COMBINATION OF NOVEL BIOMARKERS OF COLLAGEN FIBER AND IMMUNE ARCHITECTURE ARE ASSOCIATED WITH CLINICALLY RELEVANT OUTCOMES IN GYNECOLOGICAL CANCERS TREATED WITH IMMUNOTHERAPY

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Background Qualitative studies suggest collagen fiber organization (CFO) is associated with gynecological cancer (GC) prognosis.1, 2 Previous studies have shown the prognostic role of quantitative characterization of architecture of tumor-infiltrating-lymphocytes and their interplay with cancer cells in GC prognosis, known as ArcTIL.3 However, combination of CFO and immune architecture in GC prognosis is not yet studied. In this work, we use computational and machine learning tools to develop quantitative biomarkers combining collagen fiber orientation disorder (CFOD) and ArcTIL features from H&E slides and evaluate its association with progression-free-survival (PFS) in women undergoing surgical resection followed by immunotherapy.

Methods Whole-Slide-Images (WSIs) of H&E slides from surgically-resected ovarian cancer treated with adjuvant chemotherapy were obtained from TCGA used for training (St, n=95) and surgically-resected GC treated with adjuvant immunotherapy were obtained from Cleveland Clinic Foundation used for validation (Sv, n=48). ArcTIL features were derived from cell cluster graphs of nuclei within epithelial nests, surrounding stroma, and invasive tumor front compartments of WSI. The ArcTIL model previously developed by our group,3 was used for this study and prognostic subset having 7 features was selected. For calculating CFOD, WSI was partitioned into array of tumor neighborhoods and then entropy of fiber orientations in stromal regions was quantified within each neighborhood using derivative-of-Gaussian model. The first-order-statistics of CFOD feature maps were extracted for 9 different neighborhood sizes, yielding 27 features. Using these features, three Cox Regression models (CRM+LASSO) were trained that assigned risk of recurrence to each patient in St. The CRM+LASSO model trained using CFOD features selected 9 features, model trained using ArcTIL features selected 4 features and model trained using CFOD+ArcTIL features selected 6 features (4 ArcTIL and 2 CFOD features) for predicting risk scores in St and Sv. For each model, the mean risk score obtained in St was used to stratify patients as low, high-risk in Sv.

Results In Sv (figure 1, table 1), univariate analysis yielded Hazard-Ratio= 2.74, p-value= 0.03 for high-risk CFOD+ArcTIL. Multivariable analysis controlling for prognostic clinical variables, FIGO Stage (I, II, III, IV) and Tumor Grade (1, 2, 3), showed CFOD+ArcTIL (Hazard-Ratio= 2.84, p-value= 0.02) was independently associated with PFS.

Conclusions Our results found that CFO is more ordered in high-risk patients (figure 2) and evenly distributed, smaller clusters in ArcTIL-defined low-risk patients. Independent multi-site validation should allow for deployment of CFOD+ArcTIL as a prognostic decision support tool for management of GC patients treated with immunotherapy.

REFERENCES

Abstract 61 Figure 1 Kaplan Meier Curve of CFOD+ArcTIL model, validated on 48 patients of Cleveland Clinic Foundation cohort treated with immunotherapy (p-value= 0.03, Hazard-Ratio= 2.74, 95% Confidence Interval= 1.13–6.6)

Abstract 61 Figure 2 Example 3000x3000 tile of High-risk patient (top) and Low-risk patient (bottom) predicted by the CFOD+ArcTIL model. We observe CFO to be more ordered for high-risk patients as compared to low-risk patients (as seen in the right sub-figures which is the heatmap representing the disorder in CFO)
Abstract 61 Table 1  Performance of CFOD, ArcTIL and CFOD + ArcTIL models, validated on 48 patients of Cleveland Clinic Foundation cohort treated with immunotherapy (Sv)

<table>
<thead>
<tr>
<th>Features</th>
<th>C-Index</th>
<th>p-value</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
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<tr>
<td>CFOD</td>
<td>0.54</td>
<td>0.38</td>
<td>1.35 (0.69-2.6)</td>
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<td>ArcTIL</td>
<td>0.59</td>
<td>0.13</td>
<td>1.79 (0.84-3.8)</td>
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<tr>
<td>CFOD + ArcTIL</td>
<td>0.6</td>
<td>0.03</td>
<td>2.74 (1.13-6.6)</td>
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