96 THE IMPACT OF RADIOGRAPHIC TUMOR THICKNESS ON THE COMPLEXITY OF THE TUMOR IMMUNE MICROENVIRONMENT IN MALIGNANT PLEURAL MESOTHELIOMA

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Background Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer associated with exposure to asbestos with limited treatment strategies and poor prognosis.[1] There is no curative treatment for MPM, and patients follow standard treatment options.[2,3] Radiographic tumor thickness (TT) has recently emerged as a surrogate marker associated with overall survival,[4] however, the influence of TT on the complexity of the immune component within tumor microenvironment is unknown. Our aim was to perform comprehensive profiling of the tumor immune microenvironment (TIME) relative to the TT to understand of this relationship to guide the design of novel treatment strategies.

Methods Tumor specimens (n=29) were obtained from surgically managed MPM patients. Analysis was performed based on the median tumor thickness of 80mm, which defined thick vs thin groups. Additional analysis used TT as a continuous variable for correlations with immune features. The immune cell composition in the TIME was determined by flow cytometry (n=23). Transcriptomic profiling (n=20) was assessed using Nanostring nCounter Tumor Signaling 360 panel. Expanded tumor-infiltrating lymphocytes (TIL) were utilized for further characterization by 10x Genomics single cell RNA-seq profiling (n=8) and cytotoxicity assays (n=18). Level of significance was determined using unpaired non-parametric statistical test.

Results Fresh tumor tissue cytometry showed substantial differences in the immune profiles for thick versus thin tumors, highlighting a relationship of the TT and its immune composition. Thin tumors contained more Tregs, and higher OX40 expression ($p=0.081$ for non-Treg CD4+ and $p<0.05$ for CD8+ T cells), CTLA4, LAG3, TIGIT and Ki67 in TIL, while PD-1 expression was not associated with TT. Gene expression profiling suggested an impaired adaptive immune response in thin tumors compared to thick tumors characterized by the exhausted CD8 score ($p=0.0252$), T-cell co-stimulation score ($p=0.0387$) and TNF superfamily member score ($p=0.0159$) and a subset with a myeloid immune evasion score ($p=0.0387$). TIL expansion was not impacted by baseline TT. However, TIL cytotoxicity, as measured in a redirected lysis assay, showed IFN-gamma response was negatively correlated with baseline TT ($p=0.023$, $R2=0.28$). Expanded TIL clustering based upon single cell profiling is underway.

Conclusions Utilizing multi-platform immune profiling approaches, we observed a distinct relationship between the TT and immune signatures. Understanding underlying immune signatures underpinning the biology of thick versus thin MPM tumors provides insights to potential responsiveness to immune-based therapies and may inform on the design for future novel strategies relative to the disease extent based on TT.

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Ethics Approval This study was approved by the University of Texas MD Anderson Cancer Center's IRB; approval number LAB08-0380; participants gave informed consent before taking part.

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