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REVIEW

Preoperative Imaging Assessment of Lymphovascular Invasion in Breast Cancer: Current Evidence, Technical Advances, and Future Directions

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Abstract: Lymphovascular invasion (LVI) in breast cancer is a pivotal prognostic factor that directly influences patient survival outcomes and guides the formulation of individualized treatment strategies, such as the selection of adjuvant chemotherapy regimens or the extent of surgical intervention. Accurate preoperative assessment of LVI status is therefore indispensable for optimizing clinical decision-making and improving patient management. This review systematically synthesizes the latest advancements in imaging techniques for LVI evaluation in breast cancer, including conventional ultrasound, contrast-enhanced ultrasound (CEUS), elastography, mammography (digital and contrast-enhanced), magnetic resonance imaging (MRI, encompassing DCE-MRI, DWI, and novel functional sequences like IVIM), and artificial intelligence (AI)-assisted diagnostic tools (radiomics and deep learning). A critical analysis of these modalities reveals distinct strengths and limitations: for instance, ultrasound offers broad accessibility and real-time imaging but exhibits lower sensitivity (60–75%) for subtle LVI lesions compared to MRI (sensitivity 78–90%), which provides superior soft tissue contrast but is constrained by higher cost and longer scan times. Radiomics models, while demonstrating promising AUC values (0.74–0.896) in predicting LVI, suffer from inconsistencies in feature extraction protocols and limited external validation. Additionally, this review highlights key knowledge gaps, such as the lack of standardized imaging parameters for LVI assessment across centers and the underrepresentation of rare breast cancer subtypes (eg, inflammatory breast cancer) in existing studies. We emphasize the clinical urgency of addressing these limitations—including reducing false-positive rates caused by benign vascular proliferations and false negatives from obscured lesions—to enhance diagnostic accuracy. Furthermore, we propose targeted future directions, such as the development of multicenter, prospective trials to validate AI-integrated multimodal imaging workflows and the establishment of consensus guidelines for imaging protocol standardization, ultimately aiming to translate technical advancements into improved patient outcomes.

Keywords: breast cancer, lymphovascular invasion, imaging assessment, preoperative diagnosis, artificial intelligence

Introduction

Breast cancer is the most prevalent malignancy among women globally, accounting for approximately 2.3 million new cases annually and representing a major public health burden.[1] A comprehensive understanding of its pathological mechanisms and prognostic factors is critical for refining treatment paradigms, and lymphovascular invasion (LVI) has emerged as a key determinant of disease progression. LVI, defined as the presence of cancer cells within lymphatic or vascular channels, is strongly associated with an increased risk of lymph node metastasis (hazard ratio [HR] 1.82, 95% CI 1.56–2.12) and reduced 5-year disease-free survival (DFS) (62% vs 85% in LVI-negative patients).[2,3] Historically, LVI diagnosis relied exclusively on postoperative histopathological examination—using markers like D2-40 for lymphatic vessels and CD34 for blood vessels—which delays treatment stratification and may lead to suboptimal care.[4,5]

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This limitation underscores the urgent need for non-invasive preoperative imaging techniques to assess LVI, a gap that has driven recent innovations in imaging technology.[6]

Recent breakthroughs in imaging modalities have transformed preoperative LVI evaluation. MRI, in particular, has shown exceptional utility: dynamic contrast-enhanced (DCE-MRI) parameters like the transfer constant (K^{trans}) correlate with LVI presence (AUC 0.76–0.83), while diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) thresholds (eg, <1068 × 10^-6 mm^2/s) can identify LVI-positive tumors with high specificity (82–88%).[7–9] Ultrasound-based techniques, including shear wave elastography (SWE), complement MRI by quantifying tissue stiffness—tumors with stiffness values >80 kPa are 3.2 times more likely to be LVI-positive—making them valuable for resource-limited settings.[10,11] Additionally, the integration of radiomics and machine learning has further enhanced predictive power: a 3D-CNN model analyzing breast MRI volumes achieved an AUC of 0.896 for LVI prediction, outperforming traditional radiological interpretation (AUC 0.72).[12,13]

Beyond its prognostic role, LVI provides critical insights into tumor biology, as it is frequently linked to aggressive features such as high histological grade (G3), elevated Ki-67 index (>20%), and triple-negative molecular subtype (TNBC).[2,14] For example, in TNBC patients, LVI is associated with a 2.1-fold higher risk of distant metastasis, highlighting its utility in guiding adjuvant therapy decisions.[3] Oncologists increasingly rely on LVI status to determine the necessity of neoadjuvant chemotherapy or sentinel lymph node dissection, underscoring its translational importance.[14]

This review aims to fill the gap in existing literature by providing a critical, comparative analysis of preoperative imaging techniques for LVI assessment in breast cancer. Unlike previous descriptive summaries, we systematically evaluate the sensitivity, specificity, and clinical applicability of each modality (Table 1), identify inconsistencies in current research (eg, variable ADC thresholds across studies), and synthesize evidence to determine which methods are most promising for routine clinical use. We also address unresolved challenges, such as the poor reproducibility of radiomics features and the underdiagnosis of LVI in small tumors (<1 cm), and propose actionable future directions to advance the field.[15,16]

In the era of precision oncology, the demand for reliable non-invasive LVI assessment is growing rapidly. Establishing standardized, cost-effective imaging workflows will enable more accurate risk stratification and personalized treatment, ultimately improving survival rates and quality of life for breast cancer patients.[17,18] By critically evaluating existing technologies and highlighting areas for innovation, this review seeks to accelerate the translation of imaging research into clinical practice.

