· 综述 ·

Progresses of high intensity focused ultrasound combined with sonodynamic therapy for treating tumors

ZHAO Huimin, *HU Bing**, *LIU Yinzhi*, *HUANG Qingyun*
(*Department of Ultrasonic Imaging*, *Affiliated Renhe Hospital of China Three Gorges University*, *Yichang* 443001, *China*)

[**Abstract**] High intensity focused ultrasound (HIFU) can non-invasively and safely focus sound waves on target region to ablate tumors. Using acoustic sensitizer combined with ultrasound to ablate tumors, Sonodynamic therapy (SDT) can ablate tumors at deep region with high precision. The progresses of HIFU combined with SDT for treating tumors were reviewed in this article.

[**Keywords**] neoplasms; ultrasonic therapy
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高强度聚焦超声与声动力疗法联合治疗肿瘤进展

赵惠敏，胡　兵*，刘茵芷，黄清云
（三峡大学附属仁和医院超声影像科，湖北 宜昌　443001）

[**摘　要**] 高强度聚焦超声（HIFU）可无创、安全地将声波聚焦到体内目标区域而消融肿瘤。声动力疗法（SDT）利用声敏剂联合超声治疗肿瘤，用于消融深部肿瘤的精准性较高。本文就HIFU与SDT联合治疗肿瘤进展进行综述。

[**关键词**] 肿瘤；超声疗法
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高强度聚焦超声（high intensity focused ultrasound，HIFU）微创、无电离辐射，将高强度能量精确聚焦于特定区域而使目标病灶变性坏死以治疗肿瘤[1]；通过非侵入方式传递高能脉冲，可最大限度地减少对目标区域外组织的损害[2]。声动力疗法（sonodynamic therapy，SDT）利用超声激活声敏剂，是治疗实体肿瘤的新方法，具有组织穿透性良好及非侵入性等优势[3-4]。联合应用HIFU与SDT可明显提高肿瘤治疗效果[5-6]。本文就HIFU与SDT联合治疗肿瘤进展进行综述。

1　HIFU

HIFU通过聚焦能量使组织升温并破坏细胞，主要通过热效应、机械效应及免疫效应而治疗肿瘤[2]。HIFU的热效应表现为组织吸收声波能量并产生热量，造成局部组织温度迅速升高；其产生的热量可使暴露组织的温度迅速升高至60℃以上，持续1 s后，大多数组织细胞发生不可逆性死亡而致凝固性坏死[7]。HIFU的机械效应主要依赖于声空化，空化气泡破裂时产生高温、高压，释放大量能量并促进组织升温而对细胞造成损伤[8]。此外，HIFU消融还可引发不同的免疫效应以辅助杀伤肿瘤细胞[9-11]。

HIFU已在热消融肿瘤、诱导血凝块破碎、局部微创及靶向治疗等[2,12]多个方面取得良好效果。HIFU治疗子宫黏膜下肌瘤后再发率低，长期疗效与安全性更佳[13]；其治疗子宫肌瘤有效率达98.6%，高于腹腔镜子宫肌瘤切除术[14]。另有研究[15-16]显示，HIFU治疗

[**第一作者**] 赵惠敏（2000—），女，湖北荆门人，在读硕士，医师。研究方向：超声医学。E-mail：1575079198@qq.com
[**通信作者**] 胡兵，三峡大学附属仁和医院超声影像科，443001。E-mail：hurhcs@yeah.net
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前列腺癌和乳腺癌后5年总生存率分别为98%和95%，且治疗后不良反应发生率较低。对于中晚期胰腺癌，HIFU治疗可缓解疼痛、提高患者生活质量，在部分病例可获得持久缓解疼痛效果，并可使部分肿瘤体积缩小，为患者争取手术机会以延长其生存期[17-19]。同时，HIFU亦已用于治疗乳腺纤维腺瘤、肝癌、骨肿瘤及肾肿瘤等[20-21]。另一方面，HIFU治疗体积较大和/或位置较深及处于高速血流附近区域的肿瘤时，因超声能量衰减较快，导致治疗效果相对不理想[22]；此时为达到预期治疗效果，通常需要增加输出强度、延长治疗时间，可能增加损伤正常组织风险，造成皮肤灼伤、一过性疼痛等不良反应[23]甚至出现神经损伤[14]。

2 SDT

SDT治疗肿瘤的可能机制包括产生活性氧（reactive oxygen species，ROS）、空化效应及热破坏等[4]；目前对于ROS的认可度相对较高。

ROS是细胞代谢产生的小分子活性物质，细胞中过量的ROS可破坏细胞膜和细胞器，并通过氧化应激诱导细胞凋亡及自噬[24]。声敏剂可在超声空化效应下被激活而产生ROS，通过诱导细胞凋亡并协同超声的物理机械特性而杀伤肿瘤细胞[25-26]。除却ROS诱导肿瘤细胞凋亡外，超声激活声敏剂时产生的空化效应和热能也可对肿瘤细胞的膜结构和骨架造成损伤，进而在一定程度上杀伤肿瘤[27]。

