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Tumor-Infiltrating Lymphocytes in Patients With Stage I Triple-Negative Breast Cancer Untreated With Chemotherapy

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IMPORTANCE The absolute benefit of chemotherapy for all patients with stage I triple-negative breast cancer (TNBC) is unclear, and biomarkers are not currently available for selecting patients with an excellent outcome for whom neoadjuvant or adjuvant chemotherapy may have negligible benefit. High levels of stromal tumor-infiltrating lymphocytes (sTILs) are associated with favorable survival in TNBC, but data solely in stage I TNBC are lacking.

OBJECTIVE To examine the outcomes of patients of all ages with stage I TNBC solely and who received neither neoadjuvant nor adjuvant chemotherapy, according to centrally reviewed sTIL levels at prespecified cutoffs.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used the Netherlands Cancer Registry to identify patients diagnosed with stage I TNBC between January 1, 2005, and December 31, 2015, who were not treated with chemotherapy. Only patients who did not receive neoadjuvant and/or adjuvant chemotherapy were selected. The clinical data were matched with their corresponding pathology data provided by the Dutch Pathology Registry. Data analysis was performed between February and October 2023.

MAIN OUTCOMES AND MEASURES The primary end point was breast cancer–specific survival (BCSS) at 5, 10, and 15 years for the prespecified sTIL level cutoffs of 30%, 50%, and 75%. Hematoxylin and eosin–stained slides were used for central review of histologic subtype, grade, and lymphovascular invasion. The International Immuno-Oncology Biomarker Working Group guidelines were used to score the sTIL levels; these levels were determined for 1041 patients.

RESULTS A total of 4511 females with stage I TNBC (mean [SD] age at diagnosis, 64.4 [11.1] years; median follow-up, 11.4 [95% CI, 10.9-11.9] years) were included. Most tumors (952 [91.5%]) were invasive carcinomas of nonspecial histologic subtype. Most patients (548 [52.6%]) had pT1cN0 tumors. Median (range) sTIL level was 5% (1%-99%). A total of 775 patients (74.4%) had sTIL levels below 30%, 266 (25.6%) had 30% or greater, 203 (19.5%) had 50% or greater, and 141 (13.5%) had 75% or greater. Patients with pT1abN0 tumors had a more favorable outcome vs patients with pT1cN0 tumors, with a 10-year BCSS of 92% (95% CI, 89%-94%) vs 86% (95% CI, 82%-89%). In the overall cohort, sTIL levels of at least 30% were associated with better BCSS compared with sTIL levels less than 30% (96% and 87%, respectively; hazard ratio [HR], 0.45; 95% CI, 0.26-0.77). High sTIL levels of 50% or greater were associated with a better outcome than low sTIL levels of less than 50% (HR, 0.27; 95% CI, 0.10-0.74) in patients with pT1C tumors, with a 10-year BCSS of 95% increasing to 98% with sTIL levels of 75% or greater.

CONCLUSIONS AND RELEVANCE Results of this study showed that patients with stage I TNBC and high level of sTILs who did not receive neoadjuvant or adjuvant chemotherapy had excellent 10-year BCSS. The findings further support the role of sTILs as integral biomarkers in prospective clinical trials of therapy optimization for this patient population.

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Supplemental content

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Triple-negative breast cancer (TNBC) is a heterogenous subgroup of breast tumors defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and *ERBB2* (formerly *HER2*) overexpression. While TNBC is known for its aggressive clinical behavior with early recurrences,[1,2] the long-term outcome for early-stage TNBC is similar to the outcome of a more indolent ER-positive or *ERBB2*-negative breast cancer subtype.[3] This finding indicates that there is a substantial group of patients with an excellent outcome, especially when a pathological complete response is reached with neoadjuvant chemotherapy or when the tumor harbors high levels of stromal tumor-infiltrating lymphocytes (sTILs).[4,5]

Although neoadjuvant or adjuvant chemotherapy has been associated with substantially improved survival of patients with early-stage TNBC, the absolute benefit of neoadjuvant or adjuvant chemotherapy for patients with stage I (T1N0M0) disease is unclear given that prospective clinical trials evaluating chemotherapy have often excluded these patients. In multiple small, retrospective cohorts, adjuvant chemotherapy was associated with improved overall survival (OS), breast cancer–specific survival (BCSS), and recurrence-free survival for patients with a pT1c tumor.[6-8] In contrast, patients with pT1a tumors have excellent survival after surgery alone without substantial additional benefit from adjuvant chemotherapy.[6,9-13] For pT1b tumors, the data on the magnitude of benefit from adjuvant chemotherapy are conflicting.[9,10,14-16]

The lack of consensus on the use of chemotherapy for stage I TNBC is reflected in the treatment guidelines. While the European Society for Medical Oncology guideline states that all patients with TNBC should receive chemotherapy except for low-risk special histologic subtypes or very early-stage tumors (T1aN0),[17] the St Gallen International Expert Consensus recommends chemotherapy for T1b and T1c TNBC as well as case-by-case evaluation for T1a tumors.[18] In contrast, the National Comprehensive Cancer Network guidelines advise no chemotherapy for pT1a tumors, but it might be considered for patients with high-risk features and for pT1b tumors, and recommend chemotherapy for pT1c tumors. Recently, Tarantino and colleagues[13] performed a population-based study of 8601 patients with biomarker-unselected stage I TNBC, demonstrating that the use of chemotherapy for pT1b and pT1c substantially increased over the past decade.

