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Background, Current Role and Potential Applications of Radiogenomics

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Abstract

With the genomic revolution in the early 1990s, medical research has been driven to study the basis of human disease on a genomic level and to devise precise cancer therapies tailored to the specific genetic makeup of a tumor. To match novel novel therapeutic concepts conceived in the era of precision medicine, diagnostic tests must be equally sufficient, multilayered and complex to identify the relevant genetic alterations that render cancers susceptible to treatment. With significant advances in training and medical imaging techniques, image analysis and the development of high-throughput methods to extract and correlate multiple imaging parameters with genomic data, a new direction in medical research has emerged. This novel approach has been termed radiogenomics. Radiogenomics aims to correlate imaging characteristics (i.e., the imaging phenotype) with gene expression patterns, gene mutations, and other genome-related characteristics and is designed to facilitate a deeper understanding of tumor biology and capture the intrinsic tumor heterogeneity. Ultimately, the goal of radiogenomics is to develop imaging biomarkers for outcome that incorporate both phenotypic and genotypic metrics. Due to the non-invasive nature of medical imaging and its ubiquitous use in clinical practice, the field of radiogenomics is rapidly evolving and initial results are encouraging. In this article, we will briefly discuss the background and then summarize the current role and the potential of radiogenomics in brain, liver, prostate, gynecological and breast tumors.

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Introduction to Radiogenomics

With the genomic revolution in the early 1990s and the realization that cancer is a genetic disease, medical research has been driven to study the basis of human disease on a genomic level and to devise increasingly precise cancer therapies tailored to the specific genetic makeup of a tumor. It has become evident that traditional cancer classifications based on tumor phenotypes are thus insufficient. Based on the results of the Human Genome Project which was completed in 2003, and the subsequent technological advances, molecular biomarkers have been rapidly introduced into clinical practice to guide therapeutic decisions in the individual patient. To match novel therapeutic concepts conceived in the era of precision medicine, diagnostic tests must be equally sufficient, multilayered and complex to identify the relevant genetic alterations that render cancers susceptible to treatment. Such tests must extend beyond the identification of single oncogenic defects, and, moreover, should encompass the genomic and molecular complexities of neoplastic disease to support the precise prediction, guidance, and monitoring of a therapy. Medical imaging has always been an integral part of disease diagnosis and has guided treatment decisions. With significant advances in training and medical imaging techniques, image analysis, and the development of high-throughput methods to extract and correlate multiple imaging parameters with genomic data, a new direction in medical imaging research has emerged. Radiogenomics aims to correlate imaging characteristics (i.e. the imaging phenotype) with gene expression patterns, gene mutations, and other genome-related characteristics (1–7).

Although often confused with radiomics, radiogenomics is not equivalent to radiomics. Whereas radiogenomics investigates relationships between imaging features and genomics, radiomics refers to the methodology behind the conversion of digital medical images with various data of interest including patient characteristics, outcomes and ‘omics data for an improved decision support (1,3,6,8). For a detailed review of the process of radiomics, i.e. image acquisition, volume of interest identification, segmentation, feature extraction and quantification, database building, classifier modeling, data sharing, and its challenges, refer to a recent review article by Gillies et al. (3), Sala et al. (9) and Lambin et Al. (6).

Radiogenomics represents the evolution of radiology-pathology correlation from the anatomical-histological level to the genetic level. The term radiogenomics has broadened since its initial coinage that described only the research that investigates the associations of patient genetics to variations of patient sensitivities to radiation treatment (10–12). In contrast to the current use of radiogenomics, this description focused on identification of phenotypes representing normal tissue radiation toxicity and will not be discussed in this review.

In radiogenomics, biomedical images are significantly reflective of the product of processes occurring at the genetic and molecular level. Parameters derived from advanced image processing and analysis can reflect the underlying phenotypic and genotypic characteristics

of the tissue (1,2,13). Radiogenomics is thus designed to facilitate a deeper understanding of tumor biology and capture the intrinsic tumor heterogeneity with relevant implications for patient care (9). Ultimately, the goal is to develop imaging biomarkers for outcome that incorporate both phenotypic and genotypic metrics.

Radiogenomics studies are either exploratory or hypothesis-driven. In exploratory studies, several qualitative and/or quantitative imaging features, such as intensity, shape, size, volume, or texture, are manually or semi-/automatically extracted and computed from an imaging dataset. These features are tested against a multitude of different genomic variables. Metrics, such as the false discovery rate, are often implemented to identify meaningful prospective variables in the setting of multiple hypotheses testing [63–65]. A different exploratory method is hierarchical clustering, which is used to identify similarities in large genetic datasets. In this process, individual data points that show similarities are clustered until the clustering process has established the relationship between all data points. The largest group at the top of the hierarchical clustering map is then used to define different groups within the dataset. A highly cited example of this approach is the original definition of the molecular subtypes of breast cancer by Perou et al. [66]. As opposed to exploratory methods, hypothesis-driven radiogenomics consists of research where imaging phenotypes are correlated with specific genetic alterations or signatures [44], with several potential benefits for diagnostic and therapeutic interventions. As currently no low-cost genetic testing is readily available, the development of accurate surrogates by means of radiogenomics is an active field of research with initial promising results. Alternatively, radiogenomics might be used to develop imaging surrogates for specific genetic signatures to predict outcome variables, such as response to therapy or early metastases [67, 68].

The field of radiomics/radiogenomics is relatively young. Bai et al. (2), in their review of the current state of radiogenomics research which included studies employing a “radiomics approach to radiogenomics” as well as studies that associated imaging features with specific genes and expression of specific gene subsets (e.g. tumour molecular subtype), identified a total of 65 publications between 2007–2015. However, the field of radiogenomics is expected to grow rapidly as more discoveries are made in conjunction with technological innovation, with an increasing number of papers being published (2,14–25), mostly addressing challenges in oncology. Several papers on radiogenomics have been published in lung cancer (25,26), where the main imaging modality employed is computed tomography (CT). As the focus of this article is the application of radiogenomics using magnetic resonance imaging (MRI), however, organ systems where radiogenomics research is primarily conducted with CT, i.e lung, renal and head-and-neck cancers, will not be discussed. This article intends to shed light on the current role of radiogenomics and elucidate its potential, with a focus on brain, liver, prostate, gynecological and breast tumors. In instances where MRI-based studies are lacking in brain, liver, prostate, gynecological and breast tumors, we present CT-based studies that reflect the role and potential of radiogenomics.

Brain

Radiogenomics research in the brain has primarily centered on investigations of glioblastoma, the most common and the most fatal primary brain tumor in adults despite decades of effort to treat the cancer and improve patient survival. Of all patients diagnosed with glioblastoma, the mean survival is only 1 year, and 5 year survival is <5% (27). The dismal prognosis is driven by tremendous molecular and genomic heterogeneity, which leads to evasion of successful treatment. Recent advances in technology have led to this improved understanding of glioblastoma. Beginning in 2005, The Cancer Genome Atlas (TCGA) project has sought to comprehensively profile the genomic characterization of different cancers including glioblastoma. Coordinated efforts to characterize glioblastoma using TCGA data led to the identification of four distinct molecular subtypes: Classical, Mesenchymal, Proneural and Neural. These subtypes were subsequently determined to be associated with different patient outcomes and tumor progression patterns (28,29). More recently, glioblastomas have been stratified into 3 core pathways according to RTK/RAS/PI(3)K, p53 and RB signaling alterations (30) that better correlate with different patient outcomes. Radiomic analysis of MRI data in The Cancer Imaging Archive (TCIA) matching the mutation data in the TCGA has enabled radiomic correlations and the emerging field of radiogenomics for glioblastoma.

