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Radiogenomics and Radioproteomics

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Recent whole-genome sequencing efforts have expanded on the traditional histologically-driven subtypes to further stratify cases according to the presence/absence of specific somatic mutations in oncogenes integral to cancer initiation, progression and metastasis. The development of 'targeted therapeutics' intended to specifically short-circuit regulatory pathways has led to the successful development of efficacious compounds, but only in patients that harbor the targeted mutation. Tissue confirmation is required for targeted therapy prescription. In this era of molecularly based therapeutics, it may be valuable if somatic driver mutations could be correlated to imaging parameters in order to uncover a molecular profile-imaging signature. Radiogenomics/radioproteomics or radiology imaging based phenotypes–patterns–could be used to predict the molecular subtype of cancers. Functional, morphological and molecular imaging techniques are routinely used to visualize, characterize, and measure biological processes at the cellular, subcellular, and molecular levels in living subjects. Developing a noninvasive means for identifying the molecular subtype of cancer cases that bypasses or compliments the need for tissue acquisition and assay and that can be performed in the clinic at the time of diagnosis would have the potential to be transformational in the accessibility of personalized cancer medicine.

In daily clinical practice tissue confirmation of driver mutations is required for targeted therapy prescription. Consequently, patients with contraindicated, failed or indeterminate biopsies do not receive potentially beneficial targeted therapies. Non-invasive driver mutation correlation methods could:

• Bring tissue characterization from the invasive/minimally invasive realm into the clinic and on the other hand add an additional layer of imaging information (besides standard staging) into the portfolio of clinical data necessary to guide therapeutics and prognosis. This will allow us to better stratify patient treatments and ultimately improve survival. Achieving patient specific personalized medicine by integrating multiple features provided from imaging, pathology and clinical biomarkers; as well as developing complementary synergistic systems between clinical, biochemical, imaging and cellular/subcellular (molecular/gene) biomarkers is essential.

The goal would not be to replace tissue characterization but to complement it in cases where:

• Patients are not candidates for sampling of their tumors because of poor overall performance status, significant co-morbidities or the presence of de novo disease or recurrences in anatomic locations that cannot be or are high risk to be accessed–vascular proximity.

• A biopsy sample is not diagnostic and/or does not yield sufficient viable tumor cells for mutation detection, for e.g. if that biopsy sampled necrotic, fibrotic or inflammatory regions of the tumor.

• A sampling bias may yield false negative results due to the intra and inter-lesional heterogeneous nature of molecular expression or the less sensitive (but less expensive) laboratory assays used on a standard basis (-a discordant result with the radiographic signature would therefore prompt re sampling of the tumor, or a repeat molecular analysis of tumor with standard immune histochemistry techniques or more advanced FISH techniques or another clinical option).

• A radiographic prognostic element could be added to the molecular signature information.

Additionally the efficiency of the laboratory assays themselves may often result in as many as two to three weeks of delay until the mutation results are obtained, interpreted and returned to the oncologist for therapy selection.

Information gathering and validation of these models or techniques is necessary. The use of radiogenomic and radioproteomics in a system model would then be possible. Systems biology, which focuses on understanding and characterizing organizational relationships and interactions of entities within biological systems would be incorporated into these models [1]. Systems Diagnostics can then integrate systems biology into a diagnostic platform, combining macro and micro histopathological data as well as clinical datasets, biochemical and imaging biomarkers in a synergistic fashion, therefore achieving a more comprehensive multilayered tumor profile of an individual patient [2]. This would potentiate our quest to optimize patient care and reach the ultimate individualized patient care with pharmacogenomics, radiogenomics, biochemical and bio-clinical genomics incorporated in a systems diagnostics ideal. Studying and creating models for how these systems work and may integrate together and compliment each other ultimately improving patient survival is crucial. The integration of imaging into systems diagnostics and personalized medicine is promising as it provides functional, molecular and morphological data. It is already routinely used, easily accessible, and may provide cost savings when considering the additional molecular analysis costs (including invasive sampling and tissue processing). Imaging can also be accurate, reproducible and widely available nationwide.

This rationale has been explored in research but no attempt to investigate a clinical application has been initiated. A small amount of work has already been initiated looking more specifically at radiogenomics/radioproteomics in tumors [2-9], as well as prognosis and therapy modulation. Fukuda et al. showed a significant negative correlation between the metabolic rate of oxygen and Fluorodeoxyglucose (FDG) standardized uptake value (SUV) in human liver tumors [10]. Dooms et al. on the other hand found that the percentage of viable tumor cells and Ki-67 length density after induction chemotherapy were significantly lower in metabolic responders compared with non-responders [11]. Palsakas et al. identified an "FDG signature" in the basal subtype of breast cancer and correlated that with the over expression of the transcription factor c- MYC [9]. His group identified a higher FDG score for this

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subtype of breast cancer. On the other hand, Van't Veer et al. used DNA microarray analysis on primary breast tumors to identify a gene expression signature predictive of a short interval to distant metastases ('poor prognosis' signature) in patients without loco-regional lymph node metastasis at diagnosis [12]. In an effort to correlate genotype with protein expression, Rody et al. evaluated estrogen receptor, progesterone receptor and Human Epidermal growth factor Receptor 2, in patients with breast cancer and reported more than 90% concordance when immunohistochemistry results were compared to messenger ribonucleic acid (mRNA) levels [13]. Simmons et al. among other investigators also described discordance of molecular profiling between primary and metastatic breast cancer lesions and predicted that in their study this changed management by at least 20% [14,15], which would suggest a heterogeneity also in radiographic signatures. Strauss et al. correlated compartmental parameters of FDG uptake and the gene expression values of cyclin-A [3]. Furthermore, Diehn et al. showed that a high Contrast to Necrosis ratio on MRI was a surrogate imaging phenotype for EGFR expression in Glioblastomas [6]. They also found that an infiltrative "radiographic signature" predicted a worse prognosis [6]. Zander et al. [16] and Sohn et al. [17] found that FDG and Fluorothymidine (FLT), respectively, early in the course of treatment could predict outcomes to EGFR-TKI treatment. Additional authors have explored radiolabelled nuclear techniques of direct imaging of EGFR expression [18,19]. Indirect EGFR correlations with an FDG signature have also been reported [20-24].

At Yale, we have begun exploring the association between FDG PET/CT-derived imaging parameters and molecular phenotypes on selected case examples. An FDG PET/CT scan from a Stage IV esophageal cancer patient with a liver metastasis revealed an elevated SUVmax only in the primary tumor following FOLFOX and bevacizumab therapy. Molecular profiling of the 'cold' liver lesion demonstrated it to be HER2- by FISH compared with the HER2+ primary, supporting a discordant treatment response in the primary HER2+ lesion [25]. We have also started exploring molecular imaging phenotypes in breast cancer patients in order to discriminate HER2+ from HER2- tumors or even lesions. Our strategy also allowed us to discriminate between intravascular thrombosis in a patient with an intimal sarcoma not characterized clinically or on a contrast-enhanced CT, allowing for appropriate life saving therapy to be administered [26], as well as differentiating between benign and malignant skin lesions in a patient with epidermolysis bullosa and squamous cell skin cancer [27].

This radiogenomics, radioproteomics and systems diagnostics approach would create a tool that would be used in the clinic to personalize cancer therapy by prioritize which therapies are most appropriate for an individual.

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