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Review Article

The impact of radiogenomics on breast cancer

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Abstract: Advances in radiomics and machine learning techniques have facilitated the extraction of quantitative radiomic features that can be correlated with genomic data. Breast MRI-based radiogenomics, which combines MRI radiomics and genomics, is an emerging field that non-invasively reflects tumor heterogeneity and assesses the biological behaviour of breast cancer. Studies have shown that radiogenomics has the potential to replace traditional genetic testing for breast cancer, reducing the need for invasive procedures such as biopsies. In the future, the clinical application of radiogenomics as a tool for molecular subtype identification, treatment response and prognosis prediction, and recurrence risk assessment is both necessary and feasible.

Keywords: Radiogenomics, breast cancer, magnetic resonance imaging (MRI), molecular subtype, neoadjuvant chemotherapy (NAC)

Introduction

Breast cancer is a major global health concern, ranking as the second most common cancer in 2022, with an estimated 2.3 million new cases, representing 11.6% of all cancers. It is also the fourth leading cause of cancer-related deaths worldwide, accounting for 666,000 deaths (6.9% of all cancer deaths). Among women, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths globally [1]. The high heterogeneity of breast cancer has led to the integration of whole-genome expression profiling techniques in clinical practice for improved disease management [2]. These technologies enable molecular subtyping of breast cancer, leading to more accurate predictions of recurrence, metastasis risk, and treatment response [3]. However, due to cost and technological limitations, immunohistochemical analysis of pathology remains a commonly used alternative. Immunohistochemistry results can be limited by tumor heterogeneity and volume, and pathohistology cannot comprehensively, objectively, and quantitatively analyze tumors [4]. To address these limitations, radiogenomics, an emerging field that combines radiology and genomics, offers a promising solution. It non-invasively reflects the overall heterogeneity of tumors, aiding in our understanding of tumor biology [5]. This review will illustrate the critical role of state-of-the-art MRI-based radiogenomics in precision medicine for breast cancer, with the goal of optimizing medical decisions and improving patient prognosis.

Search strategy and selection criteria

We conducted a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and local institutional ethical approval was not required as this is a review article of current literature. The search of PubMed, Web of Science, and Embase databases was performed for articles published from January 1, 2012, to May 31, 2025. This search was performed using the following headings adapted for each database: “breast cancer”, “radiomics”, “radiogenomics”, “MRI”, “dynamic contrast-enhanced”, “DCE-MRI”, “neoadjuvant chemotherapy”, “pathological complete response”, “prognosis”, and “survival”. Only studies published in English were considered for inclusion. All duplicate studies were manually removed before the titles and abstracts were screened. The full texts of studies deemed appropriate were then reviewed. This

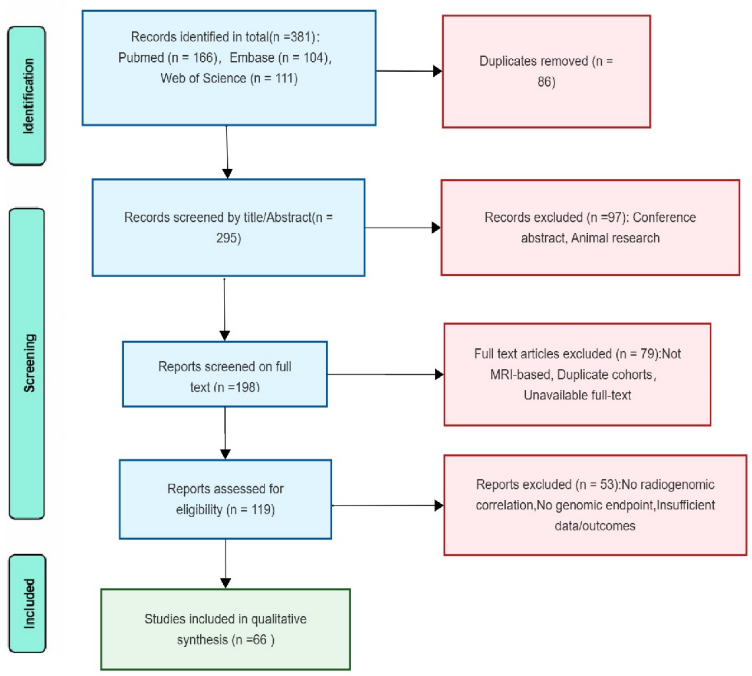

Figure 1. The PRISMA flowchart of the review process and study selection.

Table 1. Classification of surrogate molecular subtypes

Subtype	Receptor Status
Luminal A	ER positive and/or PR positive, HER2 negative
Luminal B	ER positive and/or PR positive, HER2 positive
HER2	ER negative and PR negative, HER2 positive
Basal	ER negative, PR negative, and HER2 negative

process was carried out by two independent reviewers (X.G. and C.Z.). If the reviewers disagreed, a third author (H.Z.) was asked to arbitrate. The PRISMA flow diagram is shown in **Figure 1**.

Inclusion and exclusion criteria

Studies meeting the following inclusion criteria were included: (1) Original studies (prospective or retrospective) reporting MRI-based radiomics/radiogenomics analyses in breast cancer patients; (2) Studies must link imaging features to genomic endpoints; (3) Studies reporting prediction or association for at least one of the following: molecular subtype, receptor status, proliferation index, pathologic complete response (pCR) to neoadjuvant chemotherapy, recurrence-free survival (RFS)/disease-free survival (DFS)/overall survival (OS), or validated multigene recurrence risk scores; (4) The sample size is greater than or equal to 10. Studies meeting any of the following exclusion criteria were excluded: (1) Non-human studies, editorials, letters, conference abstracts without full text, and studies lacking MRI modalities (e.g., CT-only or mammography-only without MRI radiomics); (2) Studies that did not include any genomic or molecular endpoint. Reasons for exclusion at the full-text stage were recorded (e.g., no radiogenomic endpoint, non-MRI modality, insufficient outcome data, unavailable full text); (3) Duplicate cohorts or secondary analyses without new imaging-genomic data (unless reporting a distinct validation set).

Study quality and risk-of-bias assessment

We evaluated study quality and risk of bias using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) framework, focusing on four domains: patient selection, imaging and feature extraction, genomic assay quality, and flow and timing (e.g., imaging vs tissue timing, loss to follow-up). Each included study was flagged for key bias indicators: single-center vs. multicenter, retrospective vs. prospective design, sample size, lack of external validation, no calibration reporting, and unclear segmentation reproducibility (ICC not reported). These flags are reported in **Tables 4** and **5** to assist in evaluating evidence strength.

Genomic characteristics of breast cancer

Gene testing and analysis provide valuable clinical insights into breast cancer. Breast cancer exhibits significant genomic heterogeneity, which can be categorized into three distinct levels.

Susceptibility gene mutation and single nucleotide polymorphism (SNP)

Over 70 genes have been identified as breast cancer susceptibility genes, including those

Table 2. Summary of the classification of DCE-MRI features

Category	Description	Examples
Morphological Features	General characteristics of the image	Size, shape, edge, distribution
Histogram-based Features	Features derived from the global gray-level histogram that do not consider spatial relationships	Mean, entropy, skewness, kurtosis, uniformity, standard deviation, percentiles
Texture-based Features	Second-order features that capture textural properties by analyzing spatial relationships among pixels	Autocorrelation function, gray-level co-occurrence matrix, gray-level run
Kinetic Features	Features related to the dynamic or temporal aspects of image behavior	Maximum absorption rate, peak time, absorption rate, clearance rate, transit rate

Table 3. Summary of the role of machine learning in feature extraction

Method	Requires Machine Learning	Characteristics	Typical Tools/Models
Traditional Handcrafted	No	High interpretability, relies on manual design	PyRadiomics, MaZda, IBEX
Deep Feature Extraction	Yes	Data-driven, captures complex patterns, requires large datasets	ResNet, VGG, 3D CNN
End-to-End Learning	Yes	Features highly tailored to the task, strong black-box nature	U-Net, Transformer-based models
Hybrid Method	Yes (Partial)	Balances interpretability and performance, requires feature fusion strategies	PyRadiomics + Custom CNNs

that confer high risk (BRCA1, BRCA2, PTEN, TP53) as well as moderate and low risk (ATM, BARD1, CDH1, CHEK2, NF1, PALB2, RAD51C, RAD51D, STK11) for the development of cancer, although penetrance may vary. Notably, BRCA1/2 plays a crucial role in DNA homologous recombination repair. Pathogenic mutations in these genes, often located within exonic or splice-site regions, can disrupt homologous recombination repair, increasing the likelihood of tumor development. Research has also identified at least 55 SNPs that are closely associated with breast cancer. For instance, a missense mutation in rs1800371 within the TP53 coding region can lead to p53 protein alterations, considerably elevating breast cancer risk. Additionally, SNPs in non-coding regions, such as rs4973768 in the SLC4A7 gene discovered by Ahmed et al., have also been linked to an increased risk of breast cancer development.