MRI is the primary modality for imaging glioblastoma and affords the best imaging of the brain as it is unhindered by sampling error or tumor location in eloquent or otherwise inaccessible brain. Early efforts in radiomics relied on qualitative MRI observations manually recorded by expert users in a standardized manner. The controlled vocabulary for describing 24–30 common MRI observations were then formalized by the TCIA into the Visually Accessible Rembrandt Imaging (VASARI) feature set, which subsequently became the Repository of Molecular Brain Neoplasia Data (REMBRANDT) feature set. While VASARI-based studies have revealed many promising results, they require user-marked volumes-of-interest and user-assigned qualitative descriptors. To overcome the variability and uncertainty from this manual user quantification of tumor margins and features, and facilitate high-throughput analyses, further advances in technology have since enabled semi-automated or fully automated tumor segmentations and feature extractions.

Studies using automated, quantitative feature extractions show that they can take full advantage of the multi-dimensional data captured by MRI. These studies employ voxel-based analyses and implement texture algorithms such as gray level co-occurrence matrix, local binary patterns, discrete orthonormal Stockwell transform and Gabor edge feature sets. Hundreds or even thousands of texture features are generated that require high-throughput analysis driven by advanced image analysis and machine learning techniques such as decision-tree based random forests, recursive feature elimination coupled support vector machine classifiers and principal component analyses. These techniques can be applied to predict the underlying genomic alterations in tumors, and to explicitly describe tumor heterogeneity through unsupervised clustering of different portions of the tumors.

Predicting molecular and genomic alterations, and survival

Several studies have used imaging to predict molecular and genomic alterations as well as survival. Their findings are briefly reviewed here, showing the feasibility and advantage of radiogenomics.

When examining 10 MRI features, Diehn et al (31) found that the ratio of enhancing to non-enhancing volume correlated with epidermal growth factor receptor (EGFR) overexpression ($p=0.019$), and the enhancing phenotype was correlated with angiogenesis and tumor hypoxia related genes such as vascular endothelial growth factor (VEGF), ADM and PLAUR ($p=0.012$).

A study of 104 TCGA glioblastomas found 3 VASARI features predictive for worse patient survival: ependymal enhancement (10.6 versus 18.6 months, $p=0.0018$), deep white matter tract involvement (10.9 months versus 19.9 months, $p<0.0008$) and enhancement across midline (9 months versus 14.3 months ($p<0.0003$) (32). When the first two imaging features were combined into a Class A invasive phenotype, significant associations were found with mitochondrial dysfunction ($p<0.0001$), *MYC* oncogene activation and NF-*K*B inhibitor-alpha (NFKBIA) inhibition.

Volumetric analysis of 76 TCGA glioblastomas found that TP53 mutant tumors had smaller enhancing and necrotic volumes ($p\leq0.017$) and RB1 mutant tumors had smaller edema volumes ($p=0.015$) (22).

Another study of 55 TCGA glioblastomas applied VASARI features and quantitative features to enhancement regions-of-interest (ROIs) and necrosis ROIs, and found 3 enhancement features that correlated with progression-free as well as overall survival ($p\leq0.028$) and 4 image features that correlated with TCGA molecular subgroups ($p<0.05$) (21). The implications for better stratifying survival was also described in 92 TCGA glioblastomas (33): a combinatorial phenotype consisting of volume-class (dichotomized volume greater or lesser than median volume of all cases), T1-weighted/FLAIR (fluid-attenuated inversion recovery) ratio (size of pre-contrast T1-weighted abnormality relative to the size of the FLAIR abnormality) and hemorrhage was able to stratify survival into less aggressive and more aggressive groups with median 8 month survival difference (33). These two groups demonstrated differences in genes and miRNAs involved in tumor growth, invasion and proliferation.

When examining 78 TCGA glioblastomas, Zinn et al (19) found that stratification of the non-enhancing FLAIR volumes into high volumes and low volumes correlated with upregulated genes including PERIOSTIN (POSTN) and downregulated genes including miR-219, a microRNA that binds to POSTN. The high FLAIR volume tumors demonstrated upregulated POSTN with shorter progression-free survival ($p=0.0009$) and overall survival ($p=0.0008$). POSTN upregulation is more common in Mesenchymal subtype than Proneural subtype, and thought to induce tumor invasion through epithelial to mesenchymal transformation. The non-enhancing FLAIR volume or vasogenic edema has also been correlated with oncogenes FOXP1 and PIK3IP1 (20).

Characterizing glioblastoma heterogeneity

While TCGA and TCIA are fantastic publically available resources, currently their data lack location-specific information to account for regional variations in tumor heterogeneity. However, previously demanding genomic profiling are becoming more routine due to better technology, as witnessed by the success of targeted cancer profiling tests such as Foundation One (Foundation Medicine, Cambridge, MA) and MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets, Memorial Sloan Kettering Cancer Center, New York, NY). The growing availability of such genomic profiles will enable additional correlations to be discovered between imaging, genomic and clinical data, including novel characterizations of different cell populations within the same tumor. As such, radiogenomics of cancers of the brain including glioblastoma will deepen.

In a study of 48 image-guided biopsies obtained in 13 tumors, Hu et al (34) demonstrated correlations between conventional, diffusion tensor imaging (DTI) and dynamic susceptibility contrast (DSC) perfusion metrics, and commonly implicated alterations in EGFR, PDGFRA, PTEN, CDKN2A, RB1, and TP53 ($p<0.03$)—with accuracies ranging from 87.5% for RB1 to 37.5% for TP53. A similar study of spatial diversity texture features was able to characterize local EGFR mutation status as well as patient survival in 65 glioblastomas (35). Because the various clonal populations are driven by unique genomic alterations, each with inherently different sensitivities to treatment, accurate characterization of tumor heterogeneity will become essential for success in the emerging era of targeted cancer therapies.

While efforts have thus far focused on upfront correlations before initial surgery, radiogenomics has immense untapped potential for characterizing glioblastomas during treatment. Radiogenomics has the advantage of noninvasively evaluating the entire tumor, as opposed to subjecting the patient to repeat brain tumor surgery for additional genomic profiling. Rapid, reproducible and repeatable radiogenomic quantifications can provide essential data about changes in the tumor composition induced by the treatment, which can then inform clinical treatment decisions for targeted treatment strategies. This is especially important in the case of recurrent glioblastomas which may be driven by different clonal populations with different evasion mechanisms, and some glioblastomas are even known to develop hypermutator profiles with 50–100 or more mutations.

Liver

There are limited radiogenomic studies in the liver to date, the majority of which have centered on hepatocellular carcinoma (HCC), the most common primary liver cancer. A majority of studies on liver cancers have been based on CT radiomics, with only a handful investigating the role of MRI. The potential of radiogenomics to assist the clinical management of HCC and other liver tumors is substantial, given the proliferation of treatment options available for liver cancers, such as embolization, radiation, resection and systemic therapy. The promise of radiogenomics is in helping select the best possible treatment modality for individual patients, as the genetic landscape of liver malignancies is further elucidated and shown to be predictive or prognostic for treatment response. To date, despite the central role MRI plays in the detection and characterization of liver disease, the

management of HCC patients still relies on a staging system based on the number and size of tumors identified. The need to better characterize the biology of HCC for patient stratification provides ample further motivation to develop our image analysis beyond morphological characteristics and investigate radiogenomics of liver tumors.

