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· 临床研究 ·

肝动脉导管化疗栓塞序贯经皮微波消融治疗原发性肝癌的临床应用*

张磊 赵雨冰 吴江红 张翔 万智勇[△]

(上海交通大学附属第一人民医院肿瘤中心 上海 201600)

摘要 目的:探讨肝动脉导管化疗栓塞(TACE)序贯B超/CT精准引导下经皮微波消融(MWA)在原发性肝癌中的治疗应用,分析比较疗效。**方法:**回顾性分析2016年1月至2018年7月在上海交通大学附属第一人民医院接受治疗的96例原发性肝癌患者,42例行TACE序贯联合B超/CT精准引导下MWA治疗(联合组),另54例仅行单纯TACE治疗(TACE组)。术后1月、3月、6月、1年、2年复查增强CT/MRI、AFP、肝功能,随访2年比较两组患者肿瘤坏死、复发、进展和生存情况,评价两组疗效。**结果:**联合组肿瘤坏死率92.9%,TACE组肿瘤坏死率48.1%,差异有统计学意义($P<0.05$);联合组肿瘤复发率7.1%,TACE组肿瘤复发率24.1%,差异有统计学意义($P<0.05$);联合组肿瘤进展率19.1%,TACE组肿瘤进展率27.8%,差异无统计学意义($P>0.05$);联合组肿瘤进展时间13.2个月,TACE组肿瘤进展时间7.6个月,差异有统计学意义($P<0.05$);联合组1年生存率83.3%,TACE组1年生存率57.4%,差异有统计学意义($P<0.05$);联合组2年生存率62%,TACE组2年生存率31.5%,差异有统计学意义($P<0.05$);联合组中位生存时间28.9个月,TACE组中位生存时间16.9个月,差异有统计学意义($P<0.05$)。**结论:**TACE序贯MWA治疗肝癌安全有效,互补增益,是肝癌综合治疗的新模式。

关键词:肝癌;肝动脉导管化疗栓塞;微波消融;序贯联合;疗效评价

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Clinical Value of Transcatheter Arterial Chemoembolization Followed by Percutaneous Microwave Ablation for Hepatocellular Carcinomas*

ZHANG Lei, ZHAO Yu-bing, WU Jiang-hong, ZHANG Xiang, WAN Zhi-yong[△]

(Cancer center, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 201600, China)

ABSTRACT Objective: To explore the Clinical value of transcatheter arterial chemoembolization (TACE) followed by percutaneous microwave ablation (MWA) for hepatocellular carcinomas, and to analyze the efficacy. **Methods:** A retrospective analysis of 96 patients with primary liver cancer treated at the First People's Hospital of Shanghai Jiaotong University from January 2016 to July 2018, 42 patients underwent TACE sequential combined with B-ultrasound/CT-guided MWA treatment (Combined group), another 54 patients were treated with TACE alone (TACE group). CT, MRI, AFP and liver function were enhanced at 1 month, 3 months, 6 months, 1 year and 2 years after treatment. Tumor necrosis, recurrence, progression and survival were compared between the two groups. The efficacy of the two groups was evaluated. **Results:** The tumor necrosis rate was 92.9 % in the combined group and 48.1 % in the TACE group, the difference was statistically significant ($P<0.05$). The tumor recurrence rate was 7.1 % in the combined group and 24.1 % in the TACE group, the difference was statistically significant ($P<0.05$). The tumor progression rate was 19.1 % in the combined group and 27.8 % in the TACE group, the difference was not statistically significant ($P>0.05$). The median progression time was 13.2 months in the combined group and 7.6 months in the TACE group, the difference was statistically significant ($P<0.05$). The 1-year survival rate of the combined group was 83.3 % and 57.4 % in the TACE group, the difference was statistically significant ($P<0.05$). The 2-year survival rate of the combined group was 62 % and 31.5 % in the TACE group, the difference was statistically significant ($P<0.05$). The median survival time was 28.9 months in the combined group and 16.9 months in the TACE group, the difference was statistically significant ($P<0.05$). **Conclusions:** TACE sequential MWA is safe and effective in the treatment of liver cancer, and can complement each other. It is a new model for comprehensive treatment of liver cancer.