Pathological Basis and Clinical Significance of LVI in Breast Cancer

Definition and Pathological Features of LVI

LVI is a critical pathological hallmark of breast cancer, characterized by the presence of intact tumor cells or cell clusters within lymphatic or blood vessel lumina, lined by endothelial cells.[4,5] It is imperative to distinguish LVI from blood vessel invasion (BVI), as their prognostic and therapeutic implications differ substantially: LVI involves concurrent infiltration of lymphatic and vascular systems, whereas BVI is restricted to blood vessels alone.[4] This distinction is clinically relevant because LVI is more strongly associated with lymph node metastasis (HR 1.9 vs 1.4 for BVI), while BVI correlates more closely with distant organ metastasis.[2,5]

Pathological diagnosis of LVI relies on a combination of hematoxylin-eosin (HE) staining and immunohistochemistry (IHC). HE staining identifies tumor cells within vascular spaces, but IHC is essential for distinguishing lymphatic from blood vessels: D2-40 (a podoplanin marker) is specific for lymphatic endothelium, while CD34 labels blood vessel endothelium.[4,5] Recent studies have also explored novel markers like vascular endothelial growth factor (VEGF)-C, which is overexpressed in LVI-positive tumors and correlates with increased lymphangiogenesis.[6]

Notably, LVI is closely intertwined with the tumor microenvironment (TME). Research has shown that LVI-positive tumors exhibit a pro-inflammatory stromal response, characterized by increased infiltration of tumor-associated macrophages (TAMs) and regulatory T cells (Tregs), which promote immune evasion and vascular invasion.[5,6] Additionally, LVI is strongly associated with aggressive tumor phenotypes, including larger tumor size (>2 cm), higher histological

Table 1 Comparative Analysis of Imaging Modalities for LVI Prediction in Breast Cancer

Modality	Key Parameters	Sensitivity (%)	Specificity (%)	AUC	Advantages	Limitations
Conventional Ultrasound	Indistinct margins, posterior attenuation	60-75	65-70	0.68–0.75	Non-invasive, low cost, real-time	Operator-dependent, low sensitivity for small tumors
CEUS	Peak intensity, time to peak	75-82	70-78	0.78–0.81	Visualizes microvascularity	Requires contrast, contraindicated in renal impairment
SWE	Stiffness (kPa), strain ratio	76-82	75-80	0.75–0.80	Quantifies tissue stiffness	Less reliable in dense breasts
Mammography (Digital)	Clustered/linear microcalcifications, spiculated margins	50-70	75-85	0.65–0.75	Widely available, low radiation dose	Low sensitivity in dense breasts
DCE-MRI	Type III TIC, Ktrans	78-90	80-85	0.80–0.83	High soft tissue contrast, quantitative	Expensive, long scan time, requires contrast
DWI	ADC threshold (<1068 × 10^-6 mm^2/s)	82-88	78-82	0.80–0.85	No contrast needed, short scan time	Susceptible to motion artifacts
IVIM-MRI	D, D*	80-85	78-83	0.80–0.82	Assesses diffusion and perfusion	Low spatial resolution
Radiomics (DCE-MRI)	GLCM entropy, wavelet features	78-85	75-82	0.76–0.83	Captures tumor heterogeneity	Operator-dependent feature extraction
3D-CNN (MRI)	Peritumoral enhancement patterns	85-90	82-88	0.87–0.896	End-to-end prediction	Data-dependent, "black box" interpretability
Multimodal (US + MRI)	SWE + DCE-MRI + DWI	88-92	85-90	0.88–0.91	Combines strengths of modalities	Logistically complex, high cost

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grade (G3), and positive hormone receptor status (ER/PR-negative).[2,3] For example, a retrospective study of 2000 breast cancer patients found that LVI was present in 68% of G3 tumors compared to 22% of G1 tumors, and in 52% of TNBC cases versus 31% of luminal A cases.[2,14] These associations underscore LVI's role as a surrogate marker for tumor aggressiveness.

Impact of LVI on Prognosis in Breast Cancer

The prognostic significance of lymphovascular invasion (LVI) in breast cancer is well-documented across various studies and molecular subtypes. Meta-analyses have consistently demonstrated that LVI serves as an independent predictor of decreased disease-free survival (DFS) with a hazard ratio (HR) of 1.75 (95% confidence interval [CI] 1.58–1.94) and overall survival (OS) with an HR of 1.62 (95% CI 1.45–1.81).[2,3] The negative impact of LVI is especially notable in certain subgroups. For instance, in triple-negative breast cancer (TNBC), patients with LVI face a 2.3-fold increased risk of recurrence and a 2.1-fold higher risk of mortality compared to those without LVI.[3] In the case of HER2-positive breast cancer, even among patients receiving trastuzumab, LVI continues to be a significant poor prognostic factor, with a DFS HR of 1.8 (95% CI 1.3–2.5), highlighting the necessity for more aggressive treatment approaches.[14] Additionally, in luminal B breast cancer, the presence of LVI is linked to a notable decrease in 5-year DFS rates (58% compared to 83%) and acts as an independent predictor of the benefits derived from chemotherapy.[2,14]

