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ORIGINAL ARTICLE

# Hormone receptor-negative as a predictive factor for pathologic complete response to neoadjuvant therapy in breast cancer

## Receptor hormonal negativo como fator preditivo para resposta patológica completa ao tratamento neoadjuvante de câncer de mama

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## ABSTRACT

**Objective:** To define a predictive factor for pathologic complete response, compare the oncologic outcomes associated with the degree of pathologic response after neoadjuvant chemotherapy, and to analyze pathologic complete response as a prognostic factor for overall survival and progression-free survival. **Methods:** A retrospective study of patients admitted to *Hospital Estadual Mário Covas* and *Hospital Anchieta* from 2008 to 2012, with locally advanced breast cancer. Hormone receptor status, HER2 status, histologic and nuclear grade, age upon diagnosis and histological type of the tumor were analyzed. Pathologic evaluation of the tumor was subdivided into pathologic complete response, defined by the absence of tumor; intermediate response, considered as a favorable stage; and poor response, considering low-responder patients. Data obtained were submitted to statistical analysis. **Results:** The study included 243 patients. There was an association of pathologic complete response with HER-2 negative, histological grade 3, stage III, hormone receptor negative, positive lymph node, older age and more advanced tumors. However, after multivariate analysis the only predictor of pathologic complete response was the presence of negative hormone receptor. By analyzing the prognostic factors, hormone receptor negative was considered as an independent risk factor, and pathologic complete response was considered as an independent protective factor. **Conclusion:** Hormone receptor negative is predictive of pathologic complete response and is an isolated risk factor for lower progression-free survival and overall survival. Pathologic complete response is a protective factor for these same survival analyses.

**Keywords:** Breast neoplasms/pathology; Neoadjuvant therapy; Predictive value of tests; Prognosis; Survivorship (Public Health)

## RESUMO

**Objetivo:** Definir um fator preditivo para resposta patológica completa, comparar os resultados oncológicos associados com o grau de resposta patológica, após quimioterapia neoadjuvante, e analisar a resposta patológica completa como fator prognóstico para sobrevivência global e livre de progressão de doença. **Métodos:** Estudo retrospectivo de pacientes admitidas no Hospital Estadual Mário Covas e Hospital Anchieta, no período de 2008 a 2012, com câncer de mama localmente avançado. Foram utilizados *status* dos receptores hormonais, proteína HER2, grau histológico e nuclear, idade do paciente ao diagnóstico e tipo histológico do tumor. A avaliação patológica do tumor foi subdividida em resposta patológica completa, definida com ausência de tumor;

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resposta intermediária, considerada como um estádio favorável; e resposta ruim, considerando os pacientes pouco respondedores. As informações obtidas foram submetidas à análise estatística. **Resultados:** Foram incluídas 243 pacientes. Verificou-se associação de resposta patológica completa entre HER-2 negativo, grau histológico 3, estadiamento III, receptor hormonal negativo, linfonodo positivo, maior idade e tumores mais avançados. Porém, após análise multivariada, o único fator preditivo de resposta patológica completa foi presença de receptor hormonal negativo. Ao analisar fatores prognósticos, receptor hormonal negativo permaneceu como variável independente de risco, e resposta patológica completa, como variável independente de proteção. **Conclusão:** O receptor hormonal negativo é fator preditivo isolado de resposta patológica completa e fator de risco para menor sobrevida livre de doença e sobrevida global. Já a resposta patológica completa é fator protetor para estas mesmas análises de sobrevivência.

**Descritores:** Neoplasias da mama/patologia; Terapia neoadjuvante; Valor preditivo dos testes; Prognóstico; Sobrevivência (Saúde Pública)

## INTRODUCTION

Breast cancer has been the leading cause of death in Brazilian women since 1979. Mortality rates remain high, probably because the disease is still diagnosed in advanced stages.[1] Locally advanced breast cancer is classified according to the staging system proposed by the American Joint Committee on Cancer (AJCC) as IIB, IIIA, IIIB and IIIC, 25 to 30% of which are inoperable.[2] One of the therapeutic modalities is neoadjuvant chemotherapy, which increases the likelihood of conservative surgery, also allowing initial treatment of micro metastatic disease. Furthermore, this approach allows assessing resistance to the chemotherapy regimen initially administered, offering an excellent opportunity to determine the best treatment regimen for the patient.[2,3] The MD Anderson Cancer Center has assessed more than 800 patients with disease in stages IIIA and IIIB over 25 years, and has attained objective response results in 60 to 80% of cases, complete clinical response in 15 to 20%, and pathologic complete response (pCR) in 5 to 10%, increasing the likelihood of conservative surgery.[4]

