Clínico San Carlos) was always below this value. The cut points for ER and PgR positivity were established at ≥1% of stained cells. The paraffin-embedded sections were stained with hematoxylin–eosin (H&E) for light microscopic examination. Tumor histology was assessed by analyzing the morphological features and the membrane expression of E-cadherin. Tumors showing the complete loss of the membranous E-cadherin were considered to be of the lobular phenotype.

The amplification of **ERBB2** was measured by FISH. The probes used were as follows: Centromere enumeration probe 17, labeled in green; and locus-specific identifier **ERBB2** probe, labeled in orange (Vysis-Abbott, Downers Grove, IL). Slides were prepared according to the manufacturer’s instructions for paraffin sections. A positive result was defined as an **ERBB2** gene/chromosome 17 ratio of ≥2.2. Images were visualized on a fluorescence microscope and captured on a workstation (MetaSystems, Altussheim, Germany). A minimum of 100 nuclei were counted per case. All cut points were predefined before the correlations were carried out; in all of the cases. All tumors were graded by the study pathologists according to Elston–Ellis histological grading.

**response evaluation**

Initial clinical evaluation included clinical measurement of the primary breast lesion and regional lymph nodes. Mammogram, ultrasound-based and MRI tumor measurements were obtained, as clinically indicated. After initiating the treatment, patients were assessed every 21 days for clinical response. Following the fourth neoadjuvant cycle mammogram, ultrasound and MRI evaluation as well as a surgical assessment were carried out.

The pathological response was evaluated in the surgery specimen (either lumpectomy or mastectomy; both with additional axillary clearance) by the study pathologist ([JALGA]). Pretreatment biopsies were also studied for the assessment of tumor response according to Miller and Payne classification [9]. Regarding Symmans’s et al. classification, we have evaluated both RCB index and RCB classes as described [10]. For RCB-index calculation, the RCB calculator was used (available on [http://www3.mnderson.org/app/medcalc/index.cfm?foreach=jsconvert3]). In all of the cases, the pathologist was blinded to the patient’s identity and outcome.

The clinical response was evaluated according to RECIST criteria comparing pre- and post-chemotherapy MRI assessments. CR was defined as resolution of all palpable, visible or radiology abnormalities in the breast and regional lymph nodes. PR was defined as a decrease of ≥30% in the sum of the longest diameter in the breast and regional lymph nodes. SD was assigned to patients who did not meet the criteria for CR, PR or PD. Clinical PD was defined as an increase of at least 20% in the sum of the longest diameter in the breast and regional lymph nodes or progression of other clinical manifestations of disease.

**statistical analysis**

Discrete variables are displayed as proportions, and continuous variables as means ± standard deviations (SD), unless specified otherwise. The median follow-up is summarized by its median and interquartile range (IR).

In order to assess the agreement between the three methodologies, Grade 2 and 3 of Miller and Payne classification were grouped in one category. The weighted quadratic kappa coefficient values and the corresponding 95% confidence intervals (95% CI) were used to assess the agreement between methodologies. The strength of agreement is considered to be slight when the K values are between 0.00 and 0.20; fair, 0.21 and 0.40; moderate, 0.41 and 0.60; good, 0.61 and 0.80 and almost perfect, 0.81 and 1.00.

Overall survival (OS) was defined as the time between the date of clinical assessments (i.e., date of medical appointment or admission) and the date of death. Relapse-free survival (RFS) was defined as the time between the date of clinical assessments and the date when local recurrence or distant relapses were diagnosed.

We measured the discrimination of the model for each of the treatment response variables by calculating Harrell’s C-statistic after fitting the Cox proportional hazard model. The C-statistic (c), a generalization of the area under the receiver operating characteristic curve, is the probability of concordance between observed and predicted survival based on the pairs of individuals, with c = 0.5 for random predictions and c = 1 for a perfectly discriminating model. We calculate the confidence intervals (CI) and the P-value for the differences between the predictive powers of the different models.