The decision to give neoadjuvant or adjuvant chemotherapy is mainly based on tumor size. Biomarkers for use in selecting patients with TNBC for whom chemotherapy can be safely omitted are lacking. Currently, TNBC is considered the most immunogenic breast cancer subtype with relatively high levels of sTILs.[19] The assessment of sTILs is inexpensive because it uses the diagnostic hematoxylin and eosin–stained slides and is standardized and reproducible.[20] Stromal tumor-infiltrating lymphocytes (TILs), a mixture of mononuclear cells, predominantly CD8+ T cells,[21] reflect an ongoing adaptive immune response and have been shown in 2 independent pooled analyses[22,23] to be associated with outcome in patients with early-stage TNBC who were treated with neoadjuvant or adjuvant chemotherapy. A recent study in patients younger than 40 years with early-stage TNBC without nodal involvement (stages I and II) and who had not received systemic treatment showed that TILs might be used to identify a subgroup of patients who have such high levels of TILs and excellent outcomes that the added value of systemic treatment may be limited.[24]

Given that the clinical decision to provide neoadjuvant or adjuvant chemotherapy is mainly applicable to patients with stage I TNBC, a clinically relevant question is whether there is a cutoff level of sTILs that can identify a subset of patients with stage I TNBC with excellent outcome for whom chemotherapy may have no or minimal benefit. Herein, we aimed to examine the outcomes of patients of all ages with stage I TNBC solely and who received neither neoadjuvant nor adjuvant chemotherapy, according to centrally reviewed sTIL levels at prespecified cutoffs.

Key Points

Question What is the role of stromal tumor-infiltrating lymphocytes (sTILs) in the outcome of patients with stage I triple-negative breast cancer (TNBC) who did not receive neoadjuvant or adjuvant chemotherapy?

Findings In this cohort study of 4511 females, sTILs were scored in 1041 patients with stage I TNBC. Patients with pT1c tumors and an sTIL level of 50% or greater had a 10-year survival of 95% without chemotherapy, increasing to 98% with an sTIL level of 75% or greater; an association with less magnitude was found between sTILs and outcome in patients with pT1ab tumors.

Meaning Findings of this study further support clinical trials to optimize chemotherapy for patients with stage I TNBC with a high level of sTILs.

Methods

Patient Selection

Patients with stage I TNBC diagnosed between January 1, 2005, and December 31, 2015, were identified from the Netherlands Cancer Registry. The Netherlands Cancer Institute Institutional Review Board approved the study and waived the informed consent requirement because of the study's retrospective design and use of anonymized data.

Patients with TNBC were defined as having less than 10% of the tumor cells expressing ER and PR and the absence of *ERBB2* overexpression and/or gene amplification in original local pathology reports. Axillary staging was based on sentinel node procedure or axillary lymph node dissection. Only patients who did not receive neoadjuvant and/or adjuvant chemotherapy were selected. These clinical data were matched with their corresponding pathology data provided by the Dutch Pathology Registry (PALGA). Patients were excluded if they received any type of systemic therapy (hormonal therapy, targeted therapy, immunotherapy, and/or chemotherapy) in the neoadjuvant or adjuvant setting; had ER-expression levels over 10% and/or overexpressed *ERBB2,* according to the original pathology report; had a multifocal tumor, defined as 2 or more distinct invasive carcinomas without intervening ductal carcinoma in situ; and/or had a prior malignant neoplasm in the

ipsilateral or contralateral breast that required treatment. Cause-of-death data provided by Statistics Netherlands (CBS) were linked to clinicopathological characteristics per patient. Data on vital status were obtained through February 1, 2022.

Pathological Assessments and TIL Scoring

A trained pathologist (R.S.), who was blinded for clinicopathological variables and outcome, scored sTILs according to the guidelines of the International Immuno-Oncology Biomarker Working Group. Moreover, histologic subtype, grade, and lymphovascular invasion (LVI) were centrally reviewed (R.S.) according to the 2019 *WHO Classification of Breast Tumours* (5th edition).[25]

Statistical Analysis

Clinicopathological characteristics were assessed and summarized using descriptive statistics. Analysis of variance and χ^2 tests were used to compare clinicopathological variables at baseline among pathological tumor stages (pT1a, pT1b, and pT1c). Associations between TIL scores and clinicopathological variables were assessed using Spearman correlations and Kruskal-Wallis with Dunn post hoc test.

