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Analysis on complete pathological response and estimated survival among breast cancer patients undergoing neoadjuvant chemotherapy in a private institution in the state of Rio de Janeiro

Análise da resposta patológica completa e sobrevida estimada em pacientes com câncer de mama em quimioterapia neoadjuvante em instituição privada do estado do Rio de Janeiro

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ABSTRACT

Objective: Breast cancer is the most common malignancy among women, both in developed and in developing countries. Indications for neoadjuvant treatment have been expanded so that pathological responses can be evaluated. Diversified therapeutic approaches may thus be indicated in accordance with each residual disease profile. This was a real-life study, in which the aim was to analyze the complete pathological response (CPR) and estimated survival among breast cancer patients undergoing neoadjuvant chemotherapy in a private institution in the state of Rio de Janeiro. **Methods:** This was a prospective observational cohort study on patients diagnosed with breast cancer and treated with neoadjuvant chemotherapy, in a private institution. The primary objective of this study was to analyze CPR. As secondary endpoints, we evaluated the disease-free survival (DFS) and overall survival (OS) of these patients and correlated them with clinical-pathological variables. **Results:** CPR was achieved in: 12.5% of luminal A cases; 19.5% of luminal B/HER-2-negative cases; 38.5% of luminal B/HER-2-positive cases; 65% of HER-2-enriched cases; and 37.8% of triple negative cases. There was a significant correlation between CPR and histopathological subtypes ($p<0.001$). At the end of 36 months, the DFS for patients with CPR was 89.1% vs. 72.4% for the others ($p=0.01$). OS could not be calculated for patients who achieved CPR, because there was no event. **Conclusion:** We confirmed in this study that a correlation exists between CPR and overall survival. In addition, we were able to show that even in developing countries, such as Brazil, appropriate treatments can be offered in accordance with international guidelines, such that our results were consequently similar to those in the worldwide literature.

Keywords: Neoadjuvant therapy; Breast neoplasms; Pathology, Surgical; Neoplasm, Residual.

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RESUMO

Objetivo: O câncer de mama é a neoplasia maligna mais comum entre as mulheres, tanto em países desenvolvidos quanto em desenvolvimento. As indicações para o tratamento neoadjuvante foram expandidas para que as respostas patológicas possam ser avaliadas. Abordagens terapêuticas diversificadas podem, portanto, ser indicadas de acordo com o perfil de cada doença residual. Trata-se de um estudo da vida real, cujo objetivo foi analisar a resposta patológica completa (RCP) e a estimativa de sobrevida em pacientes com câncer de mama em quimioterapia neoadjuvante em uma instituição privada do estado do Rio de Janeiro. **Métodos:** Estudo de coorte prospectivo observacional em pacientes com diagnóstico de câncer de mama e tratamento com quimioterapia neoadjuvante, em instituição privada. O objetivo principal deste estudo foi analisar a RCP. Como desfechos secundários, avaliamos a sobrevida livre de doença (SLD) e a sobrevida geral (SG) desses pacientes e as correlacionamos com as variáveis clínico-patológicas. **Resultados:** A RCP foi alcançada em: 12,5% dos casos luminal A; 19,5% dos casos luminais B/HER-2 negativos; 38,5% dos casos luminais B/HER-2 positivos; 65% dos casos enriquecidos com HER-2; e 37,8% de casos triplo negativos. Houve uma correlação significativa entre a RCP e os subtipos histopatológicos (p<0,001). Ao final de 36 meses, a DFS para pacientes com RCP foi de 89,1% vs. 72,4% para os demais (p=0,01). SG não pôde ser calculado para pacientes que alcançaram RCP, porque não houve nenhum evento. **Conclusão:** Confirmamos neste estudo que existe uma correlação entre a RCP e a sobrevida global. Além disso, pudemos mostrar que mesmo em países em desenvolvimento, como o Brasil, tratamentos adequados podem ser oferecidos de acordo com as diretrizes internacionais, de forma que nossos resultados foram, consequentemente, semelhantes aos da literatura mundial.

Descritores: Terapia neoadjuvante; Neoplasias mamárias; Patologia Cirúrgica; Neoplasia residual.