Expression profile characteristics

Breast cancer exhibits unique gene and protein expression patterns, reflecting its diverse nature. Perou et al. pioneered the use of cDNA microarray data to perform differential analysis of breast cancer gene expression profiles, highlighting the variations in gene expression levels across different tumors. As sequencing technologies have advanced, RNA sequencing data has largely replaced microarray data for differential analysis. However, protein expression profiles offer a more comprehensive understanding of breast cancer's expression characteristics. Consequently, reverse-phase protein arrays (RPPA) data have been widely employed to reveal protein expression profiles in breast cancer.

Molecular subtype characteristics

Molecular subtypes of breast cancer are used to explain differences in response to treatment and clinical outcomes beyond what can be achieved with nuclear grade and tumor size alone [6]. Based on gene expression profiling, breast cancer is classified into different molecular subtypes. Although the field is still evolving, the currently commonly accepted molecular subtypes classified by surrogate biomarkers include luminal A, luminal B, HER2-enriched (human epidermal growth factor receptor 2), and basal-like subtypes [7], as shown in **Table 1**. Molecular subtyping of breast cancer is of significant clinical importance as different subtypes exhibit distinct patterns ranging from

Table 4. Representative studies: molecular subtype classification

Study (year)	Cohort size	MRI sequences	Feature/model	Validation type	Best metric
Grimm/Mazurowski et al. (Radiology/ JMRI; 2015-2017).	Retrospective, multiple cohorts (e.g., TCGA subsets and institution cohorts).	DCE features (kinetics), multiparametric MRI.	Regression/ML on kinetic and texture features.	Internal and some external cohort comparisons in later works.	Reported moderate AUCs/discriminative stats (varies by dataset); typical AUCs in 0.65-0.75 range depending on subtype task.
Holli-Helenius et al. (2017).	Retrospective, N = 27 (15 Luminal A, 12 Luminal B).	T1-weighted non-fat-saturated pre- and post-contrast MRI.	Co-occurrence matrix (COM) texture features; binary logistic regression model.	Leave-one-out cross-validation.	Combined model (sum entropy + sum variance): AUC = 0.878 (Sens 91.7%, Spec 86.7%); Single features: Sum entropy AUC = 0.828, Sum variance AUC = 0.833.
Saha et al., Br J Cancer (2018).	Retrospective, N = 922 (split 461 train/461 test).	DCE-MRI (preop).	529 DCE features; ML models (multivariate).	Internal hold-out test (split).	Luminal A AUC = 0.697 (95% CI 0.647-0.746); TNBC AUC = 0.654 (0.589-0.727); ER AUC = 0.649 (0.591-0.705); PR AUC = 0.622 (0.569-0.674).
Xie et al. (2018).	Retrospective, N = 134 (22 TN, 26 Luminal A, 68 Luminal B, 18 HER2+).	Multiparametric MRI: DWI (ADC map) and DCE (washin, washout maps).	Whole-tumor histogram analysis; first-order texture features from ADC, washin, washout maps; univariate analysis + ROC.	Internal, statistical validation (no hold-out set).	TN vs HER2+: AUC = 0.763 (Sens 86.4%, Spec 72.2%); TN vs Luminal A: AUC = 0.710; TN vs non-TN: AUC = 0.683.
Leithner et al., Breast Cancer Res (2019).	Retrospective multi-center-ish design; Training N = 91, Validation N = 52 (total 143).	CE-MRI (3T).	Radiomic signature (LDA + k-NN classification).	Independent validation dataset from second institution.	Validation accuracies: Luminal A vs Luminal B ~79.4%, Luminal B vs TN ~77.1%; several pairwise accuracies in training > 80%.
Wang et al. (2020).	Retrospective, N = 51 (19 Luminal A, 32 Luminal B).	DCE-MRI.	Texture analysis (kurtosis, inhomogeneity, entropy); manual ROI delineation; statistical comparison (t-test, ROC).	Internal, statistical validation (no hold-out set).	Entropy AUC = 0.891 (Sensitivity 90.62%, Specificity 78.95% at cutoff ≤ 4.22).
Leithner et al. (2020).	Retrospective, N = 91 (49 LumA, 8 LumB, 11 HER2+, 23 TN).	DWI with ADC mapping.	Multiple radiomic feature types (HIS, COM, RLM, etc.); feature selection + LDA + k-NN classifier.	Leave-one-out cross-validation.	Luminal B vs HER2+: Acc = 100% (direct ADC segmentation); Luminal A vs B: Acc = 91.5%; Luminal B vs others: Acc = 91.1%.
Du et al. (2021).	Retrospective, N = 200 (41 LumA, 66 LumB, 32 Lum-HER2, 25 HER2+, 36 TN).	Multiparametric: Synthetic MRI (T1, T2, PD), DCE-MRI, DWI (ADC).	Multiple quantitative parameters; univariate + multivariate logistic regression; combined parameter models. No radiomics texture features reported.	Internal statistical validation; no external validation set.	Luminal A vs others: Combined (T2 + ADC + Volume) AUC = 0.765; TN vs others: Combined (T1 + Rim enhancement) AUC = 0.742; Single parameters: T2 for LumA (AUC = 0.702), T1 for TN (AUC = 0.699).
Huang et al., Front Oncol (2021).	Retrospective, single-center; N = 162 women (T2-T4 invasive breast cancer).	3.0 T multi-parametric MRI: DCE-T1WI, fat-suppressed T2WI, ADC map.	4,198 radiomics features extracted using Pyradiomics; feature selection with LASSO + RFE, mRMR, Boruta; classifiers: RF, SVM, LR, LDA, GNB, MLP; LOOCV used for all models.	Leave-one-out cross-validation (internal).	MLP model: AUC 0.907 (AR expression, ACC 85.8%), AUC 0.965 (TNBC vs non-TNBC), 0.840 (HER2+ vs HER2-), 0.860 (HR+/HER2- vs others); micro-AUC 0.896 overall.
Tsai et al., Korean J Radiol (2021).	Prospective, single-center; N = 306 patients (308 tumors).	DCE-MRI and IVIM-DWI (1.5T, 11 b-values).	Quantitative kinetic (Tofts model: Ktrans, kep, vp, ve, IAUGCBN90) and IVIM parameters (D, Dp, f, S0); regression and ROC analyses/Tofts model used.	Internal statistical validation only (logistic/ linear regression, ROC).	Significant group differences (P < 0.05): lower Ktrans, kep, vp, IAUGCBN90 and higher ve, D in subtype III/VI and Luminal A/normal-like; ROC analysis showed discriminatory ability (no AUC explicitly reported).
Ming et al., Cancers (2022).	Multi-cohort radiogenomic (N = 246 combined).	DCE-MRI (174 features).	Unsupervised clustering → imaging subtypes; then tested association with PAM50 and outcomes.	Internal discovery + validation cohort (s) reported.	Imaging-subtype separation validated; no single AUC for subtype prediction reported (focus on subtyping & outcome associations).
Sheng et al., Front. Oncol. (2022).	Retrospective, single-center, N = 190 patients (99 Luminal, 59 HER2+, 32 TNBC).	3-T DCE-MRI (T1, T2, DWI, DCE) Vibrant + sequence 8 dynamic phases.	1130 Radiomic Features (Shape, First-order, Texture, Wavelet, LOG) Feature Selection: LASSO Models: LR, RF, NB, SVM, XGBoost.	Internal 5-fold cross-validation Train/Test split (70:30).	1. Luminal vs. Non-Lumina: XGBoost, AUC = 0.828. 2. HER2+ vs. Non-HER2: Random Forest, AUC = 0.805. 3. TNBC vs. Non-TNBC: XGBoost, AUC = 0.903.