The primary end point was BCSS, which was defined as time from diagnosis to death due to breast cancer with landmark estimates at 5, 10, and 15 years for the prespecified sTIL level cutoffs of 30%, 50%, and 75%. For the potential omission of chemotherapy, only patients with excellent survival should be selected. Prior work indicated that the cutoffs of 30%,[26] 50%,[4,27] and 75%[25] may be used.

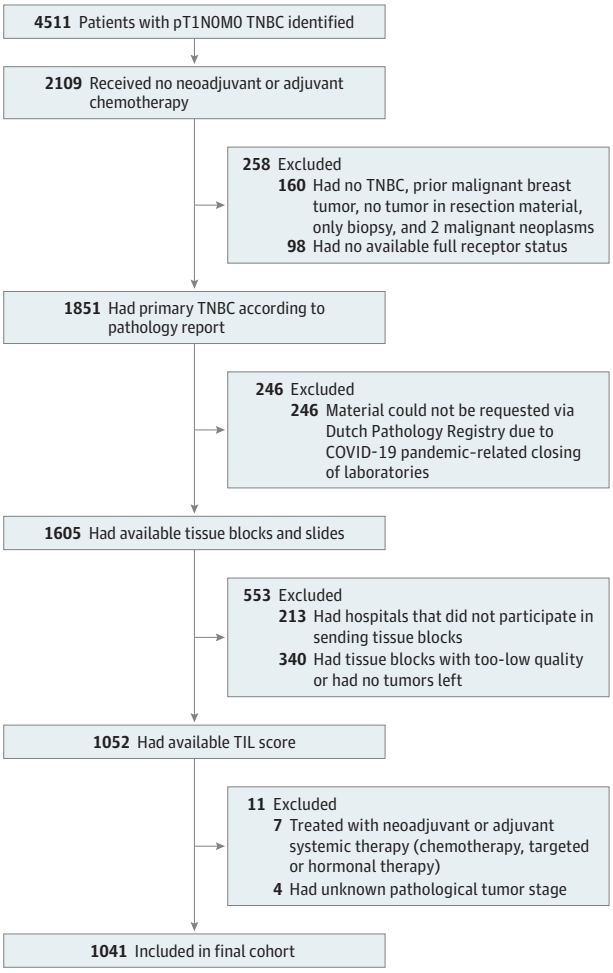
Secondary end points were BCSS per pathological tumor stage and OS. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for sTIL levels. A likelihood ratio test was used to compare a model with clinicopathological variables and sTIL levels as well as a model with only clinicopathological variables. Linearity of sTIL levels was evaluated using a restricted cubic spline analysis. Two-sided $P < .05$ was considered to be statistically significant. Data analysis was performed between February and October 2023 using R, version 4.2.3 (R Project for Statistical Computing).

Results

We identified 4511 patients with stage I TNBC diagnosed across 33 pathology centers in the Netherlands (**Figure 1**), of whom 2109 did not receive neoadjuvant or adjuvant chemotherapy. Tissue blocks were received for 1605 patients, and sTIL levels were ascertained for 1041 patients.

Patients were all females and had a mean (SD) age at diagnosis of 64.4 (11.1) years. Among these patients, 90 (8.6%) had a pT1a tumor, 403 patients (38.7%) had a pT1b tumor, and 548 patients (52.6%) had a pT1c tumor (**Table**). The majority of patients (952 [91.5%]) had an invasive carcinoma of nonspecial histologic subtype. Median (IQR) TIL score among all patients was 5% (1%-30%); eFigure 1 in Supplement 1 provides the distribution of sTILs scores. A total of 775 patients (74.4%) had sTIL levels below 30%, 266 (25.6%) had 30% or greater, 203 (19.5%) had 50% or greater, and 141 (13.5%) had 75% or greater. An increase in sTIL level as a continuous variable was associated with higher tumor grade and invasive carcinoma of nonspecial histologic subtype, but not with age (eFigure 2 in Supplement 1). Median follow-up was 11.4 (95% CI, 10.9-11.9) years in which 335 patients died, of whom 107 died because of breast cancer.

Figure 1. Flowchart



Patients with stage I triple-negative breast cancer (TNBC) diagnosed between January 1, 2005, and December 31, 2015, were identified from the Netherlands Cancer Registry. TIL indicates tumor-infiltrating lymphocyte.

BCSS and TILs in Overall Cohort

Patients with pT1ab tumors had a more favorable outcome than patients with pT1c tumors (HR, 0.47; 95% CI, 0.32-0.72) (eFigure 3 in Supplement 1). The 10-year BCSS was 92% (95% CI, 89%-94%) for patients with pT1ab tumors and 86% (95% CI, 82%-89%) for patients with pT1c tumors. In the overall cohort, sTIL levels of at least 30% were associated with better BCSS compared with sTIL levels less than 30% (HR, 0.45; 95% CI, 0.26-0.77), with 10-year BCSS of 96% (95% CI, 0.93%-0.98%) and 87% (95% CI, 0.84%-0.90%), respectively (**Figure 2**; eTable 1 in Supplement 1). At an sTIL level of 50% or greater, the 10-year BCSS was 92% (95% CI, 0.88%-0.96%) compared with 88% (95%

