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Histopathological predictors of response to treatment in patients with hormone receptor-positive her2-negative breast cancer. A single-center study

Cristina Elisa Cabrera Mañay[1], **Tannia Mariella Rivera Rivera**[2]

1. Postgraduate in Internal Medicine, Postgraduate Faculty, Universidad de Especialidades Espiritu Santo, Samborondón- Ecuador.
2. Pneumology Service, National Oncology Institute "Dr. Juan Tanca Marengo," Society for the Fight Against Cancer, Solca, Guayaquil, Ecuador.

***Correspondence:**

c.cabrera@uess.edu.ec

Address: V48M+MH Samborondón. Av. Samborondón 5, Samborondón. Guayaquil. CP: 092301. Edificio de posgrado. Universidad de Especialidades Espíritu Santo. Teléfono [593] (04) 500-0950. Ext 1021.

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Abstract

Introduction: One in every 18 women develops breast cancer throughout her life, which is the leading cause of death from cancer in women. The purpose of the present study was to establish the predictive value of the histopathological factors present in malignant breast tumors positive for the hormone receptor Her2 in a group of patients in an oncology reference center.

Methodology: This longitudinal study was carried out at the National Oncology Institute" Dr. Juan Tanca Marengo" in Guayaquil, Ecuador. The inclusion period was from 2007 to 2009, with an observation period until December 2020. With a nonprobabilistic sample, women with hormone-positive Her2 Neu-negative breast cancer who had received adjuvant treatment during a follow-up period were included. Demographic, clinical, tumor-related, TNM classification and survival variables were measured. A descriptive univariate analysis of the sample is performed, a bivariate analysis comparing the group of deceased patients with the group of living patients; a correlation analysis between variables in scale; a survival analysis; and a Cox regression is presented to predict survival based on the variables.

Results: A total of 105 patients, 54.1 ± 11.4 years old, entered the study. A total of 58.1% of cases were in the early stage, and 41.9% were in the locally advanced stage. Overall survival (OS) was 67.6% at 14 years, and progression-free survival (PFS) was 59.05%. Hormone blocking therapy was associated with PFS (R=0.544, P<0.01) and OS (R=0.399, P<0.05). Lymph node involvement in stage N0 had a PFS of 11.9 ± 0.4 years; lymph node involvement in stage N3 was 6.8 ± 1.6 years (P<0.01). The Cox regression model to predict progression-free or disease-free life was statistically significant with hormone-blocking therapy (R^2=0.607, P <0.001).

Conclusion: Hormone blockade therapy maintained for more than five years positively impacts the survival of patients with hormone-positive Her2 Neu-negative breast cancer.

Keywords:
DeCS: breast neoplasms, ErbB-2 receptor, survival analysis, regression analysis, tamoxifen.

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Introduction

One in 18 women develops breast cancer throughout her life, the leading cause of cancer death in women [1]. Seventy-five percent of these patients are hormone receptor-positive [2], with a more favorable prognosis up to the first seven years after diagnosis, after which the risk of relapse is greater than that of subtypes whose hormone receptors are negative [3]. The human epidermal growth factor receptor (HER2) gives the tumor a more aggressive behavior [4].

The natural course of breast cancer goes beyond the expression of hormone receptors. It includes a series of molecular markers that confer a wide tumor heterogeneity that would explain why there are differences in recurrence and survival rates in patients within the same group [5], and changes in cell subtype have even been reported in the same metastatic tumor.

Longitudinal studies establish the actual pattern of behavior in this particular cell subtype of patients with positivity for hormone receptors (HR) and negativity for Her2. Receptors, which have changed the therapeutic approach in breast cancer depending on the benefit of individualized treatments, are currently based on genetic signatures [6]. The report of the status of the hormone receptors (HR) and the Her2 receptor helps to subtype groups with similar results and therapeutic response rates; however, other traditional pathologic parameters, such as favorable histologic type, size, lymph node status, and Nottingham grade, have shown clinical relevance in early-stage cancers [7], which is mainly relevant for the most common subtype. Breast cancer is positive for estrogen receptors and negative for HER2, which, despite having a better prognosis, presents a constant risk of late recurrence [8].

