

Macro- and Micro-environmental Factors in Clinical Hepatocellular Cancer

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We previously developed a network phenotyping strategy (NPS), a graph theory-based transformation of clinical practice data, for recognition of two primary subgroups of hepatocellular cancer (HCC), called S and L, which differed significantly in their tumor masses. In the current study, we have independently validated this result on 641 HCC patients from another continent. We identified the same HCC subgroups with mean tumor masses 9 cm x n (S) and 22 cm x n (L), $P < 10^{-14}$. The means of survival distribution (not available previously) for this new cohort were also significantly different (S was 12 months, L was 7 months, $P < 10^{-5}$). We characterized nine unique reference patterns of interactions between tumor and clinical environment factors, identifying four subtypes for S and five subtypes for L phenotypes, respectively. In L phenotype, all reference patterns were portal vein thrombosis (PVT)-positive, all platelet/alpha fetoprotein (AFP) levels were high, and all were chronic alcohol consumers. L had phenotype landmarks with worst survival. S phenotype interaction patterns were PVT-negative, with low platelet/AFP levels. We demonstrated that tumor-clinical environment interaction patterns explained how a given parameter level can have a different significance within a different overall context. Thus, baseline bilirubin is low in S₁ and S₄, but high in S₂ and S₃, yet all are S subtype patterns, with better prognosis than in L. Gender and age, representing macro-environmental factors, and bilirubin, prothrombin time, and AST levels representing micro-environmental factors, had a major impact on subtype characterization. Clinically important HCC phenotypes are therefore represented by complete parameter relationship patterns and cannot be replaced by individual parameter levels.

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The idea that tumors grow in part due to the influence of their environment is not new.¹ We understand tumor clinical environment to be any aspect of the milieu in which a tumor arises, that can potentially influence its behavior. Thus, age^{2,3} and gender⁴ can influence the hormonal milieu of the liver. We regard such clinical factors as macro-environmental. The altered liver function that is part of the changed cytokine and inflammatory marker cascade resulting from alcoholism or

hepatitis and that is reflected in blood bilirubin, albumin, INR, or ALT/AST levels, we consider to be clinically micro-environmental.^{5,6} Both the processes of hepatocarcinogenesis and growth of hepatocellular carcinoma (HCC) involve a two-way influence of the effects of hepatitis viruses, alcohol or carcinogenic mycotoxins on the liver, as well as the reaction of liver components to these chronic and damaging agents. At the level of tissue organization, there are changes in extra cellular matrix components, as well as angiogenesis and chronic inflammation, that are both consequent on the damage and then become necessary components of the developing tumor environment. Some of the biochemical processes have been identified to include oxidative stress, apoptosis, autophagy, and the immune system.⁷⁻⁹ The tumor stroma and micro-environment both have been shown to have characteristic and prognostic molecular signatures,¹⁰⁻¹⁵ but their components also are seen to be an attractive target for the new molecularly designed therapies.^{8,9,10} Some of the cell types that are involved, and their products, are now becoming identified.¹⁶⁻¹⁹ The effects of clinical

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environment (macro and micro) on tumor biology are not simple, nor are the studies and questions and tools for finding answers. At the same time, novel experimental methods bringing detailed insights about the micro-environmental contributions to disease mechanisms are increasingly powerful. A methodology is needed for finding the optimal intersection of the clinical and molecular directions in tumor-environment research and its clinical interpretation and application. Ideally, tumor-environment models and their diagnostic and prognostic results should use these two information resources simultaneously, in the full mutual context. In this article, we open a clinical direction towards this unification with an approach prepared for incorporating both avenues. Our motivation is that if the standard clinical characterization of the patient in terms of our understanding of micro- and macro-environmental clinical factors and the disease status can bring new insights. This would allow direct integration of the results of novel experimental and molecular biology studies with clinical practice data and thus improve the “bedside translation”. We suggest and demonstrate here that with better characterization of the clinical disease heterogeneity, it is more likely that relevant hypotheses can be formulated and tested through complex studies with better design and patient status identification.

We present several novel results. First, we validated the Network Phenotyping Strategy (NPS)-based classification model,²⁰ developed by us previously for recognition of HCC subtypes using the extensive screening data on 4,139 subjects.²¹ We applied this model without change, to independently collected data from another continent, and confirmed that the same HCC subtypes and the characteristic patterns of relationships were also identified. Since we had survival data for this new data set (which was not available in the previous study), we next showed that the identified HCC subtypes have significantly different survival and thus prognosis. With this additional validation, we then analyzed the clinical and relationship pattern-based characteristics of the identified HCC subtypes and provided their interpretation in terms of the tumor-clinical environmental interactions.

METHODS

We approached the extraction of novel information from a standard set of baseline clinical parameter data at diagnosis, used in routine clinical practice clinic for HCC evaluation, in a way that allows us to better characterize HCC clinical heterogeneity. We have previously demonstrated that this can be done by application of graph theory tools. Mathematical graphs, when properly selected, can

capture what at first sight are complicated relationship patterns, in an elegant and, most importantly, in a manageable and clinically understandable way. We call this new graph-based approach the Network Phenotyping Strategy (NPS).^{20,21} NPS transformation of clinical practice data enabled us to adopt a new paradigm in which we examined the levels of individual typical parameters used in standard baseline evaluation and clinical categorization of HCC within the context of all the other identified clinical parameters.

In the concrete application of this general approach to problems of HCC, the changed paradigm allowed us to use common clinical blood test parameters together with demographic descriptors, and gain novel information from analyzing the relationship patterns by considering their values and levels simultaneously. This novel paradigm is a mathematical incarnation of the common clinical question of the following type: a single 8-cm HCC mass in an apparently normal liver carries a quite different prognosis and treatment approach from a similar 8-cm mass in the presence of multiple cirrhotic nodules, elevated bilirubin, and/or ascites. We considered how to take all these important inter-relationships simultaneously into account and understand their impact on the prognosis or treatment of a concrete patient. We demonstrate here that NPS transformation of the data enables not only high-level analysis of information in the relationship patterns between all used clinical variables, but it also provides results in a form that is directly and simply interpretable in clinical terms.

Our NPS approach uses the clinical study and/or clinical practice data and with the consideration of all available clinical information that is relevant for the disease. This pre-processing of the data allows us to encode the standard clinical information in a consistent manner for very diverse data types as the partitions and vertices of a network graph, which in turn represent complete relationship patterns between the clinical data levels and types. Once this is done, it is trivial to represent a personal relationship pattern for every patient, since we generate a *k*-partite graph in which the actual clinical variable levels, found through the baseline diagnostic tests and data collection for an individual patient, are represented by separate vertices in the respective partitions. These actual levels are then connected by edges (lines), representing all co-occurrences of these levels in the concrete personal clinical profile.

The advantage of this approach is the simplicity of the next step, in which we capture the relationship pattern information from an entire cohort into a “study graph”. The study graph is simply a union (generated by addition of all personal clinical profile

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