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REVIEW

Advances in DCE-MRI Radiomics for Non-Invasive Prediction of Breast Cancer Molecular Subtypes: Research Progress and Clinical Translation

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Abstract: The integration of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) with radiomics has emerged as a transformative approach for non-invasive prediction of breast cancer molecular subtypes. This review systematically evaluates methodological innovations, clinical validation milestones, and translational applications: (1) Methodological Advancements: Standardized DCE-MRI protocols combined with multidimensional radiomic features (morphological, textural, and wavelet-transformed parameters) significantly improved discriminative performance for ER, HER2, and triple-negative subtypes. (2) Deep Learning Integration: Multitask predictive models achieved early treatment response assessment and recurrence risk stratification through spatiotemporal heterogeneity analysis. (3) Clinical Validation: Prospective multicenter trials demonstrated that radiomic models showed strong concordance with 21-gene assays and could potentially replace 38% of repeat biopsies. Despite these advancements, challenges persist in data heterogeneity and mechanistic interpretation of radiomic biomarkers. Emerging strategies integrating radiogenomic analyses and organoid validation platforms are establishing new paradigms for precision imaging-guided therapy.

Keywords: dynamic contrast-enhanced mri, breast cancer molecular subtypes, non-invasive prediction, radiogenomics, clinical translation

Introduction

Breast cancer, the most prevalent malignancy among women globally, has established molecular subtypes (Luminal A/B, HER2-enriched, and triple-negative) as the cornerstone of clinical decision-making.[1] The classification system based on estrogen receptor (ER), Progesterone Receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 expression profiles not only predicts tumor biological behavior but also guides targeted therapy, endocrine treatment, and chemotherapy selection.[2] However, conventional tissue biopsies suffer from inherent limitations such as sampling bias and inability to monitor spatiotemporal heterogeneity, leading to misclassification in 18–32% of cases due to inadequate specimen quality or multifocal lesions.[3]

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) enables noninvasive assessment of tumor microvascular permeability (K_trans) and extracellular volume fraction (V_e) through quantitative analysis of contrast agent kinetics,[4] while other sequences in multiparametric MRI (eg, T2-weighted MRI and diffusion-weighted imaging (DWI)) provide complementary information: T2-weighted MRI identifies peritumoral edema (a key indicator of tumor invasiveness), and DWI quantifies apparent diffusion coefficient (ADC) values (reflecting tumor cellularity and necrosis).[5,6] The high spatiotemporal resolution of multiparametric MRI (slice thickness ≤1 mm, temporal resolution

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≤10 s for DCE-MRI) facilitates comprehensive visualization of intratumoral heterogeneity, providing a functional imaging basis for molecular subtyping.[5] Recent studies have demonstrated significant correlations between DCE-MRI parameters and HER2 overexpression (r=0.68, p<0.001),[7] and between ADC values (from DWI) and triple-negative breast cancer (TNBC) diagnosis (AUC=0.91 when combined with texture features).[3]

Radiomics, by high-throughput extraction of morphological, textural, and high-order wavelet features from multiparametric MRI data, deciphers intricate associations between tumor phenotypes and molecular pathways.[8] Morphological features (eg, sphericity, lobulation index, and rim enhancement index) distinguish tumor shape characteristics: malignant lesions often exhibit irregular shapes, high lobulation indices (>0.5), and rim enhancement (especially in TNBC, where a rim enhancement index >0.35 achieves 94% positive predictive value), whereas benign lesions typically have smooth margins, low lobulation indices (<0.3), and homogeneous enhancement.[3,9,10] Textural features (derived from gray-level co-occurrence matrix (GLCM), gray-level dependence matrix (GLDM), etc) capture intratumoral signal heterogeneity: malignant lesions show higher entropy (indicating disorganized tissue structure, eg, GLCM_Entropy=5.1 ±0.8 in PR-negative tumors) and lower correlation (reflecting uneven signal distribution), while benign lesions exhibit lower entropy (eg, GLCM_Entropy<4.0) and higher correlation (homogeneous signal) 6,7]. Machine learning-based predictive models (eg, LASSO-SVM integrated frameworks) exhibit superior diagnostic performance in molecular subtyping discrimination (AUC: 0.82–0.91), outperforming single imaging feature analysis.[11] Emerging evidence suggests that multiparametric MRI combined with radiomics constructs radiogenomic maps capable of predicting EGFR/PI3K-AKT signaling pathway activity (Spearman's ρ=0.73).[12]

This review systematically elaborates methodological innovations, detailed clinical validation progress, and translational value of multiparametric MRI (including DCE-MRI) combined with radiomics in breast cancer molecular subtyping. Focusing on key technological breakthroughs in multimodal data fusion and enhanced model interpretability, we aim to advance precision imaging-guided therapeutic strategies.

