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REVIEW

The role of radiomics in predicting the response to neoadjuvant chemotherapy for breast cancer

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ABSTRACT Breast cancer exhibits profound biological and spatial heterogeneity, which contributes to variable responses to neoadjuvant chemotherapy (NAC) and challenges precision treatment planning. Radiomics, an emerging discipline that converts standard medical images into high-dimensional quantitative data, offers a non-invasive and reproducible means to capture tumor phenotype, heterogeneity, and treatment-induced changes. This review provides a comprehensive overview of recent advances in radiomics for breast cancer NAC, emphasizing the roles in predicting a pathologic complete response (pCR), monitoring early therapeutic efficacy, and quantifying intratumoral heterogeneity. Among imaging modalities, magnetic resonance imaging (MRI)-based radiomics, particularly utilizing dynamic contrast-enhanced and diffusion-weighted sequences, demonstrates robust predictive performance for the pCR, with multi-center studies reporting area under the curve (AUC) values >0.80. Longitudinal and delta-radiomics approaches further enhance early response evaluation by tracking temporal alterations in imaging features that precede measurable morphologic regression. Radiomic assessment of tumor heterogeneity, especially in triple-negative breast cancer (TNBC), reveals strong associations with immune infiltration, metabolic reprogramming, and therapeutic resistance, providing mechanistic insight into radiomic biomarkers. Integrative multi-omics frameworks, combining radiomics with genomics, transcriptomics and pathomics, are increasingly elucidating the biological underpinnings of imaging phenotypes, improving both model interpretability and clinical relevance. Despite these advances, widespread clinical adoption of radiomics is limited by methodologic variability, lack of standardization, and insufficient external validation. Future efforts should focus on harmonized imaging protocols, explainable artificial intelligence, and prospective multi-center trials to translate radiomics into a clinically actionable tool. Collectively, radiomics represents a transformative approach for individualized response prediction and dynamic treatment optimization in precision breast cancer management (**Figure 1**).

KEYWORDS Breast cancer; radiomics; neoadjuvant chemotherapy; deep learning; pathologic complete response

Introduction

Clinical and biological background of breast cancer and NAC

Breast cancer remains one of the leading causes of cancer-related mortality among women worldwide owing to the distinct epidemiologic patterns and profound biological heterogeneity[1-3]. Such heterogeneity contributes to heterogeneous responses to systemic therapies and complicates precision treatment planning.

Neoadjuvant chemotherapy (NAC), defined as the administration of systemic therapy before definitive breast surgery, was originally introduced to downstage locally advanced or inoperable tumors[4,5]. NAC can convert previously inoperable cases into operable cases by decreasing the tumor burden, and even in patients with operable disease at time of presentation, NAC enables tumor downstaging that increases breast-conserving surgery rates by 7%–12%[6-10]. Over time, NAC has evolved from a specialized intervention for advanced disease into a standard therapeutic approach that confers broader clinical benefits[11,12]. Beyond improving local tumor control and curative potential in early-stage breast cancer, neoadjuvant trials also offer a rapid and efficient means to evaluate drug efficacy, accelerating the development and regulatory approval of new treatments[13]. Importantly, NAC provides an

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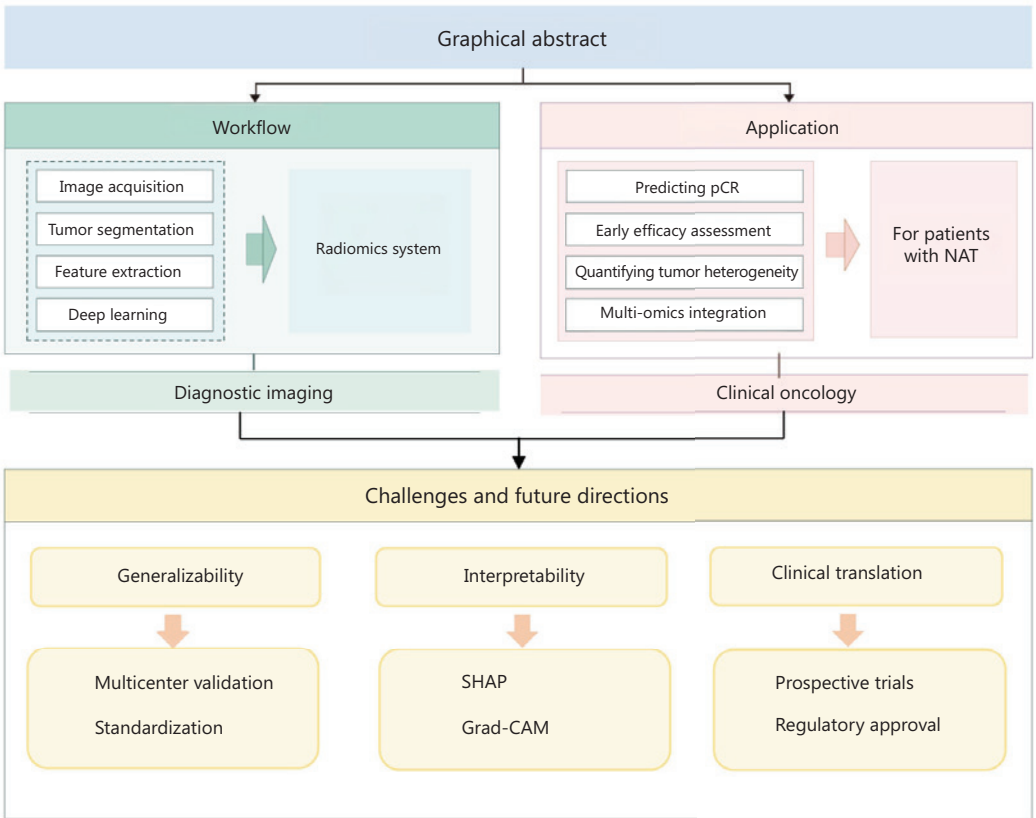


Figure 1 Graphical abstract. This figure summarizes the radiomics workflow in breast cancer across multiple imaging modalities, and discusses its potential clinical applications, the prospect of radio-multiomics, as well as the challenges and future directions for clinical integration.

opportunity to observe *in vivo* tumor response, offering valuable biological insights that inform personalized adjuvant treatment strategies[8,14]. For example, the presence of residual disease following NAC identifies HER2-negative patients who derive substantial benefit from subsequent capecitabine therapy[15]. Notably, a pathologic complete response (pCR) after NAC has been validated as a surrogate endpoint predictive of long-term clinical outcomes, such as disease-free survival and overall survival, with the strongest correlation observed in triple-negative and HER2-positive subtypes[16-20]. Achieving a pCR consistently correlates with a markedly reduced risk of disease recurrence, underscoring the prognostic value in clinical practice[12,21].

Challenges in conventional evaluation of the neoadjuvant treatment response

Given the substantial therapeutic complexity and marked biological heterogeneity of breast cancer, achieving precise prognostic prediction of the treatment response remains a major clinical and research challenge. Conventional prognostic evaluation predominantly depends on clinicopathologic indicators, including TNM staging, histologic grading, and molecular subtyping. While these factors provide essential insights into disease burden and biological behavior, clinicopathologic indicators often fail to capture the dynamic and spatial heterogeneity within the tumor microenvironment. Accurate assessment of the therapeutic response, particularly following NAC, is pivotal for optimizing personalized treatment strategies because assessment of the therapeutic response informs decisions on systemic therapy adjustment, surgical planning, and the need for additional local interventions.

Furthermore, current medical imaging has a central role in this process by providing a non-invasive, whole-breast assessment that captures intra- and peri-tumoral characteristics, effectively bridging macroscopic phenotypic patterns with underlying molecular and genomic signatures[22]. Through advanced imaging modalities, such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), diffusion-weighted imaging (DWI), and positron emission tomography (PET), clinicians can evaluate treatment-induced biological alterations across the entire breast, including regions not accessible by biopsy, thereby achieving a more comprehensive evaluation of therapeutic efficacy. However, these approaches often demonstrate limited sensitivity for

early response assessment due to a failure to capture subtle biological or microstructural changes that precede measurable tumor shrinkage.

Ultimately, confirmation of a pCR still relies on post-surgical histopathologic examination, which is inherently retrospective and therefore cannot inform treatment adjustments during the neoadjuvant period.

Radiomics as an emerging paradigm in cancer imaging

The continuous evolution of imaging technologies and analytical methods has significantly enhanced the potential for monitoring responses to NAC. These developments enable longitudinal, quantitative, and reproducible assessments, thereby contributing to more precise and individualized breast cancer management[23].

