ORIGINAL ARTICLE
https://doi.org/10.29289/2594539420230011

Five-year retrospective study of HER2+ breast cancer in a referral hospital in the state of Amazonas

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ABSTRACT

Introduction: Breast carcinoma is considered the most common malignancy in women, with a high incidence in Brazil and in the North region, surpassed only by non-melanoma skin cancer and cervical cancer. The HER2+ molecular subtype tends to grow and spread more quickly than other subtypes, resulting in the second worst outcome, behind only the triple-negative subtype. **Methods:** This was a retrospective, descriptive epidemiological study, using data from the medical records of 192 patients with HER2+ breast cancer treated at the Fundação Centro de Controle de Oncologia do Amazonas (FCECON), from 2014 to 2018. **Results:** The mean age of patients was 52±12 years. The predominant origin was Manaus. AM (53.1%). The most common education level was complete secondary education (36.5%) and the occupation was self-employed (37%). Most diagnoses were made in 2014 (23.4%). Regarding staging, the most common ones were stages IIIA and IIIB, both 20.83%. Concerning treatment, all patients (100%) underwent radiotherapy and chemotherapy, and surgery in 80.2%, including mastectomy (58.33%) and quadrantectomy (21.87%). Local recurrence and distant metastasis were both found in 7.3% of patients. With respect to the outcome, patients in follow-up predominated (53.6%), while mortality rate was 0.5%. **Conclusions:** The series demonstrated that patients with HER2 breast cancer present advanced staging and undergo neoadjuvant chemotherapy and surgery. The center in the present study is an institution that receives patients from several municipalities in the countryside of Amazonas and other states, and thus, many patients with advanced stages are cared for, since many such cities have no resources to perform mammography, compromising screening.

KEYWORDS: breast câncer; women; Amazonas.

INTRODUCTION

With the exception of non-melanoma skin cancer, malignant breast cancer is the cancer that most affects females throughout Brazil, with the exception of Amazonas and Amapa, states of the north region of the country, where it ranks second behind only cervical cancer. Annually, there are approximately 27.63 and 21.84 new cases of cervical cancer for every 100 thousand inhabitants in these two states respectively. According to data from the José Alencar Gomes da Silva National Cancer Institute (INCA) on breast cancer, 73,610 new cases were predicted in Brazil for the years 2023 to 2025, representing 30.1% of cancer cases, except for melanoma among women. Furthermore, for the state of Amazonas, it was estimated that there will be 500 new cases of breast cancer, of which 84% are predicted for the capital[1]

Breast cancer is a disease with diverse clinical and histopathological presentations, and therefore, it has treatments, procedures and prognoses that are directly influenced by immunohistochemistry (IHC) markers such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki67 (a proliferation index), along with assessment of tumor size, tumor grade and nodal status[2].

Among the subtypes of breast cancer, we will address the HER2-positive subtype, in which there is HER2 overexpression, resulting in a more aggressive subtype with a worse prognosis in the absence of targeted therapy[3,4].

Compared to 5 years ago, there are currently more options for treating a patient with HER2-positive early-stage and locally advanced breast cancer. The treatment consists of administering a drug that targets HER2, which aims to prevent cell growth and dissemination. In cases both with metastasis and localized tumors, monoclonal antibodies that attack HER2 are used, whether or not combined with chemotherapy[5,6].

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Conflicts of interests: nothing to declare. **Funding:** none.
Received on: 08/04/2023. **Accepted on:** 10/20/2023.

The different subtypes of breast cancer result in different forms of evolution. However, attention should be paid to the HER2 subtype, which tends to grow and spread faster than the other subtypes, in addition to having the second worst prognosis, behind only the triple negative subtype. However, through target-specific therapy, a marked improvement in the prognosis of these patients is observed[2].