Notes: Many subtype-classification studies report moderate discrimination, which is better for some pairwise subtype tasks than for full multi-class classification. The most robust studies are those with separate external validation cohorts (e.g. Leithner, 2019) or a very large sample size with test splits (Saha, 2018).

Table 5. Representative studies: treatment response and prognosis

Study (year)	Cohort size	Timepoint	Feature/Model	Validation	Endpoint	Best metric	Calibration
Ashraf et al., Radiology (2014).	Retrospective; N = 56 (ER+ patients).	Preoperative DCE-MRI.	Multiparametric imaging phenotype vector (morphologic, aggregate kinetic, heterogeneity kinetic features); Hierarchical clustering for intrinsic phenotypes; Multivariate logistic regression.	Leave-one-out cross-validation.	Recurrence risk (Oncotype DX Recurrence Score: High vs. Low/Medium).	AUC 0.82 (SE 0.060) when including imaging phenotype category as a predictor.	Not reported.
Li et al., Radiology (2016).	Retrospective (TCGA/TCIA), N = 84 (multi-institutional).	Preoperative DCE-MRI.	Computer-extracted image phenotypes (CEIPs): size, shape, margin, enhancement texture, kinetics. Logistic regression classifier.	Leave-one-case-out cross-validation (internal).	Agreement with research versions of multigene assay risk groupings (MammaPrint, Oncotype DX, PAM50 ROR-S, PAM50 ROR-P).	AUCs for distinguishing good vs. poor prognosis: MammaPrint 0.88 (SE 0.05); Oncotype DX 0.76 (SE 0.06); PAM50 ROR-S 0.68 (SE 0.08); PAM50 ROR-P 0.55 (SE 0.09).	Not reported.
Wan et al., Sci. Rep. (2016).	Retrospective; N = 96 (ER+ patients, multi-institutional).	Pre-treatment DCE-MRI (1.5T).	176 features (Shape, PK, EK, IK, TK, DHoG, DLBP); LDA classifier with top 6 feature combination.	2-fold cross-validation.	OncotypeDX Recurrence Score (High vs. Low Risk).	AUC 0.87 (95% CI: 0.78-0.96) for the combined feature model.	Not reported.
Drukker et al., Cancer Imaging (2018).	Retrospective (ACRIN 6657/I-SPY 1), N = 162.	Pre-treatment and early treatment (after 1st cycle of NAC).	Automated Most Enhancing Tumor Volume (METV) from DCE-MRI.	Internal (cohort analysis within trial).	Recurrence-free survival (RFS).	statistic for association with RFS: Pre-treatment: 0.69 (95% CI 0.58-0.80). Early-treatment: 0.72 (95% CI 0.60-0.84).	Calibration not explicitly reported for the C-statistic model. Performance was comparable to a semi-manual FTV model (C-statistic 0.70).
Chitalia et al., Clin Cancer Res. (2020).	Retrospective; Discovery: N = 95, Validation: N = 163.	Pre-operative DCE-MRI.	22 radiomic features (morphology, texture from SER maps); Unsupervised hierarchical clustering for intrinsic phenotypes.	Independent validation cohort (TCIA/ISPY-1).	10-year Recurrence-free survival (RFS).	C-statistic improved from 0.55 (baseline model: HR + HER2) to 0.73 (baseline + imaging phenotypes).	Not reported.
Lee et al., Sci. Rep. (2020).	Retrospective; N = 267.	Pre-treatment DCE-MRI.	Multivariable Cox model (Model D) with clinicopathologic factors, morphologic features (ipsilateral vascularity), and quantitative parameters (texture skewness, Kep 25th percentile).	Internal validation via statistical models.	Disease Recurrence (ipsilateral, contralateral, distant metastasis).	C-index: 0.825 (95% CI: 0.755-0.896) for the comprehensive model (Model D).	Not reported.
Magbanua et al., NPJ Breast Cancer (2021).	Prospective pilot, N = 84 (I-SPY 2 TRIAL).	Pre-treatment (T0), 3 weeks after treatment start (T1), between regimens (T2), post-NAC pre-surgery (T3).	Combined serial Functional Tumor Volume (FTV) from DCE-MRI and circulating tumor DNA (ctDNA) levels (Signatera test).	Internal (pilot analysis).	Pathological complete response (pCR) and Distant Recurrence-Free Survival (DRFS).	pCR Prediction (T1): • FTV only AUC: 0.59 • FTV + ctDNA AUC: 0.69 (P = 0.25 vs FTV alone, NS) DRFS Prognosis (T3): • ctDNA positivity post-NAC provided significant additive value to FTV (Multivariable Cox model: ctDNA HR = 14.25, P = 0.0046; FTV HR = 1.03, P = 0.0191).	Calibration not explicitly reported for the combined model. The model with FTV, pCR, subtype, and ctDNA had the best fit to survival data (lowest AIC score).

Fan et al., Radiology (2022).	Multicohort retrospective, N = 381 (130 + 116 + 135).	Preoperative DCE-MRI.	Radiogenomic model predicting Oncotype DX Recurrence Score (RS); combined predicted RS + complementary features for NACT response.	External validation across independent prognostic (n = 116) and treatment (n = 135) assessment cohorts.	Predicted Oncotype DX RS; Association with survival (OS/RFS) and NACT response.	AUC 0.85 for predicting NACT response (combined model). Predicted RS > 29.9 associated with worse OS (HR = 8.6) and RFS (HR = 2.7).	Not reported.
Zhang et al., J Transl Med (2022).	Retrospective, N = 112 (TNBC patients).	Baseline + after 2 cycles of NAC.	Radiogenomic model (LightGBM) combining radiomic features (from tumoral & peritumoral regions on CE-MRI) and genomic Variant Allele Frequency (VAF) features.	Training/validation split (2:1 ratio) internal validation.	Pathological complete response (pCR) in TNBC.	Radiogenomic Model AUC: • Training set: 0.89 (95% CI 0.74-0.95) • Validation set: 0.87 (95% CI 0.73-0.91) *Significantly higher than radiomics-only models (AUCs 0.71-0.73)*.	Not reported.
Wang et al., Front. Oncol. (2022).	Retrospective, N = 227.	Preoperative.	DWI/IVIM/DKI parameters (ADC, D, D*, f, MD, MK) and combined models.	Training/validation split (2:1) internal validation.	Prediction of Nottingham Prognostic Index (NPI), Ki-67 expression status, and molecular subtypes (Luminal vs. non-Luminal; Triple-negative).	Combined model AUCs: • NPI (D* + MK): 0.734 • Ki-67 (D + D* + f + MK): 0.755 • Luminal vs. non-Luminal (D + D* + MD + MK): 0.830 • Triple-negative (f + MK): 0.756	Good agreement per calibration curves (Hosmer-Lemeshow test P = 0.22 for Luminal model; P = 0.74 for TNBC model).

Notes: Several MRI-derived volumetric features (METV and FTV) and radiogenomic signatures demonstrate moderate-to-good prognostic discrimination. The most compelling studies for predicting prognosis and response combine imaging with genomic biomarkers (e.g., Fan 2022 combining predicted RS; Zhang 2022 radiogenomic for TNBC; Magbanua 2021 FTV + ctDNA).

gene mutations and SNP characteristics to expression profile features and ultimately clinical characteristics such as pathological manifestations and treatment regimens. For example, luminal A and B subtypes are more prone to developing osteoblastic metastases, while basal-like subtypes are more likely to cause pulmonary and brain metastases. Preoperative chemotherapy is generally more effective for HER2-overexpressed subtypes, whereas luminal A and B subtypes typically undergo postoperative radiotherapy.

