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Advancements in Ultrasound Imaging for Assessing the biological behavior of Hepatocellular Carcinoma

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Abstract: Since the advent of contrast-enhanced ultrasound technology in 1968, with the continuous innovation of contrast agents, the increasing refinement of the resolution of ultrasound equipment, and the vigorous development of new imaging technologies, this technology has gradually demonstrated its irreplaceable unique advantages in many fields such as the diagnosis, treatment, and efficacy evaluation of hepatocellular carcinoma (HCC). It can not only provide more accurate medical imaging support, but also is expected to reveal more biological characteristics of HCC, providing a solid basis for personalized treatment decisions in the era of precision medicine.

Keywords: Contrast-enhanced Ultrasound; Hepatocellular Carcinoma; Biological Behavior.

1. Introduction

Hepatocellular carcinoma (HCC) represents a significant contributor to cancer-related mortality globally, with both its incidence and fatality rates on the rise[1]. A majority of HCC-related fatalities stem from chronic liver conditions induced by hepatitis B or C viral infections, alcohol-induced liver damage, and a growing prevalence of non-alcoholic fatty liver disease. HCC is the predominant form of primary liver cancer, comprising roughly 75-85% of all cases[2]. Although radical resection remains the primary approach for achieving long-term survival, post-treatment recurrence is prevalent in HCC patients. Studies indicate that following surgical removal, the 5-year recurrence rate can be as high as 70%, while after liver transplantation, this figure stands between 15-30%[3]. The biological behavior of hepatocellular carcinoma (HCC) is strongly correlated with the histological features of hepatocytes, the level of differentiation, and the presence of microvascular invasion, which serve as key independent indicators for predicting post-treatment recurrence and survival outcomes[4].

The degree of differentiation of hepatocellular carcinoma can be categorized into four grades according to the Edmondson-Steiner classification system. Higher grades indicate lower differentiation and greater biological behavior[4]. Microvascular invasion (MVI), a prominent research focus in recent years, is defined as the microscopic observation of cancer cell clusters within the lumen of blood vessels lined by endothelial cells. MVI is considered the initial stage of both intrahepatic and extrahepatic metastasis in primary liver cancer. The presence of MVI can serve as an important criterion for determining a wider resection margin during surgical tumor removal[5].Furthermore, in recent years, biomarkers such as Ki-67, GPC3, and CD34 have emerged as significant research focal points for predicting the recurrence and metastasis of hepatocellular carcinoma[6].

However, at present, these pathological indicators can only be diagnosed through biopsy or after tumor resection[4]. Therefore, the use of non-invasive and reliable diagnostic tools before surgery will provide important reference for the surgical treatment plan of liver cancer. In recent years, with the development of two-dimensional ultrasound, contrast-enhanced ultrasound, and ultrasound elastography, the diagnostic efficiency has been improved, and they are increasingly used to predict the prognosis of hepatocellular carcinoma. This article reviews the research progress of ultrasound examination in evaluating the biological behavior of hepatocellular carcinoma.

2. Two-dimensional Grayscale Ultrasound as a Diagnostic Tool for Assessing the Biological Behavior of Hepatocellular Carcinoma

Two-dimensional (2D) gray-scale ultrasound constitutes the foundation of hepatocellular carcinoma (HCC) diagnosis and serves as the primary imaging modality for HCC screening. Ultrasound examination reliably detects liver nodules, with their characteristics varying according to tumor size. Previous studies have demonstrated that nodules smaller than 2 cm often lack definitive characterization, whereas those larger than 2 cm typically exhibit characteristic ultrasound features[7]. Small nodules ar categoried into two groups based on the classification proposed by Moribana et al., depending on the presence or absence of a halo: type 1 (with a halo) and type 2 (without a halo)[8]. Type 2 is further subdivided into three subgroups: type 2a, which is homogeneous hyperechoic; type 2b, which is hypoechoic with a smooth edge; and type 2c, which is hypoechoic with an irregular or blurred edge. The malignant potential progressively increases across these three subtypes. Research on the ultrasound characteristics of liver nodules has highlighted differences in malignancy among the various subtypes of small nodules, indicating that this classification aids in early diagnosis and assessment.

