

doi: 10.13241/j.cnki.pmb.2020.07.019

肝动脉化疗栓塞联合射频消融对中晚期肝癌患者血清肿瘤活性因子、肝功能和预后的影响*

王少雷 魏 宏[△] 刘德华 史国栋 吴丽娜

(中国医科大学肿瘤医院 / 辽宁省肿瘤医院医学影像科 辽宁 沈阳 110042)

摘要 目的:探讨肝动脉化疗栓塞(TACE)联合射频消融(RFA)对中晚期肝癌患者血清肿瘤活性因子、肝功能和预后的影响。**方法:**选取2012年2月~2016年6月期间我院收治的中晚期肝癌患者103例,根据随机数字表法将患者分为对照组(n=51)和研究组(n=52),对照组患者给予RFA治疗,研究组给予TACE联合RFA治疗,比较两组临床总有效率,比较两组治疗前后肝功能、血清肿瘤活性因子水平,统计两组患者并发症情况和预后。**结果:**治疗后研究组临床总有效率为53.85%(28/52),高于对照组的33.33%(17/51)($P<0.05$)。两组患者治疗后总胆红素(TBIL)、丙氨酸转氨酶(ALT)、氨基酸转氨酶(AST)较治疗前降低($P<0.05$),但两组治疗后TBIL、ALT、AST比较差异无统计学意义($P>0.05$)。两组患者治疗后甲胎蛋白(AFP)、糖类抗原199(CA199)、基质金属蛋白酶(MMP)均较治疗前降低,且研究组低于对照组($P<0.05$)。两组患者并发症发生率比较无差异($P>0.05$)。研究组患者治疗后1年、2年复发率低于对照组,生存率高于对照组($P<0.05$)。**结论:**TACE联合RFA治疗中晚期肝癌,疗效确切,可有效降低血清肿瘤活性因子水平,未加重肝功能损伤,且可改善患者的预后。

关键词:肝动脉化疗栓塞;射频消融;中晚期;肝癌;肿瘤活性因子;肝功能;预后

中图分类号:R735.7 **文献标识码:**A **文章编号:**1673-6273(2020)07-1293-04

Effects of Transcatheter Arterial Chemoembolization Combined with Radiofrequency Ablation on Serum Tumor Activity Factor, Liver Function and Prognosis in Patients with Advanced Hepatocellular Carcinoma*

WANG Shao-lei, WEI Hong[△], LIU De-hua, SHI Guo-dong, WU Li-na

(Department of Medical Imaging, Cancer Hospital Of China Medical University/Liaoning Cancer Hospital, Shenyang, Liaoning, 110042, China)

ABSTRACT Objective: To investigate the effects of transcatheter arterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) on serum tumor activity factors, liver function and prognosis in patients with advanced hepatocellular carcinoma. **Methods:** 103 patients with advanced hepatocellular carcinoma who were admitted to our hospital from February 2012 to June 2016 were selected, they were randomly divided into control group (n=51) and study group (n=52), the control group was treated with RFA, and the study group was treated with TACE combined with RFA. The clinical total effective rate was compared between the two groups. Liver function and serum levels of tumor active factors in two groups were compared before and after treatment. The complications and prognosis of the two groups were observed. **Results:** After treatment, the total clinical effective rate of the study group was 53.85% (28/52), which was significantly higher than that of the control group 33.33% (17/51)($P<0.05$). After treatment, total bilirubin (TBIL), Alanine aminotransferase (ALT) and amino acid aminotransferase (AST) were lower than those before treatment ($P<0.05$), but there were no significant differences in TBIL, ALT and AST between the two groups ($P>0.05$). After treatment, the alpha-fetoprotein (AFP), carbohydrate antigen 199 (CA199) and matrix metalloproteinase (MMP) in both groups were lower than those before treatment, and those in the study group were lower than those in the control group ($P<0.05$). There was no significant difference in the incidence of complications between the two groups ($P>0.05$). The recurrence rate of 1 year and 2 years after treatment in the study group was lower than that in the control group, and the survival rate was higher than that in the control group ($P<0.05$). **Conclusion:** TACE combined with RFA is effective in the treatment of advanced hepatocellular carcinoma. It can effectively reduce the level of serum tumor active factors, without aggravating liver function damage, and improve the prognosis of patients.

