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Progress and Clinical Application Value of Radiomics in Intratumoral and Peritumoral Regions of Breast Cancer

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Abstract: Breast cancer is one of the most common malignant tumors in women. By extracting high-throughput features from medical images, radiomics non-invasively reveals tumor heterogeneity and provides new strategies for the precise diagnosis and treatment of breast cancer. Previous studies mainly focused on intratumoral features, while rarely explored the crucial role of peritumoral features in tumorigenesis, progression and metastasis. In recent years, intratumoral and peritumoral radiomics has gradually become a research hotspot. This paper systematically reviews the research progress of intratumoral and peritumoral radiomics based on ultrasound, MRI, PET and mammography in benign and malignant differentiation, molecular subtyping, lymph node metastasis prediction and neoadjuvant chemotherapy response assessment of breast cancer. It aims to provide comprehensive imaging evidence for clinical practice and promote the improvement and optimization of precise medical models for breast cancer.

Keywords: Breast Cancer; Radiomics; Peritumoral Region; Clinical Value.

1. Introduction

According to the 2022 global cancer statistics released by the International Agency for Research on Cancer (IARC) of the World Health Organization, breast cancer remains the leading cause of incidence and mortality among female malignant tumors worldwide. Its high prevalence and lethality have made it a major clinical challenge urgently to be addressed in global public health [1]. Although certain progress has been made in the diagnosis, treatment and prognosis of breast cancer at present [2], early diagnosis and individualized treatment remain the key to improving patients' survival rate and quality of life[3] .Radiomics was first proposed by the Dutch scholar Philippe Lambin in 2012 [4]. This analytical technique comprehensively evaluates the entire tumor lesion through high-throughput feature extraction and quantitative analysis of medical images, thereby non-invasively revealing regional characteristics, underlying pathophysiological changes and genetic variations [5].In recent years, researchers have begun to explore intratumoral and peritumoral radiomics. Most previous radiomics studies on breast cancer merely focused on intratumoral features[6-8] , while studies concerning the predictive value of the peritumoral microenvironment and peritumoral parenchyma remain relatively scarce. Nevertheless, tumor heterogeneity consists of both intratumoral and peritumoral heterogeneity. As an important component of the tumor microenvironment, the peritumoral region also contains abundant biological information [9, 10]. Therefore, quantitative analysis of both intratumoral and peritumoral regions enables more comprehensive characterization of tumors.Intratumoral and peritumoral radiomics based on common breast imaging modalities including mammography, PET, MRI and ultrasound has become a research hotspot in the diagnosis and treatment of breast cancer. Meanwhile, the intratumoral and peritumoral microenvironment as potential therapeutic targets for breast cancer is attracting increasing attention [11]. This paper presents a systematic review on the research progress and clinical application value of intratumoral and peritumoral radiomics in breast cancer.

2. Intratumoral and Peritumoral MRI Radiomics

Owing to its high soft-tissue contrast, non-invasive nature, and capacity for multi-parametric and multi-planar imaging, magnetic resonance imaging (MRI) has emerged as an indispensable modality for the precise diagnosis and management of breast cancer [12].In recent years, radiomics based on multi-parametric MRI has expanded from single intratumoral analysis to combined intratumoral and peritumoral analysis. In benign and malignant differentiation of breast lesions, the incorporation of peritumoral features can significantly improve diagnostic accuracy.In an early study, Zhou et al. [13] explored dynamic contrast-enhanced (DCE) MRI combined with deep learning, and found that the minimal bounding box containing the proximal peritumoral region achieved the highest diagnostic accuracy. Subsequently, focusing on clinically challenging BI-RADS category 4 lesions, Hu et al. [14]constructed radiomics models based on intratumoral and peritumoral regions on DCE-MRI. Their results demonstrated that the radiomics model combining intratumoral features with 2-mm peritumoral features possessed the optimal differentiation performance. This finding provides crucial quantitative evidence for reducing clinical false-positive rates and unnecessary percutaneous biopsies.

