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Progress on radiomics and radiogenomics and their applications in breast cancer: A survey

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ABSTRACT

Radiomics is an emerging analytical approach in the medical field that extracts high-throughput quantitative features from multiple imaging data and builds models for cancer diagnosis, prognosis, and treatment by machine learning or deep learning. Radiomics allows radiologists to obtain a more complete picture of the tumor in a noninvasive way than by reading radiographs. Radiogenomics incorporates genomics on top of radiomics to analyze the potential relationship between imaging features and tumor genetic status, enabling biological profiling of the causes of tumor heterogeneity, and its development of biomarkers will be of great help for personalized treatment. Breast cancer is the most prevalent cancer among women worldwide today, and this survey aims to summarize the progress on radiomics and radiogenomics, their applications in breast cancer, and discuss the issues that need to be addressed before radiomics and radiogenomics can be used in clinic. From the literature, it can be concluded that radiomics and radiogenomics have a high potential for differentiating malignant and benign breast lesions to assess breast cancer types and lymph node status, as well as to predict neoadjuvant chemotherapy response, risk of recurrence and survival outcomes, especially in the context of the rapid development of artificial intelligence technologies, promising early realization of precision medicine.

KEYWORDS

Radiomics; Radiogenomics; Breast cancer; Application; Medical image

1 Introduction

Breast cancer is a common form of cancer in women worldwide, and its incidence has remained high in recent years. Early diagnosis and treatment are important for controlling mortality in breast cancer patients (Ginsburg et al., 2020). Diagnosis and screening of breast cancer is often performed through various medical imaging modalities, such as digital mammography (DM), ultrasound (US), digital breast tomosynthesis (DBT), computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) (Chong et al., 2019; Kashyap et al., 2022; Sollini et al., 2021). In the identification and diagnosis of lesions, MRI is of high specificity and sensitivity (Mann et al., 2019). However, due to the limitations of the imaging technology itself, it is difficult to ensure the accuracy of diagnosis by

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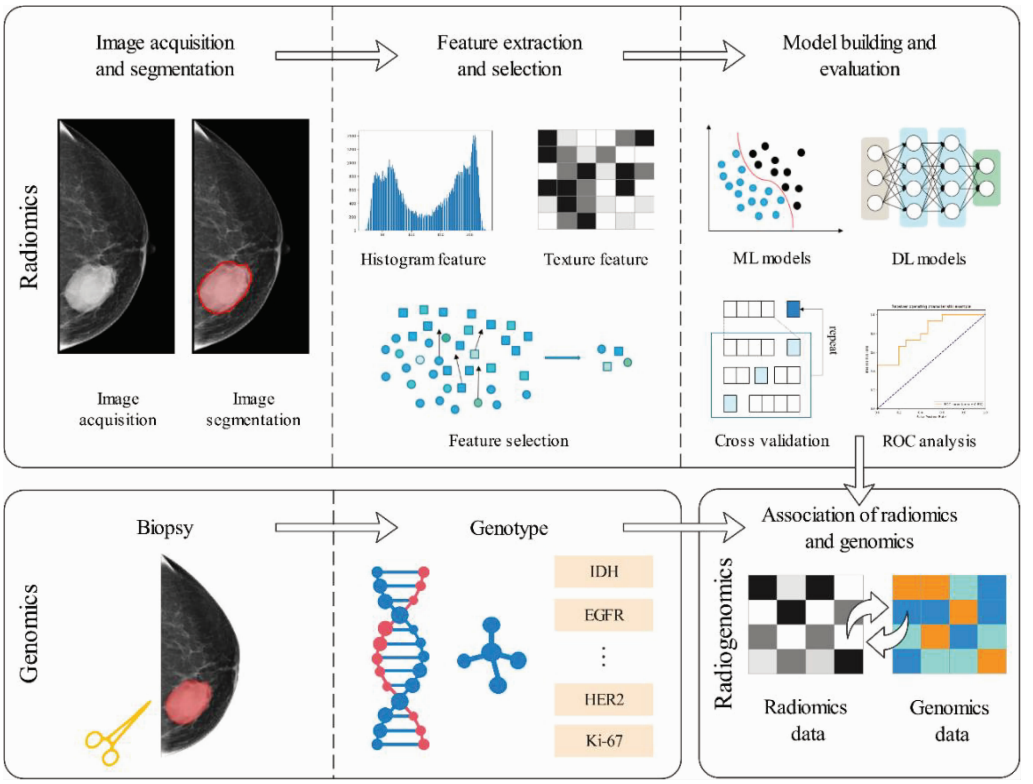
qualitatively evaluating the medical images alone (Satake et al., 2022). To avoid false positives, patients often need to receive invasive and expensive biological examinations (Bi et al., 2019; Tagliafico et al., 2020).

With the advancement of medical image analysis and artificial intelligence technology, radiomics has proven to be a promising tool for providing a comprehensive representation of tumor biology (Pinker, Chin, et al., 2018). Radiomics extracts a variety of quantitative features that the naked eye cannot see from large-scale radiological images and links quantitative imaging data with meaningful clinical endpoints, thereby enhancing the identification and predicting potential of medical imaging (van Timmeren et al., 2020). Indeed, the existence of tumor heterogeneity, both intratumoral and peritumoral (Pesapane et al., 2021), leads to the fact that no treatment is a one-size-fits-all approach and may have different clinical outcomes or different treatment responses in different patients or even in different tumor sites in the same patient (Bonin & Stanta, 2020). Radiogenomics incorporates genomics on top of radiomics, which focuses on the relationship between extracted radiomic features and underlying molecular features at the genomic level (Gallivanone et al., 2022), which may improve the identification of the underlying biological basis of the imaging phenotype (Wu et al., 2018). In the new era of precision medicine, the generation of imaging biomarkers can help to develop personalized immunotherapy regimens and improve the prediction of clinical outcomes (Conti et al., 2021; Pinker, Shitano, et al., 2018).