The most common primary liver malignancy is HCC, followed by intrahepatic cholangiocarcinoma (ICC). For each of these tumors, biomarkers are increasingly sought for prediction of genetic heterogeneity and clinically relevant parameters such as microvascular invasion (MVI). A limited number of studies to date have centered on radiogenomics of HCC. Based on the hypothesis that gene expression patterns may correlate with dynamic imaging features, a combination of 28 imaging features were found to reconstruct 78% of global gene expression profiles in HCC (36). This initial study showed the potential relationships found between tumoral imaging features and genetics, but the importance of individual genes or gene groups in HCC were not clear at that time. The imaging traits reported in this study were qualitatively assessed by radiologists from multiphasic contrast-enhanced CT, and include, for example, the presence or absence of internal arteries, the presence or absence of a capsule, and the heterogeneity in enhancement pattern (mosaic, target, or homogeneous). In a subsequent study of 157 patients with HCC, CT-based imaging features were also used to predict MVI and clinical outcomes (37). In this study, a radiogenomic venous invasion (RVI) score was devised from only 3 CT features to predict MVI, which was derived from a 91-gene HCC “venous invasion” gene expression signature. Narrowing the prediction to a biologically relevant RVI score showed how 3 qualitative imaging features could achieve a diagnostic accuracy of 89% with sensitivity and specificity of 76% and 94% respectively. In their patients, a positive RVI score was also significantly associated with lower overall survival (69 vs > 147 months), confirming the biological relevance of this investigation. Of note, five radiologists who assessed the RVI score demonstrated substantial interobserver agreement (kappa = 0.705) (37).

A study of HCC using MRI to predict pathologic MVI in 125 patients with 140 nodules was also conducted, identifying predictive imaging features related to the tumor border such as peritumoral enhancement and nonsmooth margins (38). While similar to the prior study using CT, the pathologic identification of MVI may not correspond directly to a venous invasion genetic signature and the results are not directly comparable. More recently, gene signatures of aggressive HCC phenotype were found to be associated with certain imaging traits in HCC imaged by contrast enhanced CT (26 patients) and MRI (12 patients), with an infiltrative pattern on imaging showing the highest number of positive associations (39). Interestingly, the authors did not find associations between enhancement ratios and gene expression signatures, but they propose the use of DCE-MRI for future prospective analyses given the limitation inherent to measurements of tumoral enhancement on arterial and portal venous phases alone. Multiparametric MRI was later performed in a study of 14 patients with available HCC gene expression profiles at the same institution (40). No differences were found between genetic subclasses in their MRI parameters, and none of the parameters could distinguish between HCC grades. However, individual gene expression levels did correlate with several MRI parameters, for example poor tumor perfusion (by DCE-MRI parameters) was associated with high expression of VEGFA. The authors discuss the potential benefit of quantitative multiparametric MRI compared with qualitative assessments

of HCC imaging features that are subject to interobserver variability, but the reproducibility of advanced MRI techniques including DCE-MRI, DWI and BOLD imaging in the liver needs further investigation as well.

One study has investigated the potential of texture analysis in predicting HCC biological aggressiveness on MRI, without directly addressing underlying genetic differences. In 46 patients with HCC who underwent contrast-enhanced MRI, gray-level run-length nonuniformity features calculated from arterial phase images were different between patients with low (Edmonsond grades I and II) and high grade (grades III and IV) HCCs (41). Interestingly, the authors investigated the effect of intensity normalization on the application of texture analysis, and found that, unsurprisingly, certain features performed better with, and others without normalization. The study also acknowledges the difficulty in standardizing arterial phase imaging across patients with HCC, potentially limiting the clinical applicability of their results. Performing a similar analysis in patients who undergo DCE-MRI with the associated parametric maps would be an alternative approach to consider.

A single radiogenomics study to date has investigated the potential of image analysis to predict molecular profiles of ICC, with a focus on hypoxia markers. In 24 patients, both qualitative and quantitative imaging phenotypes (based on texture analysis) correlated with a few hypoxia markers, including VEGF, EGFR, and CD24 (42). A number of qualitative and quantitative descriptors of ICC have also been investigated for their prognostic value alone, with four studies identifying the potential of tumoral vascularity in differentiating short and long term survivors (43–46). Three of these studies were performed based on retrospective analysis of CT imaging, while one employed DCE-MRI acquired from prospective clinical trials (44). While it is possible that these imaging phenotypes predict underlying genetic differences, such hypotheses remain areas of active investigation.

To date, there has been no radiogenomic study focused on liver metastases. CT texture analysis has been applied to patient with colorectal liver metastases, to investigate correlations with tumor grade, tumor response, or to predict recurrent disease (47–50). Given the increasing number of patients with colorectal liver metastases undergoing locoregional therapies as well as liver resections with a wide range of outcomes, further investigations into the role of radiogenomics in this population are warranted.

The visible heterogeneity of liver malignancies on display on CT and MR images across different patients is obvious and the desire to translate this heterogeneity into biomarkers guiding patient management is also evident. However, quantifying tumoral heterogeneity to predict patient outcomes or tumor genetics remains a challenge. From the limited available studies to date, the variability in imaging protocols and methodological approaches to quantify tumor heterogeneity limits our ability to compare results and draw conclusions about the potential role of radiogenomics. The outcomes explored are also different, including patient survival, histologic grade, genetic expression profiles, and microvascular invasion in the setting of HCC. The single-institutional approach and retrospective nature of most investigations further limits the development of this field. Multi-center collaborations

will eventually be needed to develop validated radiogenomic biomarkers for liver malignancies.

The choice between qualitative, quantitative, or dual approaches to image analysis to address tumoral heterogeneity also remains to be determined. Each has their own limitations, such as interobserver variability, technical reproducibility and costs. While the quantitative parameters offered by MRI such as DWI or DCE-MRI are attractive, these require dedicated efforts by investigators and their institutions to promote the use of advanced MR imaging techniques in select patients with liver malignancies, who in reality are more often imaged with CT given current imaging guidelines and staging needs. Even if multiparametric MRI becomes more prevalent in the routine imaging of HCC, the number of imaging features that need to be validated for reproducibility will remain a practical challenge. Texture analysis of conventional imaging techniques, including contrast enhanced CT, also present statistical challenges due to the shear number of features extracted, with potential overfitting of data to small sample sizes (51). Ultimately, radiogenomic studies for liver malignancies are bound to increase due to the need to better tailor our approaches to treatment; a collaborative approach and further guidance from national societies is needed to move us from the “bench to the bedside”.

Prostate

Among men in Western societies, prostate cancer is the most common non-cutaneous cancer (52) and exhibits an extraordinary variable biological behavior. A number of autopsy studies have revealed a disease prevalence of up to 76% in men who have never had a clinical diagnosis of prostate cancer (i.e., clinically indolent disease) during their lifetime (53). However, a subgroup suffer from a more aggressive, metastasizing type of disease that commonly evades systemic treatments (54). Thus, one of the most urgent objectives in prostate cancer research is to differentiate these populations as early as possible, allowing for individualized risk-adapted management. While risk stratification has been traditionally based on clinical examination, biopsy data (e.g. Gleason grade), and serological markers (e.g. Prostate Specific Antigen) (55), more recently, genomic (56) and MRI-derived imaging biomarkers (57) have been incorporated into the assessment of newly diagnosed prostate cancer.

A good number of radiomics studies have shown that MRI-derived first- and higher-order quantitative data analysis could be helpful in the detection (58,59) and staging (60) of prostate cancer, as well as the prediction of histopathological features (61–64) and biochemical tumor recurrence after surgery (65) and radiotherapy (66). Recently published radiogenomics studies from different institutions on the other have investigated the association of MR imaging biomarkers and genomic data with more mixed results.

