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ADVANCES IN CLINICAL RADIOLOGY

Radiogenomics of Oncology

Current Trends and Future Directions

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KEY POINTS

- Radiogenomics aims to identify potential associations between clinical imaging and cellular and molecular profiling to characterize disease phenotypes.
- The field has grown considerably in the last 10+ years with growing numbers of studies in tumors of breast, brain, liver, kidney, and prostate, among others.
- Radiogenomic association maps identify correlations that do not necessarily reflect causal relationships and generally require further experimental evaluation.
- The growing body of work in the field suggests that applications of radiogenomics extends beyond just disease classification and may also guide treatment decision making and clinical management.

The continued growth and development of high-throughput technologies in recent decades have made the objectives of precision medicine more tangible, although the causal implications of some of these measurements are not always clear. Thus the richer phenotypic characterization of disease processes through "omic" measurements presents a challenge for all fields of medicine to embrace the new information, while also avoiding overinterpretation. Radiology has embraced many of these new capabilities through radiogenomics (or imaging genomics) as it strives to use molecular classifications of tissues to link radiologic findings to pathologic diagnoses. Although radiogenomics is a young area of investigation, it has steadily grown in the past 10+ years and continues to mature. In this review we provide a brief summary of the solid organ oncologic radiogenomic studies, trying to highlight a few notable areas that either portend future promise or areas that serve as weaknesses/gaps that need to be addressed in the future.

Radiology has largely been built on the "Rad-Path Correlation"; pathologic evaluation/confirmation of radiologic findings. As the purview of radiology expands into cellular and molecular characterization through improved imaging resolution, new MR pulse sequences, new contrast agents, and so forth, there is an implicit requirement to move past correlation and to begin to explore causal mechanisms. There is an ever-present recognition that limitations exist in the ability to detect cellular phenotypes; molecular imaging probes targeting specific receptors can address these

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issues in part. Applications of radiogenomics can be seen from 3 perspectives:

1. Surrogacy for pathology/histopathology,
2. Complementary information to the biopsy, and
3. Information that the biopsy cannot provide.

Investigations in the published literature to date have focused on the first point, thus this review will be confined to the examples focused in cross-sectional imaging surrogates of molecular phenotypes, keeping in mind that this is one aspect of its potential use and that we do not expect that there will always be a robust imaging signature for molecular phenotypes; every radiogenomic study should in principle involve evaluation of a hypothesis linking imaging phenotypes with molecular profiles or signatures [1]. Furthermore, this review reinforces the feature in radiogenomics in identifying specific oncologic diseases in which imaging can provide a surrogate role for molecular signatures, as well as malignancies that are outside the limits of current imaging protocols.

BRAIN

There is a growing understanding that the imaging phenotype is the result of a wide breadth of malignant gene expression. In fact, there is increased interest in classifying central nervous system (CNS) tumors via phenotypic and genotypic signatures, as demonstrated by the 2016 WHO classification [2]. However, this classification is still largely dependent on histopathology and immunohistochemistry, requiring tools that are limited due to logistic and economic factors. Radiogenomics has become a viable method for extracting large amounts of imaging data that can be further correlated with diagnostic and prognostic biomarkers [3]. There is strong evidence demonstrating that MRI signatures is correlated to specific underlying cellular processes and may be predictive in clinical outcomes [4]. This information is useful because more aggressive and experimental treatments may be justified in a patient with radiogenomic features that confer a likelihood of poor prognosis.

The initial systematic, radiogenomic study of glioblastoma (GBM) identified an infiltrative versus edematous imaging feature that was predictive of patient outcome and other features (such as the contrast to necrosis ratio) associated with gene expression signatures related to oncologic processes such as hypoxia and cellular proliferation [4]. The identification of these signatures suggests to the potential to develop imaging biomarkers for various categories of anti-GBM therapeutic agents such as antiangiogenesis and epidermal growth factor receptor (EGFR)-based therapies. A series of subsequent studies then expanded up this work and explored associations between (primarily MR) imaging and transcriptomics, epigenetics, copy-number variations, noncoding RNA elements, and genomic sequence variants [5–10]; future studies on these features may further support their role in noninvasive characterization of GBM.

