Radiology

REVIEWS AND COMMENTARY • REVIEW

The Biological Meaning of Radiomic Features

Michal R. Tomaszewski, PhD • *Robert J. Gillies, PhD*

From the Department of Cancer Physiology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Dr, Tampa, FL 33612. Received June 5, 2020; revision requested July 20; revision received July 30; accepted August 17. **Address correspondence to** R.J.G. (e-mail: *Robert.Gillies@moffitt.org*).

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Radiomic analysis offers a powerful tool for the extraction of clinically relevant information from radiologic imaging. Radiomics can be used to predict patient outcome through automated high-throughput feature extraction, using large training cohorts to elucidate subtle relationships between image characteristics and disease status. However powerful, the data-driven nature of radiomics inherently offers no insight into the biological underpinnings of the observed relationships. Early radiomics work was dominated by analysis of semantic, radiologist-defined features and carried qualitative real-world meaning. Following the rapid developments and popularity of machine learning approaches, the field moved quickly toward high-throughput agnostic analyses, resulting in increasingly large feature sets. This trend took the focus toward an increase in predictive power and further away from a biological understanding of the findings. Such a disconnect between predictor model and biological meaning will inherently limit broad clinical translation. Efforts to reintroduce biological meaning into radiomics are gaining traction in the field with distinct emerging approaches available, including genomic correlates, local microscopic pathologic image textures, and macroscopic histopathologic marker expression. These methods are presented in this review, and their significance is discussed. The authors predict that following the increasing pressure for robust radiomics, biological validation will become a standard practice in the field, thus further cementing the role of the method in clinical decision making.

Radiomics is an emerging field of research focused on the development of novel biomarkers based on data-driven analysis of radiologic images. It is predicated on the hypothesis that medical images reflect underlying pathophysiologic characteristics and hence, quantitative analyses can be useful to describe the biology of the imaged volume. Automated extraction of a large number of quantitative imaging features enables efficient elucidation of subtle characteristics within images that may be informative for disease diagnosis, prognosis, and treatment response. The development of advanced analytical and machine learning tools has led to rapid expansion of radiomics research and successful detection of patterns not available through qualitative radiologic analysis. Since it first appeared in print in 2012, publications referring to "Radiomics" have increased exponentially, numbering almost 1000 in 2019 (1).

Modern medicine benefits from an enormous number of measurement techniques capable of informing disease characteristics that may not be accessible to physicians through manual examination. Biological processes can be tracked at spatial scales ranging from the level of the whole body all the way to single molecules, with imaging methods spanning most of that range. Radiomic analyses are predominantly based on anatomic and metabolic imaging, as shown in Figure 1. Through direct quantification of the tumor imaging phenotype at the spatial scale within the resolution of the imaging technique used, radiomics aims to provide surrogate, indirect insight into multiple aspects of the disease, including tumor grade, histologic and genetic subtype, and predicted outcome. These characteristics are reflective of alterations occurring at different spatial scales to the data provided by radiomics. Hence, the biological basis of the indirect relationships enabling radiomic predictions remains largely unexplained in most studies. Importantly, as the radiomic data can be captured longitudinally, it can be used to quantify the response of the underlying "biome" to external perturbations.

Radiomic biomarker development is almost entirely data driven. In contrast, traditional biomarker development is generally driven ab initio by biology-based hypotheses. Preclinical experiments can often enable validation of the mechanism of action and informational content of the developed metric before translation and verification of clinical use. Approaches such as genomics, transcriptomics, proteomics, and radiomics are used to screen large-parameter spaces to find sensitive markers for prediction of outcome and thus often involve posthoc generation of hypotheses. Without an underlying biological rationale, the black box–like nature of "omics" methods significantly hinders its wider use and makes validation particularly challenging. Providing the biological context of the informative radiomics features will constitute an important step toward general acceptance of radiomics as a standalone diagnostic, predictive, or prognostic method in the radiology and oncology communities. As the field develops and joins the mainstream, the emerging radiomic signatures will need to adopt the reporting guidelines (2) and evaluation standards, as used by other novel clinical diagnostic and prognostic approaches, including comparison to existing reference standard methods. Biological validation will be essential as part of this process.

In addition, understanding of the biological underpinning of the observed relationships, where possible, can strengthen the conclusions and can provide additional validation and opportunities for investigation. For example, if a highly prognostic radiomic feature were found to be highly correlated to the expression of a particular protein, one could then investigate the relationship between

Abbreviation

IHC = immunohistochemistry

Summary

This review discusses the recent advances in the accelerated search for biological meaning of radiomics signatures, as the biological validation is gradually recognized as essential for the field to enter routine clinical practice.

Essentials

- Radiomic analysis involves the automated extraction of clinically relevant information from radiologic images.
- The data-driven nature of the radiomic method offers no direct insight into the biological meaning of the findings, thus highlighting the need for external validation.
- Recent advances in the field are enabling biological validation of the radiomic signatures using a variety of correlates, including genetic and histologic data.
- We predict that biological correlation will soon become standard in the field of radiomics, thus increasing the reproducibility of the findings and cementing the role of the method in clinical practice.

the protein and the outcome. This review discusses the studies constituting notable developments in biological validation of radiomic findings, as perceived by the authors, and postulates the implementation of new standards for validation, thus prioritizing the efforts to establish a biological basis of the findings.

Importance of Validation

Radiomics is intrinsically data-driven by screening a high volume of features for reproducibility and information content. However, because many features are considered, there is a real danger of overfitting or overinterpreting the derived models. Together with increased sophistication of the analytics, more stringent validation of the findings is increasingly required. Most published radiomics studies present no validation of the proposed signatures beyond the use of an independent test set. This approach does not address much of the critique concerning the practical value of the findings because the causal relationship between radiomics and outcome may remain unclear. This limitation has been recognized in the development of a "radiomics quality score," which is based on different evaluative metrics during construction of radiomic models (3). Key to this are the standardization of feature extraction and statistical approaches (4), the use of separate validation cohorts from multiple institutions (5), and an increasing involvement of radiomics in prospective clinical studies (6). Further efforts for standardization and streamlining of the radiomic analysis process are led by the Radiomic Ontology project (7), which provides a comprehensive analytical platform for clinical use, including solutions for multicenter studies (8). Although these approaches contribute to improved reproducibility and impact of the findings, biological validation remains a critically important and elusive metric and is necessary to transform radiomic analysis into an actionable part of the routine clinical decision process.