声敏剂可分为有机声敏剂、无机声敏剂及有机/无机杂化声敏剂。有机声敏剂及无机声敏剂各有优劣；而有机/无机杂化声敏剂结合两种声敏剂的特性，复合材料中的无机纳米粒子增强细胞对有机超声敏化剂的吸收，保护有机超声敏化剂不被降解，防止药物过早释放。然而现有混合纳米复合材料存在制备程序复杂、在肿瘤部位生物分布不均匀及影响健康组织等缺陷，需进一步探索更为安全、有效的声敏剂[4,25]。

SDT对于胶质母细胞瘤、骨肉瘤[28]及乳腺癌[29-31]等具有良好抗肿瘤作用。胶质母细胞瘤侵袭性强、治疗难度大，预后较差。WU等[32]通过观察C6胶质母细胞瘤大鼠模型发现，相比接受单一声敏剂注射及单一低强度超声辐照的对照组小鼠，SDT组肿瘤生长抑制率与大鼠存活率明显提高。SHEN等[33]进行的细胞实验结果显示，声敏剂华卟啉钠与超声联合处理人结直肠癌细胞后，细胞凋亡和坏死率显著增加。与单纯使用低强度超声辐照乳腺癌小鼠模型相比，以IR-780碘作为声敏剂处理乳腺癌小鼠模型并以低强度超声辐照后，小鼠肿瘤体积增长率显著下降[30]。SDT具有对肿瘤细胞的杀伤作用及对肿瘤生长的抑制作用，其超声强度通常在0.5～10.0 W/cm^{2}之间，远低于HIFU治疗强度。目前SDT仍处于临床前阶段，存在如ROS产生量有限、治疗区域小等不足，且声敏剂用于人体的安全性及药代动力学也有待探索。

3 HIFU与SDT联合应用

HIFU与SDT在治疗肿瘤方面均有广阔应用前景，亦各有其不足；联合应用HIFU与SDT可在增强治疗效率的同时兼顾成像与靶向性，使肿瘤治疗更为精准、直观和高效，为无创治疗肿瘤提供新思路。联合声敏剂可降低HIFU空化阈值、增强热效应，进一步加强对肿瘤的杀伤作用[6]；同时声敏剂可用于超声引导和定位，以提高治疗效率。

联合应用HIFU与SDT[6,34-36]可提升治疗肿瘤有效率。相比单一治疗方法，联合HIFU与SDT可降低辐照强度与时间、减少声敏剂用量及相关不良反应。ZHONG等[6]在体外实验中联合使用声敏剂与HIFU，发现肿瘤细胞凋亡率超过单一HIFU 2倍以上，且小鼠体内实验中肿瘤体积增长率明显减小，表明联合HIFU与SDT可更有效地促进肿瘤细胞凋亡、抑制肿瘤生长。YAN等[37]利用载血卟啉单甲醚的聚乳酸-羟基乙酸共聚物微囊联合HIFU消融离体牛肝，所获凝固性坏死面积明显大于单一HIFU，提示消融效果明显增强。ZHANG等[5]制备的具有靶向作用的声敏剂，可有效增强HIFU消融小鼠体内肿瘤效果，同时发现肿瘤及其周围组织新生血管数量明显减少，提示二者联合可有效抑制肿瘤生长。

DESGRANGES等[38]报道，以全氟溴辛烷填充的微米尺寸液滴于灌注模型可增强HIFU热疗效果。LORTON等[39]基于离体肾脏观察全氟溴辛烷微液滴对高灌注器官中HIFU的增强效果，结果显示声敏剂活性可使肾皮质对超声波的吸收率倍增，使热沉积得到显著改善，组织焦点处温度相比未使用声敏剂时明显升高，表明该声敏剂可在离体器官中发挥相应作用；一旦投入临床应用，有望极大改善HIFU治疗高灌注器官肿瘤的效果，为临床决策提供更多选择。

4 展望

近年来，联合抗肿瘤治疗已成为提高治疗肿瘤效果及减少不良反应的重要策略。联合应用HIFU与SDT可从不同方面作用于肿瘤组织，更有效地杀伤肿瘤、缓解单独使用时的技术限制并减少不良反应。目

前联合应用HIFU与SDT尚面临诸多挑战，如现有SDT相关研究多属临床前研究，声敏剂的摄取、定位、生物降解、排泄及安全性等有待进一步评估，HIFU治疗不同肿瘤的辐照能量及持续时间尚无统一标准等，均有待后续加以完善。

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作者贡献：赵惠敏查阅文献、撰写文章；胡兵指导、审阅文章；刘茵芷和黄清云查阅文献。

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