Table. Baseline Characteristics of the Overall Cohort and Per Pathological Tumor Stage

Characteristic	Patients, No. (%)			
	pT1a Tumor (n = 90)	pT1b Tumor (n = 403)	pT1c Tumor (n = 548)	Total (N = 1041)
Age, y				
Mean (SD)	57.5 (11.0)	61.2 (9.61)	67.8 (10.9)	64.4 (11.1)
Median (range)	58.0 (29.0-81.0)	62.0 (26.0-90.0)	70.0 (36.0-96.0)	65.0 (26.0-96.0)
Tumor grade				
Grade 1	8 (8.9)	32 (7.9)	61 (11.1)	101 (9.7)
Grade 2	37 (41.1)	139 (34.5)	181 (33.0)	357 (34.3)
Grade 3	35 (38.9)	214 (53.1)	291 (53.1)	540 (51.9)
Unknown	10 (11.1)	18 (4.5)	15 (2.7)	43 (4.1)
Histologic subtype				
Ductal carcinoma	86 (95.6)	377 (93.5)	489 (89.2)	952 (91.5)
Lobular carcinoma	1 (1.1)	7 (1.7)	12 (2.2)	20 (1.9)
Special histologic subtypes	3 (3.3)	19 (4.7)	47 (8.6)	69 (6.6)
LVI				
Yes	0 (0)	7 (1.7)	3 (0.5)	10 (1.0)
No	87 (96.7)	393 (97.5)	533 (97.3)	1013 (97.3)
Unknown	3 (3.3)	3 (0.7)	12 (2.2)	18 (1.7)
Type of surgery				
Mastectomy	31 (34.4)	76 (18.9)	170 (31.0)	277 (26.6)
Lumpectomy	59 (65.6)	327 (81.1)	378 (69.0)	764 (73.4)
sTIL level, %				
Mean (SD)	22.7 (31.6)	24.8 (31.9)	19.6 (28.5)	21.9 (30.2)
Median (range)	5.00 (1.00-95.0)	10.0 (1.00-99.0)	5.00 (1.00-99.0)	5.00 (1.00-99.0)
TIL categories				
Low: <30%	62 (68.9)	285 (70.7)	428 (78.1)	775 (74.4)
Intermediate: 30%-74%	14 (15.6)	53 (13.2)	58 (10.6)	125 (12.0)
High: 75%	14 (15.6)	65 (16.1)	62 (11.3)	141 (13.5)

Abbreviations: LVI, lymphovascular invasion; sTILs, stromal tumor-infiltrating lymphocytes; TIL, tumor-infiltrating lymphocyte.

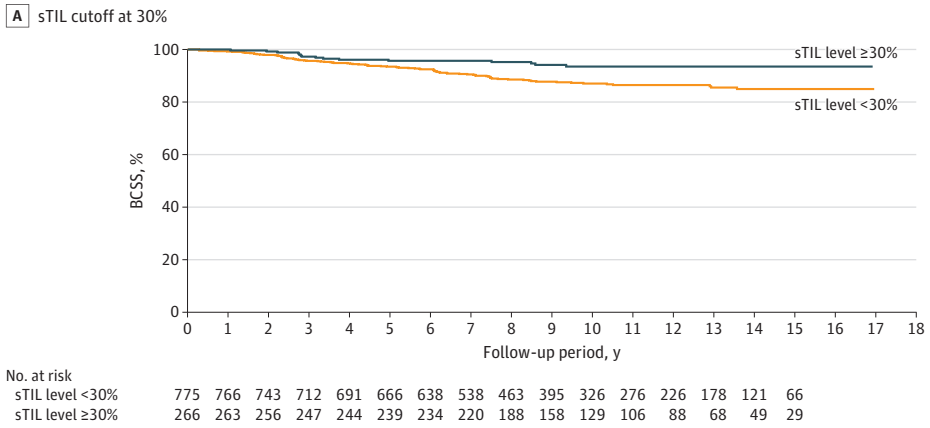
CI, 0.86%-0.90%) for patients with sTIL levels less than 50% (HR, 0.59; 95% CI, 0.33-1.04). In univariable Cox proportional hazards regression models, sTIL levels (as continuous variable) were associated with BCSS (HR, 0.99; 95% CI, 0.98-1.00; $P < .01$) (eTable 2 in Supplement 1). Pathological tumor size (pT1ab vs pT1c) was associated with BCSS in a univariable Cox proportional hazards regression model (HR, 2.08; 95% CI, 1.39-3.12), whereas histologic subtype, tumor grade, and LVI were not (eTable 2 in Supplement 1). The addition of sTIL level to clinicopathological variables was associated with improved BCSS in a multivariable analysis compared with a model not considering sTIL level (likelihood ratio test $\chi^2 = 9.25$; $P < .01$). Multivariable analyses with sTIL level as the continuous variable showed similar results as the multivariable model with sTIL level as the categorical variable (eTable 3 in Supplement 1). No evidence of nonlinearity of the univariable sTIL level model was observed (eFigure 4 in Supplement 1).

