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Research Progress on the Correlation and Predictive Value of Multimodal Ultrasound Imaging Features with Immunohistochemical Subtypes of Intrahepatic Cholangiocarcinoma

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Abstract

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy and is characterized by substantial biological heterogeneity and poor prognosis. Immunohistochemical (IHC) biomarkers, including cytokeratin-19 (CK-19), Ki-67, and S100P, provide important information regarding tumor differentiation, proliferative activity, and aggressive behavior. However, definitive evaluation of these biomarkers typically relies on postoperative pathological examination or invasive biopsy procedures. Therefore, identifying reliable non-invasive imaging biomarkers capable of predicting IHC phenotypes before treatment is of considerable clinical importance. Multimodal ultrasound (US), integrating conventional B-mode imaging, color Doppler flow imaging (CDFI), contrast-enhanced ultrasound (CEUS), and elastography, enables comprehensive characterization of tumor morphology, vascular perfusion dynamics, and mechanical tissue properties. Increasing evidence suggests that these imaging features reflect underlying tumor microenvironment and molecular characteristics. In particular, CEUS enhancement patterns—such as arterial-phase peripheral rim enhancement, heterogeneous perfusion, and early washout—together with increased stiffness measured by elastography, have been associated with aggressive biological behavior and higher proliferative activity in ICC. Recent advances in quantitative imaging analysis, radiomics, and artificial intelligence (AI) have further expanded the potential of ultrasound-based biomarkers for predicting tumor biology. By extracting high-dimensional imaging features and integrating clinical variables, machine-learning models have demonstrated promising performance in predicting Ki-67 expression, microvascular invasion, and tumor subtype. This review summarizes current evidence regarding the correlation between multimodal ultrasound features and IHC markers in ICC, discusses emerging quantitative imaging techniques, and highlights future directions for developing imaging-based predictive models that may facilitate individualized treatment planning and precision oncology.

Keywords

Intrahepatic Cholangiocarcinoma, Multimodal Ultrasound, Contrast-Enhanced Ultrasound, Immunohistochemistry

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) originates from epithelial cells of the intrahepatic bile ducts and represents approximately 10% - 20% of primary liver malignancies. The global incidence of ICC has increased steadily over the past several decades. Despite advances in surgical techniques and systemic therapies, the overall prognosis remains poor, with five-year survival rates typically below 30%.

One major challenge in the management of ICC is its remarkable biological heterogeneity [1]. Tumor behavior varies widely among patients and depends on molecular and histopathological characteristics. Immunohistochemical biomarkers such as CK-19, Ki-67, and S100P have been widely investigated because they reflect tumor differentiation, proliferation, and aggressiveness. High Ki-67 expression, for instance, indicates increased proliferative activity and is frequently associated with poor prognosis, microvascular invasion, and higher recurrence rates. Similarly, S100P overexpression has been linked to the large-duct subtype of ICC and more aggressive clinical behavior [2].

However, assessment of these biomarkers generally requires histopathological analysis after surgical resection or biopsy [3]. Biopsy procedures are invasive and may be limited by sampling error or tumor heterogeneity. Consequently, there is increasing interest in developing imaging biomarkers capable of predicting tumor biology non-invasively. Among available imaging modalities, ultrasound has several advantages, including real-time imaging capability, wide availability, absence of ionizing radiation, and relatively low cost [4] [5]. The concept of multimodal ultrasound integrates structural, functional, and mechanical information derived from several complementary techniques, including B-mode ultrasound, color Doppler imaging, contrast-enhanced ultrasound, and elastography [6]. These modalities provide detailed insights into tumor morphology, vascular architecture, perfusion dynamics, and tissue stiffness. Because these characteristics are closely related to tumor microenvironment and stromal composition, they may serve as indirect indicators of molecular phenotype [7].

