Prognostic Value of TILs Variation in Breast Cancer Undergoing Neoadjuvant Chemotherapy

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INTRODUCTION

Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is associated with improved event-free and overall survival, particularly in triple-negative and HER2-positive breast cancer. Tumor-infiltrating lymphocytes (TILs) are promising prognostic and predictive biomarkers, correlating with higher pCR rates in these subtypes. However, the clinical relevance of TILs variation between pre- and post-NAC specimens remain poorly understood.

OBJECTIVE

This study aimed to investigate associations between TILs variation, pCR, Residual Cancer Burden (RCB), and pre-NAC TILs with clinical outcomes.

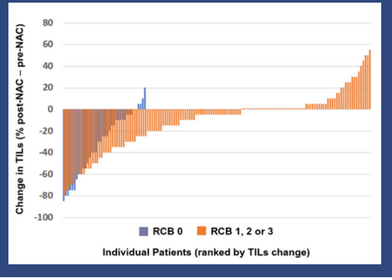
MATERIALS & METHODS

This multicenter retrospective cohort included 302 patients treated with NAC followed by surgery at two tertiary centers in Curitiba, Brazil, from 2016 to 2020. Data were extracted from electronic medical records. Pre-NAC core biopsies and post-NAC surgical specimens were reviewed by a dedicated breast pathologist. TILs were assessed per International TILs Working Group guidelines, and analyzed as categorical variables (low ≤10%, intermediate 11–49%, high ≥50%). Post-NAC TILs were quantified in stroma adjacent to the residual tumor bed. Pathologic response was defined using the RCB classification. Statistical analysis included the Wilcoxon signed-rank and Stuart-Maxwell tests. ROC curves identified outcome-related cut-offs.

Table 1 – Clinicopathological characteristics of the participants

	Total (n=302)
Mean age ‡ SD (yr.)	50,4 ‡ 12,7 (26-89)
Menopausal status	
Pre	150 (51,5%)
Post	141 (48,5%)
Histological type	
Ductal	275 (92%)
Mixed ductal	13 (4,3%)
Lobular	4 (1,3%)
Others	7 (2,3%)
Molecular subtype	
Luminal B	113 (39%)
Triple negative	65 (22,3%)
Luminal B- Her	49 (16,8%)
Her-2 pure	39 (13,4%)
Luminal A	26 (9%)
T	
1	23 (8,3%)
2	164 (59,2%)
3	53 (19,1%)
4	37 (13,4%)
N	
0	100 (36,1%)
1	145 (52,3%)
2	26 (9,4%)
3	6 (2,2%)
Pathologic complete response (pCR)	
Yes	90 (30%)
No	210 (70%)
RCB	
0	92 (31,6%)
1	14 (4,8%)
2	136 (46,7%)
3	49 (16,8%)

Graph 1. Variation in Tumor-Infiltrating Lymphocytes (TILs) Following Neoadjuvant Chemotherapy, Stratified by Residual Cancer Burden (RCB)



RESULTS

Of 302 patients, 30% achieved pCR (Table 1). TILs were evaluated in 183 paired samples. TILs levels significantly declined post-NAC (p<0.001), especially in pCR cases, with median decreases of 25% in RCB 0, 15% in RCB 1, and 5% in RCB 2 and 3 (Graph 1). Post-NAC, 78% had TILs ≤10% and 8% ≥50%, versus 43% and 25% at baseline. Pre-NAC TILs >25% were associated with reduced distant recurrence risk. No significant association was found with locoregional recurrence or mortality (Table 2).

Table 2 - Association Between Pre-NAC TIL Levels and Oncologic Outcomes

Outcome	Median Follow-up (months)	Median Time to Event (months)	Pre-NAC TILs >25%	Pre-NAC TILs ≤25%	SHR (95% CI)	p-value
Locoregional recurrence	53.9	25.0	6 (4.7%)	3 (2.3%)	1.99 (0.49–8.10)	0.336
Distant recurrence	54.8	25.4	8 (6.2%)	18 (14.1%)	**4.43 (1.83–10.7)**	**0.001**
Death	55.9	20.6	6 (4.7%)	9 (7.0%)	1.51 (0.54–4.25)	0.433

Abbreviations: NAC = Neoadjuvant Chemotherapy; TILs = Tumor-Infiltrating Lymphocytes; CI = Confidence Interval; SHR = Subdistribution Hazard Ratio. *p-values calculated using competing risks regression.

CONCLUSION

TILs declined after NAC, particularly in pCR cases. Pre-NAC TILs >25% were linked to lower risk of distant recurrence, supporting their prognostic value in the neoadjuvant setting.

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