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Tumor-infiltrating lymphocytes in triple-negative and HER2-positive breast cancer: a current analysis

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ABSTRACT

Introduction: The assessment of tumor-infiltrating lymphocytes in breast cancer is strengthened as evidence points to the clinical relevance of this immunological biomarker, especially in triple-negative and HER2-positive subtypes. **Objectives:** To evaluate the prognostic value of tumor-infiltrating lymphocytes in patients with triple-negative and HER2-positive breast cancer subtypes, especially their association with pathological complete response and survival. **Methods:** A cross-sectional study was conducted at the Liga Norte Riograndense Contra o Câncer, Natal, Brazil, which included patients who underwent neoadjuvant chemotherapy from June 2013 to June 2018, in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines, obtaining a sample of 216 patients. **Results:** There was no statistically significant difference between the variables tumor-infiltrating lymphocytes (mild, moderate, and intense) and overall survival (p=0.52). It was observed that patients with intense tumor-infiltrating lymphocytes had a 100% five-year survival rate, although this data was not statistically significant. Variables such as the presence of metastasis (p=0.0024), clinical staging (p<0.0001), and local recurrence (p<0.0001) impacted overall survival. **Conclusions:** In this study, no association was demonstrated between the concentration of tumor-infiltrating lymphocytes and prognosis (overall and disease-free survival).

KEYWORDS: Breast cancer; neoadjuvant chemotherapy; tumor-infiltrating lymphocyte; immunohistochemistry.

INTRODUCTION

Breast cancer (BC) is the most common malignant neoplasm in the world, excluding non-melanoma skin cancer. In 2020, approximately 2.3 million people worldwide, mostly women, were diagnosed with the disease, and of these, 684,996 died[1]. For Brazil, an estimated 73,610 new cases of breast cancer were expected in 2023, with an estimated risk of 66.54 cases per 100 women[2].

Cancer cells have several genetic abnormalities that allow them to proliferate spontaneously and survive, but the surrounding environment (cancer microenvironment) also influences these cells and is involved in the intrinsic characteristics of cancer. The tumor's immunological environment influences not only the effects of immunotherapy, but also of other anticancer drugs and treatment outcomes[3].

The morphological assessment of tumor-infiltrating lymphocytes (TILs) in breast cancer is gaining prominence as evidence points to the clinical relevance of this immunological biomarker. Numerous recent clinical studies have evaluated the prognostic and predictive importance of TILs in breast cancer[4-6]. Salgado et al. They cited adaptive immunity mediated by T and B lymphocytes as the basis for effective and sustained antitumor responses[4]. Extensive tumor infiltration by cytotoxic CD8+ T cells was strongly associated with patient survival, as reported by Mahmoud et al.[5], and to the response to therapy, as reported by Seo et al.[7]

A more strongly targeted antitumor immune response against the broad range of breast cancer antigens would potentially have a greater likelihood of controlling cancer cells present in large primary tumors and metastases. This hypothesis is reinforced by Almendro et al.[8], which showed that the degree of lymphocyte infiltration is predictive of a better local response to neoadjuvant treatment and of the long-term disease control prognosis.

In triple-negative breast cancer (TN), the more stromal TILs a patient has at diagnosis, the better the outcome will be after adjuvant anthracycline-based chemotherapy[4]. Thus, according

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to Simon et al.[9], the results for the prognostic value of TILs in TN breast cancer are considered high evidence. However, given the lack of prognostic information for patients with TN breast cancer not treated with chemotherapy, TILs should not be used as biomarkers to suspend or omit chemotherapy[4]. A study of 256 TN tumors demonstrated that each 10% increase in TILs was correlated with a 17% reduction in the risk of recurrence (p=0.023; HR (hazard ratio) 0.83; 95%CI 0.71–0.98) and a 27% reduction in the risk of death (p=0.035; HR 0.73; 95%CI 0.54–0.98)[10].