As the size of hepatocellular carcinoma (HCC) lesions increases, the likelihood of microvascular invasion (MVI) also rises due to the involvement of a greater number of liver tissues and microvessels. Research has demonstrated that larger tumor volumes are associated with increased microvascular formation, thereby elevating the risk of MVI. However, certain studies have observed that in patients with

solitary HCC, tumor size correlates with poorer postoperative recurrence and survival rates, even in the absence of MVI[9]. Long-term follow-up studies have shown that for patients with solitary HCC, tumor size remains a significant factor influencing postoperative outcomes and survival rates, independent of MVI status[10]. Despite this, a larger tumor volume continues to serve as an important reference point. In assessing the prognosis and formulating treatment plans for HCC patients, clinicians must consider tumor volume as a critical indicator[11].

3. Doppler Ultrasound Assessment of the Biological Behavior of Hepatocellular Carcinoma

As a vital medical imaging technique, Doppler ultrasound offers detailed visualizations of blood flow within and around hepatocellular carcinoma (HCC) lesions. This technology encompasses several imaging modalities, such as color Doppler flow imaging, power Doppler imaging, superb Micro-vascular Imaging (SMI), and micro-flow imaging (MFI).

Power Doppler imaging is a well-established and extensively utilized method that excels in detecting low-velocity blood flow and fine vascular structures. Extensive research has demonstrated its effectiveness in capturing blood flow signals from tiny vessels, providing crucial insights for diagnosing various conditions[12]. By presenting vessel details through energy-based signals, this technique demonstrates superior sensitivity to traditional methods when identifying small vessels and slow-moving blood flow.

Relevant studies have shown that color Doppler ultrasound, with its unique imaging mechanism, can present the blood flow conditions of tumors and their surrounding tissues in real time and dynamically, providing important technical support for in-depth research on the hemodynamic characteristics of hepatocellular carcinoma. Through this technology, researchers can gain a more comprehensive understanding of the changes in blood vessels within and around the tumor, thereby providing more accurate basis for the diagnosis and treatment of hepatocellular carcinoma. A wealth of research has underscored the intricate relationship between tumor blood flow dynamics and critical factors such as tissue differentiation and the degree of vascular invasion. The blood flow data obtained via color Doppler ultrasound aids clinicians in more accurately evaluating these aspects, which is essential for early HCC diagnosis and critical for tailoring treatment strategies. For instance, it can precisely identify suitable blood vessels for transarterial chemoembolization (TACE), thereby assisting doctors in achieving better therapeutic outcomes[13]. In contemporary clinical settings, color Doppler ultrasound has emerged as an indispensable tool due to its unique advantages in both diagnosing and managing HCC.

In recent years, superb Micro-vascular Imaging (SMI) and Micro-flow Imaging (MFI) have emerged as advanced Doppler micro flow imaging techniques capable of visualizing low-velocity and small blood vessels without the need for contrast agents[14]. Research indicates that these technologies, built on enhanced Doppler principles, can detect extremely faint blood flow signals, thereby achieving high-resolution imaging of low-speed microcirculation while eliminating the risks and discomfort associated with contrast agent administration.

Compared to traditional Color Doppler Flow Imaging (CDFI), MFI has demonstrated superior performance in depicting blood vessels within liver lesions[15]. It provides more detailed and clearer images of blood flow distribution. Multiple comparative studies have shown that MFI can identify numerous small blood vessels that are often overlooked by conventional CDFI, offering a more precise and nuanced view of blood flow patterns. This enhanced visualization aids clinicians in conducting a more comprehensive assessment of lesion vascularity.