In this survey, we first outline the workflow of radiomics and radiogenomics, particularly for the extraction, selection, and analysis of radiomic features. Next, by reviewing previously published studies, we summarize the application of radiomics and radiogenomics in differentiating benign and malignant breast cancer lesions, assessing tumor staging and grading, predicting response to neoadjuvant chemotherapy (NAC), and predicting risk of recurrence and survival outcomes. We conclude with a discussion of the limitations and challenges faced by radiomics and radiogenomics analysis methods in the present day, and the significance of artificial intelligence technologies in facilitating relevant research to make them more useful in clinical practice.

2 Radiomics and radiogenomics workflow

Radiomics studies use quantitative imaging methods to correlate multimodal image features with clinical outcomes. Radiogenomics expands the scope of radiomics by correlating the phenotypic information of each cancer patient with its genotypic information (e.g., IDH, EGFR, PTEN, HER2, and Ki-67) (Story & Durante, 2018). Specifically, on the one hand, based on the extraction of radiomics data and genomics data, genotype-phenotype association analysis can be further performed. For example, through the commonly used genome-wide association analysis method, we can find the genetic variants associated with certain disease phenotypes; or the association analysis of gene expression and imaging features can be used to screen the imaging markers that reflect the gene expression activities, which can be used as a reference guide for the screening and diagnosis of diseases. On the other hand, by fusing radiomics data with genomics data as input to the machine learning algorithms, the results of disease diagnosis, risk or prognosis can be predicted. The workflow of radiomics and radiogenomics is shown in Figure 1.



ML: machine learning; DL: deep learning; ROC: receiver operator characteristic curve

Figure 1 Radiomics and radiogenomics workflow

2.1 Image acquisition and segmentation

The standardized acquisition of images is the first step in radiomics. DM, US, DBT, CT, PET, and MRI examinations are often used for breast imaging, and these multimodal images can provide different information. It is important to note that the images acquired differ when the same tumor is visualized using different imaging machines, imaging parameters, and image reconstruction parameters (Hoshino & Yokota, 2021). Therefore, for quantitative image analysis, uniformity of imaging equipment at the time of image acquisition and standardization of image data acquisition methods are necessary; otherwise, this can reduce the reproducibility and repeatability of radiomics models (European Society of Radiology, 2020; C. Huang et al., 2021). In addition, preprocessing means such as pixel or voxel resampling and image alignment can also reduce the impact of the acquisition/reconstruction protocol (Scapicchio et al., 2021).

Next, the region of interest (ROI) needs to be segmented. There are many reliable semiautomatic and automatic segmentation methods that overcome the subjectivity and time-consuming problems associated with manual segmentation by radiologists, especially when dealing with large datasets (Huang et al., 2018; Jiang et al., 2019; Maffei et al., 2021; Xu et al., 2019). Semiautomatic methods include threshold-based and region-based segmentation methods, and automatic methods include fuzzy C-mean automatic segmentation and U-Net. U-Net is a deep learning method that requires supervised training, while fuzzy C-mean clus-

tering is an unsupervised method that can classify images into different clusters. However, in cases where expert knowledge is needed, manual segmentation by experienced radiologists is still the "golden standard" (Lee et al., 2020). There is no universal segmentation method with high accuracy, and it is necessary to choose a suitable segmentation method according to the actual conditions.

2.2 Feature extraction and selection

The segmentation of the ROI determines the size and location of the tumor or lesion and prepares for the feature extraction and feature selection that follows. Feature extraction is the process of generating candidate parameters or biomarkers for classification or prediction by various image processing methods or convolutional neural networks (CNNs) (Tran et al., 2019; B. Zhang et al., 2020). Feature extraction requires the extraction of a large number of features, often more than 1000, and the number may even larger in the case of feature extraction by means of deep learning networks. The process of feature selection requires analyzing and computing statistical associations between features and specific tasks or outcomes to remove redundant features, leaving independent and repeatable features, and to prevent overfitting from occurring (Fusco et al., 2022; Park et al., 2019; Rogers et al., 2020; Shur et al., 2021). Overfitting refers to the fact that the performance of the model in the testing phase is significantly different compared with the training phase, resulting in a model that is too unstable and thus unable to meet the needs of model prediction or classification (Mutasa et al., 2020).

Manually extracted radiometric features can be broadly classified into four categories: morphological features, histogram-based features, texture-based features, and transformation-based features (Aerts, 2016; Aerts et al., 2014). Morphological features here are different from the qualitative description of morphological structure in semantic features (Yip et al., 2017), which reflect physical features such as shape and size of ROI by calculation, including surface area, volume, compactness (Tello & Ibanez, 2018), and sphericity (van Griethuysen et al., 2017). Histogram-based features are also known as first-order statistical features, which characterize the intensity information of pixels or voxels in the ROI, such as the mean, standard deviation, kurtosis, and skewness. Texture features are second-order statistical features that express the relationship between adjacent pixel or voxel intensities and thus can be used to measure tumor heterogeneity (Chitalia & Kontos, 2019). The grayscale covariance matrix (GLCM) is one of the most commonly used second-order features in radiomics studies, which combines the grayscale and gradient information of the image, through which statistics such as entropy, contrast, and energy can also be calculated (Bartoli et al., 2020). Additionally, the local binary pattern is a representative model for texture analysis (Kolla et al., 2022). The transform-based features can be obtained by fractal analysis and wavelet transform (Parmar et al., 2015). They provide richer detailed information and belong to higher-order statistics. Today, when open sharing of resources is encouraged, there are many convenient tools to extract these radiomics features, such as PyRadiomics, TexRAD and ITK.