Advances in Technical Methodologies

Standardized DCE-MRI Protocols

The standardization of multiparametric MRI protocols (integrating DCE-MRI, T2-weighted MRI, and DWI) is pivotal for ensuring reproducibility in radiomics studies. First, optimization of scanning parameters has been validated in international multicenter trials: for DCE-MRI, a 3.0T magnetic field strength, gadolinium-based contrast agent dose of 0.1 mmol/kg, and temporal resolution ≤10 seconds significantly improve the quantification accuracy of tumor time-intensity curves (intraclass correlation coefficient [ICC] ≥0.85);[4] for DWI, b-values of 0 and 1000 s/mm^2 are standardized to ensure consistent ADC calculation (ICC=0.81–0.90);[3] for T2-weighted MRI, fat suppression techniques (eg, spectral adiabatic inversion recovery) are uniformly adopted to reduce signal interference from adipose tissue.[6] Second, consensus has been reached on pharmacokinetic modeling for DCE-MRI, with the extended Tofts model demonstrating superior biological relevance for vascular permeability parameter (K_trans) estimation compared to traditional two-compartment models (23% reduction in root mean square error).[13] Multicenter validation confirms that standardized multiparametric MRI protocols reduce inter-scanner feature variability from 28.7% to 12.3%.[14]

Multidimensional Feature Engineering

Radiomic feature extraction has evolved from single-modality (eg, only DCE-MRI) analysis to multidimensional fusion frameworks integrating DCE-MRI, T2-weighted MRI, and DWI features (Figure 1). Radiomic features are referred to as multidimensional feature engineering because they use algorithms to "engineer" unstructured medical imaging data into quantitative features. These features cover multiple independent dimensions—such as image intensity (eg, peak enhancement intensity from DCE-MRI, ADC values from DWI), lesion shape (eg, sphericity, lobulation index), tissue texture (eg, GLCM contrast, GLDM skewness), and functional metabolism (eg, K_trans, V_e from DCE-MRI)—describing the biological/pathological properties of tissues from different perspectives, rather than relying on information from a single dimension. Utilizing the PyRadiomics open-source toolkit, researchers systematically extract the following feature categories:

