

热消融治疗在结直肠癌肝转移中的应用进展

周福波, 于晓玲, 梁萍, 程志刚, 韩志宇, 于杰, 刘方义, 孙亚
解放军总医院 介入超声科, 北京 100853

摘要: 约 60% 的结直肠癌患者疾病进展过程中伴发肝转移, 手术切除为结直肠癌肝转移的标准疗法, 但 80% ~ 90% 的患者无法接受手术治疗。热消融技术是利用局部热能破坏肿瘤的治疗方法, 近年来在多种无法切除的实体肿瘤中获得较好的临床疗效。在结直肠癌肝转移患者中, 可使用的热消融技术主要为射频消融、微波消融、激光消融、不可逆电穿孔及冷冻消融。本文对热消融治疗后局部肿瘤进展、患者总体生存情况及并发症进行归纳, 同时对热消融技术在消化道肿瘤肝转移中的应用前景进行展望。

关键词: 热消融; 结直肠癌; 肝转移

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Perspective of thermal ablation in colorectal cancer with liver metastases

ZHOU Fubo, YU Xiaoling, LIANG Ping, CHENG Zhigang, HAN Zhiyu, YU Jie, LIU Fangyi, SUN Ya

Department of Interventional Ultrasound, Chinese PLA General Hospital, Beijing 100853, China

Corresponding author: YU Xiaoling. Email: dyuxl301@aliyun.com

Abstract: Approximately 60% of colorectal cancer patients will develop liver metastases during their disease course, and surgery is commonly believed as the standard treatment for colorectal cancer liver metastases (CRLM). However, 80%- 90% CRLM patients are not candidates for surgical resection. Thermal ablation has been regarded as an alternative for treatment to unresectable solid tumors during the last decade. Radiofrequency ablation, microwave ablation, laser-induced thermal therapy, and cryoablation have been most commonly administered for patients with unresectable CRLM. In this review, we will summarize the efficacy of thermal ablation on CRLM, including local tumor progression, cumulative survival, and complications. Additionally, further evaluation of thermal ablation in patients with liver metastases from gastrointestinal tumors will be discussed.

Keywords: thermal ablation; colorectal cancer; liver metastasis

全球每年结直肠癌新发患者约 140 万, 结直肠癌致死人数约 69 万^[1]。约 60% 的结直肠癌患者在疾病进展过程中伴发肝转移 (colorectal liver metastases, CRLM), 未经治疗的 CRLM 患者中位生存期为 6 ~ 9 个月^[2-3]。肝切除为 CRLM 的标准疗法, 部分患者手术切除后 5 年生存率可达 50%^[4]。但由于疾病进展、肿瘤部位、伴发疾病、肝功能低下等多种因素, 80% ~ 90% 患者无法行手术切除^[4]。热消融技术为利用热能对肿瘤细胞进行毁损的治疗方法, 在消融过程中热能可有效地破坏肿瘤细胞, 从而控制肿瘤的局部进展。近年来, 热消融技术已应用于多种不可切除的实体瘤, 并取得较好的疗效, 包括肝细胞癌、肝转移癌、肾细胞癌等^[5-7]。本文将对热消融治疗 CRLM 的安全性、有效性及并发症进行总结, 并对其未来的应用前景进行展望。

1 射频消融 (radiofrequency ablation, RFA)

射频消融为目前最常用的热消融技术, 可经皮或开

腹进行。RFA 治疗过程中, 消融针插入肿瘤内部, 应用电极使得凝固坏死范围覆盖整个肿瘤。当组织温度升高至 50℃ 时, 细胞蛋白发生永久性损伤, 进而产生凝固性坏死^[8]。当达 60℃ 时, 细胞即刻坏死。通常对于直径 3 ~ 5 cm 的肿瘤, 常用的消融时间为 15 ~ 30 min^[9]。多项研究证实, 对于无法手术切除的 CRLM, RFA 可获得有效的局部控制^[10]。此外, 对于可切除的 CRLM, RFA 可作为手术切除的辅助疗法。部分对化疗敏感的无法切除的 CRLM 可采用 RFA 进行局部控制。此外, 术后复发的 CRLM 也可采用 RFA 治疗。

表 1 对近 2 年发表的 RFA 治疗 CRLM 的文献进行汇总, CRLM 患者 RFA 治疗后中位生存期为 25 ~ 49 个月, 1 年、3 年、5 年总体生存为 80.4% ~ 92.2%、48% ~ 63%、16.3% ~ 8.2%, 局部复发率为 4.8% ~ 28.8%。Shady 等^[20]对 162 位 CRLM 患者 RFA 治疗后长达 10 年的随访显示, 有无肝外转移、CRLM 最大径、CEA 水平显著影响患者总体生存, 而患者性别、RFA 术前肝切除、术前肝动脉灌注治疗、CRLM 最大径、消融边界为 RFA 术后局部复发的影响因素。Facciorusso 等^[13]对 127 例 CRLM 患者 RFA 治疗预后分析显示, 淋巴细胞比例、CEA 水平、CRLM 数目、最大径均为患者总体生存、局部进展的影响因素。