Furthermore, MFI technology is effective in differentiating the blood flow characteristics across various differentiation stages of malignant liver tumors. Through extensive analysis of blood flow in patients with malignant liver tumors, researchers have found that MFI can accurately evaluate tumors at different stages of differentiation and assign appropriate blood flow grades[16]. This capability offers valuable insights for clinical diagnosis and treatment planning, helping physicians better understand tumor biology and progression.

In summary, superb Micro-vascular Imaging and Micro-flow Imaging not only enhance the visualization of low-velocity microcirculation but also provide significant advantages in detecting liver lesions and evaluating the differentiation stages of malignant tumors. These techniques offer new tools and methodologies that advance clinical applications in this field.

4. Evaluation of the Biological Behavior of Hepatocellular Carcinoma by Ultrasound Elastography.

Chronic viral infections and fatty liver diseases are primary contributors to the development of chronic liver diseases. According to World Health Organization (WHO) data, the global incidence of chronic liver diseases has shown a steady upward trend, with chronic viral infections and fatty liver diseases being significant factors. As the disease advances, viral or lipotoxic insults progressively impair hepatocytes, triggering their repair and regeneration mechanisms[17]. Nevertheless, in this process, should any anomalies arise, severe consequences might ensue. These abnormalities may lead to defects or disorders in the repair of liver parenchyma, and then result in the formation and development of liver fibrosis and liver cancer[18]. Studies have shown that liver fibrosis is not only related to the pathogenesis of HCC but also may affect the early recurrence of HCC patients after surgery. Real-time assessment of the degree of liver fibrosis in patients with chronic liver diseases is crucial for monitoring liver stiffness[19].

Currently, ultrasound elastography technology has gradually become a widely recommended and recognized non-invasive method, including two major categories: strain elastography (SE) and shear wave elastography (SWE). SWE, with its advantages such as quantitative and real-time assessment of tissue stiffness, has been recommended as the first-line method for evaluating the degree of liver fibrosis by major domestic and international guidelines.

Research has indicated that hepatocellular carcinoma (HCC) patients exhibiting higher liver stiffness measurements (LSM) prior to therapy tend to experience elevated post-surgical recurrence rates and diminished long-term survival[20]. A comprehensive long-term follow-up

investigation involving a substantial cohort of HCC patients demonstrated that pre-treatment LSM monitoring revealed a notable correlation: individuals with greater liver stiffness were more likely to face recurrent disease following surgery and had poorer long-term survival outcomes compared to those with lower stiffness levels. In terms of tumor differentiation, findings suggest that the rigidity of HCC tissue tends to increase as the condition advances. Both foundational and clinical studies highlight that as HCC progresses, alterations in the biological properties of tumor tissues contribute to increased hardness, which is linked to the extent of tumor differentiation[21].

The latest research indicates that tumor cells appear in the microvessels of the tumor margin tissue, leading to a reduction in the number of blood cells within the microvessels and causing an increase in tissue stiffness[22]. The infiltration of tumor cells in the microvessels at the tumor margin can interfere with normal blood flow and cell composition within the microvessels, resulting in a decrease in the number of blood cells and subsequently causing changes in tissue stiffness.

Studies have shown that liver fibrosis is common in liver diseases and can alter the physical properties of liver tissue. When measuring the stiffness of liver tissue around liver cancer lesions, the presence of liver fibrosis may interfere with the accuracy of the measurement results. Even if there is no microvascular invasion (MVI) in the lesion, the liver tissue around the lesion may still exhibit a high stiffness value similar to that of the tumor. Some scholars have observed and tested a large number of liver cancer patients and found that in some patients without MVI, the stiffness value of the liver tissue around the lesion is similar to that of the tumor tissue. This situation may interfere with the prediction of MVI and reduce the specificity of the study. Research indicates that due to the complexity of the relationship between the high stiffness value of liver tissue around the lesion and MVI, there is a certain error in predicting MVI through stiffness values, thereby reducing the specificity of related studies[23].