Multigene assays

Multigene assays provide valuable insights into breast cancer heterogeneity and help guide personalized treatment strategies. A growing number of commercially available multigene assays are becoming increasingly accessible for widespread clinical use, including PAM50/Prosigna, Oncotype DX, MammaPrint, EndoPredict, and Breast Cancer Index. For example, PAM50 stands for Prediction Analysis of Microarray 50 and is a molecular typing method for breast cancer. By analyzing the expression levels of 50 specific genes, it classifies breast cancers into five subtypes: Luminal A, Luminal B, HER2-enriched, Basal-like, and Normal-like [8]. This typing can be used to predict the likelihood of metastasis in patients with estrogen receptor (ER)-positive, HER2-negative breast cancer and guide clinical decisions regarding hormone therapy and chemotherapy [9]. Oncotype DX is a validated expression assay based on 21 genes strongly associated with ER-positive early-stage breast cancer [10]. This assay scores the risk of recurrence of early invasive breast cancer within 10 years. A large prospective multicenter trial (TAILORx) involving 10,253 women demonstrated that a low Oncotype DX Recurrence Score (ODxRS) was associated with very low rates of breast cancer recurrence in women treated with endocrine therapy alone [11]. For eligible women, chemotherapy could be avoided, reducing patient morbidity and healthcare costs.

MRI-based radiogenomics in breast cancer

The convergence of artificial intelligence and genomic sequencing has propelled radiogenomics to the forefront of personalized medicine. Currently, radiogenomics studies in breast cancer primarily utilize magnetic resonance imaging (MRI) and mammography, with a smaller number of studies employing ultrasound and PET data [12, 13]. Mammography and ultrasound also provide valuable radiomic features. However, DCE-MRI uniquely offers pharmacokinetic information. Since Yamamoto et al. conducted the first radiogenomics study of breast cancer in 2012 [14], dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) data have been widely used in related research due to their high resolution and spatio-temporal continuity, allowing for the assessment of vascular permeability [15]. A simplified workflow for MRI-based radiogenomics is shown in **Figure 2**.

Feature extraction

The primary methods for DCE-MRI feature extraction can be classified into four categories: morphological features, histogram-based features, texture-based features, and kinetic features, as shown in **Table 2**. Most DCE-MRI feature values are calculated on a voxel-by-voxel basis. Although the imaging features of commonly used mammography and ultrasound are largely similar to those of DCE-MRI, they lack features related to enhanced kinetic, pharmacokinetic, and thin-walled tissue enhancement, all of which are unique to DCE-MRI [16]. It's important to note that this classification of feature types is not absolute and can be adjusted as needed [17]. These features can be handcrafted or automatically learned using machine learning, especially deep learning methods. For example, tools such as PyRadiomics, MaZda, and IBEX implement imaging feature extraction based on mathematical and statistical methods, which are highly interpretable and have a deterministic process [18]. In recent years, machine learning, especially deep learning, has been widely used to automatically learn MRI features and is suitable for pattern mining of high-dimensional data. The automatic data-driven MRI features perform better in predicting clinical features of breast cancer, which are more significantly associated with genomic features, than traditional semi-automatic MRI features [19]. They can capture complex patterns such as tumor heterogeneity and edge blurring, but with low interpretability. Identifying scientifically sound feature extraction methods to obtain accurate feature data remains a significant challenge, and increasingly studies are

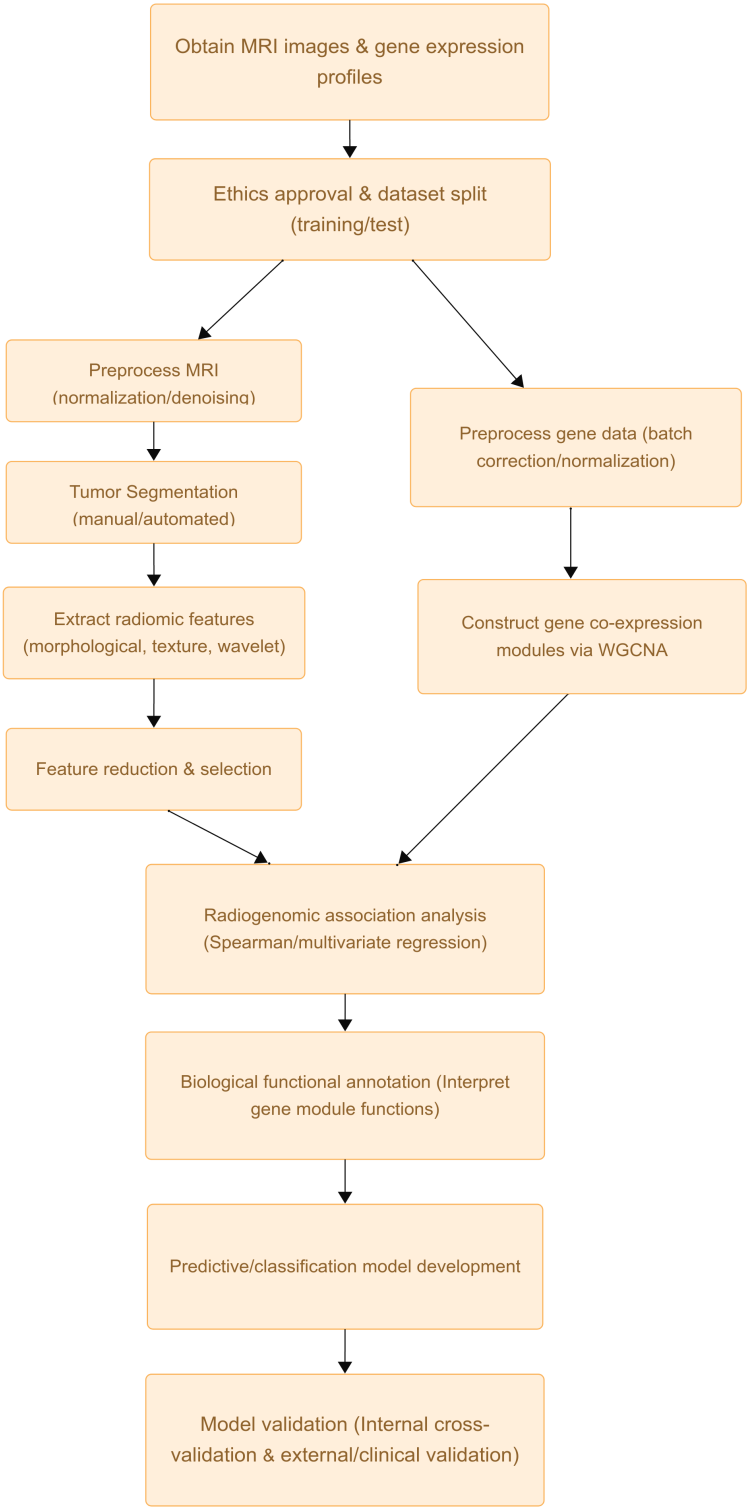

Figure 2. The MRI-based radiogenomic workflow.

exploring hybrid approaches that combine these two paradigms to improve model performance. We summarize the role of machine learning in feature extraction as shown in **Table 3**.

Feature selection

After extracting a large number of high-throughput imaging features, feature selection methods are employed to identify the most informative subset. This subset is then used to train machine learning algorithms to build prediction and classification models based on histological image features. Common feature selection approaches include Least Absolute Shrinkage and Selection Operator (LASSO), Recursive Feature Elimination (RFE), Minimum Redundancy Maximum Relevance (mRMR), mutual information, Pearson or Spearman correlation, intra-class correlation, and Principal Component Analysis (PCA), among others. Of these, LASSO - an embedded technique that adds an L1 penalty to a linear regression model - is the most commonly used, as it forces the coefficients of less important predictors to zero [20]. The next most popular methods are RFE and mRMR. RFE is a wrapper strategy that repeatedly fits a classifier, ranks features by a chosen metric, and removes the lowest scoring ones, making it adept at finding the best subset for a given model. In contrast, mRMR is a filtering method that selects features with the highest relevance to the target while minimizing redundancy between features, thereby achieving dimensionality reduction [21]. These techniques are favored in radiomics because they effectively handle redundant information. Other commonly used reduction techniques, either alone or combined, include PCA, the t-test, and the Mann-Whitney U-test.

Specifically, PCA transforms continuous variables into orthogonal principal components that capture maximum variance, effectively creating new features by linearly combining the originals [22].