Key words: Hepatocellular carcinomas; Transcatheter arterial chemoembolization; Microwave ablation; Combination therapy; Therapeutic evaluation

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作者简介:张磊(1988-),男,硕士,住院医师,主要从事肿瘤介入方面的研究,电话:18817821690, E-mail: 429592009@qq.com

[△] 通讯作者:万智勇(1962-),男,博士,副主任医师,主要从事肿瘤介入方面的研究, E-mail: wan_zhy@163.com

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前言

原发性肝癌的发病率和死亡率分别居我国恶性肿瘤的第4位和第3位^[1],首选的治疗方法是外科手术切除或肝移植。肝移植由 Starzl 于 1963 年开始实施,是肝癌最有效的治疗方法,但在供体来源、受体条件、手术难度和费用以及术后长期抗排斥等方面均存在较大难度和风险,故适用范围小。肝癌手术切除的优势在于能彻底去除病灶,是早期肝癌的首选治疗,但由于肝癌本身的隐匿性,大多数肝癌患者在早期不易被发现,就诊时已处于中晚期^[2],诊断伊始就失去了手术机会,还有相当一部分患者因为高龄、严重肝硬化、病灶多发,预计切除后残留肝脏无法代偿以及合并肝门淋巴结转移、门脉癌栓等手术风险大而无法行外科手术切除。对于无法行外科手术切除的肝癌患者,以肝动脉导管化疗栓塞(TACE)、瘤内酒精注射、微波消融(MWA)、射频消融、氩氦冷冻消融、I125 粒子植入、分子靶向药物等治疗为主。

自 1974 年 Doyon 等首次报道通过肝动脉导管化疗栓塞(TACE)治疗肝脏肿瘤以来,TACE 已成为国内外肝癌非手术切除的首选姑息性治疗^[3]。但由于肿瘤丰富的新生侧支血管,单纯依靠 TACE 常常碘化油沉积不完全,肿瘤完全坏死率较低,术后肿瘤残余导致肝癌复发的可能性大,另外 TACE 治疗次数过多会加重肝功能损伤,影响预后。

自 1994 年 Seki 等用微波消融(MWA)治疗小肝癌以来,其临床应用越来越广,MWA 在小肝癌的治疗已获得手术相当的疗效^[4]。2017 版美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)指南^[5]、我国 2017 版原发性肝癌诊疗规范^[6]均将手术和消融列为早期肝癌的推荐方案。MWA 具有导入能量大、升温速度快、消融时间短、局部灭活彻底等优点,对<3 cm 肝癌,MWA 治疗可使肿瘤完全坏死率达 90%以上,对 3-5 cm 的肿瘤,也具有很强的可操作性,单针多点、多针多点可达到更大消融范围,与 TACE 联合可互补增益,使肿瘤灭活更彻底^[7]。

一些国内学者提出肝动脉导管化疗栓塞(TACE)序贯联合微波消融(MWA)治疗肝癌,并通过 Meta 分析证实比单纯 TACE 疗效更好^[8]。消融不完全导致的肿瘤复发是影响患者预后的重要因素,TACE 可使肿瘤边界更为清晰,为消融的穿刺过程提供明确方向,减少血流的热沉效应,病灶内沉积的碘化油也有利于消融过程热量的传导。动脉造影还可能发现术前影像学检查中难以发现的微小卫星灶,大大减少消融后肿瘤残留或遗漏的概率。目前 TACE 联合 MWA 在治疗中晚期肝癌、大肝癌和肝转移瘤等方面均有应用^[9,10],可以明显提高疗效,提高患者生存率^[11]。

本文对 TACE 联合 MWA 与单纯 TACE 治疗 96 例原发性肝癌的临床疗效进行了回顾性分析,旨在评价 TACE 序贯联合 MWA 在肝癌综合治疗中的价值。

1 材料与方法

1.1 材料

1.1.1 选择标准和剔除标准 选择标准:①病理诊断或临床诊断(肝炎病史、影像学、肿瘤标志物)为原发性肝癌;②因高龄、肝硬化、肿瘤毗邻大血管、侵犯门静脉分支、肝门和周围淋巴结转移等无法行外科手术;③肿瘤最大病灶直径≤5 cm、多发病灶数目≤3 个④肝功能 Child A 或 B 级;⑤心肺功能、肾功能、凝血功能基本正常;⑥肝癌病灶之前未接受过 TACE 或消融治疗。剔除标准:①肝功能 Child C 级;②肝内弥漫性病灶或门静脉主干癌栓;③不可纠正的凝血功能障碍和血象异常,具有明显出血倾向者;④心、肺、肾和脑等重要脏器功能衰竭。

