The Predictive Potential of the Spatial Signature of Lymphocytes In Breast Cancer Patients

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INTRODUCTION

- Tumor-infiltrating lymphocytes (TILs) in breast cancer have emerged as both a prognostic and a potentially predictive immunotherapy biomarker.
- Advancements in artificial intelligence can extract pathology-based immune fingerprints for use as treatment decision support tools.
- We hypothesized that a spatial analysis of TILs in the Tumor Microenvironment (TME) by a novel AI-based model may predict prognosis of early stage ER+ breast cancer patients.

METHODS

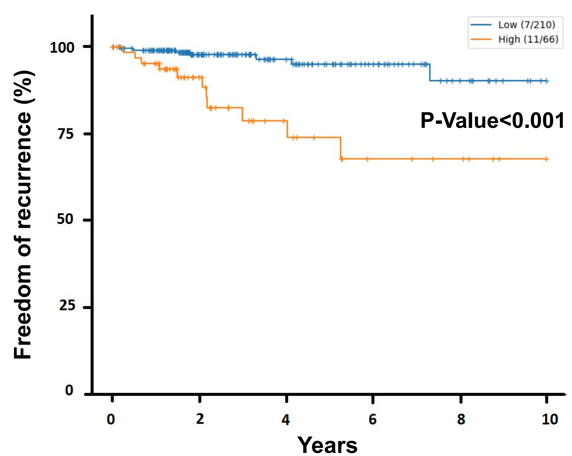
- We examined 399 ER+ stage I-II breast cancer patients with whole slide images (WSI) available from TCGA database. 276 patients (70%) were used for training and 123 patients (30%) for validating the model.
- Digital structuring of WSIs, including automated detection of lymphocytes, tumor and tumor adjacent stroma, was performed using a novel deep learning-based semantic segmentation system (Nucleai, Tel Aviv).
- A Cox Survival analysis was used to detect prognostic spatial features. Prognosis was defined as progression free interval (PFI) - the time between diagnosis to progression or death.
- A principal component analysis (PCA) was used to reduce and decorrelate significant features. The resulting PCA features were used to fit the final model.
- The model was then validated on an independent database of 42 WSI of breast lumpectomies from two tertiary hospitals in Israel - Sheba Medical Center and Kaplan Medical Center,

RESULTS

- The **detection performance** for tumor area and lymphocytes in the TCGA validation set reached scores of **99% and 97% respectively**, in comparison to human annotation.
- In a Kaplan-Meier (KM) analysis, several spatial features, like a **high number of TIL clusters were significantly associated with longer PFI (P<0.005)**. In a multivariate analysis, the model remained significantly associated with PFI after adjusting to age and stage, in both the training and validation sets.
- We used the model to determine a high and a low risk groups. The rates of distant recurrence at 10 years in the low-risk, and high-risk groups were **3% vs 16% (P<0.001).**
- The independent validation cohort was underpowered. However, in a preliminary analysis low risk patients had longer PFI (P=0.046).

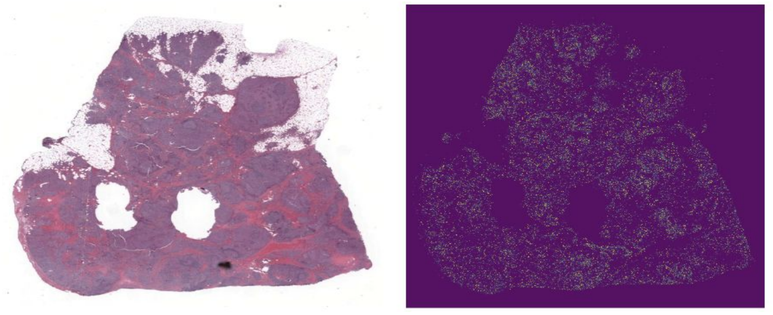
A multivariate Cox Proportional Analysis of Age, Stage and prognostic score in relation to progression free interval

Variable (training set)	P-Value	Hazard Ratio (95% CI)
Age at diagnosis	0.12	1.14 (0.97-1.35)
Stage	0.2	2.07 (0.68-6.31)
Spatial Recurrence Score	**<0.001**	6.61 (2.51-17.46)

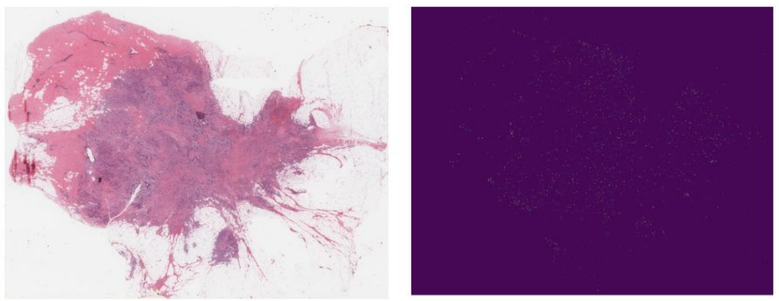


RESULTS (Continued)

A biopsy of a patient identified as a **low risk** patient by the algorithm and the heatmap showing a high density of TILs (PFI: 2632 days)



A biopsy of a patient identified as a **high risk** patient by the algorithm and the heatmap showing a low density of TILs (PFI: 756 days)



CONCLUSIONS

- Using a novel AI-based system for the characterization of tumor infiltrating lymphocytes in breast cancer biopsies, we showed that various spatial features can predict patient prognosis.
- Higher number of TIL clusters is associated with longer PFI and a lower recurrence rates, suggesting that the spatial organization of the immune system is prognostic for ER+ early stage breast cancer patients.

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