Endocrine therapy is the treatment of choice in hormone receptor-positive patients, even in the presence of metastatic disease, unless there is a visceral crisis, with a level of evidence I/A according to the 5th ESO-ESMO international consensus guideline for advanced breast cancer [9]. However, despite the significant reduction in recurrence rates during and after hormone therapy, breast cancer recurrences continue to occur consistently for up to 20 years after diagnosis [10]. The cumulative risk for contralateral breast cancer after the same period has been estimated at 40% for BRCA1 carriers and 26% for BRCA2 carriers [11]. Several gene expression panels have been investigated in HR-positive breast cancer, providing predictions about the potential benefit of chemotherapy beyond endocrine therapies [12]. However, it represents high costs compared to traditional immunohistochemistry.

This research aims to establish the predictive value of the histopathological factors present in malignant breast tumors positive for the hormone receptor Her2 in a group of patients treated at a regional reference center.

Materials and methods

Study design

Descriptive, longitudinal, and retrospective study.

Study area

The study was carried out in the clinical oncology department of the National Oncological Institute" Dr. Juan Tanca Marengo" of the Society for the Fight Against Cancer, SOLCA -

Guayaquil in Ecuador. The inclusion period was for patients diagnosed from January 1, 2007, to December 31, 2009. The survival observation period was from January 1, 2010, to December 31, 2020.

Universe and sample

The population was made up of patients admitted to the hospitalization of the institution. The sample calculation was nonprobabilistic for census-type convenience, in which all possible cases that can be analyzed are included.

Participants

Patients of legal age were included with breast cancer, hormone-positive Her2 Neu negative with histopathological confirmation, who had received adjuvant treatment during a follow-up period. Cases in which data were incomplete were excluded from the analysis. Patients who had presented a previous diagnosis of breast cancer were also excluded, the current disease being classified as local recurrence, patients with a history of previous malignant neoplasms, the current disease being classified as the second primary, and patients with a history of previous malignant neoplasms, the current disease being classified as the second primary, patients with the presence of multiple synchronous primary malignant neoplasms detected simultaneously or up to 6 months after the primary tumor, patients with immunohistochemistry with the absence of estrogen and progesterone receptors, patients with immunohistochemistry with positivity for the her2-Neu marker (++ or +++), patients whose cell subtype is unknown or triple negative, and patients who have received neoadjuvant treatment.

Variables

The following variables were included: age, menopause, laterality, tumor size, primary tumor, number of lymph nodes, lymph node involvement, histological type, grouped histological grade, infiltration, estrogen receptor, progesterone receptor, KI67, anatomical stage, prognostic stage, surgery, chemotherapy, radiotherapy, hormone therapy, and hormone therapy time. Progression-free survival, overall survival, progression, or death.

Procedures, techniques, and instruments.

The data were collected from the clinical history in a form designed exclusively for that purpose. The institutional electronic system was used for case investigation. The database was coded with serial numbers, thus protecting the confidentiality of the information and identity of the patients.

Bias avoidance

To guarantee the reliability of the information, the researchers were trained in data collection. A double checklist was used to include all cases. The data were validated and curated by the researchers CECM and TMRR. To avoid possible interviewer, information, and memory biases, the data were guarded at all times by the principal investigator with appropriate guidelines and records. Observation and selection bias was avoided by applying the participant selection criteria.

Statistical analysis

Initially, a descriptive univariate analysis of the sample is performed. Subsequently, a bivariate analysis is performed, comparing the group of deceased patients with those of living patients. A second analysis of the correlation between variables in scale and survival analysis is presented. Finally, Cox regression is presented to predict survival based on the variables. The statistical package used was SPSS version 22.0 for PC (IBM, Armonk, USA), licensed to the researchers.

Results

Study participants

The study included 105 analyzable cases (Figure 1). The majority of excluded cases are Her2+.