The aim of this review is to summarize current knowledge regarding the relationship between multimodal ultrasound imaging features and immunohistochemical subtypes of ICC, with particular emphasis on CK-19, Ki-67, and S100P. In addition, emerging technologies such as radiomics and artificial intelligence are discussed [8], as they may further enhance the predictive value of ultrasound imaging in the era of precision medicine.

2. Multimodal Ultrasound Techniques in ICC

Ultrasound plays a central role in the evaluation of liver tumors. Modern ultrasound technology has evolved beyond conventional grayscale imaging and now includes several complementary techniques that provide both structural and functional information [9].

B-mode ultrasound remains the first-line imaging modality for detecting focal liver lesions. Typical ICC lesions appear as irregular hypoechoic masses with lobulated or ill-defined margins. Associated findings may include bile duct dilatation, capsular retraction, and satellite nodules. These morphological characteristics may reflect infiltrative growth patterns and fibrotic stromal reactions within the tumor [10].

Color Doppler flow imaging (CDFI) provides information about macroscopic vascularity. ICC lesions often demonstrate relatively sparse internal vascular signals but increased peripheral vascularity due to tumor angiogenesis and desmoplastic stromal reaction. Although Doppler imaging alone has limited sensitivity for detecting microvascular flow, it may provide useful supplementary information regarding tumor vascular architecture [11].

Contrast-enhanced ultrasound (CEUS) has emerged as one of the most important tools for evaluating focal liver lesions [12]. CEUS utilizes microbubble contrast agents that remain strictly intravascular, enabling real-time visualization of tumor perfusion dynamics during arterial, portal, and late phases. ICC typically demonstrates peripheral rim-like hyperenhancement in the arterial phase followed by early washout during portal or late phases [13]. This characteristic enhancement pattern reflects abundant neovascularization at the tumor periphery and reduced vascular density within central fibrotic regions.

Elastography techniques, including shear-wave elastography and strain elastography, allow quantitative or semi-quantitative assessment of tissue stiffness [14]. ICC lesions are generally stiffer than surrounding liver parenchyma because of their abundant fibrous stroma. Measurements of tumor stiffness may therefore provide indirect information regarding stromal composition and tumor microenvironment.

The integration of these modalities forms the basis of multimodal ultrasound imaging, which offers a comprehensive evaluation of tumor morphology, vascular perfusion, and mechanical properties [15].

For clarity and consistency across studies, several key terms are defined as follows:

- Large-duct subtype: A histological subtype of ICC arising from large intrahepatic bile ducts, typically associated with mucin production, ductal dilatation, and more aggressive behavior.

- Early washout: A reduction in contrast enhancement relative to surrounding liver parenchyma occurring within approximately 60 seconds after contrast injection on CEUS, reflecting rapid contrast clearance.
- Hypovascular or non-perfused core ratio: The proportion of intratumoral regions showing little or no enhancement during the arterial phase, often corresponding to necrosis or dense fibrosis.

3. Correlation between Imaging Features and Immunohistochemical Markers

To enhance methodological transparency, the evidence discussed in this section is explicitly categorized as direct evidence or extrapolative evidence. Direct evidence refers to studies that specifically evaluate correlations between ultrasound (particularly CEUS) features and immunohistochemical (IHC) biomarkers in ICC cohorts. Extrapolative evidence includes findings derived from MRI-based studies, hepatocellular carcinoma (HCC), or combined hepatocellular-cholangiocarcinoma (cHCC-CCA), where overlapping biological mechanisms are assumed but not directly validated in ICC using ultrasound [16]. Given the limited number of ICC-specific ultrasound-IHC studies, some associations discussed below should be interpreted as biologically plausible but not yet conclusively validated.

3.1. Ki-67 (Relatively Strong Evidence)

Ki-67 is a well-established marker of tumor proliferative activity and has been the most extensively studied biomarker in imaging-pathology correlation research. Studies have demonstrated that ICC lesions with high Ki-67 expression often exhibit aggressive imaging features, including irregular margins, heterogeneous internal structure, and rapid perfusion kinetics on CEUS [17]. Arterial-phase peripheral hyperenhancement followed by early washout has been associated with increased proliferative activity and higher likelihood of microvascular invasion.