Importantly, the prognostic value of LVI varies by lymph node status. In node-negative patients, LVI identifies a high-risk subgroup: a study of 1,200 node-negative patients found that LVI-positive cases had a 5-year recurrence rate of 28% versus 12% for LVI-negative cases, justifying consideration of adjuvant chemotherapy.[3] In node-positive patients, LVI further stratifies risk: LVI-positive patients with 1–3 positive nodes had a 5-year OS of 65% versus 82% for LVI-negative patients.[2]

These findings have led to the integration of LVI into clinical practice guidelines. For example, the American Society of Clinical Oncology (ASCO) guidelines recommend LVI assessment in all invasive breast cancers to guide adjuvant therapy decisions.[14] However, inconsistencies in LVI diagnosis (eg, inter-pathologist variability) remain a challenge, with agreement rates ranging from 65% to 85% for HE staining alone.[5] The adoption of standardized IHC panels (D2-40 + CD34) has improved reproducibility to >90%, highlighting the need for uniform diagnostic criteria.[4,5]

Application of Ultrasound Technology in LVI Assessment

Characteristic Analysis of Conventional Ultrasound

Conventional ultrasound is a cornerstone of breast cancer imaging due to its non-invasiveness, real-time capability, and low cost, making it widely accessible in both high- and low-resource settings.[19,20] Key ultrasound features associated with LVI include indistinct tumor margins, posterior acoustic attenuation, irregular shape, and hypoechogenicity.[10,19] Among these, indistinct margins are the most predictive: a multicenter study of 850 invasive ductal carcinoma (IDC) patients found that tumors with poorly defined edges were 4.1 times more likely to be LVI-positive (sensitivity 72%, specificity 68%).[19] This association is attributed to the infiltrative growth pattern of LVI-positive tumors, which disrupts surrounding tissue architecture and creates irregular interfaces with normal breast parenchyma.[10]

Posterior acoustic attenuation, another important feature, occurs when dense tumor tissue absorbs ultrasound waves, and is linked to increased cellularity and fibrosis—both hallmarks of aggressive tumors with LVI.[10] A study by Liu et al (2021) reported that posterior attenuation was present in 63% of LVI-positive tumors versus 29% of LVI-negative tumors, with an odds ratio (OR) of 3.8.[10] However, conventional ultrasound has limitations: it cannot directly visualize lymphatic/vascular channels, and its performance is operator-dependent, with sensitivity ranging from 60% to 75% across studies.[19,20] For example, in tumors <1 cm, the sensitivity of conventional ultrasound for LVI prediction drops to 45%, due to the inability to resolve subtle margin irregularities.[19]

Advances in Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) overcomes the limitations of conventional ultrasound by using microbubble contrast agents (eg, SonoVue) to visualize microvascular perfusion, providing direct insights into tumor angiogenesis

—a key driver of LVI.[4,20] Quantitative CEUS parameters, including peak intensity (PI), time to peak (TTP), and wash-in rate (WIR), have been shown to correlate strongly with LVI status.[4,20] A recent study by Li et al (2023) demonstrated that LVI-positive tumors had significantly higher PI (28.5 ± 5.2 dB vs 19.3 ± 4.1 dB) and shorter TTP (18.2 ± 3.5 s vs 25.6 ± 4.3 s) compared to LVI-negative tumors, with an AUC of 0.81 for LVI prediction.[4] These parameters reflect increased vascular density and permeability in LVI-positive tumors, which facilitate cancer cell invasion into lymphatic/vascular channels.

CEUS also enables the detection of "peritumoral vascularity"—abnormal vessels surrounding the tumor—which is a strong predictor of LVI. A retrospective study of 420 breast cancer patients found that peritumoral vascularity (defined as >3 tortuous vessels within 5 mm of the tumor) had a sensitivity of 78% and specificity of 73% for LVI, outperforming conventional ultrasound features.[20] However, CEUS has drawbacks: it requires intravenous contrast administration, is contraindicated in patients with renal impairment, and has limited availability in some regions.[18] Additionally, inter-observer variability in quantifying CEUS parameters (eg, PI) remains a challenge, with intraclass correlation coefficients (ICCs) ranging from 0.65 to 0.80.[20]

Value of Elastography Techniques

Elastography techniques, particularly shear wave elastography (SWE), quantify tissue stiffness, which correlates with tumor fibrosis and cellularity—key factors associated with LVI.[10,11] SWE measures stiffness in kilopascals (kPa), and studies have consistently shown that LVI-positive tumors have higher stiffness values: a meta-analysis of 5 studies (n=1,200) reported a mean stiffness of 85.3 ± 12.5 kPa in LVI-positive tumors versus 48.2 ± 10.3 kPa in LVI-negative tumors.[10,11] A threshold of >80 kPa has been proposed for LVI prediction, with a pooled sensitivity of 76% and specificity of 79%.[10]

Other elastography parameters, such as the strain ratio (SR, ratio of tumor stiffness to normal tissue stiffness) and maximum elasticity (E_max), also show promise. Bai et al (2024) developed a nomogram combining SR (>3.5) and E_max (>85 kPa) with clinical factors (tumor size, grade), achieving an AUC of 0.83 for LVI prediction in a multicenter cohort.[11] This model outperformed SWE alone (AUC 0.75), highlighting the value of integrating elastography with clinical data.[11]

However, elastography has limitations: it is less reliable in dense breast tissue (which affects 40% of premenopausal women), and artifacts from patient motion can reduce accuracy.[10,11] Additionally, there is no standardized cutoff for stiffness values across different SWE devices, which hinders cross-center comparisons.[17] Future research should focus on harmonizing SWE protocols and validating stiffness thresholds in diverse patient populations.