Pathologic complete response is defined as the absence of residual invasive tumor in surgical tissue specimens from breast and axillary lymph nodes.[2,4] Tumor size, hormone receptor status, human epidermal growth factor receptor 2 (HER-2), molecular subtype and histological type are factors known to be associated with the pathologic response of the tumor.[5]

Currently the most common molecular breast cancer is the luminal subtype, characterized as luminal A and luminal B. Luminal A accounts for approximately 60% of breast carcinomas and has the best prognosis when compared to other breast carcinomas. Most of them are estrogen receptor positive and low histologic grade.[6] Luminal B is characterized by expressing genes associated with HER2, and by more cell proliferation genes, including the expression of MKi67 (Ki-67), CCNB1 and MYBL2 genes. Its higher cell proliferation rate is related to worse prognosis when compared to luminal A.[7] Overexpression of HER2 occurs in 10 to 15% of breast cancers, is frequently hormone-receptor-negative, and has the second worst prognosis when compared to patients who do not show this gene amplification, although molecularly targeted therapy improves the prognosis.

The triple negative clinical phenotype is negative for hormonal receptors and for HER2 overexpression. It mainly comprises the basal-like molecular subtype and shows substantial heterogeneity. In a study of DNA and RNA utilization, four stable subtypes were identified: luminal/androgen receptor, mesenchymal, basal-like immune suppressed, and basal-like immune activated.[8] These four subtypes have the worst prognosis, with lower progression-free survival and overall survival, which can be attributed to their biological characteristics.[9] The triple-negative breast cancer proliferation rate and BRCAness are two characteristics that illustrate these facts.[10]

Anthracycline and taxane regimen-based chemotherapy has increased the rate of complete pathologic response.[5,11] In contrast, the pCR rate is low in the luminal A molecular subtype, reaching only 6.7%.[11-14]

The role of persistent *in situ* lesion is controversial. A meta-analysis from a German group demonstrated that persistence of a residual *in situ* lesion is associated with shorter disease-free survival (DFS) when compared to pCR (absence of invasive component and *in situ* component).[15]

## OBJECTIVE

To define the predictive factors for pathologic complete response, as well as to analyze its role as a prognostic factor for overall survival and progression-free survival.

## METHODS

A retrospective study including patients aged over 18 years, with invasive breast carcinoma confirmed by pathology examination, locally advanced (stages II and III, according to AJCC), performance status between zero and 2, and without previous oncological therapy, treated with neoadjuvant chemotherapy followed by radical or conservative surgical resection.

We reviewed the medical records of the hospitals linked to the *Faculdade de Medicina do ABC* (FMABC), Santo André (SP), from 2008 to 2012. Patients with distant metastasis upon diagnosis and/or with a second primary tumor were excluded. The study was approved by the Research Ethics Committee of FMABC, opinion 394.576, CAAE: 20730713.2.0000.0082.

We used hormone receptor status, HER2 protein status, histological and nuclear grade, patient age at diagnosis, lymph node presence, and clinical and pathological tumor staging. Estrogen and progesterone receptors were considered positive if ≥10% of the stained positive or if Remmele score ≥3,[16] taking into consideration frequency and intensity of staining. Human epidermal growth factor receptor 2 protein status was assessed by immunohistochemistry, and considered positive if the score was equal to 3, or fluorescence *in situ* hybridization (FISH) positive. Histologic and nuclear grades were used to describe cell proliferation. The pathology assessment of the tumor after resection was subdivided into three groups: pathologic complete response defined by absence of tumor (ypT0ypN0), intermediate response considered as favorable stage (ypT1-2ypN0) and poor response considering low-responder patients (ypT3-4ypN1-3). Among histopathological factors with prognostic value, tumor size and lymph node involvement are variables that have a greater impact on the definition of individual risk,[17] and also on the 5 to 20-year distant recurrence rates, which for T1N0 patients is 14%, for T2N0 is 21%, and rates range from 23% to 47% for TxN+.