INTRODUCTION

Breast cancer is the most common malignancy among women both in developed and in developing countries[1]. In Brazil, it has been estimated that there will be 66,280 new cases of breast cancer for each year of the triennium 2020-2022, which corresponds to an estimated risk of 61.61 new cases per 100,000 women[2].

Breast cancer treatment strategies are defined according to clinical and pathological findings and predictive and prognostic factors such as staging and molecular subtype. In practice, breast cancer subtypes are identified by means of immunohistochemistry and are classified as luminal, amplified HER2 or triple negative (TN). TNM is the international system that is used to evaluate the extent of neoplasia. In the latest (eighth) edition of the TNM system, published by the American Joint Committee on Cancer (AJCC) in 2018, pathological prognostic factors were incorporated[3].

Neoadjuvant treatment has been used for many years for patients with locally advanced tumors, with the aims of enabling surgery in inoperable cases and increasing the rate of conservative surgical procedures[4]. Recently, indications for neoadjuvant treatment have been expanded so that pathological responses can be evaluated. Diversified therapeutic approaches may thus be indicated in accordance with each residual disease profile[5].

The pathological response or extent of residual disease in the surgical specimen correlates inversely with prognosis and survival. Residual tumor load is a predictor of distant recurrence-free survival, such that cases with minimal residual disease and complete pathological response (CPR) have a better prognosis[6]. Different classifications of pathological response have been used by different authors over the years. However, it is known that CPR, defined as absence of invasive carcinoma in the breast and axilla, confers significantly increased disease-free and overall survival[7,8], especially in cases of negative receptor tumors (HER2-positive and TN)[5]. Thus, CPR has frequently been used in chemotherapy studies as an intermediate outcome measuring the efficacy of treatment because it can be rapidly evaluated and reproduced.

This is a real-life study, in which the objectives are to analyze and correlate CPR with disease-free survival and overall survival among patients with breast cancer of different subtypes undergoing neoadjuvant chemotherapy in a private institution in a developing country, offering treatments in accordance with international guidelines. Periodic analysis of results obtained in an institution not only has relevance as a management tool, thus helping to ensure the best clinical practices, but also contributes to validation of results obtained in clinical trials.

MATERIALS AND METHODS

Methodology

This is a prospective observational cohort study on patients diagnosed with breast cancer (men and women) who were treated with neoadjuvant chemotherapy between 2012 and 2018 in the six units of Americas Oncology, a private institution in the state of Rio de Janeiro.

Patients were included through a prospective search, using the OpenClinica system, Enterprise edition, for new cases of breast cancer patients who received neoadjuvant chemotherapy. Data were collected by consulting physical and electronic medical records. This study was approved by the Research Ethics Committee. Written informed consent was signed by all participants.

The following patients were excluded: those who discontinued the initially planned treatment without justifiable cause (which could be due to progression or adverse events); those who were lost from the follow-up at the institution during neoadjuvant chemotherapy; and those who were already in stage IV at diagnosis.

Histopathological and immunohistochemical analyses were performed in different local laboratories. Immunohistochemistry was evaluated using estrogen receptors (ER) and progesterone receptors (PR), HER2 and Ki67.

Clinical variables such as age, sex, stage and treatment protocols were collected. Age was evaluated as age groups. For clinical and pathological staging, the TNM system of the American Joint Committee on Cancer (AJCC), eighth edition, published in 2018, was used. The chemotherapy regimens used for neoadjuvant treatments were as follows. For patients who were HER2-positive: taxane + trastuzumab; taxane + anthracycline + trastuzumab; or associations containing double blockade with trastuzumab and pertuzumab. For patients presenting luminal and TN disease: dense-dose regimens (dose-dense AC followed by dose-dense paclitaxel or dose-dense AC followed by weekly paclitaxel); taxane alone; anthracycline alone; taxane + anthracycline; and others such as platinum. The choice of surgical procedure (conservative or radical) was at the discretion of the mastologist and the patient. Radiotherapy and hormone therapy were performed on patients with indications for these, in accordance with international recommendations.