In addition, Frulio et al. found that as the tumor grows, the surrounding tissues will be fibrosed due to compression, forming a relatively hard pseudo-capsule. However, the disordered internal structure and central hemorrhage and necrosis of the tumor may lead to a decrease in hardness. Therefore, the VTQ values at different locations may vary, which can reflect the degree of differentiation and biological behavior of hepatocellular carcinoma to a certain extent.

At present, there are still relatively few related studies on ultrasound elastography technology in hepatocellular carcinoma. To fully understand the complex relationship between tissue hardness and tissue components, more studies are still needed.

5. Contrast-enhanced Ultrasound for Predicting Microvascular Invasion of Hepatocellular Carcinoma

In the development of ultrasound imaging, enhanced ultrasound contrast technology represents a significant innovation. This technology dynamically observes blood vessel and tissue perfusion information in liver nodules during contrast agent injection, diffusion, and absorption, improving diagnostic accuracy. Moreover, it has expanded beyond diagnosis to guide tumor biopsies, assist in radiofrequency ablation surgery, and monitor tumor recurrence. Continuous improvements aim to enhance its role in diagnosing and treating hepatocellular carcinoma (HCC).

Currently, among the second-generation ultrasound contrast agents, SonoVue and Sonazoid are widely utilized. SonoVue serves as a pure blood pool contrast agent, whereas Sonazoid represents a novel type of microbubble contrast agent that has recently been introduced in China. Unlike SonoVue, Sonazoid can be phagocytosed by mononuclear phagocytes. Specifically, Kupffer cells, which function as macrophages within the hepatic sinusoids, can phagocytose Sonazoid upon contact, leading to a unique "Kupffer" phase. However, liver malignant tumors, characterized by abnormal liver cells, lack the functional attributes of Kupffer cells, resulting in low enhancement during the Kupffer phase. Leveraging this characteristic, Huang et al. discovered that the peak energy difference in the Kupffer phase for the high Ki-67 expression hepatocellular carcinoma (HCC) group was notably lower, aiding in the diagnosis of high Ki-67 expression HCC. Moreover, elevated Ki-67 expression suggests potential deterioration of HCC, characterized by poor histological differentiation and increased microvascular invasion[24].

After conducting comprehensive research and experiments, it was determined that the blood supply pattern of hepatocellular carcinoma (HCC) markedly differs from that of normal liver tissue. Specifically, HCC no longer depends on the conventional dual blood supply system of the portal vein and hepatic artery, but almost exclusively relies on the hepatic artery for blood supply. In comparison, the contribution of the portal vein to blood supply is minimal [14]. This distinctive vascular characteristic has emerged as a crucial imaging marker for identifying liver cancer during contrast-enhanced ultrasound examinations.

During the staging process of contrast-enhanced ultrasound examination, there are mainly three stages: arterial phase, portal venous phase and delayed phase. Studies have shown that the enhancement characteristics of tumor lesions in different stages can reflect their biological properties, such as vascular density and tissue differentiation degree, etc.

Relevant studies have found that small liver cancer (with a diameter of < 30mm) lesions showing high enhancement in the arterial phase may have a higher degree of tumor differentiation and a more significant degree of malignancy.

In addition to the hyper-enhancement feature observed in the arterial phase, scholars have demonstrated significant interest in the correlation between the onset and degree of washout and the differentiation grade of hepatocellular carcinoma (HCC) lesions. Multiple consistent studies have revealed that in the early stages, the washout phenomenon typically becomes pronounced within 2 minutes for moderately to poorly differentiated HCC lesions. In contrast, for moderately to well-differentiated HCC lesions, the washout phenomenon occurs later and is relatively mild[25]. Furthermore, additional research has corroborated this perspective, indicating that if washout occurs within 60 seconds, it may suggest the presence of poorly differentiated HCC or non-hepatocellular malignant tumors[26].