- Direct evidence (ICC-specific ultrasound studies): Several CEUS-based studies have demonstrated that high Ki-67 expression is associated with: Irregular or infiltrative tumor margins, Heterogeneous internal echotexture, Arterial-phase peripheral rim hyperenhancement, Early washout in portal or late phases. These findings suggest that aggressive proliferative activity corresponds to disorganized tumor angiogenesis and reduced vascular integrity.
- Inferential evidence: MRI radiomics and elastography studies further support that higher Ki-67 expression correlates with: Increased tissue stiffness, Higher intratumoral heterogeneity [18].

Ki-67 currently has the strongest and most consistent imaging correlation, particularly with CEUS perfusion dynamics.

3.2. S100P (Limited Direct Evidence, Moderate Biological Plausibility)

S100P is a calcium-binding protein that has been linked to tumor invasion and metastasis. S100P is associated with the large-duct subtype of ICC, which is characterized by more aggressive biological behavior [19]. Imaging features suggestive of this subtype include segmental bile duct dilatation, infiltrative growth patterns, and heterogeneous enhancement on CEUS. Although direct imaging predictors of S100P expression remain limited, the association between large-duct morphology and S100P positivity suggests potential imaging correlations.

- Direct evidence: Currently, ultrasound-based studies directly correlating S100P expression are scarce.
- Inferential evidence: Large-duct ICC often presents with: Bile duct dilatation, Periductal infiltrative growth, and heterogeneous enhancement patterns.

These features have been observed in CEUS and cross-sectional imaging. The association between imaging features and S100P remains indirect and hypothesis-driven, primarily inferred from morphological subtype characteristics rather than direct validation [20].

3.3. CK-19 (Widely Expressed, Weak Discriminatory Value)

CK-19 is a marker of biliary epithelial differentiation and is expressed in the majority of ICC cases.CK-19 is a marker of biliary epithelial differentiation and is strongly expressed in most ICC cases. Imaging findings reflecting biliary differentiation—such as ductal dilatation and infiltrative growth along portal tracts—may indirectly indicate CK-19 positivity [21]. However, because CK-19 expression is highly prevalent in ICC, imaging studies often focus more on biomarkers with greater biological variability, such as Ki-67.

- Direct evidence: Limited ICC-specific ultrasound studies have evaluated CK-19 due to its high baseline positivity rate.
- Inferential evidence: Imaging features suggesting biliary differentiation include: Ductal dilatation, Portal tract infiltration.

Studies in HCC indicate CEUS/radiomics may predict CK-19 positivity, but extrapolation to ICC is limited [22]. Although biologically important, CK-19 has limited value as an imaging prediction target in ICC due to low variability. Overall, the correlation between imaging features and immunohistochemical markers highlights the potential of ultrasound-based imaging biomarkers to predict tumor biology non-invasively [23].

4. Quantitative Imaging Biomarkers

Beyond qualitative imaging assessment, quantitative imaging parameters derived from CEUS and elastography have attracted increasing attention [24]. For example, the proportion of non-enhancing intratumoral regions during the arterial phase—often described as the hypovascular or non-perfused core ratio—may reflect necrosis or dense fibrosis within the tumor. Larger hypovascular cores have been associated with aggressive tumor behavior and higher proliferative indices [25].

Another important parameter is contrast washout timing. Early washout during the portal phase may indicate abnormal tumor microcirculation and poor vascular integrity [26]. Quantitative analysis of time-intensity curves allows objective measurement of perfusion kinetics, including peak intensity, time to peak, and washout slope.

Elastography measurements provide quantitative assessment of tissue stiffness. Higher stiffness values may reflect increased fibrotic stroma and desmoplastic reaction, both of which are common features of aggressive ICC [27]. Combining perfusion-related parameters with stiffness measurements may improve the predictive accuracy of imaging biomarkers.