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作者简介: 周福波, 女, 在读博士, 医师。研究方向: 介入超声学。

Email: myzhoufubo@126.com

通信作者: 于晓玲, 女, 主任医师, 教授, 博士生导师。Email: dy

uxl301@aliyun.com

表1 结直肠癌肝转移患者射频消融疗效总结 (2015-2016)

时间	国家	患者数	肿瘤数	总体生存率 (%)			中位生存期 (月)	局部复发率 (%)	参考文献
				1年	3年	5年			
2016	德国	113	279			16.3	25.0	4.8	[11]
2016	加拿大	71	127					25.0	[12]
2016	意大利	127	193	89.4		33.3	38.0	28.8	[13]
2016	荷兰	51	325	90.0	63.0		49.0		[14]
2016	美国	198				27.6		7.6	[15]
2015	荷兰	52	144				32.6	12.0	[16]
2015	丹麦	49	105	92.0	51.0	29.0	28.5	4.8	[17]
2015	韩国	51		92.2	62.4	48.2			[18]
2015	中国	56		80.4		41.0	27.0		[19]
2015	美国	162	233	90.0	48.0	31.0	36.0		[20]

RFA治疗后并发症发生率 $<5\%$ 。并发症主要与肿瘤大小、消融次数、电极类型及操作者熟练程度有关。消融后综合征为腹部实性肿瘤消融后常见症状。包括低热、腹痛、腹部不适、肌肉疼痛、恶心、呕吐等^[4]。多数患者在术后7~10 d即可恢复正常活动。并发症包括肩部疼痛、胆囊炎、胆管损伤等，进而引起胆管阻塞、肠道损伤、出血、血肿、气胸、胸腔积液、腹腔内出血、腹水、感染、门脉癌栓、针道种植等^[4]。Livraghi等^[8]的多中心研究对3 554例肝恶性肿瘤进行RFA治疗，结果显示，0.3%患者RFA术后死亡，2.2%患者发生严重并发症，包括腹腔出血、针道种植、肝脓肿、肠穿孔、心搏骤停、肺栓塞、气胸、胆汁瘤及胆囊炎等。

2 微波消融(microwave ablation, MWA)

MWA利用频率 ≥ 900 MHz的能量对肿瘤进行破坏，MWA过程中偶极子旋转为产热的主要方式^[22]。此外，微波场内离子极化也可产热。目前MWA使用的频率主要有915 MHz及2 450 MHz两种。其中2 450 MHz临床上更为常用，而915 MHz的穿透能力更强^[22]。和RFA相比MWA有以下优势：消融范围更大、不会导致组织碳化、消融温度更高、消融时间更短等。此外，MWA几乎不受热沉降作用影响，这使得MWA在实体瘤的局部治疗中得到越来越多的应用^[5]。

表2对近年发表的MWA治疗CRLM的文献进行汇总。CRLM患者MWA治疗后中位生存期为11~55个月，1年、3年、5年总体生存为46.7%~98.1%、36%~78.7%、18%~27.9%，局部复发率为6%~39.4%。我科对199例CRLM患者MWA治疗预后分析显示，年龄、CRLM数目、最大径、MWA术后化疗为MWA治疗后影响总体生存的影响因素，而CRLM数目、最大径及分布为MWA治疗后无进展生存的影响因素^[25]。Correa-Gallego等^[28]对134例CRLM患者热消融治疗预后分析显示，患者年龄为影响局部复发的因素，且MWA较RFA可显著降低CRLM局部复发率。

表2 结直肠癌肝转移患者微波消融疗效总结 (2013-2016)

时间	国家	患者数	肿瘤数	总体生存率 (%)			中位生存期 (月)	局部复发率 (%)	参考文献
				1年	3年	5年			
2016	中国	30	43	46.7			11.0		[23]
2016	美国	100					42.2		[24]
2016	中国	199	318			27.9			[25]
2015	美国	33	49					39.4	[26]
2015	英国	28	45	82.0	45.0	18.0			[27]
2014	中国	115	164	98.1	78.7				[6]
2014	美国	67	127				55.0	6.0	[28]
2013	英国	15		90.0	36.0		28.0	6.9	[29]

与RFA类似，MWA治疗CRLM的并发症发生率较低，常见的为疼痛、发热、肝功能损伤、胸腔积液、腹水、膈肌损伤及针道种植等。我科对1 136例肝恶性肿瘤患者行MWA治疗，严重并发症发生率为2.6%，包括肝脓肿、胆道损伤、肠穿孔、针道种植、需处理的胸腔积液、出血、需处理的皮肤热损伤等。轻度并发症包括发热、疼痛、无症状胸腔积液、胆囊壁增厚、动脉-门脉瘘、胆管狭窄、无需治疗的皮肤热损伤等^[5]。此外，我科对115例CRLM患者进行MWA治疗，4.3%患者发生胸腔积液，不良反应主要为局部疼痛、发热及肝功能损伤^[6]。

3 激光消融(laser-induced thermotherapy, LITT)

