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Research Article

CORRELATION OF TUMOR-INFILTRATING LYMPHOCYTES WITH CLINICOPATHOLOGICAL FEATURES AND TREATMENT OUTCOMES IN NON-METASTATIC BREAST CANCER PATIENTS

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A B S T R A C T

Introduction: Breast cancer is the second most common cancer in the world. Tumor-infiltrating lymphocytes impact tumor progression and response to therapies. Here we aimed to study TILS using the International Immunooncology Biomarkers Working Group guidelines and correlating TILS with clinicopathological characteristics, disease free and overall survival in non-metastatic breast cancer patients.

Methods: Non metastatic breast cancer patients (N = 86) who presented to our department between 2013 - 2015 were retrospectively evaluated. The eligible patients were reviewed retrospectively and primary treatment information was extracted from the medical records. For all of the patients, disease-free survival and overall survival were calculated.

Results: The majority of the patients were 45 years of age or less. The TILS percentage was measured using image analysis. Samples had a range of 1-100%, with a mean 22%. There was 9.3% of the patients having lymphocyte predominant (≥50%), while 90.3% had TILS percentage of <50%. Dividing the patients into low (0-20%), intermediate (20-<50%) and high (50-100%).

The distribution of TILS according to age showed trend towards decreasing TILS with increasing age. The majority of tumors in the study T1 and T2 tumors that had significantly higher TILS percentages compared to T3 and T4 with $p<0.006$. Patients who were N0 had a significantly higher TILS percentage when compared with N1 and N2 with a $p<0.032$.

There were 74.4% tumors of the luminal subtype, 11.6% of the Her-2 enriched and 12.8% of the triple negative. There was no statistically significant correlation between any molecular subtype and TILS, but a tendency for Her-2 enriched tumors and triple negative tumors to have a higher percentage of TILS.

Discussion: We noticed that there is a subgroup of patients with exceptionally high TILS, had a beneficial response to treatment and confer additional survival benefit with delayed relapse.

INTRODUCTION

Breast cancer is one of the most common cancers affecting women in the world. [(1)] It has accounted for 29 % of all new cancer cases and 14 % of all cancer deaths, becoming the second highest cause of cancer death in women after lung cancer. [(2)] Breast cancer is a heterogeneous disease, which is categorized into subtypes according to gene expressions and clinicopathological features. [(3)]

The choice of adjuvant therapy for non- metastatic breast cancer patient based on the pathological diagnosis which includes histological classification, tumor grade, the Ki67 labeling index (LI) and lymph node metastasis [(4,5).]

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However, regardless of adjuvant therapy, some tumors recur which is a critical problem that must be overcome to improve patient survival. [(5)]

The importance of tumor infiltrating lymphocytes (TILs) has increasingly been recognized in recent years. [(6)] The host immune system appears to influence the development and prognosis of breast carcinoma. [(7)] However, the relationships between TIL distributions and either histopathological types or the efficacies of systemic therapies still remain poorly understood.

We retrospectively collected data for non-metastatic breast cancer cases, and then identified clinicopathological factors

The intent of this retrospective study was to collect data of patients with breast cancer presented to clinical oncology and nuclear medicine department from January 2013 to December

2015 aiming at determining the prevalence of TILS in this sample of Egyptian cancer patients. Also we correlated the distribution of TILS with different histopathological criteria, clinical outcome of breast cancer patients, disease free survival and overall survival.

MATERIAL AND METHODS

A total of 901 patients with invasive breast cancer who presented to the Clinical Oncology and Nuclear Medicine Department, Alexandria Main University Hospital during this period, were retrospectively evaluated. Of these, 123 patients had corresponding pathology files and sufficient formalin-fixed and Paraffin-embedded tissue blocks for immunostaining in the Pathology Department, Faculty of Medicine

The exclusion criteria were as follows: patients with distant metastasis at initial presentation, bilateral breast carcinoma, male breast carcinoma, and patients with comorbidities that affected levels of inflammatory parameters, including, hematological disorders, and collagen disease. After review of these patients' files and their pathology slides, 86 were eligible for this study.