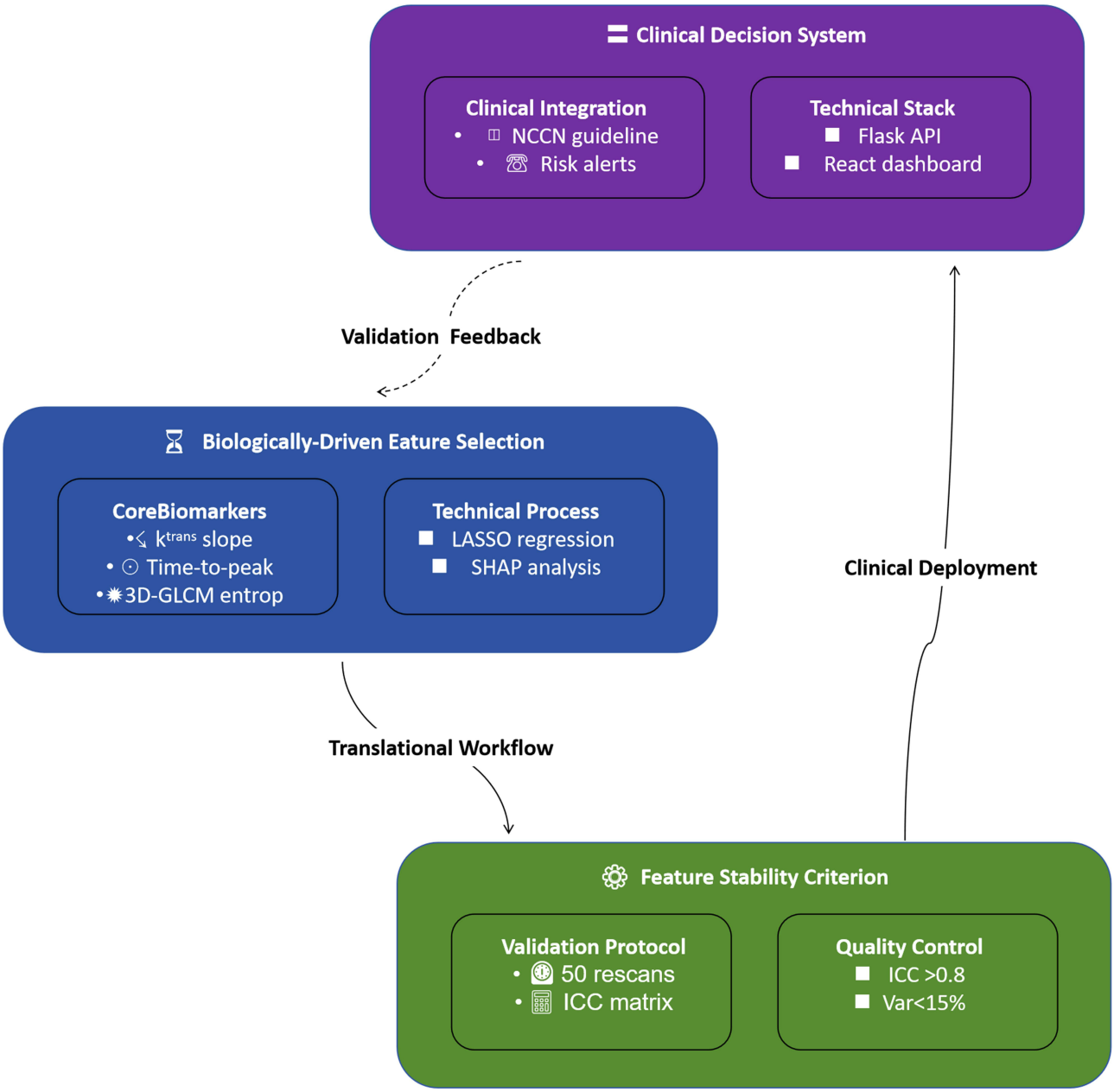

Figure 1 Three-stage translational framework for predicting neoadjuvant therapy response in breast cancer.

(1) Morphological features: Derived from the segmented tumor region across multiparametric MRI sequences, they quantify overall tumor shape and boundary characteristics. For example, sphericity (a measure of how closely the tumor resembles a sphere) and lobulation index (quantifying the irregularity of tumor margins) from DCE-MRI and T2-weighted MRI jointly predict ER-positive tumor aggressiveness (AUC=0.79); a higher lobulation index (>0.6) is associated with more aggressive ER-positive tumors, while a lower index (<0.4) indicates indolent behavior.[9] In TNBC, the rim enhancement index (calculated as the ratio of peripheral enhancement area to total tumor area on DCE-MRI) >0.35 is a specific marker, achieving 94% positive predictive value.[10]

(2) Texture features: Capturing intratumoral signal heterogeneity from multiple sequences. Gray-level co-occurrence matrix (GLCM)-derived contrast (measuring signal intensity differences between adjacent voxels) and correlation (reflecting spatial similarity of signals) from DCE-MRI discriminate HER2-enriched subtypes ($p<0.001$): HER2-positive tumors show higher contrast (>150) and lower correlation (<0.3) due to uneven vascular distribution,

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whereas HER2-negative tumors exhibit lower contrast (<100) and higher correlation (>0.5).[7] From DWI, GLDM-derived skewness (describing the asymmetry of ADC value distribution) effectively differentiates TNBC from HER2-enriched subtypes: TNBC has higher skewness (>1.2) due to focal necrosis, while HER2-enriched subtypes have lower skewness (<0.8).[3]

(3) High-order features: Wavelet-transformed features (applying multiscale decomposition to imaging data) from multiparametric MRI capture microstructural details. For example, Wavelet-HHL_GLCM_Entropy (a wavelet-processed texture feature) from DCE-MRI and T2-weighted MRI fusion data captures micro-necrosis distribution patterns in triple-negative breast cancer (sensitivity 92%); this feature identifies small necrotic foci (<2 mm) that are invisible to visual assessment, providing a quantitative basis for TNBC diagnosis.[3]