The treatments included neoadjuvant chemotherapy with doxorubicin, cyclophosphamide, paclitaxel (AC-T); dose-dense AC-T; or other chemotherapy regimens, associated or not to trastuzumab (in HER2 positive tumors), followed by surgery, which included radical mastectomy, lumpectomy or quadrantectomy.

### Statistical analysis

Continuous variables were described using means and standard deviation, or medians and minimum and maximum values. Categorical variables were described by absolute and relative frequencies. Student's *t* test was used to compare the means of two sample populations, and ANOVA with Bonferroni's auxiliary test was used for the comparison among the means of three or more populations. Comparisons of the frequency of a phenomenon between groups of categorical variables were performed using Fisher's exact test and $\chi^2$ test. Multivariate analysis to determine the predictive factors of pCR was performed by logistic regression, and all variables that presented $p<0.2$ in the univariate analysis were tested. The Kaplan-Meier method was used for progression-free survival and overall survival analyses. Patients were censored on the date of the event (death and/or progression) or most recent contact. Curves were compared using the log-rank test. For both multivariate analysis and univariate analysis, the Cox regression model was used to determine prognostic factors for calculating hazard ratio (HR), 95% confidence interval (95%CI), and $p\leq0.2$ value was considered for all variables. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 17.0 (SPSS® Inc., Illinois, USA). An alpha or type I error with a value ≤5% ($p<0.05$). was established for all comparisons.

## RESULTS

A total of 243 patients were identified with locally advanced invasive breast cancer and submitted to neoadjuvant chemotherapy. The median age of patients was 52 years, ranging from 27 to 87 years. Clinical and pathological characteristics are described on tables 1 and 2, respectively.

**Table 1.** Descriptive analysis of the clinical characteristics of all patients included

| Characteristics | n (%)† |
|---|---|
| Age, years | |
| <65 | 199 (81.9) |
| >65 | 44 (18.1) |
| Median | 52.0±13* |
| Surgery | |
| Quadrantectomy | 50 (20.6) |
| Lumpectomy | 9 (3.7) |
| Mastectomy | 184 (75.7) |
| Clinicla staging | |
| II | 74 (30.5) |
| III | 169 (69.5) |
| Tumor | |
| T2 | 44 (18.1) |
| T3 | 122 (50.2) |
| T4 | 76 (31.3) |
| Lymph node | |
| N0 | 69 (28.4) |
| N+ | 174 (71.6) |
| Neoadjuvant CT regimen | |
| AC-T | 174 (71.6) |
| AC-T dose-dense | 20 (8.2) |
| Others | 49 (20.2) |
| Herceptin | |
| Yes | 47 (19.3) |
| No | 196 (80.7) |
| Disease progression | |
| Yes | 171 (70.4) |
| No | 72 (29.6) |
| Local recurrence | |
| Yes | 32 (13.2) |
| No | 211 (86.8) |

* mean±standard deviation, in years; † total number of patients included, not necessarily corresponding to the sum of items of each variable, due to lack of information in the charts.
T2: tumor >2cm and ≤5cm; T3: tumor >5cm; T4: tumor of any size, with direct extension to the chest wall, skin or both, or inflammatory tumor; N0: absence of lymph node involvement; N+: presence of lymph node involvement; CT: chemotherapy; AC-T: doxorubicin, cyclophosphamide, paclitaxel.

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**Table 1.** Descriptive analysis of the clinical characteristics of all patients included

| Characteristics | n (%)† |
|---|---|
| Systemic recurrence | |
| No | 185 (76.1) |
| Bones | 22 (9.1) |
| Lung | 19 (7.8) |
| Central nervous system | 9 (3.7) |
| Liver | 4 (1.6) |
| Others | 4 (1.6) |
| Death | |
| No | 206 (84.8) |
| Yes | 37 (15.2) |

* mean±standard deviation, in years; † total number of patients included, not necessarily corresponding to the sum of items of each variable, due to lack of information in the charts.
T2: tumor >2cm and ≤5cm; T3: tumor >5cm; T4: tumor of any size, with direct extension to the chest wall, skin or both, or inflammatory tumor; N0: absence of lymph node involvement; N+: presence of lymph node involvement; CT: chemotherapy; AC-T: doxorubicin, cyclophosphamide, paclitaxel.