Fundação Centro de Controle de Oncologia do Amazonas (FCECON), located in Manaus-AM, is a referral center for cancer treatment in the North region of the country and serves both the population of Amazonas and patients referred from other states[7]. Analysis of the clinical profile of patients treated at the institution and the various therapies frequently used make it possible to anticipate future problems and adequately qualify care. The present study aimed to identify the clinical and epidemiological profile of women with HER2-positive breast malignancy in the institution described and how their treatment and follow-up are carried out.

METHODS

This was an observational epidemiological study of the retrospective descriptive type, carried out through a review of medical records of patients diagnosed with HER2 breast cancer treated at FCECON in the period from 2014 to 2018. The study was carried out in Manaus, the capital of Amazonas.

The medical records of 192 breast cancer patients were analyzed, where 100% of patients were diagnosed as HER2-positive. Recruitment was carried out through the analysis of reports issued by the Department of Pathological Anatomy at FCECON, where the patients were treated from 2014 to 2018. For this reason, the sample size calculation for the study was not carried out.

As a selection criterion, patients aged over 18 years, female and with care provided within the period from 2014 to 2018 were included. On the other hand, an exclusion criterion was the case of medical records not properly completed.

Therefore, we included patients diagnosed with breast cancer (primary) who had already undergone anatomopathological and immunohistochemical studies, thus evaluating the HER2-positive molecular classification. The results had the scores: 0, 1+, 2+ or 3+. If the results were 0 or 1+, the cancer was HER2- (negative). If the score was 2+, the HER2 status of the tumor was not conclusive, requiring fluorescence in situ hybridization testing. However, if the result was 3+, the cancer was HER2+ (positive)[8].

Breast cancer staging of the patients treated in this study was based on diagnoses made up to 2018, and thus, it was done based on the different groupings possible by the Tumor-Lymph Node-Metastasis (TNM) system. As of 2018, through the American Joint Committee on Cancer[1] update, the TNM-8 system is used, which includes prognosis. Currently, part of the assessment is therefore HER2 expression, tumor grade (divided into grades I, II and III according to the level of cellular differentiation), and ER and RP, as well as the inclusion of genomic tests[9].

The variables evaluated in the study were: age, origin, education level, occupation, body mass index (BMI), date of diagnosis, staging, treatment used, recurrence and outcome. The classification regarding the BMI is based on the formula weight (kg)/height (m) squared used by the Ministry of Health. The stratification of the result is done following the values: below 18.5 kg/m^2 – underweight; between 18.5 and 24.9 kg/m^2 – normal weight; between and 29.9 kg/m^2 – overweight; 30 to 34.9 kg/m^2 – grade I obesity; 35–39.9 kg/m^2 –grade II obesity; and greater than or equal to 40 kg/m^2 – grade III obesity.

We followed the ethical precepts of Resolution No. 466/2012 of the National Health Council (CNS), respecting the confidentiality of the participating subjects. The data were stored anonymously, without any nominal identification or other information that would allow the participants to be identified. The project was approved by the Research Ethics Committee of the Federal University of Amazonas (UFAM), under Approval No. 3.729.179.

Statistical analysis was conducted using the software R version 3.5.3 (R Core Team10 (2019). R: a language and environment for statistical computing[10].

To verify the normality of the patients' age, the Shapiro-Wilk test was considered at a significance level of $p < 0.05$ and a 95% confidence interval. The test provides us with evidence of symmetry of ages around the mean age.

RESULTS

When evaluating the epidemiological profile of the patients included in our study, it is possible to observe that the mean age was 52±12 (SD) years (Table 1) – which followed a normal (symmetric) distribution, with p=0.3718. Still according to Table 1, more than half (53.1%) of the patients came from Manaus.

The majority of patients had completed high school (36.5%). Furthermore, it is important to note that more than 60% were self-employed or housewives, and if we consider domestic workers, this percentage exceeds 70%. The occupation indicated as "Other" represents patients who were: retired (1), baby-sitter (1), accountant (1), public defender (1), nutritionist (1) and cashier (2) (Table 2).

