Evaluation of Treatment and Recurrence-Free Survival in Patients with Early HER2-Positive Breast Cancer: Real-Life Data Comparing Public and Private Healthcare

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Abstract

Introduction The present study was designed to compare the treatment provided in private and public health care facilities for women positive for early breast cancer of the human epidermal growth factor receptor 2 (HER2) subtype, who received anti-HER2 therapy in neoadjuvant or adjuvant settings, with an evaluation of the recurrence-free survival (RFS) and pathological complete response (pCR) rates.

Materials and Methods The current is a retrospective study carried out at the Instituto Brasileiro de Controle do Cancer (IBCC Oncologia), in the city of São Paulo, Brazil. We included patients treated between 2015 and 2020.

Results The study included 472 medical records of early HER2-positive breast cancer patients treated in the public and private health care systems who received neo-adjuvant or adjuvant treatments. The pathological complete response (pCR) was related to a lower recurrence rate and a longer recurrence-free survival (RFS). The results showed no statistically significant difference between the public and private health care systems in terms of RFS.

Discussion Although the public health care patients were diagnosed with more advanced diseases than the private health care patients, both presented similar survival rates. In spite of the small number of patients evaluated, the dual HER2 blockade did not improve the clinical outcomes. These findings should be confirmed through studies with a larger number of patients and a longer follow-up period.

Keywords
- breast neoplasms
- HER2-positive
- treatment
- neoadjuvant therapy
- adjuvant chemotherapy

Introduction

Among all the neoplasms that affect women, breast cancer is the leading cause of death. The Brazilian National Cancer Institute (Instituto Nacional de Cancer, INCA, in Portuguese) estimates 73.610 cases in Brazil in 2023 and 11.71 deaths per 100 thousand women in 2021.[1]

The human epidermal growth factor receptor 2 (HER2) subtype represents about 20% of diagnosed breast cancers, and it is characterized by the high expression rates of HER2 protein as indicated by immunohistochemistry (IHC) and fluorescent in-situ hybridization (FISH), which indicate cell proliferation, differentiation, and survival. Overexpression of HER2 may be associated with a high risk of frequent recurrence

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and a poor prognosis. Despite early detection, this subtype has a 15% recurrence rate. The expression of hormonal receptors tends to be lower in patients with HER2 overexpression.[2]

Breast cancer patients who test positive for HER2 at an early or metastatic stage are generally treated with anti-HER2 therapy. Patients with this subtype benefit from anti-HER2 therapy in terms of overall survival (OS). Due to their cost, some medications were incorporated late into the Brazilian Unified Health System (Sistema Único de Saúde, SUS, in Portuguese), despite clearly demonstrating beneficial effects. Initially, their use was restricted to clinical trials.[2]

A persistent activation of signaling pathways associated with HER2 amplification in patients with HER2-positive breast cancer leads to a biologically-aggressive malignancy that is highly sensitive to cytotoxic chemotherapy. Targeted therapy designed to block the activation of these pathways increases the chemosensitivity of HER2-positive breast cancer, resulting in a greater chance of complete response.[3] As well as increasing the rate of pathological complete response (pCR), neoadjuvant chemotherapy enables the elimination of micrometastases and the reduction of tumor size, favoring conservative surgery.[4] Trastuzumab was the first anti-HER2 drug approved by the United States Food and Drug Administration (in 1998) and by the European Medicines Agency (in 2000) for the treatment of metastatic cancer.[5] The Brazilian government approved its use in the private sector in 1999, while it only became available in SUS in 2013.[6]

As a result of the efficacy of the anti-HER2 therapy with trastuzumab, new drugs were developed to blocking HER2, including pertuzumab, a recombinant humanized monoclonal antibody which acts selectively on the extracellular domain of HER2 dimerization, leading to programmed cell death (apoptosis). In recent years, additional drugs have been discovered and incorporated into the treatment guidelines for HER2-positive cancer, such as ado-trastuzumab emtansine, fam-trastuzumab deruxtecan, tucatinib, and neratinib.[7] Through the publication of Ordinance no. 57 in 2017, the Brazilian Ministry of Health announced the incorporation of trastuzumab into the SUS as a first-line metastatic treatment.[6] The combination of trastuzumab and chemotherapy creates a complementary anti-HER2 mechanism, resulting in a higher rate of response to treatment.[8]

In our clinical practice, neoadjuvant chemotherapy is recommended for patients with HER2 subtypes, although it is not directly associated with survival when compared to adjuvant chemotherapy.[9] The present study aimed to investigate the treatment of women with early HER2-positive breast cancer who received anti-HER2 therapy in neoadjuvant or adjuvant settings, comparing data from the private and public health care systems in Brazil, analyzing the recurrence-free survival (RFS) and pCR rates, as well as variables and limitations within each scenario.