Furthermore, recent data from randomized clinical trials suggest the importance of immunity in the HER2-positive subtype of the disease. Loi et al.[11], the FinHER study demonstrated that higher TILs in baseline samples resulted in better responses to trastuzumab treatment. Furthermore, they suggested that "immuneenriched" tumors show better results when treated with trastuzumab. Considering trastuzumab as the gold standard in treatment, it is essential to highlight TILs as a prognostic factor in HER2-positive subtype disease[9]. Thus, Perez et al. stated that for every 10% increase in stromal TILs, there is an 18% increase in overall survival (OS) (HR 0.82; 95%CI 0.69–0.96)[12].

This study aimed to evaluate the prognostic value of TILs in patients with TN and HER2-positive breast cancer.

METHOD

Study design

This retrospective cross-sectional study was conducted at the Liga Norte Riograndense Contra o Câncer (North Rio Grande League Against Cancer), Natal, Brazil, from June 2013 to June 2018, in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines. This study was approved by the Research Ethics Committee of the Liga Norte Riograndense Contra o Câncer, under CAAE registration number 6.036.496.

Participants

Patients >18 years old diagnosed with invasive breast cancer, triple-negative and HER2-positive subtypes, with histopathological examination results measuring TILs and undergoing neoadjuvant chemotherapy. Patients with concomitant cancers and metastatic disease, as well as patients with positive hormone receptors, were excluded.

Sample size

The sample was based on data from the Hospital Cancer Registry of the aforementioned institution. Parise et al.[13] They highlighted that the prevalence of luminal subtypes corresponds to approximately 80% of cases, with TN subtypes accounting for about 13% and HER2-positive subtypes for about 23%. Of these, 67% and 33% are hormone receptor-positive and negative, respectively. From June 2013 to June 2018, 3,876 new cases of breast cancer of all histological subtypes were reported, of which only 216 patients presented with the TN or HER2-positive subtype, who underwent neoadjuvant chemotherapy and did not present with metastasis at diagnosis.

Sociodemographic, clinical, and health characteristics

We collected data on sex, age, education level, and race. Clinical variables included staging, presence of metastasis (yes/no), molecular subtype (triple-negative and HER2-positive), histological type (ductal, lobular, and sarcoma), histological grade (I, II, and III), local recurrence (yes/no), death from any cause (yes/no), and follow-up. Additionally, treatment-related variables collected included: surgery, chemotherapy, radiotherapy, and/or immunotherapy. The outcome of TILs was described based on the analysis of the quantity of infiltrating lymphocytes in the stromal portion of the invasive tumor in samples obtained from pre-treatment biopsies, either through *core biopsy* or incisional biopsy, and the quantity of TILs classified as mild (up to one-third of the stromal space occupied by TILs), moderate (from one-third to two-thirds of the stromal space occupied by TILs) and intense (more than two-thirds of the stromal space occupied by TILs), according to the classification established by Stanton and Disis[14].

Statistical methods

A descriptive analysis was performed, indicating the relative frequencies for categorical variables. The dependent variables of the study corresponded to three categories of TILs: mild, moderate, and severe. For these categories, prevalence was calculated with a 95% confidence interval (95%CI). Pathological response, classified as complete or incomplete, was evaluated considering the results obtained in postoperative samples from patients after neoadjuvant chemotherapy.

Bivariate analysis was applied using the $\chi 2$ test (or Fisher's exact test, when necessary) and the linear $\chi 2$ test, for dichotomous and ordinal variables, respectively. Student's *t*-test (or non-parametric Mann-Whitney test) was used for quantitative variables. As a measure of association, the ***odds ratio*** (OR) was calculated, with a 95% confidence level.

Survival analysis utilized the Kaplan-Meier model, and the *log-rank* test was used to differentiate the groups. A p-value <0.05 was considered statistically significant. Data were analyzed using R version 27 (SPSS Inc., Chicago, IL).