Multivariate Cox proportional hazards analyses were used to determine the significance of each methodology in the prediction of prognosis. HRs for OS and RFS from the Cox proportional hazards model were adjusted for ER, HER2, histological grade and treatment branch. Survival curves were estimated by the Kaplan–Meier method. P < 0.05 was considered to be statistical significance.

The statistical analysis was carried out using software Stata 11.0.
patients’ characteristics and tumor response
We report data from 151 LABC patients, who received primary neoadjuvant chemotherapy. The pathological characteristics of study population are summarized in Table 1. Among the 151 patients, 76 (50.3%) were treated with single-agent doxorubicin and 75 (49.7%) were treated with single-agent docetaxel. No significant differences were found in OS and RFS when patients were stratified according to therapy. All women underwent surgery after treatment. After surgery, patient treatment assignment was crossed-over to receive four cycles of the opposite drug, plus radiation therapy. Patients with HER2-positive tumors also received adjuvant trastuzumab for 1 year. In addition, patients whose tumors were positive for hormone receptors received tamoxifen, or aromatase inhibitors, or a sequence of both for at least 5 years.

The study population involved Caucasians aged 26 to 77 years, with 52.1 being the mean age at diagnosis (SD 12.8). Disease recurrence was noted for 66 (43.7%) women and 37 deaths (24.5%) were recorded. The median follow-up was 53.9 months (IR 36.9–72.3).

Table 2 shows the neoadjuvant tumor response rates, number of deceased patients and recurrences according to each methodology.

agreement between methodologies
The proportion of observed agreement between RCB classes and Miller and Payne classification was 70.2% with $K = 0.82$ (95% IC 0.78–0.84), indicating a very high agreement between both the methodologies. However, the proportion of observed agreement between RCB classes and RECIST criteria was 19.2% with $K = 0.38$ (95% IC: 0.29–0.46), showing a fair agreement. Also, we found a moderate agreement between Miller and Payne classification and RECIST criteria ($K = 0.52$; 95%IC: 0.47–0.57) with 29.1% of observed agreement.

correlation between chemotherapy tumor response with survival
To evaluate the ability of each methodology to discriminate between deceased and non-deceased patients and relapsed and non-relapsed patients, we calculated the Harrell’s C-statistic. Table 3 shows the C-statistic to predict OS and RFS for each methodology. As shown, all methods demonstrated statistically significant capacity to discriminate patients with different prognosis according to tumor response ($c > 0.5$). The RCB index yielded a C-statistic to predict OS of 0.74 and was significantly superior to 0.68 given by RECIST criteria ($P = 0.013$). Similarly, the C-statistic of RCB index (0.70) to predict RFS was significantly higher than the C-statistic of RECIST criteria (0.61) ($P = 0.001$). Because trastuzumab and endocrine therapy could bias the correlation between neoadjuvant chemotherapy tumor response and survival, we also calculated the C-statistic adjusted by ER and HER2 receptor (Table 3). The adjusted C-statistic to predict OS of the RCB index (0.77) and RCB classes (0.73) was significantly higher than the C-statistic for the RECIST criteria (0.69) ($P = 0.008$ and $P = 0.035$, respectively). In addition, the adjusted C-statistic to predict RFS for RCB index (0.71), RCB classes (0.71) and Miller and Payne classification (0.67) were superior than the corresponding RECIST criteria (0.61) ($P = 0.005$, $P = 0.006$ and $P = 0.028$, respectively). These results indicate that, in this cohort of patients, the measurement of the RCB after neoadjuvant chemotherapy predicted better the OS than the RECIST criteria. Also, the predictive accuracy of the RCB method and the Miller and Payne classification was superior to the predictive accuracy of RECIST criteria when RFS was evaluated, suggesting the superiority of the pathological evaluation of the tumor response in the prediction of survival.

Additionally, Cox models were tested using RCB index, RCB classes, RECIST criteria and Miller and Payne classification alone and together with clinical variables. Table 4 shows the multivariate analyses of these models. As shown, all methods predicted survival independently of the clinical variables that were tested (treatment branch, ER, HER2, histological grade).