The Role of Mammography in the Assessment of LVI

Correlation Between Microcalcifications and LVI

Microcalcifications, detected in 30–50% of breast cancers on mammography, are important indirect markers of LVI, particularly in ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC).[21,22] The distribution and morphology of microcalcifications—including clustered, linear, or pleomorphic patterns—correlate with LVI risk.[21] Clustered microcalcifications (defined as >5 calcifications per cm^2) are the most predictive: a study of 122 IDC patients found that clustered calcifications were present in 67% of LVI-positive tumors versus 32% of LVI-negative tumors, with an OR of 4.2.[21] This association is attributed to the fact that clustered calcifications often arise from necrotic tumor cells, which release calcium phosphate crystals into ductal spaces—an environment that promotes lymphatic invasion.

Linear or branching microcalcifications, though less common (15–20% of cases), are even more strongly linked to LVI: a retrospective analysis of 350 breast cancer patients reported that linear calcifications had a sensitivity of 82% and specificity of 85% for LVI, compared to 72% and 68% for clustered calcifications.[21] These patterns are thought to reflect tumor invasion along ductal-lymphatic pathways, directly indicating LVI potential.[22]

Digital mammography and contrast-enhanced mammography (CEM) have improved microcalcification detection compared to conventional film mammography. CEM, which uses iodine contrast to enhance vascularity, can identify "calcification-associated enhancement"—a sign of increased angiogenesis and LVI risk.[22] A study by Wang et al found

that CEM improved the AUC for LVI prediction from 0.71 (digital mammography) to 0.78 by combining microcalcification patterns with contrast enhancement.[22] However, mammography has limitations: it is less sensitive in dense breasts (sensitivity 50–60% vs 80–90% in fatty breasts), and microcalcifications can also be present in benign conditions (eg, fibrocystic changes), leading to false positives.[16,21]

Imaging Features of Tumor Margins

Tumor margin characteristics on mammography—including spiculated, indistinct, or circumscribed margins—are strong predictors of LVI.[22,23] Spiculated margins, defined as radiating linear densities extending from the tumor edge, are the most specific: a multicenter study of 600 breast cancer patients found that spiculated margins were present in 78% of LVI-positive tumors versus 29% of LVI-negative tumors, with a specificity of 81%.[22] This feature reflects the infiltration of tumor cells into surrounding stroma and lymphatic channels, a key step in LVI.

Indistinct margins (blurred interfaces between tumor and normal tissue) are also associated with LVI, though with lower specificity (68%).[23] A study by Yeom et al (2025) reported that indistinct margins were an independent risk factor for LVI (OR 3.5, 95% CI 2.1–5.8) after adjusting for tumor size and grade.[23] In contrast, circumscribed margins (well-defined tumor edges) are rarely associated with LVI (<10% of cases), making them a reassuring feature.[23]

Digital breast tomosynthesis (DBT), a 3D mammography technique, has improved the detection of margin features compared to 2D mammography. DBT reduces overlapping tissue artifacts, enabling clearer visualization of spicules and indistinct margins. A meta-analysis of 4 studies (n=1,800) found that DBT increased the sensitivity of margin-based LVI prediction from 68% (2D mammography) to 79%.[22] However, DBT has higher radiation dose than 2D mammography and is not universally available.[18] Additionally, inter-radiologist variability in margin assessment remains a challenge, with ICCs of 0.65–0.75 for spiculated margins.[23]

Multimodal Evaluation of MRI in Breast Cancer LVI

Quantitative Parameters of Dynamic Contrast-Enhanced MRI

Dynamic contrast-enhanced MRI (DCE-MRI) is a gold standard for breast cancer imaging, as it quantifies vascular permeability and perfusion—key biomarkers of LVI.[7,15,24] The time-signal intensity curve (TIC), derived from DCE-MRI, classifies tumors into three types: Type I (persistent enhancement), Type II (plateau), and Type III (washout). Type III TIC is strongly associated with LVI: a study of 500 breast cancer patients found that Type III TIC was present in 82% of LVI-positive tumors versus 31% of LVI-negative tumors, with an AUC of 0.80.[7] This pattern reflects rapid contrast uptake (due to increased vascular density) followed by washout (due to high vascular permeability), which facilitates cancer cell invasion into lymphatic/vascular channels.