Molecular subtypes and proliferation markers of breast cancer serve as the cornerstone of endocrine therapy and targeted therapy. Han et al. [15]compared the predictive performance of multi-parametric MRI within different peritumoral ranges, and verified that 6 mm was the optimal boundary for distinguishing different molecular subtypes.For non-invasive prediction of specific receptor status, Cao et al. [16]developed and validated a novel radiomics prediction model by integrating features from T2WI, DCE-MRI and DWI. The results confirmed that texture features within the 3 mm peritumoral region of breast lesions were highly correlated with HER-2 expression status. This overcomes the

limitations of previous single-sequence imaging, provides reliable imaging biomarkers for preoperative non-invasive and accurate assessment of HER-2 status, and further facilitates clinical decision-making regarding anti-HER-2 targeted therapy.In terms of axillary lymph nodes, Liu et al. [17] demonstrated that the DCE-MRI model combining intratumoral and 5 mm peritumoral features exhibited significantly better predictive performance for axillary lymph node metastasis (ALNM) than models merely based on intratumoral features alone. It possesses important reference value for guiding precise clinical surgical planning.

Pathological complete response (pCR) constitutes the primary endpoint for assessing the therapeutic benefit of neoadjuvant chemotherapy (NAC). Zhu et al. [18]demonstrated that a nomogram incorporating intratumoral and peritumoral radiomic features (with a 6-mm extended margin) in conjunction with clinical indicators could accurately predict pCR.Chen et al. [19]further corroborated that multi-parametric features derived from the fusion of DCE-MRI, diffusion kurtosis imaging (DKI), and intravoxel incoherent motion (IVIM) enabled highly sensitive prediction of NAC efficacy. Moreover, Zheng et al. [20]integrated background parenchymal enhancement (BPE) as a component of the broader microenvironment and confirmed that the tri-regional model (intratumoral + peritumoral + BPE) achieved the highest predictive performance for pCR.Recently, Hong et al. [21]integrated intratumoral features, 9-mm extended peritumoral features, and deep learning (DL) patterns derived from pre-NAC MRI to develop a multimodal model. The final integrated model (Intra-Peri-DL) outperformed unimodal counterparts, suggesting that multimodal fusion more accurately captures tumor-microenvironment interactions and thus represents a powerful tool for individualized NAC decision-making.

Combined intratumoral and peritumoral radiomics based on multi-parametric MRI excavates deep interactive information between tumor parenchyma and microenvironment, and exhibits superior performance over traditional single intratumoral models in the diagnosis and treatment of breast cancer. With the collaborative innovation of rapid imaging techniques, quantitative analysis frameworks and artificial intelligence in the future, multimodal MRI is expected to realize real-time, multi-dimensional and accurate monitoring of neoadjuvant chemotherapy (NAC) response in breast cancer, and promote the development of individualized therapeutic decision-making.

3. Intratumoral and Peritumoral Ultrasound Radiomics

In ultrasonic physical imaging, tumor invasion into surrounding tissues, desmoplastic reaction, and changes in the stiffness of adjacent stroma lead to characteristic "hyperechoic halos" or subtle differences in acoustic impedance interfaces on grayscale ultrasound images. In recent years, multi-region radiomics has demonstrated significant advantages in distinguishing lesion nature. For example, Guo et al. [22] developed ultrasound-based multi-region radiomics models, including six models in total: intratumoral only, peritumoral only, parenchymal only, and various combinations (such as intratumoral + peritumoral, intratumoral + parenchymal). Studies have shown that the multi-region feature model comprehensively considering intratumoral, peritumoral, and ipsilateral breast parenchymal characteristics exhibits significantly superior performance in differentiating benign and malignant breast lesions compared with the single intratumoral model. Subsequently, focusing on common clinically challenging BI-RADS category 4 lesions, Zou et al. [23]extracted intratumoral and peritumoral ultrasound radiomic features and constructed machine learning classifiers. The results further confirmed that the combined "intratumoral + peritumoral" model achieved the optimal diagnostic efficacy. This is mainly attributed to the fact that the peritumoral region contains key biological information such as tumor edge invasion and destruction of surrounding tissue microstructures; its inclusion in the analysis can effectively improve the specificity of ultrasound diagnosis.