In an analysis of prostate biopsy samples from 6 patients, a group of investigators from the University of Miami (67) correlated 49 multiparametric MRI features with 69 genes from three commercially available prostate cancer gene signatures, i.e., Oncotype DX® Genomic Prostate Score™, Decipher® Prostate Cancer Classifier and Prolaris® Cell Cycle Progression. They separately analyzed regions that were suspicious for harboring tumor as

well as regions with normal appearing prostatic tissue and reported strong associations of imaging features with the expression of genes associated with immune/inflammatory response, metabolism, cell and biological adhesion (Figure 1). From all evaluated imaging features, the apparent diffusion coefficient (ADC) values were most highly associated with distinct biological processes.

In another study with multiparametric prostate MRI, a group from the Pierre-et-Marie-Curie University in Paris correlated pre-prostactomy MRI features of prostate cancer in 106 patients with the Prolaris® Cell Cycle Progression (CCP) score, which is based on the expression of cell cycle proliferation genes (68). MRI features included Prostate Imaging Reporting and Data System (PI-RADS) scores, as well as diameters and mean ADC values of suspicious lesions. The authors reported a significant correlation of PI-RADS and CCP scores (ρ=0.26, p=0.007). However, unlike the University of Miami study, no significant correlation was found between CCP scores and mean ADC, respectively. CCP scores were also not correlated with lesion diameter.

McCann et al. from the University of Chicago extracted MRI features from 45 peripheral zone prostate cancer lesions of 30 patients and correlated the results with PTEN expression on prostatectomy specimen (69). They found a weak correlation of PTEN expression and one quantitative perfusion parameter (i.e. reverse reflux rate constant between the extracellular space and plasma, r=−0.35, p=0.02), but did not find significant associations with first-order statistical data from ADC-maps and T2-weighted images, or other perfusion parameters (69).

In a recently published whole-exome DNA sequencing study in 6 patients with higher-grade prostate cancer from the University of California Los Angeles, the authors were able to identify 77 mutations involving 29 cancer-associated genes (70). However, while the assessment of multiparametric MRI on a five-point ranked scale correctly identified high-grade lesions on whole-mount histopathology in all patients, there was no significant difference in mutation profiles between histopathologically normal tissue, high-grade prostate cancer, MRI-normal and MRI-suspicious regions (p=0.3), meaning that the background mutation spectrum in non-cancerous prostate tissue may be greater than expected.

Further studies are warranted to identify the most powerful imaging biomarkers that could potentially contribute to the prediction of high-risk genomic features, more accurate risk assessment and better management decisions in patients with prostate cancer.

Gynecological Tumors

Data on radiogenomics in gynecological tumors are scarce with only a few recent studies focusing on this emerging field. MRI for gynecological malignant tumor, including T2WI, T1WI, DWI/ADC maps and dynamic contrast enhanced (DCE) MRI, plays an added role for assessment of local staging and recurrence and is an important tool in the preoperative characterization of complex, sonographically indeterminate adnexal mass (71–74). CT and ^{18}F-FDG PET-CT are useful for staging in advanced malignancy and treatment follow-up

(75–78). Although studies in MRI related to radiogenomics are limited, they are valuable in continuing to improve our ability for using vast amounts of quantitative imaging data and understanding the molecular underpinnings of tumors and their response to treatment.

Studies in cervical cancer

Studies in patients with advanced cervical cancer have mainly evaluated the predictive value of radiogenomics/radiomics for patients undergoing chemoradiotherapy. In a study of 78 patients with locally advanced cervical cancer, Andersen et al. reported that several pharmacokinetic Brix and Tofts models parameters of DCE-MRI images were associated with progression-free survival and locoregional control (79). The A_{Brix} parameter was most significantly associated with patient outcomes. Following this study, Halle et al conducted further assessment in the 78 patients to determine the predictive ability of this parameter, using a radiogenomic approach (80). A gene set analysis of 46 of 78 tumors found that the A_{Brix} parameter correlated with hypoxia gene sets. In the remaining 32 of 78 tumors, immunohistochemistry analysis was performed, with the result that a low A_{Brix} was associated with upregulation of HIF1α protein expression. A DCE-MRI hypoxia gene signature consisting of 31 hypoxia genes upregulated in tumors with low A_{Brix} was constructed which showed prognostic impact (Fig. 1).

Studies in ovarian cancer

In a hypothesis-generating radiogenomics study of 46 patients with stage IIIC or IV high grade serous ovarian cancer, morphologic preoperative CT imaging features were associated with the Classification of Ovarian Cancer (CLOVAR) genomic subtypes of high grade serous ovarian cancer and predicted survival (81). The CLOVAR genomic subtypes were described as differentiated, immunoreactive, mesenchymal, and proliferative; this was done by integrating gene expression profiles into a prognostic framework named “CLOVAR” based on analysis by TCGA Research Network (82,83). Presence of mesenteric infiltration and pattern of diffuse peritoneal involvement at pre-treatment CT imaging were significantly associated with the CLOVAR mesenchymal subtype. Presence of mesenteric infiltration was also significantly associated with shorter progression-free survival and overall survival, thus providing important prognostic information.

Following this study, a multi-institutional study of 92 patients with high grade serous ovarian cancer was performed in order to generate risk scores based on combinations of CT imaging features that can predict either time-to-disease (TTP) or CLOVAR profile. Multiple preoperative CT imaging features were significantly asociated with TTP progression and CLOVAR genomic subtypes, (84). Presence of peritoneal disease in the right upper quadrant, supradiaphragmatic lympoadenopathy, more peritoneal disease sites and nonvisualization of a discrete ovarian mass were determined to be associated with a shorter time-to-disease progression. More peritoneal disease sites (also associated with a shorter time-to-disease progression) and presence of pouch of Douglas implants were determined to be associated with the CLOVAR mesenchymal subtype, which indicates the worst prognosis.

A study of 38 patients with stage IIIC or IV high grade serous ovarian cancer showed that radiomics-derived inter-site spatial heterogeneity metrics across multiple metastatic lesions

on preoperative CT were associated with clinical outcomes i.e., shorter overall survival and incomplete surgical resection, as well as amplication of 19q12 involving cyclin E1 gene (CCNE1) (85). CCNE1 amplification has been associated with higher chemoresistance (86) and higher rates of primary treatment failure (87). Inter-site spatial heterogeneity metrics may therefore predict outcomes and facilitate more effective treatment.

So far radiogenomics data in gynecological tumors are limited and more studies are needed combining qualitative and quantitative multi-parametric imaging features and genetic alterations, with the aim of developing and validating quantitative imaging biomarkers that can guide personalized therapy in patients with gynecologic malignancies

Breast

The field of radiogenomics in breast imaging is just emerging with the publication of the first paper in 2012 and is currently exclusively dominated by MRI (88). MRI is an essential tool in breast imaging, with multiple established indications; further, it is the most sensitive test for breast cancer detection (89–91). Nowadays, state-of-the-art breast MRI is usually performed as multiparametric imaging and comprises high resolution DCE-MRI, T2-weighted and DWI (92–94). DCE-MRI provides morphological as well as functional information about neo-angiogenesis as a tumor-specific feature (95,96). DWI, which has been explored and implemented in clinical routine breast imaging, provides functional parameters to overcome limitations in specificity (93,97–99). To date, breast MRI radiogenomics has mainly focused on DCE-MRI and the analyses of either individual genomic signatures, breast cancer molecular subtypes or clinically used recurrence scores, with encouraging results.