In recent years the conventional diagnostic paradigm of medical imaging has undergone a profound transformation with the emergence of radiomics, which extends imaging analysis far beyond visual interpretation[24]. By converting standard medical images into high-dimensional, quantifiable data, radiomics enables the extraction of complex features that reflect underlying tumor phenotypes and microenvironmental characteristics. This approach provides complementary insights that augment traditional clinical and pathologic indices across various malignancies, including breast cancer[25,26]. In parallel, artificial intelligence (AI)-driven computer-aided detection and diagnostic systems have become increasingly integrated into breast cancer screening and diagnostic workflows, assisting radiologists in identifying subtle imaging patterns that may escape human perception[27]. The convergence of AI and radiomics has catalyzed a paradigm shift in oncologic imaging, promising significant advances in early tumor detection, refined risk stratification, and individualized therapeutic planning[28-30]. Despite this growing enthusiasm and rapid technological progress, most radiomics-based studies are in exploratory phases, often limited by retrospective designs, small sample sizes, and lack of external validation. Consequently, only a handful of radiomic models have achieved regulatory clearance or clinical implementation, with few receiving approval from the United States Food and Drug Administration (FDA)[31]. These challenges underscore the urgent need for standardized methodologies, large-scale prospective validation, and transparent model reporting to bridge the gap between research innovation and clinical translation in the era of precision imaging.

Aims and scope of the present review

The purpose of this review is to provide a comprehensive overview of the role of radiomics in the context of neoadjuvant systemic therapy for breast cancer with particular emphasis on the potential to predict a pCR, monitor early therapeutic efficacy, quantify intratumoral heterogeneity (ITH), and facilitate the integration of multi-omics data. By systematically examining the current state of evidence, we aim to elucidate how radiomics, through advanced quantitative imaging analytics, can serve as a non-invasive surrogate biomarker that captures tumor biology and therapeutic dynamics beyond conventional imaging interpretation. Furthermore, this review compares the performance of diverse artificial intelligence-based radiomic models, including traditional handcrafted feature approaches and deep learning-driven architectures, in terms of predictive accuracy, reproducibility, and clinical generalizability. These comparisons highlight the emerging role of radiomics as an integral component of precision oncology, capable of complementing histopathologic and molecular information for personalized treatment stratification. Finally, we discuss the translational and clinical implications of these findings, underscoring the need for standardized workflows, robust multi-center validation, and interdisciplinary collaboration between radiologists, oncologists, data scientists, and pathologists. Through this multidisciplinary lens, we propose a conceptual framework aimed at bridging methodologic innovation with clinical utility, thereby promoting the integration of radiomics into evidence-based decision-making in routine breast cancer management.

Identification of patients with a pCR to NAC

pCR prediction and the emerging "digital biopsy" paradigm

Neoadjuvant systemic therapy (NST) has become an increasingly integral component in the multidisciplinary management of breast cancer, offering both therapeutic and prognostic advantages. By enabling the direct evaluation of a tumor response during treatment, NAC provides a valuable opportunity to tailor subsequent therapeutic decisions. Clinically, NAC can effectively downstage locally advanced tumors, thereby increasing the feasibility of breast-conserving surgery and enhancing the likelihood of achieving a pCR, a state characterized by the absence of residual invasive disease in the breast and axillary lymph nodes. A tumor pCR serves as a robust surrogate endpoint, demonstrating a strong association with improved long-term outcomes, including extended disease-free survival (DFS) and overall survival (OS)[4,12,13,15,32-36]. Consequently, a pCR has become the most widely accepted and clinically meaningful biomarker for assessing the efficacy of NAC in breast cancer with multiple large-scale trials and meta-analyses confirming the predictive value for favorable prognosis[12]. However, the therapeutic response to NAC remains highly heterogeneous across patients, reflecting the

profound biological diversity of breast cancer. Some patients achieve complete tumor eradication, while others exhibit a minimal response or even disease progression despite intensive treatment[37]. The current gold standard for determining a pCR depends on the histopathologic examination of resected surgical specimens obtained after completion of NAC, a method that is inherently retrospective, invasive, and potentially subject to sampling bias. Therefore, developing reliable, non-invasive, and forward-looking tools to accurately predict a pCR before surgery is of paramount clinical importance. While traditional imaging provides morphologic assessments, imaging often fails to capture the underlying physiologic and molecular shifts driven by therapy. By integrating radiomics with pathomics and molecular data within an integrative framework, we can move toward a "digital biopsy" paradigm (**Figure 2**). Such predictive capability would enable refined surgical planning, improved risk stratification, and more personalized treatment optimization, transitioning from a "one-size-fits-all" approach toward a biologically informed precision oncology framework, ultimately advancing precision oncology in breast cancer care.

Imaging platforms for radiomics in pCR prediction

A wide range of clinical and pathologic characteristics, such as tumor size, histologic grade, and hormone receptor or HER2 status, have been investigated as potential predictors of a pCR

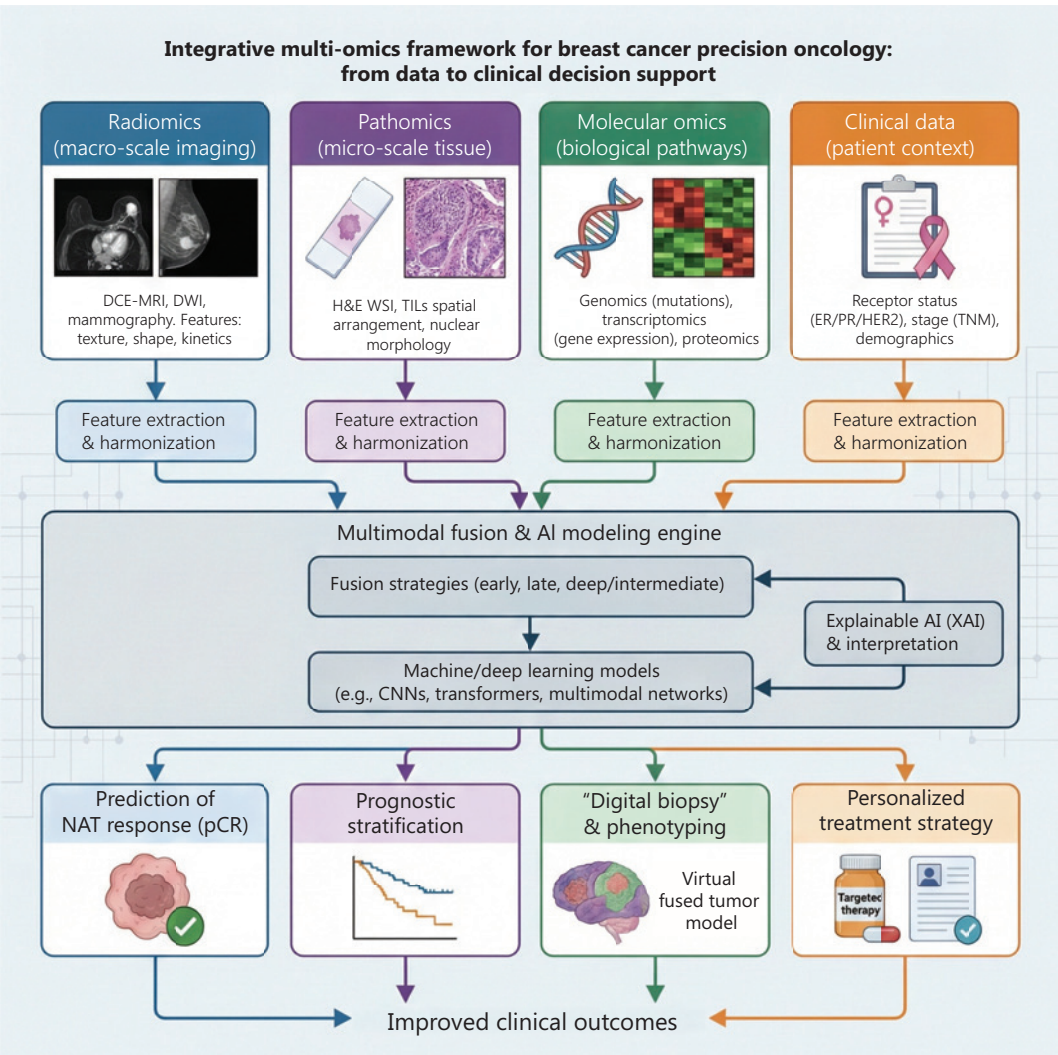


Figure 2 The standardized radiomics and multi-omics integration pipeline in breast cancer. The workflow comprises five key stages: (1) data acquisition, collecting multimodal imaging (DCE-MRI, DWI, mammography, and US); (2) preprocessing, image harmonization, ROI delineation, and resampling; (3) feature extraction, extracting handcrafted (texture/shape) and deep learning-based features; (4) modeling, feature selection, and model construction *via* machine learning or deep learning with external validation; and (5) clinical application, providing decision support for pCR prediction, efficacy monitoring, and personalized treatment. CNNs: convolutional neural networks; DCE-MRI: dynamic contrast-enhanced MRI; DWI: diffusion-weighted imaging; TILs: tumor-infiltrating lymphocytes; WSI: digitizing whole-slide images.