The level of biological insight and tools used in other high-throughput data-driven studies are largely not available for radiomics. For example, the genes and pathways identified in genomics screenings can be interrogated in vitro and, thanks to the large body of research available, embodied into powerful resources such as the Gene Ontology (9), which combines

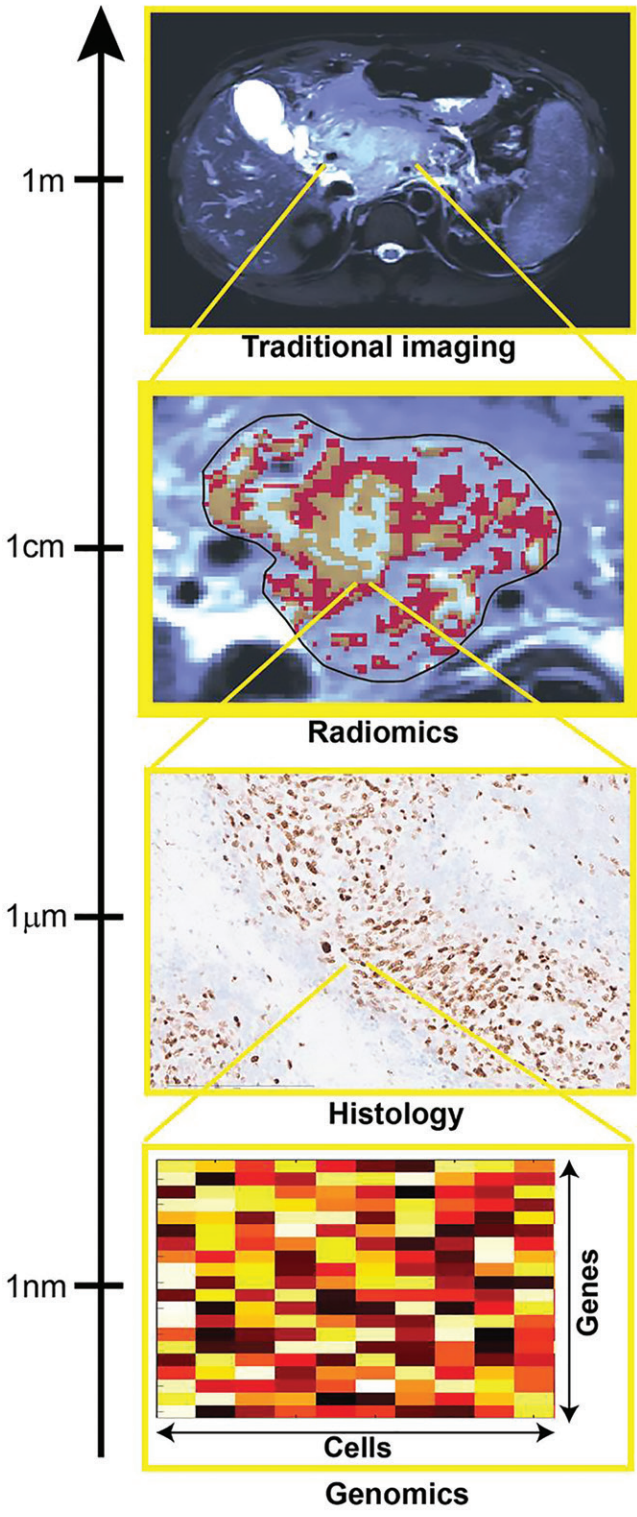

Figure 1: Image shows how multiscale quantification provides complementary tumor insight. Histologic and genomic analysis can provide specific small-scale insight useful for validation of radiomic results, focused on quantification of spatial patterns of size exceeding image resolution.

the functional information available on each gene and pathway. We believe that as the field of radiomics grows, and more information related to biological underpinning of different features becomes available, a similar database may be compiled and published. Stringent standardization of the analytical methods, as described herein, will be paramount for this task.

In this review, the major efforts for biological validation of radiomic findings are presented and are divided into main sections focused on the main classes of biological correlates available for comparison.

The relationship between data-driven radiomics and visual image content, described by semantic features, is first discussed, followed by separate sections describing the biological insight available for radiomics validation from the notable correlates—genetic and histopathologic data. Finally, habitat imaging is discussed as a radiomic approach that holds significant promise for effective validation of the biological findings underlying the image heterogeneity.

The review aims to summarize and discuss the approaches available and practiced in the field for biological validation to promote their more widespread use. Although many studies present relationships between radiomic features and biological correlates, such as histologic tumor grade or gene expression, emphasis in this review is placed on reports where additional independent correlates were discussed to validate the biological source of the findings. We strongly believe that introduction of biological validation into standard practice for radiomic model building will accelerate clinical acceptance and routine use of the method in patient care.

Semantic Analyses

Semantic features are generally radiologist-defined accepted metrics that describe tumor morphologic characteristics and location. Examples include *spiculation*, *lepidic*, *concavities*, and *central necrosis*, among other terms. Before the use of more sophisticated approaches and data-driven features, early work in the field of radiomics can be associated with combining multiple semantic features (10) into more complex signatures (eg, for gene expression prediction) (11,12). The visual nature of the considered characteristics (13) ensured the findings remained relatively grounded in physical, if not biological, understanding. Following the rapid development and popularity of computer vision and machine learning approaches, the field of radiomics moved quickly toward high-throughput agnostic analysis and complex combined signatures. This led to increased throughput and lower cost of the analysis, at the price of biological understanding.