RESULTS

The total eligible cohort of the study consisted of 216 women diagnosed with TN and HER2 breast cancer and with available data on TILs. Demographic, clinical, and biopsy report data can be found in Table 1. There was no statistically significant relationship between the TIL categories and the variables in Table 1.

Table 1. Relationship between classification of tumor-infiltrating lymphocytes, sociodemographic information, and cancer characterization, with information regarding patient treatment.

Characteristics	Total	TILs Classification			p-value *
	n=216 (%)	Light	Moderate	Intense	
		n=148 (%)	n=3 (%)	n=5 (%)	
Age range (years)					
25–34	10 (4.6)	8 (5.4)	2 (3.2)	0 (0)	0.44
35–44	47 (22)	29 (20)	17 (27)	1 (20)	
45–54	71 (33)	48 (32)	19 (30)	4 (80)	
55–64	52 (24)	36 (24)	16 (25)	0 (0)	
65 or more	36 (17)	27 (18)	9 (14)	0 (0)	
Molecular subtype					
HER2 positive	106 (49)	69 (47)	32 (51)	5 (100)	0.06
Triple-negative	110 (51)	79 (53)	31 (49)	0 (0)	
Clinical staging at TNM diagnosis					
IA	13 (6.0)	7 (4.7)	6 (9.5)	0 (0)	0.50
IB	7 (3.2)	3 (2.0)	4 (6.3)	0 (0)	
IIA	48 (22)	35 (24)	10 (16)	3 (60)	
IIB	41 (19)	30 (20)	11 (17)	0 (0)	
IIIA	65 (30)	44 (30)	20 (32)	1 (20)	
IIIB	36 (17)	24 (16)	11 (17)	1 (20)	
IIIC	6 (2.8)	5 (3.4)	1 (1.6)	0 (0)	
Metastasis					
No	162 (75)	112 (76)	45 (71)	5 (100)	0.36
Yes	54 (25)	36 (24)	18 (29)	0 (0)	
Histological type					
CI NST	183 (93)	139 (94)	60 (95,2)	3 (60)	0.06
invasive LC	5 (2.5)	4 (2.6)	0 (0)	1 (20)	
Mixed	4 (2)	2 (1.4)	2 (3.2)	0 (0)	
Mucinous	1 (0.5)	1 (0.6)	0 (0)	0 (0)	
Papillary	1 (0.5)	0 (0)	1 (1.6)	0 (0)	
Others	3 (1.5)	2 (1.4)	0 (0)	1 (20)	
Local recurrence					
No	189 (88)	129 (87)	56 (89)	4 (80)	0.94
Yes	27 (13)	19 (13)	7 (11)	1 (20)	
Death from any cause					
No	169 (78)	115 (78)	49 (78)	5 (100)	0.58
Yes	47 (22)	33 (22)	14 (22)	0 (0)	
Therapeutic approach					
Surgery	205 (95)	139 (94)	61 (97)	5 (100)	1.00
Chemotherapy	209 (97)	144 (97)	60 (95)	5 (100)	
Radiotherapy	185 (86)	131 (89)	49 (78)	5 (100)	
Hormone therapy	24 (11)	13 (8.8)	10 (16)	1 (20)	
Immunotherapy	50 (23)	36 (24)	10 (16)	4 (80)	
Staging after neoadjuvant chemotherapy					
0	49 (23)	35 (24)	12 (19)	2 (40)	0.65

It continues...

Table 1. Continuation.

