·专家论坛·

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肝细胞癌超声诊疗基础研究进展：从诊断、治疗到诊疗一体化

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摘要：肝细胞癌（HCC）的精准诊疗面临肿瘤微环境复杂、治疗抵抗及易复发转移等重大挑战。近年来，超声技术已突破传统筛查定位功能，逐渐发展为兼具能量激活、靶向递送、局部消融、免疫调控和疗效反馈能力的多维治疗平台。本文系统综述了超声技术在HCC治疗及诊疗一体化基础研究中的最新进展。在治疗方面，以微泡/纳泡递送、声动力疗法、高强度聚焦超声及组织碎化术为代表的干预策略，不仅实现了病灶的原位物理毁损，更通过与声遗传学、代谢重编程及免疫化疗的深度协同，有效逆转了肿瘤的免疫耐受网络。在诊疗一体化方面，新型声敏纳米递送系统构筑了能量激活与靶向控释的平台。针对该领域面临的转化瓶颈，建议未来建立标准化的临床前治疗声学参数共识，以期为HCC的个体化精准诊疗确立新的转化范式。

关键词：癌，肝细胞；超声检查；分子成像；声动力疗法；体外冲击波疗法；诊断；治疗学

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Advances in basic research on ultrasound diagnosis and treatment of hepatocellular carcinoma: From diagnosis and treatment to integrated management

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Abstract：The precise diagnosis and treatment of hepatocellular carcinoma（HCC）face major challenges such as the complexity of tumor microenvironment，treatment resistance，and a high risk of recurrence and metastasis. In recent years，ultrasound technology has moved beyond its traditional role in screening and localization，gradually evolving into a multidimensional therapeutic platform capable of energy activation，targeted delivery，local ablation，immune modulation，and therapeutic feedback. This article systematically reviews the latest advances in the basic research on ultrasound techniques in HCC treatment and integrated management. In terms of treatment，intervention strategies represented by microbubble/nanobubble-mediated delivery，sonodynamic therapy，high-intensity focused ultrasound，and histotripsy not only enable *in situ* physical destruction of lesions，but also effectively reverse tumor immune tolerance networks through deep synergy with sonogenetics，metabolic reprogramming，and immunochemotherapy. In terms of integrated management，novel sonosensitive nanodelivery systems provide a platform for energy activation and targeted controlled release. To address the translational bottlenecks in this field，it is recommended to develop standardized consensus on preclinical therapeutic ultrasound parameters，in order to establish a new translational paradigm for individualized precise diagnosis and treatment of HCC.

Key words：Carcinoma，Hepatocellular；Ultrasonography；Molecular Imaging；Sonodynamic Therapy；Extracorporeal Shockwave Therapy；Diagnosis；Therapeutics

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肝细胞癌（hepatocellular carcinoma，HCC）占所有原发性肝癌的80%以上，其起病隐匿，多数患者确诊时已至晚期，是当前面临的重大公共卫生挑战[1-3]。目前，超声被多项指南列为HCC高危人群监测的重要工具[4-6]，其在HCC的临床管理中发挥着不可替代的作用。然而，传统超声主要依赖于宏观物理结构成像，难以揭示决定肿瘤预后的深层生物学特征。

随着近年基础研究的深入，超声已从单一的结构显像工具，变为兼具分子精准诊断与靶向治疗功能的关键诊疗手段。超声可作为外源性能量输入，通过声空化、声敏剂激活、声辐射力及聚焦热效应等方式直接参与治疗，实现药物递送、声动力治疗（sonodynamic therapy，SDT）杀伤、基因转染、免疫激活及组织消融等多种生物学效应[7]。超声既是成像方式，也可作为能量和药物的递送平台，二者结合形成诊疗一体化思路，是近年HCC超声基础研究最活跃的方向。

本文围绕HCC超声治疗相关基础研究进展，重点梳理近年来在细胞与动物模型中，超声介导治疗及诊疗一体化策略的作用机制、技术特点与临床转化潜力，为后续HCC精准诊疗研究提供参考（图1）。