Key words: Transcatheter arterial chemoembolization; Radiofrequency ablation; Advanced; Liver cancer; Tumor active factor; Liver function; Prognosis

* 基金项目:辽宁省临床能力建设项目(LNCCC-D47-2015)

作者简介:王少雷(1979-),男,硕士,副主任医师,研究方向:肿瘤介入, E-mail: wang797@126.com

[△] 通讯作者:魏宏(1961-),男,本科,主任医师,研究方向:肿瘤介入, E-mail: hongvip82@126.com

(收稿日期:2019-07-28 接受日期:2019-08-23)

Chinese Library Classification(CLC): R735.7 Document code: A

Article ID: 1673-6273(2020)07-1293-04

前言

原发性肝癌是消化系统常见的恶性肿瘤之一,病死率位于全球恶性肿瘤第2位^[1]。我国作为原发性肝癌的多发地区,肝癌病例约占全球的55%,可见我国肝癌高发的形势十分严峻^[2]。该病起病隐匿,早期无特异性症状,病情进展迅速,多数患者确诊时已到达中晚期或发生远处转移,错过最佳治疗时机,预后极差^[3]。肝动脉化疗栓塞(Transcatheter arterial chemoembolization, TACE)是较为成熟的治疗中晚期肝癌的非手术疗法之一^[4],但较多临床实践证实单纯的TACE无法彻底阻断肿瘤血供,需经多次治疗^[5,6]。射频消融(Radio frequency ablation, RFA)是近年来新兴的靶向治疗肝癌的最新微创介入手术,可彻底杀灭肿瘤细胞并使之脱落^[7]。本研究通过对我院收治的部分中晚期肝癌患者采用TACE联合RFA治疗,疗效较好,报道如下。

1 资料与方法

1.1 一般资料

选取辽宁省肿瘤医院于2012年2月~2016年6月间接收的103例中晚期肝癌患者,纳入标准:(1)均符合《原发性肝癌诊断标准》^[8]中有关肝癌的诊断标准;(2)影像学、实验室检查及肝组织活检确诊,无外科手术适应证者,无化疗禁忌证者;(3)肿瘤单个最长直径3~10 cm;(4)肝功能Child-Pugh分级^[9]为A级或B级,巴塞罗那临床肝癌^[10]分期B期或C期;(5)患者以及家属知情本次研究,且已签署了知情同意书。排除标准:(1)实验室检查存在TACE、RFA禁忌证者;(2)合并心肺肾等脏器损伤者;(3)肿瘤体积>70%肝脏体积者;(4)合并有严重黄疸、转移者;(5)预计生存期<3个月者;(6)合并其他部位恶性肿瘤者、不能完成治疗者。本研究已获我院伦理学委员会批准进行。根据随机数字表法将患者分为对照组(n=51)和研究组(n=52),其中对照组男29例,女22例,年龄31~65岁,平均(46.18±4.09)岁;Child-Pugh分级:A级27例,B级24例;肿瘤直径3~10 cm,平均(5.93±1.16)cm。研究组男30例,女22例,年龄32~68岁,平均(45.97±3.86)岁;Child-Pugh分级:A级25例,B级27例;肿瘤直径3~9 cm,平均(5.86±1.05)cm。两组患者一般资料比较无差异(P>0.05)。

1.2 治疗方法

对照组患者予以TACE治疗,操作如下:治疗前禁食4 h,肌注地西洋,常规消毒铺巾,局麻,采用经皮股动脉穿刺,将5F TACE导管(日本泰尔茂公司)插入至患者肝动脉,行肝动脉造

影,确定并将导管置入肝癌供血血管后,注入化疗药物奥沙利铂10~30 mg,羟基喜树碱15~30 mg,随后注入吡柔比星20 mg以及7~20 mL非离子型对比剂碘化油混合物行供血血管栓塞,其中栓塞不彻底者则使用明胶海绵,肿瘤较大者可分次栓塞。栓塞完成后拔出导管,加压包扎。研究组经TACE治疗后5~7 d给予RFA治疗,选择美国达隆公司RF-2000、RF-3000射频机器,具体如下:对插入部位进行消毒、局麻,扫描定位后将15G或20G RFA针经皮穿刺至肿瘤中心位置,靶温105℃,功率150 W,消融范围直径5 cm,采用多方向叠加消融范围、单点穿刺的方式进行。RFA为1个月治疗一次,共治疗4次。

1.3 观察指标

(1)比较两组患者治疗后的临床疗效,疗效判定标准参考世界卫生组织制定的相关实体瘤疗效标准^[11],具体为病情进展:病灶面积未见减少或增加;病情稳定:病灶面积减少<30%;部分缓解:病灶面积减少≥30%,且持续1个月;完全缓解:病灶消失,且消失时间>1个月。总有效率=部分缓解率+完全缓解率。(2)于治疗前后抽取患者清晨空腹静脉血6 mL,4000 r/min离心10 min,离心半径9 cm,取上清液,置于-4℃冰箱中待测。采用日本OLYMPUS-AU600型全自动生化分析仪检测丙氨酸转氨酶(Alanine aminotransferase, ALT)、总胆红素(Total bilirubin, TBIL)、氨基酸转氨酶(Aspartate aminotransferase, AST)水平。采用酶联免疫吸附试验检测甲胎蛋白(Alpha-fetoprotein, AFP)、糖类抗原199(Carbohydrate antigen 199, CA199),基质金属蛋白酶(Matrix metalloproteinase, MMP)水平,试剂盒购自武汉华美生物科技有限公司,操作进行严格按照试剂盒说明。比较两组并发症发生情况。随访2年采用电话或其他社交平台联络等方式,观察两组患者复发情况、生存情况,以患者死亡为随访终止指标。复发判定标准:肝动脉造影发现肿瘤明显染色可认定为肝内复发。