BCSS and TILs in Patients With pTab and pT1c Tumors

The association between sTIL level and outcome was evaluated separately for pT1ab and pT1c tumors. A 30% or greater sTIL level was not associated with improved BCSS compared with low an sTIL level less than 30% in patients with a pT1ab tumor (HR, 0.93; 95% CI, 0.44-1.94) (**Figure 3**; eTable 1 in Supplement 1). Similar results were found for sTIL levels 50% or greater vs levels less than 50% (HR, 1.35; 95% CI, 0.65-2.82) and for levels 75% or greater vs those less than 75% (HR, 1.52; 95% CI, 0.69-3.35). In univariable Cox proportional hazards regression models, sTIL level as both a continuous variable (HR, 1.00; 95% CI, 0.99-1.01; $P = .84$) and a categorical variable with TIL levels less than and greater than 30% (HR, 0.93; 95% CI, 0.44-1.94), and none of the clinicopathological variables, was associated with BCSS (eTables 2 and 3 in Supplement 1).

In contrast, patients with pT1c tumors with an sTIL level 30% or greater compared with a level less than 30% (HR, 0.24; 95% CI, 0.10-0.60) as well as a level 50% or greater vs less than 50% (HR, 0.27; 95% CI, 0.10-0.74) were found to have better outcome, with an excellent 10-year BCSS of 95% (95% CI, 0.89%-1.00%) (**Figure 4**; eTable 1 in Supplement 1). The BCSS further increased to 98% (95% CI, 0.95%-1.00%) for an sTIL level of 75% or greater (HR, 0.09; 95% CI, 0.01-0.68), whereas the 10-year BCSS in patients with sTIL levels less than 30% was only 83% (95% CI, 0.79%-0.87%). Again, histologic subtype, tumor grade, and LVI were not associated with BCSS; however, the addition of sTIL level (continuous variable) to a multivariable model was associated with improved BCSS ($\chi^2 = 15.947$; $P < .01$) (eTable 2 in Supplement 1). Multivariable analyses with sTIL levels as continuous variables showed similar results as the multivariable model with sTIL levels as categorical variables (eTable 3 in Supplement 1).

Figure 2. Breast Cancer–Specific Survival (BCSS) of Patients in the Overall Cohort



A, Ten-year BCSS was 96% for a stromal tumor-infiltrating lymphocyte (sTIL) level 30% or greater and 87% for a level less than 30% (hazard ratio [HR], 0.45; 95% CI, 0.26-0.77). B, Ten-year BCSS was 92% for an sTIL level 50% or greater and 88% for a level less than 50% (HR, 0.59; 95% CI, 0.33-1.04). C, Ten-year BCSS was 87% for an sTIL level less than 30%, 94% for a level between 30% and 74% (HR, 0.38; 95% CI, 0.17-0.87), and 93% for a level 75% or greater (HR, 0.50; 95% CI, 0.25-1.00). TIL indicates tumor-infiltrating lymphocyte.