1　超声在HCC治疗中的基础研究进展

超声波作为一种非侵入性机械波，主要通过对组织产生热效应和机械效应（包括空化效应和声辐射力等）发挥治疗作用[8]。空化效应被认为是超声治疗中最重要且被最广泛接受的核心机制。基于超声的多种生物效应，目前已衍生出丰富多样的超声治疗策略，包括以空化效应为主导的微泡治疗、SDT与组织碎化术，以压电催化为机制的声压电治疗，兼具热效应与空化效应的高强度聚焦超声（high-intensity focused ultrasound，HIFU）等[9-10]。

1.1　*空化介导的微泡/纳泡递送与治疗增敏*　在超声作用下，微泡振荡与破裂可增加细胞膜通透性、促进外源分子入胞并改善局部组织灌注，由此发展出的超声靶向微泡破坏（ultrasound-targeted microbubble destruction，UTMD）技术可进一步实现治疗分子的时空可控释放[11-12]（附录A）。

利用超声激发临床常用造影剂SonoVue微泡产生空化效应，可显著增加HCC血管通透性并降低间质液压力，从而有效促进化疗药物多柔比星在HCC局部的富集[13]。UTMD技术还可以高效递送多种功能性核酸，通

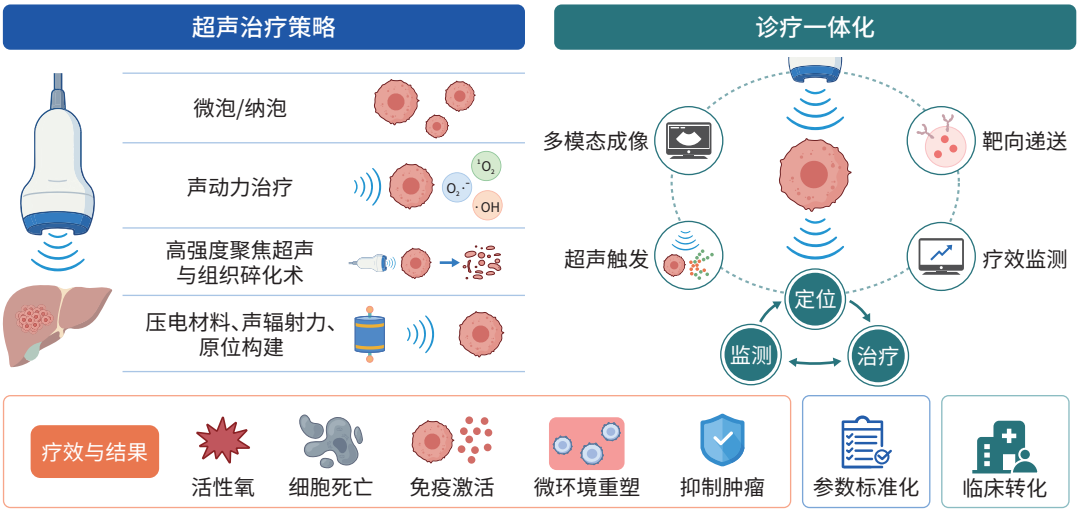


图1　肝细胞癌超声治疗与诊疗一体化的主要研究策略

Figure 1　Major research strategies for ultrasound therapy and theranostics in hepatocellular carcinoma

过调控肿瘤细胞或免疫细胞功能来增强抗肿瘤免疫反应[14-16]。另有研究将载药微泡整合于经动脉化疗栓塞体系中，通过超声触发促进药物向HCC渗透，从而显著提高局部治疗效率并增强对肿瘤边缘区域的杀伤作用[17]。以上提示微泡技术与介入治疗的结合为其临床转化提供了重要路径。

由此可见，微泡技术已由单纯的药物载体发展为连接超声物理效应与组织生物响应的重要平台，而实现空化过程的精准调控与实时监测，是推动UTMD走向临床的关键。

1.2 SDT：活性氧（reactive oxygen species，ROS）杀伤与免疫激活

SDT是近年来HCC超声治疗基础研究中最活跃的方向之一（附录B），其基本原理是利用低强度超声激活声敏剂，通过空化、声致发光、热解及电子转移等过程生成单线态氧（$^1O_2$）、羟基自由基（·OH）等ROS，从而诱导肿瘤细胞氧化应激、线粒体损伤、免疫原性细胞死亡及多种非凋亡性细胞死亡[9, 18]。