**Table 2.** Pathological characteristics of all patients

| Characteristics | Total n (%) |
|---|---|
| Histological type | |
| Invasive ductal | 217 (89.3) |
| Invasive lobular | 12 (4.9) |
| Others | 14 (5.8) |
| Histological grade | |
| I | 13 (5.4) |
| II | 155 (64.0) |
| III | 74 (30.6) |
| Nuclear grade | |
| I | 4 (1.6) |
| II | 118 (48.6) |
| III | 121 (49.8) |
| Hormone receptor | |
| Positive | 150 (61.7) |
| Negative | 93 (38.3) |
| HER2 protein | |
| Positive | 58 (23.9) |
| Negative | 185 (76.1) |
| Pathological response | |
| Pathological complete response | 75 (30.9) |
| Intermediate response | 50 (20.6) |
| Poor response | 118 (48.6) |
| Tumor (ypT) | |
| ypT0 | 80 (32.9) |
| ypT1 | 32 (13.2) |
| ypT2 | 66 (27.2) |
| ypT3 | 45 (18.5) |
| ypT4 | 20 (8.2) |
| Lymph node (ypN) | |
| ypN0 | 141 (58.0) |
| ypN+ | 102 (42.0) |

HER-2: human epidermal growth factor receptor 2.

The median follow-up of patients was 32 months, ranging from 4 to 69 months. Overall survival and progression-free survival did not reach the median (63.7% and 53.4%, respectively), and are shown in figure 1.