1.1.2 病例资料 2016 年 1 月-2018 年 7 月我院符合纳入标准的原发性肝癌患者 96 例,TACE 联合 MWA 治疗 42 例(联合组),单纯 TACE 治疗 54 例(TACE 组)。两组患者的性别、年龄、肿瘤数目、肿瘤直径、AFP 值、巴塞罗那(BCLC)分期、肝功能、肝炎、肿瘤包膜、ECOG 评分等一般临床资料差异无统计学意义($P>0.05$),详细资料见表 1。

表 1 96 例原发性肝癌患者的一般临床资料

Table 1 General clinical data of 96 patients with primary liver cancer

Parameter	Combined group Number of cases (proportion)	TACE group Number of cases (proportion)	χ^2 value	P value
Gender			0.977	0.508
Male	36(85.7 %)	42(77.8 %)		
Female	6(14.3 %)	12(22.2 %)		
Age			0.067	0.323
<60	9(21.4 %)	15(27.8 %)		
≥ 60	33(78.6 %)	39(72.2 %)		
Number of tumors			0.476	0.795
1	19(45.2 %)	23(42.6 %)		
2-3	23(54.8 %)	31(57.4 %)		
Tumor size			0.138	0.710
<3 cm	11(26.2 %)	16(29.6 %)		
3-5 cm	31(73.8 %)	38(70.4 %)		

AFP			0.786	0.375
<200 ng/ml	7(16.7 %)	13(24.1 %)		
≥ 200 ng/ml	35(83.3 %)	41(75.9 %)		
BCLC staging			0.633	0.426
Phase B	8(19.0 %)	14(25.9 %)		
Phase C	34(81.0 %)	40(74.1 %)		
Child rating			0.018	0.894
Class A	15(35.7 %)	20(37.0 %)		
Class B	27(64.3 %)	34(63.0 %)		
hepatitis B			0.249	0.618
yes	30(71.4 %)	36(66.7 %)		
no	12(28.6 %)	18(33.3 %)		0.554
Tumor envelope			0.350	
Yes	22(52.4 %)	25(46.3 %)		
no	20(47.6 %)	29(53.7 %)		
ECOG score			0.024	0.876
0-1 score	24(57.1 %)	30(55.6 %)		
2 score	18(42.9 %)	24(44.4 %)		

1.2 方法

1.2.1 TACE 治疗 所有患者均先行 TACE 治疗。经皮股动脉穿刺(seldinger 法),置入 5F 血管鞘,使用 4F/5F 导管行腹腔干动脉、肝动脉和肠系膜上动脉造影,必要时行膈下动脉、胃左动脉造影。明确肿瘤供血动脉后,使用微导管(商品名:Progreat,日本泰尔茂株式会社)超选择插管至肿瘤的供血动脉,在供血动脉内灌注化疗药物:奥铂 100 mg+ 亚叶酸钙 200 mg+5-Fu 1 g,然后透视下缓慢注入含有表阿霉素 40 mg 和碘化油 10-20 mL

的混悬液进行栓塞,剂量视病灶大小和血管富乏程度而定,栓塞至造影显示肿瘤血供完全消失或减少 95 %以上。如造影时发现存在肝动脉 - 门静脉瘘或肝动脉 - 肝静脉瘘的存在,则先使用聚乙烯醇颗粒(PVA)或明胶海绵堵塞后,再行碘化油栓塞。栓塞完毕后再行 DSA 造影,与栓塞前造影做对比(图 1)。两组 TACE 治疗时使用的化疗药物和碘化油剂量差别无统计学意义。