Materials and Methods

We conducted a population-based retrospective cohort study of patients with early breast cancer treated at IBCC Oncologia, a tertiary referral hospital in the city of São Paulo.

Study Population

The sample was obtained through a search in our database for the use of pertuzumab and trastuzumab. We included all cases of patients diagnosed with breast cancer, HER2-positive subtype (hybrid luminal or pure HER), who received adjuvant or neoadjuvant chemotherapy from 2015 to 2020. We excluded cases of patients who were metastatic at diagnosis, patients with neoplasia in the 5 years prior to the diagnosis of breast cancer (except non-melanoma skin cancer and cervical cancer), and patients who received the first therapy (except surgery) in other institutions.

Study Variables

We considered the following variables: age at diagnosis; tumor characteristics, such as size (T), axillary lymph node invasion (N), and initial clinical staging and pathological staging according to the seventh edition of the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC); hormone receptor status; evaluation of HER2 by IHC or FISH; treatments performed in neoadjuvance or adjuvance; disease progression (DP) throughout time; and anatomical and cardiotoxicity.

Data Analysis

Demographic data were presented using descriptive statistics according to the type of variable analyzed. The differences in demographic characteristics between patients who received public versus private care were evaluated using the two-sample *t*-test (for the continuous variables) and the Chi-squared test (for the categorical variables). Differences in the types of treatment received were adjusted according to the staging at diagnosis and biological factors through logistic regression.

To evaluate the risks of recurrence associated with demographic characteristics, clinical data, and the type of medical care received, data were analyzed through multivariate Cox proportional risk regression modeling and univariate log-rank analyses for subgroups of interest (public versus Private; double blockade versus isolated trastuzumab; T staging; and N staging). All analyses were performed using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, Unted States) software, version 20.0, and the significance level of 5% was adopted for the analyses.

Results

From 2015 to 2020, 1,115 patients treated with pertuzumab associated with trastuzumab or with trastuzumab monotherapy were identified in the institutional database through active searches. Based on the established selection criteria, 472 medical records were screened for eligibility, and 359 of these patients were from the public health care system (SUS), while 113 were from the private health care system. The median follow-up was of 2.4 years (28.8 months).

►**Table 1** presents the general characteristics of the sample. Regarding age, SUS patients averaged 52 years, while those from the private health system averaged 50 years.

Table 1 Distribution of study variables regarding public and private health care system patients

Variables		Public health care (n = 359)	Private health care (n = 113)	*p*
Age (years): mean ± SD		52 ± 11	50 ± 12	0.075
T stage	T1–T2	58%	71%	**0.009**
	T3–T4	42%	29%	
N stage	N0	45%	57%	**0.034**
	N+	55%	43%	
Hormone receptor	Positive	74%	74%	0.845
	Negative	26%	26%	
Treatment	Neoadjuvant	64%	50%	**0.006**
	Adjuvant	36%	50%	
Neoadjuvant treatment	Trastuzumab	85%	32%	< **0.001**
	Dual HER2 blockade	1%	59%	
	Isolated chemotherapy	14%	9%	

Abbreviations: HER2, human epidermal growth factor receptor 2; N, axillary lymph node invasion; SD, standard deviation; T, tumor size.

The SUS patients had larger tumors (T3–T4) and higher levels of positive axillary lymph node invasion compared to patients from the private health care system, resulting in a higher proportion of neoadjuvant treatment among SUS patients. In the private health care setting, 59% of the patients were treated with anti-HER2 therapy with dual HER2 blockade. To identify cPR predictors, a multivariate logistic regression analysis was performed. The absence of expression of hormonal receptors was positively correlated with the pCR rate (►**Table 2**). It has been demonstrated that small tumors and pCR are protective factors (►**Fig. 1**).

There was no statistically significant difference between SUS patients and those from private health care in terms of RFS (►**Fig. 2**). ►**Fig. 3** shows that dual HER-2 blockade did not result in a statistically significant increase in RFS. The sample size in this subgroup (N = 40) should be noted. ►**Fig. 4** shows that pCR was associated with increased RFS.