Some notable recent studies including semantic and conventional (agnostic) image features suggest that these approaches may provide valuable intuitive and biological insight, as they clearly relate to the visual phenotype. Yip et al (14) quantified the correlations between manual semantic features and automatically computed radiomic features in non–small cell lung cancer, showing relationships between the two approaches. Importantly, the authors used the observed relationships to discuss the physical and biological source of radiomic feature changes. Similarly, Tunali et al (15) introduced an automated framework for robust quantification of the tumor-stromal interface features, showing its association with survival in non–small cell lung cancer. The visual interpretation of the novel features was then verified by showing significant correlation to semantically scored features such as lobulation and border definition. An example of this quantitative approach is shown in Figure 2. The introduction of decision trees into model design may also simplify intuitive understanding of the features' informational content. Gevaert et al (16) used this approach for the successful prediction of mutation status using semantic and computed features. The authors highlight, however, an important shortcoming of the semantic analysis—its poor interobserver reproducibility related to subjective assessment, expressed in low Cohen κ.

Some studies have focused on automated quantification of particular visual characteristics of the tumor to improve reproducibility and standardization of the analysis. Koay et al (17,18) focused on quantitative assessment of the visual conspicuity of pancreatic tumors in CT images, presenting its power for survival prediction. This approach could then be evaluated against histologic and genomic data to shed more light on the microscopic characteristics underlying the measured phenotype. This hypothesis-driven study employs a few custom image features in place of a standard radiomic approach, which, when feasible, may be preferable for identification of an unambiguous relationship between the image-based and biological information.

Similarly, multiple quantitative metrics of tumor heterogeneity have been proposed, as detailed in a review by Davnall et al (19). Notably, only a small proportion of studies attempting to quantify heterogeneity discuss the informational content of the chosen metrics, with important examples coming from dynamic contrast-enhanced MRI (20,21) and fluorine 18 fluorodeoxyglucose PET (22). Most other studies instead consider panels of textures, such as gray-level co-occurrence matrix radiomic features, which describe the internal image intensity patterns, assuming an implicit relationship between these and heterogeneity. Although relatively little data are available on the relationships between the qualitative definition of heterogeneity and image texture features, some studies report indirect relationships. Skogen et al (23) demonstrated in glioma that tumor grade, known to be associated with visual heterogeneity (24), correlated to a standard deviation of intensity distributions in filtered CT images. Conversely, Liu et al (25) reported no correlation between tumor grade and visual heterogeneity, as assessed manually, whereas texture features commonly associated with tumor heterogeneity showed a strong link. More studies validating the relationships between the visual characteristics, semantic features, and quantitative metrics assumed to represent them may be required.

Radiogenomics Relationship with Gene Expression

Data-driven image feature extraction can also be combined with genetic analysis to inform mutation status beyond survival and tumor grade prediction. This is referred to as *radiogenomics*, not to be confused with the same term used to define relationships between genomics and radiosensitivity. Radiogenomics is a rapidly developing high-throughput method aimed at extracting and correlating multiple image

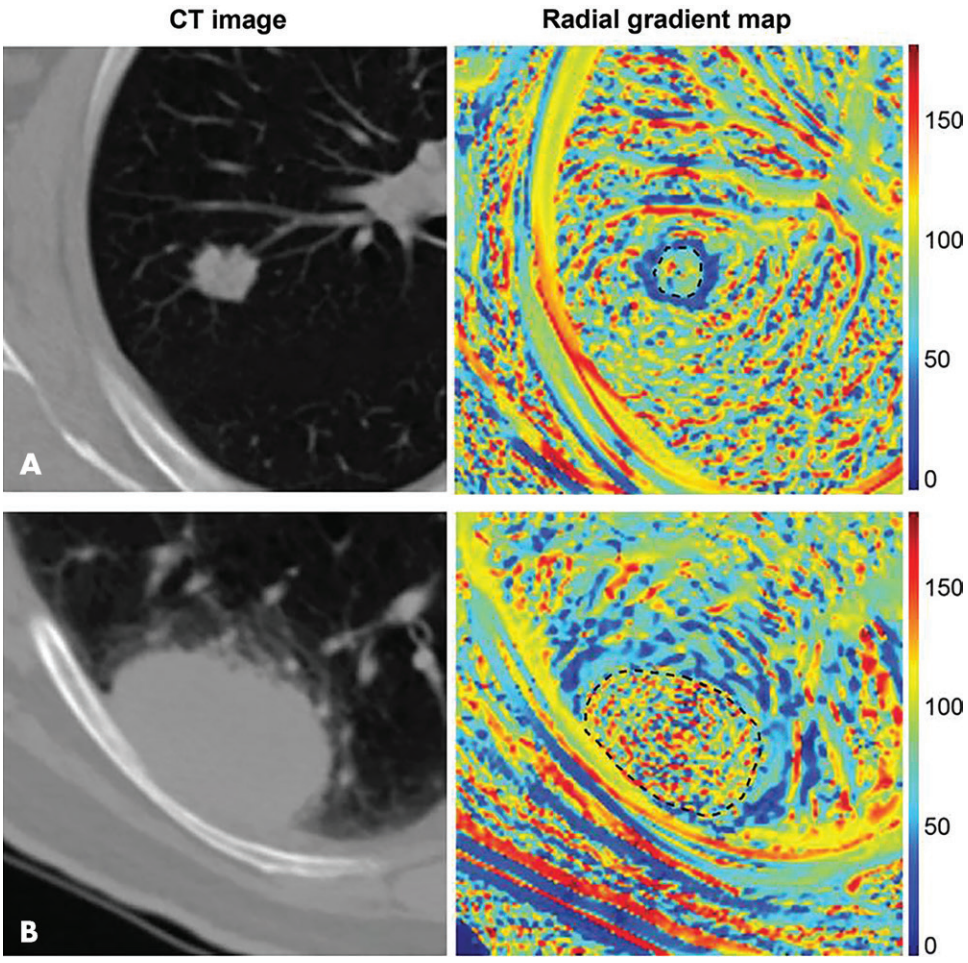

Figure 2: Radiomics can quantify visual tumor characteristics. CT images (left) of lung cancer lesions from two patients (*A* and *B*) were used by Tunali et al to calculate radial gradient maps (right) that describe tumor edge interface (tumor outlined in black dotted line). Quantification of simple mean and standard deviation of map in peritumoral region is associated with survival and correlates to qualitative semantic descriptors of tumor edge, such as border definition. Source.—Reference 14.