Heterogeneity and Atypical CEUS Patterns in ICC. Although peripheral rim enhancement and early washout are considered characteristic CEUS features of ICC, substantial heterogeneity exists [28]. A subset of ICC lesions may exhibit: Homogeneous hyperenhancement in the arterial phase, Delayed or mild washout, even HCC-like vascular patterns in cirrhotic livers. This variability may be influenced by: Tumor size, Fibrotic content, Underlying liver disease (e.g., viral hepatitis). This heterogeneity limits the reliability of single imaging features as predictors of IHC biomarkers. Overreliance on "typical" patterns (e.g., rim enhancement + early washout) may lead to oversimplified biological interpretation.

5. Radiomics and Artificial Intelligence

Radiomics refers to the extraction of large numbers of quantitative imaging features from medical images using advanced computational algorithms. These features capture subtle patterns related to tumor heterogeneity that may not be visible to the human eye [29]. When combined with machine-learning techniques, radiomic features can be used to build predictive models for tumor classification, prognosis, and treatment response.

Recent studies have applied radiomics analysis to ultrasound and CEUS images of liver tumors. Texture features derived from CEUS images have shown potential in differentiating ICC from hepatocellular carcinoma and in predicting biological characteristics such as Ki-67 expression [30]. Deep-learning models based on convolutional neural networks have also demonstrated promising results for automatic lesion detection and classification [31].

The integration of radiomics features with clinical variables and laboratory biomarkers may further improve predictive performance [32]. However, most current studies are retrospective and involve relatively small cohorts. Prospective multicenter validation is needed before these models can be widely implemented in clinical practice [33].

6. Clinical Implications

The clinical value of multimodal ultrasound lies in its ability to provide biomarker-oriented risk stratification [34].

- Ki-67-related applications: CEUS features such as arterial-phase rim enhancement, early washout, and high hypovascular core ratio are most relevant for identifying tumors with high proliferative activity. These findings may inform: Surgical aggressiveness, Need for adjuvant therapy, and Prognostic assessment.

- S100P-related implications: Imaging features suggestive of large-duct subtype (e.g., bile duct dilatation, infiltrative growth) may indicate potential S100P positivity, although further validation is required.
- CK-19-related implications: Due to its high prevalence, CK-19 has limited utility for imaging-based stratification in ICC, and its prediction remains secondary compared with proliferation markers.

Overall, current evidence supports a Ki-67-centered imaging strategy, while predictions of S100P and CK-19 remain exploratory [35].

7. Limitations and Future Perspectives

Despite promising findings, several limitations remain in the current literature. Many studies are retrospective and involve small sample sizes, which limits statistical power. Ultrasound imaging is also operator-dependent, and variations in scanning technique or equipment settings may influence imaging features.

Future research should focus on establishing standardized imaging protocols and quantitative measurement methods. Large multicenter studies with external validation are necessary to confirm imaging-biomarker correlations. The integration of multimodal imaging data with genomic and transcriptomic information may further enhance our understanding of tumor biology. Emerging technologies such as targeted molecular contrast agents and advanced AI algorithms may also expand the capabilities of ultrasound imaging in precision oncology [36] [37].

8. Conclusions

Multimodal ultrasound provides a comprehensive and non-invasive approach for evaluating intrahepatic cholangiocarcinoma. By integrating morphological assessment, perfusion analysis, and tissue stiffness measurements, ultrasound imaging can capture key aspects of tumor biology [38]. CEUS features—particularly peripheral arterial enhancement, heterogeneous perfusion, and early washout—together with increased elastographic stiffness, have been associated with aggressive tumor phenotypes and higher proliferative activity.

Advances in quantitative imaging analysis, radiomics, and artificial intelligence are expected to further enhance the predictive value of ultrasound-based biomarkers. Although additional validation studies are needed, multimodal ultrasound holds significant promise for the non-invasive prediction of immunohistochemical subtypes and personalized management of ICC patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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