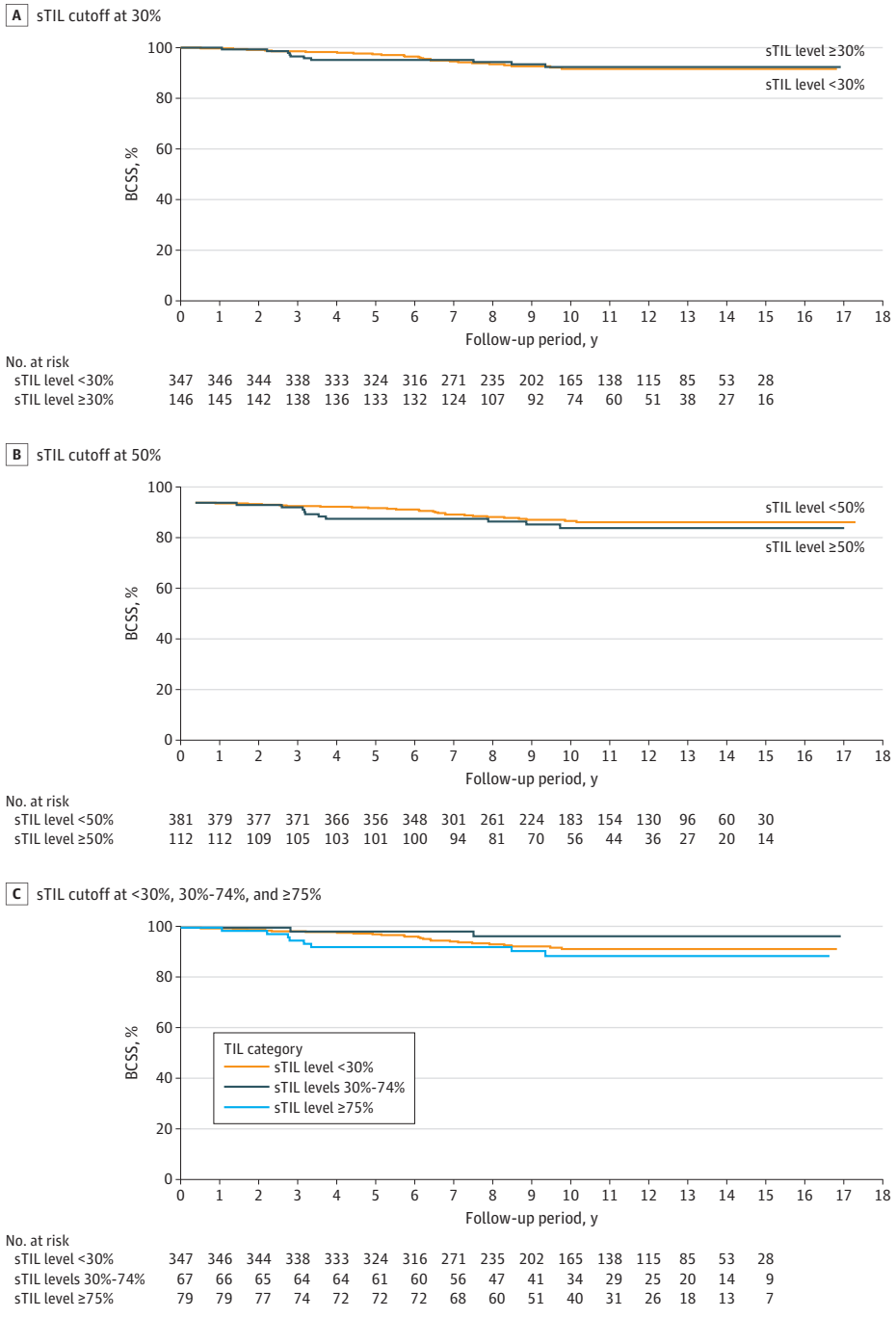
Overall Survival

In the overall cohort, an sTIL level of at least 30% was associated with better OS compared with a level less than 30% (HR, 0.64; 95% CI, 0.49-0.84) (eFigure 5 in Supplement 1). A similar pattern was observed if the sTIL level was 50% or greater (HR, 0.75; 95% CI, 0.56-1.00) (eFigure 5 in Supplement 1). High sTIL levels were not associated with better OS in patients with pT1ab tumors (eFigure 6 in Supplement 1). In contrast, patients with pT1C tumors with sTIL levels 30% or greater had better OS compared with patients with levels less than 30% (HR, 0.65; 95% CI, 0.46-0.91) (eFigure 7 in Supplement 1). A similar pattern was observed if sTIL levels were 50% or greater or 75% or greater (eFigure 7 in Supplement 1).

Discussion

To our knowledge, this study was the first to investigate the association of various sTIL levels with TNBC outcome in a large cohort of patients with stage I TNBC only who did not receive