The pathological variables evaluated were histopathological subtypes and CPR. The following subgroups were identified by means of immunohistochemistry and were defined as: luminal A (ER-positive, PR-positive, HER2-negative and Ki67 up to 14%); luminal B/HER2-negative (ER-positive, PR-positive, HER2-negative and Ki67 ≥ 14%); luminal B/HER2-positive (ER-positive, PR-positive, HER2-positive and Ki67 ≥ 14%); HER2-enriched (HER2e) (HER2-positive, ER-positive and PR-negative); and triple negative (TN) (ER-negative, PR-negative and HER2-negative)[9]. Cerb2 scores were identified as 0, 1+, 2+ or 3+, and fluorescence *in situ* hybridization (FISH) was performed for 2+ results. Those whose results were presented as 3+ and amplified FISH (2+ cases) were included as HER2-positive. To grade Ki67, we used the 2013 St. Gallen Consensus, which considers that values below 14% are low or negative[9,10].

The Food and Drug Administration (FDA) has defined CPR as the absence of residual invasive neoplasia in breast and lymph node specimens after neoadjuvant chemotherapy, while allowing the presence of residual noninvasive disease, including carcinoma *in situ* (ypT0/Tis ypN0, in the AJCC 8th edition)[11].

Statistical analysis

The results from this study were exploratory and descriptive. Overall survival was estimated using the Kaplan-Meier method and was defined as the interval between the date of diagnosis and death. Disease-free survival (DFS) was defined as the time interval between the date of diagnosis and recurrence of local or distant disease. For patients included in this study who remained alive or were lost from the follow-up, the data were censored at the time of the last contact. $P \leq 0.05$ was considered significant. Multivariate analyses were performed between the clinical-pathological variables and the outcomes. The statistical analysis was done using the SPSS statistical software, version 17, IBM.

The primary objective of this study was to analyze the complete pathological response (CPR) of patients who underwent neoadjuvant chemotherapy in a private institution in the state of Rio de Janeiro. As secondary endpoints, we evaluated the disease-free survival and overall survival of these patients and correlated these with clinical-pathological variables.

RESULTS

We evaluated 198 patients, all female, with a median follow-up of 35 months. They had ages ranging from 26 to 78 years, with a median of 48 years. Twelve percent (12.1%) corresponded to luminal subtype A; 38.9% to luminal B/HER2-negative; 13.6% to luminal B/HER2-positive; and 10.6% to HER2-enriched. Nine patients (18.8%) underwent FISH for diagnostic definition. Twenty-four percent (23.7%) were of the TN subtype (as shown in Table 1). Regarding clinical staging (cTNM grouped), stage I accounted for only 2.5% of the cases, while stage III accounted for 43.9%. Stage II was the one most frequently present, in 53.5% of the patients in the study.

Regarding the chemotherapy used, regimens containing taxane and anthracycline were the ones most used, followed by dense dose. The most commonly used anti-HER2 therapy consisted of double blockade containing trastuzumab and pertuzumab. Conservative surgery occurred in the cases of 27.8% of the patients, while 72.2% underwent radical surgery. Regarding the axillary lymph node evaluation, 32% only underwent sentinel lymph node excision, while 65.5% underwent axillary emptying. Adjuvant radiotherapy was performed in 85.6%, and hormone therapy in 64.6% of the cases (Table 1).

Table 1. General characteristics of patients and treatment.

	n	%
Age		
20-49	112	56.6%
50-59	49	24.7%
60-69	30	15.2%
≥70	7	3.5%
Receptor status subgroups		
Luminal A	24	12.1%
Luminal B/HER-2-negative	77	38.9%
Luminal B/HER-2-positive	27	13.6%
HER-2e	21	10.6%
Triple negative	47	23.7%
Not classified	2	1.0%
Type of neoadjuvant chemotherapy		
Anthracycline + taxane	114	57.9%
Anthracycline alone	8	4.1%
Taxane alone	2	1.0%
Dense dose	28	14.2%
Platinum	3	1.5%
Therapy directed to HER-2		
Trastuzumab + pertuzumab + chemotherapy	25	12.7%
Trastuzumab alone + chemotherapy	17	8.6%
Type of breast surgery		
Conservative	54	27.8%
Radical	140	72.2%
Type of axillary surgery		
Sentinel lymph node biopsy	62	32%
Axillary emptying	127	65.5%
Unspecified	5	2.5%
Adjuvant radiotherapy		
Yes	166	85.6%
No	19	9.8%
Unspecified	9	4.6%
Adjuvant hormone therapy		
Yes	128	64.6%
No	59	29.8%
Unspecified	11	5.6%