following NAC. However, the prognostic precision remains limited, largely due to the multifactorial nature of the treatment response and the substantial biological heterogeneity of breast cancer. Clinicians routinely use several diagnostic modalities to assess therapeutic efficacy during NAC, including physical examination, ultrasonography (US), computed tomography (CT), mammography, magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT), each offering complementary insights into tumor morphology and burden[38-41]. Among these diagnostic modalities, breast MRI has emerged as the reference standard for response evaluation during NAC, owing to superior soft-tissue contrast, high spatial resolution, and an ability to delineate tumor extent and internal architecture more comprehensively than mammography or US[42]. Breast cancer response is categorized into complete response, partial response, stable disease, and progressive disease based primarily on volumetric or linear tumor measurements, according to the Response Evaluation Criteria in Solid Tumors (RECIST)[43]. Nevertheless, RECIST-defined assessments frequently fail to correspond with a histopathologic pCR, reflecting the inherent limitation of size-based assessments in capturing microscopic residual disease or subtle biological alterations. Conventional imaging approaches primarily focus on morphologic or dimensional changes and therefore lack sufficient sensitivity and specificity to reflect the underlying tumor microenvironment and biological heterogeneity. The advent of radiomics has opened new avenues to overcome these constraints by extracting high-dimensional quantitative features that describe tumor phenotype beyond visual perception. DCE-MRI is widely utilized in this context because DCE-MRI effectively differentiates malignant from normal tissue by characterizing vascular permeability and hemodynamic patterns. Functional MRI techniques, such as DWI, which assesses tissue cellularity through apparent diffusion coefficient (ADC) values, and magnetic resonance spectroscopy, which profiles metabolic alterations, have further expanded the diagnostic and monitoring capabilities of MRI in breast cancer. These advanced imaging modalities serve as critical inputs for the multi-omics fusion frameworks (**Figure 2**) necessary to achieve precision oncology[44-46].

The ACRIN 6657/I-SPY trial provided compelling evidence that early changes in tumor size measured by MRI during the initial stages of NAC can serve as a reliable indicator for predicting a pCR[47]. MRI demonstrates superior performance in delineating tumor extent, morphology, and treatment-induced alterations, both before and after NAC, owing to high spatial resolution and comprehensive imaging capability compared to mammography and US[48]. Among MRI modalities, DCR-MRI has proven particularly effective in monitoring residual disease due to sensitivity to perfusion and vascular permeability, while DWI-derived ADC maps offer complementary quantitative insights into tumor cellularity and microstructural changes[49,50]. Recent studies have further highlighted that integrating conventional clinicopathologic variables with MRI-based radiologic features can substantially improve predictive accuracy for a pCR following NAC[38,39]. Nonetheless, evidence-based meta-analyses have revealed that MRI alone achieves only moderate sensitivity (64%) in predicting a pCR[51] and the detection of axillary lymph node metastasis after NAC. Specifically, MRI demonstrated sensitivity and specificity of 77% and 54%, respectively, compared to 50% and 72% for US, indicating room for improvement in diagnostic precision[52]. These diagnostic gaps indicate that morphologic and simple functional metrics are insufficient for capturing the full spectrum of a therapeutic response. Emerging computational imaging approaches, particularly radiomics and deep learning, are reshaping this landscape by enabling large-scale quantitative extraction of imaging biomarkers that capture intratumoral heterogeneity beyond human perception[24,53-56]. These technologies bridge medical imaging and data science, offering transformative potential to refine therapeutic response prediction, facilitate individualized treatment planning, and advance precision oncology in breast cancer care.

Advanced modeling strategies for radiomics-based pCR prediction

Among all imaging modalities, MRI-based radiomics combined with advanced machine learning algorithms has emerged as having a consistently high predictive performance for predicting a pCR in breast cancer patients undergoing NAC. DCE-MRI provides insights into tumor perfusion and vascular permeability, while DWI captures information related to cellular density and tissue microstructure. Quantitative texture and shape features extracted from these functional MRI sequences have demonstrated strong discriminatory power between pCR and non-pCR cases. Integrating MRI-derived radiomic signatures with machine learning algorithms has yielded consistently high predictive performance with area under the receiver operating characteristic curve (AUC) values frequently > 0.80 across independent studies, underscoring the robustness and reproducibility of these models[38,57-59]. Liu et al. developed an MRI-based radiomics model (RMM) in a notable multi-center study that achieved excellent predictive accuracy with AUCs ranging from 0.71–0.80 across validation cohorts[38]. These findings highlight the clinical importance of early and precise pCR prediction as a foundation for individualized treatment optimization. Building upon this finding, a 2023 multi-center study that included 1262 patients demonstrated subtype-specific pCR rates of 10.6% in $HR^+/HER2^-$, 54.3% in $HER2^+$, and 37.5% in triple-negative breast cancer (TNBC). Using subtype-tailored feature sets of 20, 15, and 13 variables, respectively, machine learning models, particularly a multi-layer perceptron (MLP), achieved the best diagnostic performance. The integration of pre-, post-, and delta-radiomic features

through a stacking ensemble approach further enhanced predictive accuracy, achieving AUCs of 0.959, 0.974, and 0.958 in the primary cohort, respectively, with external validation AUCs up to 0.929. Tracking these temporal shifts during NAT allows for dynamic monitoring of tumor evolution, as shown in the longitudinal and delta-radiomics workflow (**Figure 1**). The model demonstrated accuracies between 85.0%–88.9%, sensitivities of 80.0%–86.3%, and specificities of 87.4%–91.5% across external datasets, suggesting strong generalizability and clinical utility for guiding post-NAC surgical strategies[60]. Complementary efforts have explored multiparametric and -timepoint MRI approaches, integrating baseline, interim, and post-treatment data to capture dynamic tumor heterogeneity. Specifically, spatial habitat radiomics, linking functional subregions within the tumor to underlying biological behavior, has shown superior predictive value compared to conventional whole-lesion radiomics, providing a non-invasive and reliable method for identifying pCR candidates and supporting breast-conserving therapy[61]. Building on these advances, multimodal imaging fusion has emerged as a promising strategy to further improve model robustness and interpretability. By combining MRI-derived features with data from US and PET/CT within an integrative multi-omics fusion framework (**Figure 2**), researchers can capture hemodynamic, mechanical, and metabolic dimensions of tumor biology[62]. Such integrative frameworks have demonstrated enhanced predictive accuracy, stability, and cross-cohort generalizability, underscoring the growing role of multimodal radiomics in refining precision oncology paradigms for breast cancer management[63].

Recent advances in deep learning (DL) have markedly transformed the prediction of a pCR in breast cancer. Modern network architectures, including convolutional neural networks (CNNs) and transformer-based models, are capable of autonomously learning of complex and latent imaging representations directly from raw medical images, thereby minimizing reliance on predefined handcrafted radiomic features[63]. Such data-driven approaches enable the extraction of subtle phenotypic variations linked to therapeutic outcomes, offering a more holistic reflection of tumor biology. In comparative studies, DL-based frameworks have consistently outperformed traditional radiomics methods in predicting a pCR, demonstrating higher robustness and generalizability across imaging protocols and patient cohorts[60]. A comprehensive systematic review encompassing 51 studies further revealed that multimodal DL models, integrating information from multiple imaging modalities or data sources, consistently achieved superior predictive performance over single-modality systems. Notably, one representative multimodal fusion model combining MRI, histopathology, and clinical data achieved external validation area under the curve values of 0.88–0.91, underscoring the promise of integrative learning for robust response prediction[64]. Building on this concept, Gao et al. proposed a longitudinal multimodal framework (MRP) that combined serial MRI assessments with clinical parameters, demonstrating strong potential for accurately predicting NAC outcomes[65]. In addition to imaging, the convergence of radiomics with multi-omics data has emerged as a rapidly evolving frontier, enabling the creation of highly individualized predictive models. Integrating quantitative imaging signatures with clinical factors, molecular biomarkers (Ki-67, HER2, and PD-L1) and features of the tumor immune microenvironment allows for deeper biological contextualization of imaging phenotypes[66]. As depicted in the integrative multi-omics framework (**Figure 2**), extracted features from radiomics, pathomics, and molecular omics undergo harmonization before entering an AI engine utilizing advanced fusion strategies. Preliminary evidence suggests that specific radiomic patterns may serve as non-invasive indicators of tumor immune infiltration, thus offering potential utility in forecasting responses to neoadjuvant immunotherapy and expanding the role of radiomics as a surrogate for immune-oncologic characterization[67,68].

