SPATIAL ARRANGEMENT AND DENSITY OF TUMOR-INFILTRATING LYMPHOCYTES (TILS) PREDICTS RESPONSE TO IMMUNOTHERAPY IN HEAD AND NECK SQUAMOUS CELL CARCINOMA PATIENTS

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Background Anti-PD-1 immunotherapies (IOs) have robust clinical benefit in a subset of head and neck squamous cell carcinoma (HNSCC) patients and is considered as a standard of care option in the recurrent/metastatic setting. Previous studies showed association of higher number of lymphocytes and density of tumor-infiltrating lymphocytes (TILs) with better survival probability and prognosis in HNSCC patients. In this study, we evaluate whether the spatial interplay between TILs with surrounding nuclei and TIL density from digitized H&E-stained slides was associated with better immunotherapy response in HNSCC patients.

Methods Whole slide images (WSIs) from 43 HNSCC patients treated with IO at University Hospitals, Cleveland were selected. Response to immunotherapy was defined as per RECIST v1.1. Computerized algorithms identified and built clusters for nuclei of TILs and TIL density and spatial arrangement of the clusters was quantified using network graph-metrics. To assess the predictive ability of the combination of spatial arrangement and density features of TILs, a cross-validation scheme was used as follows: at each iteration, the dataset was randomly split into training (60%) and validation sets (40%). The Wilcoxon method selected top two features in the training set, then used to train a Naïve Bayes classifier to differentiate between responders and non-responders. Next, the classifier was applied to the validation set and its performance was evaluated by computing the area under the curve (AUC) for the receiver operating characteristic (ROC) curve. This process was repeated 250 times. For comparison, the same cross-validation procedure was used on (1) TIL arrangement and (2) TIL density features.

Results Figure 1(A) and 1(B) show the violin plots corresponding to the two selected top features across the cross-validation iterations for responders and non-responders. Figure 1(C) illustrates the average ROC curves for the three assessed models and corresponding AUC. The average AUCs for the model based on combination (TIL arrangement + TIL density), TIL arrangement and TIL density only yielded an average AUCs of 0.84+0.14, 0.81+0.02 and 0.74+0.06 respectively. After DeLong assessment of the ROC curves, significant difference was found for TIL combination vs. TIL density (p=0.03) whereas no significant difference was found for TIL combination vs. TIL arrangement (p=0.55).

Conclusions We present a predictive model based on image biomarkers i.e. spatial interplay between TILs and surrounding nuclei along with TIL density in order to distinguish HNSCC patients responding and not responding to immunotherapy. The model based on TIL combination performed better in comparison to only TIL density.