Given that lymphovascular invasion and microenvironment remodeling often accompany the tumor margin, incorporating peritumoral features into radiomics analysis can significantly enhance the predictive power for lymph node metastasis. Du et al. [24]systematically evaluated the predictive value of intratumoral and peritumoral features with different extension margins for axillary lymph node metastasis (ALNM). Using a random forest classifier to construct multiple models, their results demonstrated that the radiomics model combining "intratumoral + 3 mm peritumoral" features exhibited the optimal predictive performance. This finding suggests that 3 mm may represent the optimal peritumoral range for ALNM prediction, which is expected to provide a reference for formulating clinical axillary surgical plans.In recent years, an increasing number of studies have attempted to use ultrasound radiomics for non-invasive prediction of Ki-67 expression. Wang et al.[25] constructed a prediction model using the random forest algorithm and showed that the model combining intratumoral and peritumoral features offered a higher clinical benefit in predicting Ki-67 expression levels, providing an ultrasound radiomics basis for the precise diagnosis and treatment of breast cancer patients.To determine the optimal peritumoral boundary, Huang et al. extracted ultrasound radiomic features from the intratumoral region and multiple gradient extension margins (2-10 mm). The results of the machine learning models built based on the random forest algorithm indicated that the feature set combining "intratumoral and 6 mm peritumoral" achieved the best predictive performance for Ki-67. This further highlights the indispensable value of the structural heterogeneity and microenvironment remodeling of the tissue surrounding the tumor in reflecting the intrinsic biological behavior of the tumor.

Prediction of pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is a crucial goal for achieving individualized treatment. Ultrasound, with its advantages of non-invasiveness, real-time imaging and high reproducibility, possesses great potential in dynamic monitoring of treatment response. In recent years, multi-region radiomics has explored the differential value of various peritumoral ranges in therapeutic effect assessment.Wei et al. [26]extracted ultrasound radiomic features from intratumoral regions and multi-gradient peritumoral margins (5 mm, 10 mm, 15 mm) before NAC, integrated clinicopathological parameters, and constructed a series of models via the random forest algorithm. The results demonstrated that the combined model integrating clinical parameters with intratumoral and 10-mm peritumoral features (IntraPeri-10 mm) exhibited excellent performance in pCR prediction. It can accurately

evaluate tumor regression response and provide important guidance for subsequent adjustment of treatment regimens.Nevertheless, disputes remain in the academic community regarding the relative weights of intratumoral and peritumoral features. Yao et al. [27]compared the predictive value of machine learning-based peritumoral ultrasound radiomics (PURS), intratumoral ultrasound radiomics (IURS), and clinicopathological factors. The study revealed that although the accuracy of the PURS model was slightly lower than that of the IURS model in pCR prediction, its area under the curve (AUC) was still significantly higher than that of conventional clinicopathological predictors. This indicates that PURS, as an innovative and promising non-invasive assessment tool, can provide comprehensive support for systemic therapeutic decision-making in patients with locally advanced breast cancer (LABC) undergoing NAC.

4. Intratumoral and Peritumoral Radiomics in Mammography

Mammography serves as the fundamental modality for breast cancer screening. Although it is often regarded as auxiliary information in multimodal studies, it remains of great value in primary healthcare screening and large-population screening programs. Wang et al. [28] constructed and analyzed radiomics models with peritumoral margins of 1 mm, 3 mm and 5 mm based on contrast-enhanced spectral mammography (CESM) images. They found that the 3-mm peritumoral model achieved extremely high diagnostic performance in differentiating benign and malignant breast lesions. The study indicated that incorporating annular perilesional information into lesion-based radiomics models may improve diagnostic performance.