The eligible patients were reviewed retrospectively regarding the demographic status and clinical parameters (such as age, menopausal status, tumor size, lymph node status, histologic grade, lymphovascular invasion (LVI), estrogen receptor (ER) status, progesterone receptor status, human epidermal growth factor receptor 2 (HER2) status, and primary treatment information (including surgery, radiotherapy, and chemotherapy) were extracted from the medical records.
Follow-up

All patients underwent a physical examination at 3-month intervals after surgery, pelviabdomen U/S and chest CT at 6-month intervals and breast mammogram at 1-year intervals. For all of the available patients, disease-free survival (DFS) was defined as the interval between the date of diagnosis for breast cancer and the date of having evidence of recurrent events and overall survival (OS) was calculated from the date of diagnosis to death (of any causes) or the date of the last follow-up.

All patient samples were obtained before any treatment modality using core needle biopsies, and samples were fixed in 10% formaldehyde solution and then embedded in paraffin. The formalin-fixed paraffin-embedded specimens were cut into 3 µm thick sections for IHC staining. The methodology for assessment of TILS distribution was based on the TILS International Working Group 2014 recommendations [8] as summarized below and in Figure 1:

1. Scoring of TILS was done on 4-5µ sections of PEFF tissues obtained either from core biopsies or surgical specimens and stained with H&E stains.
2. For each case one section was examined with microscope magnification ranging from ×200–400.
3. For each section five different fields were examined, without focusing on hot or cold spots, and the mean was calculated for each case.
4. TILS were reported as the % stromal TILS. The denominator used to determine the % stromal TILS is the area of stromal tissue (i.e. area occupied by mononuclear inflammatory cells over total intratumoral stromal area), using image analysis for all cases.
5. TILS were evaluated within the borders of the invasive tumor.
6. TILS outside the tumor border, around DCIS, around normal lobules, at crushed areas, necrosis and showing regressive hyalinization were excluded.
7. All mononuclear cells (including lymphocytes and plasma cells were scored, while polymorphonuclear leukocytes were excluded.
8. TILS were assessed as a continuous parameter. For the purpose of this study the 50% mark was used as the threshold for lymphocyte predominant breast cancer (LPBC).

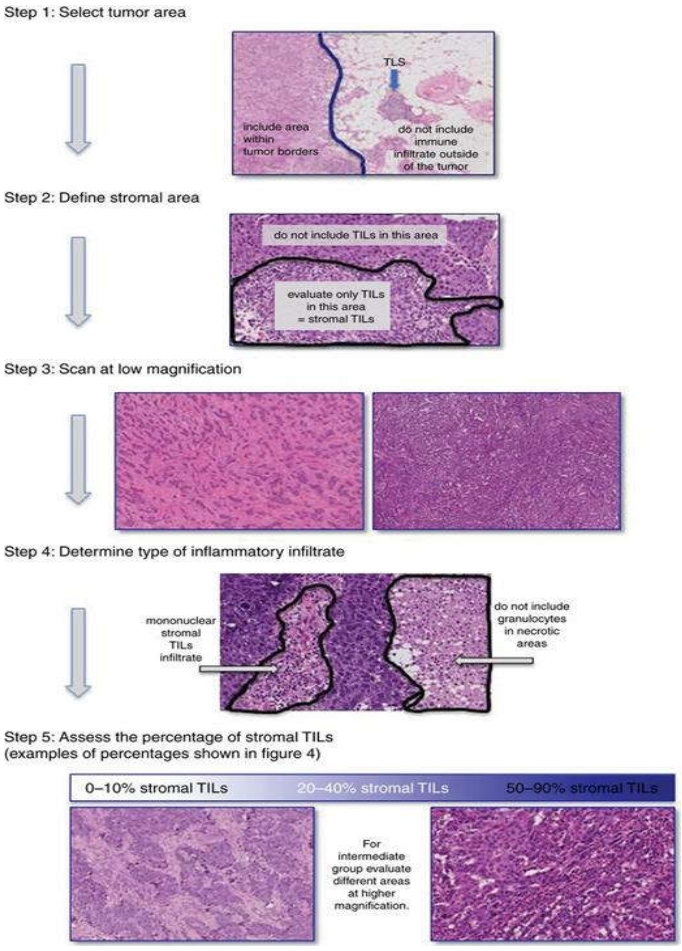

Figure 1 Figure showing assessment of TILS according to TILS international collaborative group guidelines. (8)

