



The Application Progress of Multimodal Ultrasound New Technology in Solid Liver Lesions

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Abstract

With the rapid development of medical imaging technology, ultrasound technology, as the preferred method for the screening and diagnosis of liver diseases, has revolutionary progress in recent years. From traditional two-dimensional grayscale ultrasound to today's intelligent multimodal fusion imaging, ultrasound technology is experiencing profound changes from empirical diagnosis to datafication, from single examination to multi-technique collaboration. This article will systematically expound the application progress of eight major technology fields, including ultrasound contrast imaging, elastography microvascular imaging, three-dimensional ultrasound and fusion imaging, laparoscopic ultrasound, molecular imaging, radiomics and artificial intelligence-assisted diagnosis, 5G remote ultrasound,, in liver lesions, analyze the advantages and limitations of each technology, and look forward to the future development direction, providing references for clinical practice and scientific research.

Keywords: Liver solid lesions, New ultrasound technology, Ultrasonic artificial intelligence, Ultrasonic molecular imaging, 5G remote ultrasound robot

Preface

Liver space-occupying lesions are common clinical diseases. In addition to benign cystic lesions, clinical multi-modal ultrasound new technology can be used for their differential diagnosis, interventional therapy and efficacy evaluation in order to further clarify the nature of liver solid lesions and treatment options.

Contrast Enhanced Ultrasound Examination

Contrast-Enhanced Ultrasound (CEUS), by intravenously injecting microbubble contrast agent containing inert gas, generates strong echo signal by utilizing its nonlinear oscillation characteristics in the ultrasound field, and selectively receives the second harmonic signal of microbubbles through harmonic imaging technology, thus displaying the hepatic blood perfusion in real time. By observing the difference of enhancement patterns in the arterial phase, portal venous phase delayed phase, it can achieve the differential

diagnosis of hepatic space-occupying lesions. This technique has the advantages of non-radiation, real-time dynamic, high spatiotemporal resolution, and can accurately evaluate the hemodynamic changes of hepatic microcirculation [1]. The dual blood supply system of hepatic artery and portal vein is the best target organ for contrast-enhanced, and benign hepatic lesions generally show high or equal enhancement in the arterial phase in CEUS, and continue to the venous phase and delayed phase without change or show equal enhancement; malignant lesions show high enhancement in the arterial phase, and rapid regression in the venous and delayed phases, low enhancement, and the maximum difference between benign and malignant lesions lies in the venous and delayed phases [2]. Conventional CEUS diagnosis is highly dependent on the doctors, and there is a large difference in diagnostic consistency among doctors with different seniority. The AI intelligent diagnosis model (Model-DCB) based on CEUS represents the level of current

CEUS technology [3]. This model integrates 4 million frames of CEUS videos, biomarkers and 17 clinical parameters of 3,75 cases of FLL patients to construct a six-category (hepatocellular carcinoma, hepatic metastatic carcinoma, intrahepatic cholangiocarcinoma, hepatic hemangioma, hepatic abscess and other rare types) diagnosis system, which consists of three major modules: disease module, biomarker, clinical module. This innovative model has a diagnostic accuracy rate of up to 90%, which is significantly better than junior CEUS doctors and comparable to senior CEUS and doctors. The research of Chen and others shows that CEUS also has excellent diagnostic performance in children's benign and malignant multiple hepatic lesions, with accuracy (0.85-0.86). The future development direction of CEUS will tend to the development of molecular targeted contrast agents, multi-parameter quantitative analysis and the clinical promotion of AI-assisted diagnosis system [4].