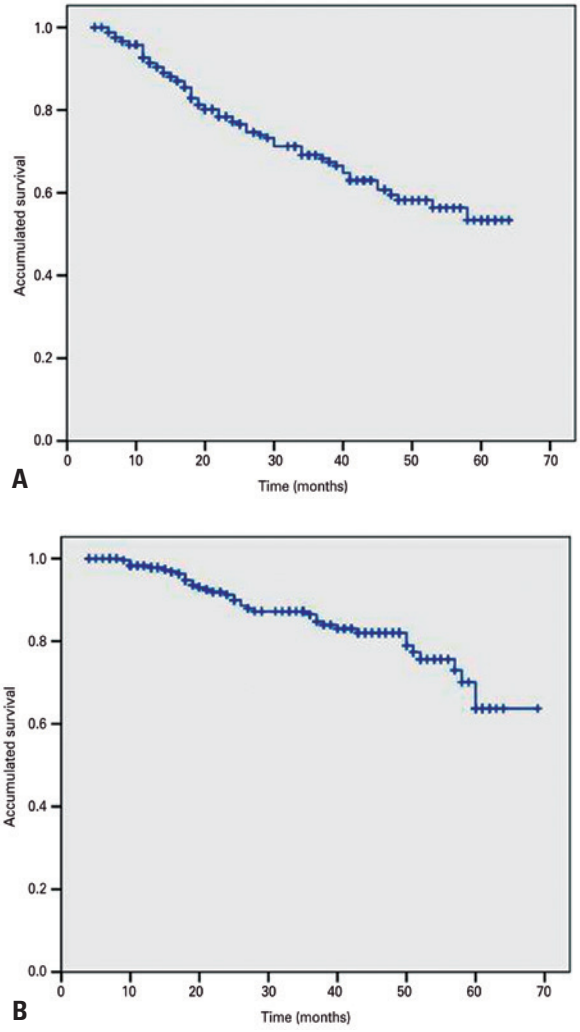



**Figure 1.** Kaplan-Meier survival curves. (A) Disease-free survival and (B) Overall survival

## Predictive factors of pathologic complete response

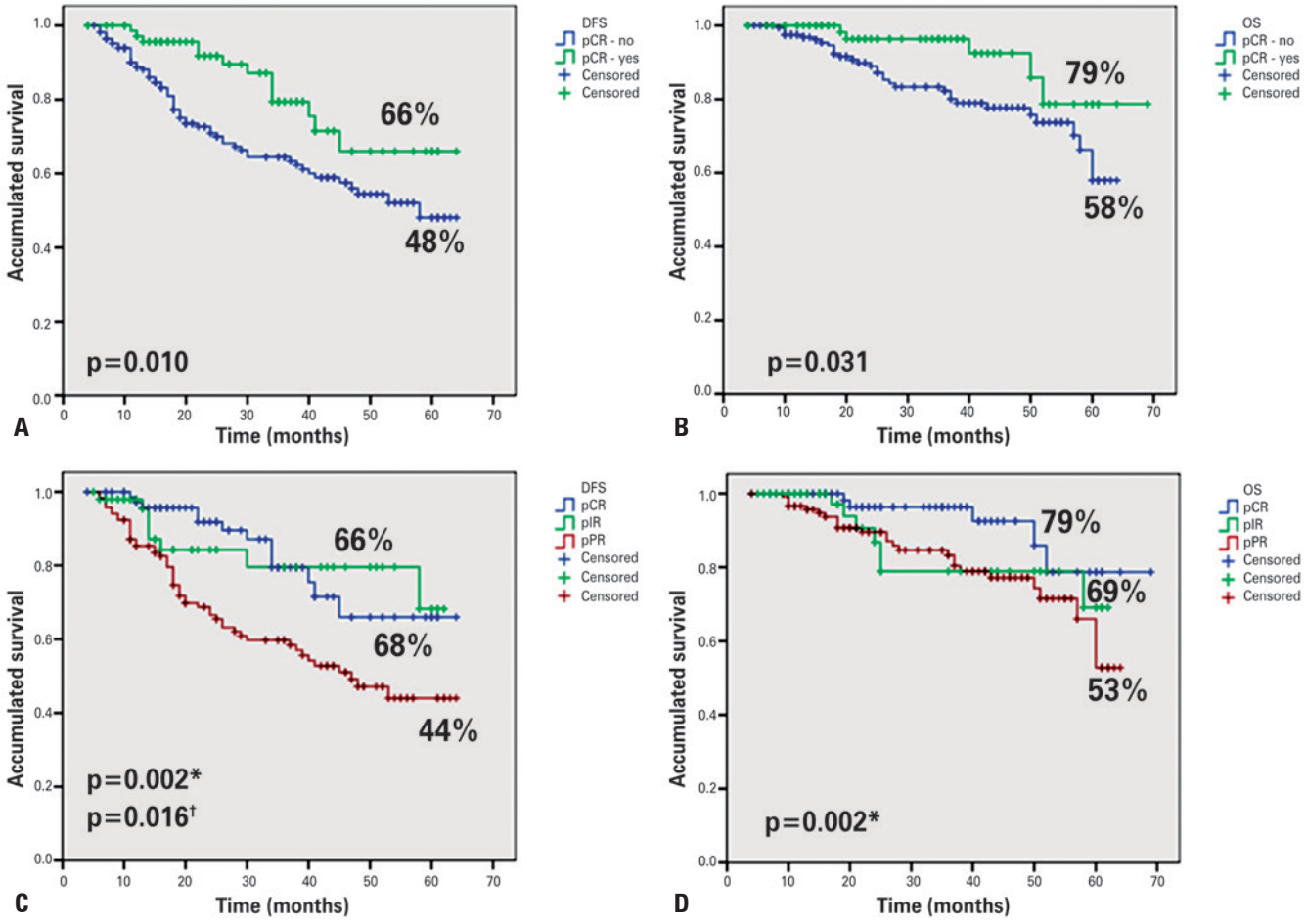
In order to assess the predictive factors of pCR, associations were made among all variables. The univariate analysis showed that pCR was associated with

HER2 negative, histologic grade 3, stage III, negative hormone receptor, positive lymph node, older age and more advanced tumors (T3/T4). However, after the multivariate analysis, the only predictive factor of pCR was the presence of negative hormone receptor (HR = 2.2; 95%CI: 1.25-3.89; p=0.006, logistic regression).