Individual genomic signatures

The first radiogenomic breast MRI study was an exploratory analysis of the correlations of global gene expression characterization with DCE-MRI, which set the stage for the radiogenomic age in breast imaging. In this groundbreaking study, Yamamoto et al. (24) investigated ten patients who underwent preoperative DCE-MRI and global gene expression analysis, and presented a preliminary radiogenomic association map linking MRI phenotypes to underlying global gene expression patterns in breast cancer. High-level analysis identified 21 imaging traits that were globally correlated with 71% of the total genes measured in patients with breast cancer ($p<0.05$). Moreover, there were significant correlations between heterogeneous enhancement patterns and the interferon breast cancer subtype ($p<0.01$). In addition, 12 imaging traits significantly correlated with breast cancer gene sets and 11 traits correlated with prognostic gene sets (false discovery rate < 0.25, respectively).

In their most recent study, the same investigators (23) pursued this analyses and investigated the multiscale relationships among quantitative computer vision-extracted DCE-MRI phenotypes, early metastasis and long noncoding RNA (lncRNA) expression using high-resolution next-generation RNA sequencing. Radiogenomic analysis allowed the identification of eight lncRNAs that were significantly associated with the enhancing rim fraction score ($p<.05$). The enhancing rim fraction score is associated with early metastasis

and the expression of Homeobox transcript antisense intergenic RNA, a known predictor of poor metastasis-free survival in patients with breast cancer.

Molecular breast cancer subtypes

Most data for breast MRI radiogenomics are available pertaining to molecular breast cancer subtypes (100–103). Based on gene expression profiling, breast cancer has four distinct molecular subtypes: luminal A [estrogen receptor (ER)- or progesterone (PR)-positive and human epidermal growth factor receptor 2 (HER2)-negative]; luminal B (ER- or PR-positive and HER2-positive); HER2-enriched (ER- and PR-negative and HER2-positive) and Triple negative (TN)/basal-like (ER-, PR-, and HER2-negative) (104–106). These subtypes are unevenly distributed among women with breast cancers, with differences per race, menopausal status and age (107). More importantly, distinct differences in molecular tumor types are not only associated with different tumor phenotypes but also with distinct variations in response to therapy and in patient survival (105).

Currently, no low-cost genetic testing is readily available and therefore immunohistochemical (IHC) surrogates are often used to define the molecular breast cancer subtypes: Triple negative/Basal-like; Luminal A (ER/PR+, Her2 −, ki67 <15%); Luminal B (ER/PR+, Her2 −, ki67 >15%); Her2-enriched (ER/PR+/−, Her2 +). However, although these IHC surrogates can provide clinical guidance, there is variable agreement with formal genetic testing (41–100%) and IHC surrogate markers have been shown to be less robust in predicting patient outcomes (108). Therefore, there is a strong demand for more accurate means of differentiating molecular breast cancer subtypes and radiogenomics could provide an attractive alternative.

Several authors have investigated DCE-MRI enhancement kinetics and molecular breast cancer subtypes (104,109,110). For example, Blashke et al. correlated IHC surrogates of molecular breast cancer subtypes and found that HER2-positive cancers showed a more rapid initial phase enhancement compared with other subtypes (110). Mazurowski et al. studied 48 patients with formal genetic testing and found an increased ratio of tumor-to-background parenchymal enhancement in HER2-positive cancers (104). Both author groups attributed their findings to the increased tumor neoangiogenesis induced by HER2 overexpression in these particular subtypes. Yamaguchi et al. assessed the delayed phase of enhancement in 192 cancers and correlated these with the IHC surrogates of molecular breast cancer types. They found that luminal A and basal-like cancers demonstrated less washout, and they attributed their findings in luminal A cancers to the association with ductal carcinoma in situ in their study sample and their findings in basal-like cancers to the existence of tumor necrosis and central scarring (109).

Recently, other functional MRI parameters such as DWI have been implemented in clinical routine as several studies have demonstrated that DWI with ADC mapping improves diagnostic accuracy in breast cancer (111–115). In addition, DWI with ADC mapping has been assessed for correlations of ADC values and molecular breast cancer subtypes (116–118). All studies independently discovered that HER2-positive cancers had the highest ADC values whereas luminal B cancers without HER2 overexpression had the lowest ADC values. An explanation for this surprising finding might be an increased tumor neo-

angiogenesis as HER2 overexpression induces VEGF, which in turn leads to increased vessel diameters, vascular permeability and extracellular fluid. These interesting findings indicate that functional parameters can significantly contribute to our understanding of tumor biology and highlight their potential for radiogenomics in breast cancer.

One of the main objectives of radiogenomics in breast imaging is to develop imaging biomarkers as surrogates for genetic testing and three studies have so far approached this task. Whaugh et al. explored texture analysis from 220 imaging features for identifying molecular breast cancer subtypes with limited success. They achieved a classification accuracy of 57.2% with an area under the curve of 0.754 (119). Grimm et al. developed a model that incorporated 56 imaging features, including lesion morphology, texture as well kinetic features. On multivariate analysis, they demonstrated a strong association between the collective imaging features and both luminal A ($p=0.0007$) and luminal B ($p=0.0063$) molecular breast cancer subtypes (120). In a study by Li et al. radiomics analysis was performed on 91 DCE-MRI data sets of biopsy-proven invasive breast cancers from the multi-institutional TCGA/TCIA. The performance of a classifier model for molecular subtyping was evaluated using receiver operating characteristic analysis and the computer-extracted tumor phenotypes was shown to distinguish between molecular prognostic indicators (Fig. 2). The results indicate that computer-extracted image phenotypes show promise for high-throughput discrimination of breast cancer subtypes and may yield a quantitative predictive signature for advancing precision medicine (101).

Recurrence Scores

Breast cancer MRI features have also been correlated with clinically available genomic assays [OncotypeDx (Genomic Health, CA), MammaPrint (Agendia, CA), Mammostrat (Clarient Diagnostic Services, CA), PAM50/Prosigna (NanoString, WA)], which provide scores to predict recurrence and guide treatment decisions (100,103,121–123). Ashraf et al. investigated radiogenomic correlations of DCE-MRI features and the 21-gene recurrence score assay OncotypeDx (122,124). They were able to identify four dominant imaging phenotypes, two of which were exclusively associated with low- and medium-risk tumors. DCE-MRI kinetic features and imaging phenotypes were predictive of recurrence risk with an AUC of 0.82 ($p<.01$) and tumors with greater neo-angiogenesis were associated with an increased risk of recurrence.

Sutton et al. assessed the correlations of morphological and texture-based image features extracted from breast MRI with OncotypeDx and a median Oncotype Dx Recurrence Score of 16 (range: 0–45) in 95 patients with invasive ductal cancer. Combining imaging and pathology information, they developed a model that correlated with the OncotypeDx Recurrence Score, and showed that this model was also predictive of recurrence and therapeutic outcome (Fig. 3) (103).

A more recent study by Li et al. investigated the relationships of computer-extracted breast MRI phenotypes with MammaPrint, Oncotype DX and PAM50/Prosigna to assess the role of radiogenomics in evaluating the risk of breast cancer recurrence. In this study, there were significant associations between breast cancer MRI radiomics signatures and multigene

assay recurrence scores, specifically Mammaprint, Oncotype Dx and PAM50/Prosigna risk of relapse based on subtype (Figs. 4 and 5) (100).