Ultrasonic Elastography

Ultrasound Elastography (UE) technology induces tissue deformation by applying vibrations or Acoustic Radiation Force Impulse (ARFI) through the probe, and uses ultrasound to detect the degree of tissue deformation. According to the characteristic that the hardness of the tissue is inversely proportional to the deformation (the harder the tissue, the smaller the deformation), the tissue elastic information is converted into quantitative values (such as Young's modulus, unit kPa) or color elastic maps, so as to evaluate the degree of liver fibrosis invasively. At present, it mainly includes three categories: transient elastography (TE), Acoustic Radiation Force Impulse Imaging (ARFI) and Shear Wave Elastography (SWE) in the clinic. Among them, transient elastography (FibroScan) uses a one-dimensional shear wave measurement, while two-dimensional shear wave elastography (2D-SWE) can achieve real-time and multi-point hardness detection and is increasingly widely used in clinical applications Ren, et al., [5]. showed that the average Young's modulus increased gradually in patients with chronic hepatitis B virus infection a fibrosis stage less than F2, which had reliable liver stiffness measurements; Wang, et al., [6]. confirmed that the diagnostic performance of ultrasound elastography was superior to of serum biomarkers in terms of liver staging in CHB patients. In view of the problem that the success rate of measurement in obese patients is low in traditional SWE,oscopic ultrasonic shear wave elastography (EUS-SWE) can avoid the interference of abdominal wall thickness on the results through EUS-SWE measurement through the wall or duodenal wall in obese NAFLD patients, which is more accurate than transabdominal SWE [7]. This technique is expected to establish a standard for fibrosis grading in NAFLD/ NASH patients with a BMI \geq 25.

Superb Microvascular Imaging

Superb Microvascular Imaging (SMI), by combining high-frequency ultrasound probes with adaptive Doppler signal processing algorithms, clearly display the low-speed blood flow

of the order of microns that are difficult to detect by traditional ultrasound, eliminate tissue interference by using motion artifact filtering technology, and enhance the vascular imaging by using high-sensitivity blood flow signal extraction. Through real-time dynamic overlay technology, it improves the signal-to-noise ratio, and finally achieves high resolution visualization of the hepatic microvascular network, providing important hemodynamic evidence for the early diagnosis of hepatocellular carcinoma and the differentiation of hepatic lesions It has two display modes: grayscale (mSMI) mode and color (cSMI) mode. The third-generation SMI technology can detect microflow with flow velocity of <1 cm/s. Since SMI can detect even lower flow velocities than those detected by ordinary color Doppler ultrasound examination, it is more sensitive than color Doppler and Doppler imaging. Zeng QQ, [8] and others showed that in the application of liver lesions, SMI can detect tumor neovascularization earlier, and the detection rate microhepatocellular carcinoma (≤ 1 cm) is significantly improved. The "twisted vessel sign" in the nodular hyperplasia of cirrhosis has a warning sign of precancerous lesions. Super-resolution ultrasound (SR-US) imaging can be used to visualize and quantify the microvessels of solid FLLg [9] and others showed that SMI combined with CEUS can improve the specificity of the benign and malignant differentiation of FLL, especially in the diagnosis of smallcellular carcinoma in the background of cirrhosis, and the display of hepatic vascular abnormalities such as hepatic artery-portal vein fistula by MI is also superior to conventional color Doppler, which provides a new tool for the assessment of portal hypertension. However, SMI still has limitations such as low sensitivity to deep lesions and influence of patient breathing, and needs to be combined with other techniques. Synergistic analysis of SMI and other ultrasound parameters can significantly improve the diagnostic efficacy, which represents future direction of functional assessment of liver ultrasound.

Three-Dimensional Ultrasonography

Three-dimensional ultrasonography, based on the propagation characteristics of ultrasound in human tissue, forms three-dimensional images through the processing and superposition of computer software, which can clearly show the surface contour and internal structure of lesions. When combined with ultrasound angiography, it can more clearly show origin and course of tumor vessels, as well as the size, shape, and spatial relationship with surrounding blood vessels. TV, et al., [10] conducted a prospective study of 39 patients with Focal Liver Lesions (FLLs), confirming that the 3D-CEUS technique provided consistent data measurement results for the calculation of FLL volume among researchers, and the consistency of the volume calculation was almost perfect. However, three-dimensional ultrasound is still limited by the balance between high and low resolution and large and small field view, which does not show deep small lesions well, and it places high demands on the operator's technical skills.