features with genomic information. It is increasingly accessible thanks to The Cancer Genome Atlas initiative (26), in particular in combination with the resources offered by associated The Cancer Imaging Archive (27). Although mainly focused on providing surrogate imaging signatures for genetic information, radiogenomic (28) tools can also provide some biological validation of radiomic signatures. The similarities between the analytical approaches used in feature extraction from radiologic and genetic data can also be exploited (29) for cross-validation between the methods. In a comprehensive study of the relationship between somatic mutations and radiographic CT phenotype in lung cancer, Rios Velazquez et al (30) showed significant associations between multiple radiomic features and several relevant mutations, including epidermal growth factor receptor, or EGFR, and Kirsten rat sarcoma viral oncogene homolog, or KRAS, in non–small cell lung cancers. Aerts et al (31) used genetic information to shed light on the biological characteristics of a developed radiomic signature of survival in lung and head and neck cancers. Conversely, Gevaert et al (32) used the genetic signatures as a starting point to predict image features, thus further reinforcing the strong link between genomic and radiomic information.

Epidermal growth factor receptor status in non–small cell lung cancer is a widely researched subject because of its high frequency and the fact that this mutation is actionable for treatment with tyrosine kinase inhibitors (33,34). Multiple studies reported CT signatures associated with epidermal growth factor receptor mutation status as determined with genetic testing. As pointed out by Yip et al (35), many of them have, however, shown conflicting conclusions (36–38) that undermine the reproducibility of the approach. Combining the genomic correlations with other biological metrics as provided by histologic analysis may prove necessary to ultimately verify such inconsistent findings. In a study following these principles, Sun et al (39) developed a radiomic signature of immune infiltration, relating the score to relevant gene expression panel, pathologic findings, and survival data. Similarly, Tunali et al (40) demonstrated that the CT radiomic features that were most predictive of survival following immunotherapy were also strongly associated with hypoxia according to genetic profiling and immunohistochemistry (IHC). Mu et al (41,42) have used PET/CT radiomics to develop predictors of both programmed death-ligand 1, or PD-L1, status and epidermal growth factor receptor mutation status. When combined, these generated a powerful decision support tool, as these two phenotypes are generally mutually exclusive. Beyond additional validation, the combination of multiple correlates in these studies informs on the biological driving forces of the radiomic relationships. Beig et al (43) took advantage of the known relevance of oxygenation status in cancer by developing a radiomic signature of tumor hypoxia from patient MRI scans and subsequently showing it to relate strongly to the survival of patients with glioblastoma. Grossman et al (44) presented an alternative approach with the aim to reveal general themes in the relationships between radiomic feature classes and pathway information. A biclustering approach was used to identify clusters of radiogenomic correlations, linked to outcome, which were subsequently validated to show, for example, correlations with immune infiltration or nuclear factor-κB, or NF-κB, expression (also involved in immune response), with targeted IHC (Fig 3). Introduction of