Regarding the date of diagnosis of the patients, the majority were diagnosed between 2014 and 2016, with the years 2014 and 2015 being those with the highest records of diagnoses — the two years together accounted for around 46% of the total, as illustrated in Figure 1. It is worth noting that 22 (11.4%) patients did not have a recoreded diagnosis date, and therefore, they were not included in the graph.

Regarding staging, the most frequent stages were IIIA and IIIB, both representing approximately 21% of the patients. However, it should be noted that 23 (almost 12%) patients did not have a record of staging (Figure 2).

Table 3 presents a summary regarding the surgical treatment performed, as well as the record of recurrence or not, and the outcome of patients followed up at FCECON.

Around 80% of patients underwent surgery — with mastectomy being the most frequent approach — and of these, approximately 22% underwent quadrantectomy. Only 38 patients did not undergo a surgical procedure.

Recurrence was observed in 28 patients (14.6%), with 14 local recurrences and 14 distant metastases.

Table 1. Sociodemographic profile of patients with HER2 breast cancer treated at FCECON between 2014 and 2018.

Description	Patients n=192 (%)
Age	
Minimum	22
First quartile	44
Mean±standard deviation	52.1 ± 11.8
Third quartile	59
Maximum	84
Body mass index	
Underweight	3 (1.6)
Normal	45 (23.4)
Obesity 1	30 (15.6)
Obesity 2	11 (5.7)
Obesity 3	7 (3.6)
Overweight	75 (39.1)
NA	21 (10.9)
Origin	
Countryside AM	63 (32.8)
Manaus AM	102 (53.1)
Other state	24 (12.5)
NA	3 (1.6)

NA: indicates "not applied" response; that is, no response was obtained from the patient.

Table 2. Occupation profile of patients with HER2 breast cancer treated at FCECON between 2014 and 2018.

Description	Patients n=192 (%)
Education level	
Literate	1 (0.5)
Iliterate	10 (5.2)
Complete elementary school	29 (15.1)
Incomplete higher education	1 (0.5)
Incomplete elementary school	42 (21.9)
Complete high school	70 (36.5)
Incomplete high school	11 (5.7)
Complete higher education	16 (8.3)
Incompleto higher education	6 (3.1)
NA	6 (3.1)
Occupation	
Administrator	5 (2.6)
Independent	71 (37)
Compary assistant	13 (6.8)
Household	52 (27.1)
Domestic	18 (9.4)
Others	7 (3.6)
Teacher	6 (3.1)
Nursing tech	5 (2.6)
NA	15 (7.8)

NA: indicates "not applied" responses; that is, those for which it was not possible to obtain information from the patients.

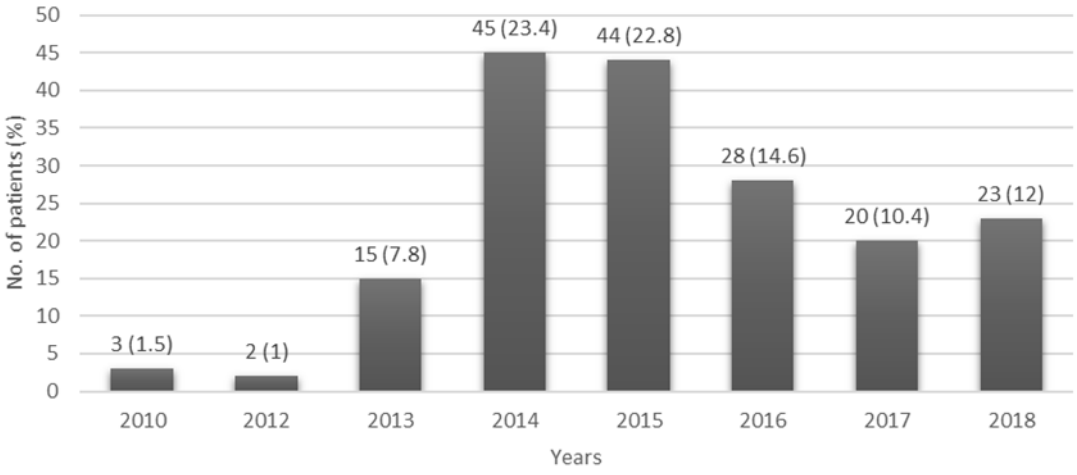

Figure 1. Distribution of patients according to date of diagnosis with HER2-type breast cancer, treated at FCECON between 2014 and 2018.