1.2.1 声敏剂创新及递送优化 声敏剂是SDT发挥治疗效应的核心，其性能决定ROS生成效率和体内可转化潜力。传统有机声敏剂如二氢卟吩e6、血卟啉单甲醚（hematoporphyrin monomethyl ether，HMME）和吲哚菁绿（indocyanine green，ICG）具有较好生物相容性，但常受激发效率、体内稳定性和肿瘤还原环境影响[19]。

近年来，研究者通过供体-受体结构、重原子配位、聚合物酞菁和刺激响应基团等分子工程策略，有效提升了声敏剂的能级匹配、系间窜越和肿瘤选择性激活能力[20-23]。与此同时，无机纳米酶、二维异质结和声-柔电催化材料等新型声敏体系，可通过类酶催化、界面电荷分离和超声诱导极化等方式提高ROS生成效率，使SDT由传统分子声敏剂激发向材料声催化方向发展[24-26]。递送体系则决定声敏剂能否真正到达并滞留于HCC病灶。红细胞膜等仿生载体、磷脂酰肌醇蛋白聚糖3抗体等肿瘤特异性配体以及工程菌主动定植策略，可分别通过延长循环、降低免疫清除、增强主动靶向和促进肿瘤内持续富集与长效滞留，进一步优化声敏剂在HCC病灶中的递送效率[27-29]。Song等[30]构建的肿瘤微环境响应型纳米体系通过形态转化和自产氧策略改善肿瘤微环境氧供来增强HCC的SDT效果。

1.2.2 肿瘤微环境与细胞稳态调控增敏 调控肿瘤内在稳态，尤其是诱导金属离子稳态失衡，已成为增强SDT效果的重要策略。Xie等[31]构建的超声响应纳米平台可通过调控HCC肿瘤细胞内铜库，在诱导铜死亡的同时伴随免疫原性细胞死亡（immunogenic cell death，ICD）的发生。Sun等[32]将铜死亡诱导剂与声敏剂协同递送，可进一步放大HCC铜死亡并增强抗肿瘤活性。除铜离子外，通过构建含铁或多金属纳米体系，可通过增强脂质过氧化并抑制谷胱甘肽过氧化物酶4等关键抗氧化通路，从而促进HCC铁死亡发生并协同增强SDT效果[33-35]。

氧化还原稳态的调控构成另一类核心策略。在HCC肿瘤ROS清除端，研究者通过构建消耗谷胱甘肽（glutathione，GSH）的体系，以削弱其抗氧化防御能力，从而增强整体氧化应激水平[36-37]。在ROS生成端，Li等[38]设计的氧气自供给纳米平台可改善局部氧供并调控HCC缺氧相关信号通路。在此基础上，多机制协同策略进一步放大氧化应激反应。Wu等[39]和Zhang等[40]分别通过GSH耗竭/过氧化氢（hydrogen peroxide，H_2O_2）级联催化以及供氧、GSH抑制和钙离子过载等多机制协同策略，进一步促进ROS积累并放大HCC细胞氧化应激反应。

1.2.3 SDT联合分子层靶向策略 靶向阻断驱动HCC发生发展的核心病理通路（如联合大鼠肉瘤病毒基因或磷脂酰肌醇3激酶/哺乳动物雷帕霉素靶蛋白抑制剂），能显著打破肿瘤的生存依赖，进而协同SDT诱发更为彻底的氧化应激损伤与细胞凋亡[41-42]。在代谢重编程方面，利用糖酵解抑制剂干扰肿瘤能量代谢并阻断GSH抗氧化网络，可大幅提升HCC对ROS的敏感性[43]。此外，破坏细胞蛋白稳态也是重要的增敏路径，Wang等[44]通过蛋白酶体抑制剂诱发错误折叠蛋白蓄积，能进一步放大SDT介导的凋亡与自噬效应，削弱HCC细胞恶性表型。SDT联合靶向策略通过整合信号传导、代谢及蛋白稳态等多维调控，实现了对肿瘤细胞生存网络的强效协同干预。