According to ►**Fig. 5**, tumor staging was directly related to RFS, which increased in cases of tumors smaller than 5 cm; this variable remained statistically significant in the multivariate analyses as well. ►**Fig. 6** illustrates that patients with axillary lymph node invasion had a shorter RFS.

Data on the recurrence pattern are shown in ►**Table 3**. In total, 95% of the patients with pCR had no recurrence, and 5% had local or distant recurrence, compared to 13% of those with partial response. This difference was statistically significant ($p = 0.043$). There was no relationship between pCR and the prevention of recurrence in the central nervous system (CNS). However, it is important to note that the number of patients with recurrences in the CNS was small, making it difficult to interpret the results.

►**Table 4** shows that there was no statistically significant difference between dual HER-2 blockade and trastuzumab monotherapy in terms of CNS metastasis, recurrence rate, or cardiotoxicity.

Discussion

About 76% of the patients in the present study received treatment in the public health care system. In comparison

Table 2 Pathological complete response of the study sample

Variables	pCR: no (n = 184)	pCR: yes (n = 98)	*p*
Public health care system	65%	35%	0.518
Private health care system	63%	37%	
Dual HER2 blockade	55%	45%	0.153
Isolated trastuzumab	66%	34%	
HR positive	72%	28%	< **0.001**
HR negative	47%	53%	
N+	63%	37%	0.527
N0	69%	31%	
T < 5cm	65%	35%	0.543
T ≥ 5cm	65%	35%	

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, axillary lymph node invasion; pCR, pathological complete response; T, tumor size.