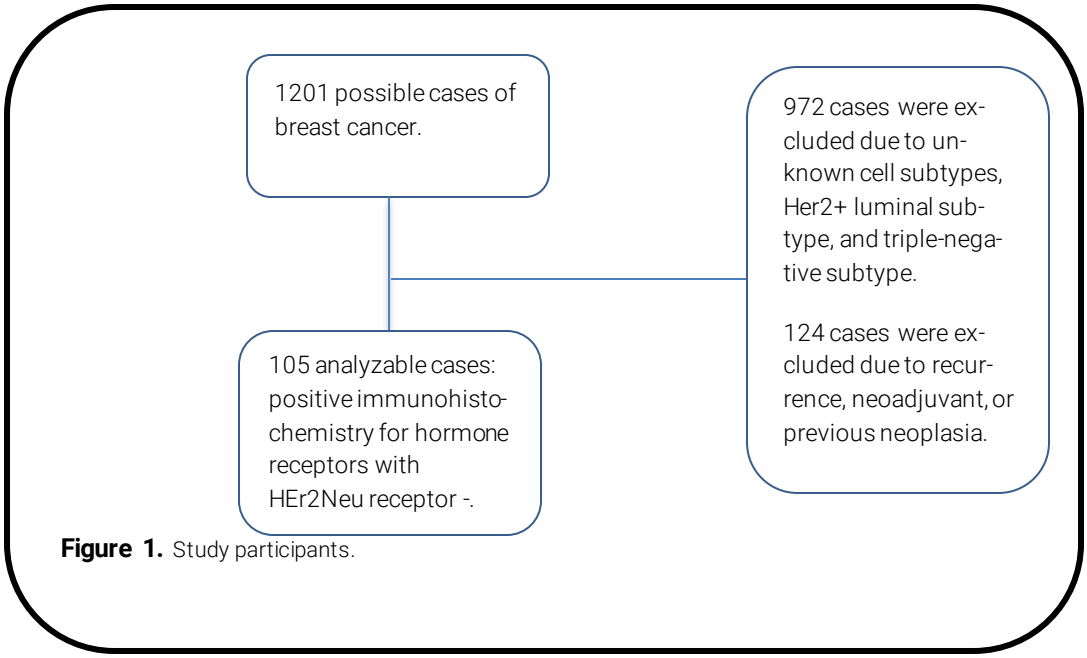

Figure 1. Study participants.

Sample characterization

The average age was 54.05 ± 11.35 years. A total of 31.4% of patients were in the range of 45 to 54 years of age; at the time of diagnosis, 58.10% of the patients were menopausal. Tumor measurement was 3.02 ± 1421 cm, with a range of 20 to 50 mm (T2) in 59% of cases.

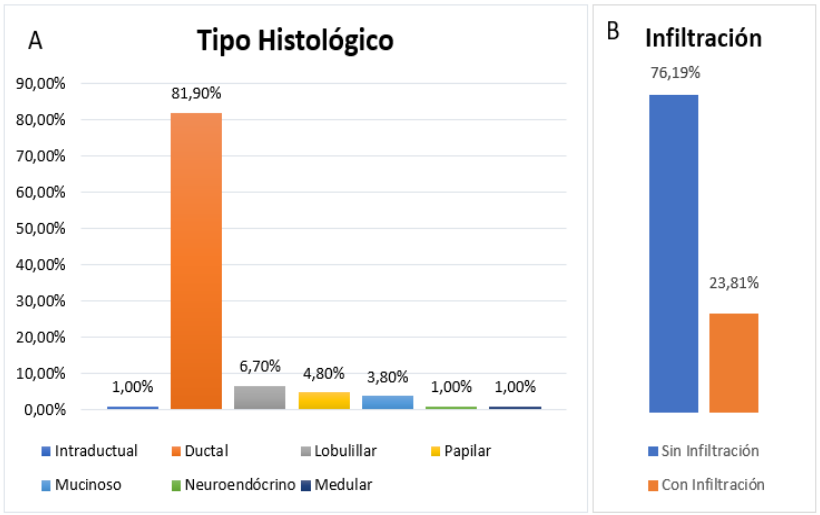

Figure 2. Prevalence of histological types.