Although there are too many exciting developments in this area to discuss all at length, we highlight 2 notable developments in GBM; methylation status correlates and potential biomarkers of isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) variants. Epigenetic silencing of DNA repair enzyme O^6-methylguanine DNA methyltransferase (MGMT) has been identified as an important prognostic biomarker associated with temozolomide treatment response [11]. Methylation of the MGMT promoter can be induced via tumor resection or chemotherapy and loss of the methylation has been associated with resistance to temozolomide therapy [12]. Exploring the possibility that restricted diffusion, as reflected by the apparent diffusion coefficient (ADC), is correlated with methylation status, Pope and colleagues [13] identified a significant association between pretreatment ADC values and methylation status, observing increased methylation in tumors with lower ADC values, as well as longer progression-free survival in patients treated with bevacizumab. Increased MGMT methylation has also been positively associated with radiation-induced pseudoprogression [14]. Recently Qian and colleagues [15] identified associations between MR features and 2 genes (IRF5 and XRCC1) to differentiate true progression from pseudoprogression. Potentially compelling subsequent investigations could focus on pseudoprogression and MGMT status assessment by MR.

The identification of IDH1 and IDH2 mutants in gliomas [16] was a milestone triggering a fervor of studies in the genetics, biochemistry, and molecular biology of the disease and, accordingly, revision of the WHO classification of brain tumors [17]. The discovery that many diffusely infiltrating gliomas had acquired IDH1 and IDH2 mutations resulting in altered catalytic activities provided a means to phenotypically characterize a subset of tumors. This biochemical phenotype was fortuitously also amenable to detection using proton spectroscopy. Mutations of IDH1 and IDH2 in gliomas lead to the overproduction of 2-hydroxyglutarate (2HG). 2HG was subsequently demonstrated to be detectable via MRI, and in turn provide utility as an imaging marker for diagnosis of infiltrating gliomas and provide important prognostic information regarding treatment response [18,19].

As the WHO defines CNS tumors based on genetic phenotypes, radiogenomics of CNS tumors will need to embrace its role in tumor classification. A major challenge necessitating the WHO update of CNS tumor classification was the frustration in confronting tumor heterogeneity. Treatment failure is often attributed to intratumoral heterogeneity found on biopsy (or with a lack of causality of the omic phenotype). A targeted therapy that is dependent on the genomic analysis of a single biopsy site has often been found to be ineffective, presumably from tumor heterogeneity. Cross-sectional imaging allows for analysis of an entire tumor phenotype and may more accurately capture the variations in tumor phenotypic characteristics. The use of radiogenomics, which combines the subtleties of genomic analysis with the thoroughness of imaging provides an attractive approach to painting a more accurate picture of gliomas and can help stratify their response in clinical trials.

Specific hurdles that radiogenomics will need to resolve involve correctly organizing the large amounts of imaging data that are derived from comparatively low numbers of sample size. The nature of MRI has multiple inherent limitations. Specifically, many MR studies, especially those that involve diffusion imaging requires coregistration between multiple sequences. This can be an issue, particularly if the slice thicknesses between pulse sequences are not the same. Secondly, due to low sample size and short follow-up of the clinical studies there are inherent inconsistencies between patient groups with regard to previous treatment. Many radiogenomics studies are based off of a subset of a larger study and may be subject to previous selection bias that cannot be removed [13]. As acknowledged in many radiogenomic studies of the brain, many of the aforementioned results need to be confirmed in a prospective study with a larger cohort of patients.

LUNG

Most literature comprises of non-small cell lung cancer (NSCLC), which is the leading cause of death in the United States [20], consequently most thoracic radiogenomic studies target NSCLC. The role of computed tomography (CT) and PET/CT imaging in the screening and management of lung cancer is well established; however, the potential for radiogenomic analyses to provide added value via phenotyping of lung cancers points to an exciting advancement in the management of lung cancer [21,22].

Viable therapeutic targets that have gained traction commercially has been within the tyrosine kinase family. One type of NSCLC that has been targeted is the one that has an activated ALK gene (also known as an EML4-ALK translocation) and is responsive to the small-molecule ALK inhibitor crizotinib (Xalkor; Pfizer, New York, NY) [23]. A retrospective radiogenomic analysis identified statistically significant associations between CT imaging features (central tumor location, absence of pleural tail, and pleural effusions) and ALK + status with sensitivity and specificity of 83% and 80%, respectively [24]. These findings are compelling in that the CT imaging findings are correlated to a genotypic signature that is amenable to targeted therapy. A confirmatory study in a separate group using resected NSCLC results found that CT phenotypes such as lobulated margins with solid, hypoattenuating lesions were associated with ALK + lung cancer [25]. Although the individual studies are encouraging, given that different imaging features were identified in each of the studies speaks to the preliminary nature of the results and the need to further evaluate the specific features.