Figure 3. Breast Cancer–Specific Survival (BCSS) of Patients With pT1ab Tumors

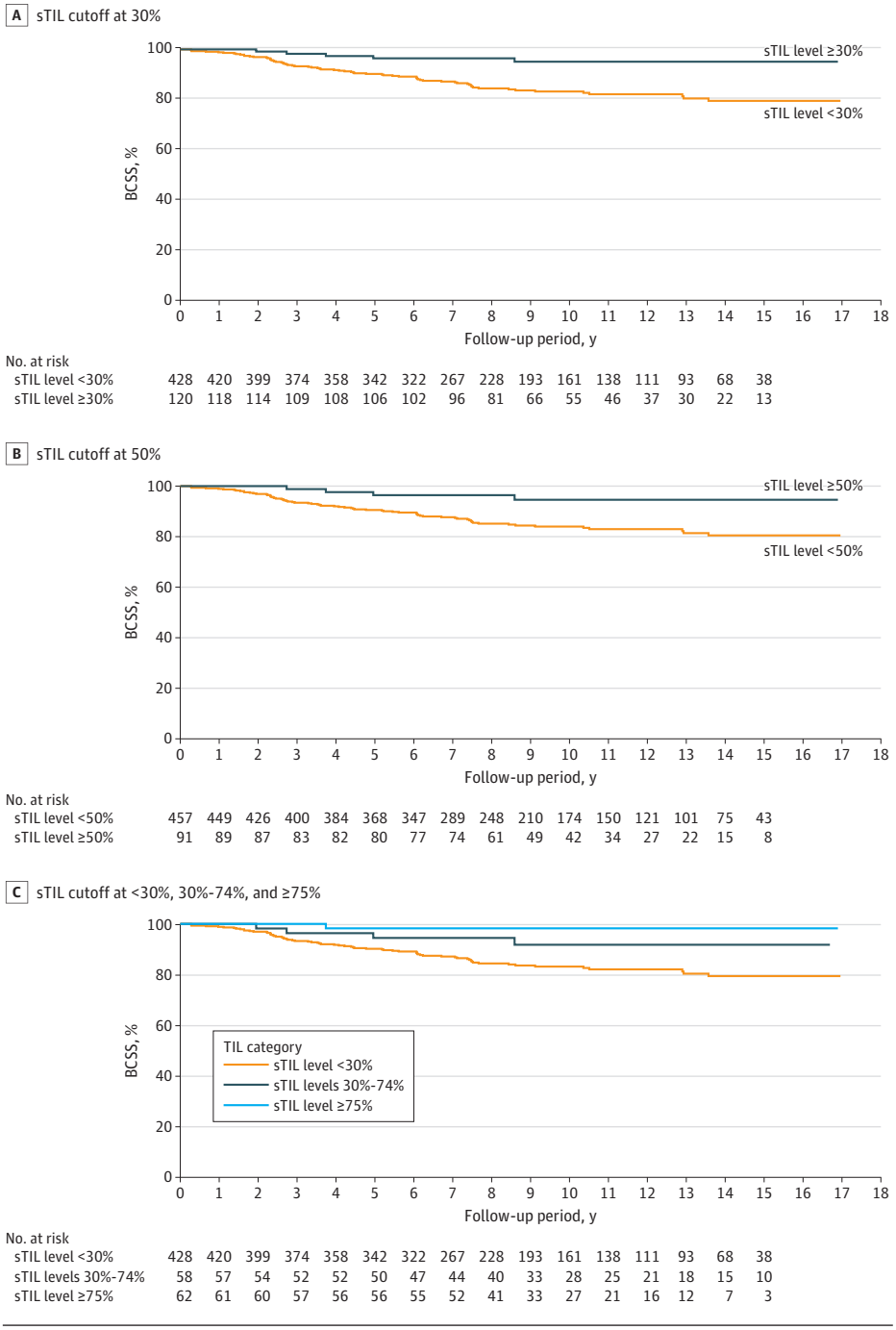


A, Ten-year BCSS was 92% for a stromal tumor-infiltrating lymphocyte (sTIL) level 30% or greater and 92% for a level less than 30% (hazard ratio [HR], 0.93; 95% CI, 0.44-1.94). B, Ten-year BCSS was 90% for an sTIL level 50% or greater and 92% for a level less than 50% (HR, 1.35; 95% CI, 0.65-2.82). C, Ten-year BCSS was 92% for an sTIL level less than 30%, 97% for a level between 30% and 74% (HR, 0.41; 95% CI, 0.10-1.73), and 89% for a level 75% or greater (HR, 1.37; 95% CI, 0.62-3.05). TIL indicates tumor-infiltrating lymphocyte.

chemotherapy. We observed a 10-year BCSS of 96% for all patients with stage I TNBC with an sTIL level of at least 30% . Patients with pT1c tumors and sTIL levels 50% or greater had an excellent outcome, with a 10-year BCSS of 95% without neoadjuvant or adjuvant chemotherapy and a 10-year BCSS that increased to 98% if the sTIL levels were 75% or greater. Overall, patients with pT1ab tumors had good outcomes, and sTIL levels at the prespecified cutoffs were not associated with BCSS in this subset. These results support the use of sTIL level as a biomarker in selecting patients with stage I TNBC for whom chemotherapy can be optimized while preserving excellent outcomes.

Prior studies evaluating the role of sTILs in TNBC have predominantly focused on sTIL levels in patients who received neoadjuvant or adjuvant chemotherapy.[22,23] To substantiate treatment optimization decisions, data derived from chemotherapy-naive patients are needed to understand the natural history of the disease, especially in patients with stage I TNBC who may not all benefit from adjuvant chemotherapy. The results of the present study are in line with prior studies dem-

Figure 4. Breast Cancer–Specific Survival (BCSS) of Patients With pT1c Tumors



A, Ten-year BCSS was 95% for a stromal tumor-infiltrating lymphocyte (sTIL) level 30% or greater and 83% for a level less than 30% (hazard ratio [HR], 0.24; 95% CI, 0.10-0.60). B, Ten-year BCSS was 95% for an sTIL level 50% or greater and 84% for a level less than 50% (HR, 0.27; 95% CI, 0.10-0.74). C, Ten-year BCSS was 83% for an sTIL level less than 30%, 91% for a level between 30% and 74% (HR, 0.40; 95% CI, 0.15-1.10), and 98% for a level 75% or greater (HR, 0.09; 95% CI, 0.01-0.68). TIL indicates tumor-infiltrating lymphocyte.

onstrating sTILs' independent association with outcome in patients with early-stage TNBC who were not treated with chemotherapy.[4,24] The excellent 5-year survival, with a distant disease-free survival of 97% in the subset of patients with stage I disease and the sTIL level cutoff of 30% or greater, was confirmed in the present analyses at the 10-year and 15-year follow-ups.[4] Most of the prior studies lacked a central revision of pathology, including central assessment of TILs, and most were not based on formal registries.[4,22,23] This study, using a nationwide registry, adds to the existing knowledge of the role of sTILs in early-stage TNBC outcome by focusing on patients with stage I TNBC.