It is important to note that more than half of the patients were still being monitored, and around 14% were undergoing treatment, at the time of writing. Among the medical records analyzed, there was one death record. On the other hand, 30 patients were discharged — representing around 15.6% of participants.

DISCUSSION

Yang et al.[11], through a retrospective analysis of data from 168 participants from a prospective study carried out with patients with HER2-positive tumors in Shanxi province, China, demonstrated that the average age at the time of surgery was 52 years. In the case series of Oliveira et al.[12], conducted a retrospective analysis in the city of Vassouras (RJ) and observed that the average time was 57.4 years, with a predominance of the age group of 50 to 59 years. Both studies were corroborated by finding of the present study, as the average age of the patients at surgery was 52 years.

From this perspective, FCECON's 2015 Annual Management Report[13] notes the occurrence of 124 cases of breast cancer in 2015 in Amazonas, with 25.8% in the 50-59 age group.

It is also noted that the dates of diagnosis of the patients in this study were between the years 2010 and 2018, with a higher prevalence between 2014 and 2016, with 2014 being the year with the highest diagnosis record with 23.4% .

In another descriptive and quantitative study, with 32 women in 2016, Reis et al.[14] outlined the sociodemographic aspects of the women cared for, observing a predominance of those completing high school (65.6%) and referring to domestic workers in 53.1% of cases; agreeing with the data from the present study, with a prevalence of those finishing high school (36.5%) and disagreeing with the prevalence of self-employed occupations (37%), given that domestic workers represented 9.4%.

In 2020, Motoki[15], through a cross-sectional clinical study with 189 women, highlighted the profile in terms of BMI, which was 28.5±5.5 kg/m² (overweight). Furthermore, Pinheiro and Monteiro[16], in an integrative literature review with six studies, identified worse survival in two patients with higher BMI, in agreement with the present study, in which the prevalence of overweight was 39.1% of the patients evaluated.

The BMI data are important, as it has already been described that patients with tumors that are hormone receptor positive (HR+), overweight or obesity were generally associated with a decreased probability of achieving a pathological complete response (PCR) independently of other clinical variables, including planned surgery, lymph node status and tumor size[17]. Furthermore, specifically in relation to neoadjuvant chemotherapy, some retrospective studies have already pointed out that obesity can, independently and negatively, affect PCR, which is a favorable prognostic marker in HER2-positive patients[17-19].

In the results of the present study, the majority of patients (53.1%) were residents of Manaus, while the countryside showed 32.8% of cases; this finding agreed with the observational study carried out by Lucia with 364 patients, 100 of which were considered HER2-positive, where it was found that living in an area far from large urban centers may have a correlation with a lower incidence of HER2 breast cancer (p<0.0099)[20].

Lucia[20] also points out that breast cancer of the HER2+ molecular subtype more frequently has a stage II at the time of diagnosis in that institution, when compared to HER2-; conflicting with the staging found in this study, with a higher incidence of stages IIIA and IIIB, both with 23.5% at the time of diagnosis.