Characteristics	Total	TILs Classification			p-value *
	n=216 (%)	Light	Moderate	Intense	
		n=148 (%)	n=3 (%)	n=5 (%)	
IA	42 (19)	24 (16)	17 (27)	1 (20)	0.65
IB	2 (0.9)	2 (1.4)	0 (0)	0 (0)	
IC	1 (0.5)	0 (0)	1 (1.6)	0 (0)	
IIA	55 (25)	39 (26)	15 (24)	1 (20)	
IIB	25 (12)	15 (10)	10 (16)	0 (0)	
IIIA	21 (9.7)	15 (10)	5 (7.9)	1 (20)	
IIIB	4 (1.9)	4 (2.7)	0 (0)	0 (0)	
IIIC	8 (3.7)	6 (4.1)	2 (3.2)	0 (0)	
IV	9 (4.2)	8 (5.4)	1 (1.6)	0 (0)	
Pathological response after neoadjuvant chemotherapy					
Not complete	165 (76)	113 (76)	49 (78)	3 (60)	0.44
Complete	51 (24)	35 (24)	14 (22)	2 (40)	

*χ^2 test with simulated p-value (based on 10,000 replicates).
TILs: Tumor-infiltrating lymphocytes; TNM: Tumor size (T), nodule (N), and metastasis (M); CI NST: invasive carcinoma of no special type; LC: lobular carcinoma.

Partial pathological response was predominant in the study patients (76%), and only 24% achieved complete pathological response with neoadjuvant treatment (p=0.44).

Study data related to prognosis and OS at five years are included in Table 2. There was no statistically significant difference between the variables TILs and OS (p=0.52), although a reduction in survival was noticeable in patients characterized as mild TILs in the period from 12 to 60 months (98% vs. 78%), similarly to moderate TILs in the same period (100% vs. 79%). During the 60-month clinical follow-up, the emergence of metastases (p=0.0024) and local recurrence (p<0.0001) and clinical staging (p<0.0001) impacted OS (Table 2).

Data associating variables with local recurrence-free survival (RFS) are described in Table 3.

There was a statistically significant difference in local RFS curves for patients who did or did not develop metastasis (p<0.0001). It was observed that the overall survival (OS) of those who developed metastasis after 12 months of follow-up was 96%, and decreased to 72% after 60 months, while patients who did not develop metastasis had an OS above 92% after 60 months.

Furthermore, there was a statistically significant difference in the RFS curves when comparing patients who survived with those who died from any cause (p<0.0001). In patients who completed the study's clinical follow-up at 60 months, the RFS was 93%. In the subgroup of those who died, this RFS dropped to 50%.

Figures 1 and 2 represent the Kaplan-Meier curves of OS and local RFS, according to their association with TIL classification. It was not possible to demonstrate statistical significance in relation to TIL concentration and survival.

DISCUSSIONS

Currently, there is growing interest in analyzing TILs and immune subpopulations in clinical practice to explore their potential as prognostic and predictive biomarkers. Tumors with high immune infiltration generally present better clinical outcomes and favorable clinicopathological characteristics[15]. In this sense, TILs have emerged as an important immunological biomarker related to the antitumor immune response in breast cancer. TILs are observed in higher concentrations in triple-negative breast cancer and HER2-positive subtypes, in which increased TIL levels have been associated with better response to neoadjuvant chemotherapy and greater survival[16].

Denkert et al.[16] evaluated the role of TILs in breast cancer and demonstrated that a 10% increase in TILs was associated with better disease-free survival in triple-negative tumors (HR 0.93 [95%CI 0.87–0.98]; p=0.011) and in HER2-positive tumors (0.94 [0.89–0.99]; p=0.017). The increase in TILs was also associated with better overall survival in triple-negative tumors (0.92 [0.86–0.99]; p=0.032). Furthermore, the authors found that the increase in TILs correlates positively with the response to neoadjuvant therapy: in the HER2-positive subtype, pathological complete response (pCR) was observed in 32% of patients with mild TILs, 39% with moderate TILs, and 48% with severe TILs; In the triple-negative subtype, pCR was achieved in 31% of patients with mild to moderate TILs and 50% with severe TILs (p<0.0001)[16].