The Kaplan–Meier curves for OS and RFS according to RCB classes, RECIST criteria and Miller and Payne classification are displayed in Figure 1. The 5-year OS and RFS probabilities, by category, are displayed in Table 5. As illustrated, RCB-0 identified the group of patients with better OS as we did not register any cancer-related death events within this category. By contrast, all patients showing a PD assessed by RECIST criteria relapsed and deceased after 5 years from diagnosis.

discussion
A number of large randomized studies have shown that pCR to primary chemotherapy is associated with long-term survival.
It has, therefore, been assumed that pCR is a suitable surrogate marker for treatment efficacy and has been considered as the primary end-point for neoadjuvant trials [3–5, 16, 17]. However, there are some controversies concerning pCR definition. While it is commonly accepted that pCR should include patients without residual invasive carcinoma, there is not a uniform consensus about how to consider the presence of nodal metastasis, minimal residual cellularity or residual in situ carcinoma. To overcome these limitations, Symmans et al. [10] defined the continuous variable RCB index which considers tumor dimension, cellularity and the nodal status. On the other hand, the Miller and Payne classification determines tumor response attending exclusively to the decrease in cancer cellularity [9]. To our knowledge, we report, for the first time, the agreement between both the methods, as well as the concordance of them with RECIST criteria. In addition, we have evaluated the predictive accuracy of the three methodologies in an independent prospective cohort.

Remarkably, we have found that, despite the Miller and Payne classification and Symmans’s et al. methodology stratify treatment response based on different variables, the agreement between them was very high ($K = 0.82$). In addition, the predictive capacity of RCB was not superior to the Miller and Payne grading system as the differences in the $c$-statistic were not statistically significant. However, the agreement dramatically falls off when these methodologies are compared with RECIST criteria. This result is not surprising as the RECIST criteria are based on the radiological assessment of tumor dimensions, whereas the Miller and Payne grading system and Symman’s classification evaluate tumor response according to pathological analysis.

In our population, all methods predicted statistically significantly OS and RFS. The $C$-statistic of RCB index and RCB classes was very similar to the $C$-statistic reported in the original article [10], therefore suggesting similar discriminatory capacity in a different cohort of patients. Also, as illustrated in Figure 1, the survival curves were similar to those previously published [9,10].

All methods showed a good-to-moderate capacity of classifying patients according to OS and RFS ($c > 0.5$). According to our results, RCB index and RCB classes gave

### Table 2. Tumor responses, number of deceased patients and relapses by category for each methodology

<table>
<thead>
<tr>
<th>RCB classes</th>
<th>No. of patients</th>
<th>Deaths</th>
<th>Relapses</th>
<th>RECIST</th>
<th>No. of patients</th>
<th>Deaths</th>
<th>Relapses</th>
<th>M&amp;P</th>
<th>No. of patients</th>
<th>Deaths</th>
<th>Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCB-0</td>
<td>16</td>
<td>0</td>
<td>3</td>
<td>CR</td>
<td>26</td>
<td>5</td>
<td>11</td>
<td>Grade 5</td>
<td>20</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>RCB-I</td>
<td>15</td>
<td>3</td>
<td>5</td>
<td>PR</td>
<td>87</td>
<td>14</td>
<td>33</td>
<td>Grade 4</td>
<td>24</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>RCB-II</td>
<td>65</td>
<td>10</td>
<td>22</td>
<td>SD</td>
<td>30</td>
<td>10</td>
<td>14</td>
<td>Grade 3</td>
<td>55</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>RCB-III</td>
<td>55</td>
<td>24</td>
<td>36</td>
<td>PD</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>Grade 2</td>
<td>22</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

RCB, residual breast cancer burden.