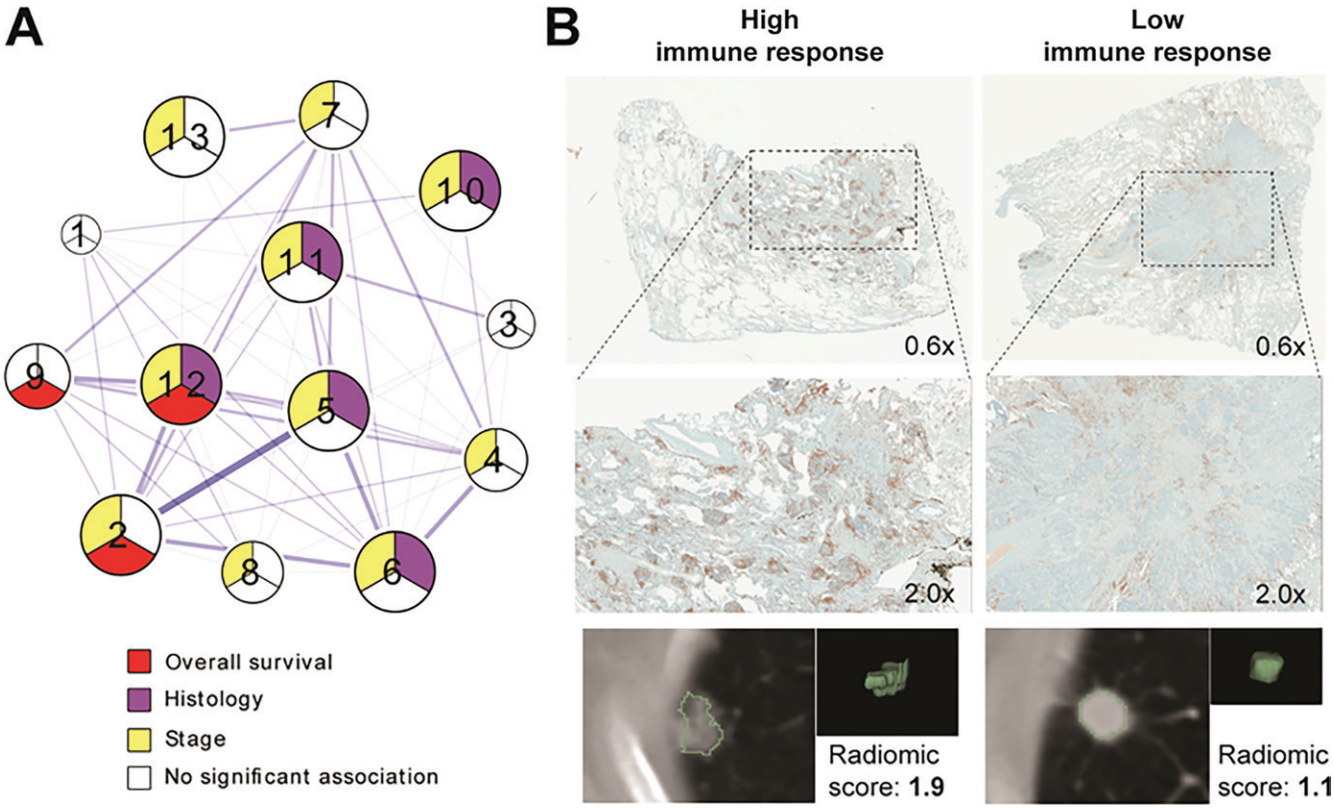

Figure 3: Associations between radiomic and pathway data can be explored histologically. *A*, Diagram depicts analysis of correlations between pathway enrichment and radiomic features presented by Grossman et al. Multiple clusters (numbers 1–13) describe relationships between distinct biological processes and image information. Further correlation of relevant radiomic features and immunohistochemical staining (nuclear CD3 expression) was performed to validate findings and to provide link to understand interaction between genetics and imaging characteristics of tumor. *B*, Example tumors with strong immune response and/or high radiomic score (left) and low immune response and/or radiomic score (right) are shown. Source.—Reference 43.

histologic information can provide the necessary link to understand the relationships between genetics and seemingly distant radiomic features describing the macroscopic tumor textures.

Instead of considering the tumor volume, Wu et al (45) focused on the image features of tumor-adjacent parenchyma and concluded that their predictive power for patient survival was likely associated with the related dysregulation of relevant signaling pathways, such as tumor necrosis factor-α, or TNF-α. Modules of features of similar informational content were grouped and related first to genetic data for screening to later evaluate their power for survival prediction. In a similar study, this same group performed an analysis of breast cancer, demonstrating the use of radiomic analysis of contrast-enhanced MRI to identify tumor subtypes of distinct survival and molecular pathway characteristics, likely underlying the survival differences (46). Itakura et al (47) took a distinct approach by using unsupervised analysis to define main clusters of tumors, defined strongly by their shape and enhancement pattern. Following confirmation of differential survival of the clusters, corresponding genetic pathway upregulation differences were identified, providing potential biological underpinning of the outcome disparity.

Treatment response information can further verify the biological mechanism behind a radiomic model. Liu et al (48) used MRI perfusion imaging data to identify subgroups of patients with glioblastoma with distinct survival. This was further interrogated with associated genomic data to relate contrast enhancement to angiogenic properties of the tumor, and the model was shown to correctly predict response to antiangiogenic treatment, confirming its biological underpinning.

The relationships observed in radiogenomic studies may often still be biologically ambiguous, given the complexity of the genetic code and its link to the phenotype, which is often indirect. Additionally, the large number of correlated parameters, both image- and genome-derived, results in an often overwhelming number of comparisons, which can blur conclusions.

Demonstration of a causal relationship between tumor characteristics and image features remains beyond the reach of most radiomic studies, as the predominantly clinical and retrospective nature of the work precludes an intervention to test observed correlations. This may be informed by preclinical studies. Panth et al (49) argued causality between genetic changes and radiomic features with the aid of an inducible gene mouse model, shown to affect specifically tumor hypoxia. In a broader coclinical study, Zinn et al (50) demonstrated a causal link between gene expression and radiomic signature changes through analysis of wild type versus knockdown mouse tumor models and related these to patient data. These studies offer more detailed and powerful

insight into the mechanism of action and biological underpinning of the findings and should therefore be encouraged.

Additional Validation of Histopathologic Findings and IHC

One step closer to the anatomy is the histopathologic information describing the phenotypes of the tumor cell population and its surrounding microenvironment. Establishing the relationship between observed radiomic signatures and pathologic findings could provide a powerful link to the biological drivers of patient outcomes, potentially more specific than genetic profiles.

Multiple studies have used histologic data to provide more detailed end point information compared with standard survival metrics, thus demonstrating the potential for radiomics to predict, for example, the histologic tumor type (51–53) or pathologic response (54,55). Others focused on prediction of yet more specific analysis, for example, with Yin et al (56) relating PET/MRI radiomics to vascular density derived from pathologic samples. This study did not, however, use the biological correlates available from histologic data for validation and improvement of radiomic findings. In a novel approach to pathologic finding–supported radiomic model development, Tang et al (57) stratified patients according to two immune-pathologic markers and used this as an additional screening step. They arrived at a survival predictor correlated to the relevant immunologic phenotype, known to be relevant for patient outcome.

Sun et al (39) have used IHC staining information to validate the biological underpinnings of a proposed survival signature, which was related to immune infiltration. Ha et al (58) demonstrated the use of histopathologic correlations in evaluation of unsupervised radiomic models. The clusters of tumors based on radiomic features were shown to display differential response to treatment and recurrence risk. They were also observed to present differential expression of relevant IHC markers, thus providing an insight into the probable biological source of the difference in outcomes.

Biological validation of the mechanism linking a radiomic signature to patient outcome requires careful selection of a meaningful correlate. Sone radiomic studies have focused on relating the signatures to tumor oxygenation status (hypoxia), measured through association to relevant genetic pathways, as described earlier, and/or with the aid of histopathologic analysis, relying on the known strong link between tumor hypoxia, disease progression, and treatment response across multiple cancer types (59,60). Tunali et al (40) confirmed a relationship between the radiomic model of survival in non–small cell lung cancer and IHC of a hypoxia marker, carbonic anhydrase IX, which was originally identified in a radiogenomic screening. Similar to Sun et al (39), IHC analysis was used to bridge the imaging and genetic information, thus overcoming the limited specificity of pathway data to direct phenotypical insight.