Challenges and future directions in radiomics-based pCR prediction

In summary, radiomics represents a transformative yet pragmatic approach for predicting a pCR to NAC in breast cancer, offering a level of precision that surpasses traditional imaging metrics. By extracting high-dimensional quantitative features that capture tumor heterogeneity and spatial complexity, radiomics provides an opportunity to stratify patients according to the likelihood of achieving a pCR and to refine individualized treatment pathways. However, several critical barriers still hinder widespread clinical implementation, including small and often single-institutional study cohorts, lack of standardized imaging protocols, inconsistent feature reproducibility, and limited external and prospective validation across diverse populations. Overcoming these limitations will require large-scale, multi-center collaborations, harmonized data acquisition frameworks, and adherence to rigorous methodologic standards.

Looking ahead, the integration of multimodal imaging data with complementary multi-omics information, such as genomics, transcriptomics, and digital pathology, together with advanced artificial intelligence algorithms, holds great promise for constructing robust, interpretable, and generalizable predictive models. The future of pCR prediction lies in the construction of robust, interpretable, and generalizable models that combine multimodal imaging with genomics and digital pathology. Such integrative frameworks are expected to enhance the accuracy of pCR prediction and ultimately reshape personalized NAC in breast cancer. By enabling real-time, data-driven clinical decision-making, these approaches may facilitate more precise treatment stratification and optimize therapeutic outcomes[69].

Early efficacy assessment and monitoring tumor change

Limitations of conventional treatment monitoring

The early and precise evaluation of treatment response is fundamental to guiding clinical decision-making and improving outcomes in patients receiving NAC. Timely assessment allows clinicians to adjust therapeutic regimens, identify non-responders, and implement personalized strategies that can maximize efficacy while minimizing unnecessary toxicity. Traditionally, treatment monitoring has relied on morphologic criteria, such as RECIST 1.1, which primarily assess changes in tumor size through modalities, like US and MRI. However, these diameter-based methods are intrinsically limited by delayed sensitivity, as tumor shrinkage often occurs only after several cycles of therapy, long after the underlying biological changes have begun. Consequently, non-responding patients may continue to receive ineffective chemotherapy for two or more additional cycles before disease resistance becomes apparent, subjecting non-responding patients to avoidable adverse effects and financial strain[70].

Radiomics for early detection of treatment response

In recent years radiomics has emerged as a promising paradigm to address these limitations by providing an earlier and more nuanced evaluation of therapeutic efficacy. Through the extraction of high-dimensional quantitative features from sequential imaging data and the analysis of temporal variations, an approach (delta-radiomics), which refers to the quantitative analysis of the longitudinal change in radiomic features between two or more imaging time points (e.g., pre-treatment *vs.* post-treatment scans) to capture the dynamic evolution of tumor heterogeneity, this method can detect microstructural, textural, and functional alterations that precede observable anatomic changes, thereby allowing response prediction at an earlier stage[24,25,57]. Evidence has increasingly demonstrated that radiomics applied to multi-parametric MRI, including DCE-MRI, T2-weighted imaging, and DWI with ADC mapping, can quantitatively characterize tumor vascularity, cellular density, and heterogeneity during treatment[71]. Notably, early shifts in radiomic features, often detectable after the first treatment cycle, have shown strong correlations with an eventual pCR[72]. Tracking these temporal alterations allows for the dynamic evaluation of tumor evolution, as illustrated in the standardized radiomics pipeline (**Figure 1**). These dynamic alterations mirror fundamental biological processes, such as the homogenization of tumor texture following cellular apoptosis, modifications in enhancement kinetics indicative of microvascular disruption, and reductions in entropy corresponding to decreased ITH. Together, these findings underscore the potential of radiomics to transform response monitoring in breast cancer NAC, enabling earlier, non-invasive, and biologically informed therapeutic evaluation that could ultimately facilitate more adaptive and personalized treatment strategies.

Multicenter validation and clinical evidence of radiomics models

At the level of multi-center prospective trials, the ACRIN 6698 study[50] provided compelling evidence that DWI and ADC parameters are significantly associated with the pathologic response to NAC, thereby establishing diffusion imaging as a cornerstone for early functional assessment in breast cancer. This foundational work has since informed a broad spectrum of radiomics research aimed at improving the reproducibility and predictive performance of response modeling. Subsequent multicenter investigations have demonstrated that multi-parametric MRI radiomics, integrating kinetic information from DCE imaging with microstructural metrics derived from diffusion sequences, consistently outperform single-modality or purely volumetric metrics in predicting a pCR. These findings underscore the translational importance of combining structural and functional "dual-channel" information for robust early response prediction. More recently, longitudinal or delta-radiomics approaches, defined as the quantitative analysis of temporal feature changes between serial scans (**Figure 1**), have advanced this paradigm by incorporating temporal dynamics to capture treatment-induced changes. Integrating feature variations between baseline and mid-treatment scans has been shown to substantially enhance pCR prediction accuracy. For example, Huang et al. developed a longitudinal MRI-based fusion ensemble model that combined multi-parametric features across timepoints, achieving superior performance compared to single-timepoint models and highlighting the additive value of temporal feature fusion for individualized therapy adaptation[60]. Specific mid-treatment imaging biomarkers, such as increased ADC values, reflecting reduced cellular density, and diminished enhancement heterogeneity on DCE-MRI, indicating vascular normalization, are now widely recognized as radiologic correlates of a favorable response[73].

Challenges and strategies for radiomics implementation

Conversely, persistent or increased enhancement heterogeneity has been linked to therapeutic resistance, signaling the need for timely modification of treatment regimens[74]. Despite these promising developments, substantial challenges remain before radiomics can be seamlessly incorporated into clinical workflows. Feature stability is highly sensitive to differences in

acquisition protocols, reconstruction algorithms, and segmentation variability across institutions, emphasizing the urgent need for harmonized imaging and analysis standards. Notably, the current evidence base is dominated by single-center, retrospective studies, underscoring the necessity of large-scale, prospective, multi-center validation to establish generalizability. Future directions should prioritize automated and standardized analytic pipelines, DL-based feature discovery to reduce human bias, and multimodal integration frameworks that combine imaging phenotypes with circulating biomarkers, such as circulating tumor (ct)DNA. Addressing these methodologic and translational barriers will be essential for embedding radiomics into routine breast cancer management, where radiomics holds the potential to guide timely therapeutic adjustments and enable dynamic, personalized treatment strategies.

Radiomics in the quantification of tumor heterogeneity

Clinical significance and assessment challenges of intratumoral heterogeneity

NAC has become an established first-line approach for patients with locally advanced disease within the evolving landscape of breast cancer treatment, offering the opportunity for tumor downstaging, breast conservation, and early assessment of the therapeutic response[75]. Despite widespread use, patient outcomes after NAC vary dramatically, ranging from a pCR-to-disease progression[76-78]. Such variability is largely attributed to the pervasive phenomenon of ITH, a defining hallmark of malignancy that reflects the co-existence of distinct genetic, phenotypic, and microenvironmental subclones within a single tumor[79-81]. This heterogeneity exerts a profound influence on tumor behavior, drug resistance, and treatment efficacy, rendering uniform therapeutic responses unlikely[82,83]. Conventional clinicopathologic and molecular biomarkers, typically derived from spatially limited core-needle biopsies, often have sampling bias and fail to capture the spatial and temporal complexity of ITH, thereby limiting the predictive accuracy for NAC outcomes[84]. Consequently, the development of robust, quantitative metrics that can non-invasively characterize the full spectrum of ITH has emerged as a major research focus. Briefly, radiomics addresses this clinical imperative by providing a "virtual biopsy" of the entire tumor volume, thereby reflecting the biological diversity of the whole lesion rather than a single point. Such measures could more accurately reflect the biological diversity of the entire tumor, provide a dynamic assessment of treatment sensitivity, and ultimately facilitate individualized therapeutic strategies. Recognizing and quantifying tumor heterogeneity represent a clinical imperative to refine prognostication, guide adaptive therapy, and enhance precision oncology in breast cancer management.