Among the patients evaluated, four did not undergo surgery (three due to disease progression during neoadjuvant chemotherapy and one died without known cause), which made it impossible to evaluate their pathological response. CPR was achieved in 12.5% of luminal A cases; 19.5% of luminal B/HER2-negative cases; 38.5% of luminal B/HER2-positive cases; 65% of HER2-enriched cases; and 37.8% of TN cases. There was a significant correlation between CPR and histopathological subtypes ($p < 0.001$; as shown in Table 2). Among the patients in stage I (total of five), only one reached CPR. Among the 105 patients in stage II, 34 (58.6%) achieved CPR; and among the 84 in stage III, 23 (39.7%) achieved CPR. Among all the patients who achieved CPR (n = 58), 91.4% (53) were under 60 years of age ($p = 0.054$). Regarding Ki67, CPR was achieved in 87.3% of the cases with Ki67 that was considered positive, but without statistical significance ($p = 0.23$).

Table 2. Evaluation of complete pathological response (CPR) according to subtypes.

Subtypes	CPR yes	CPR no	Total
Luminal A	3 (12.5%)	21 (87.5%)	24 (100%)
LuminalB/HER-2- negative	15 (19.5%)	62 (80.5%)	77 (100%)
LuminalB/HER-2- positive	10 (38.5%)	16 (61.5%)	26 (100%)
HER-2e	13 (65%)	7 (35%)	20 (100%)
Triple negative	17 (37.8%)	28 (62.2%)	45 (100%)
Total	58 (30.2%)	134 (69.8%)	192 (100%)

$p<0.001$.

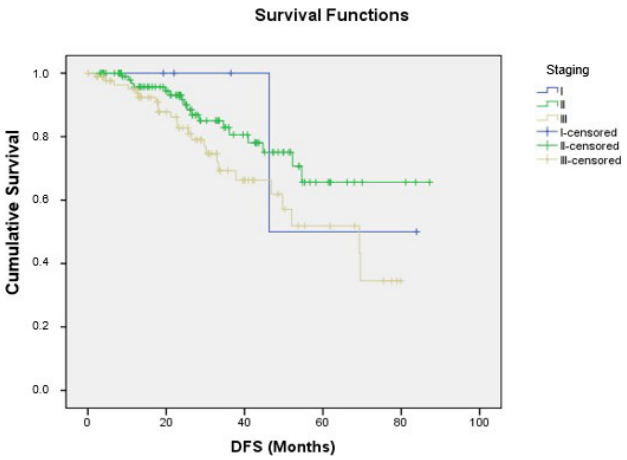
Disease-free survival (DFS) at the end of 24 months of follow-up, was found to be about 90% for the patients in stage II and 80% for those in stage III ($p = 0.11$) (Graph 1). Regarding the subtypes, the DFS was worse for patients classified as TN and HER2-enriched, and this was statistically significant ($p = 0.019$), as shown in Graph 2. At the end of 36 months, the DFS for patients with CPR was 89.1%, versus 72.4% for the others, and this was also significant ($p = 0.01$) (Graph 3).

Overall survival was similar for stages I, II and III. At 24 months of follow-up, it was slightly worse for stage III, but without statistical significance, with $p = 0.12$ (Graph 4). Regarding the subtypes, the overall survival was about 97% and 94% for the luminal B/HER2-negative and luminal B/HER2-positive groups, respectively ($p = 0.025$) (Graph 5). For patients who reached CPR at the end of 36 months of follow-up, overall survival could not be calculated, since there was no event ($p = 0.08$) (Graph 6).