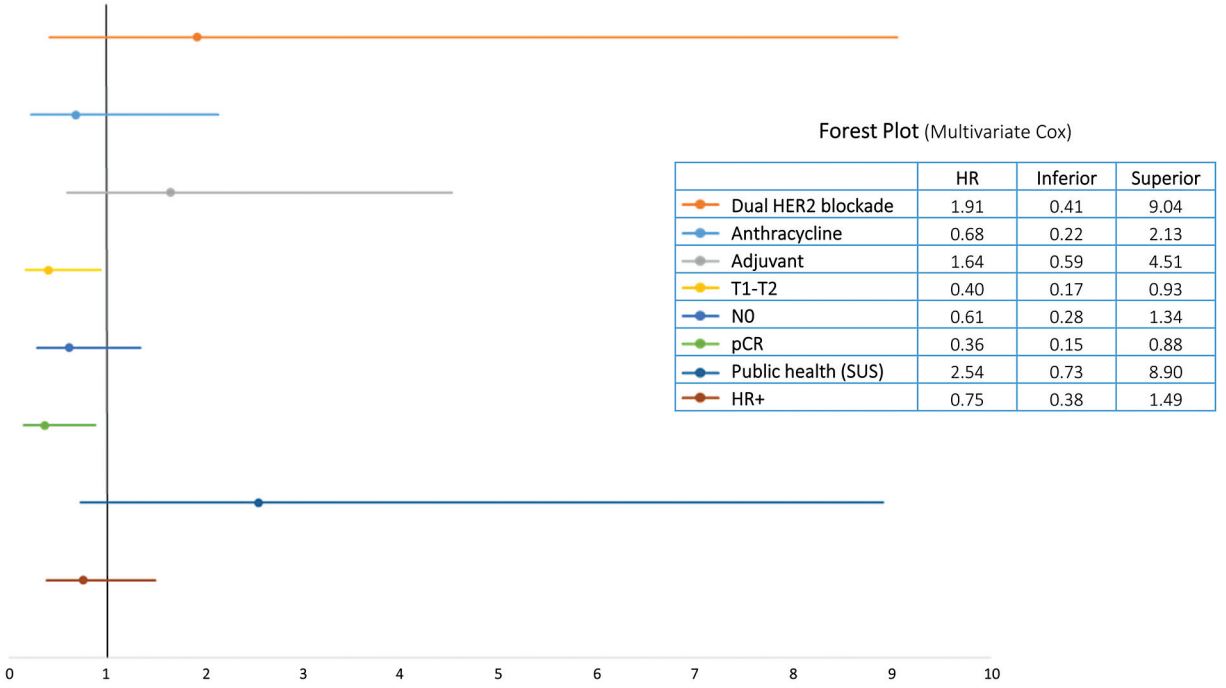

Fig. 1 Forest plot (multivariate Cox regression analysis

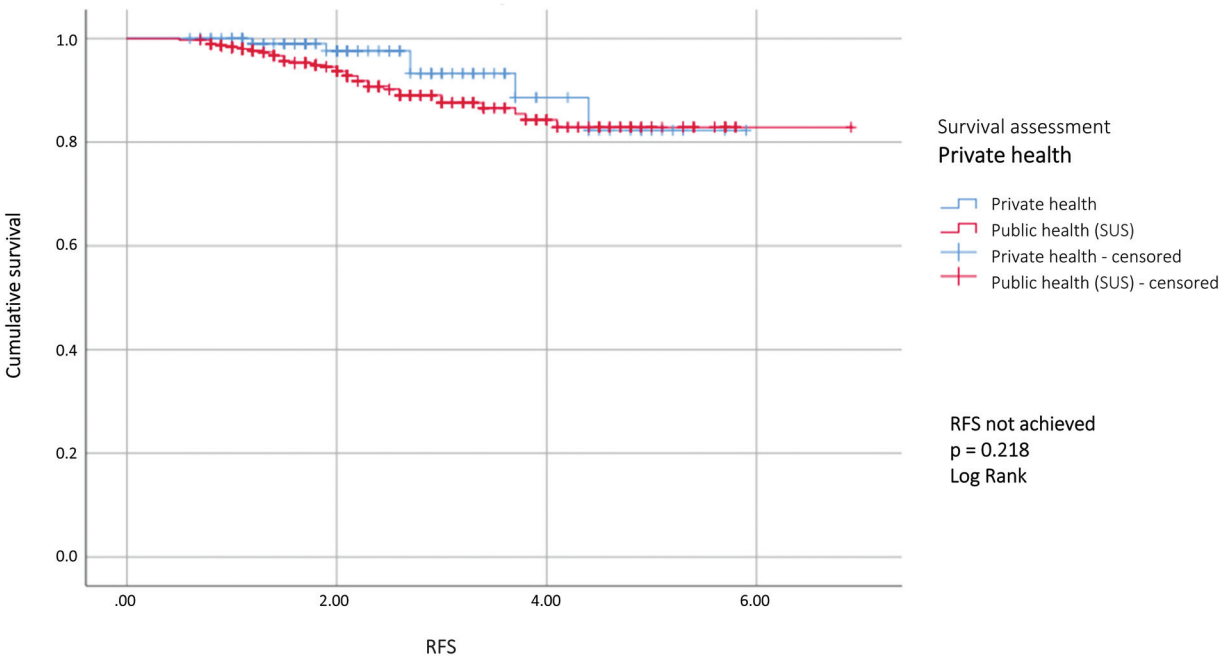

Fig. 2 Recurrence-free survival curve – public versus private health care system.

with patients treated in the private health care system, late staging was a significant factor. Those findings are in agreement with those reported in the literature, which discusses barriers in the public health care system that make it difficult to detect cancer at an early stage, resulting in a worse prognosis. Breast tumors are diagnosed at advanced stages in more than 50% of the cases, implying that late diagnosis is closely associated with metastatic disease.[10]

A study published in 2020 by Rosa et al.[11] with 2,950 women with breast cancer demonstrated that SUS patients were more frequently diagnosed with symptomatic disease, at advanced stages, and with more aggressive subtypes when compared with patients with private health system coverage.[11] According to Boukai et al.[12] (2018), middle-income countries such as Brazil have a dichotomous health system, in which patients can either receive public or private care, with different levels of access to diagnostic and therapeutic services. According to the authors,[12] patients treated in private care are more likely to present with the disease at its earliest stage, indicating a favorable prognosis. The results