EGFR mutation is a major subtype of NSCLC, with 95% being found in adenocarcinomas, the most common subtype of NSCLC [26]. Given that EGFR mutation status has been associated with response to tyrosine kinase inhibitors, there is relevance for identifying noninvasive characterization of EGFR mutation status. An increasing number of studies have reported associations with various EGFR mutations and CT imaging features [25,27–31], with cohort sizes in the hundreds for the more recent studies. Whereas some of the features overlap, there is a concomitant increase in the number of reported imaging features including nonspecific features such as emphysema and "airway abnormalities" to more specific features such as ground glass opacities and texture of nodule margins, which speaks to the need for a systematic evaluation of all features and all studies.

Novel efforts in the last decade have looked at using nuclear imaging, specifically fluorine-18 (F-18) fluoro-2-deoxyglucose (FDG) uptake, as a source of imaging phenotype. F-18 FDG PET is routinely used for tracking metastatic disease, resistance to chemotherapy, and outcomes in NSCLC. An initial exploratory study in a cohort of 25 patients identified PET imaging features that were correlated with gene expressions and linked to survival [32]. Another study tracked a molecular phenotype known as the epithelial-mesenchymal transition (EMT), a phenotypic alteration that is seen in a range of physiologic behaviors, but has also been implicated in metastatic transitions in numerous malignancies, including breast cancer [33,34]. Yamamoto

and colleagues [35] observed increased F-18 FDG uptake in patients with upregulated EMT gene expression that were concordant with experimental evidence of enhanced glucose transporter 1-mediated glucose uptake and hexokinase activity. This study took steps to link molecular imaging measurements with a specific cellular phenotype, thus resulting in a more causal interpretation of radiogenomic associations in NSCLC [35]. For both of the preceding studies, however, it should be recognized that there is a non-negligible nonspecificity for these associations and so the interpretation as a radiogenomic marker depends on the clinical context and other relevant findings.

Tissue biopsies play an important role in determining disease progression, targeted therapy approach, and posttreatment progression. Whereas it is unclear whether radiogenomics will reach the stage at which it can supplant actual lung biopsies, there is strong evidence that pulmonary radiogenomic studies can assist in performing lung biopsies by highlight the areas of higher risk based on genomic signatures. Genomic sequencing and profiling that more accurately profiles the spatial heterogeneity are quickly becoming validated clinical tools that can help guide clinical management [36]. This will lead to an increased unmet need to define genomic sample adequacy and not simply the histopathologic adequacy of biopsy specimens.

LIVER

The primary guideline that drives the staging and management of primary hepatocellular carcinoma is known as the Barcelona Clinic Liver Cancer staging system [37]. There have also been advances in imaging assessment of liver lesions, such as the Liver Imaging Report and Data System (LI-RADS) for hepatocellular carcinoma (HCC) [38], which, in the context of specific imaging findings, obviates the need for tissue biopsies. However, there is still a large gap in categorizing primary liver malignancies and their respective subtypes via histopathological analysis.

The first formal radiogenomic study created a gene module-CT imaging map for HCC composed of 28 imaging traits linked to 116 gene modules [39]. Validation was performed via histologic findings of microvascular invasion. A critical observation in that study was that the presence of internal arteries and the absence of hypodense halo were associated with microvascular invasion and matrix invasion genes. This seminal study confirmed that localized HCC gene expression patterns could be mapped out using conventional contrast-enhanced CT imaging. A subsequent study demonstrated proof of concept using functional genomic approaches to identify gene expression themes associated with tumor treatment response [40]. Specifically, the group used an HCC dataset with CT and gene expression to delineate response of HCC to chemotherapy using a tumor margin score that was correlated against a previously characterized doxorubicin response gene expression profile. This score also was significantly associated with liver tumor differentiation and venous invasion at the gene expression level as well as the tumor TMN staging levels. The group concluded that imaging-genomic associations are not random and can be structured in a way to classify HCC responses to various treatments [40].