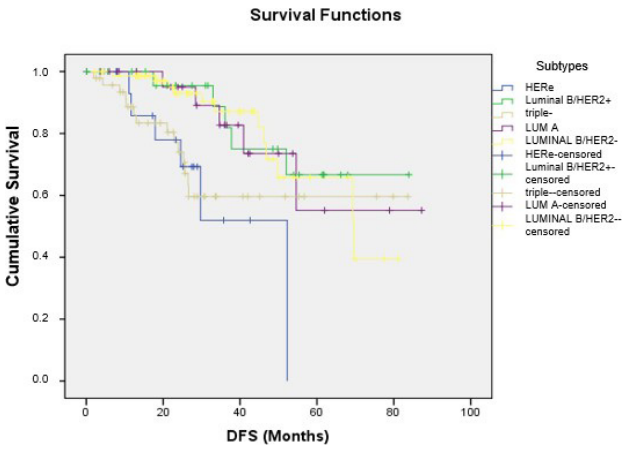
DISCUSSION

Neoadjuvant chemotherapy, initially used in patients with inoperable breast cancer to improve resectability, is now commonly used for its impact on surgery, downstaging tumours convert patients from mastectomy to breast-conservation candidates. In large studies in the literature, the breast conservation rate with neoadjuvant chemotherapy is around 65% compared to 49% when surgery is the initial treatment[12].

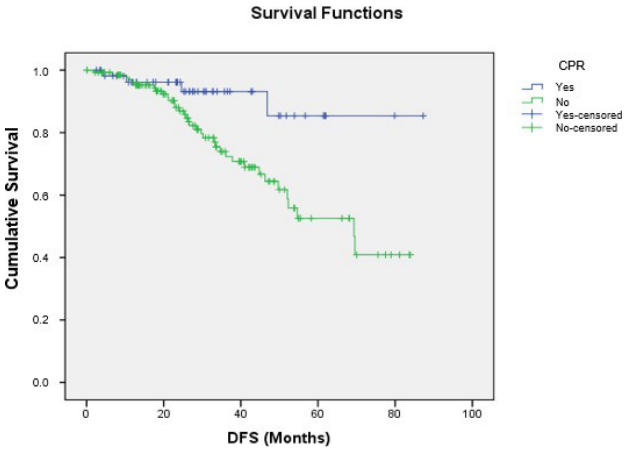
In our study, the results showed that conservative surgery occurred in only 27.8% of patients and



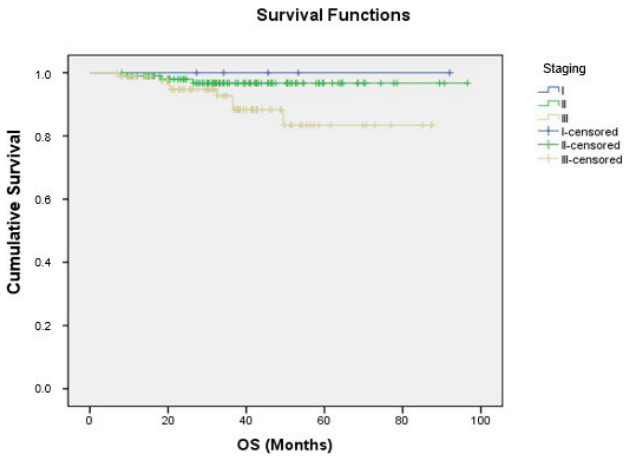
Graph 1. Disease-free survival and staging (p=0.11).



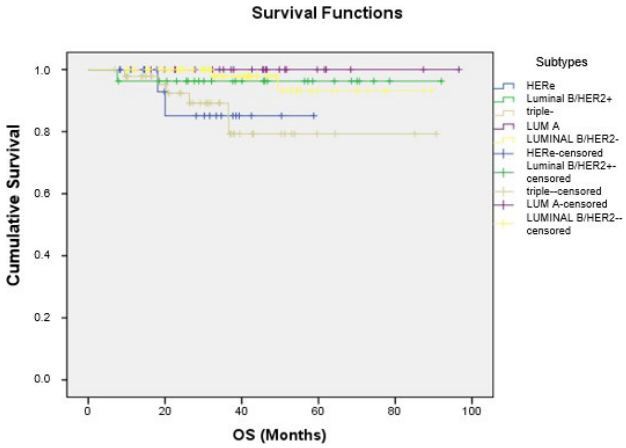
Graph 2. Disease-free survival and subtypes (p=0.019).