The current evaluation of ITH in breast cancer largely depends on genomic assays derived from single-region biopsies or histopathologic examination of tumor sections, methods that, although informative, are fundamentally limited by sampling bias and the practical difficulty of obtaining multiple spatially distinct, high-quality tissue specimens[85,86]. Because pathologic evaluation typically encompasses only a small portion or a single plane of the tumor, pathologic evaluation often fails to reflect the full spatial and molecular complexity of the lesion. This limitation underscores the urgent clinical need for non-invasive, comprehensive strategies capable of characterizing ITH across the entire tumor volume[24,26].

Radiomics as a virtual biopsy for assessing ITH

Over the past decade radiomics has emerged as a transformative solution, offering distinct advantages over traditional biopsy-based assessments. Radiomics is entirely non-invasive and can be performed repeatedly throughout the course of treatment and follow-up. Such longitudinal capability enables dynamic monitoring of tumor evolution, including spatial and temporal shifts in biological behavior, therapeutic response, and resistance mechanisms[87-89]. As a "virtual biopsy," radiomics extracts high-dimensional imaging features that capture the underlying tissue heterogeneity, serving to bridge the gap between radiologic phenotype and genomic architecture. As illustrated in the integrative multi-omics framework (**Figure 2**), this approach offers a scalable, patient-friendly means to assess ITH and support precision oncology in breast cancer.

Radiomics-based models for predicting ITH

Radiomic features quantify complex imaging textures and spatial heterogeneity that mirror underlying biological diversity within tumors and are strongly associated with patient prognosis. Radiogenomic studies have further established links between these mesoscopic imaging phenotypes and microscopic molecular alterations, such as somatic mutations, gene expression patterns, and signaling pathway activity[24,35,90]. Among available modalities, MRI remains the most sensitive technique for evaluating the response to NAC in breast cancer[91] and radiomics significantly augments the diagnostic and prognostic value[38,92,93]. For example, DCE-MRI-based radiomic analyses have enabled stratification of patients into low-, intermediate-, and high-ITH groups, each demonstrating distinct prognostic trajectories[92]. In parallel, histopathology-derived heterogeneity indices have been independently correlated with survival outcomes, highlighting the consistency between imaging-based and microscopic measures of tumor complexity[94]. Earlier texture-based radiomic investigations consistently found that greater imaging heterogeneity predicted inferior outcomes, reinforcing the prognostic relevance of spatial disorder in breast tumors[95,96]. Notably, Chitalia et al. demonstrated that MRI-derived radiomic features could categorize 95 patients with primary invasive breast

cancer into discrete ITH groups[92]. However, to address the granularity limitations of categorical assessments, more recent multicenter efforts have advanced this field by integrating a pre-treatment MRI-derived ITH index with a composite radiomic (C-radiomics) score and molecular subtype, resulting in a robust predictive framework for a pCR, achieving an AUC of 0.90 in the training cohort and 0.83–0.87 across external validation datasets[57]. Collectively, these findings underscored the capacity of radiomics to bridge imaging phenotypes and molecular biology, refining early response prediction and paving the way toward individualized treatment adaptation in breast cancer.

TNBC, which accounts for 15%–20% of all newly diagnosed breast cancers, represents one of the most aggressive and therapeutically challenging subtypes due to rapid progression, high rates of early relapse, and poor long-term prognosis[80,97-103]. Increasing recognition of the profound biological heterogeneity within TNBC has underscored the urgent need to identify subtype-specific biomarkers and therapeutic targets that can guide individualized treatment strategies. Histologic and genomic analyses have revealed that TNBC exhibits striking ITH with spatial variations in cellularity, angiogenesis, and immune infiltration contributing to treatment resistance and disease evolution[102-104]. DCE-MRI provides semi-quantitative and quantitative parameters that mirror key biological processes, such as tumor proliferation, vascular permeability, and microenvironmental dynamics, making DCE-MRI an ideal modality for characterizing spatial heterogeneity in TNBC[96]. Recent advances in radiomics, particularly clustering and voxel-wise analyses based on native DCE images and kinetic parameter maps, have demonstrated that imaging-derived metrics of ITH serve as powerful predictors of NAC response and recurrence-free survival[57,84]. Notably, a pre-treatment radiomics score derived from DCE-MRI pharmacokinetic parameters achieved an AUC of 0.80 for predicting a pCR in TNBC patients receiving NAC. The discriminatory power of the model improved to an AUC of 0.86 when integrated into a nomogram with clinicopathologic factors. Higher radiomics scores were significantly associated with larger tumor size, washout enhancement patterns, and increased androgen receptor and PD-L1 expression, suggesting a biologic link between imaging heterogeneity and the tumor immune microenvironment[72]. Further supporting this concept, Jiang et al. identified radiomic features capable of distinguishing ITH in TNBC and developed a prognostic peritumoral signature associated with immunosuppressive and metabolically reprogrammed phenotypes.[105] Building on these insights, multimodal models that integrate spatial-habitat radiomics from dynamic MRI with transcriptomic and single-cell sequencing data have emerged as promising non-invasive frameworks for pCR prediction across molecular subtypes[60]. As illustrated in our integrative multi-omics framework (**Figure 2**), bridging radiomic signatures with underlying tumor ecology allows for a more comprehensive pCR prediction. These integrative approaches capture dynamic remodeling of intratumoral habitats during therapy, thereby bridging radiomic signatures with underlying tumor ecology. Nevertheless, these models require rigorous external and prospective validation in diverse patient populations before clinical translation can be fully realized.

In summary, radiomics, especially when integrated with longitudinal imaging analyses and molecular profiling, offers a powerful, non-invasive framework for capturing the spatial and temporal complexity of breast cancer. By quantifying ITH across the entire tumor volume, radiomic approaches enable a more comprehensive understanding of tumor biology and therapeutic dynamics, ultimately enhancing the accuracy of response prediction to NAC. Through advanced computational modeling, these techniques bridge phenotypic imaging signatures with molecular and genomic alterations, supporting a more biologically informed and individualized approach to treatment evaluation. However, to achieve reliable clinical translation, the following critical steps are necessary: rigorous methodologic standardization; reproducible feature extraction; and robust biological validation across multi-institutional cohorts. Furthermore, prospective clinical trials integrating radiomic biomarkers into real-world treatment decision pathways are essential to confirm the predictive value, optimize workflow integration, and ensure that these tools evolve from research prototypes into dependable components of precision breast cancer care.

Exploration of multi-omics integration models in NAC

Rationale for integrating radiomics with multi-omics data

NAC represents both a clinical opportunity and a biological challenge in breast cancer management. NAC enables real-time, *in vivo* assessment of drug sensitivity and offers the potential to downstage tumors before surgery. In contrast, treatment response is markedly heterogeneous across patients and tumor subtypes[106-108]. Although a pCR remains a well-established surrogate endpoint for favorable long-term survival, current predictive models based primarily on clinical, histopathologic, or molecular parameters fail to fully capture the complexity of tumor behavior. The breast tumor microenvironment, which is composed of malignant epithelial cells, immune infiltrates, vascular networks, and stromal components, has a pivotal role in determining therapeutic efficacy. However, dynamic remodeling of the breast tumor microenvironment under NAC presents significant challenges for precise monitoring and prediction. Multi-omics approaches integrating genomic, transcriptomic, proteomic, metabolomic, and digital pathology data have

shown strong potential to elucidate these complex biological mechanisms. Recent investigations have emphasized the predictive significance of malignant cell proliferation rates, immune activation states, and immune evasion mechanisms in modulating NAC outcomes[80,109-112]. However, despite the biological depth, biopsy-based assays are fundamentally limited by invasiveness, temporal constraints, and sampling bias, which hinder the ability to reflect the full spatial and temporal spectrum of ITH. This limitation underscores the urgent need for non-invasive, dynamic biomarkers capable of capturing comprehensive tumor characteristics across space and time. Radiomics, by extracting high-dimensional quantitative features from standard medical imaging, has emerged as a powerful method for characterizing ITH at the whole-lesion level[84,113-115]. The advent of radiogenomics has further bridged the gap between imaging phenotypes and molecular alterations, allowing the integration of macroscopic imaging signatures with genomic profiles. This synergy enhances the biological interpretability of imaging-derived features and facilitates non-invasive prediction of actionable mutations, as well as molecular subtypes of breast cancer[116-121]. Specifically, studies in TNBC integrating MRI-based radiomics with transcriptomic and metabolomic analyses have revealed that peritumoral heterogeneity correlates strongly with immunosuppressive signaling and aberrant lipid metabolism, providing mechanistic validation for radiomics-derived biomarkers[105]. Collectively, these findings indicated that radiogenomic models are evolving beyond mere correlative tools to become functional frameworks that elucidate tumor microenvironment interactions, identify therapeutic vulnerabilities, and enhance precision risk stratification, ultimately bridging the divide between biological insight and clinical application.