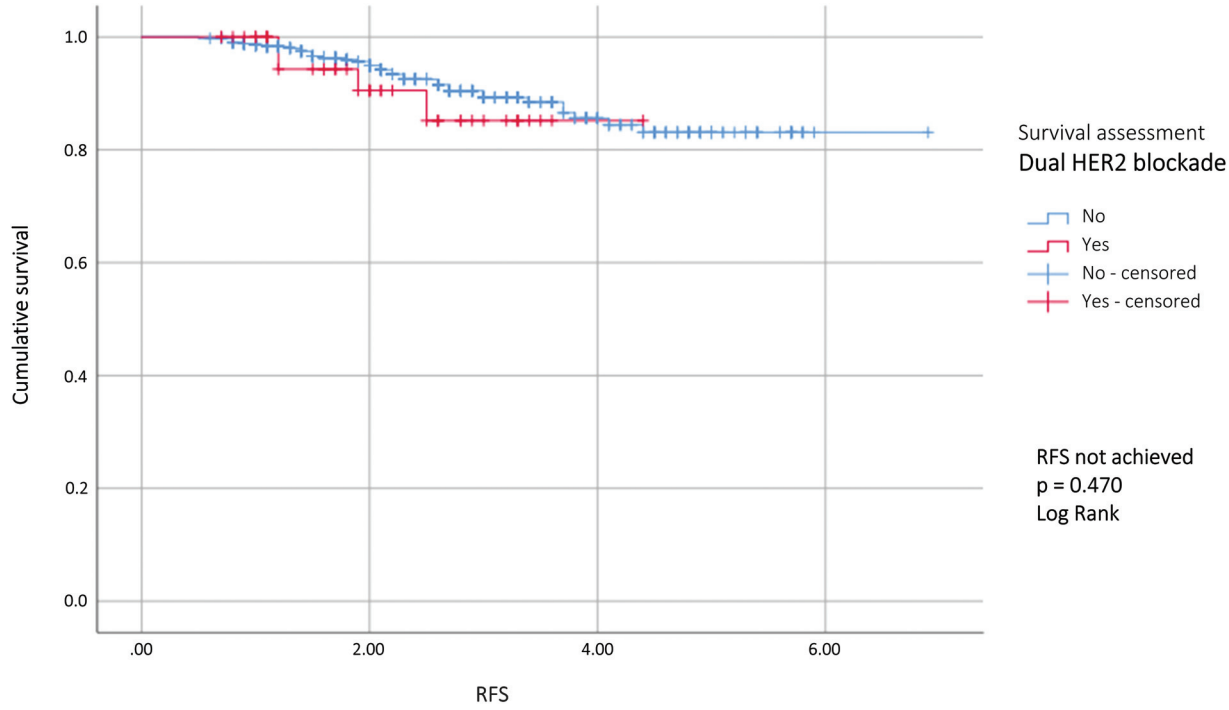

Fig. 3 Recurrence-free survival curve based on treatment (trastuzumab versus dual HER2 blockade).

