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

Nora Balint-Lahat¹*, Chen Mayer¹*, Noa Ben-Baruch², Ady Yosepovich², Kira Sacks³, Shahar Ish-Shalom², Dana Morzaev-Sulzbach¹, Einav Nili Gai-Yam¹, Albert Achtenberg⁴, Yuval Gabay³, Roman Gluskin⁴, Alon Griosman³, Yuval Shachaf³, Amir Luchtenstein³, Ori Zelichov³, Kathrina Alexander³, Alexander J. Lazar⁴, Iris Barshak¹

¹Chaim Sheba Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, ²Kaplan Medical Center, Rehovot, Israel, ³Nucleai. Ltd, Israel, ⁴The University of Texas MD Anderson Cancer Center, Houston, TX. *The two authors contributed equally to this work

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.

- The independent validation cohort was underpowered. However, in a preliminary analysis low risk patients had longer PFI (P=0.046).

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.

Corresponding Authors: nora.balintlahat@sheba.health.gov.il, chen.mayer@sheba.health.gov.il