To date, radiogenomics in breast imaging has focused mainly on DCE-MRI, molecular breast cancer subtypes and recurrences scores. However, due to the large number of clinically relevant genetic variables in breast cancer as well as established and emerging functional breast imaging techniques such as DWI or multi-nuclei MR spectroscopy (93,97) more radiogenomic multi-dimensional studies will emerge. Ideally, in the future, radiogenomics in breast cancer will combine multiple qualitative and quantitative parameters with genomic alterations to devise meaningful imaging biomarkers to achieve the ultimate goal of precision medicine in breast cancer.

Future Directions

Thus far, radiogenomics has shown great promise to allow deeper insights into tumor biology by means of integration of genomic and imaging data. The most currently used imaging techniques for radiogenomics comprise CT, PET and MRI. In this context, MRI is an extremely versatile imaging technique as it can provide multifaceted data derived from both morphologic and functional imaging biomarkers. To date radiogenomic studies have mainly used morphologic and contrast-enhanced MRI and to some extent DWI and DTI for its application in brain, abdomen, pelvic and breast diseases. However, the field of imaging biomarkers development with MRI is rapidly growing. In DWI advanced techniques such as intravoxel incoherent motion (IVIM), stretched exponential DWI and DW kurtosis imaging (DKI) are being investigated and show promise to provide additional robust imaging biomarkers that can be incorporated in radiogenomic studies (125). Other MRI techniques that can potentially provide imaging biomarkers for radiogenomic research include spectroscopy [proton (126), phosphorus (127), lipid (128,129)], sodium imaging(130–134), chemical exchange saturation transfer (CEST) imaging (135,136), blood oxygen level–dependent (BOLD) (137–139), or arterial spin labeling MRI (140–142). In this respect radiogenomics is still in its infancy and data still scarce. There is plethora of advanced and emerging imaging biomarkers and further large scale studies utilizing the full wealth of information that MRI can offer have to be conducted to identify which imaging biomarker are most valuable and to establish the role of radiogenomics in clinical practice.

Another future direction is the incorporation of the whole spectrum of “omics” technologies, i.e transcriptomics (143–146), proteomics (147) and metabolomics (148–150) in radio-”omics” research. It can be expected that the integration of multiple “omics” technologies - genomics, transcriptomics, proteomics, metabolomics- with advanced imaging techniques will further open up new avenues in the diagnosis and treatment of diseases with initial data being promising (2,9,151–153).

Radio-”omics” studies mandate the availability of large datasets, patient characteristics and in particular standardization of imaging technqiues to provide meaningful and clinically applicable results. It has to be noted that to date there often is a substantial inter- and intra-institutional heterogeneity in datasets stemming from differences in hardware, sequences, and post-processing approaches. Considerable efforts in standardization and quality control

will be necessary to allow a generalizability of results and consequently implementation in the clinical work-flow.

Conclusion

Radiogenomics investigates the correlations of imaging phenotypes with disease genomic characteristics and enables a deeper understanding of underlying pathologic processes. Due to the non-invasive nature of medical imaging and its ubiquitous use in clinical practice, the emerging field of radiogenomics offers many potential applications in medical imaging to improve patient care. Initial results with DCE-MRI and to some extent DWI and DTI, mainly in oncology, particularly in brain, liver, prostate, ovarian, cervical and breast cancer are encouraging yet it is potentially applicable to all diseases. Our vision for radiogenomics is optimistic. It can be expected that the exploration of additional functional imaging data such as perfusion, spectroscopic and PET data in conjuction with more “omics” technologies will open new avenues of multi-dimensional radiogenomic research. Radiogenomic analysis promises to increase precision in diagnosis, assessment of prognosis, and prediction of treatment response and we anticipate that the implementation of radiogenomics in clinical practice will enhance further the role of radiology. Nevertheless, additional efforts and rigorous standardization will be necessary to validate already described radiogenomic correlations, discover new correlations and define clinically relevant imaging biomarkers, which can then be translated into the clinical arena. In conclusion, it can be expected that radiogenomics will play an important role in medical and particularly cancer research and it has the potential to revolutionize diagnosis, treatment and prognosis of cancer patients.

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Abbreviations

ADC	apparent diffusion coefficient
CCNE1	cyclin E1 gene
CCP	Cell Cycle Progression
CLOVAR	Classification of Ovarian Cancer
CT	computed tomography
DCE	dynamic contrast enhanced
DTI	diffusion tensor imaging
DSC	dynamic susceptibility contrast
DWI	diffusion weighted imaging
EGFR	epidermal growth factor receptor
ER	estrogen receptor

FLAIR	fluid-attenuated inversion recovery
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
ICC	intrahepatic cholangiocarcinoma
IHC	immunohistochemical
lncRNA	long noncoding RNA
MRI	magnetic resonance imaging
MVI	microvascular invasion
NFKBIA	NF-*K*B inhibitor-alpha
PI-RADS	Prostate Imaging Reporting and Data System
POSTN	PERIOSTIN
PR	progesterone
REMBRANDT	Repository of Molecular Brain Neoplasia Data
ROI	region of interest
TCGA	The Cancer Genome Atlas
TCIA	The Cancer Imaging Archive
TTP	time-to-progression
VASARI	Visually Accessible Rembrandt Imaging
VEGF	vascular endothelial growth factor

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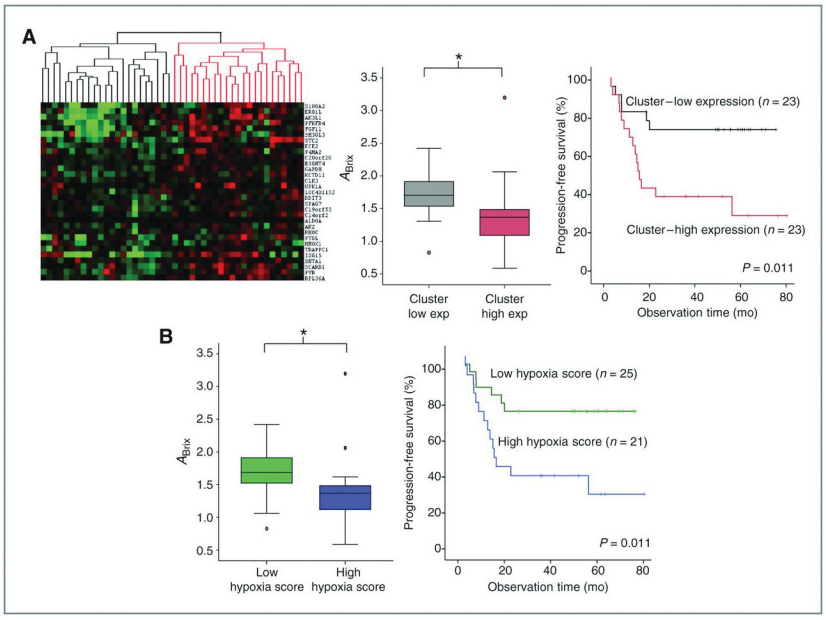
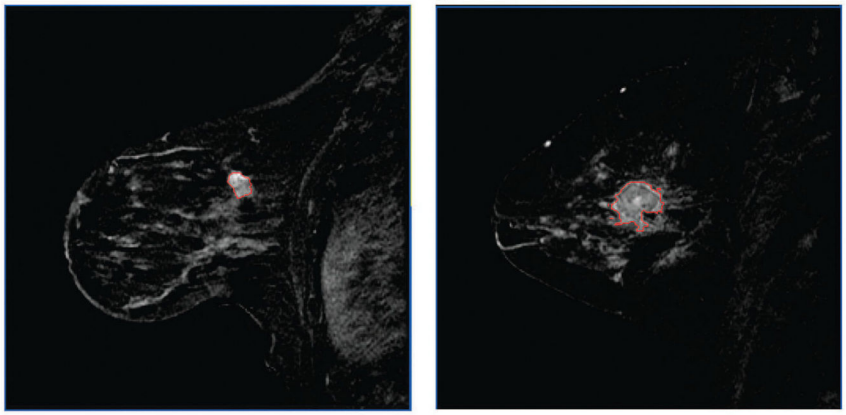


Figure 1.