Quantitative DCE-MRI parameters, such as the transfer constant (Ktrans), extracellular volume fraction (Ve), and rate constant (Kep), further improve LVI prediction. Ktrans, which measures contrast leakage from blood vessels to the extracellular space, is the most predictive: LVI-positive tumors have significantly higher Ktrans values (0.85 ± 0.25 min^{-1} vs 0.42 ± 0.18 min^{-1} in LVI-negative tumors).[7,15] A threshold of Ktrans >0.6 min^{-1} has been proposed, with a sensitivity of 85% and specificity of 82% for LVI.[15] A radiomics model combining Ktrans with TIC type achieved an AUC of 0.83 in a multicenter validation cohort, outperforming qualitative DCE-MRI interpretation (AUC 0.72).[15]

However, DCE-MRI has limitations: it requires intravenous gadolinium contrast (contraindicated in patients with severe renal impairment), has long scan times (30–45 minutes), and is expensive. Additionally, background parenchymal enhancement (BPE)—common in premenopausal women—can obscure tumor vascular features, leading to false negatives.[16,25] Standardization of DCE-MRI protocols (eg, contrast dose, temporal resolution) is needed to improve reproducibility across centers.[17]

Application of Diffusion-Weighted Imaging

Diffusion-weighted imaging (DWI) evaluates water molecule diffusion in tissues, which is restricted in highly cellular tumors—an important correlate of LVI.[8,9] The apparent diffusion coefficient (ADC), derived from DWI, quantifies diffusion restriction: lower ADC values indicate higher cellularity and aggressiveness. LVI-positive tumors have

significantly lower ADC values: a meta-analysis of 10 studies (n=1,800) reported a pooled mean ADC of 980 ± 120 × 10^-6 mm^2/s in LVI-positive tumors versus 1,250 ± 150 × 10^-6 mm^2/s in LVI-negative tumors.[8] An ADC threshold of <1068 × 10^-6 mm^2/s has been validated for LVI prediction, with a sensitivity of 82% and specificity of 80%.[8,9]

The peritumoral-tumoral ADC ratio (P/T ratio) is another promising parameter. Peritumoral tissue (within 5 mm of the tumor) often exhibits increased diffusion restriction due to stromal reaction and lymphatic invasion. A study by Xu et al found that a P/T ratio >1.2 was associated with LVI (OR 4.8, 95% CI 3.1–7.4), and a model combining P/T ratio with ADC threshold achieved an AUC of 0.85.[9] This ratio is particularly useful for small tumors (<1 cm), where ADC alone may be less reliable.[9]

DWI has several advantages over DCE-MRI: it does not require contrast, has shorter scan times (5–10 minutes), and is more reproducible.[8,9] However, DWI is susceptible to artifacts from patient motion and magnetic susceptibility (eg, from metallic implants), which can reduce accuracy.[25] Additionally, ADC values vary by MRI scanner and b-value (diffusion weighting factor), highlighting the need for standardization.[17]

Novel Functional MRI Techniques

Emerging functional MRI techniques, such as intravoxel incoherent motion (IVIM) imaging and magnetic resonance spectroscopy (MRS), offer new insights into tumor biology and LVI risk.[26,27] IVIM distinguishes between true diffusion (D, water diffusion in tissues) and perfusion-related diffusion (D*water diffusion in microvessels), providing simultaneous assessment of cellularity and angiogenesis.[26,27] LVI-positive tumors have lower D values (0.85 ± 0.15 × 10^-6 mm^2/s vs 1.12 ± 0.18 × 10^-6 mm^2/s) and higher D* values (25.3 ± 5.2 × 10^-6 mm^2/s vs 18.2 ± 4.1 × 10^-6 mm^2/s) compared to LVI-negative tumors.[26] A study by Jiang et al (2024) developed an IVIM-based radiomics signature that achieved an AUC of 0.82 for LVI prediction, outperforming conventional DWI (AUC 0.75).[27]

MRS identifies metabolic biomarkers of aggressiveness, such as choline (Cho, a marker of cell proliferation) and creatine (Cr, a reference metabolite). The Cho/Cr ratio is elevated in LVI-positive tumors (2.8 ± 0.6 vs 1.5 ± 0.4 in LVI-negative tumors).[26] A study of 200 breast cancer patients found that a Cho/Cr ratio >2.0 had a sensitivity of 78% and specificity of 75% for LVI.[26] However, MRS has low spatial resolution (1–2 cm^3), making it unsuitable for small tumors, and requires specialized post-processing software.[18,26]

These novel techniques show promise, but they are not yet widely available in clinical practice. Future research should focus on validating IVIM and MRS parameters in multicenter trials and integrating them into routine MRI protocols.

Artificial Intelligence and Radiomics in Predicting LVI

Radiomics Feature Extraction and Model Construction

Radiomics is a quantitative imaging technique that extracts a vast array of features from medical images, enabling the assessment of tumor heterogeneity and the characteristics of the tumor microenvironment that are not discernible to the naked eye.[4,12,22,28,29] The features derived from radiomics can be classified into four main categories. First, first-order statistics provide insights into the distribution of pixel intensities, including metrics such as mean, median, and entropy. Second, shape-based features focus on the geometric properties of tumors, measuring aspects like volume and sphericity. Third, textural features analyze the spatial patterns of pixel intensities, utilizing methods such as the gray-level co-occurrence matrix (GLCM) entropy and the gray-level run-length matrix (GLRLM) energy to quantify these patterns. Lastly, wavelet features employ wavelet transformations to capture texture information across multiple scales, enhancing the understanding of the tumor's complexity.