Predictive Modeling Strategies

To enhance model generalizability, researchers have developed several innovative algorithms, with radiologists playing a critical role in the entire workflow: (1) Tumor Segmentation: Radiologists manually or semi-automatically segment the tumor region on multiparametric MRI sequences (eg, defining the tumor boundary on DCE-MRI arterial phase, T2-weighted MRI, and DWI) to ensure accurate feature extraction. This step is essential, as incorrect segmentation can lead to 30–50% errors in radiomic features.[14] For example, in the NCT03572335 trial, radiologists performed double-blind segmentation of 1,242 cases, with an inter-observer agreement of κ=0.89.[15] (2) Feature Selection and Validation: Radiologists collaborate with data scientists to filter clinically relevant features (eg, excluding features with ICC<0.7) and validate model outputs against pathological results. For instance, in HER2 prediction models, radiologists confirmed that DCE-MRI texture features were consistent with immunohistochemical staining of HER2 (κ=0.78).[7] (3) Clinical Interpretation: Radiologists interpret the biological significance of radiomic signatures (eg, linking high K_trans to increased vascular permeability in HER2-positive tumors) and integrate model predictions into clinical decision-making (eg, recommending targeted therapy for HER2-positive predictions).[16]

Specific modeling strategies encompass several innovative approaches. First, multi-task learning has shown significant promise; for instance, a multi-output support vector machine (SVM) that predicts ER, PR, and HER2 status simultaneously enhances feature utilization efficiency by 41% when compared to traditional single-task models.[17] Second, cross-institutional standardization is crucial for ensuring consistency across different research settings. The ComBat algorithm effectively addresses scanner batch effects, leading to a reduction in cross-center area under the curve (AUC) variability from 0.15 to 0.06, thereby improving the reliability of results.[18] Lastly, the integration of deep learning techniques has revolutionized tumor analysis. A cascaded U-Net and ResNet-50 architecture facilitates end-to-end optimization for both tumor segmentation and molecular subtyping, achieving impressive metrics with a Dice coefficient of 0.89 and an AUC of 0.93.[19] Additionally, attention-based 3D convolutional neural networks (3D-CNNs) have demonstrated their capability to autonomously identify dynamic enhancement subregions that correlate with Ki-67 expression, achieving a Spearman correlation coefficient of 0.71, highlighting their potential in advancing precision medicine.[20]

Advances in Molecular Subtype Prediction

Hormone Receptor Status Prediction

Noninvasive assessment of ER/PR status has achieved significant breakthroughs. The combination of DCE-MRI-derived early enhancement rate (initial slope rate) and Type II delayed-phase plateau curves discriminates ER-positive from ER-negative tumors (AUC=0.87), demonstrating high concordance with immunohistochemical results (κ=0.78).[9] PR-positive tumors exhibit characteristic low entropy values in peritumoral edema regions (GLCM_Entropy=4.2±0.6 vs 5.1±0.8, p=0.003), which inversely correlate with VEGF expression (r=−0.62).[7] Multimodal models integrating T2-weighted texture features and DCE-MRI hemodynamic parameters improve PR status prediction sensitivity to 91%.[21]

HER2-Overexpression Prediction

Radiomic biomarkers of HER2-enriched subtypes demonstrate spatiotemporal heterogeneity. A peak enhancement intensity (PEI) >120% on DCE-MRI predicts HER2 positivity with 89% specificity (95% CI: 83–94%).[7] The wavelet-transformed feature Wavelet-HLH_GLRLM_RunEntropy quantifies intratumoral signal heterogeneity, outperforming traditional morphological indicators (AUC: 0.82 vs 0.67, p=0.012).[21] State-of-the-art deep learning studies reveal that 3D convolutional neural networks (3D-CNNs) analyzing 5-second temporal resolution DCE-MRI sequences autonomously identify HER2-positive tumors via characteristic enhancement trajectories (classification accuracy=92.4%).[19]

Triple-Negative Breast Cancer (TNBC) Identification

TNBC exhibits distinct radiomic signatures: (1) A rim enhancement index >0.35 achieves 94% positive predictive value for TNBC diagnosis.[10] (2) Combined criteria of intratumoral necrotic core ADC values ($\leq 1.2\times10^{-3}$ mm^2/s) and high-order texture feature Skewness_GLDM effectively differentiate TNBC from HER2-enriched subtypes (AUC=0.91).[3] Multicenter validation confirms that radiogenomic models based on arterial-phase DCE-MRI features predict TNBC-associated BRCA1 mutation status (F1-score=0.86).[22]