Emerging radiomics-driven multi-omics fields

Radiotranscriptomics represents a rapidly expanding interdisciplinary domain that integrates radiomic features derived from medical imaging with transcriptomic signatures to elucidate the biological basis of imaging phenotypes. This approach offers promising opportunities for improving cancer diagnosis, treatment stratification, and outcome prediction by linking non-invasive imaging biomarkers with gene expression–driven tumor biology. Because transcriptomic profiles capture dynamic gene activity and reflect epigenetic and post-transcriptional regulation beyond what is detectable at the genomic level, radiotranscriptomics provides a functional layer of insight into tumor heterogeneity and therapeutic response. By directly correlating quantitative imaging features, such as texture, spatial heterogeneity, and enhancement kinetics, with transcriptome-defined molecular pathways, this field enables a deeper understanding of the biological processes that shape radiologic appearance. However, the integration of these high-dimensional data sources allows for the discovery of latent biological signals that single-modality assessments might overlook. Recent studies have identified reproducible radiomic–transcriptomic associations and have delineated transcriptome-informed imaging subtypes across multiple tumor types, suggesting that radiotranscriptomic models may serve as reliable, non-invasive biomarkers for clinical decision support[122-124].

Pathomics and radiomics provide complementary, multi-scale perspectives on breast tumor biology that together enhance the precision of predicting response to NAC. Radiomics enables quantitative assessment of the entire tumor by extracting high-dimensional features that describe the morphology, texture, temporal dynamics, and other phenotypic traits. A standard radiomics workflow, comprising image acquisition, region-of-interest segmentation, high-throughput feature extraction, feature selection, and model development, transforms conventional medical images into reproducible biomarkers with prognostic or predictive value[69,125]. Among imaging modalities, MRI is particularly valuable. DCE-MRI provides superior spatial and contrast resolution and yields quantitative insights into tumor perfusion, microvasculature, and capillary permeability, which are parameters that mammography and US cannot readily capture[126]. The predictive specificity of the model improves when integrated with DWI because the ADC serves as a quantitative surrogate for cellular density and early treatment-induced changes[127-131]. Combining radiomic features from multiple MRI sequences therefore captures distinct but complementary aspects of tumor physiology, enhancing early and accurate prediction of the therapeutic response[132-134].

Pathomics, in parallel, converts traditional hematoxylin and eosin (H&E)-stained slides into spatially resolved quantitative data by digitizing whole-slide images (WSIs) and applying machine learning algorithms to extract histomorphologic and microenvironmental attributes. Automated pathomic metrics, such as the density and spatial distribution of tumor-infiltrating lymphocytes (TILs), stromal organization, and nuclear shape irregularity, offer objective, reproducible quantification of histopathologic features linked to treatment sensitivity[135,136]. Because histopathology directly reflects local cellular composition and tissue architecture, pathomic features provide biological context that complements, and often elucidates, imaging-derived observations.

Integration frameworks and performance of multi-omics models

The integration of radiomics and pathomics thus bridges macroscopic and microscopic tumor representations, linking imaging phenotypes to underlying histologic structure and improving both the biological interpretability and robustness of predictive models. Building upon this synergy, the emerging field of radiopathomics seeks to unify imaging and histopathology data within a single analytical framework.

Radiopathomic models combine non-invasive imaging features that capture whole-tumor and temporal dynamics with digital histology descriptors that encode cellular-level context, such as immune infiltration patterns, stromal remodeling, and nuclear morphology. These models combine non-invasive whole-tumor dynamics with digital histology descriptors that encode cellular-level context, such as immune infiltration patterns and stromal remodeling. Early studies in breast cancer have demonstrated that models incorporating both MRI-derived radiomics and WSI-based pathomics outperform single-modality approaches for predicting response to NAC, supporting a "digital biopsy" paradigm in which imaging and pathology jointly inform prognosis and treatment planning without the need for additional invasive procedures. Extending this cross-scale integration to include genomic and proteomic layers further enhances biological fidelity and clinical relevance. Machine-learning frameworks that jointly analyze radiologic, pathologic, and molecular data have shown superior performance in multiple cancers[137]. For example, a multimodal model for non–small cell lung cancer integrating imaging, pathology, and genomic features achieved an AUC of 0.80 for predicting the immunotherapy response, outperforming any individual data source[138]. Similarly, Wang et al. developed an imaging-omics signature that predicted DFS in breast cancer, and through gene set enrichment and Gene Ontology analyses, linked high-risk scores to interferon-γ and immune-related pathways. Twenty-three pathomic features primarily associated with nuclear morphology and cellular organization were identified and the imaging-molecular correlations were substantiated[139].

Translational barriers and future directions for multi-omics integration

Despite notable progress, several critical barriers must be addressed before radiomics-driven multi-omics approaches can be seamlessly integrated into neoadjuvant breast cancer care. First, establishing causal relationships between imaging phenotypes and specific molecular pathways remains a fundamental challenge. Radiomic signatures frequently capture composite biological processes, such as angiogenesis, fibrosis, and immune infiltration, that are difficult to disentangle. Correlative associations alone are insufficient to elucidate the underlying mechanisms. Second, reproducibility and generalizability are constrained by technical variability in image acquisition and WSI preparation. To ensure clinical reliability, future models must adopt standardized feature extraction pipelines (e.g., IBSI-compliant software) and utilize statistical methods, like ComBat harmonization, to mitigate inter-institutional "batch effects." Third, the high dimensionality and multimodal nature of radiomics-based multi-omics models raise the risk of overfitting and compromise interpretability, limiting the clinical translation. To overcome these challenges, future research should emphasize the development of large, prospectively collected multi-center cohorts that enable rigorous external validation. Integrating circulating biomarkers, such as ctDNA and peripheral immune signatures could further complement imaging by capturing systemic treatment dynamics. Moreover, coupling radiomic data with single-cell RNA sequencing and spatial transcriptomics offers a promising avenue to spatially and functionally anchor imaging-derived features within the tumor microenvironment. As illustrated in our integrative multi-omics framework (**Figure 2**), this shift toward mechanistic validation is essential for designing interpretable and clinically actionable models. Such biologically informed validation frameworks will facilitate the shift from purely correlative radiopathomic and radiotranscriptomic studies toward mechanistic insights, ultimately supporting the design of interpretable and clinically actionable models that guide individualized NAC strategies.

Discussion

This review provides a comprehensive and critical synthesis of the evolving role of radiomics in the context of NST for breast cancer, emphasizing the multifaceted applications in predicting a pCR, monitoring early therapeutic efficacy, quantifying ITH, and facilitating integration with multi-omics frameworks. This article highlights how radiomics can non-invasively capture the complex spatial and temporal dynamics of tumor biology by systematically examining current evidence across imaging modalities and analytical methodologies. The collective data collectively demonstrate that radiomics holds significant potential to refine risk stratification, personalize treatment regimens, and support data-driven clinical decision-making. In addition, incorporation into multi-omics models underscores a broader paradigm shift toward biologically informed precision oncology, where imaging-derived phenotypes serve as quantitative biomarkers linking morphology to molecular signatures. However, as we move from bench-to-bedside, the field must transcend the "reproducibility crisis" by adopting rigorous standardization and prospective validation frameworks. Addressing these technical barriers is not merely a methodologic necessity but a clinical imperative to ensure that radiomic biomarkers are as robust as traditional histopathology. The review underscores the translational value of radiomics in bridging diagnostic imaging, tumor biology, and therapeutic optimization through this synthesis, pointing toward the future role as a cornerstone in individualized breast cancer management.