More recently, there has been an emphasis on trying to delineate microvascular invasion. Taouli and colleagues [41] constructed a prognostic model for HCC recurrence based on gene expression patterns in tumors and adjacent tissues. This single-center retrospective study looked at imaging traits such as size, enhancement ratios, wash-out ratios, and tumor-to-liver ratios was correlated with transcriptome profiling. That study revealed strong associations between imaging traits and gene signatures of more aggressive HCC, particularly with enhancement ratios and tumor-to-liver contrast ratios. A notable multicenter retrospective cohort study, using a "radiogenomic venous invasion (RVI)" biomarker that is made up of contrast-enhanced CT image linked to a 91-gene HCC gene expression signature, showed diagnostic accuracy of RVI in predicting microvascular invasion [39,42]. There have been multiple studies looking strictly at texture analysis suggesting again that absolute difference in enhancement, enhancement ratios, and size were strongly related to microvascular invasion in HCC [43–47].

At present there has only been 1 published radiogenomic cholangiocarcinoma study. Intrahepatic cholangiocarcinoma has abnormal tissue vasculature and expressions of hypoxia genes and proteins, markers that have been previously studied under imaging [48,49]. In this particular study, the researchers evaluated histologically confirmed cholangiocarcinoma and correlated immunochemistry findings associated with hypoxia such as vascular endothelial growth factor (VEGF) and EGFR. These immunochemistry genotypes were correlated with qualitative and quantitative texture features associated with hypoxia markers. The study results showed that quantitative imaging findings such as correlation, entropy, contrast, and homogeneity were significantly associated with VEGF and EGFR, whereas a positive nonsignificant trend was seen with CD24 expression. Likewise, there were some qualitative

features (tumor-liver difference and heterogeneity) that were significantly correlated with VEGF expression [50].

The aforementioned studies highlight the possibilities of using radiogenomics to guide the diagnosis of specific subtypes of primary liver malignancies and identify specific features associated with recurrence and suboptimal response to treatment. Although modern CT and MRI protocols for these malignancies have advanced to the point where interventions can be performed without biopsy, radiogenomics can further stratify them and give clinicians better insight into a patient's prognosis.

KIDNEY

Diagnostic imaging of renal malignancies is primarily based on tumor detection, cytologic subtype characterization, localization, and spread. Because of the breadth of imaging profile that can characterize renal masses, CT remains the primary basis for staging and monitoring treatment [51], and much of this focus on loss of the von Hippel-Lindau (VHL) tumor suppressor gene owing to its association with clear cell renal cell carcinoma (ccRCC). When active, the VHL gene codes for a protein that can degrade the hypoxia-induced factor alpha (HIF-α). HIF-α subsequently creates several proangiogenic factors, including VEGF, leading to angiogenesis, cell survival, and cell proliferation. However, when inactivated, the VHL gene interrupts the expected cellular degradation of HIF-α leading to excess angiogenesis. This excess angiogenesis is what leads to the hypervascularity appearance of RCC seen on CT imaging [52]. In addition to this specific imaging characterization, this pathway explains why ccRCC responds well to antiangiogenic agents [53].

Mutations of VHL have been associated with well-defined tumor margins, nodular tumor enhancement, and high vascularity [54]. Consequently, well-defined tumor margins can be suggestive of a less-infiltrative subtype of ccRCC, and thus lower in aggressiveness when compared with ccRCC tumors with poorly defined margins. A similar study also found that mutations in lysine (K)-specific demethylase 5C (KDM5C) and BRCA1-associated protein 1 (BAP1) was linked to renal vein invasion. Nodular, heterogeneous enhancement of ccRCC, along with intravascular invasion was found to be significantly associated with an underlying VHL mutation [55]. Lastly, it has been suggested that solid ccRCCs are associated with a different genotype compared with multicystic RCC (mRCC). Mutations of VHL and PBRM1 were more common among solid ccRCC, while mutations of SETD2, KDM5C, and BAP1 were absent in mRCC. These findings were supportive of previous studies that suggested that mRCCs were less aggressive than solid ccRCCs [56]. Collectively these findings revealed associations between CT findings and individual gene mutations. However, further studies are required to correlate these specific gene mutations to underlying genomic profiles and their subsequent clinical manifestations.