After feature extraction, it is vital in radiomics research to perform appropriate feature selection and dimensionality reduction to balance the number of features with model performance. There are three types of methods for feature selection: filter, wrapper and embedding methods (Avanzo et al., 2020). Filter methods rank and select features based on statistical correlations (e.g., Pearson correlation coefficient, chi-square test), where multivariate fil-

ters remove redundant features (Rizzo et al., 2018). Wrapper methods use algorithms with recursive feature elimination for further feature selection, such as the Las Vegas Wrapper. Embedding methods integrate the feature selection process with the model training process, such as the least absolute shrinkage and selection operator (LASSO), random forest, and decision tree. In contrast, principal component analysis is an unsupervised feature dimensionality reduction method that compresses features to a lower dimension (Anne-Leen et al., 2022).

The extraction and selection of deep features do not require excessive human intervention and can be performed automatically in different layers of the same CNN (Huang et al., 2022). However, due to the small number and size of medical image datasets, it is difficult to train CNN models from scratch, so pretraining of models is often performed by migration learning, such as the commonly used natural image dataset ImageNet, to alleviate the limitations of small datasets (Castiglioni et al., 2021; Le et al., 2019). Although deep learning models have difficulty in interpreting the results of feature selection, their powerful automatic analysis and big data processing capabilities will bring new possibilities to radiomics.

2.3 Model building and evaluation

A statistical or machine learning model suitable for the study task is developed based on the feature dimensionality and the sample (Anagnostopoulos et al., 2022). For the classification task, various classifiers can be used, including Naive Bayesian, support vector machine (SVM), random forest, and XGBoost classifiers, which are commonly evaluated by the area under the receiver operating characteristic (ROC) curve (AUC) (Liu et al., 2022; Nakamoto et al., 2018). For survival analysis, Cox proportional risk regression models, randomized survival forests, and support vector survival were used to predict the survival time of patients, and Harrell's concordance index (C-index) was commonly used to assess the discriminatory ability of the model (Longato et al., 2020). After training, the best way to validate the model to obtain a model with good generalization is to use independent datasets from different centers for external validation. Usually we can use some open databases, such as the Cancer Genome Atlas Initiative (the Cancer Genome Atlas, TCGA, 2012) and the Cancer Imaging Archive (TCIA) (Clark et al., 2013) to accomplish external validation. When external data is not available, then internal validation is needed. Internal validation requires splitting all sample data into training and validation datasets, and the most commonly used methods are cross-validation (CV), k-fold CV and leave-one-out CV (LOOCV) (Collins et al., 2015; Little et al., 2017; Wong, 2015).

3 Radiomics and radiogenomics application in breast cancer

By extracting quantitative features from a variety of medical images and combining them with tumor genomic analysis, radiomics and radiogenomics have yielded numerous applications in breast cancer to inform the diagnosis, treatment, and prognosis of the patients. These applications include differentiation of benign and malignant lesions, evaluation of tumor types and grades, prediction of lymph node metastasis, prediction of response to NAC, prediction of cancer recurrence risk and survival outcomes.

3.1 Differentiation between malignant and benign lesions

Early detection of breast cancer can contribute to patient prognosis. Recent studies have shown that radiomics has positive implications in the differentiation of benign and malignant

breast lesions, and a summary of these studies is presented in Table 1. Wang et al. (2020) demonstrated that DM-based radiomics can accurately discriminate between benign and malignant round-like tumors with circumscribed or obscured margins but without suspicious malignant or benign macrocalcifications. The authors retrospectively studied 112 patients with round tumors treated for diabetes mellitus within 20 days prior to surgery, and ten radiomic features were extracted from DM images of each patient, which included one shape feature, one histogram feature, one texture feature and seven GLCM features, resulting in an AUC of 0.88. Stogiannos et al. (2023) used only radiomic features derived from postcontrast T1 weighted -MRI sequences and apparent diffusion coefficient (ADC) maps for the evaluation of breast pathologies, followed by texture analysis and a 5-fold CV machine learning classification algorithm, providing a promising new tool for the differentiation of benign and malignant lesions.

Radiomic features extracted from US and DBT have also been shown to be useful in the differentiation of breast lesions. Fujioka et al. (2019) extracted deep features from US images based on CNN models to identify benign and malignant breast lesions. This study confirmed that the deep learning radiomics model had equal or better diagnostic performance than radiologists on a test dataset with 120 breast lesions. Tagliafico et al. (2018) first applied radiomic analysis to DBT in a substudy of a multicenter prospective study with good results in differentiating cancerous from normal breast tissue in patients with dense breasts. Niu et al. (2022) demonstrated that a radiomics map combining DBT radiomics features and clinical factors (age and menstrual status) could assist in the clinical diagnosis of breast cancer and showed the best discriminatory performance in the validation cohort (AUC = 0.985).