### Pathologic complete response as a prognostic factor

The accumulated DFS for pathologic complete response, intermediate response and poor response was 66%, 68% and 44%, respectively; and for overall survival, 78%, 69% and 52%, respectively. In order to better analyze the results, we divided the patients into two groups: pCR, yes or no. Thus, the following results were found: patients with pCR had overall survival of 78% *versus* 58%, and DFS of 66% *versus* 48%, as compared to those with intermediate or poor response (Figure 2).

In addition to pCR, in the univariate analysis we observed that the variables related to DFS were nuclear grade, hormone receptor and clinical tumor staging. In the multivariate analysis, we found that the only independent risk factors were negative hormone receptor for shorter DFS and pCR for longer DFS. For overall survival, the following variables were included in the multivariate analysis: nuclear grade, hormone receptor and pCR, and hormone receptor negative also remaining as an independent risk variable, and pathologic complete response as independent protection variable, as shown in tables 3 and 4.




* p value refers to comparison of pCR with pPR; † p value refers to comparison of pathological intermediate response with pPR.
DFS: disease-free survival; pCR: pathological complete response; pIR: pathological intermediate response; pPR: pathological poor response; OS: overall survival.

**Figure 2.** Comparison among the types of pathological response. (A) Disease-free survival. (pCR): yes or not. (B) Overall survival. pCR: yes or not. (C) Disease-free survival. pCR, pIR and pPR. (D) Overall survival. pCR, pPIR and pPR

**Table 3.** Univariate and multivariate analysis for disease-free survival

| Characteristics | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | p value | HR | 95%CI | p value |
| Age | 1.0 | 0.99-1.03 | 0.302 | | N/A | |
| Clinical staging | 1.66 | 0.94-2.93 | 0.081 | 1.6 | 0.89-2.79 | 0.12 |
| Tumor | 1.94 | 0.93-4.04 | 0.078 | 1.4 | 0.57-3.45 | 0.45 |
| Positive lymph node | 1.12 | 0.66-1.20 | 0.665 | | N/A | |
| Grade | | | | | | |
| Histological | 1.26 | 0.78-2.03 | 0.344 | 1.18 | N/A | 0.507 |
| Nuclear | 1.49 | 0.90-2.32 | 0.124 | | 0.721-1.95 | |
| HER2 status | 1.34 | 0.88-2.24 | 0.266 | | N/A | |
| Hormone receptor | 1.76 | 1.14-2.80 | 0.016 | 3.38 | 1.73-6.60 | <0.001 |
| pCR | 0.46 | 0.25-0.85 | 0.013 | 0.26 | 0.09-0.66 | 0.005 |

p value: probability of obtaining results, or something more extreme, if the null hypothesis is true.
HR: hazard ratio; 95%CI: 95% confidence interval; N/A: not applicable; pCR: pathological complete response.

**Table 4.** Univariate and multivariate analysis for overall survival

| Characteristics | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | p value | HR | 95%CI | p value |
| Age | 1.17 | 0.52-2.68 | 0.706 | | N/A | |
| Clinical staging | 1.24 | 0.58-2.63 | 0.580 | | N/A | |
| Tumor | 1.08 | 0.45-2.06 | 0.860 | | N/A | |
| Positive lymph node | 1.40 | 0.63-3.04 | 0.410 | | N/A | |
| Grade | | | | | | |
| Histological | 1.50 | 0.78-2.89 | 0.220 | | N/A | |
| Nuclear | 2.09 | 1.03-4.23 | 0.041 | 1.6 | 0.76-3.33 | 0.216 |
| HER2 status | 0.72 | 0.32-1.63 | 0.420 | | N/A | |
| Hormone receptor | 2.50 | 1.30-4.84 | 0.006 | 2.20 | 1.37-3.55 | 0.001 |
| pCR | 0.37 | 0.14-0.95 | 0.038 | 0.37 | 0.19-0.68 | 0.002 |

p value: probability of obtaining results, or something more extreme, if the null hypothesis is true.
HR: hazard ratio; 95%CI: 95% confidence interval; N/A: not applicable; pCR: pathological complete response.