In an effort to bring concordance between the growing mutation/gene signature classification schemes and imaging features, a radiogenomic study in ccRCC was performed in which a multifeature imaging predictor was developed to target a predefined transcriptomic signature and was validated in an independent dataset [57]. Similar to the liver RVI score previously described, this study used CT image features to noninvasively predict disease-specific survival independent of stage, grade, and performance status. In gross analogy with some of imaging features that were predictive of outcome in other malignancies, 3 of the 4 imaging traits involved characterization of the tumor margin or capsule. Perhaps most interestingly, when this multifeature predictor was applied to a phase II clinical trial evaluating the response of preoperative bevacizumab in patients with metastatic ccRCC [58], the radiogenomic classifier successfully stratified outcome in patients (progression-free survival as well as overall survival) [59]. In light of the fantastic advancements made in the immune-oncology field with checkpoint inhibitors, including for RCC [60], the potential for radiogenomic classifiers for drug treatment and response warrants further investigation. By the same token, it should be recognized that there is not expected to be an association with an imaging feature and every molecular feature or variant that is discovered [61–63].

PROSTATE

Adenocarcinoma of the prostate is the most prevalent male-specific malignancy in the United States, with an expected 1 in 6 men diagnosed in their lifetime, with countless more suspected to have clinically indolent disease. However, there is a growing acknowledgment that many patients with clinically indolent disease are actually pathologically aggressive and remain undetected. A recent study demonstrated that 45% of men with low-risk prostate cancer and scheduled for surveillance were actually found to have a higher-grade/stage and nodal metastatic disease [64]. The lack of intervention led to delayed treatment with radical prostatectomy and led to an increase in metastatic disease after surgery [65]. The necessity for a more accurate

stratification system has led to increased interest in combining genomic and imaging-derived biomarkers to more accurately assess disease burden. Patient's with higher risk would likely benefit from earlier intervention such as radiotherapy or adjuvant androgen deprivation therapy.

The Prostate Imaging Reporting and Data System (PI-RADS) [66] has been a successful means for using multiparametric MRI for risk stratification in the management of patients with suspected cancer (ie, whether to recommend biopsies) and has been successful in setting a reproducible standard across different practice settings; however, there is potentially much more information in the multiparametric MRI studies that may have further insights into possible genomic correlates from the diffusion, T2, perfusion, and spectroscopy sequences.

Initial reports of a "field effect" in prostate cancer in which "normal" tissue adjacent to malignant prostate nodules express abnormal transcriptomic features [67] has been further supported by subsequent transcriptomic studies in larger cohorts [68], as have radiogenomic studies based on transcriptomic MRI [69] and exome sequencing MRI data [70]. If these observations continue to be verified in independent cohorts, the implications will have significant bearing on clinical practice from the perspective of (1) the established use of transcriptomic gene signatures for the diagnosis of prostate cancer to take equal footing with Gleason classification and (2) use of nontargeted prostate biopsies.

Image-guided, targeted prostate biopsies are now the standard of care, with multiparametric MRI gaining more ground. However, there are reports that only a small fraction of these cancers are clinically significant, with most of them having previous negative biopsies [71]. The Miami Active Surveillance Trial, is a single-institution, prospective study looking at the role of multiparametric MRI and genomic signatures of suspicious prostate lesions [72]. MRI-ultrasound biopsies from targeted and random cores will be selected for whole genome sequencing to assess individual gene expression levels and their associated signatures. This study may provide insight and guidance into the respective roles of transcriptomic profiling and MR-targeted biopsies in the diagnosis and risk stratification of prostate cancer.

BREAST

Multiparametric MRI and breast imaging-RADS have been successful in providing a consistent means for recommendations of clinical workup of breast lesions [73]; however, as with PI-RADS the imaging data may provide further insights into biological characteristics of the masses. Breast cancer receptor status (estrogen, progesterone, and herceptin 2 [HER2]) is the diagnostic- and treatment-defining standard. Transcriptomic classifications (luminal A, luminal B, basal-like, ERBB2+, and so forth) have also found biological applications [74]. However, there is no one-to-one correlation or mapping between these transcriptomic and receptor subtyping classifications, thus prospective identification of targeted phenotypes should be performed before performing radiogenomic studies. For example, if a radiogenomic marker is developed to target clinical management, then the receptor status (ER/PR/Her2) should be the targets, not the transcript-based classifiers.