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

RESULTS

All patients were female with a median age of 48 years at the time of diagnosis. The majority of patients were 45 years of age or less; while 26.7% were above the age of 55 years. The majority of patient 68.6%, underwent modified radical

mastectomy and 88.4%, underwent complete axillary lymph node dissection.

The TILS percentage was measured using image analysis. All samples had a range of 1-100%, with a mean 22%. There was 9.3% of the patients having lymphocyte predominant breast cancer (≥50%), while 90.3% had TILS percentage of <50%. Dividing the patients into low (0-20%), intermediate (20-<50%) and high (50-100%). TILS percentage gave us 62.7%, 27.9% and 9.3% of the patients respectively as seen in figures 2,3.

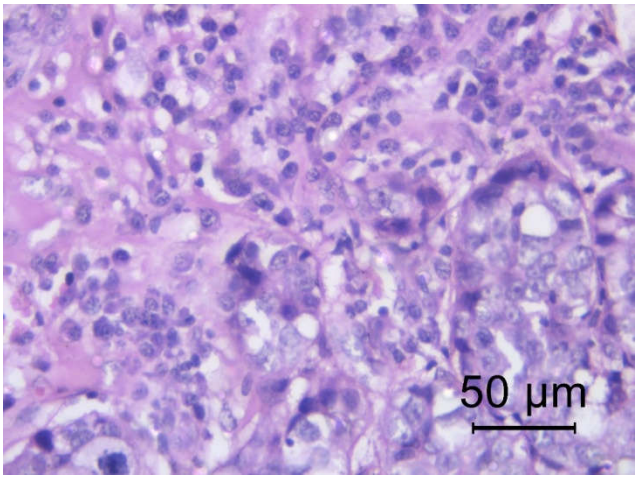

Figure 2 A postoperative image of a triple negative tumor under high magnification (x400) using simple H&E stain showing cancer cells and stroma with high infiltration of lymphocytes.

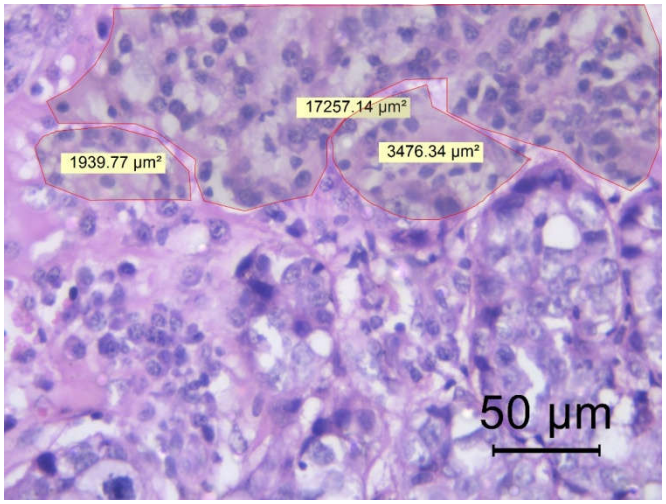

Figure 3 The same image with the stroma highlighted and its area calculated, since the stroma is separated we add all the different stromal areas to total of 22673µm^2.

The distribution of TILS according to age showed a trend towards decreasing TILS with increasing age, and this was not statistically significant. The majority of tumors in the study were T2 (60.5%) followed by T1 (15.1%). T3 and T4 tumors represented 14% and 8.1% respectively. T1 and T2 tumors had significantly higher TILS percentages compared to T3 and T4, mean 24.94% versus mean 13.37% respectively. Using the t-test this showed a p<0.006.

The majority of patients in the study were N1 at 62.8% followed by an equal percentage of 17.4% as both N0 and N2. Patients who were N0 had a significantly higher TILS percentage when compared with N1 and N2, mean 33.07% versus mean 20.0% respectively. This was statistically significant using the t-test with a p<0.032 (table 1).