Textural features, particularly GLCM entropy (a measure of heterogeneity), are most predictive of LVI. A study of 300 breast cancer patients found that GLCM entropy was significantly higher in LVI-positive tumors (6.2 ± 0.8 vs 4.5 ± 0.6 in LVI-negative tumors), with an OR of 3.9.[12] Radiomics models combining multiple features have shown excellent performance: a DCE-MRI-based radiomics signature (28 features) achieved an AUC of 0.763 in the validation cohort, and integrating clinical factors (tumor grade, ER status) improved the AUC to 0.81.[15] In esophageal squamous cell

carcinoma (ESCC), a CT-based radiomics signature (28 features) achieved an AUC of 0.77 in the training cohort and 0.74 in the validation cohort for LVI prediction, demonstrating cross-tumor applicability.[28]

Feature selection is a critical step in radiomics model construction, as it reduces dimensionality and avoids overfitting. The least absolute shrinkage and selection operator (LASSO) is the most commonly used method, as it selects relevant features and penalizes redundant ones.[29] For example, Li et also used LASSO to reduce 1,032 CT features to 12 non-redundant features, improving model reproducibility (ICC >0.85).[29] However, radiomics faces challenges: feature extraction is operator-dependent, and there is no standardized protocol for feature calculation, leading to inconsistencies across studies.[17] The Image Biomarker Standardization Initiative (IBSI) has developed guidelines to address this, but adoption remains limited.[17]

Application of Deep Learning Techniques

Deep learning, particularly convolutional neural networks (CNNs), has revolutionized medical imaging by enabling end-to-end LVI prediction without manual feature extraction.[12,13,30] CNNs automatically learn hierarchical features from images—from low-level edges to high-level tumor patterns—and have outperformed traditional radiomics in several studies.[13] A 3D-CNN model analyzing breast MRI volumes (12 convolutional layers, skip connections) achieved an AUC of 0.896 for LVI prediction, focusing on peritumoral enhancement patterns that are missed by radiologists.[12] In node-negative breast cancer, a MRI-based CNN model achieved an AUC of 0.87, outperforming radiomics (AUC 0.78).[13]

Hybrid models that combine deep learning with clinical data have further improved performance. A study by Tong et al (2023) developed a model integrating biparametric MRI (DCE + DWI) CNN features with clinical factors (Ki-67 index, molecular subtype), achieving an AUC of 0.89 for LVI prediction in rectal cancer.[30] This model outperformed CNN alone (AUC 0.82) and clinical data alone (AUC 0.65), highlighting the value of multi-modal integration.[30]

Deep learning, particularly Convolutional Neural Networks (CNNs), faces several notable limitations that impact its effectiveness in clinical settings. One major issue is data dependency; CNNs require extensive, annotated datasets—often consisting of thousands of cases—to prevent overfitting. However, many existing studies rely on small, single-center datasets with fewer than 500 cases, which restricts the generalizability of the findings.[13] Another significant limitation is interpretability; CNNs are often referred to as "black boxes" because it is challenging to identify the specific features that influence their predictions, which can diminish trust among clinicians.[13,30] Although techniques such as gradient-weighted class activation mapping (Grad-CAM) have been developed to visualize the decision-making process of CNNs, they primarily highlight regions of interest rather than pinpointing specific biological features.[13] Lastly, reproducibility is a concern, as variations in MRI and CT protocols—such as differences in scanner types and sequence parameters—can adversely affect CNN performance.[17] This is particularly problematic since models are typically trained on specific imaging datasets, making them less adaptable to diverse clinical environments. Future research should focus on developing federated learning models (to pool data across centers without sharing patient information) and improving interpretability through explainable AI (XAI) techniques.

Multimodal Imaging Combined Assessment Strategies

Complementarity of Ultrasound and MRI

The integration of ultrasound (elastography/CEUS) and MRI (DCE + DWI) leverages the strengths of both modalities, improving LVI prediction accuracy.[31] Ultrasound provides real-time, cost-effective assessment of tissue stiffness and microvascularity, while MRI offers high-resolution soft tissue contrast and quantitative vascular/perfusion parameters.[31] A study by Wang et al developed a multimodal model combining SWE (stiffness >80 kPa), CEUS (PI >25 dB), DCE-MRI (Type III TIC), and DWI (ADC <1068 × 10^-6 mm^2/s), achieving an AUC of 0.91 for LVI prediction—significantly higher than any single modality (ultrasound AUC 0.78, MRI AUC 0.83).[31] This model was particularly effective in dense breasts, where ultrasound elastography compensated for MRI artifacts from BPE.

Another example is the combination of CEUS and IVIM-MRI: CEUS quantifies macro-vascular perfusion, while IVIM assesses micro-vascular diffusion. A study of 200 breast cancer patients found that this combination achieved an

AUC of 0.88 for LVI prediction, compared to 0.81 for CEUS alone and 0.82 for IVIM alone.[31] The complementarity of these modalities lies in their ability to capture different aspects of tumor angiogenesis—CEUS focuses on large vessels, while IVIM targets microvessels—providing a comprehensive view of LVI risk.[31]

However, multimodal imaging has logistical challenges: it requires coordination between ultrasound and MRI departments, increases scan time (1–2 hours), and raises costs. Additionally, there is no standardized workflow for combining modalities (eg, which modality to perform first), leading to variability in clinical practice. Future efforts should focus on developing integrated imaging protocols and reducing scan time through parallel imaging techniques.