Ultrasonic-CT/MRI image fusion technologys real-time

ultrasound images with preoperative CT/MRI volume data in three dimensions through spatial registration algorithms, and uses electromagnetic or optical positioning systems to track the position of the probe achieving real-time overlay display of multi-modal images, which complements the real-time advantage of ultrasound with the high-resolution advantage of CT/MRI, mainly for liver interventional guidance and difficult lesion localization. For focal hepatic lesions that cannot be displayed by routine ultrasound, fusion imaging combined with ultrasound angiography can significantly improve the detection rate of lesions [11,12]. Before performing radiofrequency ablation for HCC, accurate characterization and localization of the lesion play a decisive role in formulating the plan. During radiofrequency ablation of HCC, the use of fusion imaging is conducive to accurate puncture and needle placement, as well as immediate assessment of curative and guidance of treatment. Some scholars [13] have studied 56 cases (59 lesions) of HCC patients who underwent thermal ablation treatment under the guidance of DUS FI, and collected the patient's three-dimensional ultrasound volume image before the operation and fused and registered with the real-time two-dimensional ultrasound image, and tumor and the 5 mm safety margin were segmented and marked out, and then the preoperative planning was performed under the three-dimensional visualization and the thermal ablation was guided in time, and the results showed that all lesions could be successfully registered and three-dimensionally displayed during the operation, and the post-ultrasound angiography showed that 8.5% of the lesions achieved complete ablation and the ablation margin ≥ 5 mm, and the cumulative LTP (Local tumor progression) rate of all lesions was 7.1% at 1 year and 2 years. The combined application of ultrasonic-CT/MRI fusion imaging technology and ultrasound angiography has become a research hotspot in the field of ultrasound interventional therapy.

Laparoscopic Ultrasonography

Laparoscopic Ultra Sound (LUS), by placing a high-frequency ultrasound probe in laparoscopic surgery, uses ultrasound beams to penetrate the liver parenchyma and receive reflected signals, directly enters the abdominal cavity through the operating hole, and scans the surface of the liver to avoid the interference of abdominal and intestinal gas, to obtain high-resolution cross-sectional images of the liver in real time, so as to accurately locate liver tumors (especially <1 cm) and key vascular structures (such as hepatic vein branches) in minimally invasive surgery, and provide real-time imaging navigation for hepatic resection or ablation therapy. There are studies [14] that report the safe use of laparoscopic ultrasound for precise localization in 43 cases of patients with tumors at the confluence of the hepatic vein, and the evaluation of hepatic hemodynamics is performed simultaneously during surgery, greatly improving the success rate of surgery for tumors in critical locations. In recent years, application of LUS in the diagnosis of liver lesions has been continuously optimized in the aspects of precise navigation during surgery and minimally

invasive treatment [15,16], which has high-frequency linear array (7-10MHz) and can show millimeter-level lesions, and can identify small metastatic foci <3 mm, significantly intraoperative decision-making, especially in the background of cirrhosis. The study by Arata, [17] and others showed that the combined use of real-time tissue imaging and LUS can clearly distinguish tumor hardness and improve the negative rate of the margin. The limitations of LUS are that it is only suitable for surgical patients and requires an experienced operating team to cooperate.

Ultrasonic Molecular Imaging

Ultrasonic Molecular Imaging (UMI) is an advanced development of traditional CEUS, which can image specific molecular biomarkers by targeted microbubble contrast agents, thereby evaluating liver lesions at the molecular level. UMI uses microbubble contrast agents surface-modified with specific ligands (such as antibodies, etc.), which can bind to specific molecular biomarkers in diseased tissues. When the microbubbles oscillate in the ultrasonic field, they produce strong echo signals, thus realizing the imaging of specific molecular biomarkers. The application of UMI in liver metastases [18] mainly targets tumor neovascularization biomarkers such as vascular endothelial growth factor receptor 2 (VEGFR2), $\alpha v\beta 3$ integrin, etc., to improve the early detection rate of metastases and also to assess the response to anti-angiogenic therapy for HCC at an early stage. The fourth-generation ultrasound contrast agent drug-loaded microbubble can locally release drugs under ultrasound triggering, and in the treatment of HCC, they make cystatin C proteinase-cleavage death [19], and carry out targeted treatment, and have developed from simple diagnosis to "diagnosis-treatment" integration. Although most molecular imaging studies are still in the stage of animal experiments, there is great potential and is expected to become an early diagnosis and personalized treatment management of liver diseases [20].