Modelling and evaluation

Next, various statistical and machine learning algorithms are used to build and validate radiogenomic models. Popular choices include Support Vector Machines (SVM), Random Forests (RF), K-Nearest Neighbours (KNN), Logistic Regression (LR), Decision Trees, and Artificial Neural Networks (ANNs). Among traditional methods, SVM, LR, and RF remain popular in radiogenomics due to their consistently strong performance. SVMs find the optimal linear or non-linear boundary to distinguish classes in feature space, are inherently resistant to overfitting, and can handle redundant inputs. Logistic regression is valued for its simplicity and ease of interpretation but can overfit when faced with many irrelevant or correlated variables in high-dimensional settings. Random forests combine multiple decision trees to improve robustness, although identifying truly informative features in large feature sets can be challenging. Most supervised classifiers in radiogenomics are shallow models with only a few layers or simple architectures. However, ANNs have been increasingly adopted for their ability to capture complex patterns in both classification and regression tasks [23]. Model effectiveness is typically evaluated using metrics such as true positive rate, true negative rate, overall accuracy, and area under the ROC curve (AUC) - all of which can be generalized from binary to multi-class problems.

Modeling and reporting rigor in radiogenomics

To ensure robust, reproducible, and clinically useful radiogenomic models, it is essential to follow best practices in data preprocessing, model development, and reporting. Key recommendations include:

1. Prevent data leakage: All preprocessing and feature selection steps should be performed within cross-validation folds, preferably nested cross-validation. This prevents information from the test set leaking into the training process and avoids overly optimistic performance estimates [24].

2. Report model calibration and clinical utility: In addition to discrimination metrics such as AUC, model calibration should be assessed using calibration curves, Brier scores, and calibration slopes. Decision curve analysis (DCA) is recommended to evaluate potential clinical utility and inform decision-making [25].

3. Address class imbalance: Class imbalance should be explicitly addressed using methods such as threshold adjustment, resampling (oversampling/undersampling), or reporting metrics robust to imbalance such as PR-AUC. Proper handling of imbalanced datasets ensures reliable model performance across classes [26].

4. Consider domain shift and image harmonization: For multi-center or multi-scanner datasets, domain shift due to variations in acquisition protocols should be assessed. Image harmonization techniques (e.g., ComBat, histogram matching) may be applied to improve model generalizability [27].

5. Document reproducibility: Reproducibility should be reported, including test-retest robustness and segmentation reliability (e.g., Intraclass Correlation Coefficient, ICC). Detailed documentation of preprocessing pipelines, software versions, and random seeds is critical for enabling independent replication [28].

6. Encourage adherence to established standards: Follow standardized feature definitions such as IBSI (e.g., Image Biomarker Standardisation Initiative, IBSI) and prediction model reporting guidelines (e.g., Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis, TRIPOD) to ensure transparency, reproducibility, and comparability in radiogenomic research [29].

Radiogenomics at the gene sequence level

The performance of breast MRI is critical in the evaluation of patients with cancer-predisposing pathogenic variants. It aims to establish a link between breast cancer susceptibility genes, SNP loci information, and imaging features, uncovering the correlation between breast cancer genetic characteristics and imaging phenotypes. A pilot study by Yamamoto et al. [14] analyzed 10 breast cancer patients and found that MRI phenotypes with a heterogeneous

enhancement pattern were significantly associated with immune-related genes characterizing the interferon-rich subtype, which is often associated with basal breast cancer. This study identified 12 DCE-MRI-specific traits significantly associated with high expression of immune-related genes, including STAT1, CXCL9, and IFIT1. Subsequently, Maimone et al. [30] investigated 410 breast cancer patients (2001-2020) who underwent MRI with identified pathogenic variants and found that BRCA1 (29.5%), BRCA2 (25.9%), CHEK2 (16.6%), ATM (8.0%), and PALB2 (6.3%) were the most common variants. Significant associations were observed with tumor shape, margin, grade, rim enhancement, kinetics, and necrosis. BRCA1 tumors were predominantly basal (47.9%) and exhibited distinct imaging features such as round shape (31.4%), circumscribed margins (24.0%), rim enhancement (24.0%), washout (58.7%), and necrosis (19.8%), while CHEK2 and ATM tumors were often lower grade with spiculated margins, rarely exhibiting washout or necrosis, and were mostly comprised of luminal molecular subtypes (CHEK2: 88.2%, ATM: 90.9%).

While these studies established a link between susceptibility genes and imaging features, researchers expanded upon this concept using RNA sequencing. Advances in next-generation RNA sequencing have led to the discovery of new transcriptional and epigenetic regulators. For example, Incoronato et al. [31] found that standard quantitative visualization biomarkers on MRI and positron emission tomography (PET) correlated with circulating microRNAs. Their study included 77 breast cancer patients who underwent PET/MRI analysis and blood sampling on the same day, along with 78 healthy individuals as a control group. The results demonstrated that among the 84 microRNAs identified, MIR-125b-5p, MIR-143-3p, MIR-145-5p, MIR-100-5p, and MIR-23a-3p were more frequently detected in plasma samples. A strong correlation was observed between the expression level of circulating MIR-143-3p and the mean initial area under the concentration curve in stage II breast cancer, suggesting a potential role of MIR-143-3p in tumor vascularization regulation. Additionally, a strong correlation was observed between MIR-143-3p and the maximum standardized uptake value at this stage, indicating that microRNAs play a role in cancer metabolism control.

Beyond microRNAs, long noncoding RNAs (lncRNAs), referred to as non-coding transcripts, are key regulatory RNAs implicated in breast cancer. Yamamoto et al. [32] investigated the relationship between MRI-derived enhancing rim fraction scores and the expression of 14,880 lncRNAs. Radiogenomic analysis allowed the identification of three previously uncharacterized and five named lncRNAs that were significantly associated with high enhancing rim fraction, including homeobox transcript antisense intergenic RNA (HOTAIR), a known predictor of tumor metastasis in breast cancer patients.

In a recent prospective cohort by Park et al. [33], 95 women with invasive breast cancer were evaluated using BI-RADS scoring, texture analysis, and next-generation RNA sequencing. The authors observed that tumors presenting as masses had increased CCL3L1 expression, whereas those with irregular shapes had decreased MIR421 levels. Within the ER-positive mass subgroup, CCL3L1, SNHG-12, and MIR206 were upregulated, whereas MIR597, MIR126, and SOX17 were downregulated. In basal tumors with higher texture heterogeneity on precontrast T1-weighted images, the genes CLEC3A, SRGN, HSPG2, KMT2D, and VMP1 were overexpressed, whereas IGLC2 and PRDX4 were underexpressed. Gene network analyses further linked ER-positive mass lesions with increased cell proliferation, resistance to anti-estrogen treatment, and poorer survival.

These insights support the potential of radiogenomics as an alternative to traditional genetic testing in breast cancer.

Radiogenomics at the gene pathway level

The analysis of gene pathways can reflect changes in gene activity and transcription during the occurrence and development of breast cancer. MRI-based radiogenomics utilizes gene and protein expression profiling data to reveal the relationship between the activity characteristics of breast cancer at the transcriptional and translational levels and its MRI phenotype. For instance, Janus kinases (JAK), a type of non-receptor tyrosine kinase, are crucial for

activating signal transducer and activator of transcription (STAT) proteins in breast cancer. Disruption of the JAK-STAT pathway can lead to cancer development [34]. Yeh et al. [35] analyzed 47 invasive breast cancers using radiomic techniques and gene expression data from fresh tissue samples; their Gene Set Enrichment Analysis (GSEA) linked 186 gene pathways to 38 imaging features. The results showed that radiomic size features were positively associated with replication and proliferation pathways and negatively associated with the apoptosis pathway. Notably, pathways related to immune regulation and extracellular signalling showed the most significant correlations with radiomic features. Tumors with upregulation of immune and extracellular signalling pathways were smaller, more spherical, and had a more heterogeneous texture on DCE-MRI, whereas tumors with higher expression levels of JAK/STAT and VEGF pathways had increased contrast, variance, and entropy, while homogeneity and linearity decreased. In addition, the tumor necrosis factor-alpha (TNF-α)/NF-kappaB/Snail pathway is another key molecular pathway in breast cancer, influencing epithelial-mesenchymal transition, proliferation, angiogenesis, invasion, and metastasis [36-38]. Wu et al. [39] analyzed 10 quantitative imaging features related to tumor-adjacent enhancement patterns and found that certain parenchymal imaging features associated with the TNF pathway have prognostic value.