The malignancy of breast lesions is often assessed with the aid of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS). However, lesions of BI-RADS 4 have different probabilities of malignancy (2%-95%) (Leithner et al., 2017; Strigel et al., 2017) and are considered suspicious lesions. Several studies have shown that radiomics can help improve the diagnosis of this category of lesions to reduce unnecessary biopsies. Lyu et al. (2023) demonstrated that radiomic features based on ultrafast DCE-MRI (using differential subsampling with the cartesian ordering technique) combined with artificial neural networks can classify MR BI-RADS category 4 lesions as benign or malignant with AUC values of 0.915-0.956. A retrospective study (Zhang et al., 2021) combined three MRI sequences, dynamic contrast-enhanced (DCE) imaging, diffusion weighted imaging (DWI) and T2 weighted image (T2WI), to build a radiomics model and screened 12 features by Pearson correlation, LASSO and logistic regression (LR). In the test cohort, the best model constructed from the 12 features of the three sequences had an AUC value of 0.939 and an accuracy of 0.931, demonstrating better performance of the multimodal fusion model in predicting the benignity and malignancy of BI-RADS 4 breast lesions. In fact, a combined model of radiomics and BI-RADS score has also been developed. Zhang et al. (2023) combined the BI-RADS score with three features extracted from ADC images, T2WI and DCE-derived kinetic mapping to build the model and obtained the highest AUC of 0.975 in an external cohort with 50 lesions.

In conclusion, these studies fully demonstrate the tremendous role of radiomics in differentiating benign and malignant breast lesions. Compared with traditional radiologist review, the radiomic model has significant advantages, such as reducing the false positive rate of suspicious lesions and unnecessary biopsies.

Table 1 Studies differentiating between malignant and benign breast lesions by radiomics and radiogenomics

Reference	Imaging Modality	Number of Patients	Radiomic Features	Purpose	Results
Wang et al. (2020)	DM	112	Histogram, shape and texture features	Differentiate between benign and malignant round–like (round and oval) solid tumors	AUC=0.88
Stogiannos et al. (2023)	MRI	52	First–order and texture features	Differentiate between malignant and benign breast lesions	Sensitivity=70%, Specificity=66%, Accuracy=67%
Fujioka et al. (2019)	US	355	Deep features from CNN model	Discriminate between benign and malignant breast mass images from ultrasound	Sensitivity=0.958, Specificity=0.925, Accuracy=0.925, AUC=0.913
Niu et al. (2022)	DBT	185	First–order, shape–based, texture features and deep features from VGG model	Differentiate between malignant and benign breast lesions	Sensitivity=0.909, Specificity=0.966, AUC=0.985
Lyu et al. (2023)	Ultrafast DCE–MRI	173	Histogram, shape and texture features	Differentiation of MR BI–RADS 4 breast lesions	artificial neural networks models with AUC values of 0.915–0.956
Zhang et al. (2021)	MRI	216	First –order, 3D shape –based and texture features	Differentiation of MR BI–RADS 4 breast lesions	Sensitivity=0.932, Specificity=0.923, Accuracy=0.931, AUC=0.939
Zhang et al. (2023)	MRI	222	Shape, histogram and texture features	Construct an automatic radiomics –based pipeline to improve the diagnosis of breast lesions	Sensitivity =0.920, Specificity =0.923, AUC =0.975 (The joint model using both radiomics score and BI–RADS score)

DM: digital mammography; MRI: magnetic resonance imaging; US: ultrasound; DBT: digital breast tomosynthesis; DCE: dynamic contrast-enhanced; CNN: convolutional neural network; VGG: Visual Geometry Group; BI-RADS: Breast Imaging Reporting and Data System; AUC: area under the curve

3.2 Evaluation of tumor molecular subtype and lymph node status

Molecular staging of breast cancer is performed clinically by immunohistochemistry (IHC) and is divided into four main staging categories by measuring estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), and Ki-67 index: luminal A, luminal B, HER2 overexpression, and triple-negative breast cancer (TNBC) (Blaschke & Abe, 2015; Fiordelisi et al., 2019).

In a multicenter exploratory study, Ming et al. (2022) identified heterogeneity in DCE-MRI radiomic features, indicating that different imaging subtypes have different clinical outcomes, which could contribute to the exploration of biomarkers for predicting clinical outcomes in breast cancer. For example, breast tumors that are larger in size and exhibit rapid enhancement patterns usually have the worst prognosis. Saha et al. (2018) studied the pre-

operative DCE-MRI radiomic features of 922 patients with invasive cancer, of which data from 461 patients were trained and data from the remaining 461 patients were used for external validation. The multivariate model predicted an AUC of 0.697 for luminal A, an AUC of 0.654 for TNBC, an AUC of 0.649 for ER status, and an AUC of 0.622 for PR status, demonstrating the value of DCE-MRI radiomic features. Zhang et al. (2020) demonstrated that the ADC-based radiomic LR model with 11 radiomic features from the ADC map was a feasible predictor of the Ki-67 index in patients with invasive ductal breast cancer, with an AUC of 0.75.