Integration of Imaging and Clinical Pathological Factors

The integration of imaging features with clinical and pathological factors (eg, tumor grade, ER status, Ki-67 index) significantly enhances LVI prediction, as it captures both tumor biology and imaging phenotypes.[4,12,32] A multicenter trial of 500 breast cancer patients developed a nomogram combining MRI features (tumor irregularity, Type III TIC), clinical factors (ER status, Ki-67 >20%), and a radiomics signature, achieving an AUC of 0.82 for LVI prediction.[32] This nomogram outperformed models using imaging alone (AUC 0.71) or clinical data alone (AUC 0.65), as it accounted for confounding factors like tumor grade (which correlates with both LVI and imaging features).[32]

Another example is the integration of ultrasound elastography with pathological markers: a study of 350 breast cancer patients found that a model combining SWE (E_max >85 kPa) with Ki-67 index (>20%) and HER2 status achieved an AUC of 0.84 for LVI prediction, compared to 0.75 for SWE alone.[11] This model was particularly useful for luminal A tumors, where imaging features alone are less predictive of LVI.[11]

Machine learning techniques, such as random forests and logistic regression, are essential for integrating multi-modal data. A random forest model combining 10 imaging features, 5 clinical factors, and 3 pathological markers achieved an AUC of 0.86 in a validation cohort, with excellent calibration (Hosmer-Lemeshow p=0.72).[32] However, the integration of clinical data requires electronic health record (EHR) integration, which is challenging in settings with fragmented data systems.[18] Additionally, missing data (eg, unavailable Ki-67 results) can reduce model performance, highlighting the need for imputation techniques and robust data collection.[32]

Current Limitations of Technology and Future Directions

Sensitivity and Specificity Issues in Imaging Assessment

Despite advancements in imaging technology, challenges related to sensitivity and specificity continue to affect the prediction of lymphovascular invasion (LVI), resulting in both false positives and false negatives.[16,25] False positives often arise from benign conditions that exhibit imaging features similar to those associated with LVI. For instance, inflammatory processes such as mastitis and granulomatous diseases can lead to increased vascularity observed in contrast-enhanced ultrasound (CEUS) and magnetic resonance imaging (MRI), which may mimic the angiogenesis typically seen in LVI. Additionally, these conditions can produce microcalcifications on mammography that resemble tumor-related calcifications. A study involving 200 benign breast lesions revealed that 15% were incorrectly classified as LVI-positive on CEUS due to elevated perfusion index (PI) values.[16] Furthermore, benign tumors like fibroadenomas with adenosis can show posterior acoustic attenuation on ultrasound, which can be mistaken for LVI-positive tumors, and exhibit Type II time-intensity curves (TIC) on dynamic contrast-enhanced MRI, resembling more aggressive tumors.[16]

False negatives in cancer detection often arise from technical limitations and the characteristics of tumors. For instance, small tumors measuring less than 1 cm typically exhibit fewer features associated with lymphovascular invasion (LVI), such as subtle irregularities at the margins and low vascular density. This results in a reduced sensitivity of ultrasound, which is around 45%, and mammography, which stands at approximately 40%.[19,21] Additionally, background parenchymal enhancement (BPE) in premenopausal women can obscure the vascular features of tumors on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), leading to false negatives in 12% to 18% of cases.[25] Artifacts also play a significant role; motion artifacts caused by patient breathing and magnetic susceptibility artifacts from metallic implants can diminish the accuracy of apparent diffusion coefficient (ADC) measurements, resulting in false negatives in 10% to 15% of cases.[25]

To tackle these challenges, several strategies are currently being explored. Advanced image processing techniques, such as wavelet denoising algorithms, have been shown to enhance the quality of diffusion-weighted imaging (DWI) and reduce ADC variability by 20%.[25] The use of dual-modal contrast agents, particularly nanoparticle agents that target both vascular and lymphatic markers like CD44 and D2-40, can improve specificity by effectively distinguishing between tumor and benign vascularity.[17] Furthermore, artificial intelligence-assisted interpretation, particularly through convolutional neural networks (CNNs) trained on extensive datasets of benign and malignant lesions, has demonstrated a reduction in false positive rates by 30% on mammography and 25% on MRI.[13,16]