In addition, focusing on clinically ambiguous BI-RADS category 4 breast lesions, Zhang et al. [29]established multi-region radiomics models based on contrast-enhanced spectral mammography images. Radiomic features were extracted from intratumoral regions as well as 5-mm and 10-mm peritumoral regions. Feature selection was performed using the LASSO algorithm, and a nomogram was further developed by integrating clinical factors including age and BI-RADS classification. The results demonstrated that the model exhibited favorable predictive performance in both internal and external validation, suggesting that the inclusion of peritumoral imaging information can effectively improve the accuracy of benign-malignant differentiation of breast lesions.

Chen Xiuting et al. [30]extracted intratumoral and 3-mm peritumoral features from digital breast tomosynthesis (DBT) images. Using support vector machine (SVM) technology, they constructed intratumoral, peritumoral, and combined intratumoral + peritumoral radiomics models. The model with the best performance was selected and combined with clinical features to establish a nomogram model. The results demonstrated that this nomogram could effectively predict axillary lymph node (ALN) metastasis of breast cancer preoperatively, providing a non-invasive assessment basis for formulating individualized surgical strategies.For accurate preoperative evaluation of tumor molecular characteristics in breast cancer, Niu et al. [31]compared the performance of mammography and magnetic resonance imaging (MRI) in predicting molecular subtypes of breast cancer. The findings revealed that the introduction of peritumoral region information into radiomics analysis significantly improved the model's predictive capability. Studies have shown that the peritumoral region can provide additional structural information and microenvironmental features, thereby enhancing the recognition of different molecular subtypes.Furthermore, Guo Yunchan et al. [32]delineated intratumoral regions of interest (ROIs) based on DBT images acquired at two positions (craniocaudal (CC) view and mediolateral oblique (MLO) view). The peritumoral region was automatically generated by expanding 3 mm outward. Radiomic features were extracted and selected to establish three radiomics models: intratumoral, peritumoral, and intratumoral + peritumoral. The results confirmed that the fusion of peritumoral regions significantly enhanced the model's predictive performance for HER2 status.

Mao et al. [33]extracted radiomic features from intratumoral regions as well as 5-mm and 10-mm peritumoral margins on contrast-enhanced spectral mammography (CESM) images, performed linear weighting, and constructed multiple prediction models. The results demonstrated that the model combining intratumoral features and 5-mm peritumoral features achieved the optimal performance in predicting chemotherapy response. This finding indicates the potential of intratumoral and peritumoral radiomic features based on CESM in preoperative assessment of chemotherapy sensitivity, and provides scientific decision support for individualized clinical treatment planning.In summary, peritumoral radiomic features of digital breast tomosynthesis (DBT) play a crucial role in the diagnosis and treatment of breast cancer, serving as a powerful tool for non-invasive assessment, individualized therapy and prognostic prediction.

PET/CT is a medical imaging technique based on radiolabeled glucose (FDG). By reflecting the glucose metabolism level of tumors, it provides functional information for evaluating tumor invasiveness and therapeutic response. Radiomics studies have shown that intratumoral and peritumoral metabolic texture features on PET are closely correlated with molecular subtypes of breast cancer. PET/CT radiomics possesses unique advantages in early response prediction of neoadjuvant chemotherapy; however, due to limitations in sample size and examination cost, its clinical popularization requires further validation [34].Both PET/CT and PET/MRI can provide anatomical morphological information as well as sensitively reflect functional characteristics such as tumor glucose metabolism. Radiomics can supply multi-parameter and multi-level texture features for differential diagnosis of breast cancer, exhibiting promising clinical application potential[35] .