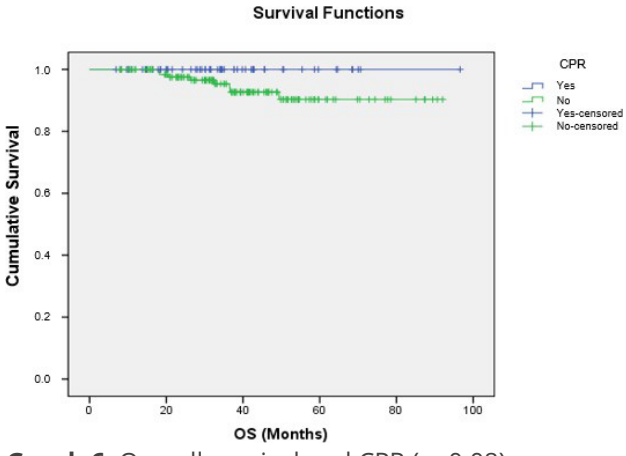
Graph 3. Disease-free survival and CPR (p=0.01).



Graph 4. Overall survival and staging (p=0.12).



Graph 5. Overall survival and subtypes (p=0.025).



Graph 6. Overall survival and CPR (p=0.08).

that 72.2% of patients underwent radical surgery and 65.5% underwent axillary dissection. This contradictory result can, in part, be explained by the high rate of patients, 43.9% in our study, who were in stage III and also by the diversity of surgical services involved in the decision-making process, involving contradictions inherent to each group.

CPR, especially in HER2-positive and TN tumors, has been consolidated as a prognostic marker. Therefore, for patients with residual breast and/or axillary disease, complementary adjuvant treatment has been recommended. Use of T-DM1 as an adjuvant after neoadjuvant therapy for patients with residual disease in the surgical specimen has given rise to reduction of the risk of death by 50%[13], which shows the benefit of neoadjuvant treatment for this type of patient. In the case of patients with the TN subtype, the CREATE-X study showed the importance of using capecitabine as an adjuvant after preoperative chemotherapy, with gains in disease-free survival and overall survival[14]. The CPR verified in the various subtypes of our study and its correlation with survival is in agreement with literature data[15].

Neoadjuvant chemotherapy protocols have been improving over the years, with higher response rates achieved. In the context of HER2-positive cases, initial studies in 2011 already showed increased proportions of CPR and gains in survival through addition of trastuzumab to chemotherapy[16]. Years later, double blockade of HER2 using pertuzumab and trastuzumab was shown to have CPR benefit, reaching response rates of 60%[17,18]. In our study, most HER2-positive patients received double blockade, with CPR of 65% in HER2-enriched cases and 38% in HER2/Hormone-receptor-positive cases. These results were similar to what has been reported in the worldwide literature. There are few Brazilian studies on CPR data. Buzatto et al. (2017)[19] observed a CPR rate of 48% with use of trastuzumab alone for the HER2-enriched subtype and 44% for HER2/Hormone-receptor-positive cases. In another Brazilian study, an even lower rate of 33% was observed among HER2-positive patients, which can be explained by the fact that trastuzumab was not used: at that time, this drug was not available through the Brazilian public healthcare system[20]. These data reveal discrepancies in the treatment used, between different services, especially between the private and public networks. This may have repercussions regarding differences in survival, among women with difficulty in accessing the therapeutic regimens recommended in international guidelines.

Minor changes were observed in neoadjuvant chemotherapy protocols for triple negative tumors. Bayratar and Arun, in 2012[21], showed that there was greater benefit through use of dense-dose chemotherapy regimens for patients with negative hormone receptors and high proliferation rates. The results in the literature regarding use of platinum derivatives and anti-angiogenic agents seem conflicting. The CALGB 40603 study did not show better results through use of carboplatin and bevacizumab[22]. On the other hand, other trials showed that adding platinum benefited the CPR, with values ranging from 53.2% to 58%[23,24]. Another agent that was tested in the neoadjuvant scenario, in TN tumors, was PARP inhibitors, but also with controversial results[24]. The use of immunotherapy in TN cases has aroused great interest. In the KEYNOTE-522 study, pembrolizumab combined with chemotherapy gave rise to CPR of 64.8%[25]. In 2020, Mittendorf et al.[26] showed data on CPR rates of 58% among TN patients who used chemotherapy consisting of nab-paclitaxel and anthracycline in combination with atezolizumab. However, it remains unknown within the immunotherapy scenario whether CPR correlates with overall survival. In our study, most patients used regimens containing a dense dose, and only three used platinum. We observed high response rates, with CPR in 37.8% of the cases of TN, which seems similar to what has been reported in the worldwide literature, as reported in the review by Asaoka et al., in 2020[27], in which the CPR rate was 34.2%. In the Brazilian literature, we found lower CPR rates (21%), again in a public institution, with low financial resources and patients with advanced disease[28].