MRI-based multiparametric radiomics combined with a machine learning approach provides a promising approach for the noninvasive prediction of molecular subtypes of breast cancer. Huang et al. (2021) performed radiomic analysis using multiparametric MRI, including DCE-MRI, T2WI and ADC maps, and used different classification algorithms to predict molecular subtypes of breast cancer. The multilayer perceptron (MLP) model showed the best performance under LOOCV, in distinguishing TNBC from non-TNBC (AUC=0.965 with 92.6% accuracy) and in identifying HER2 expression (AUC=0.840 with 79.0% accuracy). In addition, Xie et al. (2019) considered the influence of textural features by imaging parameters and evaluated the accuracy of four immunohistochemical (4-IHC) tumor subtype classifications and TNBC versus non-TNBC by radiomic analysis combining DCE images varying at six time points and DWI images varying at three b values. The authors retrospectively studied 134 patients with pathologically confirmed invasive ductal carcinoma, and in the article proposed a two-stage feature selection method combining traditional statistics and machine learning-based features. Ultimately, for the 4-IHC tumor subtype classification task, the best accuracy of 72.4% was obtained by combining 20 selected features. The highest accuracy of 91.0% was obtained when comparing TNBC and non-TNBC, while the highest accuracy was 83.6% when using DWI sequences alone. Fan et al. (2020) used a multitask learning framework to jointly predict Ki-67 and tumor histological grade by extracting morphological, statistical, and textural features on DWI and DCE-MRI sequence precontrast and subtraction images, ultimately achieving AUCs of 0.811 and 0.816, respectively, obtaining results superior to those of a single-task-based model.

Although MR imaging has been used extensively for the prediction of molecular subtypes of breast cancer, several studies have focused on radiomic features in DM, US and CT. Ge et al. (2022) reported significant differences in the performance of DM between the TNBC and non-TNBC groups ($P<0.001$) and an AUC of 0.809 in external validation to distinguish TNBC from non-TNBC, demonstrating the value of DM-based radiomic features. Wang et al. (2022) used radiomics to study 300 patients with breast cancer who underwent conventional chest CT and successfully differentiated between ductal and nonductal breast cancers in internal validation (AUC=0.842). Cui et al. (2023) developed a radiomic model based on a logistic classifier and an ultrasound radiomic feature (URF) module, which predicted HER2 status in cancer with relative accuracy (AUC=0.80). The authors used Pearson correlation analysis to calculate correlations between differential URFs and HER2-related genes, identifying eight distinct URFs ($P<0.05$). The biological function of each URF was then obtained by functional enrichment analysis. Among them, regional entropy was found to be associated with immune cell activity and could regulate the generation of cancer calcification. Fan et al. (2022) demonstrated that CT radiomics analysis could be used to assess the status of ER, PR, HER2 and Ki-67 in patients with breast carcinomatosis. In this study, CT images of 108 patients with breast carcinomatosis at three stages were used to extract radiomic features, including

nonenhanced, arterial and portal phases, and the 20 most predictive features were selected after each stage by the LASSO method, with the final combined model of radiomic features at the three stages achieving the best overall performance. The AUCs for predicting ER, PR, HER2, and Ki-67 status were 0.870, 0.797, 0.981 and 0.726, respectively.

The assessment of axillary lymph node (ALN) and sentinel lymph node (SLN) status helps to determine the clinical staging of breast cancer disease (Dong et al., 2018; Kim et al., 2018). Machine learning -based DCE-MRI radiomics is also important for the accurate prediction of ALN and SLN metastasis, and this assertion was demonstrated in a meta-analysis (J. Zhang et al., 2022). By combining features derived from DCE-MRI of the primary tumor with machine learning models, Liu et al. (2019) demonstrated the feasibility of a radiomics approach to predict SLN metastasis. These authors also compared three classification models, including LR, XGBoost and SVM classifiers, with SVM ultimately showing the best performance (AUC=0.85). Song et al. (2021) studied fluorodeoxyglucose PET/CT images and used the XGBoost algorithm to select features and build a radiomic model to predict ALN metastasis with 80% accuracy, which is higher than the accuracy of diagnosis by PET/CT images only.

In summary, radiogenomics attempts to obtain molecular subtypes of tumors in a noninvasive manner by obtaining radiomic features from various imaging modalities (DM, US, MR and PET/CT) and correlating them with the genomic status of the tumor. Some studies have also predicted lymph node metastasis and histological grade, which can assist in determining the stage of the tumor, facilitating the assessment of prognosis in different patients, and personalizing the treatment plan.

A summary of these studies can be found in Table 2.

3.3 Prediction of response to NAC

NAC is a preoperative treatment for breast cancer designed to reduce the stage of the tumor and even allow patients who need mastectomy to undergo breast-conserving surgery (Early Breast Cancer Trialists' Collaborative, 2018). Response to NAC is generally assessed by the reduction in tumor size after several cycles of NAC (Therasse et al., 2000). Pathologic complete remission (pCR) after NAC is considered clinically good outcome because patients who achieve pCR have an improved survival rate (Conforti et al., 2021). However, the mean pCR rate of breast cancer patients was only 19%, ranging from 0.3% to 50.3% (Reig et al., 2020). According to previous studies (Cortazar et al., 2014; Haque et al., 2018; Wang & Mao, 2020), different tumor subtypes lead to different pCR rates, so it is necessary to know the tumor subtypes before NAC; otherwise, not only is the treatment ineffective, but it may also lead to patients suffering from potential side effects.