Table 1 Relation between histopathological parameters and tumor infiltrating lymphocytes TILS (%)

Clinical staging	N	Tumor infiltrating lymphocytes (TILS %)		
		Min. – Max.	Mean ± SD.	Median
T				
Tx	2	4.0 – 25.0	14.50 ± 14.85	14.50
T1	13	2.0 – 100.0	24.92 ± 27.04	18.0
T2	52	2.0 – 98.0	24.94 ± 22.0	18.0
T3	12	1.0 – 40.0	12.33 ± 14.07	6.0
T4	7	2.0 – 33.0	15.14 ± 9.56	15.0
N				
Nx	2	3.0 – 25.0	14.0 ± 15.56	14.0
N0	15	5.0 – 100.0	33.07 ± 29.47	19.0
N1	54	1.0 – 62.0	20.94 ± 17.03	17.50
N2	15	2.0 – 98.0	16.60 ± 24.32	6.0
LVI				
No	28	1.0 – 100.0	23.86 ± 26.71	17.50
Yes	51	1.0 – 62.0	21.18 ± 16.35	17.0
N/A	7	2.0 – 87.0	22.29 ± 30.99	7.0
PNI				
No	40	2.0 – 100.0	23.75 ± 23.88	17.50
Yes	41	1.0 – 62.0	19.85 ± 16.28	15.0
N/A	5	2.0 – 87.0	28.0 ± 35.99	7.0
ECE				
No	70	1.0 – 100.0	23.71 ± 22.38	18.0
Yes	9	2.0 – 25.0	11.67 ± 8.41	9.0
N/A	7	2.0 – 54.0	19.86 ± 19.16	15.0

All the patients in the study underwent diagnosis by either FNA or CNB, and this was followed by either primary surgical treatment or NAC. Their histopathological data was collated and analysed and the majority (91.9%), had IDC NOS. About 70.9% of patients had grade II and 10.5% grade III.

There was a strong tendency for grade III tumors to have much higher TILS, when compared with grades I and II. This was statistically significant using logical regression and t-test to a p-value of 0.035. The majority of cases (59.3%) had positive lymphovascular invasion and 47.7% had positive Perineural invasion. there was no statistically significant correlation between the percentage of TILS with LVI and PNI as seen in table 1. The extracapsular extension was observed in 10.5% of the patients and there was a statistically significant higher percentage of TILS in patients with no ECE in comparison with those with ECE, p<0.004.

Also in this study, there were 74.4% tumors of the luminal subtype, 11.6% of the Her-2 enriched subtype and 12.8% of the triple negative subtype. There was one case (1.2%) that had no IHC analysis done on either the biopsy or the surgical specimen. Although there was no statistically significant correlation between any molecular subtype and TILS, there was a tendency for Her-2 enriched tumors and triple negative tumors to have a higher percentage of TILS in comparison with luminal subtypes as seen in table 2.

Table 2 Relation between molecular receptors and tumor infiltrating lymphocytes TILS % (n =86)

Final	N	Tumor infiltrating lymphocytes (TILS %)		
		Min. – Max.	Mean ± SD.	Median
ER				
Negative (0)	**21**	2.0 – 100.0	27.33 ± 28.93	18.0
Weak (1+)	**6**	3.0 – 40.0	19.67 ± 16.29	17.0
Moderate (2++)	**13**	5.0 – 62.0	24.38± 20.63	17.0
Strong (3+++)	**45**	1.0 – 87.0	19.78 ± 17.92	17.0
N/A	**1**		5.0	
PR				
Negative (0)	**28**	2.0 – 100.0	24.86 ± 26.19	16.50
Weak (1+)	**3**	6.0 – 12.0	8.33 ± 3.21	7.0
Moderate (2++)	**17**	1.0 – 87.0	22.12 ± 22.10	17.0
Strong (3+++)	**37**	1.0 – 62.0	21.68 ± 17.55	18.0