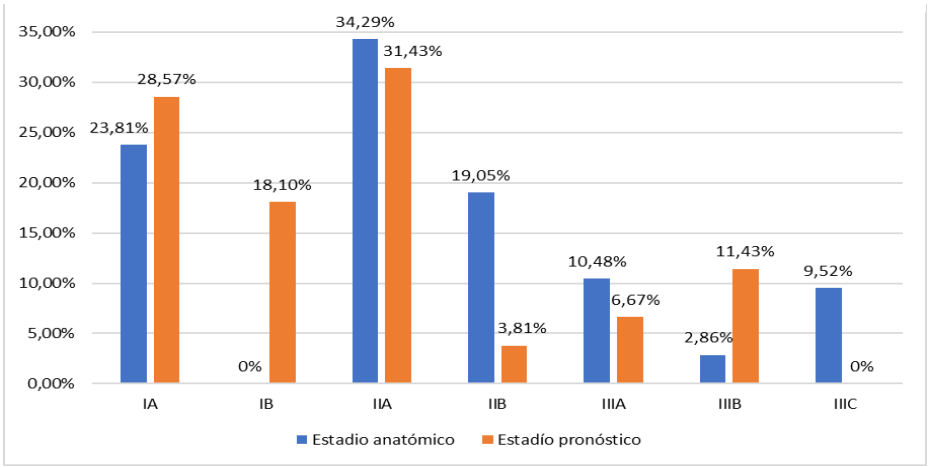

Figure 3. TNM classification of patients with breast cancer was included in the study.

Ninety-one percent of the cases presented tumors smaller than 5 cm at the time of surgery. A total of 45.7% of the tumors presented in the left breast. The median number of involved nodes was 3 (IQR 0-40); N0 classification was in 56.19% of cases, and N1 was in 23.81%. Regarding the histological type, the most frequent is infiltrating ductal carcinoma. Vasculolymphatic, skin, and adipose tissue infiltration were found in 23.81% of the patients (Figure 2).

A total of 78.10% of the cases were positive for the estrogen receptor, 86% for the progesterone receptor, and 27.62% for the Ki67 proliferation marker. By histological grade, most corresponded to anatomical/prognostic stage IIA (Figure 3).

Modified radical mastectomy was performed in 74.3% of cases, and conservative surgery was performed in 25.7% of cases. They received adjuvant therapy such as chemotherapy in 82.9% of cases, and 60% received radiotherapy. A total of 62.9% received adjuvant hormone therapy, standard hormone therapy was 44.8%, and extended hormone therapy was 18.1% of patients who completed at least five years of hormone block therapy; this was done with the selective estrogen receptor modulator tamoxifen or with aromatase inhibitors (Table 1).

Table 1. Bivariate analysis between the outcome (alive/deceased) and clinical-

Variable	Progression-free survival			Overall survival		
	Alive	Death	P.	Alive	Death	P.
Primary tumor						
T1	22.7%	9.5%	0.087	24.8%	7.6%	0.038
T2	33.3%	25.7%		38.1%	21.0%	
T3	2.9%	2.9%		4.8%	1.0%	
T4	0%	2.9%		0%	2.9%	
Lymph node involvement						
N0	37.1%	19.1%	0.055	43.8%	12.4%	0.016
N1	14.3%	9.5%		15.2%	8.6%	
N2	5.7%	4.8%		5.7%	4.8%	
N3	1.9%	7.6%		2.9%	6.7%	
Histological Grade						
Grade 1	11.4%	4.8%	0.291	14.3%	1.9%	0.047
Grade 2 or 3	47.6%	33.3%		53.3%	30.5%	
Infiltration						
Absent	50.5%	25.7%	0.007	58.1%	18.1%	0.001
Present	8.6%	15.2%		9.5%	14.3%	
Anatomical stage						
AI	18.1%	5.7%	0.065	20.0%	3.8%	0.045
BI	0%	0%		0%	0%	
IIA	21.0%	13.3%		23.8%	10.5%	
IIB	10.5%	8.6%		13.3%	5.7%	
IIIA	6.7%	3.8%		6.7%	3.8%	
IIIB	1.0%	1.9%		1.0%	1.9%	
IIIC	1.9%	7.6%		2.9%	6.7%	
Prognostic stage						
AI	21.0%	7.6%	0.107	23.8%	4.8%	0.031
BI	9.5%	8.6%		11.4%	6.7%	
IIA	20.0%	11.4%		21.0%	10.5%	
IIB	1.9%	1.9%		3.8%	0%	
IIIA	3.8%	2.86%		3.8%	2.9%	
IIIB	2.9%	8.6%		3.8%	7.6%	
Hormone therapy						
None	14.3%	22.9%	0.04	16.2%	21.0%	0.001
Standard	32.4%	12.4%		36.2%	8.6%	
Extended	13.4%	5.7%		15.2%	2.9%	
Hormone block time						
<5 years	14.3%	22.9%	0.001	16.2%	21.0%	0.001
>5 years	44.8%	18.1%		51.4%	11.4%	

The correlation analysis is presented in table 2. The variable most correlated with overall and progression-free survival is the use of hormonal blocking therapy. There is an inverse correlation between radiotherapy, number of involved lymph nodes, infiltration, age, and the presence of estrogen receptors with survival.