## DISCUSSION

Neoadjuvant chemotherapy is the initial standard treatment for locally advanced breast cancer. The correlation between the response to neoadjuvant chemotherapy and prognostic factors allows us to understand that the different subtypes of breast cancer have differentiated response profiles. Pathologic complete response is a predictor of long-term outcome and is therefore an appropriate marker for survival, although the incidence and prognostic impact of pCR vary among breast cancer subtypes.[4,15,18] The pCR rate increases in triple-negative and HER2 positive tumors (28 to 32%), according to the prospective and randomized NOAH study, which showed significantly higher event-free survival in patients treated with chemotherapy and trastuzumab (71% *versus* 56%, p=0.013) and also a significantly higher pCR rate (43% *versus* 23%, p=0.002),[19] which agrees with the series reported here. The ACOSOG Z1041 study[20] compared 4 cycles of FEC75, followed by 12 weeks of paclitaxel (80mg/m$^2$) concomitant with trastuzumab, with the experimental arm consisting of 12 weeks of paclitaxel, followed by 4 cycles of FEC75, concomitant with trastuzumab throughout the treatment. Pathological complete response rates found were high in both arms, although in the subgroup of patients with hormone receptor negative, the pCR was higher than in patients with hormone receptor positive.

In the present study, with data from two public reference hospitals in oncology, with a high percentage of cases with locally advanced disease, data obtained were similar to those in the literature. The multivariate analysis showed that the only predictive factor for pCR was the presence of negative hormone receptor. Hormone receptor negative tumors tend to have a higher rate of pathologic response to chemotherapy than hormone receptor positive tumors.[21] An important neoadjuvant study, the GeparSixto of the German AGO-B and GBG groups, also demonstrated high complete pathology response rate in triple-negative tumors.[22]

In another analysis of pathologic complete response as a prognostic factor, the only independent risk factor for shorter DFS and overall survival was hormone receptor negative, and pCR was the only protective factor for these same survival analyses. Patients with hormone receptor negative who achieve pCR present a prognosis comparable to luminal A tumors.[14] Similarly, patients with triple negative neoplasms presenting pCR have a better prognosis when compared to those with residual disease after neoadjuvance.[23] According to a study at MD Anderson analyzing post-mastectomy pathology specimens of 241 patients treated with neoadjuvant paclitaxel followed by FAC, and of 141 treated with neoadjuvant FAC, patients with extensive residual disease were observed to have a worse prognosis, regardless of hormone receptor status, adjuvant hormone therapy, or pathological stage of residual disease, according to the AJCC.[24]

The NSABP B18 study, from the National Surgical Adjuvant Breast and Bowel Project (NSABP), demonstrated increased overall survival and disease-free survival in patients who presented pCR compared with those who did not.[25]

Some studies have shown the association between pCR and the cell proliferation index measured by Ki-67.[26-28] One of the limitations of our study was the unavailability of Ki-67 to measure cell proliferation as a predictor variable, due to the lack of registration of this examination in many patient records.

## CONCLUSION

The presence of negative hormonal receptor was an isolated predictive factor of pathologic complete response and was associated with shorter overall survival and disease-free survival. Pathologic complete response was associated with longer disease-free survival and overall survival.