Conversely, radiomic approaches can be used to provide surrogate measure of tumor hypoxia. Traditionally, direct tumor hypoxia measurements (61) are attempted with molecular imaging techniques, including specific PET and optical probes (62,63). Although novel tracers are being developed (64), the imaging efforts have largely been hampered with low dynamic range and hence poor signal-to-noise ratio. In contrast, radiomic analyses of standard of care imaging have a potential to provide an indirect insight into the hypoxia status. As described previously, Beig et al (43) used a radiogenomic signature of hypoxia to predict survival in patients with glioblastoma. Pimonidazole sequesters in hypoxic volumes and can be detected with IHC. A data-driven analysis relating pimonidazole staining to tumor characteristics has previously been described using genomics (65). Ganeshan et al (66) took a more detailed look at the image texture features and histologic metrics of hypoxia and angiogenesis in coregistered radiologic and IHC images and reported multiple significant associations.

Muzi et al (67) and Sörensen et al (68) developed moderately strong survival signatures based on image feature extraction from fluorine 18 fluoromisonidazole PET uptake imaging related directly to tumor hypoxia information. No secondary correlates were reported. As fluorine 18 fluoromisonidazole PET is not widely available to patients, Crispin-Ortzuar et al (69) have developed a surrogate signature of this PET hypoxia marker using the traditional FDG/PET and CT data. Another study by de Jong et al (70) describes the use of PET/CT radiomics in an attempt to measure changes in response to a hypoxia-altering nitroglycerin treatment. No significant differences were reported.

Local Radiomic Analysis Using Pathologic Correlates

A separate approach to relate radiomic results to tumor pathologic findings relies on texture analysis of histologic images. The emerging and rapidly expanding field of pathomics (71) aims to apply high-throughput image feature extraction techniques to interrogate the microscopic patterns in pathologic data, especially from hematoxylin-eosin–stained sections. Because of the close similarity of the approaches, the features from in vivo images may be compared with the features extracted from ex vivo specimens, often benefiting from a clearer biological definition of the image patterns and hence a better understanding of the features. The quantitative analysis of histologic data has been shown to improve outcome prediction (72,73) and to aid prognosis (74) beyond the capabilities of human practitioners, mimicking the goals of radiomics. Saltz et al (75) argued that the similarities between radiomic and pathomic analysis renders the combination of the techniques promising to improve the predictive power. Direct application of radiomic tools to histopathologic images has shown promise for tumor staging (76).

Comparing the radiomic features derived from macroscopic resolution in vivo images to subcellular scale data of pathomics is a challenge and may not provide direct insight into the biological underpinning of radiomics. As with the radiogenomics analysis, a significant gap in the biological source of information from the two approaches precludes clear conclusions. In a promising early attempt, Geady et al (77) generated simulated CT images from pathologic data,