In the present study, it was not possible to demonstrate statistical significance between high TIL concentrations and increased overall survival (OS) and disease-free. Nor was it possible to demonstrate an association with complete pathological response after neoadjuvant chemotherapy. These results may

be explained by the small sample size of patients with moderate and severe TILs. Ochi et al. described that triple-negative and HER2-positive breast tumors with mild TILs prior to neoadjuvant chemotherapy had a low probability of reaching pCR[17], and the result is consistent with the findings of the sample in this study. It is noteworthy that, despite the small sample size of patients with elevated TILs, the overall survival (OS) of this subgroup of patients reached 100% at five years.

In the sample studied, 24% of patients achieved a complete pathological response. This percentage is consistent with rates reported in other studies, ranging from 16.6% to 48% of triple-negative tumors that achieved pCR. The variability in percentages

Table 2. Estimates regarding overall survival for cancer characterization.

Characteristics	12 months % (min–max)	24 months % (min–max)	36 months % (min–max)	48 months % (min–max)	60 months % (min–max)	p-value*
General	99 (97–100)	92 (89–96)	86 (81–91)	81 (76–87)	79 (73–85)	
TILs Classification						
Light	98 (96–100)	94 (91–98)	87 (81–93)	81 (74–88)	78 (72–86)	0.52
Moderate	100 (100–100)	87 (79–96)	82 (73–92)	80 (71–91)	79 (69–90)	
Intense	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	
Molecular subtype						
Triple-negative	98 (96–100)	90 (84–96)	87 (80–93)	83 (76–90)	81 (73–89)	0.99
HER2 positive	99 (97–100)	95 (91–99)	85 (78–92)	80 (72–88)	77 (69–86)	
Stadium						
IA	100 (100–100)	100 (100–100)	100 (100–100)	92 (79–100)	85 (67–100)	<0.0001
IB	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	
IIA	98 (94–100)	94 (87–100)	89 (81–99)	87 (78–97)	85 (75–96)	
IIB	98 (93–100)	92 (85–100)	90 (81–100)	81 (69–95)	78 (65–93)	
IIIA	100 (100–100)	94 (88–100)	85 (76–95)	83 (74–93)	83 (74–93)	
IIIB	97 (92–100)	85 (74–98)	72 (58–90)	69 (54–87)	65 (51–84)	
IIIC	100 (100–100)	83 (58–100)	67 (38–100)	33 (11–100)	33 (11–100)	
Metastasis						
No	100 (100–100)	96 (93–99)	94 (90–97)	93 (89–97)	91 (87–96)	0.0024
Yes	94 (88–100)	81 (71–92)	63 (51–77)	46 (34–63)	42 (31–59)	
Histological type						
CI NST	98 (97–100)	91 (87–95)	84 (78–89)	79 (73–85)	77 (71–84)	0.71
CDIS	100 (100–100)	100 (100–100)	95 (85–100)	89 (77–100)	89 (77–100)	
invasive LC	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	33 (6.7–100)	
Mixed	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	
Mucinous	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	
Papillary	100 (100–100)	100 (100–100)	0	0	0	
Others	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100(100,100)	
Histological grade						
1	100 (100–100)	100 (100–100)	67 (30–100)	67 (30–100)	67 (30–100)	0.20
2	100 (100–100)	93 (87–98)	91 (86–98)	86 (79–94)	85 (77–93)	
3	98 (95–100)	92 (87–97)	83 (76–90)	78 (71–86)	76 (68–84)	
Local recurrence						
No	98 (97–100)	92 (89–96)	87 (82–92)	85 (79–90)	83 (77–89)	<0.0001
Yes	100 (100–100)	93 (83–100)	78 (64–95)	58 (42–81)	55 (38–77)	

*Log-rank test.
TILs: Tumor-infiltrating lymphocytes; min: minimum value; max: maximum value; CI NST: invasive carcinoma of no special type; LC: lobular carcinoma; DCIS: ductal carcinoma *in situ*.

may be related to differences in chemotherapy regimens between studies[18,19]. In CALGB 40603 (Alliance), it has been shown that the association of carboplatin with the chemotherapy regimen can lead to mean pCR of 54%[20]. Furthermore, the Keynote 522 study demonstrated the benefit of pembrolizumab in neoadjuvant treatment, reaching a pCR rate of 64.8%[21]. It has not been clearly demonstrated that TILs are associated with pCR; however, of the cases in which pCR was obtained, 40% were severe TILs and 24% were mild TILs.