In recent years, the application of radiomics and radiogenomics in predicting pCR in breast cancer has evolved, especially in HER2-positive breast cancer and TNBC (Murphy et al., 2018). MRI, especially DCE-MRI, has been used extensively to assess response because DCE-MRI not only describes morphological features but also contains pharmacokinetic features of contrast agent in breast tumors with blood flow information (Pesapane et al., 2023; Tsougos et al., 2018). Caballo et al. (2023) used DCE-MRI preprocessed images to extract radiomic features of the tumor and peritumor region, and completed model training and validation with LR models and LOOCV. In this study, nine features associated with textural temporal changes and enhanced kinetic heterogeneity were significant in distinguishing cases achieving pCR from non-pCR. The LR model achieved significant AUCs of 0.707 (all cancers),

Table 2 Studies evaluating tumor molecular subtype and lymph node status by radiomics and radiogenomics

Reference	Imaging Modality	Number of Patients	Radiomic Features	Purpose	Results
Saha et al. (2018)	DCE–MRI	922	A comprehensive set of features	Evaluation of the association between tumor molecular biomarkers and imag-	AUC=0.697 (luminal A), AUC=0.654 (TNBC), AUC=0.649 (ER), AUC=0.622 (PR)
Zhang et al. (2020)	DWI–MRI	128	First–order, shape–based and texture features	Predict the Ki–67 proliferation index in patients with invasive ductal breast cancer	Sensitivity=0.71, Specificity=0.70, Accuracy=0.70 AUC=0.72
Huang et al. (2021)	MRI	162	First –order, 3D shape –based and texture features	Predict molecular subtype and androgen receptor expression of breast cancer	Accuracy =85.8% and AUC=0.907 (AR); Accuracy =92.6% and AUC=0.965 (TNBC); Accuracy =79.0% and AUC=0.840 (HER2); Accuracy =82.1% and AUC=0.860 (HR+/HER2– *vs.* others)
Xie et al. (2019)	MRI	134	Shape, texture and sequential features	Classification of IHC subtypes of breast cancer	Accuracy=72.4% (4–IHC classification), Accuracy=91.0% (TNBC)
Fan et al. (2020)	MRI	144	Morphological, statistical and texture features	Prediction of histologic grade and Ki–67 proliferation status	The multitask learning models with AUC =0.811 for prediction of Ki –67 and AUC =0.816 for prediction of histologic grade
Ge et al. (2022)	DM	319	Histogram and texture features	Prediction of TNBC	Sensitivity=72.0%, Specificity=80.7%, Accuracy=80.6%, AUC=0.809
Wang et al. (2022)	CT	300	First –order, shape and texture features	Prediction of molecular subtypes of breast cancer	The AUC, accuracy, sensitivity, and specificity of the model to distinguish luminal from the non –luminal type were 0.757, 0.713, 0.767, and 0.676
Cui et al. (2023)	US	489	First–order and texture features	Predict the status of HER2 in breast cancer	AUC=0.80
Fan et al. (2022)	CT	108	Histogram, morphologic and texture features from CT images of 3 phases	Prediction of ER, PR, HER2 and Ki–67 status of breast cancer	AUC=0.870 (ER), AUC=0.797 (PR), AUC=0.881 (HER2), AUC=0.726 (Ki–67)
Liu et al. (2019)	DCE–MRI	62	First–order, shape–based, size –based, texture and higher–order features	Predict axillary sentinel lymph node metastasis of primary breast cancer	Sensitivity =0.71, Specificity=1, Accuracy=0.85, AUC=0.83, Mean Squared Error=0.26
Song et al. (2021)	PET/CT	100	Texture features	Predict axillary lymph–node metastasis in invasive ductal breast cancer	Sensitivity=90.9%, Specificity=71.4%, Accuracy=80%

MRI: magnetic resonance imaging; DCE: dynamic contrast-enhanced; DWI: diffusion weighted imaging; DM: digital mammography; CT: computed tomography; US: ultrasound; PET: positron emission tomography; TNBC: triple-negative breast cancer; AR: androgen receptor; HER2: human epidermal growth factor receptor-2; ER: estrogen receptor; PR: progesterone receptor; AUC: area under the curve

0.824 (luminal A), 0.823 (luminal B), 0.844 (HER2 enrichment) and 0.803 (TNBC), which may help to stratify patients according to predicted response levels prior to treatment. Y. Zhang et al. (2022) extracted quantitative radiomic features from contrast-enhanced MRI scans (both baseline and after two cycles of treatment) and constructed two radiomics-only models using a light gradient boosting machine. After that, by incorporating the variant allele frequency features obtained from baseline core tissues, a radiogenomic model was constructed. This radiogenomic model (AUC=0.87) obtained higher performance in the validation set than the two radiomics-only models (AUCs of 0.71 and 0.73, respectively), demonstrating the value of the radiogenomic model in accurately predicting pCR in TNBC patients.

Compared with MRI, US is less costly, less time consuming, and can be performed repeatedly during NAC. Jiang et al. (2021) developed a deep learning radiomic nomogram (DLRN) model that extracts both manual radiomic features and deep features of US before and after treatment, which realized the preoperative evaluation of pCR in breast cancer patients. The authors studied 592 biopsy-proven patients with locally advanced breast cancer, and the DLRN model obtained a C-index of 0.94 in an independent external validation cohort and was more accurate than the prediction of pCR by two radiologists (P<0.01). In addition, Qi et al. (2022) aimed to develop a radiomics model based on CT breast images to predict NAC response in breast cancer. The authors performed CT scans of 324 patients with NAC from multiple centers in Singapore and combined clinical information to develop four different radiomic models to predict pCR. The results of the study showed that the combined model based on peritumour and tumor area texture features had an AUC of 0.765, which was higher than that of the radiomic model of tumor area (AUC=0.743). The new spatially resolved radiomics model (AUC=0.775), which used voxel-based radiomics to extract feature maps, and the DL-based radiomics model (AUC=0.772) were better than the conventional radiomics model.