Zhu et al. [16] obtained breast cancer-related gene pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) and utilized GSEA to identify gene pathways associated with 38 imaging features. The results revealed significant associations between numerous KEGG pathways and imaging features, particularly showing statistically significant positive correlations with lesion volume, effective diameter, surface area, and maximum linear dimension, while exhibiting significant negative correlations with margin sharpness and radial gradient histogram variance. Additionally, the study employed RPPA data encompassing 142 proteins such as p53 and cadherin to analyze the correlation between protein expression profiles and imaging features using linear regression models. The results demonstrated that protein expression characteristics exhibited limited correlations solely with tumor size and morphological features.

However, the complexity of gene expression and signalling pathways limits such studies.

Research of MRI-based radiogenomics in breast cancer

The role of radiogenomics in identifying molecular subtypes of breast cancer

Preoperative knowledge of breast cancer molecular subtypes is crucial for guiding individualized treatment selection, including chemotherapy, endocrine therapy, and HER2-targeted therapy. While genomic analysis remains the gold standard for classifying molecular subtypes, its high cost and time-consuming nature limit its applicability to a large patient population. Consequently, most studies often rely on receptor status as a surrogate for genomic analysis to leverage larger sample sizes.

Researchers have extensively investigated the relationship between contrast enhancement kinetics on breast MRI and molecular subtypes. MRI enhancement kinetics can be categorized into an initial phase (slow, medium, and fast) and a delayed phase (persistent, plateau, and washout). Blaschke and Abe [40] observed that the HER2-enriched subtype exhibited faster initial phase enhancement compared to other subtypes in an analysis of 112 cancer cases. Grimm et al. [41] identified two dynamic imaging features as independent predictors of the luminal A and B subtypes: 1) the ratio of tumor enhancement to fibroglandular tissue at two time points, and 2) the sequence number at which peak enhancement occurs. Further research by Grimm et al. [42] found that the shape of the breast mass is significantly associated with the basal-like subtype, whereas the mass margin is significantly associated with the HER2-enriched subtype. Notably, homogeneous mass-like and non-mass-like internal enhancement have a higher negative predictive value for the luminal B subtype. Subsequently, Ming et al. [43] utilized an unsupervised analysis of DCE-MRI features to identify and validate three novel imaging subtypes of breast cancer in two independent radiogenomics cohorts, totaling 246 patients. The study revealed that these imaging subtypes were significantly associated with Ki67 status, PAM50 intrinsic molecular subtypes, and tumor stage. There were significant differences in tumor size, enhance-

ment patterns, and clinical outcomes among the subtypes.

Other studies have focused on the role of background parenchymal enhancement (BPE) in subtype differentiation. Mazurowski et al. [44] found that luminal B breast cancer showed maximal tumor enhancement relative to background parenchyma. HER2 overexpression, often seen in luminal B and HER2-enriched breast cancer, is linked to vascular endothelial growth factor (VEGF). Dilorenzo et al. [45] found that mild BPE suggests Luminal B or HER2-negative subtypes, while severe BPE suggests the basal subtype. Wang et al. [46] found that the addition of quantitative imaging features of BPE significantly improved its ability to predict the basal subtype, increasing prediction accuracy from 86.9% to 90.0% and AUC from 0.782 to 0.883. Furthermore, Luo et al. [47] aimed to identify differences in pharmacokinetic parameters derived from DCE-MRI between luminal A and B breast cancer subtypes. They retrospectively analyzed data from 94 patients with confirmed breast cancer, applying the Mann-Whitney U-test to compare pharmacokinetic parameters (Ktrans, Kep, and Ve) along with their corresponding histogram and texture features. Their findings showed that luminal B cancers exhibited significantly higher maximum values for Ktrans, Kep, and Ve, as well as increased mean and 90th percentile values for Ve, compared to luminal A cancers. This study concluded that DCE-MRI-derived pharmacokinetic parameters could represent valuable imaging biomarkers for differentiating between luminal A and B subtypes of breast cancer.

With the advancement of MRI radiogenomics, recent studies have typically provided both quantitative and qualitative imaging biomarkers. For example, in a retrospective analysis of 51 patients with ER-positive invasive ductal carcinoma using DCE-MRI texture analysis, Wang et al. [48] found that kurtosis, heterogeneity, and entropy effectively discriminated between Luminal A and Luminal B, with entropy showing the highest diagnostic efficacy (AUC = 0.891). Saha et al. [49] performed a comprehensive analysis on a larger cohort of 922 female patients with invasive breast cancer who underwent pre-operative DCE-MRI. The researchers used a machine learning approach to extract 529 imaging features from the MRIs and developed multivariate models to predict various molecular and genomic characteristics, including tumor subtype, ER, progesterone receptor (PR), HER2 status, and the proliferation marker Ki-67. The results indicated moderate associations between the imaging features and molecular biomarkers, with the highest predictive accuracy achieved for distinguishing Luminal A subtype (AUC = 0.697) and basal breast cancer (AUC = 0.654).

Early studies of breast MRI radiogenomics were often based on T1-weighted imaging, and multiparametric imaging is the greatest strength of MRI. In the first study that investigated the utility of diffusion weighted imaging (DWI) radiomic signatures, Xie et al. [50] investigated DWI and DCE-MRI histogram features for the differentiation of basal from other molecular subtypes with AUCs up to 0.763. However, histogram features do not provide textural information regarding spatial relationships between the signal intensities of pixels/voxels across a region or volume of interest. Leithner et al. [51] found that radiomic features from DWI, such as gray-level co-occurrence matrices, can more accurately assess the receptor status and molecular subtype of breast cancer, especially for the luminal A and B subtypes (with accuracies of 91.5% and 89.5%, respectively). Meanwhile, Holli-Helenius et al. [52] achieved AUC values of 0.83-0.88 for the separation of luminal A and B cancers in a small patient cohort (n = 27) using co-occurrence matrix features alone. Siyao Du et al. [53] conducted a study involving 200 breast cancer patients who underwent synthetic MRI, DWI, and DCE-MRI examinations. The study found that T1 and T2 values were significantly different in hormone receptor-negative and Ki67 > 14% tumors, while HER2-positive tumors demonstrated higher Ktrans and Kep. The authors concluded that MRI quantitative parameters can help distinguish molecular markers and subtypes, with T1 values from synthetic MRI being associated with the basal subtype and combined parameters including T2 values showing potential in discriminating the Luminal A subtype. In a prospective study, Tsai et al. [54] evaluated 306 female patients with de novo breast cancer, specifically tumors larger than 1 cm, using DCE-MRI, DWI, and intravoxel incoherent motion (IVIM). They found that breast cancer PAM50 subtypes luminal A and normal-like exhibited

significantly higher expression of vascular normalization genes compared to other subtypes.

Building on multiparametric MRI examinations, researchers have explored the use of advanced machine learning techniques to differentiate molecular subtypes. For example, Huang et al. [55] conducted a study involving 162 female patients diagnosed with clinical stage T2-4 breast cancer to investigate the potential of multiparametric MRI-based radiomic features in predicting molecular subtypes and androgen receptor expression. They employed various machine learning algorithms and feature selection strategies to analyze a total of 4,198 radiomic features extracted from MRI sequences. The study found that the Multilayer Perceptron (MLP) model demonstrated the best performance, achieving an AUC of 0.907 for predicting AR expression and a micro-AUC of 0.896 for classifying molecular subtypes.

MRI-based radiomic features could also be used alongside other clinical variables to understand tumor biology. For example, Sheng et al. [56] conducted a study on 190 Chinese female patients with invasive ductal breast cancer. The study utilized a combination of three-dimensional imaging features extracted from DCE-MRI, pathology variables, and clinical data, applying machine learning techniques to predict molecular subtypes. The study found that the eXtreme Gradient Boosting model demonstrated superior performance in differentiating the various molecular subtypes of breast cancer, including Luminal, HER2, and basal subtypes, especially in the Luminal and basal groups, with AUC values of 0.8282 and 0.9031, respectively.