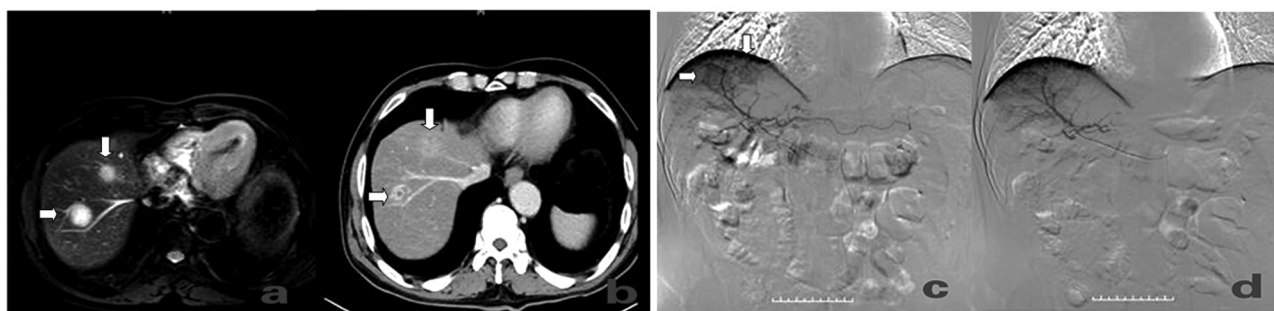


图 1 TACE 治疗前后 CT 图像和 DSA 造影图像

Fig.1 CT images and DSA images before and after TACE treatment

注:图 a 是 TACE 术前增强 CT 图像(箭头示肝内 2 病灶);图 b 是 TACE 术后增强 CT 图像(箭头示肝内 2 病灶碘油不完全沉积);图 c 是 DSA 术中碘油栓塞前造影(箭头示肝内 2 枚类圆形病灶);图 d 是 DSA 术中碘油栓塞后造影(肝内病灶血供基本完全消失)。图中标尺每格 1 cm,共 10 cm。

Note: Figure a shows the pre-TACE enhanced CT image(arrows show intrahepatic 2 tumor lesions); Figure b shows enhanced CT images after TACE (arrows indicate that the intraluminal 2 tumor lesions are not completely deposited with lipiodol); Figure c shows pre-embolization of lipiodol during DSA (Arrows show 2 round lesions in the liver); Figure d shows angiography after lipiodol embolization in DSA(The blood supply to the liver is almost completely gone). The scale in the figure is 1 cm per grid, a total of 10 cm.

1.2.2 MWA 治疗 联合组在 TACE 治疗后序贯行 MWA 治疗。富血供而碘油沉积良好者,每月 1 次 TACE,2-3 次后,对残留病灶进行 MWA;乏血供而碘油沉积较差者,第一次 TACE 治疗 5-7 天后即行 MWA。MWA 治疗首选 B 超引导,当肿瘤病灶位于膈顶、肋骨下,气体或骨头干扰导致超声显像欠佳时,改

选 CT 引导。治疗时,根据术前影像所示病变部位让患者取仰卧或俯卧位,在 B 超/CT 扫描下,选择合适的穿刺点和穿刺途径。确定穿刺点后,给予吗啡 10 mg 皮下注射镇痛,常规消毒、铺巾、利多卡因局麻、刀片扩皮,使用一次性冷循环微波消融刀(南京福中医疗高科有限公司)进行穿刺,B 超/CT 引导下调整

微波刀针芯位置,使针道位于肿瘤组织的中心,针尖超出肿瘤边界 0.5-1.0 cm。根据肿瘤大小、形状、毗邻重要脏器的距离、消融时 B 超/CT 反馈的图像以及患者的耐受程度,决定消融功率和时间,一般功率 55-60 W,时间 6-10 min(图 2)。如果肿瘤稍大或形状不规则,单次消融不能完全覆盖病灶或存疑,则行

单针多次、重叠消融,直至覆盖肿瘤完全。如果肿瘤毗邻重要脏器,如心脏、膈肌、大血管、胃肠、胆囊等危险部位,则采用人工胸腹水技术或小剂量无水乙醇注射辅助消融,保证疗效的同时可避免严重并发症发生。消融结束后,电凝状态下拔针,烧灼穿刺道防止出血和针道转移。