N/A	**1**		5.0	
HER-2				
Negative (0)	**44**	1.0 – 100.0	22.84 ± 22.97	17.50
Weak (1+)	**1**		6.0	
Moderate (2++)	**11**	4.0 – 87.0	25.09 ± 23.76	25.0
Strong (3+++)	**23**	2.0 – 65.0	18.70 ± 17.13	12.0
N/A	**7**	4.0 – 53.0	26.71 ± 22.12	25.0
BC subtypes				
Luminal A	**40**	1.0 – 62.0	21.28 ± 17.92	17.50
Luminal B	**24**	2.0 – 87.0	19.75 ± 18.90	13.50
Her2 Enriched	**10**	4.0 – 65.0	23.20 ± 21.36	16.50
Triple –ve	**11**	2.0 – 100.0	31.09 ± 35.08	19.0
N/A	**1**		5.0	

There was an OR of 0.348 (95% CI 0.06-2.02) and 0.397 (95% CI 0.07-2.27) for Her-2 enriched and triple negative tumors to be lymphocyte predominant breast cancers (LPBC), meaning they have TILS ≥50%. Also, there was a statistically significant hazard ration for Her-2 enriched and triple negative tumors with increasing TILS percentage as an interrupted variable into low, intermediate and high (low=0-20%, intermediate=20-50%, high=50-100%). For Her-2 enriched tumors this was significant with a p=value of 0.021 and for triple negative tumors the p-value was 0.025. There was no statistical significance with overall survival.as seen in figure (4).

The majority of patients in the study were disease free at the time of the study while 36% of the patients had relapse. 1.2% had local relapse in the same breast, 2.3% had locoregional relapse in the LN or mastectomy scar, 16.3% had local or locoregional plus distant relapse, and 16.3% had only distant metastasis. Of the 32.6% who had distant metastasis the largest percentage, 9.3%, had bone only metastasis, followed by 8.1% with visceral plus bone metastasis, 5.8% with visceral only metastasis, 3.5% with brain only metastasis, 3.5% with visceral plus brain metastasis and 2.3% with bone plus brain metastasis.

There was a definite tendency for favorable outcomes to have higher TILS across the board. Patients who were disease free had significantly higher TILS percentages than those who relapsed, regardless of the type of relapse, mean 25.92% versus mean 16.68% respectively. There was a statistically significant difference between patients who had distant metastasis and those who didn't, mean TILS percentage for distant disease free was 26% versus mean 14.79% for patients with distant disease Of the patients in the study 62.8% were alive at the time; 52.3% were alive and disease free and 10.5% were alive with local or distant disease; while 10.5% were confirmed dead and 26.7% were untraced.