Table 2. Association analysis between survival and study variables.

Variable	Survival time	
	Progression-free survival	Overall survival
hormone blocking therapy	**0.544****	**0.399***
Radiotherapy	**-0.256****	**-0.278****
Number of involved nodes	**-0.227***	**-0.242***
Infiltration	-0.184	**-0.328****
Age group	-0.125	**-0.251***
estrogen receptor	-0.121	**-0.221***
Tumor measurement range	-0.092	0.008
primary tumor	-0.098	-0.003
type of Surgery	-0.096	0.025
Histological Grade	-0.092	-0.097
histological type	0.063	-0.053
progesterone receptor	-0.079	-0.084
anatomical stage	-0.161	-0.142
prognostic stage	-0.138	-0.056
Laterality	-0.079	-0.11
Chemotherapy	0.168	0.145
menopausal status	-0.003	-0.106
KI67	0.078	0.171

**P value<0.01; *P value <0.05. Spearman's nonparametric correlation.

Bivariate analysis

No relationship was found between PFS and OS with the variables age, menopausal status, status of hormone receptors for estrogen or progesterone, or the Ki67 receptor. The variables that were statistically associated are presented in Table 1.

Survival analysis

The OS at 14 years of follow-up was 67.6%, less than the median survival at the end of the study. The PFS was 59.05%. The median progression-free time was 13.31 ± 0.75 years. There were 32 events (30.48%) of local or distant recurrence, with a median time to recurrence of 13.2 years, with a recurrence rate of 15% at five years and 25% at ten years. The time to relapse was longer in N0 patients without lymph node involvement (Table 3 and Figure 4).

Table 3. Association analysis between survival and study variables.

lymph node involvement	Survival time	
	Progression-free survival	95% CI
N0	11.847 ± 0.395	11.074 -12.621
N1	11.497 ± 0.893	9.748 -13.247
N2	8.633 ± 1,572	5.552 -11.714
N3	6.830 ± 1,561	3.771 – 9.889
Global	11.141 ± 0.435	10.289 – 11.993

The estimate is limited to the longest recurrence time if censored. N0 vs. N3 *P* = 0.023

Regarding the classification by hormone block therapy, of the 105 patients during 14 years of follow-up, a total of 43 events of progression or death were recorded, of which 24 occurred in the group of patients who did not receive hormone therapy or whose hormone therapy Hormone blockade was less than five years and 19 events in the group of patients who completed at least five years with hormone blockade therapy. The median progression-free survival for patients without hormone blocking therapy or who did not complete the 5-year time frame was 6.3 years; for the group that completed five years or more, it was 13.2 years (Figure 5).

Prediction model for lifetime free of progression or disease.

Table 4 shows the Cox regression model to predict progression-free or disease-free life. The model was statistically significant (R^2=0.607, P <0.001); nonsignificant variables were eliminated from the model.