Technical challenges and reproducibility in radiomics

Radiomics has shown substantial potential in identifying patients who are likely to achieve a pCR following NAC in

breast cancer. By quantitatively extracting high-dimensional imaging features from multi-parametric modalities, such as MRI, US, and PET/CT, radiomic models, especially those enhanced with machine learning and DL algorithms, have consistently surpassed the diagnostic accuracy of traditional imaging-based assessments. These approaches enable the characterization of tumor phenotypes beyond visual interpretation, providing a data-driven means to capture subtle textural, spatial, and kinetic variations associated with treatment sensitivity. The integration of multimodal imaging, particularly combining DCE-MRI, DWI, and metabolic imaging with PET/CT, further improves predictive performance by encompassing complementary dimensions of tumor physiology, including vascularity, cellularity, and metabolic activity. Crucially, the advancement of delta-radiomics, defined as the quantitative analysis of temporal changes in radiomic features between serial imaging time points (e.g., baseline *vs.* mid-treatment), allows for the dynamic tracking of tumor evolution. This temporal perspective enables early identification of non-responders, supports timely therapeutic adjustments, and ultimately contributes to the realization of precision oncology through adaptive and individualized treatment strategies.

In addition to predicting a pCR, radiomics provides a powerful non-invasive approach for quantifying tumor heterogeneity, which is a fundamental determinant of the therapeutic response, metastatic potential, and overall prognosis in breast cancer. By extracting high-dimensional quantitative features from standard medical images, radiomics enables a more granular depiction of spatial and temporal variations in tumor phenotype that are often imperceptible to the human eye. This is particularly relevant in TNBC, a subtype characterized by pronounced molecular and morphologic heterogeneity, where the innate aggressiveness and high mutation burden drive distinct imaging signatures. In addition, radiomics-based metrics of intra- and peri-tumoral heterogeneity can uncover subtle biological processes that underlie treatment resistance or sensitivity, such as differences in angiogenesis, hypoxia, immune infiltration, and lipid metabolism. Notably, recent studies have suggested that these imaging-derived heterogeneity markers may even reflect specific metabolic vulnerabilities, including susceptibility to ferroptosis, a regulated form of cell death linked to lipid peroxidation, thereby identifying novel therapeutic entry points. Bridging these macroscopic signatures with transcriptomic and metabolomic data allows for a "digital biopsy" that circumvents the sampling bias inherent in traditional tissue assays (**Figure 2**). This integrative approach is essential for identifying precision-targeted interventions in aggressive TNBC cohorts.

The convergence of radiomics with multi-omics disciplines, including genomics, transcriptomics, proteomics, and pathomics, marks a transformative step toward a systems-level understanding of breast cancer biology. As depicted in the integrative multi-omics framework (**Figure 3**), this approach bridges macro-scale imaging with molecular signatures to provide a multi-dimensional perspective on tumor behavior. By linking imaging-derived phenotypic signatures with molecular, cellular, and histopathologic information, these integrative frameworks provide a multidimensional perspective on tumor behavior that extends beyond conventional radiologic interpretation. Radiogenomic and radiopathomic models serve as critical translational bridges between macroscopic imaging features and microscopic biological processes, thereby enhancing both the interpretability and clinical applicability of imaging biomarkers. To overcome current "correlation-only" limitations, future frameworks must transition toward biologically informed validation. This includes anchoring imaging phenotypes to single-cell RNA-seq or spatial transcriptomics to provide mechanistic context for radiomic features. Such cross-scale integration enables the characterization of tumor heterogeneity, therapeutic resistance mechanisms, and immune microenvironmental dynamics with greater precision. Emerging evidence demonstrates that these integrated models outperform unimodal approaches in predicting therapeutic response, recurrence risk, and survival outcomes across diverse malignancies, reinforcing the promise of radiomics-driven digital biopsies as complementary, non-invasive surrogates for traditional tissue-based assessments.

Despite these promises, the manuscript critically evaluates the profound technical barriers to radiomics reproducibility. The lack of consistency across scanners and protocols remains a major bottleneck for technical challenges and reproducibility in radiomics. To address this issue, current research is shifting toward harmonized imaging protocols and the mandatory use of Image Biomarker Standardisation Initiative (IBSI)-compliant software to ensure mathematical consistency. We argue that "batch effect" mitigation, using tools like ComBat harmonization, is a prerequisite for any multi-center clinical application. As summarized in this review, although radiomics has shown substantial promise in enhancing clinical classification and predictive modeling for breast cancer, the integration into routine clinical workflows remains limited. Most existing studies are retrospective in nature, often based on small, single-center cohorts with limited external validation, which constrains the generalizability and hinders clinical translation. The current gap between algorithmic innovation and real-world implementation reflects several persistent challenges, including variability in imaging acquisition and feature extraction protocols, and the absence of prospective, "model-in-the-loop" clinical trials. Addressing these challenges requires a concerted effort to move beyond retrospective proof-of-concept studies toward well-designed, prospective, multi-center trials with harmonized imaging protocols and transparent analytical pipelines. Notably, future research should emphasize clinical interpretability, model calibration, and decision-curve analysis to ensure that radiomics-based models not only achieve statistical accuracy but also deliver actionable value

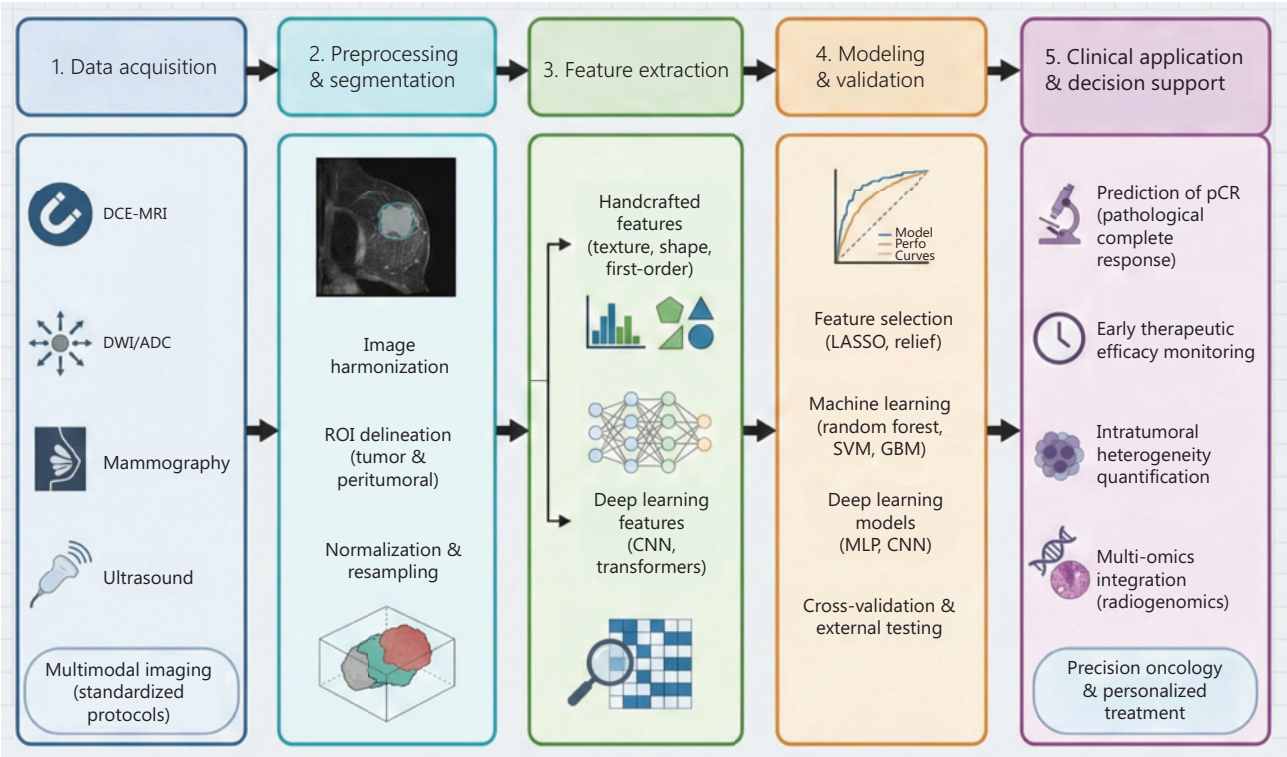


Figure 3 Multi-omics integration for precision oncology. The framework transitions from data-to-decision support: (1) inputs, merging macro-scale radiomics, micro-scale pathomics, molecular omics, and clinical data; (2) AI engine, feature harmonization followed by multimodal fusion (early/late/deep) using CNNs and transformers; (3) explainability, XAI modules for biological interpretation; and (4) endpoints, actionable insights for pCR prediction, "digital biopsies," and improved clinical outcomes. CNNs: convolutional neural networks; DWI: diffusion-weighted imaging; DCE-MRI: dynamic contrast-enhanced MRI; GBM: Gradient Boosting Machine; MLP: Multi-Layer Perceptron; CNN: Convolutional Neural Network; SVM: Support Vector Machine.

in personalized treatment planning. The establishment of open, annotated imaging databases and adherence to emerging reporting standards, such as TRIPOD-AI and CLAIM, will be essential to promote transparency, reproducibility, and regulatory readiness. Ultimately, bridging the translational gap in radiomics will depend on integrating robust methodologic rigor with clinically meaningful endpoints to facilitate its adoption as a reliable decision-support tool in precision breast cancer management.

