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TOPIC HIGHLIGHT

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Radiogenomic imaging-linking diagnostic imaging and molecular diagnostics

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Abstract

Radiogenomic imaging refers to the correlation between cancer imaging features and gene expression and is one of the most promising areas within science and medicine. High-throughput biological techniques have reshaped the perspective of biomedical research allowing for fast and efficient assessment of the entire molecular topography of a cell's physiology providing new insights into human cancers. The use of noninvasive imaging tools for gene expression profiling of solid tumors could serve as a means for linking specific imaging features with specific gene expression patterns thereby allowing for more accurate diagnosis and prognosis and obviating the need for high-risk invasive biopsy procedures. This review focuses on the medical imaging part as one of the main drivers for the development of radiogenomic imaging.

Key words: Radiogenomic imaging; Personalized medicine; Diagnostic imaging

Core tip: Radiogenomic imaging has the potential to catalyze the health system by creating imaging biomarkers that identify the genomics of a disease. The use of noninvasive imaging for gene expression profiling is a fast and reliable technique which has the potential to replace high-risk invasive biopsy procedures.

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INTRODUCTION

Recent developments in high-throughput molecular techniques promise to generate biomarkers driving the future of personalized medicine[1-3]. Gene expression profiling has the potential to gather key information regarding biology and its relationship to diagnosis, prognosis and therapy. However, a main limitation of these techniques is the need to acquire tissue for gene expression profiling through invasive biopsy thereby limiting the clinical application of this method in an everyday patient care setting. In addition, in these biopsies samples are frequently obtained from only a part of the lesion and therefore do not entirely represent the lesion's unique anatomic, functional, and physiologic properties, such as size, location, and morphology. Many of these features are obtained in routine clinical imaging exams and are very useful for diagnosis, staging, and treatment planning. Although these image features provide anatomical and morphological information, only few studies[4-6] have generated a "radiogenomics map" integrating the genomic and image data thereby introducing the field of "radiogenomics" or "radiogenomic imaging"[3]. Specific radiological tumor phenotypes can be used as surrogates for signatures of gene expression. If imaging can be linked to these treat-

ment-response gene-expression patterns routine clinical imaging is able to predict the likely response to specific chemotherapeutics and helps to choose the best form and duration of treatment.

DIAGNOSTIC IMAGING AS A PLATFORM FOR GENE EXPRESSION PROFILING

Radiologic imaging plays an important part in every stage of cancer treatment. Besides screening, detection and staging of disease, imaging is used to predict and evaluate individual patient's responsiveness to therapies in every stage of cancer treatment. Diagnostic imaging is a safe and accurate tool to noninvasively assess location, morphology and physiology of tissues[3]. This crucial role for imaging biomarkers in cancer treatment is reflected by the fact that more than 90 percent of cancer patients are evaluated by imaging. However, much of the data generated by radiologic imaging remains largely unspecific at a molecular level. The integration of these noninvasive imaging tools with functional genomic assays has the power for a quick clinical translation of high-throughput technology.

IMAGING FOR MOLECULAR ASSESSMENT OF TUMOR STAGING AND DIAGNOSIS

A study by Kuo *et al*[6] in patients with liver cancer demonstrated the relationship between imaging traits, histopathologic markers, and several predefined gene-expression programs. The study found that a liver-specific gene expression program was highly correlated with the imaging trait "tumor margin score, arterial phase". The data suggest that this radiophenotype could potentially form the basis to categorize hepatocellular carcinomas (HCCs).

Segal *et al*[4] also demonstrated that dynamic imaging traits in computed tomography (CT) strongly correlated with the global gene expression programs of primary HCC. The authors managed to reconstruct 78% of the gene expression profiles by combining twenty-eight imaging traits, thereby showing cell proliferation, liver synthetic function, and patient outcome. Therefore, noninvasive imaging could decode genomic activity of human liver cancers, allowing for a noninvasive, frequent and quick molecular work-up on an individual level.

In patients with glioblastoma multiforme (GBM) Zinn *et al*[7] introduced a new diagnostic imaging technique to assess molecular cancer subtypes and genomic correlates of cellular invasion using quantitative magnetic resonance imaging (MRI) volumetrics and large-scale gene- and microRNA expression profiling in GBM. Based on The Cancer Genome Atlas, discovery and validation sets with gene, microRNA, and quantitative

MRI data were created. Zinn *et al*[7] showed that in patients with GBM the used fluid-attenuated inversion recovery sequence reliably detected main cancer genomic components responsible for cellular migration and invasion. In addition it revealed genes and microRNAs highly associated with mesenchymal transformation and invasion. As cellular invasion is one of the main causes of treatment failure, the surgical extent of resection and adjuvant treatment planning are highly important. Thus, the authors conclude that the used method has potential therapeutic significance since successful molecular inhibition of invasion will improve therapy and patient survival in GBM.

In a recently published study in patients with GBM Jamshidi *et al*[8] could show that MRI, messenger RNA expression and DNA copy number variation can identify MR traits which are associated with some known high-grade glioma biomarkers and associated with genomic biomarkers that have been identified for other malignancies but not GBM. Further work is needed to determine the clinical value of these findings.

IMAGING FOR MOLECULAR ASSESSMENT OF TUMOR PROGNOSIS

Radiogenomic imaging is a useful tool for molecular assessment of tumor staging and diagnosis; however, for its success in a clinical setting it is crucial that radiogenomics has the potential to also impact clinical management. Despite much recent activity in developing imaging biomarkers of disease, it is challenging to link these biomarkers to clinical outcomes as it takes years to obtain these outcomes in cohort studies[9].