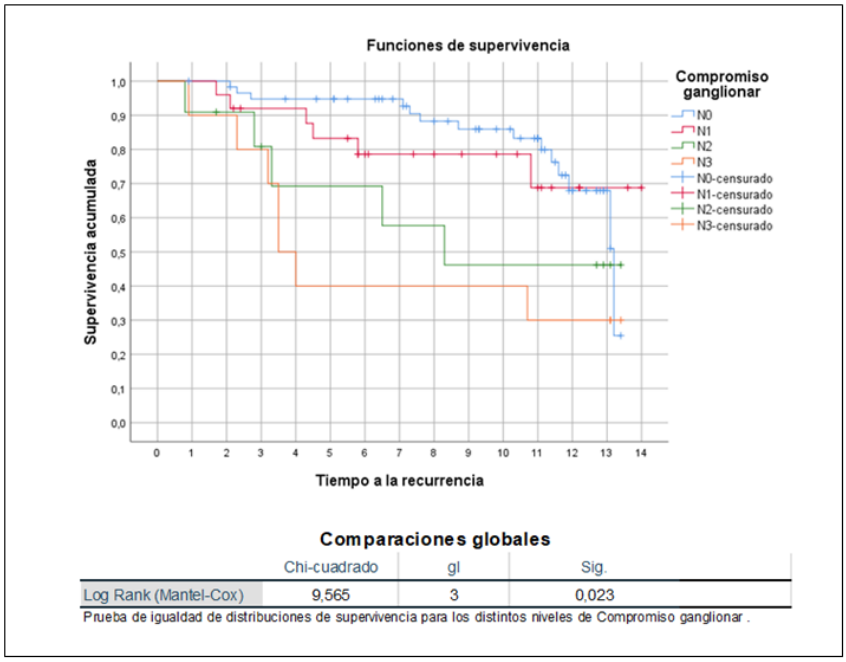

Figure 4. Recurrence time due to lymph node involvement. Kaplan-Meier plot.

Table 4. Progression-free survival time estimation model.

Lymph node involvement	Nonstandardized coefficient B.	Standardized coefficient Beta	Relative weight	t	*P*
Constant	4,954			6,949	
LVI	-1,317	-0.168	-0.266	-1,385	0.174
HBT	3,185	0.607	0.640	5.01	0.001

LVI: lymphocytic vascular infiltration of the skin or adipose tissue. HBT: hormone-blocking therapy

Discussion

Two studies were conducted in populations with hormone receptor-positive and HER2-negative breast carcinoma with a large number of participants, the first with 5,342 and a predominance of 67% of age >50 years [13] and the second study with 3,198 and the median age of 56 years [14] had histologic grade 2 in 54% and 62%, respectively, and nodal stage N0 in 58% of both. With similar results to those obtained in the present investigation, where the mean age in the population was 54.05 ± 11.35, the most common histological grade was grade 2 in 62%, and in terms of lymph node involvement, the N0 number of nodes was 58.8%. In this study, ductal carcinoma comprised 81.9% and lobular carcinoma 6.7%.

The most common histological subtype reported in previous studies was ductal carcinoma in 74%, followed by lobular carcinoma in 13% [13]; the tumor size at diagnosis was 30 mm above the median reported by other studies in which the mean did not exceed 20 mm [14, 15].

A study in the United Kingdom in patients of all cell subgroups demonstrated a strong association between histological grade and progression-free survival, also finding a positive association between low tumor grades with smaller sizes of the primary tumor and the absence of involved nodes [16]. The present study differs from these results because it failed to demonstrate that histological grade was correlated or an independent predictor of progression-free survival or overall survival. There was no evidence of an association between histological grade and other histopathological characteristics, such as tumor size or lymph node involvement. Another study reported that the formation of tubules and the mitotic rate, which are values included in the estimation of the histological grade, are independent predictors of cancer-specific survival [17]; however, in the present investigation, these values were not considered since they were not reported in the pathological anatomy in the study period.

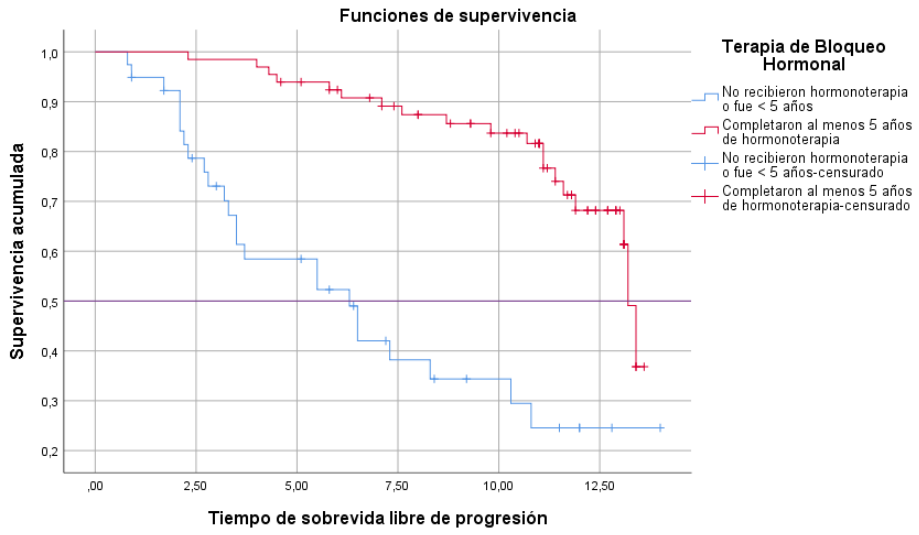

Figure 5. Progression-free survival time for hormonal blockade therapy.