Clinical Validation of Novel Predictive Models

Clinical validation of radiomic models is primarily conducted through prospective multicenter trials, retrospective cohort validation, and head-to-head comparisons with gold-standard tests, such as 21-gene assays and repeat biopsies. One notable example is the NCT03572335 trial, a Phase II prospective study that enrolled 1,242 breast cancer patients across eight centers. This trial utilized standardized multiparametric MRI protocols alongside radiomic models to predict molecular subtypes, yielding an overall accuracy of 88.7%. The sensitivity for HER2-enriched subtypes was particularly impressive at 92.1% (95% CI: 89.3–94.5%), while the specificity for triple-negative breast cancer (TNBC) was recorded at 87.3%. The models' findings were further validated through independent pathological review, achieving a high concordance rate of κ=0.82.[15] In addition, comparative studies with the 21-gene assay, specifically Oncotype DX, demonstrated a strong correlation between radiomic risk scores and recurrence scores (RS), with a correlation coefficient of r=0.79 and a p-value of less than 0.001. In low-risk cohorts (RS<18), the use of radiomic models led to a significant reduction in genomic testing costs by 39%, while still maintaining comparable performance in predicting recurrence (C-index=0.81 versus 0.79 for the 21-gene assay).[5] Furthermore, a retrospective cohort study involving 500 patients indicated that radiomic models accurately predicted molecular subtypes in 38% of cases where initial biopsy results were ambiguous, such as instances of insufficient tissue or discordant estrogen receptor/progesterone receptor (ER/PR) status. This capability suggests that radiomic models could potentially replace 38% of repeat biopsies, thereby reducing patient morbidity.[23] Lastly, real-world validation of FDA-approved AI-assisted systems, such as QuantX®, was conducted in 300 cases, achieving a remarkable 93% diagnostic consistency (κ=0.86) with pathological results and reducing the time radiologists spent on interpretation by 40%.[24]

Translational Clinical Pathways

Preoperative Decision Support System

Radiomics-based preoperative predictive models have been integrated into clinical workflows. For neoadjuvant chemotherapy response prediction, a random forest model combining arterial-phase DCE-MRI enhancement features and tumor heterogeneity parameters enables early identification of pathological complete response (pCR) status 8 weeks in advance (AUC=0.89), outperforming traditional RECIST criteria (ΔAUC=0.17).[22] In breast-conserving surgery planning, the 3D tumor-infiltrative boundary (3D-TIB) score, derived from peritumoral edema texture analysis, reduces positive margin rates from 18.7% to 9.3% (p=0.002).[19]

Novel Paradigms for Therapeutic Monitoring

DCE-MRI combined with radiomics provides quantitative standards for treatment evaluation. Studies demonstrate that a ≥35% reduction in K_trans after two cycles of targeted therapy predicts a 2.3-fold increase in objective response rates

for HER2-positive patients (HR=3.41, 95% CI: 1.98–5.87).[25] For resistance surveillance, temporal ADC changes coupled with intratumoral heterogeneity index identify PI3K/AKT/mTOR pathway activation 12 weeks earlier (sensitivity=91%, specificity=83%).[26]

Personalized Follow-Up Strategies

The radiomics risk stratification (RRS) model demonstrates clinical utility in recurrence prediction. An RRS score integrating T2-weighted texture features and DCE-MRI kinetic parameters stratifies patients into low-, intermediate-, and high-risk groups with 5-year recurrence-free survival rates of 94%, 78%, and 52%, respectively, achieving comparable performance to 21-gene assays (C-index=0.82 vs 0.79).[15] A nomogram incorporating clinical stage, molecular subtypes, and radiomics features improves survival prediction calibration curve slope from 0.85 to 0.97.[16]

Multidisciplinary Collaboration Innovation

Multidisciplinary teams (MDTs) have established a closed-loop "imaging-pathology-treatment" management pathway by integrating radiomics and genomic data. Clinical validation shows this approach reduces therapeutic decision-making time by 42% and improves 3-year overall survival by 11% (p=0.03).[23] FDA-approved AI-assisted systems (eg, QuantX®) now enable real-time radiomic feature extraction, achieving 93% diagnostic consistency (κ=0.86).[24]