As with prostate cancer, breast cancer in radiogenomics is only starting to gain traction and also nearly exclusively dominated by MRI. Current metrics to diagnose, manage, and predict treatment responsiveness of breast cancer is largely determined by histologic analysis of tumor grade, lymph node involvement, and the expression of hormone receptors such as estrogen, progesterone, ERRB2, as well as p53 mutations. However, there is a considerable gap in correlating these markers to treatment response and outcomes. The application of genome signature profiling using transcriptomic signatures is becoming a standard tool for molecular analysis and allows for genome-wide evaluation of the tumors that can reveal the underlying mechanisms behind the tumor biology. These advances can also improve breast cancer classification and allow for individually tailored treatment based on these molecular features [75]. Current indications for MRI in breast cancer include staging disease, quantifying response to neoadjuvant chemotherapy, and screening for high-risk patients. Parallel development in MRI with global gene expression has lent itself well to radiogenomic analysis.

An initial exploratory study identifying groups of genes associated with different preoperative quantitative computer vision-extracted dynamic contrast material-enhanced MRI features [76] gave way to a subsequent study that focused on long noncoding RNA expression and metastasis-free survival [77]. A enhancing rim fraction metric was found to be associated with early metastasis in women with invasive ductal breast carcinoma. Furthermore, this enhancing rim fraction score was significantly associated with 4 long noncoding RNAs that are known to be a surrogate markers for metastasis-free survival.

Subsequent radiogenomic studies have aimed at identifying radiomic features that correlated with US Food and Drug Administration-approved transcriptomic signatures [78,79]. The initial findings are encouraging, although to compete with the transcriptomic signatures there needs to be significant improvement in the sensitivity and specificity of the imaging predictors. There have been imaging associations with the HER2-positive subtype, including rapid early contrast enhancement of breast cancer lesions, as well as increased ratio of tumor-to-background parenchymal enhancement, and diffusion restriction [80–84]. The results were attributed to tumor angiogenesis upregulation induced by HER2 overexpression in these breast cancer subtypes. Multiparametric imaging biomarkers have also been performed to classify molecular breast cancer subtypes, incorporating textural analysis, combined with contrast kinetics, with promising results [85–87], although, as noted earlier, blurring between transcriptomic and receptor subtyping in a single study is ill-advised.

Genetic testing for these immunohistochemistry markers remains expensive and unreliable, while surrogate markers are variable in their usefulness in predicting patient outcomes. Consequently, there is an unmet need to more accurately categorize these patients using radiogenomic analysis. Breast cancer recurrence and treatment guidance has also been a topic of interest regarding clinically available genomic assays. A radiogenomic study evaluated a 21-gene recurrence score assay identified 4 dominant imaging phenotypes, 2 of which were associated with lower-risk tumors. MRI enhancement curves, along with quantitative morphologic and spatial heterogeneity features were predictive of recurrence risk, as well as tumor with larger levels of neoangiogenesis genes [88,89].

There is currently no low-cost, easily accessible genetic testing to date and characterizing molecular subtypes of breast cancer require invasive tissue sampling to guide clinical decisions. As with biopsies of other organ systems, tissue samples are not representative of the entire tumor and its associated genetic and phenotypic characteristics. Immunohistochemistry can provide a surrogate marker for these genetic alterations but there is variability in their agreement with genetic analysis. Although the status of the field is still largely exploratory, results to date suggest that radiogenomics has the potential to provide an alternative means for differentiating between different molecular subtypes of breast cancer and can also serve as a means for monitoring progression of disease and response to treatment. Further evaluation into novel MRI sequences, including intravoxel incoherent motion diffusion-weighted imaging and higher-order statistics have shown to be promising imaging biomarkers that can potentially be linked to underlying genomic signatures [90].

