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Evaluation of tumor-infiltrating lymphocytes as a predictive biomarker of recurrence in patients with ductal carcinoma *in situ* of the breast

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Objective: The objective of this study was to evaluate the association between tumor-infiltrating lymphocytes (TILs) in ductal carcinoma *in situ* (DCIS) samples and disease recurrence. **Methodology:** This is a retrospective cohort study with patients diagnosed with DCIS and treated at the University of São Paulo. We included women over 18 years old with a diagnosis of DCIS who underwent treatment from January 2007 to December 2020. Male patients, patients with a diagnosis of invasive or microinvasive disease in the anatomopathological examination of the surgical specimen, or patients with a history of any neoplasm were excluded. The main outcome was survival analysis according to the quantification of TILs, adjusted for potential confounders. Two pathologists evaluated TILS in the sample with the highest tumor representation and numerically quantified it as a percentage. Kaplan-Meier curves, log-rank tests, and Cox regression models were used to evaluate survival. Chi-square tests were used to evaluate the association between categorical variables. **Results:** A total of 283 patients met the eligibility criteria. The mean follow-up was 77.2 months, with a recurrence rate of 9.2%. The mean age of patients was 55 years. Clustered amorphous microcalcifications were the most prevalent mammographic presentation. The most frequent histological and IHC features were cribriform presentation (73%) and ER positivity (86%), respectively. We observed that tumors with focal necrosis (HR 6.4 [1.39–34.71] p=0.018) or comedo necrosis (HR 4.53 [1.34–15.28] p=0.015) had higher risks of recurrence. Patients with a percentage value of TILs, greater than or equal to 17% also had a higher risk of recurrence (HR 2.97 [95%CI 1.17–7.51] p=0.02). These patients were mostly under 65 years of age (OR 0.45 [95%CI 0.21–0.97] p=0.049). In a multivariate model, CN and TILs>17% remained significantly associated with recurrence (p=0.034 and p=0.035, respectively). **Conclusion:** In our cohort, the high value of TILs (>17%) and the presence of CN were independently associated with DCIS recurrence.

Keywords: ductal carcinoma *in situ* of the breast; recurrence; tumor-infiltrating lymphocytes; immunological microenvironment.