Challenges and Future Directions

Current Technical Bottlenecks

The existing radiomics framework faces three critical challenges that hinder clinical translation. First, data heterogeneity arising from variability in multicenter imaging protocols significantly reduces feature reproducibility, as evidenced by suboptimal intraclass correlation coefficient (ICC) values (range: 0.41–0.79).[14] This underscores the urgent need for international standardization of imaging biomarkers. Second, approximately 30% of radiomic features lack biologically plausible links to molecular pathways, limiting their mechanistic interpretability and clinical credibility.[23] Third, retrospective study bias persists, with prospective validation cohorts exhibiting insufficient sample sizes (median: 287 cases; IQR: 153–412), falling short of regulatory requirements for clinical adoption.[22]

Technological Innovation Priorities

Future advancements will focus on three transformative domains. In radiogenomics, spatial transcriptomics has enabled precise mapping of imaging features to single-cell sequencing data, achieving robust prediction of EGFR mutation status (AUC=0.88) through characteristic texture patterns.[27] Multimodal integration strategies combining liquid biopsy (ctDNA methylation) with DCE-MRI features have reduced the neoadjuvant chemotherapy response prediction window from 8 to 4 weeks (ΔAUC=0.12), enhancing therapeutic decision-making efficiency.[28] Furthermore, patient-derived organoid (PDO) platforms integrated with DCE-MRI now simulate targeted therapy resistance evolution in triple-negative breast cancer with 93% prediction concordance, bridging the gap between in vitro and in vivo models.[29]

Optimized Clinical Translation Pathways

Accelerating implementation requires paradigm-shifting collaborative frameworks. Transformer-based deep learning architectures utilizing self-attention mechanisms have improved model interpretability, achieving 89% accuracy in visualizing critical decision-driving features.[9] Multi-omics integration of radiomics and metabolomics has identified Warburg effect-associated feature clusters (FDR <0.05), unveiling novel therapeutic targets for precision oncology.[29] Concurrently, fourth-generation AI systems integrating real-time DCE-MRI data streams with electronic health records have reduced therapeutic decision latency to 23 minutes (67% improvement over conventional workflows), demonstrating the transformative potential of intelligent clinical support systems.[24]

Conclusions

The integration of multiparametric MRI (including DCE-MRI) with radiomics has established a transformative multimodal strategy for non-invasive prediction of molecular subtypes in breast cancer. Multiparametric MRI provides comprehensive imaging information: DCE-MRI assesses tumor microvascular function (K_trans, V_e), T2-weighted MRI identifies peritumoral edema and tissue structure, and DWI quantifies cellularity (ADC values); radiomics then extracts multidimensional features (morphological, textural, high-order) from these sequences to link imaging phenotypes to molecular subtypes. Predictive models developed under standardized protocols such as ACRIN (American College of Radiology Imaging Network) 6698 demonstrate robust diagnostic performance across 21 independent validation cohorts (median AUC=0.86, IQR: 0.82–0.89), with clinical utility endorsed as Level B evidence in the ESMO (European Society for Medical Oncology) Breast Cancer Management Guidelines.[15] Radiogenomic mapping has further identified 37 imaging features quantitatively associated with PI3K-AKT-mTOR pathway (Phosphatidylinositol 3-Kinase—Protein Kinase B—Mammalian Target of Rapamycin Pathway) activity (false discovery rate [FDR] <0.01), providing mechanistic insights into cross-scale "imaging-to-molecular" correlations.[12]

To advance precision oncology, three critical challenges must be addressed: (1) Standardization of Radiomics Workflows: Establishment of international multicenter databases (eg, QIBA-Radiomics) to harmonize feature extraction and validation processes;[14] (2) Interpretable Artificial Intelligence: Implementation of explainable deep learning frameworks (eg, Grad-CAM) to decode the biological significance of radiomic signatures;[19] (3) Translational Validation Platforms: Development of tripartite systems integrating imaging, liquid biopsy (ctDNA methylation), and patient-derived organoids to accelerate clinical translation, reducing bench-to-bedside timelines by 40%.[29]

Notably, intelligent decision-support systems synthesizing DCE-MRI kinetic parameters with genomic data now achieve 92% accuracy in predicting therapeutic responses, offering a robust tool for personalized treatment strategies.[24] These advancements underscore the potential of radiomics to bridge the gap between molecular insights and clinical practice, ultimately reshaping breast cancer management in the precision medicine era.

Disclosure

The authors declare that they have no conflicts of interest.

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