The variables that most impacted survival were initial staging and progression to metastatic disease. Overall survival (OS) for stage IIIC after 48 months fell to 33%, and patients who

Table 3. Estimates regarding local recurrence-free survival for cancer characterization.

Characteristics	12 months % (min–max)	24 months % (min–max)	36 months % (min–max)	48 months % (min–max)	60 months % (min–max)	p-value*
Global	97 (95–99)	94 (91–97)	93 (90–97)	89 (85–94)	87 (83–92)	
Classification of TILs						
Light	97 (94–100)	94 (91–98)	93 (89–97)	90 (85–95)	87 (82–93)	0.78
Moderate	100 (100–100)	95 (89–100)	95 (89–100)	88 (80–98)	88 (80–98)	
Intense	80 (52–100)	80 (52–100)	80 (52–100)	80 (52–100)	80 (52–100)	
Molecular subtype						
Triple-negative	99 (97–100)	94 (89–99)	93 (88–98)	91 (85–97)	88 (82–95)	0.98
HER2 positive	95 (91–99)	94 (90–99)	93 (88–98)	88 (82–95)	87 (80–94)	
Stadium						
IA	100 (100–100)	92 (79–100)	92 (79–100)	92 (79–100)	92 (79–100)	0.28
IB	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	
IIA	100 (100–100)	100 (100–100)	98 (93–100)	93 (85–100)	93 (85–100)	
IIB	100 (100–100)	92 (83–100)	92 (83–100)	85 (74–98)	82 (69–96)	
IIIA	97 (93–100)	95 (90–100)	93 (87–100)	91 (85–99)	89 (82–98)	
IIIB	89 (79–100)	89 (79–100)	89 (79–100)	84 (71–99)	79 (64–97)	
IIIC	100 (100–100)	83 (58–100)	83 (58–100)	83 (58–100)	83 (58–100)	
Metastasis						
No	97 (95–100)	97 (94–100)	95 (92–99)	94 (90–98)	92 (87–96)	<0.0001
Yes	96 (91–100)	86 (76–96)	86 (76–96)	72 (59–88)	72 (59–88)	
Histological type						
CI NST	97 (94–99)	94 (90–97)	92 (88–96)	89 (85–94)	88 (83–93)	0.38
CDIS	100 (100–100)	95 (85–100)	95 (85–100)	95 (85–100)	95 (85–100)	
invasive LC	100 (100–100)	100 (100–100)	100 (100–100)	75 (43–100)	75 (43–100)	
Mixed	100 (100–100)	100 (100–100)	100 (100–100)	75 (43–100)	50 (19–100)	
Mucinous	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	
Papillary	100 (100–100)	100 (100–100)	0	0	0	
Others	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	
histological grade						
1	100 (100–100)	67 (30–100)	67 (30–100)	67 (30–100)	67 (30–100)	0.62
2	98 (94–100)	95 (90–100)	95 (90–100)	91 (84–98)	87 (79–95)	
3	97 (94–100)	94 (90–99)	92 (88–97)	89 (84–95)	88 (82–95)	
Death from any cause						
No	99 (97–100)	98 (95–100)	97 (94–100)	95 (91–98)	93 (89–97)	<0.0001
Yes	91 (83–100)	80 (69–94)	77 (64–92)	58 (41–84)	50 (31–80)	

*Log-rank test.
TILs: Tumor-infiltrating lymphocytes; min: minimum value; max: maximum value; CI NST: invasive carcinoma of no special type; LC: lobular carcinoma; DCIS: ductal carcinoma *in situ*.