A meta-analysis carried out in 64,196 patients concluded that the histological marker Ki-67 has an independent prognostic value in terms of overall survival in patients with breast cancer, associating it with a higher risk of death with a positivity cutoff of > 25%. Compared to lower expression rates [18]. The present study failed to demonstrate a correlation or association between the proliferative marker Ki67 and survival variables.

A meta-analysis that included 62,923 patients reported a constant risk of cancer recurrence up to 20 years after diagnosis despite having used five years of adjuvant endocrine therapy, correlating this risk with the original TN status, with risks ranging from 10 to 41%, depending on TN status and tumor grade [10]. The 14-year follow-up of the study patients allowed us to determine that the risk of recurrence for patients who completed five years of treatment remained latent until the cutoff date of the study, demonstrating a median progression-free survival of 13.2 years in those patients, unlike those who did not receive it for five years of treatment who reached a median progression-free survival of 6.3 years. Although a correlation was shown between the risk of recurrence and lymph node involvement, similar to the study above, it was impossible to establish the relationship between the risk of recurrence and tumor size.

A Chilean study in 130 patients found in its univariate analysis that tumor size, the proportion of metastatic lymph nodes examined, and the absence of hormone receptors were significant predictors of complete pathological response. These findings were not replicated in multivariate analyses. However, they support using cheap, classical biomarkers as predictive tools [19]. At the end of the study, once the survival prediction models were applied, the only variable that showed a high significance (P =0.001) was hormone blockade therapy, which presented a good correlation with PFS (R=0.607) and with OS (R=0.734), finding no predictive power in any of the histopathological factors studied; however, it can be concluded that there is a correlation between the microscopic variables lymphatic infiltration and the tumor grade with the survival of the patients as well as between the macroscopic variables primary tumor and lymph node involvement and overall survival.

Conclusions

The patients in the study presented in more than 80% of the cases an infiltrating ductal carcinoma of the breast, with a low expression of Ki67 in 27.62%, in its majority 95.24% with histological grades 1 and 2. There was a statistical association between the presence of infiltration and progression-free survival, as well as the histological grade and infiltration with overall survival. It was shown that the greater the lymph node involvement, the greater the risk of locoregional or distant recurrence. The time to occurrence of these events was 13.2 years for N0 patients and 3.5 years for N3 patients. In the survival prediction models, hormonal blockade and its duration greater than five years strongly correlated with progression-free survival and overall survival.

Abbreviations

PFS: progression-free survival.
OS: Overall survival.

Administrative information

Additional Files

The authors declare none.

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Author contributions

1. Conceptualization: Cristina Elisa Cabrera Mañay, Tannia Mariella Rivera Rivera.
2. Formal analysis: Cristina Elisa Cabrera Mañay.
3. Research: Cristina Elisa Cabrera Mañay.
4. Methodology: Cristina Elisa Cabrera Mañay.
5. Project administration: Cristina Elisa Cabrera Mañay.
6. Supervision: Tannia Mariella Rivera Rivera.
7. Validation: Tannia Mariella Rivera Rivera.
8. Visualization: Tannia Mariella Rivera Rivera.
9. Writing - draft or original: Tannia Mariella Rivera Rivera.
10. Writing - revision and editing: Cristina Elisa Cabrera Mañay, Tannia Mariella Rivera Rivera.

All authors read and approved the final version of the manuscript.

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Availability of data and materials

Data availability is available upon request to the corresponding author. No other materials were reported.

Statements

Ethics committee approval

It does not apply to observational studies with a review of databases or medical records.

Consent to publication

This does not apply to studies that do not publish explicit images such as CT scans, MRIs, and physical exam images.

Conflicts of interest

The authors declare that they have no conflict of interest or competence.

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