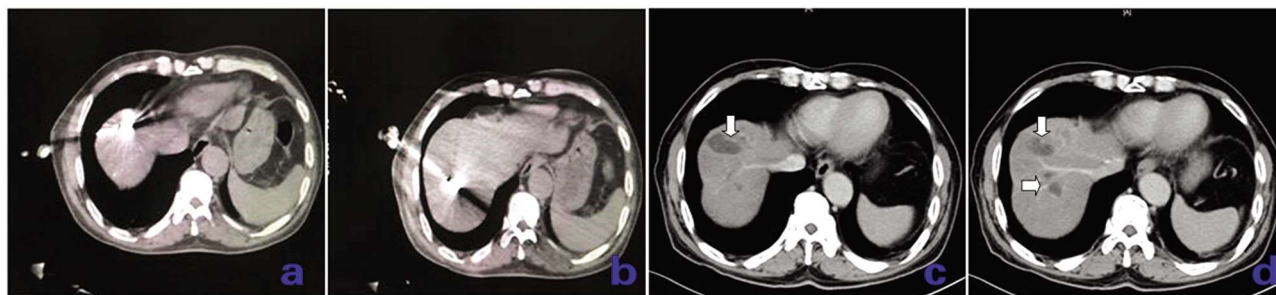


图 2 微波消融 CT 图像

Fig.2 Microwave ablation CT image

注:图 a-b 为 CT 引导下穿刺消融过程,图 c-d 为消融后 1 个月复查增强 CT 结果(箭头示原肿瘤所在高密度影转变为低密度影)。

Note: Figure a-b shows the CT-guided microwave ablation procedure, and Figure c-d shows the enhanced CT image 1 month after ablation (the arrows indicate that the high-density image of the original tumor is converted to an inactive low-density shadow).

1.3 疗效评价

所有患者术后 4-6 周复查增强 CT/MRI、AFP、肝功能,如果发现肿瘤残余,联合组再次行 MWA 治疗,TACE 组继续 TACE 治疗,直至肿瘤完全坏死或病人无法耐受。随后 1 个月、3 个月、6 个月、1 年、2 年门诊和电话随访,记录两组患者的肿瘤坏死、复发进展和生存情况,比较评估疗效。肿瘤坏死、复发和进展评价标准:(1)肿瘤坏死:增强 CT/MRI 检查病变区无强化,AFP 转阴。(2)肿瘤复发:肿瘤完全坏死后在原病灶的边缘出现新的病灶,新病灶与原病灶相连。(3)肿瘤进展:肝内其它部位出现新发病灶或发生远处转移。

CT/MRI 阅片、TACE/MWA 操作均为同一组医师,诊断和治疗标准一致。

1.4 统计学分析

采用 SPSS 20.0 进行统计学分析,计数资料用 χ^2 检验,计量资料用 t 检验,用 Kaplan-Meier 法画出生存曲线,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 联合组

全组 42 例患者共 64 个肿瘤病灶,共行 TACE 治疗 72 次,MWA 治疗 54 次,平均每人 TACE 治疗 1.71 次,每人 MWA 治疗 1.29 次。其中 10 例患者行 2 次 MWA 治疗,1 例患者行 3 次 MWA 治疗。3 例发生原肿瘤病灶复发,6 例出现肝内其它部位新发病灶,2 例发生肺部转移。全组患者术后肿瘤完全坏死率 92.9 % (39/42),肿瘤复发率 7.1 % (3/42),肿瘤进展率 19.1 % (8/42)。所有治疗结束至肿瘤进展时间平均为 13.2 个月,中位生存时间 28.9 个月,1 年、2 年生存率分别为 83.3 %、62 %。

2.2 TACE 组

全组 54 患者共 78 个肿瘤病灶,共行 TACE 治疗 185 次,平均每人 TACE 治疗 3.4 次。其中 26 例患者碘油沉积良好,肿瘤完全坏死;13 例患者碘油沉积不完全,肿瘤不完全坏死,肝内无新发病灶;10 例发生肝内多发转移;5 例发生肺转移。全组患者术后肿瘤完全坏死率 48.1 % (26/54),肿瘤复发率 24.1 % (13/54),肿瘤进展率 27.8 % (15/54)。所有治疗结束至肿瘤进展时间平均为 7.6 个月,中位生存时间 16.9 个月,1 年、2 年生存率分别为 57.4 %、31.5 %。

2.3 随访

两组的随访结果见表 2 和图 3。

表 2 TACE 联合 MWA 组与单纯 TACE 组的随访结果

Table 2 Follow-up results of TACE combined with MWA group and simple TACE group

Parameter	Combined group Number of cases	TACE group Number of cases	χ^2 value	P value
Tumor necrosis rate (%)	92.9	48.1	21.599	<0.001
Tumor recurrence rate (%)	7.1	24.1	4.876	0.027
Tumor progression rate (%)	19.1	27.8	0.988	0.320
Tumor progression time (months)	13.2	7.6	20.582	<0.001
Median survival time (months)	28.9	16.9	12.616	<0.001
1-year survival rate (%)	83.3	57.4	7.391	0.007
2-year survival rate (%)	62	31.5	8.843	0.003