1.2.4 SDT协同基因治疗：从靶向沉默到声遗传学 SDT不仅可作为单一治疗方式发挥抗肿瘤作用，也可作为治疗增敏平台，与基因治疗等多种策略联用。

在靶向沉默层面，研究者利用SDT产生的ROS诱导载体破裂，实现了针对凋亡抑制因子（Bcl-2）和ROS抵抗因子的干扰小RNA（small interfering RNA，siRNA）在HCC深部精准释放[21, 45]。还有研究将声敏金属有机框架与靶向程序性死亡受体1（programmed death-1，PD-L1）的siRNA共载于仿生细菌膜囊泡中，构建出超声响应型仿生基因控制系统[46]。在此基础上，Yin等[47]将SDT联合基因治疗拓展至CRISPR/Cas9编辑层面，构建超声控释

HMME包载CRISPR/Cas9共载脂质体(HMME@Lip-Cas9),共同递送声敏剂和Cas9/单链指导RNA。该系统在超声作用下产生ROS杀伤肿瘤,并利用ROS诱导溶酶体破裂释放Cas9,通过敲低核转录因子红系2相关因子2削弱HCC抗氧化防御,从而增强细胞凋亡和SDT效果。Xiong等[48]进一步提出"声遗传代谢疗法",利用单原子钌金属有机框架纳米平台递送靶向CD73的反义寡核苷酸,一方面通过催化增氧增强SDT,另一方面通过超声控释反义寡核苷酸抑制CD73表达,阻断腺苷介导的免疫抑制。该声控寡核苷酸递送系统,也为未来基于寡核苷酸的全身性代谢疾病干预开辟了全新的转化视角。

SDT协同基因治疗策略在HCC中从siRNA沉默、CRISPR/Cas9编辑拓展至声遗传代谢重编程,为核酸递送和"基因-代谢"联合干预提供了新思路。

1.2.5 联合治疗策略:化疗与免疫治疗增敏 近年来,SDT被进一步拓展为一种治疗增敏平台,通过与化疗及免疫治疗等传统抗肿瘤手段协同,大幅放大了整体治疗效应。

在化疗增敏方面,SDT可通过促进药物释放、调控药物胞内分布、激活前药及逆转耐药等机制增强HCC的化疗敏感性。超声可促进脂质体阿霉素从溶酶体向非溶酶体区域转移,增强细胞毒性[49]。ROS响应型前药和多响应纳米体系则可在超声或内源性H_2O_2刺激下实现局部按需释药[50-51]。此外,特定设计的声敏功能复合体还可通过抑制P-糖蛋白表达逆转多药耐药[52]。

SDT与免疫治疗联合可将局部氧化应激转化为系统性抗肿瘤免疫激活。SDT诱导的ROS可触发ICD,促进肿瘤抗原释放和树突状细胞成熟。同时,结合免疫佐剂、免疫检查点阻断、干扰素基因刺激因子激动剂、仿生纳米平台或基因递送系统,可进一步增强抗原呈递、促进巨噬细胞M1极化、激活先天免疫或训练性免疫,并提高T细胞介导的抗肿瘤效应[46, 53-56]。

综上所述,SDT在HCC中的角色,正由单纯局部杀伤手段发展为协同化疗增敏和免疫微环境重塑的重要治疗平台。建议未来研究应要求"治愈-再挑战"模型来证明真正的免疫记忆效应,而非仅靠肿瘤体积缩小说明问题。

1.2.6 气体治疗与微泡/纳泡协同SDT增效 气体治疗和微泡/纳泡体系为SDT提供了另一类可触发、可放大的协同路径。负载氧气的纳米气泡可以缓解HCC缺氧并协同铁死亡诱导来增强SDT效应[57]。同时,Tian等[58]利用ICG纳米气泡的空化释药与声穿孔效应,协同紫草素成功诱发HCC发生坏死性凋亡,放大了SDT的杀伤力。同样依托气泡的UTMD优势,微泡联合SDT通过改善HCC乏氧微环境、激活免疫系统、诱导HCC死亡方式重编程等多重机制,在HCC中实现了对声动力效应的系统性放大。