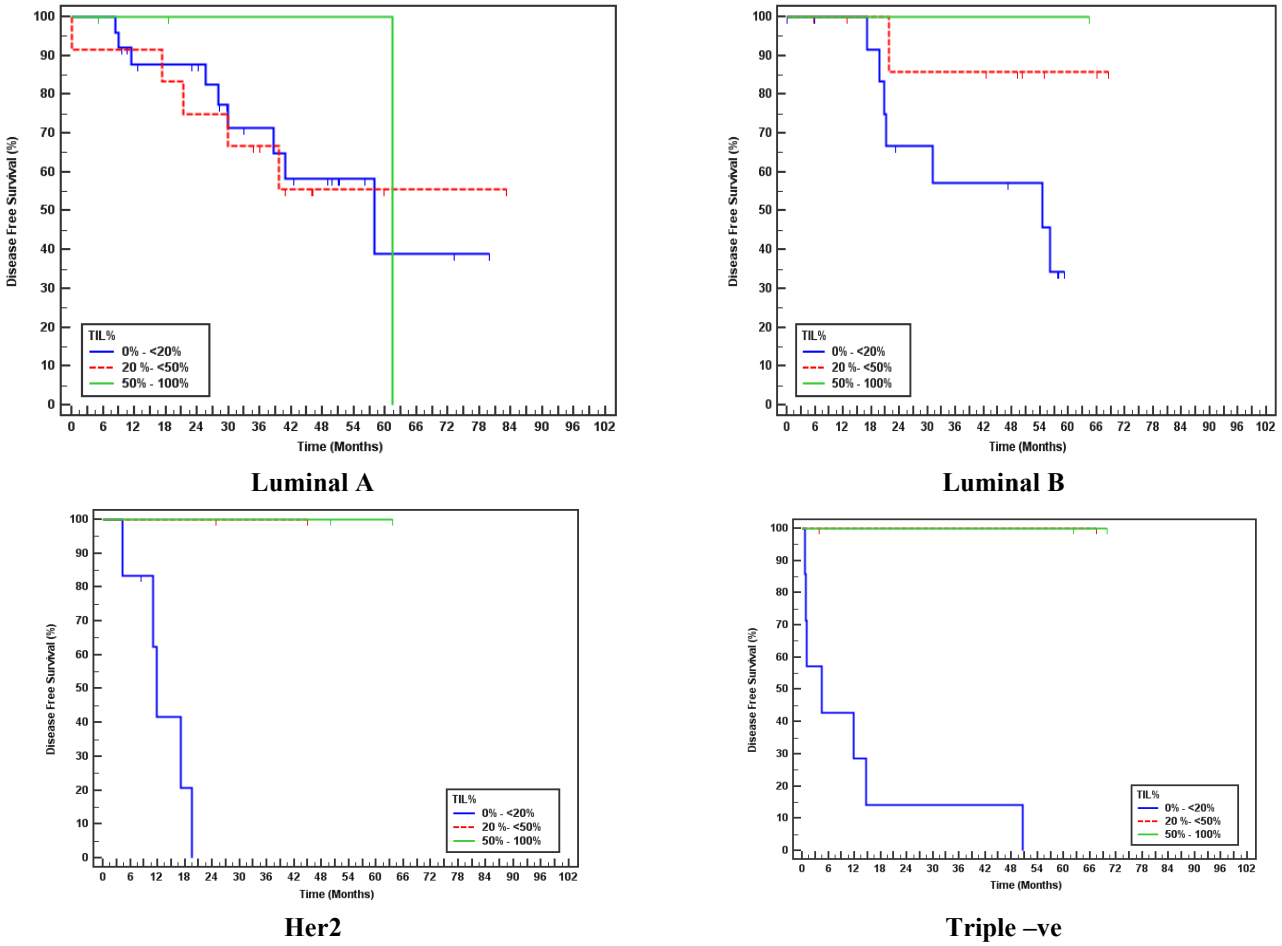

Figure 4 Kaplan-Meier curves for disease free survival by molecular subtype and TILS (%) divided into low, intermediate and high

The majority of our patients, 64%, did not receive neoadjuvant chemotherapy, while only 34.9% received NAC. The most common regimen used was FAC (Flurouracil, Adriamycin and Cyclophosphamide). Patients who received NAC had a statistically significant lower percentage of TILS than those who did not using univariate logical regression, p=0.008.

The mean period for disease free survival was 52.45 months, with 1 year DFS of 85.3% and 5 year DFS being 47.1%. The mean of overall survival was 74.63 months, with 1 year OS being 85.3% and 5 year OS being 47.1%.

Patients who were disease free had a much higher percentage of TILS in comparison with either those who were alive with disease or dead, mean 27.84% versus 16.11% and 18.22% respectively as seen in table10 and 11. Using the Pearson coefficient there was a strong correlation between TILS percentage and both DFS and OS that was statistically significant, p=0.002 for DFS and p=0.027 for OS. (Figure 5,6)

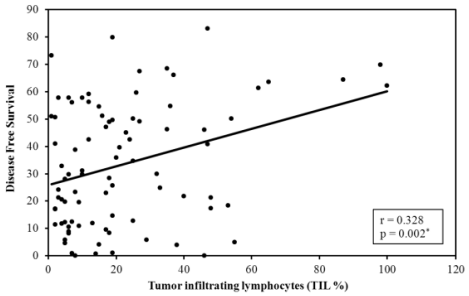

Figure 6 Correlation between TILS % and OS.