1.4 统计学方法

通过SPSS21.0软件处理统计数据。计数资料用率表示,实施 χ^2 检验。计量资料用($\bar{x} \pm s$)表示,实施t检验, $\alpha=0.05$ 为检验水准。

2 结果

2.1 两组患者临床疗效比较

研究组治疗后临床总有效率为53.85%(28/52),高于对照组患者的33.33%(17/51)(P<0.05),如表1。

表1 两组患者临床疗效比较例(%)

Table 1 Comparison of clinical efficacy of two groups of patients n(%)

Groups	Complete remission	Partial remission	Disease stabilization	Disease progression	Total effective rate
Control group(n=51)	5(9.80)	12(23.53)	19(37.26)	15(29.41)	17(33.33)
Study group(n=52)	10(19.23)	18(34.62)	17(32.69)	7(13.46)	28(53.85)
χ^2					4.404
P					0.036

2.2 两组患者治疗前后肝功能指标比较

($P<0.05$), 但两组治疗后 TBIL、ALT、AST 比较无统计学差异

两组患者治疗前 TBIL、ALT、AST 比较差异无统计学意义 ($P>0.05$), 详见表 2。

($P>0.05$), 两组患者治疗后 TBIL、ALT、AST 较治疗前降低

表 2 两组患者治疗前后肝功能指标比较($\bar{x}\pm s$)

Table 2 Comparison of liver function before and after treatment in two groups($\bar{x}\pm s$)

Groups	TBIL($\mu\text{mol/L}$)		ALT(U/L)		AST(U/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group($n=51$)	18.54 $\pm$ 5.64	16.07 $\pm$ 3.35*	62.12 $\pm$ 5.89	47.35 $\pm$ 5.56*	96.05 $\pm$ 10.31	51.24 $\pm$ 11.86*
Study group($n=52$)	18.49 $\pm$ 4.93	16.10 $\pm$ 2.27*	61.83 $\pm$ 6.13	46.41 $\pm$ 5.62*	97.87 $\pm$ 9.87	49.05 $\pm$ 12.03*
t	0.048	0.053	0.245	0.853	0.915	0.930
P	0.962	0.958	0.807	0.396	0.362	0.354

Note: compared with before treatment, * $P<0.05$.

2.3 血清肿瘤活性因子比较

治疗后两组患者 AFP、CA199、MMP 均较治疗前降低, 且研究

治疗前, 两组患者 AFP、CA199、MMP 比较无差异($P>0.05$), 组较对照组降低($P<0.05$), 详见表 3。

表 3 血清肿瘤活性因子比较($\bar{x}\pm s$)

Table 3 Comparison of serum tumor factors($\bar{x}\pm s$)

Groups	AFP($\mu\text{g/mL}$)		CA199(U/L)		MMP(ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group($n=51$)	485.68 $\pm$ 72.32	206.08 $\pm$ 31.86*	88.16 $\pm$ 13.74	56.44 $\pm$ 8.37*	124.97 $\pm$ 19.34	68.21 $\pm$ 9.78*
Study group($n=52$)	486.35 $\pm$ 63.48	101.27 $\pm$ 22.41*	87.99 $\pm$ 14.59	33.82 $\pm$ 7.63*	125.17 $\pm$ 18.23	37.84 $\pm$ 8.02*
t	0.050	19.341	0.061	14.339	0.054	17.248
P	0.960	0.000	0.952	0.000	0.957	0.000

Note: compared with before treatment, * $P<0.05$.

