Spatial intratumoral heterogeneity of proliferation in immunohistochemical images of solid tumors

Nektarios A. Valous[a)]
Applied Tumor Immunity Clinical Cooperation Unit, National Center for Tumor Diseases, German Cancer Research Center, Heidelberg 69120, Germany

Bernd Lahrmann and Niels Halama
Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg 69120, Germany

Frank Bergmann
Institute of Pathology, Heidelberg University Hospital, Heidelberg 69120, Germany

Dirk Jäger
Department of Medical Oncology, National Center for Tumor Diseases, German Cancer Research Center, Heidelberg 69120, Germany and National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg 69120, Germany

Niels Grabe
Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg 69120, Germany

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Purpose: The interactions of neoplastic cells with each other and the microenvironment are complex. To understand intratumoral heterogeneity, subtle differences should be quantified. Main factors contributing to heterogeneity include the gradient ischemic level within neoplasms, action of microenvironment, mechanisms of intercellular transfer of genetic information, and differential mechanisms of modifications of genetic material/proteins. This may reflect on the expression of biomarkers in the context of prognosis/stratification. Hence, a rigorous approach for assessing the spatial intratumoral heterogeneity of histological biomarker expression with accuracy and reproducibility is required, since patterns in immunohistochemical images can be challenging to identify and describe.
Methods: A quantitative method that is useful for characterizing complex irregular structures is lacunarity; it is a multiscale technique that exhaustively samples the image, while the decay of its index as a function of window size follows characteristic patterns for different spatial arrangements. In histological images, lacunarity provides a useful measure for the spatial organization of a biomarker when a sampling scheme is employed and relevant features are computed. The proposed approach quantifies the segmented proliferative cells and not the textural content of the histological slide, thus providing a more realistic measure of heterogeneity within the sample space of the tumor region. The aim is to investigate in whole sections of primary pancreatic neuroendocrine neoplasms (pNENs), using whole-slide imaging and image analysis, the spatial intratumoral heterogeneity of Ki-67 immunostains. Unsupervised learning is employed to verify that the approach can partition the tissue sections according to distributional heterogeneity.
Results: The architectural complexity of histological images has shown that single measurements are often insufficient. Inhomogeneity of distribution depends not only on percentage content of proliferation phase but also on how the phase fills the space. Lacunarity curves demonstrate variations in the sampled image sections. Since the spatial distribution of proliferation in each case is different, the width of the curves changes too. Image sections that have smaller numerical variations in the computed features correspond to neoplasms with spatially homogeneous proliferation, while larger variations correspond to cases where proliferation shows various degrees of clumping. Grade 1 (uniform/nonuniform: 74%/26%) and grade 3 (uniform: 100%) pNENs demonstrate a more homogeneous proliferation with grade 1 neoplasms being more variant, while grade 2 tumor regions render a more diverse landscape (50%/50%). Hence, some cases show an increased degree of spatial heterogeneity comparing to others with similar grade. Whether this is a sign of different tumor biology and an association with a more benign/malignant clinical course needs to be investigated further. The extent and range of spatial heterogeneity has the potential to be evaluated as a prognostic marker.
Conclusions: The association with tumor grade as well as the rationale that the methodology reflects true tumor architecture supports the technical soundness of the method. This reflects a general approach which is relevant to other solid tumors and biomarkers. Drawing upon the merits of computational biomedicine, the approach uncovers salient features for use in