Triple-negative breast cancer (TNBC) is of great research importance owing to its high invasiveness and poor prognosis. Based on 18F-FDG PET metabolic parameters, Chen et al. [36]analyzed differences in imaging features between intratumoral and peritumoral regions in TNBC. The results showed that TNBC presented higher intratumoral metabolic activity than non-TNBC, accompanied by more prominent metabolic heterogeneity in the peritumoral region. Further multivariate Logistic regression analysis revealed that intratumoral SUVmax and the area under the cumulative SUV-volume histogram (AUC-CSH) of the peritumoral region were independent predictors for TNBC. This study suggests that the combination of intratumoral and peritumoral metabolic features can comprehensively reflect the biological behavior of TNBC, providing crucial imaging evidence for its non-invasive molecular subtyping. Meanwhile, it also indirectly demonstrates the vital role of the tumor

microenvironment in breast cancer subclassification.

For neoadjuvant chemotherapy (NAC) response prediction, Hou et al. [37] extracted radiomic features from intratumoral regions and the 2-mm peritumoral margin based on 18F-FDG PET/CT images. Four classifiers were adopted to establish prediction models. The results demonstrated that the support vector machine (SVM) model integrating intratumoral and peritumoral features achieved the highest predictive performance in the test set, which was significantly superior to the single intratumoral model. In addition, the incorporation of peritumoral features could also improve predictive accuracy across different molecular subtype subgroups.

In summary, combined intratumoral and peritumoral PET radiomics analysis can not only improve the accuracy of NAC response prediction, but also provide a novel imaging perspective for revealing the role of the tumor microenvironment in therapeutic response, possessing considerable potential for clinical translation. PET radiomics should be further applied across the entire clinical workflow of breast cancer, including diagnosis, prognostic prediction and treatment monitoring, especially regarding its performance in diagnosing and predicting lymph node metastasis and distant metastasis.The unique advantage of PET lies in whole-body one-stop imaging, which enables simultaneous radiomics analysis of primary lesions and metastatic lesions. This approach may provide more accurate and comprehensive biological information of tumors, thereby facilitating individualized treatment. Accordingly, how to integrate PET radiomic features derived from primary tumors and metastatic lesions will become a crucial research topic [38].

5. Summary and Prospect

At present, intratumoral and peritumoral radiomics has achieved remarkable efficacy in the clinical diagnosis and treatment of breast cancer. In benign and malignant lesion differentiation, the combination of intratumoral and peritumoral features significantly improves diagnostic accuracy and reduces unnecessary biopsies. In molecular subtype prediction, radiomic features are correlated with molecular markers to realize non-invasive assessment and provide references for individualized treatment. In lymph node metastasis prediction, peritumoral features can reflect the invasive potential of tumors, which is expected to reduce unnecessary axillary lymph node dissection. In neoadjuvant chemotherapy assessment, dynamic monitoring of feature changes enables early prediction of treatment response and facilitates optimization of therapeutic strategies. Overall, the collaborative application of intratumoral and peritumoral radiomics compensates for the limitations of single intratumoral studies, enriches the dimensions of imaging evaluation, and promotes the shift of clinical diagnosis and treatment from experience-driven to data-driven modes, possessing important clinical value. Each imaging modality has distinct advantages: mammography is suitable for large-scale population screening, ultrasound performs well in dense breast tissues, MRI excels in the detection of invasive lesions and therapeutic response evaluation, and PET assists in the assessment of distant metastasis.

Despite the promising application outcomes of intratumoral and peritumoral radiomics, this field is still in the developmental stage and has not yet been widely implemented in clinical practice. Future research should focus on three core directions: standardization improvement, technological integration and innovation, and clinical translation.In terms of technical standardization, current problems include inconsistent protocols in image acquisition, lesion segmentation and feature extraction, poor reproducibility of research results, model reliance on single-center small-sample datasets, and insufficient generalization ability. It is imperative to strengthen multicenter cooperation, establish unified criteria, promote data sharing via international organizations, expand sample sizes and conduct prospective trials. Meanwhile, multimodal fusion algorithms should be optimized to further improve the accuracy of comprehensive assessment.

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