Emerging Technologies and Standardization Needs

Emerging imaging technologies show great potential for enhancing the assessment of LVI, but achieving standardization is essential for their integration into clinical practice.[17] Notable advancements in this area include Optical Coherence Tomography (OCT), which offers high-resolution images of breast tissue microstructures, allowing for direct visualization of lymphatic and vascular channels. A preclinical study involving breast cancer xenografts demonstrated that OCT could detect LVI with a sensitivity of 90% and specificity of 88% by identifying tumor cells within lymphatic vessels.[17] Another promising technology is nanoparticle-enhanced imaging, specifically the use of superparamagnetic iron oxide (SPIO) nanoparticles that accumulate in lymph nodes, thereby enhancing MRI visualization of lymphatic invasion. A Phase II trial involving 50 breast cancer patients revealed that SPIO-MRI improved the sensitivity of LVI detection from 78% with conventional MRI to 92%.[17] Additionally, photoacoustic imaging (PAI) merges ultrasound and optical imaging to quantify hemoglobin concentration, a marker of angiogenesis. A preclinical study indicated that PAI could effectively differentiate between LVI-positive and LVI-negative tumors, achieving an area under the curve (AUC) of 0.87 by detecting increased peritumoral hemoglobin.[17] However, the need for standardization is urgent to ensure reproducibility across these imaging modalities. For instance, the International Breast Imaging Society (IBIS) has proposed standardized dynamic contrast-enhanced MRI (DCE-MRI) protocols, such as a gadolinium dose of 0.1 mmol/kg and a temporal resolution of 60 seconds, yet adoption remains below 50% across various centers.[17] Furthermore, while the IBSI has established standardized definitions for radiomics features, only 30% of studies adhere to these guidelines, resulting in inconsistent findings.[17] Additionally, there is no consensus on reference standards for LVI, such as whether to rely solely on hematoxylin and eosin (HE) staining or to include immunohistochemistry (IHC), which contributes to variability in reported sensitivity and specificity. Future research should prioritize the development of international consensus guidelines and the mandatory registration of imaging protocols for studies to enhance the reliability and applicability of these emerging technologies in clinical settings.

Challenges in Clinical Translation

Despite the promising results seen in preclinical studies and single-center trials, many imaging technologies encounter significant obstacles when it comes to clinical implementation.[18] One of the primary challenges is cost and accessibility; advanced imaging modalities such as MRI and optical coherence tomography (OCT) are prohibitively expensive and are not available in 40% of low- and middle-income countries (LMICs).[18] Even in high-income nations, contrast-enhanced ultrasound (CEUS) is only accessible in 60% of hospitals, largely due to the high costs associated with contrast agents.[18] Another significant barrier is the training requirements for radiologists; many AI models and new imaging techniques, like intravoxel incoherent motion MRI (IVIM-MRI), necessitate specialized training.[18] A survey involving 200 radiologists revealed that 70% felt they lacked adequate training to interpret radiomics results, and 65% had no experience with IVIM. Additionally, the majority of studies in this field are conducted at single centers, with 75% of radiomics studies featuring small sample sizes of fewer than 300 participants. A meta-analysis focusing on AI models for lymphovascular invasion (LVI) prediction indicated that only 15% of these models had undergone external multicenter validation, which often leads to an overestimation of their performance.[13,18] Regulatory approval also poses a challenge, as AI models must obtain clearance, such as the FDA 510(k) in the United States, a process that can take 1 to 2 years and incur significant costs. Alarmingly, only 5% of AI models for breast cancer have received such regulatory approval. To address these barriers, several strategies can be implemented.[18] First, reducing costs through the use of low-field MRI machines, which are priced around $500,000, and portable ultrasound devices costing between $10,000 and $50,000, can

enhance accessibility in LMICs. Second, establishing training programs, including online courses from organizations like the Radiological Society of North America and hands-on workshops, can help improve radiologists' proficiency in AI and emerging imaging modalities.[18] Lastly, fostering public-private partnerships that bring together academic institutions, industry stakeholders, and government entities can provide the necessary funding for multicenter trials and facilitate the regulatory approval process, as exemplified by initiatives like the NIH's Bridge2AI program.[18]

Conclusion

Preoperative imaging assessment of LVI in breast cancer has made significant strides in recent years, with advancements in ultrasound, MRI, and AI transforming clinical practice. This review has critically synthesized the evidence, highlighting that multimodal imaging—combining ultrasound elastography/CEUS with MRI (DCE + DWI)—achieves the highest accuracy for LVI prediction (AUC 0.88–0.91), outperforming single modalities.[31,32] AI-assisted tools, particularly 3D-CNNs and radiomics nomograms, further enhance performance by capturing subtle tumor heterogeneity, though their clinical adoption is limited by data dependency and interpretability issues.[12,13]

However, substantial limitations remain: variable sensitivity/specificity across modalities (eg, ultrasound sensitivity 60–75% vs MRI 78–90%), lack of standardization (eg, inconsistent ADC thresholds, radiomics protocols), and barriers to clinical translation (eg, cost, training, regulatory approval).[7,8,17–19] These gaps underscore the need for urgent action to harmonize imaging protocols, validate AI models in multicenter trials, and improve accessibility in resource-limited settings.

The future of LVI assessment lies in integrated, patient-centric workflows: combining novel technologies (OCT, nanoparticle-enhanced MRI) with AI and clinical data to deliver personalized risk stratification.[17] For example, a federated learning model trained on global datasets (to address data scarcity) and integrated with EHRs could provide real-time LVI prediction at the point of care. Additionally, standardization initiatives—led by organizations like IBIS and IBSI—will be critical to ensuring reproducibility and trust in imaging results.[17]

In conclusion, preoperative imaging for LVI assessment has the potential to revolutionize breast cancer care, by enabling earlier, more accurate treatment decisions. However, realizing this potential requires collaboration between researchers, clinicians, industry, and policymakers to address technical, logistical, and regulatory challenges. By prioritizing standardization, validation, and accessibility, we can translate scientific advancements into improved outcomes for breast cancer patients worldwide.

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