Radio(gen)omics
From Genome to Anatome and Back Again.

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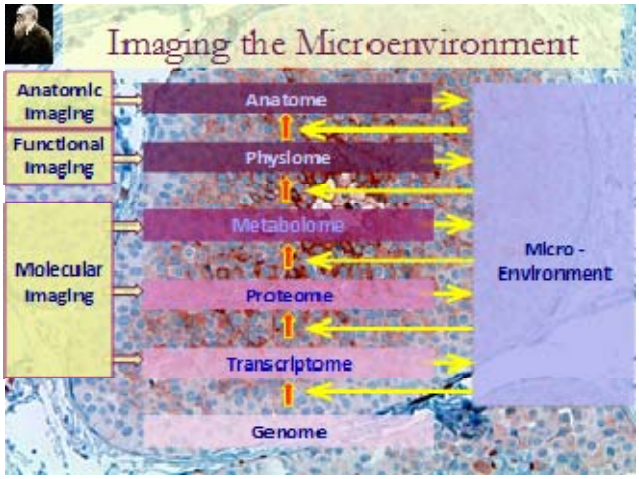
Target audience: – Clinical cancer radiologists and imaging informaticists
Objectives: –

1. Understand relationship between physiome and functional imaging
2. Describe and differentiate agnostic, semantic and habitat features.

Background



While it is commonly assumed that "cancer is a genetic disease", it is significantly more complicated than that. Cancers are complex, evolving, multiscale ecosystems that are characterized by profound spatial and temporal heterogeneity. Understanding a cancer requires a detailed understanding of complex dynamical systems. The interactions are nonlinear in that small changes in one variable can have large changes on another. Imaging is central to this investigation because it can non-destructively and longitudinally characterize spatial and behavioral variations in the tumor phenotype and environment as they evolve. The effect of an altered "genome" is manifested by the complement of genes that are expressed, the "transcriptome". The conversion from gene to transcript is non-linear process and can be affected by genetic and epigenetic events as well as an interaction with the surrounding microenvironment. Similarly, the conversion from transcriptome to "proteome", "metabolome" and "physiome" is also strongly influenced by interactions with the microenvironment. This is further made complex by products of gene expression, metabolism and physiology, in turn, being exported from the cell to the microenvironment, providing conduits for cell-cell communication. The microenvironment contains cells, proteins and small molecules, all of which can impact tumor growth and response to therapy. In human cancers, the microenvironment is an integral part of the tumor itself, whereas it is often physically separated from tumors in animal models.

These different levels of organization can be interrogated with non-invasive molecular, functional or anatomic imaging. All three types of imaging are interrelated and the delineations are somewhat arbitrary, they each have distinguishing characteristics. Molecular imaging is relegated to measuring the levels or activities of specific macromolecules or metabolic pathways in vivo. Functional imaging is devoted to measuring specific organ functions such as perfusion and cell density. At the highest level of organization, anatomic imaging can be very quantitative and can identify underlying heterogeneity in microenvironmental conditions, gene expression, and metabolic phenotypes.

These complex interactions between intra- and extracellular processes give rise to intra-tumoral heterogeneity, i.e. gene expression and cell phenotypes are highly variable, even within the same lesion. The consequences of this cellular heterogeneity are enormous and challenging. For example, phenotypic heterogeneity is the most significant factor underlying evolution rates. An emerging concept states that tumors with the most heterogeneity are to be more readily adaptable to perturbations such as chemotherapy and hence, have the worst prognosis. As a result of selection pressure (e.g. from treatment), a phenotypic convergence occurs. This convergence maybe transient and need not involve a convergence in genotype. In fact, multiple

genotypes can produce similar phenotypes. Such transient convergence at the phenotype scale is precisely the sort of thing that modern imaging can highlight.

Intratumoral variability dramatically confounds our ability to study in-vivo cancers by molecular diagnostics. Typical molecular characterizations such as microarray studies measure the transcriptome in a large number of cells. The relevance of this single, average measurement in a population of high phenotypic and genotypic variance will likely be very limited. In such studies, the impact of heterogeneity can only be appreciated with large data sets from a large study population. Consequently, the applicability of these data to individual patients is limited. Modern imaging and, more to the point, modern image analyses, have begun to explore the importance of tumor heterogeneity in progression and response and have the potential to improve diagnosis, prognosis and prediction for individual patients.

Radio(gen)omics

"Radiomics" is an emerging field that aims to classify tumor heterogeneity at the molecular, functional and anatomic levels. The central hypothesis of cancer radiomics is that molecular, functional or anatomic tumor imaging features reflect underlying gene expression patterns. Over the last few years, it has become clear that distinct sub-regions of tumors, identifiable by MR imaging, have distinct gene expression patterns. In the simplest cases, changes in expression of specific genes can affect specific imageable parameters, such as vascular-endothelial growth factor (VEGF) effects on perfusion or survival gene effects on tumor density, both of which are measurable by MRI. That imaging features reflect underlying differences in gene expression is also evidenced by image-guided biopsy, which has clearly shown that tumors exhibit distinct regional variations in gene expression that are correlated with image features, such as perfusion. In Radiomics, the use of image features is being elevated to a new level through extraction of many more features and their relationships to gene expression patterns and tumor behavior. In multiple cases, these 'omic data have improved classifier models for improved prediction and prognosis.

As the discipline of radiomics has grown, image feature have been defined to occur at three different levels.

"Agnostic" features are primarily texture features, captured by Haralick classifiers, grey-length co-occurrence matrixes, wavelets, etc. In practice hundreds of texture features can be extracted from single images, or parts of images. Because of the large number of texture features, care must be taken to eliminate redundancies, to prevent overfitting data during classifier modeling. Hence, correlation matrixes are useful for reducing the dimensionality of texture space, and can result in reducing the number of features by an order of magnitude. These texture features are important components to identify intratumoral heterogeneity.

"Semantic" features are primarily size, location and shape features that reflect descriptors that are commonly used by radiologists in their analysis of images. Hence, semantic features quantitatively capture roundness or irregular shape, spiculation, central necrosis, volume, etc. These features are important because they have proven prognostic value, and are used in the assessment of response for solid tumors.

"Habitats" are identified by combining multiple MR images with orthogonal information. This was originally used by van Bruggen to identify necrosis and adipose from viable tissue, but has recently been expanded to identify hypoxic and acidic habitats, among others. The individual data elements are used to build data cubes in each voxel that can then be combined with fuzzy clustering algorithms to identify bounded habitats with unique characteristics. Importantly, these bounded habitats can then be parsed as regions of interest from which "agnostic" or "semantic" features can likewise be extracted. To date, this has been performed in GBM, pancreatic cancer, breast cancer, prostate cancer and sarcomas. The challenge going forward is to relate these distinct habitats to underlying molecular pathophysiology via image guided biopsies.

FURTHER READING

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