1.3 超声消融与组织碎化术:局部毁损与免疫重塑 基于聚焦超声的消融治疗是HCC超声治疗中最接近临床应用的一类策略(附录C)。近年来,聚焦超声相关技术已从传统热消融逐渐拓展至机械空化、靶向递药、免疫激活及联合治疗等方向[59-60]。

HIFU是目前应用广泛的超声治疗技术,其通过将声能精准聚焦于靶组织,在局部产生快速温度升高(通常>60 ℃),从而诱导蛋白质变性及凝固性坏死[61]。Shen等[62]构建了中性粒细胞载药系统,其巧妙之处在于将HIFU消融术后炎症微环境作为主动趋化信号,引导药物富集于残余HCC,为抑制HIFU后复发提供了新策略。

机械消融主要依赖超声诱导的空化效应产生机械力对肿瘤组织进行破坏,其中机械高强度聚焦超声(mechanical HIFU, mHIFU)及组织碎化术是代表性技术。Yang等[63]引入全氟己烷纳米液滴作为空化增强剂,在小鼠体内显著提高HCC杀伤率并诱导损伤相关分子模式释放,从而激活抗肿瘤免疫反应。组织碎化术则完全依赖非热机制,通过高幅度短脉冲超声产生密集空化泡,对HCC进行机械性粉碎,实现高精度、可控的非热消融[64]。

未来通过精细优化声空化与热效应的联合参数,并进一步验证其重塑免疫微环境的长期疗效,基于聚焦超声的综合治疗策略有望为HCC临床治疗提供新的选择。

1.4 其他声控前沿策略:压电、声辐射力与原位构建除微泡、SDT和超声消融外,近年来一些新型超声响应策略也逐渐应用于HCC基础研究,进一步拓展了超声治疗的机制边界(附录D)。

超声激活的压电材料可通过机械变形诱导电荷分离,产生电流及ROS,直接介导肿瘤细胞损伤。Wang等[65]研究表明,该过程还可通过Ca^{2+}内流激活核因子κB等信号通路,促进巨噬细胞极化及$CD8^+$ T细胞浸润,从而实现对HCC肿瘤免疫抑制微环境的重塑。此外,Li等[66]构建声-光协同催化体系,利用超声激活纳米片的压电效应实现H_2和H_2O_2高效生成,联合声动力治疗后显著增强原位肝肿瘤治疗效果,为深部肿瘤治疗提供了新的可能。多焦点声辐射力冲击则可在不直接引起细胞损伤的情况下诱导组织微结构改变,从而改善纳米药物在HCC的渗透并增强化疗效果[67]。超声响应策略的另一前沿方向是将"药物递送"转变为"原位生成",实现病

灶区域的药物长效蓄积。Chen等[68]基于化疗药物美法仑构建了超声响应性水凝胶，其在超声作用下可快速自组装形成纳米纤维网络，从而实现药物的持续释放与局部高浓度的长效维持。

总体来看，HCC超声治疗基础研究已从局部物理损伤拓展为能量触发的精准干预，其应用现状以细胞和动物实验为主，部分消融技术已有临床应用基础。超声作用的效果包括提高药物/核酸递送效率、增强肿瘤细胞杀伤、诱导免疫原性细胞死亡和改善联合治疗反应。当前局限主要集中在超声参数、空化剂量、材料安全性和模型外推性不足。未来突破有赖于可监测、可量化、可重复的声学剂量体系，并推动与介入、免疫和分子影像平台的深度融合。