In conclusion, MR-based radiomics and radiogenomics play a great role in predicting pCR of NAC, and some other studies have improved the accuracy of other imaging modalities (US, CT) in predicting pCR by deep learning methods (see Table 3 for a summary).

3.4 Prediction of recurrence and survival outcomes

Cancer recurrence is an important clinical issue in patient management. The high heterogeneity of breast tumors leads to completely different outcomes for patients after treatment, and the prediction of patient risk of recurrence and survival after surgery is key to improving breast cancer cure rates (Chitalia et al., 2020; Engstrom et al., 2013; Kim et al., 2017). Recent studies have demonstrated the success of radiomics and radiogenomic analysis approaches in predicting recurrence risk and survival outcomes.

Mazurowski et al. (2019) retrospectively studied 892 female invasive breast cancer patients and selected 20 radiomic features with high prognostic value from conventional breast MRI and found a correlation between signal enhancement ratio partial tumor volume (C-index = 0.768), tumor long axis length (C-index = 0.742), and distant recurrence-free survival. A study by Fudan University Shanghai Cancer Center (Jiang et al., 2022) showed that low variance among the MRI sequences of dependence nonuniformity extracted from peritumoral ROIs (Peri_V_DN) predicted better recurrence-free survival (RFS) and overall survival in TNBC patients. Eun et al. (2021) demonstrated the superior diagnostic performance of RF model-based texture analysis over conventional MRI and clinicopathological features in predicting breast carcinomatosis recurrence after NAC(AUC: 0.94 *vs.* 0.83, P<0.05). Chen et al. (2022)

Table 3 Studies predicting response to NAC by radiomics and radiogenomics

Reference	Imaging Modality	Number of Patients	Radiomic Features	Purpose	Results
Caballo et al. (2023)	DCE–MRI	251	First postcontrast texture, time –dependent texture, pseudo4D texture, enhancement kinetics heterogeneity and morphology features	Identify patients achieving pCR after NAC	AUC=0.707 (all cancers), AUC=0.824 (luminal A), AUC=0.823 (luminal B), AUC=0.844 (HER2 enriched), AUC = 0.803 (triple negative)
Y. Zhang et al. (2022)	contrast–enhanced MRI	52	First–order, wavelet and texture features	Predict pCR in triple? negative breast cancer	The radiogenomic model with AUC of 0.87
Jiang et al. (2021)	US	592	Histogram, morphology, intensity, laws, wavelet and texture features; deep features from Dense – Net–201	Develop and validate a deep learning radiomic nomogram for preoperatively assessing breast cancer pCR after NAC	AUC=0.94 (all cancers), AUC=0.90 (HR+/HER2–), AUC=0.95 (HER2+), AUC=0.93 (triple negative)
Qi et al. (2022)	CT	324	Shape, first –order, texture features, wavelet and Laplace of Gaussian features	Predict response to NAC	Space –resolved model improves the clinical AUCs of pCR prediction from 0.743 to 0.775 and deep learning model improved it from 0.743 to 0.772

MRI: magnetic resonance imaging; DCE: dynamic contrast-enhanced; US: ultrasound; CT: computed tomography; pCR: pathologic complete response; NAC: neoadjuvant chemotherapy; HR: hormone receptor; HER2: human epidermal growth factor receptor-2; AUC: area under the curve

proposed a multiparametric MRI-based radiomic model (T2WI, DWI, DCE) to predict the Oncotype DX 21 gene recurrence score (RS) in patients with ER+/HER2- breast cancer disease. These authors used a linear SVM classifier model to distinguish between high RS (RS ≥ 26) and low RS (RS<26), demonstrating that a multiparametric MRI-based radiomics model (AUC=0.77) can help distinguish recurrence risk in patients with ER+/HER2- breast cancer. Radiomic features extracted from DM can also be used to predict the risk of recurrence. Mao et al. (2021) selected three radiomic features from DM and developed a multivariate logistic regression model including radiomic features and clinical risk factors (tumor grade and HER2). The radiomic model showed a good predictive effect in predicting the risk of ER-positive, lymph node -negative invasive breast cancer recurrence based on Oncotype DX.

Several other studies have demonstrated that radiomic nomograms incorporating radiomic features can improve individualized disease-free survival (DFS) estimates. Park et al. (2018) used univariate and multivariate Cox proportional risk models and Kaplan-Meier analysis to determine the correlation between radiomic features, MRI findings, and clinicopathologic variables and DFS, demonstrating the potential of MRI radiomic features to be used as DFS risk stratification biomarkers. Similarly, Xiong et al. (2021) constructed a radiomic nomogram based on the radiomic features of preoperative US combined with clinicopathological pre-

dictors, which also successfully predicted DFS in patients with invasive breast cancer.

In addition, Fan et al. (2020) demonstrated by means of radiogenomic analysis that unsupervised backfolding of gene expression profiles can reveal genomic subclones affecting biological functions associated with breast carcinomatosis and patient survival, thereby capturing potential tumor heterogeneity to better inform prognosis. Jiang et al. (2022) extracted quantitative radiomic features from contrast-enhanced MRI and demonstrated that a radiomic feature that captures peritumoral heterogeneity is a prognostic factor for RFS (P= 0.01) and overall survival (P= 0.004) in TNBC.