### Table 3. $C$-statistic to predict OS and RFS and their CI by RCB index, RCB classes, RECIST criteria and M&P and the corresponding $C$-statistic and CI adjusted by ER and HER2 status

<table>
<thead>
<tr>
<th></th>
<th>C-statistic (OS)</th>
<th>CI</th>
<th>Adjusted C-statistic (OS)</th>
<th>CI</th>
<th>C-statistic (RFS)</th>
<th>CI</th>
<th>Adjusted C-statistic (RFS)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCB index</td>
<td>0.74</td>
<td>0.65–0.83</td>
<td>0.77</td>
<td>0.68–0.86</td>
<td>0.70</td>
<td>0.63–0.77</td>
<td>0.71</td>
<td>0.64–0.78</td>
</tr>
<tr>
<td>RCB classes</td>
<td>0.70</td>
<td>0.63–0.77</td>
<td>0.75</td>
<td>0.66–0.84</td>
<td>0.69</td>
<td>0.63–0.75</td>
<td>0.71</td>
<td>0.64–0.78</td>
</tr>
<tr>
<td>RECIST</td>
<td>0.67</td>
<td>0.58–0.77</td>
<td>0.69</td>
<td>0.59–0.79</td>
<td>0.60</td>
<td>0.53–0.67</td>
<td>0.61</td>
<td>0.54–0.69</td>
</tr>
<tr>
<td>M&amp;P</td>
<td>0.72</td>
<td>0.62–0.81</td>
<td>0.74</td>
<td>0.65–0.85</td>
<td>0.67</td>
<td>0.60–0.73</td>
<td>0.67</td>
<td>0.60–0.75</td>
</tr>
</tbody>
</table>

CI, confidence intervals; OS, overall survival; M&P, Miller and Payne classification; RCB, residual breast cancer burden.

### Table 4. Multivariate Cox proportional hazards analyses of the four variables. Hazard ratios were adjusted by ER, HER2, treatment branch and histological grade

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>Relapse-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>(95% confidence interval)</td>
</tr>
<tr>
<td>RCB index</td>
<td>2.109</td>
<td>0.000</td>
</tr>
<tr>
<td>RCB classes (III versus 0-II)</td>
<td>4.240</td>
<td>0.000</td>
</tr>
<tr>
<td>RECIST (PD versus CR-SD)</td>
<td>7.254</td>
<td>0.000</td>
</tr>
<tr>
<td>M&amp;P (grade 1 versus others)</td>
<td>5.211</td>
<td>0.000</td>
</tr>
</tbody>
</table>

M&P, Miller and Payne classification; RCB, residual breast cancer burden.
significantly higher C-statistic to predict OS and RFS than those given by RECIST criteria. In addition, the adjusted C-statistic to predict RFS for Miller and Payne classification was significantly higher than that of the RECIST criteria. These results might suggest that the predicting ability of the methodologies based on pathological analysis, as the evaluation of the cellularity of residual tumors cells, might be superior to traditional radiological assessment of tumor response. It has

Table 5. Five-year OS probability and 5-year RFS probability by categories of response for each methodology

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Category</th>
<th>Five-year OS</th>
<th>Standard error</th>
<th>Five-year RFS</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCB classes</td>
<td>RCB-0</td>
<td>1.00</td>
<td>0.781</td>
<td>0.113</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCB-I</td>
<td>0.867</td>
<td>0.088</td>
<td>0.66</td>
<td>0.124</td>
</tr>
<tr>
<td></td>
<td>RCB-II</td>
<td>0.867</td>
<td>0.044</td>
<td>0.775</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>RCB-III</td>
<td>0.547</td>
<td>0.075</td>
<td>0.322</td>
<td>0.069</td>
</tr>
<tr>
<td>RECIST</td>
<td>CR</td>
<td>0.883</td>
<td>0.064</td>
<td>0.687</td>
<td>0.092</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>0.841</td>
<td>0.043</td>
<td>0.651</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.681</td>
<td>0.09</td>
<td>0.544</td>
<td>0.094</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>0.900</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>M&amp;P</td>
<td>Grade 5</td>
<td>0.95</td>
<td>0.049</td>
<td>0.662</td>
<td>0.114</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>0.847</td>
<td>0.083</td>
<td>0.812</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0.888</td>
<td>0.043</td>
<td>0.682</td>
<td>0.064</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>0.736</td>
<td>0.105</td>
<td>0.495</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>0.38</td>
<td>0.098</td>
<td>0.315</td>
<td>0.086</td>
</tr>
</tbody>
</table>

CI, confidence intervals; OS, overall survival; M&P, Miller and Payne classification; RCB, residual breast cancer burden.
been previously reported that the accuracy of breast ultrasound, mammography, MRI and clinical examination in predicting pCR is rather poor [18–21] and might be limited by chemotherapy-induced fibrosis and reactive inflammation, which are both difficult to differentiate from residual disease [21, 22]. Also, although it is believed that MRI is an accurate method for predicting the extent of residual tumor after neoadjuvant chemotherapy, it may overestimate or underestimate the residual disease in a non-negligible proportion of patients [21, 23].

