DIGITAL FUNCTIONAL IMAGING AT MICROSCALE: A STUDY OF OSTEOSARCOMA TREATMENT RESISTANCE

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Abstract

INTRODUCTION

Osteosarcoma is a malignant primary bone tumor that primarily affects children and young adults. It is characterized by the disorganized production of bone by tumor cells. The high genomic complexity of osteosarcoma has hindered the identification of recurrent therapeutic molecular targets or specific biomarkers of treatment resistance. This complexity results in both intra-tumoral and inter-individual heterogeneity (1), which can be analyzed at various scales: genomic, molecular, metabolic, cellular, tissue, or macroscopic. Additionally, the structural and fluid mechanical effects acting on osteosarcoma components further complicate the understanding of the tumor microenvironment.

To investigate treatment resistance, this study focused on the tissue scale, guided by clinical routine histological images. At this scale, tumoral tissue can be modeled as a spatially heterogeneous porous medium, consisting of fluid, cellular, fibrous, and osseous solid phases.

METHODS

Using machine learning techniques, we developed a methodology to explore the correlation between tissue porosity and microenvironment cell density (2), aiming to uncover relationships between cells and the extracellular matrix, which differ in their characteristic dimensions. This approach involves the development of efficient segmentation and statistical tools tailored for large-scale images (50 000 px × 50 000 px) extracted from histological and immunohistological slices obtained during clinical routines.

From the segmentation results, the solid phase was isolated, and using porous media theory, we developed a novel digital functional imaging technique to analyze the mechanical and transport properties of the tissue based on human histological and immunohistological data. We propose a robust upscaling method to characterize the mechanical properties of the tumor microenvironment, which can be modeled as a strongly heterogeneous porous medium. This method employs a sequential grid-block approach (3,4), following image segmentation. Interstitial fluid transport and elastic models were investigated, and piece-wise

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constant equivalent parameters, such as tissue permeability and stiffness coefficients, were reliably determined.

RESULTS
From the geometrical analysis of the data, we identified a negative correlation between bone matrix porosity and macrophage density, which served as a marker of favorable response to chemotherapy in osteosarcoma patients. Additionally, a relatively high lymphocyte density was found to correlate with patient survival without metastasis or relapse.

From the mechanical analysis, we identified correlations between elastic properties, transport properties, and cell distribution in the microenvironment, depending on treatment response. These findings highlighted the impact of the microarchitecture of neo-formed bone on chemotherapy patients' response. Specifically, chemotherapy was found to be more effective in lacy-like neo-formed bone regions compared to trabecular-like regions. Areas with favorable treatment response corresponded to a decreasing number of residual cells and reduced local tissue permeability and stiffness.

CONCLUSION
In conclusion, we developed an innovative approach based on heterogeneous porous media theory and clinical data to investigate the properties of the tumor microenvironment. This novel *in silico* functional imaging technique is generic and can be adapted to different physical properties and other cancer types. Currently being validated on a large patient cohort, the new osteosarcoma response and prognostic signatures identified in this study could be integrated into post-surgical therapeutic stratification algorithms to optimize patient-specific therapies.

References

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