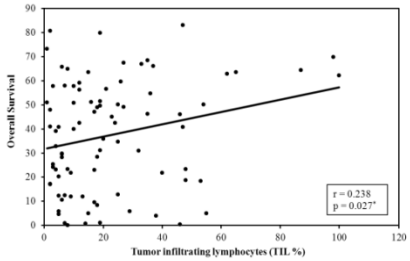

Figure 5 Correlation between (TILS %) and DFS

There was also a statistically significant linear regression between DFS and TILS as both a LPBC and non-LPBC variable and as an interrupted variable (low, intermediate and high), with p=0.048 and 0.003 respectively. This statistical significance failed to be achieved with OS, despite there being a tendency for patients with higher TILS to have longer OS.

DISCUSSION

Tumor infiltrating lymphocytes represent the emergence of the tumor microenvironment as a target for both prognosis and treatment. [(9)] Most of the studies done on TILS have focused on the relationship between NAC using different regimens with TILS as a predictor of pathological complete response [(10)] We evaluated the reproducibility of the International TILS Working Group recommendations for the evaluation of TILS and as well as correlating TILS percentages with the histopathological characteristics of the patients, disease free and overall survival in non-metastatic breast cancer patients.

We used image analysis to evaluate the TILS for all the patients, using the guidelines by the International TILS Working Group in 2014 and updated in 2017. All the analysis was done on H&E stained samples and we evaluated the tissue samples on low magnification then on high magnification. We highlighted the stroma excluding the tumor cell nests and the computer calculated its area. We then started highlighting the TILS in the stroma and the computer calculated the area occupied by them. We excluded areas of necrosis or crush injuries, as well as other immune infiltrates in the stroma or inside the tumor.

We observed that there was a tendency for patients with increasing TILS to be younger in age that was in accord with the finding of Denkert *et al* 2010.[(9)] The T1 and T2 tumors had statistically significant higher TILS than T3 and T4 (mean 24.94% ± 22.86% versus 13.37% ± 12.38% respectively with p=0.006). This difference indicates that high TILS indicate an active immune response that prevents disease progression. In Denkert *et al* 2010 they found no significance with TILS and tumor size, but they used tumor size <4 and ≥4cm [(9)] while Lee *et al* they found a significant disease free survival hazard ratio for T1 versus >T1 with increasing TILS, HR 2.53 (95% CI 1.10–5.83) p=0.029. [(11)]

When comparing N0 patients with N1 and N2 we had statistically significant difference in their TILS%, mean 33.07% ± 29.47% for N0 patients and 20.0% ± 18.74% for N1 patients. This gave us a p-value of 0.032 using the t-test and univariate linear regression. In Denkert *et al* 2010 and 2016 they had the same division of N0 versus >N0 but failed to achieve any statistical significance.[(9,10)] This is further evidence of the active role of TILS in preventing disease progression, especially considering the importance of LN status as both a prognostic and predictive factor in BC.

Tumors with grade III had much higher TILS, mean 32.62% ± 28.34%, when compared with grades I and II, mean 20.9% ± 19.30% with p-value of 0.035. This result was consistent with what was seen by Wang *et al*, in their meta-analysis, where they found an OR was 0.45 (95% CI, 0.30–0.68, P < 0.001), suggesting that TILS are associated with a high histological grade and this is explained by the fact that the higher grade tumors cause higher recruitment of immune cells thus initiating a more robust immune response in an attempt to control what is considered an aggressive characteristic. [(12)]

Although there was no statistically significant correlation between the percentage of TILS with LVI and PNI, there was a tendency for tumors with negative LVI and negative PNI to have higher TILS percentages. However there was a statistically significant higher percentage of TILS in patients with no ECE in comparison with those with ECE, using the t-test, p<0.004. The data for the relationship between LVI and TILS was investigated in Lee *et al*.[(11)]

In our study, tumors that were ER/PR negative, regardless of HER-2 status tended to have higher TILS percentages than those with hormone positive, although this difference was not statistically significant. This was inconsistent with what was found in Denkert *et al*, where they found statistical significance in ER/PR- versus ER+ and/or PR+, OR 3.78 95% CI 1.52 to 9.41, p<0.004. [(9)] We believe that this difference is due to the difference in the size of the cohorts.