2 超声在HCC诊疗一体中的基础研究进展

在声动力学、微泡靶向递送及高强度聚焦超声等研究基础上，近年来超声在HCC中的应用已从传统结构显像，逐渐拓展至诊疗一体化（附录E）。

2.1 *微泡/纳泡作为诊疗一体化平台：成像引导下的精准干预* 超声微泡/纳泡是HCC诊疗一体化研究的重要平台，可实现可视化诊断与精准治疗的有机结合。

趋化因子CXC亚家族受体4靶向超声微泡可在实现HCC分子成像的同时增强抗PD-L1治疗效果[69]；磷脂酰肌醇蛋白聚糖3靶向多功能纳米体系结合超声与光声成像，不仅提高小肝癌检出率，还可通过级联反应产生ROS抑制肿瘤进展[70]。此外，靶向热敏型超声造影剂可结合超声引导、射频消融及免疫治疗，进一步拓展诊疗一体化模式[71]。

多功能纳泡如双药纳米气泡和纳米造影剂可同步实现超声成像、SDT与化疗或免疫治疗协同增效[72-73]。值得注意的是，目前的诊疗一体化平台已不再局限于单一的超声模态。多项研究引入了磁共振成像、光声、荧光等多模态成像技术，在实现病灶多维精确定位的同时，亦能高效触发SDT与光动力疗法等联合干预策略[74-76]。

2.2 *多功能纳米平台与仿生递送：拓展诊疗一体化设计* 多功能纳米与仿生系统丰富了HCC超声诊疗策略。三氧化二砷/全氟己烷纳米颗粒负载金-环状精氨酸甘氨酸天冬氨酸多肽纳米平台在超声作用下通过全氟己烷相变增强显影并能同步介导光热与免疫治疗[77]。超声激活的仿生“细胞炸弹”则利用巨噬细胞的肿瘤趋化性递送药物，超声触发相变以增强成像并促使载体破裂，实现HCC深部实时追踪和精准释药[78]。

值得注意的是，利用分子、免疫等诊断信息直接指导治疗策略，正逐渐将“所见即所治”的构想落到实处。但受限于小动物模型，长期安全性、超声参数标准化以及临床设备的适配问题依然是其在临床转化前的难题。因此，后续研究的重心应逐渐从单纯拓展材料体系，转向遴选优效平台并开展大动物或非人灵长类模型的转化验证。

3 总结与展望

超声在HCC基础研究中的角色已从筛查、定位和介入引导工具，逐步转变为兼具分子成像、靶向递送、能量激活和疗效反馈能力的综合诊疗平台。超声不再只是“观察肿瘤”的手段，而正在成为调控肿瘤局部微环境和干预治疗反应的重要工具。

当前HCC超声诊疗研究主要呈现三方面趋势：从传统形态学向功能与分子评估拓展；从单一物理损伤向声促递送、细胞死亡重编程及免疫激活等多机制协同转变；从单点干预向“诊断定位-超声触发-疗效监测-反馈优化”的诊疗一体化模式发展。早期临床试验及大量荟萃分析已证实，超声介导增敏及精准递药在HCC中具备良好的安全性与临床可行性[79-82]。上述研究提示，决定其临床转化价值的核心在于机制明确、参数可控与疗效可重复，而非盲目追求平台功能的复杂化。

然而，该领域距离广泛临床转化仍面临多重挑战。其一，大量研究在声学参数（如频率、声压）与材料表征上存在高度异质性，削弱了实验数据的可比性；其二，现有诊断型临床超声设备难以满足纳米药物激活及精确空化调控的硬件需求；其三，HCC患者常伴随肝硬化等复杂背景，对正常肝组织的安全保护提出了严苛要求。

展望未来，HCC超声诊疗研究还应重点解决以下问题：首先，针对HCC易复发转移的临床困境，需依托远期转移与再挑战模型，确证超声协同治疗能否激发持久的系统性抗肿瘤免疫记忆，补齐从局部杀伤到全身保护的证据链。此外，规范参数标准，鉴于复杂肝病背景对声学响应的干扰，亟须确立超声参数报告共识，解决跨研究可比性缺失的问题。

总体而言，未来的突破有赖于声学工程、纳米医学、免疫学与人工智能的深度交叉。借助人工智能驱动的多维数据模型统筹材料筛选与声学参数优化，超声技术必将在HCC早筛、局部增敏、复发监测及个体化决策中发挥更核心的作用。

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附录A～E见二维码

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