Median sTIL levels in prior studies ranged between 10% and 20%, which is slightly higher than the median of 5% observed in the present cohort.[4,22-24,27] Some of these previous studies also included stage II TNBC or higher and patients with node-negative as well as node-positive disease. Moreover, patients in these cohorts were generally younger (median age, ≤50 years).[23,28] The distribution of sTILs in this series was comparable to prior studies, although females younger than 40

years tended to have higher sTIL levels, with half of the patients having sTIL levels less than 30% compared with three-quarters with low sTIL levels in the present cohort.[24] Although in prior series sTIL levels were associated with outcome regardless of age distribution, age may be taken into consideration while defining sTILs cutoffs in clinical trial designs.

Generally, tumors with low expression of ER (ER low) can be considered TNBC. Recently, no significant differences in sTIL levels, CD8+ T cells, and programmed cell death ligand 1 expression were found when comparing ER-low (1%-9%) tumors with ER-negative (0%) tumors, suggesting that the immune landscape of ER-low tumors and true triple-negative tumors look alike.[29] Preliminary data from an Italian study that included over 100 ER-low cases suggested that the association of various sTIL levels with ER-low tumors is similar to what has been observed in TNBC.[30] Similarly, a study in *ERBB2*-low tumors observed no significant differences in sTIL levels between *ERBB2*-low and *ERBB2*-negative breast tumors.[31] However, ER and *ERBB2* levels were not available for the present series.

Given that guidelines differ regarding chemotherapy use among patients with pT1ab TNBC, while they universally recommend adjuvant chemotherapy for pT1c TNBC, we analyzed these pT stages separately. In contrast to the role of sTIL levels in pT1c tumors, the role of sTIL levels in pT1ab tumors is less clear. Ascertaining the size of very small tumors on histopathologic slides might be less accurate given that even the smallest variation of 1 mm changes stage I subclassification, and also measuring tumor size fresh or formalin fixed, already can give a change of a few millimeters.[32] The favorable outcome of patients with pT1ab tumors and low event rates in this subgroup suggests that large patient cohorts with longer follow-up are needed to define the role of sTIL level in pT1ab TNBC.

Although the association between sTIL level and OS follows a similar pattern as the pattern seen with BCSS, this association had a smaller magnitude. Given that only 107 of the 335 deceased patients died of breast cancer, these OS results are mainly associated with deaths from other causes. Moreover, the non-breast-cancer–related events were not equally distributed over the various TIL groups. Therefore, OS may not accurately reflect the role of sTILs in this cohort.

This study adds to the current 1B level of evidence of sTILs, indicating that sTILs may add outcome information on the risk of recurrence. Hence, recurrent risk cannot be ascertained based on standard clinicopathological factors alone and should, therefore, include a metric of preexisting cancer-immune interactions, namely sTILs. The global cumulative data on sTILs in the early setting support sTILs as an integral biomarker in future chemotherapy optimization trials for a broad population of patients with early-stage TNBC. Clinicians and patients should be aware of the association of sTILs with outcome, which is linear in a Cox proportional hazards regression model. Therefore, any cutoff for sTILs is debatable and should be considered in the context of other variables such as age, size, and nodal status.

Strengths and Limitations

The strengths of this study include the use of a nationwide registry to select patients with stage I TNBC alone, central pathology revision, and central scoring of sTILs who did not receive neoadjuvant and/or adjuvant chemotherapy. This study also has some limitations. First, the starting cohort consisted of a large yet observational set of patients, of whom half received adjuvant chemotherapy.[6] Since patients with favorable tumor characteristics may likely not have received adjuvant chemotherapy, the results might be skewed due to bias by indication, emphasizing the urge for a prospective clinical trial.[33] However, such a prospective de-escalation trial might also recruit patients with slightly more favorable clinicopathological characteristics, as this is the population for which the question of potential overtreatment is most relevant. Second, despite a relatively large cohort of patients with pT1ab tumors, the number of events in this subgroup was low. Merging data of pT1ab tumors with other similar cohorts will allow further exploration of BCSS and the role of sTILs in this patient population. Third, as expected from registry studies depending on historical cohorts, data on *BRCA1* and *BRCA2* germline status were lacking. Fourth, no data on recurrences and/or distant metastases were available. Fifth, the nationwide registry in the Netherlands does not include data on ethnicity, as most Dutch patients are White.

Conclusions

To our knowledge, this cohort study was the first to analyze the role of sTILs in the outcomes of a large cohort of patients with stage I TNBC solely and who did not receive neoadjuvant and/or adjuvant chemotherapy. Results were in line with previous studies that found some patients with early-stage TNBC had excellent outcomes for which the added value of chemotherapy can be debated. Recent US Food and Drug Administration approval for a continuing medical education course on sTIL level assessment as well as rapid development of artificial intelligence pipelines to digitize sTILs scoring will further facilitate the implementation of sTIL level in daily clinical practice. This study supports treatment-optimization clinical trials in patients with stage I TNBC using sTIL level as an integral biomarker to prospectively confirm the observed excellent survival when neoadjuvant or adjuvant chemotherapy is not administered to patients with TNBC.

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