Pearson's correlation analysis of imaging features and 65 genes from commercially available prostate cancer classifiers. Hierarchical clustering on Pearson's correlation distance between radiomic features and genes from commercially available prostate cancer classifiers: CCP (Cell Cycle Progression), Decipher and GPS (Genomic Prostate Score). Genes in these signatures that are up-expressed in aggressive cancers are indicated by a dark red box over the gene's column while those that are down-expressed are indicated with a blue box. Groups of radiomic features are indicated along the dendrogram on the left. Group1 (left) connects the radiomic feature with location (TZ, PZ and ROI); Group 2 is related to the image modality/function: T2w, ADC and DCE-MRI.

Buerki C, Castillo R, Jorda M, Ashab HA, Kryvenko ON, Punnen S, Parekh D, Abramowitz MC, Gillies RJ, Davicioni E, Erho N, Ishkanian A. Association of multiparametric MRI quantitative imaging features with prostate cancer gene expression in MRI-targeted prostatebiopsies. Oncotarget. 2016 Aug 16;7(33):53362–53376. doi: 10.18632/oncotarget.10523.

a b



c

	ER Positive Case (a)	ER Negative Case (b)
Cancer Subtype	Luminal A	HER2-enriched
MRI CEIP Size (Effective Diameter) Range [7.8 54.0]	12.9 mm	23.8 mm
MRI CEIP Shape (Irregularity) Range [0.40 0.84]	0.452	0.602
MRI CEIP Enhancement Texture (Entropy) Range [6.00 6.59]	6.30	6.46

Figure 2.

The relationship between the DCE-MRI hypoxia gene signature, A_{Brix} and clinical outcome of 46 cervical cancer patients with both DCE-MRI and gene expression data. **A:** Hierarchical clustering (left) was performed based on the expression of 31 genes that were upregulated in tumors with low A_{Brix} and extracted to construct the DCE-MRI hypoxia gene signature.

Box plot of A_{Brix} (middle) and Kaplan-Meier curves for progression-free survival (right) show patients with high (red) expression cluster had lower A_{Brix} and poorer outcome than patients with low (black) expression cluster. **B:** Box plot of A_{Brix} (left) and Kaplan-Meier curves for progression-free survival (right) show patients with high (blue) hypoxia score had lower A_{Brix} and poorer outcome than patients with low (green) hypoxia score. The hypoxia score was calculated by averaging the median centered expression levels for the 31 genes. Reprinted by permission from the American Association for Cancer Research: Halle C, Andersen E, Lando M, Aarnes E-K, Hasvold G, Holden M, Syljuåsen RG, Sundfør K, Kristensen GB, Holm R, Malinen E, Lyng H, Hypoxia-Induced Gene Expression in Chemoradioresistant Cervical Cancer Revealed by Dynamic Contrast-Enhanced MRI, *Cancer Research*, 2012, 72(20);5285–5295. doi: 10.1158/0008-5472.can-12-1085.

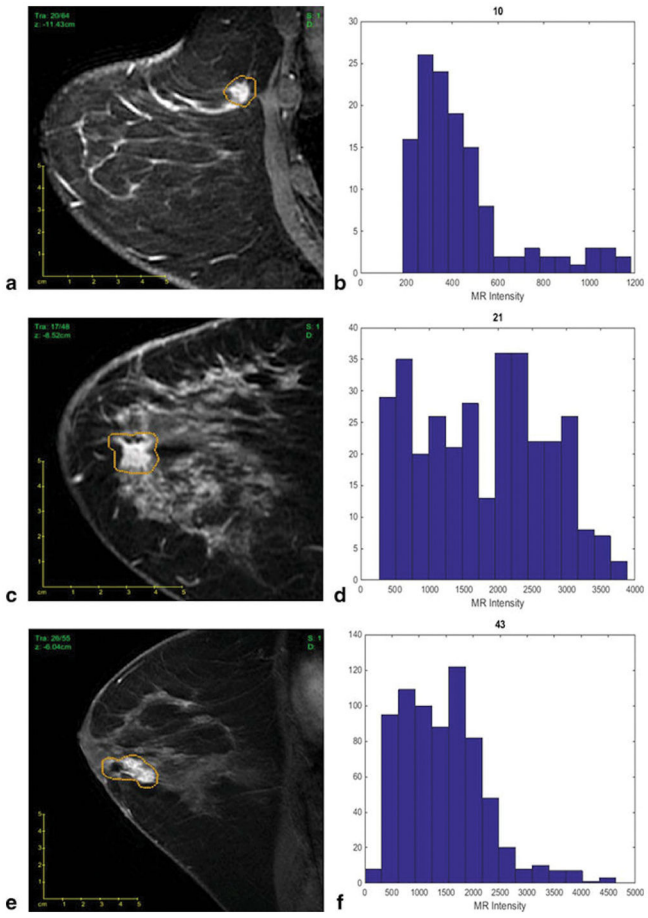


Figure 3.

Figure 2 illustrates the computer segmentation method in example cases of one estrogen receptor positive tumor and one estrogen receptor negative tumor. The tumor segmentation outlines are shown along with computer-extracted image phenotype (CEIP) values (and ranges) for size, irregularity, and contrast enhancement heterogeneity.

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NPJ Breast Cancer. 2016;2. pii: 16012. Epub 2016 May 11. Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA data set. Li H, Zhu Y, Burnside ES, Huang E, Drukker K, Hoadley KA, Fan C, Conzen SD, Zuley M, Net JM, Sutton E, Whitman GJ, Morris E, Perou CM, Ji Y, Giger ML.