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## REFERENCES

1. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Estimativa 2012: incidência de câncer no Brasil [Internet]. Rio de Janeiro: INCA; 2011. 118p [citado 2018 Jan 29]. Disponível em: http://portal.saude.sp.gov.br/resources/ses/perfil/gestor/homepage/estimativas-de-incidencia-de-cancer-2012/estimativas_incidencia_cancer_2012.pdf
2. Mieog JS, van der Hage JA, van de Valde CJ. Neoadjvant chemotherapy for operable breast cancer. Br J Surg. 2007;94(10):1189-200. Review.
3. Gralow JR, Zujewski JA, Winer E. Preoperative therapy in invasive breast cancer: reviewing the state of the science and exploring new research directions. J Clin Oncol. 2008;26(5):696-7. Review.
4. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol. 1999;17(2):460-9.
5. Schott AF, Hayes DF. Defining the benefits of neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2012;30(15):1747-9.
6. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A. 2003;100(14):8418-23.
7. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki-67 Index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101(10):736-50.
8. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SA, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clin Cancer Res. 2015;21(7):1688-98.
9. Lin NU, Vanderplas A, Hughes ME, Theriault RL, Edge SB, Wong YN, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer. 2012;118(22):5463-72.
10. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-33. Erratum in: N Engl J Med. 2017;377(17):1700.
11. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998;16(8):2672-85.
12. Rouzier R, Extra JM, Klijanienko J, Falcou MC, Asselain B, Vincent-Salomon A, et al. Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. J Clin Oncol. 2002;20(5):1304-10.
13. Mazouni C, Peitinger F, Wan-Kau S, Andre F, Gonzalez-Angulo AM, Symmans WF, et al. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. J Clin Oncol. 2007;25(19):2650-5.
14. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30(15):1796-804.
15. von Minckwitz G, Kaufmann M, Kuemmel S, Fasching PA, Eiermann W, Blohmer JU, et al. Correlation of various pathologic complete response (PCR) definition with log-term outcome and the prognostic value of PCR in various breast cancer subtypes: results from the German neoadjuvant meta-analysis. J Clin Oncol. 2011;29(15 suppl):1028.
16. Remmele W, Schicketanz KH. Immunohistochemical determination of estrogen and progesterone receptor content in human breast cancer. Computer-assisted image analysis (QIC score) vs. subjective grading (IRS). Pathol Res Pract. 1993;189(8):862-6.
17. Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T, Eusebi V, et al. Breast cancer prognostic classification in the molecular era: the role of histological grade. Breast Cancer Res. 2010;12(4):207. Review.
18. Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: a n update. J Clin Oncol. 2006;24(12):1940-9. Erratum in: J Clin Oncol. 2006; 24(19):3221.
19. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with Her-2 positive locally advanced breast cancer (the NOAH Trial): a randomized controlled superiority trial with a parallel Her-2 negative cohort. Lancet. 2010;375(9712):377-84.
20. Ewer M, Suman VJ, Buzdar A, McCall LM, Meric-Bernstam F, Leitch AM, et al. ACOSOG Z1041 (Alliance): Cardiac events (CE) among those receiving neoadjuvant anthracyclines (A) and Taxanes with transtuzumab (T) for Her-2 + breast cancer. J Clin Oncol. 2013;31(15 suppl):526.
21. Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, Margolese R, Theoret H, Soran A, Wickerham DL, Wolmark N; National Surgical Adjuvant Breast and Bowel Project Protocol B-27. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003;21(22):4165-74.
22. von Minckwitz G, Schneeweiss A, Salat C, Rezai M, Zahm DM, Klare P, Blohmer JU, Tesch H, Khandan F, Jud S, Jackisch C, Mehta K, Loibl S, Untch M; German Breast Group. A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple – negative and Her-2 positive early breast cancer (GeparSixto). J Clin Oncol. 2013;(15 suppl):1004.
23. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, et al. Response to neoadjuvant therapy and long–term survival in patients with triple–negative breast cancer. J Clin Oncol. 2008;26(8):1275-81.
24. Wesolowski R, Budd GT. Neoadjuvant therapy for breast cancer: assessing treatment progress and managing poor responders. Curr Oncol Rep. 2009; 11(1):37-44. Review.
25. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol. 2008;26(5):778-85. Erratum in: J Clin Oncol. 2008;26(16):2793.
26. Yoshioka T, Hosoda M, Yamamoto M, Taguchi K, Hatanaka KC, Takakuwa E, et al. Prognostic significance ofpathologic complete response and Ki67 expression after neoadjuvant chemotherapy in breast cancer. Breast Cancer. 2015;22(2):185-91.
27. Esserman LJ, Berry DA, DeMichele A, Carey L, Davis SE, Buxton M, et al. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL--CALGB 150007/150012, ACRIN 6657. J Clin Oncol. 2012;30(26):3242-9.
28. Zhang GC, Qian XK, Guo ZB, Ren CY, Yao M, Li XR, et al. Pre-treatment hormonal receptor status and Ki67 index predict pathologic complete response to neoadjuvant trastuzumab/taxanes but not disease-free survival in HER2-positive breast cancer patients. Med Oncol. 2012;29(5):3222-31.