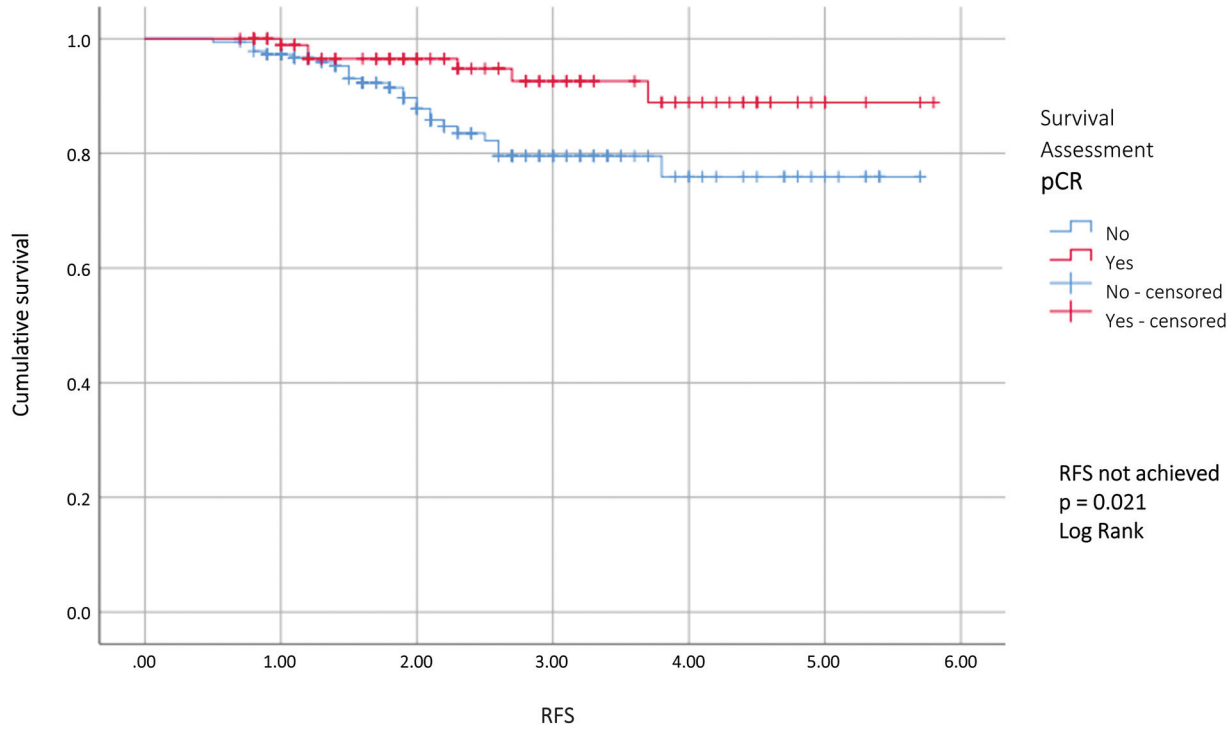

Fig. 4 Curve of recurrence-free survival curve according to pathological response.

of a review[13] of 87,969 Brazilian women with breast cancer based on cancer records mostly from Brazilian public health hospitals, support this conclusion. In this series,[13] 58.9% of the patients had the disease in stages I or II, reflecting the high rate of late diagnosis among the general population.

Studies have shown[14] that the pCR rate after the neoadjuvant treatment with trastuzumab is almost double that of the neoadjuvant treatment without trastuzumab (35% versus 18%). As a result of the use of anti-HER2 therapy in the current study, we observed an increase in the pCR rate, despite the fact that the dual HER2 blockade did not show a

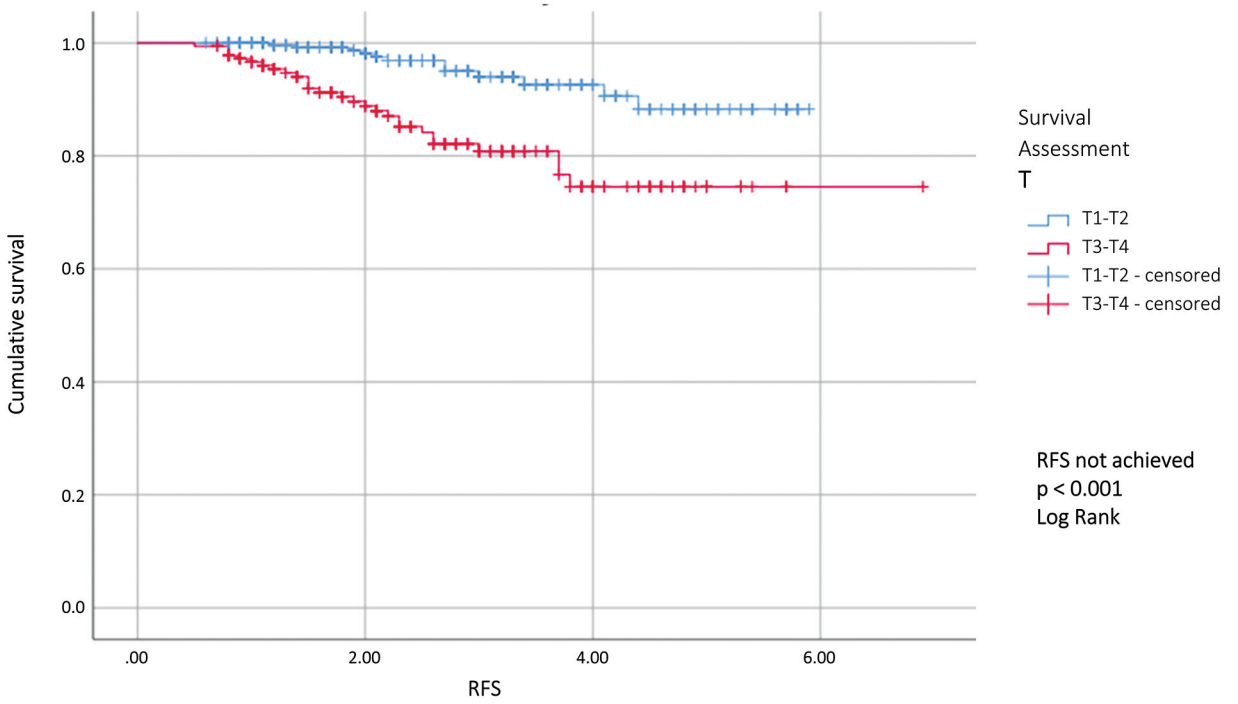

Fig. 5 Recurrence-free survival curve according to T-staging.