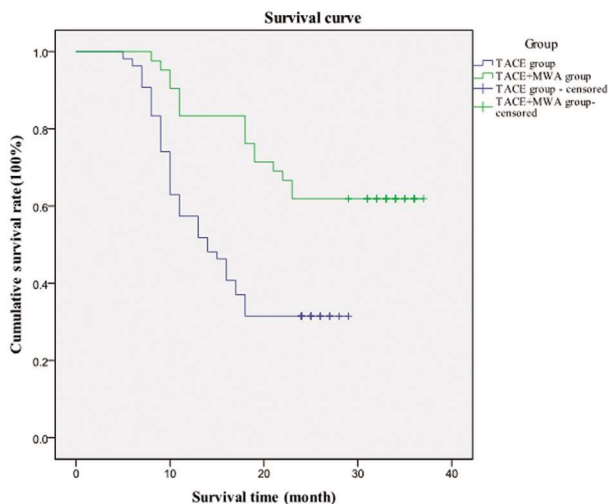


图3 TACE联合MWA组与单纯TACE组的生存曲线图

Fig.3 Survival curve of TACE combined with MWA group and simple TACE group

表2和图3示联合组与TACE组在肿瘤坏死率、肿瘤复发率、肿瘤进展时间、1年生存率、2年生存率、中位生存时间均存在统计学差异($P < 0.05$),但肿瘤进展率无统计学差异($P > 0.05$)。

2.4 并发症

两组患者术后均出现不同程度的肝区胀痛、发热、恶心、呕吐、腹胀、厌食,另有部分患者发生一过性谷丙转氨酶和总胆红素升高,经保肝、止痛、吸氧、褪热、静脉水化等对症支持治疗后好转。无严重并发症,无手术相关死亡。

3 讨论

肝脏由门静脉和肝动脉双重供血,正常组织供血80%由门静脉提供,而原发性肝癌的供血90%~99%由肝动脉提供,仅小部分由门静脉供血^[12],这是TACE治疗原发性肝癌的理论基础。TACE在抗血管治疗中发挥较为重要的作用,但对乏血供肿瘤,效果不佳,肿瘤坏死率低,次数过多会加速肝硬化^[13],影响预后。消融是对肿瘤的局部针对性治疗,消融尤其是MWA可做为TACE的补充,特别是对乏血供肿瘤,减少TACE次数,减轻肝功能损害。

介入治疗是对传统外科手术或肝移植的补充,消融也是对TACE的补充,它们可产生协同治疗作用^[14],MWA还有助于提高抗肿瘤免疫作用^[15,16]。MWA的局限性在于对>5cm的大病灶消融不完全、易残留,对靠近肺、胆囊、胃肠、肝包膜、膈肌、心脏、大血管等"危险部位"的肿瘤有损伤邻近脏器的风险,人工胸腹水技术和乙醇注射消融有助于减少危险部位的消融风险^[17]。

单纯应用TACE或MWA治疗肝癌均有局限性,两者序贯联合治疗可以发挥协同放大作用^[17,18],笔者认为合理的方法是先行TACE后再行MWA治疗。TACE治疗的关键是使用微导管超选择靶血管进行栓塞,避开非靶血管,最大程度地减少对正常肝组织的损害,保护患者的肝功能储备。消融治疗的关键是使用CT/B超引导对肿瘤进行精准灭活,在保证肿瘤消融完全无残留的基础上,尽量减少对周围正常肝组织的损伤,其核心是对肿瘤边界范围的精准确认。超声造影技术(Contrast enhanced ultrasound, CEUS)有助于确认肿瘤的实际形态和边界,界定肿瘤范围,为消融手术提供了可靠参考,实现肿瘤精准灭

活^[19]。我们的体会是优先选择超声引导、尽量保持消融体位与术前CT/B超扫描时一致、缩短消融手术与CT/B超检查的时间间隔,尽量减少肝脏解剖结构的变化,可以明显提高消融对位准确的成功率。