Ultrasound Radiomics

Ultrasonic radiomics can construct predictive models by high-throughput extraction of texture, morphological and functional features in ultrasound images with machine learning algorithms, which are used for the differential diagnosis of benign and malignant liver focal lesions, staging of liver fibrosis and evaluation of curative effect. In the differential diagnosis of well-differentiated hepatocellular carcinoma and typical benign focal hepatic lesions, the AUCs of the radiomics model and the combined model were 0.905 and 0.951, respectively, and the AUCs were 0.826 and 0.912 in the test cohort. The combined model was significantly better than the radiomics model, indicating that the Kupffer-based radiomics combined model can assist clinicians in making accurate diagnosis and unnecessary surgical treatment for benign diseases. Dong, et al., [21] conducted a prospective analysis of 100 hepatocellular lesions confirmed by histopathology, and evaluated a machine learning model based on grayscale and ultrasound contrast for the

prediction of microvascular invasion preoperatively in patients with hepatocellular carcinoma, which the final prediction model of Kupffer 0.804 (95% CI: 0.723, 0.878), the was 75.0%, the sensitivity was 87.5%, and the specificity was 69.1%. In comparison with traditional ultrasound, omics ultrasound has significantly improved diagnostic specificity, and it can also be combined with AI technology to achieve automated analysis in the future.

Ultrasonic Artificial Intelligence (AI) and 5G Tele-Ultrasound

Ultrasonic intelligence is a new technology that uses AI algorithms (such as deep learning technology) to automatically analyze the characteristics of ultrasound images, automatically detect and identify liver tumors, intelligently segment diseased area of the image, and assist physicians in the prognosis evaluation of diseases, providing real-time diagnosis and treatment support [22]. AI technology can discover the ment of lesions, deep learning can extract image features that are difficult for the human eye to recognize, discover the heterogeneity of the tumor microenvironment, and enable patients with liver cancer choose treatment in the early or extremely early stage [23]. AI technology optimizes the workflow, automatically generates reports and archiving saves the doctor's time, Lu RF, et al., [24] analyzed 21,934 liver ultrasound images of 11,960 patients, the artificial intelligence detection was compared with the ultrasound's detection, the sensitivity (0.956 vs.0.991) was matched, and specificity was improved (0.787 vs..698), which reduced 54.5% of the work of the imaging physician. Due to the lack of interpretability of the model and the lack of ification of multi-center data, there are still some limitations in the AI technology of ultrasound.

5G remote ultrasound combines the 5G network with high bandwidth and low latency and the precise operation capability of robotic technology, providing a more brand-new solution for the diagnosis and treatment of liver lesions. Early diagnosis and precise treatment of hepatocellular carcin require high-quality imaging support, 5G remote ultrasound can transmit high-definition ultrasound images in real time, combined with AI auxiliary diagnostic system, to help experts remotely identify the, size and characteristics of liver tumors [25], this technology is especially suitable for remote areas, emergency situations and scenarios that require multidisciplinary consultation. Remote multi dis collaboration is another important application of 5G ultrasound, through the integration of ultrasound, CT/MRI and laboratory data through the cloud platform, hepatology, radiology, surgical experts different regions can work together to formulate diagnosis and treatment plans, and guide personalized treatment options. The limitations of 5G remote ultrasound at present are uneven network coverage, unstable signal in mountainous areas, and large-scale application still needs to solve problems such as equipment cost and data security.

Summary

Multimodal ultrasound new techniques significantly improve the detection rate and diagnostic accuracy of liver solid lesions, and with the application of molecular probes, quantum, brain-computer interface and other technologies, ultrasound has the potential to provide non-invasive pathological diagnosis of liver solid lesions. Although some new techniques currently have some limitations future breakthroughs need to rely on the integration of multimodal imaging technology, clinical and basic research integration and so on. In conclusion, multimodal technology has the advantages of real-, precision and efficiency in liver solid lesions, and provides strong support for minimally invasive treatment and personalized medicine, and has gradually developed from a pure examination tool to a comprehensive system that can doctors formulate diagnosis-treatment plans.

Acknowledgment

None.

Conflict of Interest

None.

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