LITT治疗后，组织内吸收光转化为热，进而组织发生热损伤。目前LITT常用的激光源为钕铝石榴石晶体(Nd:YAG)，其波长为1 064 nm，穿透深度可达8 mm^[30]。组织吸热取决于激光束的特征、组织吸收特征，当能量增强致局部高热时可发生光热效应。局部温度达43~45℃时，细胞内酶失活。若维持43~45℃超过25 min，即发生永久性酶失活。局部温度达60~140℃时，组织即可发生肉眼可见的凝固性坏死^[31]。LITT可采用多个光纤对相对较大的肿瘤进行治疗。此外，其不受热沉降作用影响。

与上述两种消融治疗相比，目前LITT治疗CRLM的临床研究相对较少，近期发表的文献汇总见表3。CRLM患者LITT治疗后中位生存期为19.1~36个月，1年、3年、5年总体生存为78%~95.7%、19%~72.4%、4.5%~33.4%，局部复发率为2%~48%。Thomas等对594例CRLM患者行LITT治疗，患者平均年龄为61.2岁，中位生存期达25个月，无进展生存期为13个月。生存分析结果显示，CRLM的数目及最大径为患者LITT治疗后总体生存及无进展生存的预后因素。此外，初次治疗时有无淋巴结转移也将影响CRLM患者的长期生存。Christopher等^[36]对80例CRLM患者行LITT治疗，结果显示CRLM数目、肿瘤分化程度、LITT术前接受手术、化疗为影响患者生存的因素。

表3 结直肠癌肝转移患者激光消融疗效总结(2004-2016)

时间	国家	患者数	肿瘤数	总体生存率(%)			中位生存期(月)	局部复发率(%)	参考文献
				1年	3年	5年			
2016	中国	43	113				19.1	[30]	
2015	埃及	594	1 545	78.0	28.0	7.8	25.0	2.0	[31]
2012	埃及	224	492	88.0	19.0	4.5	23.0	3.6	[32]
2009	德国	87	180	95.7	72.4	33.4	54.0	10.0	[33]
2007	德国	66	117				23.0		[34]
2006	意大利	44	75				35.0	48.0	[35]
2004	澳大利亚	80	168				48.3	6.7	[36]
2004	德国	1 259	3 440				36.0		[37]

根据目前已发表的文献统计, LITT治疗CRLM的并发症较RFA及MWA高。Puls等^[33]对87例CRLM患者行LITT治疗, 7%患者治疗后出现并发症, 包括胸腔积液、膈下血肿、脓肿、气胸、胸膜炎、肝内出血、胆汁瘤等。Christopher等对80例CRLM患者LITT治疗后, 并发症发生率为16%, 包括心动过缓、气胸、持续发热、黄疸、小肠瘘等。

4 不可逆电穿孔(irreversible electroporation, IRE)

不可逆电穿孔是基于电场的脉冲原理(1 000 ~ 1 500 V/cm), 在肿瘤中插入电极进而灭活肿瘤的治疗方法。电脉冲改变原有跨膜电位、产生“纳米孔”, 进而破坏细胞膜。在足够的脉冲强度及脉冲持续时间作用下, 细胞稳态破坏进而死亡。临床预研究证实IRE会导致消融范围内的细胞死亡, 而胞外基质完整, 这可保护近肿瘤部位的血管及胆管结构。

2011年, IRE首次应用于人体, 其安全性在随后的多项研究中得到证实^[38-39]。目前, IRE应用于CRLM的相关文献较少。Scheffer等^[40]纳入10例CRLM患者, 均成功行IRE治疗, IRE术后平均84(51 ~ 153) min后行手术切除。1例患者IRE术后发生心律失常。Hasein等^[41]纳入29例CRLM患者的58个转移灶进行IRE治疗, 术后2年无进展生存率18%, 2年总体生存率62%, 1例患者术后出现心率失常, 1例疼痛。

5 冷冻消融(cryoablation)

冷冻消融术是应用冷冻对靶组织进行消除的治疗, 其在肝及肺肿瘤的治疗中应用较多, 在CRLM中应用的报道较少。Bang等^[42]对59例CRLM患者的151个CRLM病灶行冷冻消融, 8%患者出现严重并发症, 包括出血、血胸、死亡等。患者术后中位生存期为23.6个月, 3年生存率为30%, 局部复发率为12%。Ng等^[43]对293例CRLM患者行冷冻消融, 患者术后中位生存期为29个月, 10年生存率为13.3%, 局部复发率为23%。

6 结语

热消融技术可有效控制无法切除的CRLM患者局部肿瘤进展。据2013年国际消融专家组提出的CRLM操作规范^[44], 热消融治疗CRLM的适应证: 由于肿瘤部位、分布等原因导致肿瘤无法切除, 患者应接受消融(+化疗), 而非单纯化疗; 前期接受切除或肿瘤分布广泛, 导致残余肝量不

足; 肿瘤虽可切除, 但存在重要脏器并发症、患者意愿等。在临床热消融治疗前, 不仅需要多学科综合讨论, 确定患者可否行消融治疗, 还需结合患者临床特征及肿瘤特性, 制订最佳治疗方案, 方可达最优疗效。

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