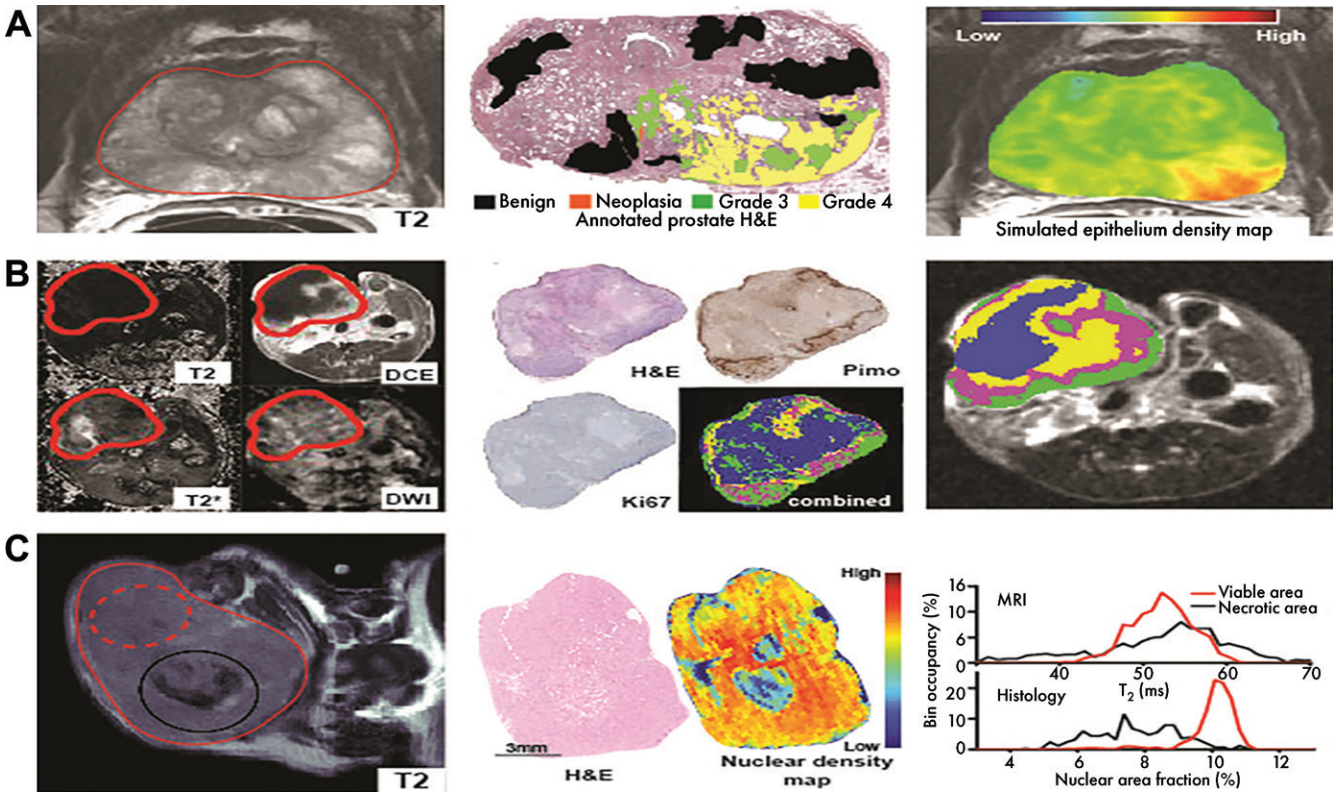

Figure 4: Coregistered histologic findings provide biological insight into image features. H&E = hematoxylin-eosin. *A*, McGarry et al (additional data provided by authors) developed model using multiparametric MRI information (left), trained on coregistered annotated hematoxylin-eosin–stained slides (middle) to model prostate epithelium density (right), relevant for tumor staging. *B*, Jardim-Perassi used multiparametric MRI (left), coregistered with histologic maps of viability, proliferation, and hypoxia (middle) to understand biological meaning of imaging habitats (right). DCE = dynamic contrast enhanced, DWI = diffusion-weighted imaging, Pimo = pimonidazole. *C*, Tomaszewski et al proposed T2-weighted MRI (left) histogram biomarker of radiation therapy response and used coregistered histologically derived nuclear density maps (middle) to demonstrate source of observed imaging changes through similarities in histogram features (right). Source.—References 79, 80, 89.

thus showing good correlations between the underlying microscopic information and derived texture features.

Other approaches have been proposed to overcome this limitation by focusing on histologic information at spatial scales that were matched to the in vivo imaging. Bobholz et al (78) coregistered MRI and hematoxylin-eosin–stained histologic images that were downsampled to the MRI resolution to compare the local texture information in both data sets. Comparison of the radiomic features from matching areas of the images identified a subset of metrics closely related between the two modalities. Although not directly revealing the biological underpinning of the metrics, these findings bring us closer to a solution as the biological meaning of hematoxylin-eosin stain patterns is significantly less ambiguous than are most MRI scans. In addition, knowing the close correlation between the low-resolution radiomic and pathomic features, the latter can then be related to the local phenotype with the help of pathologists. A step in this direction is described by McGarry et al (79,80), again using coregistered hematoxylin-eosin stain and multiparametric MRI data sets to develop local radiomic predictions of histologic parameters related to tumor grade in prostate cancer, although the unsupervised nature of the model does not reveal the direct contributions of different multiparametric MRI components to the predictions. Matched quantification of MRI and pathologic images was also used by Tomaszewski et al (81) for validation of the proposed feature of radiation therapy response. These examples illustrate the value in coregistration of in vivo and ex vivo images for detailed, spatially resolved insight into the relationships, shown pictorially in Figure 4. The local nature of the findings does not always translate directly to the main aim of radiomic analysis, which is focused on general per-patient signatures of survival and response. However, the local comparisons and observed correlation can shed light on the biological meaning of the radiomic metrics and can provide additional validation for observed signatures of outcome, thus enabling screening of features for relationships to histologic findings.

Habitat Imaging

Radiomic analysis has been widely applied in attempts to inform and quantify tumor heterogeneity. A separate approach explicitly aimed at identifying distinct tumor areas and cell subpopulations is represented by habitat imaging, which represents a middle ground between traditional whole-tumor and local per-voxel analysis as presented earlier. Combining images from multiple techniques, such as multiparametric MRI (82), or PET/CT (83), enables establishment of quantitative signatures used for delineation of distinct functional regions (habitats) within the tumor

Table 1: Summary of Classes of Biological Correlates with Their Advantages and Disadvantages

Biological Correlate	Description	Advantage	Disadvantage
Genomic data	High-throughput screening methods can reveal possible links between radiomic features and molecular pathways underlying tumor biological characteristics	Highly sensitive to many possible relationships because of volume and availability of data	Unclear underlying mechanism of correlations, risk of overfitting, and requires further validation
Immunohistochemistry	Providing insight into tumor phenotype, direct correlations between immunohistochemistry and radiomic signatures have been used to shed light on radiogenomic and outcome associations of image textures	Direct phenotypic information from histologic findings likely to explain image features	Analysis requires tissue blocks often not available in sufficient numbers and additional processing
Local pathologic analysis	Quantitative pathologic image features can be directly compared with radiomics to explain structural characteristics underlying radiologic textures	Like-to-like comparison using reference standard pathologic analysis includes spatial information not available to other validation methods	A need for specially collected and usually coregistered tissue blocks limits analysis to prospective studies
Habitat imaging	Comparison of tumor subregions between imaging and histologic findings facilitates understanding of underlying biological characteristics of radiomically defined habitats	Accounts for intratumor heterogeneity and provides specific local radiomic and histologic signatures	Unsupervised clustering of multidimensional imaging data (eg, multiparametric MRI) may not reveal details of biological relationships

mass (84). The use of complex signatures from multidimensional information, an approach shared with radiomic analysis, leads to shared challenges in biological interpretation and validation of the findings. Relative habitat volumes have been reported as a predictor of survival (85) and genetic pathway dysregulation (86) using MRI or PET/CT data (87) for clustering. Limited insight into the biological meaning of the habitats can be provided by independent delineation of apparent tissue phenotypes such as necrosis and edema (86). With the help of careful histologic validation, Henning et al (88,89) tracked temporal dynamics of hypoxic, viable, and necrotic MRI habitats in a preclinical model of sarcoma following radiation therapy. Efforts to provide even more detailed biological insight are already available preclinically through per-pixel spatial coregistration of the images and corresponding histologic findings, thus demonstrating the use of MRI habitats for delineation of hypoxia, necrosis, and other conditions (90). The retrospective design of many clinical quantitative imaging studies prevents access to such insight. Prospective radiomic studies, including coregistered pathologic collection in the protocol, and early reports, such as the ovarian cancer case study (91) and continued efforts in renal carcinoma (92) or the Total Tumor Mapping trial in pancreatic cancer (ClinicalTrials.gov identifier: NCT03718650), will be necessary to shed light on the biological meaning of clinical image habitats.

Division of tumor and surrounding tissues into distinct physiologic subregions can also be used to focus the radiomic analysis to informative areas. Beig et al (93) performed feature extraction separately in edema, necrotic, and enhancing regions of brain tumors, showing their different informational content for progression-free survival prediction and association with gene expression. A similar approach was also used (94) to relate radiomic signatures to metabolic traits, as measured by MR spectroscopy. However, the increased number of features due to analysis of multiple regions requires larger cohort sizes and careful validation.