The methods used in the above studies varied in their ability to identify molecular subtypes of breast cancer. Consequently, Davey et al. [57] performed a meta-analysis to assess the diagnostic accuracy of radiogenomics in differentiating molecular subtypes. The authors evaluated 41 studies (from 2015 to 2020) involving 10,090 breast cancer patients. This analysis supports the reliability of preoperative MRI-based radiogenomics in independently differentiating the therapeutically relevant luminal A (sensitivity: 0.78 and specificity: 0.83) and HER2+ (sensitivity: 0.87 and specificity: 0.88) subtypes from each other. It also supports the refinement of deep learning and convolutional neural networks (CNN) as the most favorable means of radiogenomic analysis. The authors concluded that radiogenomics has the potential to differentiate breast cancer into its clinically relevant subtypes, while preserving invasive approaches until the time of surgical resection.

Predictive value of radiogenomics for treatment response and prognosis

Prognostic risk analysis is crucial for post-operative treatment selection and survival assessment in breast cancer. Radiogenomics has shown significant potential in predicting treatment response and prognosis, which could guide personalized therapy in breast cancer management, ultimately improving patient survival and quality of life.

A secondary analysis of the "Multimodality Analysis and Radiologic Guidance in Breast-Conserving Therapy" (MARGIN) study evaluated 21 MRI-based imaging characteristics, focusing on six key parameters: tumor size, shape, contours, initial and late signal enhancement, and intensity, in relation to gene expression profiles obtained from RNA sequencing in 295 patients. A significant link was found between tumor proliferation and size, indicating that larger, highly proliferative tumors have worse prognoses [58]. Building upon this paradigm, Ming et al. [59] conducted a radiogenomic analysis based on DCE-MRI and RNA sequencing data from 246 patients across multiple centers. The expression of genes including RBP4, MYBL2, and LINC00993 was found to correlate significantly with imaging features. Based on these findings, the researchers developed a prognostic signature using eight imaging-associated genes. Experimental results showed that high expression of this signature indicated a poor prognosis. Incorporating five genomic features and three MRI radiomic features, Chen et al. [60] developed and validated a radiogenomic model to predict axillary lymph node metastasis in breast cancer, achieving a higher AUC value of 0.84.

Further expanding the clinical applicability of imaging biomarkers, Wang et al. [61] conducted a retrospective study involving 227 breast cancer patients to explore the clinical value of advanced diffusion MRI techniques, including apparent diffusion coefficient (ADC), intravoxel

incoherent motion (IVIM), and diffusion kurtosis imaging (DKI), in predicting genotypes and prognostic factors. The researchers found that perfusion-related diffusion coefficient (D*) and mean kurtosis (MK) values were significantly higher in high-grade Nottingham prognostic index (NPI) groups, while lower ADC and true diffusion coefficient (D) values were associated with high Ki-67 expression. The combination of DWI, IVIM, and DKI could enhance diagnostic efficiency in breast cancer patients. Concurrently, Wu et al. [62] analyzed two cohorts (discovery cohort: 60 patients; validation cohort: 186 patients) to investigate intratumoral spatial heterogeneity at perfusion MR imaging of locally advanced breast cancer treated with neoadjuvant chemotherapy. The authors developed a two-stage clustering method to identify three intratumoral subregions (poorly, moderately, and highly perfused), quantified spatial heterogeneity using multiregional spatial interaction (MSI) matrices, and performed network-based patient stratification. Results showed that MRI-based heterogeneity was an independent predictor of recurrence-free survival beyond traditional clinicopathologic and genomic factors. In another multicohort study, Fan et al. [63] aimed to identify preoperative radiomic signatures associated with ODxRS in ER-positive breast cancer patients. They utilized DCE-MRI data from three independent cohorts, comprising a total of 332 patients, to develop and validate these signatures. The study found that high ODxRS predicted values were significantly associated with a favorable response to neoadjuvant chemotherapy, and the identified radiomic signatures have the potential to serve as promising non-invasive biomarkers for prognosis and treatment response in breast cancer.

Neoadjuvant chemotherapy (NAC) is the standard treatment for localized and advanced breast cancer, aiming to reduce tumor size and potentially enable breast-conserving surgery. However, not all breast cancers benefit from NAC treatment, as some biologically aggressive lesions may not be effectively controlled after months of treatment and may even increase the risk of tumor metastasis. Therefore, it is crucial to distinguish between patients who benefit from NAC treatment and those who are insensitive to NAC treatment as early as possible during treatment. Drukker et al. [64] conducted a study using DCE-MRI data from the American College of Radiology Imaging Network (ACRIN) trial 6657, which included 162 women with breast cancer undergoing NAC. They employed an automated method to calculate the most enhancing tumor volume (METV) as a radiomic feature for predicting recurrence-free survival. The results indicated that METV was predictive of recurrence-free survival both pre-treatment and after the first cycle of chemotherapy, with C-statistics of 0.69 and 0.72, respectively.

Pathologic complete remission (pCR) is closely related to good patient prognosis and can be used as an indicator to evaluate the effectiveness of NAC treatment. Several studies have investigated the potential of radiogenomics to predict pCR and assess the effectiveness of NAC treatment. For example, Tsukada et al. [65] showed that the tumor growth direction parallel to the Cooper ligament (i.e., the tumor anteroposterior diameter is longer than the mediolateral diameter) and the pre-treatment multi-parametric MRI clearance rate are predictive indicators of pCR. Chamming et al. [66] found a statistically significant difference in the relationship between kurtosis with a spatial proportion factor of 2 and prognosis in non-basal breast cancer patients. Kim et al. [67] showed that patients with higher tumor entropy values on T2-weighted imaging had lower recurrence-free survival rates. Additionally, Parikh et al. [68] detected changes in tumor entropy and homogeneity (gray level distribution) during treatment and found that tumors became more homogeneous after NAC treatment, with an increase in signal homogeneity and a decrease in entropy on T2-weighted imaging, which may indicate pCR earlier than changes in tumor size. Zhang et al. [69] developed a radiogenomic model to predict pCR in patients with basal breast cancer undergoing NAC. The prediction model, which integrated imaging and genetic data, showed excellent predictive performance, achieving an AUC of 0.87. They also discovered that the MED23 p. P394H mutation correlated with increased epirubicin resistance in vitro.

Concurrently, Magbanua et al. [70] conducted a pilot study involving 84 high-risk early breast cancer patients to investigate the predictive value of circulating tumor DNA (ctDNA) and functional tumor volume (FTV) measured by

MRI in assessing NAC response and recurrence risk. The researchers employed serial measurements of ctDNA and FTV at multiple time points during treatment, analyzing their correlations and their combined predictive capabilities for pCR and distant recurrence-free survival. They found that ctDNA levels were significantly correlated with FTV, and while the addition of ctDNA to FTV-based predictors improved the prediction of pCR, the change was not statistically significant. However, ctDNA positivity after NAC significantly enhanced the identification of patients at increased risk of metastatic recurrence and death. The study concluded that combining ctDNA and FTV could provide a more robust framework for predicting treatment outcomes in early breast cancer patients undergoing NAC.

Correlation between imaging phenotype and recurrence in breast cancer

MRI imaging characteristics hold promise as radiomic biomarkers for predicting breast cancer recurrence risk. In an earlier study, Mazurowski et al. [71] examined the relationship between MRI enhancement dynamics and recurrence-free survival in 275 breast cancer patients. Using semi-automated computer algorithms, they quantified enhancement dynamics from preoperative MRI scans. Their multivariate analysis revealed that these enhancement dynamics were independently predictive of recurrence-free survival ($P = 0.024$) among patients newly diagnosed with breast cancer, even after controlling for patient age, race/ethnicity, menopausal status, tumor grade, and tumor size. This dynamic feature represents the rate of enhancement of the tumor versus the background breast parenchymal enhancement, and the survival regression model indicated that a higher feature value was associated with an increased risk of disease recurrence. Consequently, Chitalia et al. [72] identified and validated imaging phenotypes of breast cancer heterogeneity using preoperative DCE-MRI scans from two cohorts of women with invasive breast cancer (discovery cohort: 95 patients; validation cohort: 163 patients). The researchers employed radiomic feature extraction, unsupervised hierarchical clustering, and survival analysis. They identified three phenotypes of tumor heterogeneity (low, medium, and high) that were reproducible and demonstrated significant prognostic value ($c = 0.73$) in predicting 10-year recurrence-free survival.

