

**Prognostic Value of Stromal Tumor-Infiltrating Lymphocytes in Young, Node-Negative, Triple-Negative Breast Cancer Patients Who Did Not Receive (neo)Adjuvant Systemic Therapy**

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Objective: Triple-negative breast cancer (TNBC) is considered aggressive and therefore, virtually all young patients with TNBC receive (neo)adjuvant chemotherapy. Increased stromal tumor-infiltrating lymphocytes (sTILs) have been associated with a favorable prognosis in TNBC. However, whether this association holds for patients who are node-negative (N0), young (<40 years), and chemotherapy-naïve, and thus can be used for chemotherapy de-escalation strategies, is unknown.

Methods: We selected all patients with N0 TNBC diagnosed between 1989 and 2000 from a Dutch population-based registry. Patients were <40 years at diagnosis and had not received (neo)adjuvant systemic therapy, as was standard practice at the time. FFPE blocks were retrieved (PALGA: Dutch Pathology Registry) and a pathology review including sTILs was performed. Patients were categorized according to sTILs (<30%, 30-75%, ≥75%). Multivariable Cox regression was performed for overall survival, with or without sTILs as a covariate. Cumulative incidence of distant metastasis or death was analyzed in a competing risk model, with second primary tumors as competing risk.

Results: Stromal TILs were scored for 441 patients. High sTILs (≥ 75%; 21%) translated into an excellent prognosis with a 15-year cumulative incidence of a distant metastasis or death of only 2.1% (95%CI 0-5.0), whereas low sTILs (<30%; 52%) had an unfavorable prognosis with a 15-year cumulative incidence of a distant metastasis or death of 38.4% (32.1–44.6). In addition, every 10% increment of sTILs decreased the risk of dying by 19% (adjusted hazard ratio: 0.81; 95%CI 0.76 to 0.87), which are an independent predictor adding prognostic information to standard clinicopathological variables ( $\chi^2=46.7$ ,  $p<0.001$ ).

Conclusions: Chemotherapy-naïve, young, N0 TNBC patients with high sTILs (≥ 75%) have an excellent long-term prognosis. Therefore, sTILs should be considered for prospective clinical trials investigating (neo)adjuvant chemotherapy de-escalation strategies.