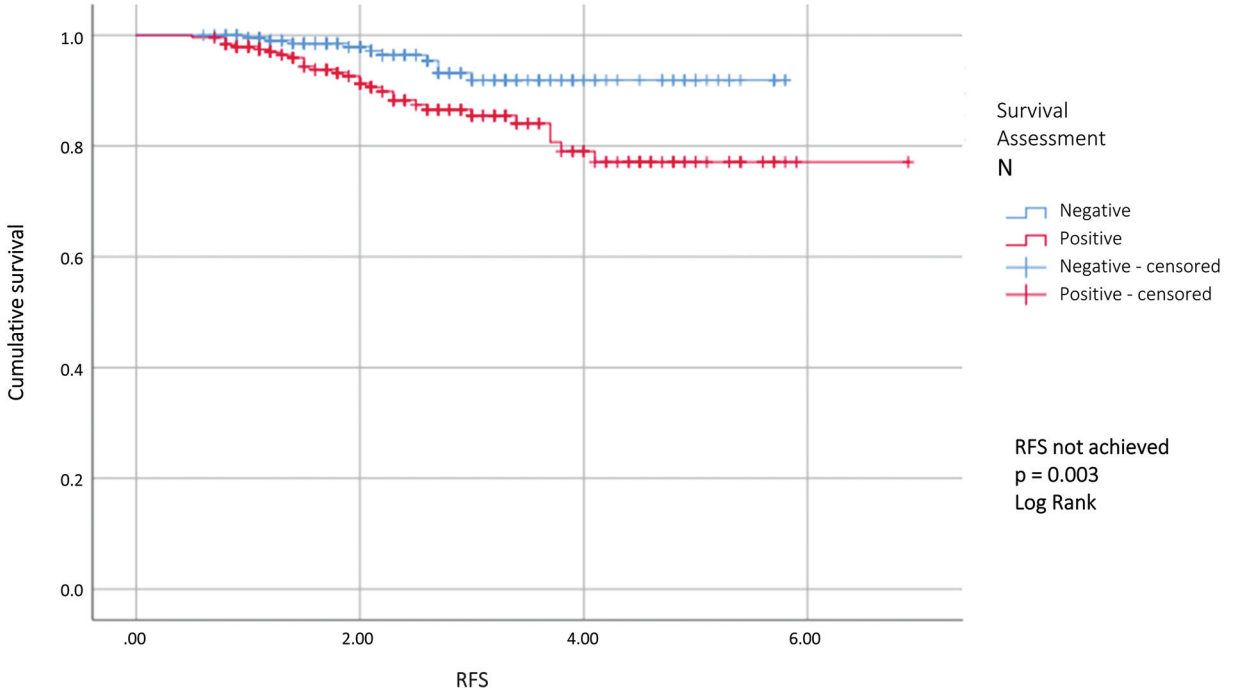

Fig. 6 Recurrence-free survival curve according to N-staging.

statistically significant increase in the pCR rate. This finding may be directly related to the small sample size (40 patients) in this subgroup.

The use of targeted anti-HER2 therapy may extend the survival of patients with HER2-positive early breast cancer. During the HERA study,[14] patients with HER2-positive breast cancer treated with neoadjuvant or adjuvant chemotherapy were compared to those who were observed for 1 or 2 years. In patients treated with trastuzumab for 1 year following adjuvant chemotherapy, the recurrence rate (particularly distant recurrences) decreased by approximately 50%.[14]

According to the NeoSphere study,[15] patients who received neoadjuvant pertuzumab, trastuzumab, and docetaxel showed a pCR rate that was significantly higher than the rate found among those who received adjuvant trastuzumab and docetaxel.

Table 3 Recurrence patterns of the study sample

Recurrence	Complete response rate	Partial response rate	*p*
No	95%	87%	0.043
Local and/or distant	5%	13%	
Recurrence	**Complete response rate**	**Partial response rate**	***p***
No	95%	87%	0.067
Local	2%	2%	
Distant	3%	11%	
Recurrence	**Complete response rate**	**Partial response rate**	***p***
No	97%	97%	0.905
Central nervous system	3%*	3%*	

Note: *Limited number of individuals.