Improving model interpretability and clinical usability

The interpretability of radiomic features and models is crucial for clinical confidence yet remains challenging, particularly for DL-based approaches. For conventional hand-crafted features, tree-ensemble algorithms, such as random forests and gradient-boosting decision trees, provide feature-level contributions to model outputs, improving transparency by ranking features according to the relative importance[140]. However, ensemble-based importance estimates may be unstable, prompting the adoption of game-theory-driven methods, such as Shapley additive explanations (SHAP), which quantify each feature contribution to individual predictions[141]. SHAP, including its DeepExplainer extension, enables interpretation of DL-derived features by leveraging gradients within neural networks and has been applied in breast cancer radiomics to elucidate handcrafted and DL feature relevance[142]. Spatial interpretability techniques, such as class activation maps (CAMs), Grad-CAM, and adaptive learning-based CAM, highlight salient image regions associated with diagnostic predictions for CNN models, facilitating visual validation of model reasoning[143]. Future DL radiomics research should explore architectures incorporating attention mechanisms, transformers, and graph-based networks, as well as longitudinal designs that integrate on-treatment imaging, given preliminary evidence suggesting performance improvements with mid-treatment data. Concurrently, addressing the "black-box" of DL models remains imperative. Methods, such as saliency mapping, layer-wise relevance propagation, and concept-based explanations or hybrid frameworks combining DL feature extraction with transparent classifiers, offer potential to

reveal biologically and clinically meaningful imaging patterns. Sustained evaluation and publication of DL feature reproducibility will be essential to advance interpretable radiomics and DL tools toward dependable clinical application. Ultimately, interpretability must bridge the gap between "black-box" predictions and biological "ground truth," such as anchoring imaging phenotypes to spatial transcriptomics or single-cell RNA-seq to decode the underlying tumor microenvironment.

The reproducibility of radiomic findings across external cohorts and public databases largely depends on model robustness, which can be compromised by methodologic limitations, such as small sample sizes, inadequate quality control, overfitting, and batch effects arising from imaging heterogeneity. To mitigate these challenges, robustness assessments have been implemented. For example, Robinson et al. applied a two-state evaluation across mammography vendors[144], while Granzier et al. demonstrated that 41.6% and 32.8% of RadiomiX and Pyradiomics features, respectively, remained stable despite segmentation variability[145]. Establishing large, high-quality datasets remains fundamental. Lambin et al. emphasized the "4Vs" of big data (volume, variety, velocity, and veracity[69]) and initiatives, such as CancerLinQ are consolidating clinical data to facilitate robust model validation[146]. Well-structured studies further exemplify this standard, as occurs in an axillary lymph node metastasis prediction model validated across large discovery, external, and prospective cohorts (N = 234, 723, and 81, respectively), which achieved accuracies of 0.93, 0.90, and 0.97, respectively, underscoring the importance of rigorous validation[147]. Nonetheless, for clinical implementation, predictive performance alone is insufficient. Interpretability and user engagement are equally critical. Integrating explainable AI frameworks to elucidate key imaging or genomic determinants, establishing clinician feedback loops, promoting data-sharing participation, and maintaining continual model reassessment will be essential to strengthen trust, ensure robustness, and enhance the generalizability of radiomic models.

We propose a roadmap where future validation strategies focus on meaningful clinical endpoints, not just AUC, but survival benefit, morbidity reduction, and resource utilization. Prospective, real-time clinical trials should enroll patients in which imaging and omic data are processed through the model to generate predictive outputs with resulting model-guided treatment decisions compared to those trials following standard-of-care protocols. These studies must assess not only diagnostic performance metrics, such as sensitivity and specificity for predicting pCR, but also real-world clinical impact, including whether model-guided therapy improves survival outcomes, decreases treatment-related morbidity, or enhances resource utilization. Randomized trial designs may compare standard NAC with model-adapted NAC regimens to determine, for instance, whether patients predicted as non-responders can safely avoid ineffective or toxic treatments. Only through prospective evidence demonstrating both predictive accuracy and tangible clinical benefit can radiomic methodologies transition from investigational tools to validated components of routine clinical decision-making.

Validating the robustness and generalizability of radiomic models necessitates external testing on large, multi-center cohorts or publicly accessible databases, which in turn requires close collaboration among medical institutions, ideally spanning multiple countries. Integrating data from diverse centers and shared repositories enables the inclusion of variations arising from different imaging devices and patient populations, thereby providing a more comprehensive assessment of model stability across heterogeneous clinical environments. Increasingly, recent breast cancer studies have underscored the importance of such rigorous external validation and early investigations, both from other groups and our own center, have demonstrated the utility of independent evaluation on external datasets. Looking ahead, broader multi-center collaborations and open-access consortia are expected to accelerate large-scale, independent validation; only through consistent performance across diverse clinical contexts can radiomic models achieve the level of generalizability necessary for widespread clinical implementation.

The clinical translation of radiomics is currently impeded by significant hurdles regarding reproducibility and standardized validation. A primary source of instability is the variability in image acquisition parameters, such as reconstruction kernels, slice thickness, and tube current across different scanner manufacturers. These variations can introduce non-biological noise that outweighs the underlying tumor-specific signals.

To mitigate these effects, preprocessing standardization, including voxel resampling, gray-level discretization, and intensity normalization, is no longer optional but a prerequisite for multi-center studies. Furthermore, the lack of transparency in feature calculation formulas has historically led to disparate results across different software platforms. We emphasize the critical necessity of employing IBSI-compliant software to ensure that extracted features are mathematically consistent and verifiable. Without such rigorous adherence to technical standards, the "radiomic signature" remains a local phenomenon rather than a robust clinical biomarker.

Radiomics represents a critical interface connecting macroscopic imaging phenotypes with the underlying biological mechanisms. Future modeling efforts are anticipated to not only assist clinical decision-making but also elucidate associations between quantitative imaging features and pivotal molecular events. An emerging and promising trend is the evolution from radiogenomics toward radio-multi-omics, which integrates genomics, transcriptomics, proteomics, metabolomics, epigenomics, pathomics, and clinical data. This integrative framework leverages the complementary strengths of different omic layers, enabling a more comprehensive understanding of tumor biology and enhancing predictive accuracy. For example, imaging-derived features can correspond to specific genetic

mutations, immune activity signatures, or epigenetic alterations, and recent breast cancer studies have identified actionable biomarkers, such as the RRP9–JUN/AKT axis and immune modulatory pathways, that influence therapeutic response. Incorporating these molecular correlates into radiomic models holds the potential to improve pCR prediction and yield mechanistic insights extending beyond imaging alone. To realize this vision, future research should prioritize the systematic collection of paired imaging-omic datasets and the development of DL architectures capable of integrating heterogeneous data sources, thereby advancing radio-multi-omics toward clinically robust and biologically meaningful applications.

Conclusions

In conclusion, this review summarizes the current applications of radiomics in NAC for breast cancer, emphasizing its emerging role in assisting radiologists and clinicians in clinical decision-making. Although challenges to clinical translation persist, radiomics shows strong potential to enhance neoadjuvant treatment strategies through early response evaluation, improved outcome prediction, and individualized therapeutic planning. With continuous technological advancement and closer interdisciplinary collaboration, radiomics is poised to become an essential component of precision oncology, bridging diagnostic imaging with clinical oncology practice.

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Conflicts of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Kun Wang.
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Wrote the paper: Yilin Chen, Teng Zhu, Yuhong Huang.

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