Moreover, Lee et al. [73] investigated prognostic factors for breast cancer recurrence by analyzing a cohort of 267 patients who underwent DCE-MRI prior to surgery. The researchers employed univariable and multivariable Cox proportional hazards regression analysis to identify associations between various imaging parameters, including morphologic features, quantitative MRI metrics, and clinicopathologic factors, with disease recurrence. Their findings revealed that increased ipsilateral vascularity, higher positive skewness in texture analysis, and advanced pathologic stage were significant predictors of recurrence. The comprehensive model incorporating both imaging and clinicopathologic factors demonstrated excellent discrimination for identifying high-risk patients, with a C index of 0.825. Meanwhile, in another study, Lee et al. [74] focused on the imaging characteristics of young age breast cancer (YABC) in 53 patients under 40 years of age, utilizing pre-treatment DCE-MRI to obtain quantitative parameters such as tumor-stroma ratio (TSR), microvessel density (MVD), and endothelial Notch 1 (EC Notch 1). The findings revealed that several MRI parameters could serve as imaging biomarkers for the tumor microenvironment and predict disease recurrence, particularly highlighting the significant association of the basal subtype and low CD34 MVD positivity in Notch 1 hotspots with tumor recurrence. Texture parameters reflecting tumor sphericity and homogeneity were also associated with disease recurrence. The study concluded that several quantitative MRI parameters can be used as imaging biomarkers for the tumor microenvironment and can predict disease recurrence in YABC.

The use of multigene assays to predict the risk of tumor recurrence has been introduced into clinical practice. While these assays provide valuable information, their high cost and the requirement for offsite laboratory analysis limit their accessibility. MRI-based radiogenomics has emerged as a promising tool for assessing breast cancer recurrence risk, offering a non-invasive alternative to biopsies in less time and at lower cost. As Oncotype DX is the most widely used assay in clinical practice, multiple studies have explored the correlation between

MRI imaging features and ODxRS. For example, Ashraf et al. [75] conducted a study involving 56 patients and found that tumors with high ODxRS tended to exhibit significantly rapid enhancement. During dynamic contrast enhancement, high-risk breast cancers occupied a larger proportion of enhancement in relatively faster-enhancing phases, with their peak enhancement often occurring in the first enhancement phase and declining in proportion by the third phase. Through unsupervised cluster analysis of imaging features, the tumors were categorized into four imaging phenotypes. A multiple linear regression model was then established to analyze the correlation between imaging features and recurrence risk. The results demonstrated that DCE-MRI imaging features of ER-positive breast cancers showed a moderate correlation with genetically predicted tumor recurrence risk, achieving an AUC of 0.77. When the imaging phenotype classification results were added as additional variables to the classifier, the AUC increased to 0.82. Subsequently, Sutton et al. [76] performed correlation analysis among DCE-MRI, clinical, and pathological features in a cohort of 95 breast cancer patients. They found that two kurtosis values from breast MRI and histological nuclear grade were significantly associated with ODxRS in luminal A breast cancer, consistent with the findings of Pickles et al. [77] and Yi et al. [78], who found that increased perfusion in luminal A breast cancer correlates with reduced disease-free survival. While both Ashraf et al. and Sutton et al. found that tumors with rapid contrast enhancement features had increased ODxRS, their studies differed in several aspects as follows: 1) the former included four major imaging phenotypes but did not mention kurtosis; 2) the former included ductal and lobular breast cancers, but the PR and HER2 status were unclear; 3) the former only considered imaging features, while the latter combined imaging, clinical, and pathological features for a more comprehensive analysis.

Wan et al. [79] analyzed the correlation between 196 imaging features and Oncotype DX risk categories in 96 ER-positive breast cancer patients. The results showed a high correlation between DCE-MRI texture features of ER-positive breast cancer and ODxRS, with AUCs of 0.84 and 0.80 for directional gradient histogram and dynamic local binary pattern, respectively. Unlike Agner et al. [80], who used a single parameter to assess lesion texture, directional gradient histogram and dynamic local binary pattern can capture dynamic texture changes over time and space. This study differs from Ashraf et al.'s work as it focuses |on texture features rather than kinetic features, which are based on assessments of time-intensity curve, peak enhancement, wash-in, and wash-out parameters. Notably, Wan et al. believe that intensity feature discrimination has the worst stability, while morphology features have the highest error rate among all classification criteria. This research marked the first systematic comparison of various kinetic and morphological features to evaluate recurrence risk in ER-positive breast cancer. The authors suggested that non-invasive radiogenomic methods may be superior to biopsy in the assessment of recurrence risk.

Li et al. [81] investigated the relationships between three multigene assays (MammaPrint, Oncotype DX, and PAM50) and MRI phenotypes to assess breast cancer recurrence risk. The research utilized a retrospective dataset of 84 deidentified breast MR examinations from the Cancer Imaging Archive (TCIA), along with clinical and genomic data from the Cancer Genome Atlas (TCGA). The authors used multiple linear regression and receiver operating characteristic analysis to evaluate the predictive ability of MR radiomic features. Their results showed significant associations between multigene assay recurrence scores and radiomic signatures (R^2 = 0.25-0.32, r = 0.5-0.56, P < 0.0001), particularly tumor size and enhanced texture, meaning that the larger and less homogeneously enhanced the tumor, the higher the risk of recurrence.

Furthermore, Thakur et al. [82] measured ADC values in ER-positive and axillary lymph node-negative invasive breast cancer and found that low-risk lesions with low ODxRS exhibited significantly higher ADC values compared to intermediate/high-risk lesions.

Limitations

Although MRI-based radiogenomics in breast cancer, which links tumor genotype with imaging phenotype, shows significant clinical value and vast application prospects, there are modeling and reporting gaps across the field.

Studies with higher clinical rigor - meaning large sample size, external validation, or prospective/multicenter design; clearly defined endpoints and performance metrics; full subtype or response prediction models, not only imaging-gene correlations - are needed. However, most studies rely on single institutions and retrospective datasets with small sample sizes, lacking representativeness. Many studies use internal hold-outs, cross-validation, or leave-one-out methods but lack independent external test sets. Very few studies report calibration metrics or decision curve analysis (DCA). Multi-class molecular subtype tasks often yield lower multi-class discrimination, and many studies present pairwise accuracy or per-class AUCs rather than robust multi-class calibration. This inflates perceived performance if readers interpret pairwise results as equivalent to multi-class accuracy. Large multi-institutional pools (TCGA/TCIA/multi-center cohorts) introduce scanner and protocol variability, but only a minority of studies explicitly harmonize imaging or test robustness to scanner differences. The lack of standardized protocols, varying software and imaging equipment, and inter- and intra-institutional heterogeneity of datasets restrict the reproducibility of results. This is a major limitation for clinical translation. Some studies [16, 81] link radiomic signatures to gene assays and pathways (strong biological anchor), which improves interpretability. Others present black-box deep learning models without pathway linkage, which require stronger external validation and explainability for clinical uptake. Additionally, the complexity of gene expression and signaling pathways, coupled with the expense and operational intricacies of gene testing, hinder large-scale radiogenomics research. Manual or automatic segmentation methods for regions of interest can also influence feature extraction and subsequent analysis. Future research should focus on overcoming these hurdles to establish radiogenomics as a reliable tool in clinical practice.

Conclusion and future direction

Studies have demonstrated moderate relationships between radiomic features and genomic features. MRI-based radiogenomics offers a rapid and non-invasive approach to obtain valuable imaging biomarkers, holding promise to improve the accuracy of molecular subtype identification, treatment response and prognosis prediction, and recurrence risk assessment. Moving forward, radiogenomics should aim to obtain multicenter and larger sample sizes to conduct prospective and validation studies, as well as to develop standardized protocols for feature extraction and normalization. Translating these research findings into clinical practice to address real-world challenges will facilitate the advancement of personalized treatment and precision medicine.

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Disclosure of conflict of interest

None.

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