Table 4 Effects of the dual HER-2 Blockade and trastuzumab in the study sample

Variables		Dual HER-2 blockade	Trastuzumab	*p*
CNS metastasis	Yes	2%	3%	0.867
	No	98%	97%	
Cardiotoxicity	Yes	2%	9%	0.106
	No	98%	91%	
Relapse	No	94%	92%	0.720
	Local	0%	1%	
	Distant	6%	7%	

Abbreviations: CNS, central nervous system; HER2, human epidermal growth factor receptor 2.

Several randomized clinical trials[16,17] have demonstrated that trastuzumab, along with adjuvant chemotherapy, increases disease-free survival (DFS) and OS in women with early breast cancer that expresses the *HER2* gene.

In 2012, a meta-analysis[16] of 8 studies with 12 thousand patients demonstrated that trastuzumab improved DFS (odds ratio [OR]: 0.60; 95% confidence interval [95%CI]: 0.50–0.71), regardless of the duration of the drug treatment or the chemotherapy regimen associated with it. In addition, the OS increased (OR: 0.66; 95%CI: 0.57–0.77),[16] and this increase was associated with the use of trastuzumab for 12 months, which is the current standard treatment (OR: 0.67, 95%CI: 0.57–0.80). Trastuzumab was associated with an adverse event of cardiotoxicity of 0.5 to 4.1%, primarily congestive heart failure, and a reduction in left ventricular ejection fraction.[16] The results of the present study indicated that 9% of the patients treated with trastuzumab monotherapy experienced cardiotoxicity (a reduction in the ejection fraction) compared to 2% of those treated with dual HER2 blockade therapy. The discrepancy may result from the small sample of patients who received dual HER2 blockade therapy.

The present study did not find a statistically significant difference between SUS patients and those in the private health care system in terms of RFS. It has been demonstrated that certain factors contribute to the disparity in breast cancer survival between public and private health care. The mortality rate in public health care hospitals is twice as high, highlighting the need for greater efforts to improve the quality, availability, and equity of breast cancer treatment services.

In the Brazilian context, the staging of HER2-positive breast cancer at diagnosis often reveals a tendency for diagnosis at more advanced stages, particularly among SUS patients. Studies show that, in middle-income countries like Brazil, the proportion of diagnoses at advanced stages is high due to barriers in accessing early diagnostic and treatment services. Rosa et al.[11] demonstrated that SUS patients are more frequently diagnosed with symptomatic disease and at advanced stages compared to patients with private health coverage. The literature indicates that approximately 50% of breast cancer cases in Brazil are diagnosed at stages III or IV. This scenario is supported by data from the current study, which showed that 42% of patients treated in the SUS were diagnosed with T3 to T4 tumors, while only 29% of private network patients presented such advanced stages. A significant limitation of the present study was the small number of patients who received dual anti-HER2 therapy (trastuzumab and pertuzumab). Only 1% of SUS patients and 59% of private network patients received this therapy. This inequality highlights a critical problem in accessing more advanced and effective treatments. The criteria to undergo dual blockade are as follows: 1) patients with positive lymph nodes (N+); and 2) patients who received neoadjuvant followed by

adjuvant treatment. In the current study, 55% of SUS patients and 43% of patients in the private healthcare system had positive lymph nodes. Additionally, 64% of SUS patients and 50% of private healthcare patients received neoadjuvant treatment. Based on these percentages, there would be approximately 126 eligible SUS patients and around 24 in the private healthcare system. Consequently, approximately 150 patients in total would be eligible for the dual blockade, considering both positive lymph nodes and neoadjuvant treatment. When we compare this to the actual number of patients who received the dual therapy, a significant disparity becomes evident, indicating a substantial underutilization of this potentially beneficial treatment within the public health system.

Conclusion

According to the findings of the present study, there was no difference between SUS patients and those in the private health care system in terms of pCR and RFS. Additionally, SUS patients were diagnosed with more advanced tumors, and most underwent the neoadjuvant treatment. Despite the limited number of individuals treated with HER2 dual blockade in the present study, there was an increase in the pCR rate when anti-HER- antibodies were used. However, anti-HER2 dual blockade did not cause a statistically significant increase in the pCR rate. The main limitations of the study were the size of the sample and the length of the follow-up (median of 28.8 months).

Author's Contributions

MPC: collection and assembly of data, conception and design, data analysis and interpretation, final approval of the manuscript, manuscript writing; VL: final approval of the manuscript and manuscript writing; and PAJ: data analysis and interpretation, final approval of the manuscript, and manuscript writing.

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Clinical Trials

None.

Conflict of Interests

The authors have no conflict of interests to declare.

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