TACE联合MWA治疗肝癌安全有效,既能减少TACE治疗的频次,又可提高MWA治疗的肿瘤一次完全消融率,减少肿瘤复发,提高患者的生存质量和延长生存时间^[20]。目前关于联合治疗的顺序(先行TACE再行消融和先行消融再行TACE)和时间间隔方面尚有争论。在联合治疗的顺序方面,大多主张先行TACE治疗,然后再行MWA治疗,主要原因在于肿瘤局部供血动脉大多在MWA治疗后受损闭塞,MWA之后再行TACE则会给超选择过程带来困难,影响其疗效。有诸多研究均表明,先行TACE更有利于联合疗法充分发挥作用,原因如下:其一,TACE可使肿瘤坏死、缩小,获得消融机会^[21];其二,TACE可发现CT/MRI/B超遗漏的小病灶;其三,阻断肿瘤病灶周围及其内部的血流,可以有效降低"热沉效应"对MWA治疗效果的影响,并减少消融时肿瘤的血行转移;其四,TACE术后病灶内沉积的碘化油,有利于消融过程中热量的传导,同时具有定位作用,提高治疗的准确性^[22,23]。在联合治疗的时间间隔方面,目前尚未能达成共识,笔者认为这一时间间隔并非规定不变,应在综合患者TACE术后的恢复情况与残余肿瘤的急迫情况后,个体化决策。

目前不同国家、不同医院、不同科室在肝癌的治疗上还有分歧^[24],缺乏多中心随机对照研究^[25]。Lyu等^[26,27]研究表明经肝动脉灌注化疗药物治疗晚期肝癌患者,中位无进展生存时间7.4个月,中位生存时间14.5个月。石明等^[28]于2010年回顾性研究了经TACE治疗的肝癌患者,1年、5年、10年生存率分别为47%、10%、7%,中位生存时间10.37个月。Chen等^[29]于2017年回顾性研究了TACE-MWA或TACE治疗的肝癌患者,TACE-MWA组的肿瘤坏死率为92.1%,高于TACE组的46.3%。本研究回顾性研究了96例原发性肝癌患者,联合组术后肿瘤完全坏死率92.9%,TACE组术后肿瘤完全肿瘤率48.1%,联合组肿瘤进展时间13.2个月,TACE组肿瘤进展时间7.6个月,联合组1年生存率83.3%,TACE组1年生存率57.4%,联合组2年生存率62%,TACE组2年生存率31.5%,联合组中位生存时间28.9个月,TACE组中位生存时间16.9个月。结果与国内外大多数研究报道基本一致,研究报道≤5cm的肝脏肿瘤,建议一次TACE后序贯消融;>5cm的肿瘤,2~3次TACE后联合消融,根据随访结果,再次TACE或联合其它治疗^[30,31]。

我国约80%的肝癌患者伴有乙型肝炎病毒(Hepatitis B virus, HBV)感染,HBV感染是肝癌发生、发展、复发的危险因素,对HBV感染且复制活跃的患者,抗病毒治疗应贯穿于肝癌治疗的全过程,可以降低术后复发率^[32,33]。另外,我们观察到肿瘤有无包膜也是影响患者预后的重要因素,Benvenegut等^[34]报道肝癌包膜完整组患者1年、3年生存率比浸润型肝癌组高;Kneuert等^[35]报道浸润型肝癌患者生存率低,中位生存时间仅10个月。

总之,肝癌的治疗是一个综合治疗,综合治疗体现在序贯联合之中,在着重消灭肿瘤的同时,还要注意保护肝功能,同时关注患者肝炎病毒、机体免疫力和体能状态。在治疗肿瘤时,要

合理选用方法,适当掌握力度,既要狠狠打击肿瘤,又要最大程度保护肝脏,延长患者生存期是肝癌治疗的唯一目的,生存质量才是硬道理!

本研究对肝癌治疗的模式进行了探索,积累了宝贵经验,建立了肝癌综合治疗的临床路径,为肝癌治疗提供了新的选择。但也有不足:① 本研究是回顾性研究,不是前瞻性的随机对照研究。② 患者样本数还不够多,还需要大样本、多中心的随机对照研究证实。③ 随访时间相对较短,还需要更长时间的随访来确认患者的预后。

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