2.4 并发症发生情况比较

对照组主要并发症为栓塞后综合征 2 例、胆囊炎 2 例、胆红素升高 2 例、胃肠道反应 3 例, 经对症处理后好转, 并发症发生率为 17.65%(9/51); 研究组主要并发症为栓塞后综合征 1 例、局部出血 3 例、肝性脑病 1 例、胆红素升高 2 例, 经对症处

理后好转, 并发症发生率为 13.46%(7/52); 两组患者并发症发生率比较差异无统计学意义($\chi^2=0.344$, $P=0.558$)。

2.5 预后情况比较

本研究随访 2 年, 无失访病例, 研究组患者治疗后 1 年、2 年复发率低于对照组, 生存率高于对照组($P<0.05$), 详见表 4。

表 4 预后情况比较例(%)

Table 4 Comparison of prognosis n(%)

Groups	Recurrence rate		Survival rate	
	1 year	2 years	1 year	2 years
Control group($n=51$)	19(37.25)	29(56.86)	35(68.63)	24(47.06)
Study group($n=52$)	8(15.38)	16(30.77)	46(88.46)	36(69.23)
χ^2	6.367	7.126	6.030	5.205
P	0.012	0.008	0.014	0.023

3 讨论

据以往相关研究报道, 我国原发性肝癌的病死率占有因恶性肿瘤死亡人数的 20%, 给人类健康带来严重威胁^[12]。中晚期肝癌患者由于肝癌机体巨大, 且多并发肝硬化, 已失去最佳手术机会或肝移植的治疗机会, 虽有部分患者接受切除性根治治疗, 但受肝癌多中心性起源的生物特殊性影响, 术后复发率较高, 预后不佳^[13-15]。肝脏是一个实质性脏器, 通过门静脉和肝

动脉双重供血, 正常人体的肝脏组织供血主要来源于门静脉, 而肝癌患者 99% 的血供来自肝动脉, 因此临床阻止肿瘤细胞进展多通过阻断肝动脉供血的方式^[16,17]。近年来, 以 TACE、RFA 为代表的介入治疗在临床愈发得到重视, TACE 的治疗机制是通过碘油以栓塞患者肝动脉供血血管, 造成肿瘤部位缺血缺氧以达到抗肿瘤的目的^[18]。然而癌细胞存在多血管供血及肝脏可建立侧支循环等因素, 并且 TACE 的重复治疗可加重肝损伤, 导致单纯的 TACE 治疗效果有限^[19]。RFA 是一种新型的肿瘤治

疗办法,主要通过交变电流装置,利用射频的热损伤效应使肿瘤活体细胞产生蛋白质变性,最终坏死、脱水^[20]。然而单用 RFA 对于体积较大肿瘤患者无法完全消融,鉴于上述两种介入治疗方式单用时均存在一定局限性,故分析二者联合应用。

本研究结果表明治疗后研究组临床总有效率为 53.85%,高于对照组的 33.33%,且研究组患者治疗后 1 年、2 年复发率低于对照组,生存率高于对照组,可见 TACE 联合 RFA 治疗中晚期肝癌效果优于单用 TACE 治疗,有效降低患者复发率、提高生存率,这和刘墨等人^[21]结果基本一致。TACE 联合 RFA 的治疗优势主要有以下几点:TACE 通过栓塞患者肝动脉供血,使肿瘤内血流减少,从而降低 RFA"热沉降效应";先行 TACE 可缩小肝癌体积并使之形成炎性包膜,有利于后期 RFA 定位;RFA 的高温可提高化疗药物的疗效;栓塞药物中的碘离子反射电波可加强 RFA 的高温效应;两种介入方式联合使用发挥协同作用^[22-24]。本次研究结果还显示,两种介入治疗方式均可改善患者的肝功能,且联合治疗并不会加重对机体肝功能的损伤,这可能是由于 RFA 可减少 TACE 栓塞次数,减轻 TACE 对肝功能的进一步损害。AFP 是肿瘤相关的胚胎特异 α - 球蛋白,以往临床结果显示^[25],AFP 水平的升高与肝癌的恶性程度、患者预后密切相关;CA199 是非特异性肿瘤相关抗原,其水平与肿瘤增生以及增生程度呈正相关^[26];MMP 可降解基底膜和细胞外基质,在肿瘤血管的生成、侵袭中扮演重要角色^[27]。本研究中研究组治疗后 AFP、CA199、MMP 水平均低于对照组,提示 TACE 联合 RFA 治疗可有效阻止癌症病情进展,改善患者血清肿瘤活性因子水平。首先 TACE 可减少并阻断肝组织的血流灌注,减少 RFA 过程的热效应,同时 TACE 还可帮助 RFA 提高消融范围,提高肿瘤局部坏死率^[28-30]。另外,研究组并发症发生率低于对照组,可能是因为 RFA 的加入有助于弥补 TACE 的缺陷,但经比较却无统计学差异,可能与本次研究样本量偏小,导致结果存在一定的偏倚有关,后续报道将扩大样本量以进行更为准确的报道。

综上所述,TACE 联合 RFA 治疗中晚期肝癌,疗效显著,且不会对患者肝功能造成进一步损伤,对于改善患者血清肿瘤活性因子水平、复发率、生存率等方面效果显著。

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