Unlike TN and HER2- positive cases, in which the CPR rate correlates with the prognosis, luminal subtypes A and B do not show any close correlation, according to the 2012 publication by Journal of Clinical Oncology[29]. However, for patients with positive hormonal receptors, previous studies showed that higher clinical response rates were found through use of dose-dense chemotherapy, such that even conservative surgery became possible. In luminal tumors, the CPR rate was much lower than that of the previous subtypes, ranging in the literature from 6.4% to 22%[30] for luminal A tumors and 11% to 28%[29,31] for luminal B tumors, similar to the data found in the present study (luminal A CPR of 12.5% and Luminal B CPR of 19.5%).

This study had a median follow-up of 35 months. Disease-free survival (DFS) at the end of 24 months of follow-up, was about 90% for patients in stage II and 80% for those in stage III, and the overall survival was similar for stages I, II and III. It was slightly worse for stage III, but this difference was not statistically significant. These data differed from what had been reported the literature because it is recognized that staging is a prognostic factor for survival. This may perhaps be explained by the small number of patients at an early stage.

In an attempt to identify predictive factors for CPR and prognostic factors for survival, we conducted multivariate analysis (subtypes, staging, age and Ki67). We found a significant correlation between histopathological and CPR subtypes, as well as in relation to DFS and overall survival. Asaoka et al., in 2020[27], found response rates of 52.9% for HER2-enriched cases, 34.2% for TN cases and 14.7% for luminal cases. These data are similar to what we observed in this study (65%, 37.8% and 19.5%, respectively, for HER2-enriched, TN and Luminal B/HER2-negative cases)[32]. Regarding staging, the literature shows that cases in initial stages correlate with higher rates of CPR[29]. However, in our study, we did not find any correlation between staging and CPR ($p = 0.67$). Among the patients in stage I (total of 5), only one achieved CPR. Among the 105 patients in stage II, 34 (58.6%) achieved CPR and among the 84 in stage III, 23 (39.7%) achieved CPR. Regarding age, the median was 48 years, ranging from 26 to 78, and there was no relationship with CPR or survival. Regarding Ki67, we found that CPR was achieved in 87.3% of the cases in which Ki67 was considered positive ($p = 0.23$), with worse disease-free survival outcomes, which is consistent with data found in a meta-analysis by Tao et al.[33].

Both in our study and in the study by Minckwitz et al. (2012)[29], CPR was associated with better prognosis for HER2-enriched and TN cases, and it was correlated with better DFS in luminal B/HER2-negative, HER2-enriched and TN cases.

Thus, our data are similar to those of the worldwide literature and reflect good access to the therapies currently existing, which are already incorporated in the private healthcare system of Brazilian society. It is noteworthy that despite being a prospective study, many follow-up losses occurred through exchanges of health insurance, thereby decreasing the number of patients evaluated and impacting on some results.

CONCLUSION

In this study, we confirmed the correlation between complete pathological response and overall survival. Thus, it is essential that increased attention is given to indications for neoadjuvant treatment, especially in the triple negative and HER2-positive subgroups, for which CPR has better prognostic value. In this study, we were able to show that even in developing countries such as Brazil, adequate treatments that are in accordance with international guidelines can be offered. The consequence of this is that our results are similar to those in the worldwide literature. However, it is essential that the coverage of these therapies should be expanded to encompass the entire private network and, especially, the public network. In this manner, equal treatment, with similar and fair outcomes for breast cancer patients with locally advanced scenarios can be provided.

Further studies with assessments such as this one should be encouraged, so that better understanding of the results in countries with more deficient health structures can be obtained, thereby improving access to the most recommended therapies worldwide.

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