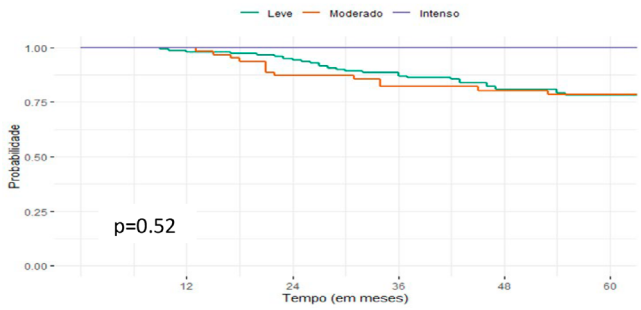

Figure 1. Overall survival, according to classification of tumor-infiltrating lymphocytes.

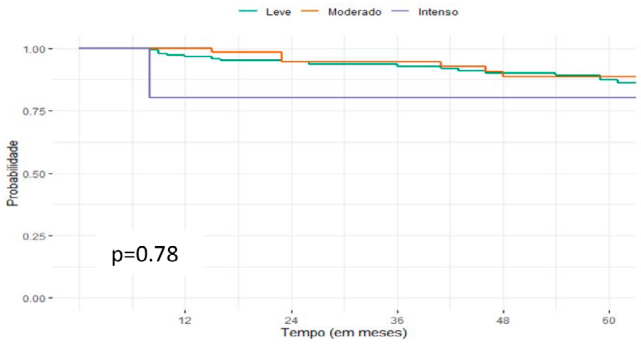

Figure 2. Relapse-free survival, according to the classification of tumor-infiltrating lymphocytes.

developed metastasis after 60 months had a survival rate of 72%, while non-metastatic patients had a survival rate above 92% at the same time. These findings confirmed how much initial clinical conditions (tumor size and lymph node status) impact prognosis[22].

Limitations of the study include the low number of patients with severe TILs (n=5). The variability between gold standard chemotherapy regimens and those available at the Liga Norte Riograndense Contra o Câncer directly influenced the selection of patients for neoadjuvant chemotherapy or upfront surgery, as well as the achievement of post-neoadjuvant treatment pCR rates. This is a reality present in a large part of underdeveloped countries.

CONCLUSION

In the study in question, it was not possible to demonstrate an association between TIL concentration and prognosis (overall survival and local recurrence-free survival), nor between TILs and complete pathological response in patients undergoing neoadjuvant chemotherapy. To date, it is not possible to justify changes in clinical protocols based on information about TIL concentration. These results encourage further studies in this subgroup of patients, aiming for greater data robustness and statistical power, for example, in multicenter studies that can validate prognostic and predictive factors for better outcomes in patients with triple-negative and HER2-positive breast cancer.

AUTHORS' CONTRIBUTIONS

MAF: Formal Analysis, Conceptualization, Data Curation, Investigation, Methodology, Visualization. WP: Formal Analysis, Writing – First Draft, Investigation, Methodology, Visualization. JO: Formal Analysis, Writing – First Draft, Investigation, Methodology, Visualization. JLAA: Conceptualization, Data Curation, Writing – First Draft, Investigation, Methodology, Validation, Visualization. FMA: Project Management, Resources, Conceptualization, Writing – First Draft, Writing – Revision and Editing, Investigation, Methodology, Resources, Supervision, Validation, Visualization. KSM: Writing – First Draft, Writing – Revision and Editing, Investigation, Methodology, Validation, Visualization. DTSMN: Project Management, Conceptualization, Writing – First Draft, Writing – Revision and Editing, Investigation, Methodology, Resources, Supervision, Validation, Visualization.

Ethical approval from CEP/CONEP on 03/05/2023 — CAAE 68937523.0.0000.5293

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