ABSCOPAL EFFECTS

One aspect of liver imaging that is amenable to disruption is the monitoring of locoregional therapies. There has been considerable literature on how thermal ablations and intravascular therapies affect surrounding tissue with a recent interest in their respective immunologic and abscopal effects [91]. One study reported substantially higher HCC incidence in populations who have undergone previous ablation as opposed to those who were not treated with ablations [92]. Tissue responses within the borders of an ablation zone have been shown to vary according to ablative modalities and thermal dose. There have been multiple reports of increases in inflammatory markers such as IL-6, c-Met, or VEGF when performing thermal ablations, that have been linked to pro-oncogenic effects [93–95]. Likewise, blocking these particular pathways via targeted therapy has shown decreases in these pro-oncogenic effects. A recent ablation study used gene microarray assays to identify a host of modulated genes in a periablational rim, genes that are linked to tissue metabolism, inflammation and tissue repair [96]. There were noted gene expression changes in untreated segments of the liver, pointing to a global effect of hepatic thermal ablation on normal liver. This study was also able to correlate periablational rims to upregulation of STAT3, a downstream signaling molecule that contributes to tumor angiogenesis. Although these studies observing the abscopal effects of ablation have been performed on animals and analyzed with immunohistochemistry, addition or incorporation of an imaging component would enable radiogenomic analyses. The ability to monitor the genomic signature of a treated lesion and its therapeutic response to targeted therapy would be an invaluable tool in pushing this field forward. Although studies to date are limited to the liver, it is expected that future work will explore abscopal effects in other organs and tumors that are ablated, such as lung and kidney.

CURRENT CHALLENGES AND LIMITATIONS

Radiogenomics has undergone significant progress since its inception, linking imaging and genomic profiles to gain insight into tumor genetics, biology, and clinical outcome. The availability of open access databases and data sharing initiatives, particularly via The

Cancer Genome Atlas (cancergenome.nih.gov/) and The Cancer Imaging Archive (www.cancerimagingarchive.net/) have been instrumental in advancing radiogenomic research. However, standardization of current protocols will remain a major challenge going forward. It is widely acknowledged that there is a lack of standardization in current literature, with imaging protocols and reporting standards differing significantly between institutions. In addition, there is a great deal of heterogeneity in these datasets. Preparing imaging data, which has traditionally been performed manually, is difficult to do consistently and is subject to interuser variability. Furthermore, within each part of the workflow, there are various types of image acquisition, segmentation, and postprocessing approaches and methodologies. Continued efforts in data organization, sharing, and standardization will allow for more robust evaluation and support of radiogenomic association maps. A recurrent challenge in many radiogenomic studies, as noted numerous times, include limited sample size and the retrospective nature of the studies. These factors contribute to potential overfitting and overinterpretation of the data; however, by adhering to rigorous methodologies, such errors can be minimized, if not avoided [94].

FUTURE DIRECTIONS

There are 2 important points to keep in mind when evaluating possible radiogenomic associations:

1. The study should be hypothesis driven and as such the null hypothesis is frequently upheld, thus no association will be identified, and
2. Even if a statistically significant association is identified (ie, the null hypothesis is false), it does not imply causation.

Thus, a positive radiogenomic association is really the scientific starting point that needs to be further explored (usually experimentally) before any presumption of causality can be inferred. Nevertheless, as highlighted by some of the examples above, there are numerous areas whereby radiogenomics can contribute to precision medicine, diagnostically and therapeutically.

Tumor heterogeneity is a confounding factor when performing biopsies of solid tumors. The ability to localize specific regions of a tumor that express a particularly aggressive genotype will likely reduce the rates of false-negative or false-positive results if combined with radiogenomic data. Similarly, an aggressive-appearing imaging phenotype may potentially be associated with a benign genotype and lead the clinician to opt for an active surveillance strategy rather than aggressive intervention. Radiogenomic analyses can also help optimize biopsy sampling procedures by identification of high-yield targets for interventionalists and decrease the risk of grabbing healthy, nonmalignant tissue. Increasing biopsy yield can lead to decreased risks for complications, decreased hospital costs and more effective medical decision making [36,97].

In the era of precision medicine, radiogenomics is also uniquely suited to track genomic changes corresponding to a positive therapeutic effect, particularly in therapies that target a specific pathway. Therapies that block inflammatory pathways will require a means to track their efficacy and progression of disease. Radiogenomics lends itself well in targeted therapy monitoring by providing a noninvasive manner to track these genomic changes temporally and spatially. This need becomes more evident when considering that combination therapies that rely on multiple targeted treatments with multiple levels of interactions and noninvasive assessment will be invaluable for physicians who are trying to tailor treatments to patient-specific tumor-molecular subtypes. In addition to these tracking these systemic therapies, there is great potential for radiogenomics to play a role in tracking locoregional therapies in organs such as the liver. Thermal ablations or intravascular therapy have begun to be associated with abscopal effects, with notable increases in genes that code for tissue inflammation and repair that may exert pro-oncogenic effects. These genomic changes may be characterized on imaging phenotypes and give clinicians a tool to prognosticate the posttreatment outcomes in a patient with cancer.

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