The above mentioned study by Kuo *et al*[6] in patients with HCC showed that the tumor margin score highly correlated with a venous invasion gene expression program as well as histologically-confirmed venous invasion.

A study by Diehn *et al*[5] sought to correlate imaging surrogates for gene-expression profiles with prognostic implications in patients with GBM. The radiogenomic maps showed a statistically significant overlap between a survival-associated gene signature and an infiltrative pattern of the edema on T2-weighted images. The hyperintense signal on the T2-weighted images allowed for a clear differentiation between edematous and infiltrative patterns reflecting the interface between a tumor and the adjacent normal brain. In a second part of the study another 110 GBMs were included; the results revealed a correlation between the infiltrative radiophenotype and a poor prognosis: a median survival of 390 d was found for those without infiltrative pattern compared to 216 for those with infiltrative pattern. The study shows a quick, easy-to-use technique to discover prognostic imaging biomarkers associated with underlying gene-expression signatures.

A study by Gevaert *et al*[9] explored the clinical prognostic value of Radiogenomic imaging by looking at features from non-small cell lung cancer (NSCLC) CT- and positron emission tomography (PET)-cases[10]. Gevaert *et al*[9] study comprised 26 patients with NSCLC whose imaging features were comprehensively extracted and statistically analyzed. To obtain survival data which were

not available the authors derived prognostic conclusions by using a genomically matched NSCLC case set with known clinical outcomes from public databases[11]. Gevaert *et al*[9] demonstrated an imaging approach able to quickly identify prognostically relevant image biomarkers requiring only the paired acquisition of image and gene expression data as well as the existence of a large public gene expression data set where survival outcomes are available. The authors conclude that by mapping image features to gene expression data, it is possible to leverage public gene expression microarray data to determine prognosis and therapeutic response as a function of image features.

In a follow-up study Nair *et al*[12] analyzed Nuclear factor-κB (NF-κB) protein expression in a group of 355 patients with NSCLC (365 tumor samples) with long-term follow-up by means of immunohistochemistry (IHC) using a Tissue Microarray.

NF-κBp65 as well as a positive uptake of fluorodeoxyglucose (FDG) was significantly associated with more advanced stage, tumor histology and invasion. Higher NF-κBp65 expression was associated with death by Kaplan Meier analysis ($P = 0.06$) while LDHA was strongly associated with recurrence ($P = 0.04$). Increased levels of combined NF-κBp65 and lactate dehydrogenase A (LDHA) expression were synergistic and associated with both recurrence ($P = 0.04$) and death ($P = 0.03$). The authors conclude that NF-κB IHC was a modest biomarker of prognosis that associated with tumor glucose metabolism on FDG PET when compared to existing molecular correlates like LDHA, which was synergistic with NF-κB for outcome.

IMAGING FOR MOLECULAR ASSESSMENT OF OPTIMAL THERAPY

By using an integrated imaging-genomic approach Kuo *et al*[6] determined whether contrast-enhanced CT was capable to assess imaging phenotypes which are associated with a doxorubicin drug response gene expression program in patients with HCC. The authors included 30 HCCs into the study and scored them individually across six predefined imaging phenotypes. An imaging phenotype related to tumor margins on arterial phase images showed a significant correlation with the doxorubicin-response transcriptional program ($P < 0.05$, $q < 0.1$). In addition it was significantly associated with HCC venous invasion and tumor stage ($P < 0.05$, $q < 0.1$). Tumors with higher tumor margin scores were more strongly associated with the doxorubicin resistance transcriptional program and had a greater prevalence of venous invasion and worse stage. Tumors with lower tumor margin scores, however, showed a converse relationship. The authors conclude that CT has the potential to identify HCC imaging phenotypes correlating with a doxorubicin drug response gene expression program. As doxorubicin is a standard treatment in regional therapies for patients with HCC, the used imaging strategy could be used to guide HCC therapy on a tumor-by-tumor basis on the basis of underlying tumor gene expression patterns.

The previously mentioned study by Diehn *et al*[5] also evaluated whether in patients with GBM the expression of a therapeutic target could be predicted based on its imaging-gene-expression association. Activation of specific gene-expression programs can be inferred from imaging traits, thereby giving insights into tumor biology on a tumor-by-tumor basis. The authors could reveal potential imaging biomarkers for several classes of anti-GBM therapeutic agents, including antiangiogenesis and epidermal growth factor receptor-based therapies. In addition, the results show that intratumoral heterogeneity of several gene-expression programs can be spatially resolved by means of imaging. Furthermore, the authors identified an imaging phenotype characterized by an infiltrative appearance that was associated with aggressive clinical behavior and expression of genes involved in central nervous system development and gliogenesis. As this imaging approach is noninvasive and widely available in clinical practice it can be applied to a broad range of human disease processes.

CONCLUSION

Radiogenomic imaging has the potential to catalyze the health system by creating imaging biomarkers that identify the genomics of a disease. The use of noninvasive imaging as a surrogate for gene expression profiling is a quick and reliable tool which has the potential to replace high-risk invasive biopsy procedures. Additional studies with larger numbers of patients are necessary to confirm links between gene expression patterns and imaging features permitting fast and reliable clinical diagnosis of tumors as well as estimation of prognosis and decision for optimal therapy.

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