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# On dynamics of growth of prostate cancer; Towards the objective fractal system of tumor grading

Cellular growth is the fundamental biological phenomenon. A mathematical model shows that the emergence of simplistic macroscopic dynamics of growth, such as Gompertzian dynamics results from a coupling of a number of events at the microscale level. The coupling is associated with the emergence of at least three features, i.e. fractal structure of space-time, in which growth occurs, conditional probability of events, which eliminates sensitivity to the initial conditions, and a temporal function of entropy. The latter one is dependent on macroscopic dynamics of growth, and determines a capability of the supramolecular system for coding or transfer of biologically relevant information. Indeed, experiments with growth of prostate cancer spheroids suggest that both intra- and intercellular interactions play a significant role in fractal dynamics of growth.

The pattern of growth during tumor angiogenesis changes. Growth in space results in formation of the spatial fractal tissue structures as reflected by the spatial fractal dimension. The spatial fractal dimension for the normal-appearing prostate epithelium was 1.451 (018) (n=18 cases), for the Gleason 3 pattern 1.469 (022) (n = 15 cases), for the Gleason 4 pattern 1.601 (019) (n=18 cases), and for the Gleason 5 pattern 1.769 (011) (n=10 cases). In addition, different areas of the same tumor possessed a similar value of the spatial fractal dimension. With regards to the morphometric cell analysis, the minimal cell radius, aspect ratio, cell roundness and compactness were all statistically different across all Gleason score cases (ANOVA $p<0.05$). Sphericity, solidity shape and circularity were statistically different between cases with Gleason score 3, and those with a score of 4 and 5 (ANOVA $p<0.05$). However, these parameters were not different between cases with a Gleason score of 4 and 5. Based on the cellular morphology parameters, discriminant analysis with leave one out showed that 60% of Gleason score 3 and 4 cases, 63% of Gleason score 4 and 5 cases and 62% of Gleason score 3 and 5 cases could be correctly classified. This dropped to 45% when all the three groups were analyzed.

Tumor growth in time during angiogenesis is not of Gompertzian nature anymore. The long-term temporal evolution of PSA in 50 prostate cancer patients during growth ($b>0$) or decay ($b< 0$) phase describes the exponential function of the algebraic form $p(t) = p0\exp(bt)$ with the coefficient of non-linear regression $R > 0.95$ and the Poisson probability distribution, in which p(t) stands for PSA concentration, p0 is the initial PSA concentration in time t0, b stands for the coefficient, t denotes scalar time. Such evolution suggests a decay of intercellular interactions. Those results define clinically relevant prostate cancer as the first order dynamic system. The novel approach based upon the parameters p0, p' and b can be used to compare objectively dynamics of growth of different prostate cancers or to identify cancer recurrence. The spatial fractal dimension allows the objective and numerical grading of prostate cancer.