Triple negative tumors tended to have the highest percentage of TILS, mean 31.09% ± 35.08% with a range of 2.0% – 100.0% and median 19%. This was followed by HER-2 enriched tumors that showed a mean of 23.20% ± 21.36% with a range of 4.0%-65.0% and median 16.5%, with the lowest TILS percentages being found in luminal tumors, mean 20.0% with a range of 1.0%-62.0% and median 15%. This was close to the results of a recent systemic review of the literature by Solinas *et al*, where they found that triple negative tumors had median TILS of 15-25%, Her-2 enriched tumors had TILS with a median of 15-20% and luminal tumors had a median of 7-10%. [(13)]

We then ran a hazard ratio analysis by molecular subtype and TILS divided into increments of low (0-20%), intermediate (20-<50%) and high (50-100%) to study whether incremental increases of TILS make a difference or only whether the tumor is LPBC or not. The disease free survival HR was significant

for both triple negative and HER-2 enriched tumors, with a p-value of 0.025 and 0.021 respectively. The HR for luminal tumors failed to reach statistical significant, as well as the overall survival HR for all subtypes. This indicates that every incremental increase of 10% in TILS confers and additional benefit for disease free survival in triple negative and HER-2 enriched patients.

This was consistent with what Denkert *et al* published in a pooled analysis of previous trials in 2017. They found that every 10% increase in TILS was associated with longer disease-free survival in triple-negative breast cancer and HER2-positive breast cancer but not in luminal HER2-negative disease. [(14)]

The majority of patients in the study, 76.7%, received adjuvant chemotherapy, the regimen most commonly used was FAC, on 34.9% of the patients, followed by 16.3% receiving AC and taxanes, then 14% received single agent taxanes. The majority of patients in the study, 61.7%, received hormonal treatment, either aromatase inhibitors or tamoxifen or both, but only 10.5% received Herceptin, while 66.3% received their radiotherapy. We found no correlation between any of these factors and TILS. We should have found a correlation between Trastuzumab and TILS, as multiple trials have demonstrated the additional benefit that high TILS confer on the patient. [(15)] There was a definite tendency for favorable outcomes to have higher TILS across the board. Patients who were disease free had significantly higher TILS percentages than those who relapsed, regardless of the type of relapse, mean 25.92% versus mean 16.68% respectively. The patients with local relapse had TILS than patients who had distant however, this did not reach statistical significant. There was a statistically significant difference between patients who had distant metastasis and those who didn't, mean TILS percentage for distant disease free was 26% versus mean 14.79% for patients with distant disease, p=0.028. This is a clear indicator that for tumors to metastasize they have to first undergo immune escape.

The mean of overall survival was 74.63 months, with 1 year OS being 85.3% and 5 year OS being 47.1%. Patients who were disease free had a much higher percentage of TILS in comparison with who were alive with disease or dead, mean 27.84% versus 16.11% and 18.22% respectively.

The high TILS confer a benefit for DFS in all tumor subtypes and this matches with what was published by Denkert *et al* 2016 and Mayoshi *et al* 2018, that found that high TILS confer benefits in luminal tumors to some extent, more specifically luminal B tumors.[(15,16)] In Savas *et al* and Solinas *et al* there were correlation between LPBC in triple-negative on OS but we failed to show this using linear regression analysis.[(17,18)] We believe that this could have been achieved in a larger study.

CONCLUSIONS

We were able to reproduce the International Immunooncology Biomarkers Working Group guidelines, using image analysis, may be considered a viable standardized method for the evaluation of TILS in clinical practice. TILS confer additional benefit to the patient in terms of disease free and overall survival. Increasing TILS correlate closely with early and localized disease, in terms of tumor size and unilaterality and may be considered a prognostic biomarker for LN negative disease. High TILS counts were particularly associated with Her-2 enriched and triple negative BC which significantly delays disease recurrence. There also may be an OS benefit conferred with higher TILS, although this needs further study.

Declaration of interest statement

The authors report no conflict of interest.

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