In conclusion, radiomics and radiogenomics allow for better, early and personalized prediction of recurrence risk and survival outcomes for cancer patients, which can help to target therapeutic measures in a timely manner to achieve a better prognosis.

A summary of these studies can be found in Table 4.

Table 4 Studies predicting recurrence and survival outcomes by radiomics and radiogenomics

Reference	Imaging Modality	Number of Patients	Radiomic Features	Purpose	Results
Eun et al. (2021)	MRI	130	Texture features	Predict recurrence in patients with breast cancer treated with NAC	AUC=0.94
Chen et al. (2022)	MRI	151	Texture, wavelet and Laplace of Gaussian features	Assess ER +/HER2 – breast cancer patients' 21 –gene recurrence score	AUC=0.77
Mao et al. (2021)	DM	304	Shape – and size – based, first – order statistical and texture features	Predict the risk of ER –positive, lymph node –negative invasive breast cancer recurrence based on Oncotype DX	The multivariate logistic regression model including radiomics signature and clinical risk factors with AUCs of 0.92, 0.88 and 0.84 in the training, internal and external test sets, respectively
Park et al. (2018)	MRI	294	Morphological, histogram –based and higher–order texture features	Estimate DFS in patients with invasive breast cancer and establish a radiomics nomogram that incorporates the radiomics signature and MRI and clinicopathological findings	C –index =0.76 (Radiomics nomogram), C–index=0.72 (clinicopathological nomogram), C–index=0.67 (Rad –score – only nomogram)
Xiong et al. (2021)	ultrasound	620	First –order, 2D shape –based, texture and wavelet features	Predict DFS in patients with invasive breast cancer	The radiomics nomogram performed better than the clinicopathological nomogram (C –index, 0.796 *vs.* 0.761)

MRI: magnetic resonance imaging; DM: digital mammography; DFS: disease-free survival; NAC: neoadjuvant chemotherapy; ER: estrogen receptor; HER2: human epidermal growth factor receptor-2; AUC: area under the curve

4 Discussion and conclusion

Radiomics works by extracting quantitative features from multiple imaging modalities and using these features to build classification or prediction models to determine the specifics of a cancer. The results of radiomics models have the advantage of being more robust and reproducible than those obtained by radiologists by reading radiographs alone. The features obtained by radiomics are generally not perceived by the human eye, so it can obtain some "hidden" information that can help to obtain more accurate results (Crivelli et al., 2018). With the emphasis on multiomics integration, radiogenomics is one of the trends in the development of radiomics, which integrates structured genetic data with unstructured imaging data to complement the intrinsic biological features of tumors (Yin et al., 2022). Radiogenomics is able to describe the molecular composition of the tumor and immune microenvironment and its evolution in a noninvasive and holistic manner, thus promising to replace biopsy (Wu et al., 2022).

In the survey study presented here, radiomics and radiogenomics have applications in identifying breast tumor lesions, differentiating tumor types and grades, predicting NAC response, and predicting recurrence risk and survival outcomes. Among them, it should be noted that artificial intelligence techniques (including machine learning and deep learning) have supported their rapid development (Bitencourt et al., 2021). Machine learning plays a role mainly in feature selection and model building, while deep learning plays a role that can be used throughout the radiomics process, including image acquisition and image segmentation (Nie et al., 2018; Padmapriya et al., 2022). The most significant difference between machine learning and deep learning is the use of hand-crafted features. In other words, machine learning extracts predefined manual features, whereas deep learning automatically learns features from data that are generalizable and can be applied to different tasks.

Although radiomics and radiogenomics have been proven in scientific research, there is still a distance to clinical applications (Ak et al., 2022; Lo Gullo et al., 2020). Faced with the problems and challenges posed by clinical translation, some work needs to be done. First, because of the differences in image acquisition protocols (van Dijk & Fuller, 2021), methods of extracting image features and acquisition of clinical and genomic data can affect the reproducibility of results, for example by producing inconsistent images as well as ROIs. As the interpretation of results may vary between or within readers, it is necessary to standardize the whole process (Saxena et al., 2022; Shui et al., 2020). Second, given that most radiomics studies are retrospective, and retrospective studies have fewer constraints and no guarantee of data completeness and accuracy, prospective studies with higher credibility are needed to validate these preliminary results (Singh et al., 2021). Finally, the reliability of the results of many studies, which were conducted in patient cohorts with small sample sizes, has yet to be validated in larger databases. Large-scale data sharing (Traverso et al., 2018) is the only solution to this problem, and TCGA and TCIA have played a leading role in this by including molecular data of tumors and corresponding imaging data, providing a great opportunity for researchers to perform radiogenomic studies (Zanfardino et al., 2019).

In addition, various new imaging technologies will provide high-quality imaging for feature extraction, such as quantitative ultrasound (Nasief et al., 2019), molecular imaging (immuno-PET) (Mayer & Gambhir, 2018), contrast-enhanced spectral mammography (Suter et al., 2020), and some emerging MRI technologies (sodium imaging) (Zaric et al., 2016), chemi-

cal exchange saturation transfer imaging (Jones et al., 2018), blood oxygen level-dependent imaging (King & Thoeny, 2016). In conclusion, the integration of quantitative features, clinical information, histopathological data and genomic data is the key for the future era of personalized treatment (Saini et al., 2019) with repeatable, robustness biomarkers in precision medicine.

Declarations of interest

There are no financial conflicts of interest to disclose.

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