Biologically validated habitat imaging will be essential for its perhaps most promising clinical application—radiation therapy planning (95). As stressed by Enderling et al (96), knowledge of the spatial distribution of physiologic tumor subregions could allow for dose painting to optimize the response according to local radiosensitivity profiles. Early developments in these data-driven dose planning approaches based on image (radiomics) and dose shape (dosiomics) features are already promising for the reduction of radiation toxicity (97,98) and for enabling personalized dose prescription (99).

Discussion

Our review showed significant recent effort in biological validation of radiomic findings. Four main classes of biological correlates and approaches used to date to inform the biological underpinnings of radiomics are identified, including gene expression data, protein expression from immunohistochemistry staining, microscopic histologic textures, and physiologic tumor habitats. The summary of these core classes and their evaluation is presented in Table 1.

In a traditional radiomic pipeline, a signature of outcome, developed and validated in an independent training set, may

Table 2: Approaches Available for Investigation of Biological Underpinnings of Radiomic Signatures

Analysis Aim	Biological Correlate	Observed Relationship	Biological Conclusion
Establishment of CT treatment response biomarkers for patients with lung cancer treated with immunotherapy (40)	Genomic analysis of risk groups was followed by immunohistochemistry analysis for carbonic anhydrase IX (CAIX).	Gray-level co-occurrence matrix, or GLCM, inverse difference, significantly associated with survival, was also related to CAIX expression	The response prediction of feature appeared to be due to its sensitivity to hypoxia, a prognostic factor
Radiomic prediction of tumor hypoxia from MRI for indirect survival analysis in glioblastoma (43)	Correlation of hypoxia pathway genes to radiomic features	Radiomic signature of hypoxia was found to also be associated with survival	Tumor hypoxia affects imaging phenotype and enables indirect survival prediction
Investigation of associations between radiomic features, molecular pathways, and clinical information (44)	Correlation of pathway clusters to radiomic features and histologic staining	For example, wavelet texture entropy was related to immune response through pathway and histologic data	Multiple molecular pathways appear to induce macroscopic tumor changes affecting image textures
Identification of tumor MRI phenotypes with distinct molecular and survival characteristics (47)	Gene expression profiles compared between clusters of tumors identified by imaging features	Tumors appearing distinct in shape and enhancement are associated with different molecular pathways and survival	Image features can distinguish tumors of separate molecular characteristics, which in turn inform survival prediction
Development of radiomic signatures of immune phenotype for survival prediction (57)	Radiomic analysis applied to immune-pathologic tumor subgroups	Signatures developed for immune phenotype identification enabled indirect survival prediction	Image characteristics can inform immune phenotype for biologically driven outcome modeling
Correlation of CT texture features from lung cancer tumors to histopathologic markers of angiogenesis and hypoxia (66)	Correlation of staining intensity in pimonidazole and CD34 immunohistochemistry slides to texture features	Standard deviation and mean value from medium- and coarse-texture filtered images is associated with pimonidazole stain intensity.	CT textures appear to be surrogate measure of tumor hypoxia
Identification of physiologic tumor subregions by multiparametric MRI habitat imaging in mouse breast models (90)	Sections stained with hematoxylin-eosin, pimonidazole, and Ki67 coregistered to MRI maps	Imaging habitats based on multiparametric MRI results strongly overlapped with normoxic, hypoxic, and necrotic areas identified ex vivo	Signature of local oxygenation and viability status is defined by MRI metrics of tumor vasculature and tissue density

Note.—Distinct methods as described in Table 2 have been employed to relate radiomic findings to the underlying tumor biological characteristics. Each row presents a different study, and the order reflects each study's reference in the article.

be subsequently investigated for its association with a particular biological metric such as gene expression or IHC staining intensity. This method, as used among others by Sun et al (39) and Tunali et al (40), can strengthen the model, retrospectively informing the possible mechanism of outcome prediction. Conversely, the biological correlate can be used explicitly for model building, arriving at a radiomic signature indirectly associated with outcome because of the biological correlation, such as the negative prognostic value of tumor hypoxia, as in the studies by Beig et al (43). Although both approaches provide important validation and insight into the tumor biological characteristics, the more hypothesis-driven focus on the second method may deem it less biased for outcome analysis. Examples of the distinct methods designed to provide a biological insight into radiomic signatures, together with the findings and their significance, are presented in Table 2.

As the field develops, studies are increasingly expected to report at least one more correlation of the proposed radiomic model beyond the primary relationship with survival or other end point metrics. These can be incorporated at different stages of the process as a prescreening tool for feature selection or as the primary source of test data before survival calculation. The microscopic texture of histologic slides can also be used for additional insight.

Coclinical and preclinical experiments may also serve an important purpose in biological validation of radiomic findings. The controlled environment of animal studies enables the experimental interventions necessary to establish causal relationships between biology and radiomics and to offer precise, spatially coregistered histologic analysis for in-depth validation. However, the direct translatability of imaging findings between the spatial scales remains a challenge. Increasingly, clinical reports (eg, in the brain [78], prostate [80], or ovarian cancer [91]) demonstrate the feasibility and high value of three-dimensional printing–aided coregistration of in vivo and ex vivo images, providing spatially resolved insight into the biological meaning of local imaging characteristics.

Conclusions

To date, many radiomic studies present no validation of the findings beyond using an independent test cohort. This trend contributes to poor reproducibility and hence limited impact. With further recognition of the importance of biological understanding of the radiomic signatures, a standardized valida-

tion roadmap should be developed and deployed within the radiomics community. Many approaches, as summarized in our review, are already available for validation and biological context of the features. Going forward, we propose that reported studies should all strive to include such analysis, either as part of the model building or subsequent validation, to provide a hypothesis for the biological mechanism of the observed relationship. This will enable the discussion of the biological characteristics underlying the findings to become a standard in the field and enforced in the peer-review process.

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