However, such qualitative analysis of CEUS also has some limitations. The first issue to be addressed is that in the process of using CEUS to diagnose HCC, there are always differences between and within observers because there are significant differences between the pathological tissues of HCC.

The quantitative analysis software of contrast-enhanced

ultrasound holds great significance in the preoperative evaluation of the contrast agent perfusion characteristics of tumor lesions. By constructing time-intensity curves, this technique is capable of extracting various quantitative indices, such as the area under the curve (AUC), peak intensity (Peak Intensity, PI), rise time (Rise Time, RT), and time to peak (Time to Peak, TTP), in order to investigate the relationship between these indices and the biological characteristics as well as prognosis of the lesions.

Research findings suggest that for hepatocellular carcinoma (HCC) lesions, factors such as reduced rise time, shortened time to peak, and decreased peak intensity are significant independent predictors of postoperative recurrence. More specifically, a lower peak intensity might be associated with suboptimal radiofrequency ablation efficacy, leading to incomplete eradication of tumor tissue. This can enhance the tumor's invasive potential and elevate the risk of recurrence[27]. Furthermore, diminished peak intensity could also indicate inadequate tumor angiogenesis or compromised blood perfusion, both of which can adversely impact treatment outcomes.

A shorter rise time could be associated with enhanced angiogenesis due to micrometastases originating from the primary tumor. In such instances, the increased number of new blood vessels facilitates a faster influx of contrast agents into the tumor region, leading to a reduced rise time. This observation not only indicates abnormal alterations in the tumor's internal vascular architecture but also implies a greater likelihood of invasive and metastatic potential in the tumor.

To further validate these findings, researchers conducted multi-center studies, gathering extensive case data and performing thorough analyses integrated with imaging and pathological findings. The results demonstrated that the aforementioned quantitative metrics can not only effectively predict postoperative recurrence risk but also offer valuable insights to clinicians, aiding in the development of more personalized treatment strategies. For instance, for patients at higher risk of recurrence, more intensive adjuvant treatments, such as targeted or immunotherapies, could be considered to enhance patient survival rates and quality of life.

In summary, the utilization of quantitative analysis software for contrast-enhanced ultrasound heralds a transformative approach to preoperative evaluation of tumor lesions. This innovative tool not only unveils deeper insights into the intricate biological behavior of these lesions but also elucidates their nuanced responses to therapeutic interventions. By offering a comprehensive and multi-dimensional understanding, this technology empowers clinicians to tailor personalized treatment strategies with unparalleled precision, ultimately enhancing patient outcomes and paving the way for a new era of precision medicine.

6. Conclusion

Multimodal ultrasound methods, such as two-dimensional ultrasound, ultrasound elastography, and contrast-enhanced ultrasound, are instrumental not only in diagnosing hepatocellular carcinoma (HCC) but also in predicting its pathological outcomes and associated biological features to some extent. These techniques support the advancement of precision medicine. Moreover, recent advancements in ultrasound technology, particularly the integration of radiomics and artificial intelligence (AI), have markedly enhanced the accuracy and efficiency of HCC diagnosis and treatment.

Radiomics leverages big data analysis and pattern recognition to derive clinically significant insights from extensive ultrasound imaging datasets, thereby improving physicians' diagnostic accuracy and staging capabilities for HCC. Concurrently, the incorporation of AI technologies, especially machine learning and deep learning algorithms, has significantly boosted the interpretation and diagnostic precision of ultrasound images while accelerating image analysis, providing robust support for clinical decision-making.

The ongoing evolution of these technologies has broadened the utility of ultrasound in HCC management, establishing it as a critical medical tool. However, factors like the operator's expertise, equipment quality, patient-related issues such as gas interference, and tumor location can influence image quality and, consequently, research outcomes. These areas warrant further investigation to optimize the effectiveness of ultrasound in HCC diagnosis and treatment.

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