According to our results, RCB-0 class identified best the group of patients with better OS. As shown in Table 2, any of the patients included in this category deceased. In contrast to the Miller and Payne classification, which is based on the decrease of the cellularity of the residual primary tumor, the RCB method considers the tumor volume, the number and size of axillary lymph node metastases in addition to the cellularity of the residual tumor. Therefore, the evaluation of nodal status might add prognostic information, especially in patients without residual carcinoma after neoadjuvant treatment. In this way, other researchers have reported that in the absence of residual invasive carcinoma, the number of positive axillary lymph nodes is inversely related to survival [24, 25]. However, although we report a better outcome in terms of RFS and OS after neoadjuvant chemotherapy for patients showing a RCB-0 response, the disease recurrence was noted for three women, indicating that a proportion of patients might remain at risk of relapse despite the achievement of pCR as defined by Symmans et al. [10]. Other researchers have reported similar results in patients reaching a pCR [26–28]. Conversely, patients with progressive disease assessed by RECIST criteria had the poorest outcome (Figure 1, Table 5).

It should be considered that the RCB index provides a continuous variable of treatment response. This might constitute an advantage, particularly in small clinical trials or studies with low pCR rates, as dichotomization of response can be avoided and therefore increasing the information that can be obtained from the clinical study. However, despite this benefit, the RCB index is seldom used in clinical studies. On the other hand, the predictive ability of RCB classes might be limited to the cut-off that defines the subgroups and larger studies in independent cohorts should be carried out in order to validate them.

In summary, the clinical information obtained from the clinical trial directly depends on how the treatment response is measured. At the moment, there is no standard method to assess the pathological response to primary chemotherapy in patients with LABC. Hence, the standardization and improvement of methods to assess the response to induction chemotherapy are sorely needed. The pathological assessment of tumor response might provide stronger prognostic information. However, further studies in a large cohort of patients with long-term follow-up are required to verify this observation, especially in highly proliferative high endocrine-sensitive tumors which remain at substantial risk of late recurrences.

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**disclosure**

The authors have declared no conflicts of interest.

**references**

Progestosterone receptor loss identifies Luminal B breast cancer subgroups at higher risk of relapse

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Background: The immunohistochemical (IHC) evaluation of estrogen receptor (ER), progesterone receptor (PgR), Ki-67 and HER2 is considered a surrogate means for identifying the molecular subtypes of breast cancer with different prognosis.

Patients and methods: We explored patterns of recurrence in 4837 women with breast cancer defined as Luminal B (ER-positive and/or PgR-positive, HER2 positive and/or Ki-67≥14%) by IHC classification. We evaluated four subgroups within the Luminal B subtype according to HER2 expression and PgR status.

Results: Patients within the ER+/PgR+/HER2– subgroup presented a 5-year breast cancer-related survival (BCS) of 97% (95% confidence interval [CI], 96–97) and overall survival (OS) of 95% [95% CI, 95–96], the best survivals of the Luminal B subgroups. In the multivariate analysis, the ER+/PgR−/HER2– subgroup was associated with a reduced BCS (HR 1.71; 95%CI, 1.25–2.35) and OS (HR 1.47; 95%CI, 1.10–1.96) compared with the ER+/PgR+/HER2– subgroup. Also patients within the ER+/PgR−/HER2– subgroup had a reduced BCS (HR 1.93; 95%CI, 1.32–2.83) and OS (HR 1.62; 95% CI, 1.14–2.30) when compared with ER+/PgR+/HER2– subgroup. On the other hand, no statistically significant differences were found with regard to BCS and OS among patients with ER+/PgR+/HER2+ and patients with ER+/PgR+/HER2– disease.