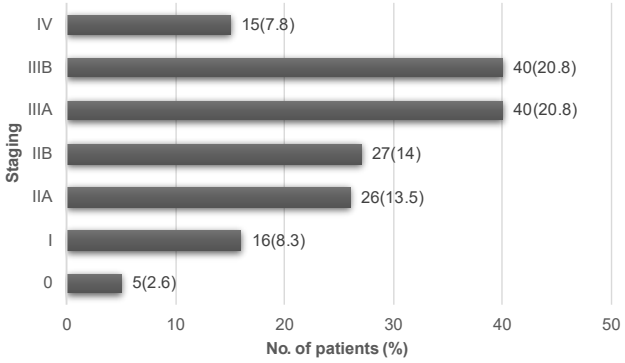

Figure 2. Distribution of staging frequencies of patients with HER2 breast cancer treated at FCECON between 2014 and 2018.

Table 3. Description of clinical data related to surgery. recurrence and outcome of patients with HER2 breast cancer treated at FCECON between 2014 and 2018.

Description	Patients n=192 (%)
Surgery	
Mastectomy	112 (58.3)
No	38 (19.8)
Quadrantectomy	42 (21.9)
Recurrence	
Local	14 (7.3)
Metastasis	14 (7.3)
No	164 (85.4)
Outcome	
Treatment abandonment	12 (6.2)
Follow-up	103 (53.6)
Awaiting surgery	4 (2.1)
Discharge	30 (15.6)
In treatment	27 (14.1)
Death	1 (0.5)
Ongoing treatment	3 (1.6)
Palliative treatment	12 (6.2)

We found that the majority of patients (69.27%) had locally advanced clinical staging at diagnosis, while only 7.81% had distant metastasis and where only 10.93% had initial disease. These results corroborated the retrospective study carried out by Soares et al.[21] in 2018, with 753 patients, which showed a metastasis rate of 14.4% in patients with HER2-positive breast camcer.

Reis et al., through a descriptive study, pointed out that the treatment used was mastectomy with lymph node dissection (53.1%), in addition to treatment with combined chemotherapy, radiotherapy and hormone therapy (75%). Furthermore, in the same study, 87.5% of those analyzed did not show metastasis, therefore obtaining similar data as ours[14].

Dagnoni et al., in a retrospective study with 135 women, found that 123 patients underwent surgery, where 71 (52.59%) had a quadrantectomy and in 52 (38.51%) a mastectomy[22]. This is in line with the results of the present study with 192 patients, where 112 (58.33%) underwent mastectomy and 42 (21.87%) quadrantectomy.

Regarding the study outcome, the highest prevalence was patients still being monitored (53.6%) and the lowest prevalence was death (0.5%). Furthermore, 6.2% are undergoing palliative treatment.

The clinical profile was a prevalent diagnosis in 2014 (23.4%), with stage IIIA and IIIB cancer, both 20.83%, as well as treatment with radiotherapy and chemotherapy (100%); and almost all patients underwent surgical treatment (80.2%), with a predominance of mastectomy (58.33%). Furthermore, the large majority had no recurrences (85.4%) and a 7.3% rate of distant metastasis. The majority of patients were still being monitored at the end of the study (71.6%).

It is worth highlighting that the data presented reveals and alerts us to some facts: the center analyzed in the present study is an institution that receives patients from different municipalities in the countryside of Amazonas and other states, thus, many patients with advanced stages are treated, since in many cities there are no resources for mammograms, compromising screening. More large-scale, multicenter and prospective studies are needed to obtain more accurate information. Still, our study presented results consistent with the literature, mainly during the analysis period, which allowed a comparative and statistical analysis of the patients' profile.

CONCLUSIONS

The epidemiological design of patients with breast cancer of the HER2+ subtype treated at FCECON from 2014 to 2018 was an average age of 52 years. The majority came from Manaus (53.1%) and had completed high school (36.5%). The prevalence of overweight was also found in 39.1% of patients, while the most prevalent occupation was self-employed (37%).

AUTHORS' CONTRIBUTIONS

LGOS: Investigation, Methodology, Writing – original draft. HFBESAP: Conceptualization, Project administration, Supervision, Writing – review & editing. DSM: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. LRMA: Data curation, Formal analysis, Investigation, Methodology. LALC: Data curation, Formal analysis, Investigation, Methodology.

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