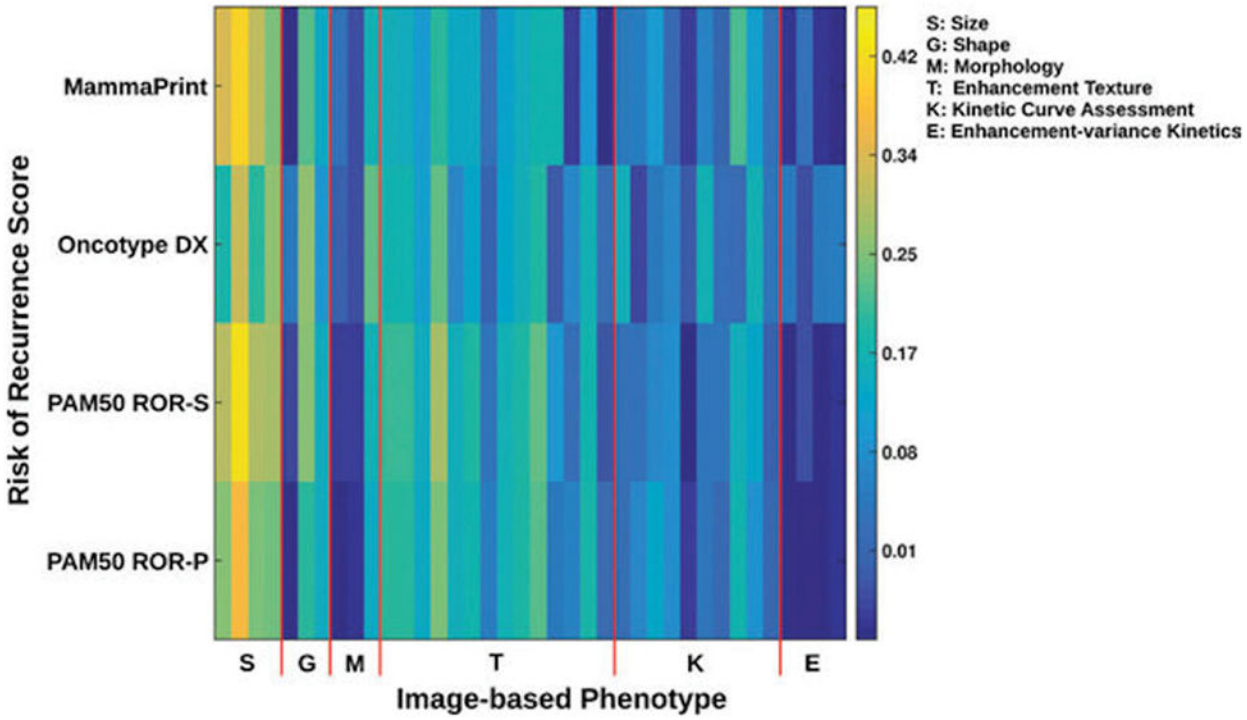

Figure 4.

The best-fit linear regression model allows imaging features to differentiate tumors with different Oncotype Dx Recurrence Score (ODxRS). **A:** Sagittal T1-weighted fat-suppressed post-contrast MRI of an invasive ductal nuclear grade 1 carcinoma with an ODxRS of 10 and **B:** corresponding kurtosis histogram, which demonstrates the frequency of MR intensity. **C:** Sagittal T1-weighted fat-suppressed postcontrast MRI of an invasive ductal nuclear grade 2 carcinoma with an ODxRS of 21 and **D:** corresponding kurtosis histogram. **E:** Sagittal T1- weighted fat-suppressed postcontrast MRI of an invasive ductal nuclear grade 3 carcinoma with an ODxRS of 43 and **F:** corresponding kurtosis histogram.

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J Magn Reson Imaging. 2015 Nov;42(5):1398–406. doi: 10.1002/jmri.24890

Breast cancer subtype intertumor heterogeneity: MRI-based features predict results of a genomic assay.

Sutton EJ, Oh JH, Dashevsky BZ, Veeraraghavan H, Apte AP, Thakur SB, Deasy JO, Morris EA.

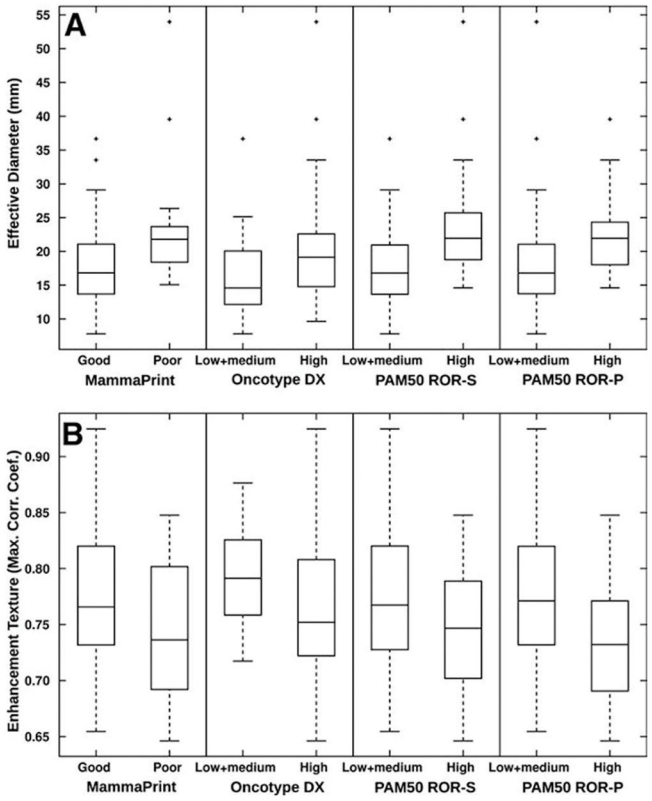

Figure 5.

Correlation heat map based on univariate linear regression analysis between each individual MR imaging phenotype and the recurrence predictor models of MammoPrint, Oncotype DX, PAM50 ROR-S, and PAM50 ROR-P. In this color scale yellow indicates higher correlation as compared with blue and the different gene assays served as the “reference standard” in this study. Some phenotypes correlate similarly (ie, similar color on the color scale) across the risk estimate models, while others do not.

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Radiology. 2016 Nov;281(2):382–391. Epub 2016 May 5. MR Imaging Radiomics Signatures for Predicting the Risk of Breast Cancer Recurrence as Given by Research Versions of MammaPrint, Oncotype DX, and PAM50 Gene Assays. Li H, Zhu Y, Burnside ES, Drukker K, Hoadley KA, Fan C, Conzen SD, Whitman GJ, Sutton EJ, Net JM, Ganott M, Huang E, Morris EA, Perou CM, Ji Y, Giger ML.

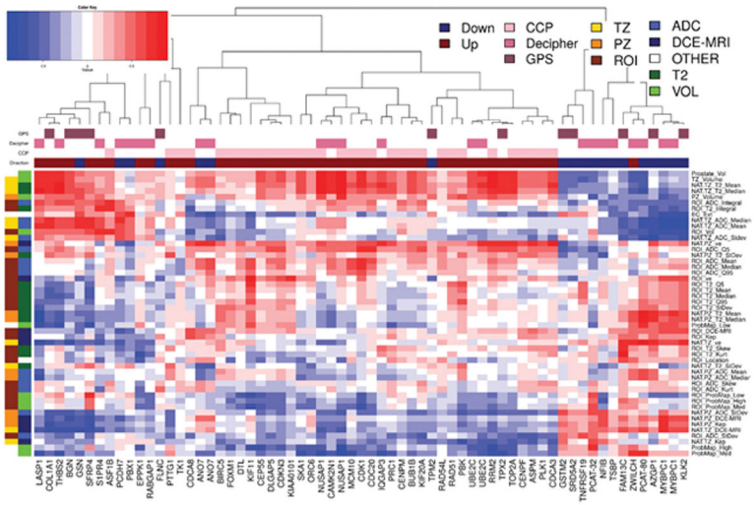

Figure 6.

Box and whisker plots show the relationship of the MRI based phenotypes of, **A:** size (effective diameter) and, **B:** enhancement texture (maximum correlation coefficient) with the recurrence predictor models of MammaPrint, Oncotype DX, PAM50 ROR-S, and PAM50 ROR-P. A positive correlation between the selected MR imaging phenotypes of size (effective diameter) and negative correlation with enhancement texture (maximum correlation coefficient) and increasing levels of risk of recurrence for MammaPrint, Oncotype DX, PAM50 ROR-S, and PAM50 ROR-P were observed. A low value of this enhancement texture feature indicates a more heterogeneous enhancement pattern.

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Radiology. 2016 Nov;281(2):382–391. Epub 2016 May 5. MR Imaging Radiomics Signatures for Predicting the Risk of Breast Cancer Recurrence as Given by Research Versions of MammaPrint, Oncotype DX, and PAM50 Gene Assays. Li H, Zhu Y, Burnside ES, Drukker K, Hoadley KA, Fan C, Conzen SD, Whitman GJ, Sutton EJ, Net JM, Ganott M, Huang E, Morris EA, Perou CM, Ji Y, Giger ML.