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TACE 结合立体定向体部 X- 刀治疗肝癌的临床疗效研究 *

曾 俊¹ 谭利华^{1Δ} 伍玉枝¹ 郭杨钰¹ 付秀根²

(1 中南大学湘雅二医院放射科 湖南 长沙 410011; 2 华中科技大学同济医学院附属同济医院放疗中心 湖北 武汉 430030)

摘要 目的:探讨经肝动脉化疗栓塞(transarterial chemoembolization, TACE)结合立体定向体部 X- 刀治疗肝癌的临床疗效和安全性。**方法:**选取 2015 年 12 月至 2017 年 8 月在我院接受治疗的原发性肝癌患者 120 例,并将其随机分为 X- 刀组、TACE 组以及联合组,每组患者各 40 例。X- 刀组患者给予单纯 X- 刀治疗,TACE 组给予单纯 TACE 治疗,联合组给予 X- 刀联合 TACE 治疗。观察并比较三组患者临床疗效、生存期、治疗前后肝功能的变化及治疗过程中毒副作用的发生情况。**结果:**联合组患者临床总有效率为 47.5%,明显高于 X- 刀组和 TACE 组($P<0.05$);X- 刀组患者临床总有效率为 27.5%,显著高于 TACE 组($P<0.05$)。X- 刀组、TACE 组、联合组患者生存时间分别为 0.73 ± 0.18 年、 0.48 ± 0.18 年、 1.10 ± 0.22 年,联合组患者生存时间显著长于 X- 刀组和 TACE 组($P<0.05$),X- 刀组患者生存时间长于 TACE 组($P<0.05$)。三组患者治疗后血清血清谷丙转氨酶(alanine aminotransferase, ALT)、谷草转氨酶(aspartate aminotransferase, AST)、 γ - 谷氨酰转肽酶(Gamma - glutamyl transpeptidase, γ -GT)、总胆红素(total bilirubin, TBil)水平与本组治疗前比较均显著降低($P<0.05$);联合组患者治疗后血清 ALT、AST 水平与 TACE 组和 X- 刀组比较差异均无统计学意义($P>0.05$),而血清 γ -GT、TBil 水平均显著低于 TACE 组和 X- 刀组($P<0.05$)。三组患者毒副作用情况比较差异无统计学意义($P>0.05$)。**结论:**TACE 结合立体定向体部 X- 刀治疗肝癌的临床疗效明显优于单用 TACE 或 X- 刀治疗,且三种治疗方法的安全性相当。

关键词:原发性肝癌;X- 刀;经肝动脉化疗栓塞;临床疗效

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Effect of TACE Combined with Stereotactic Body X- knife on the Patients with Hepatocellular Carcinoma*

ZENG Jun¹, TAN Li-hua^{1Δ}, WU Yu-zhi¹, GUO Yang-yu¹, FU Xiu-gen²

(1 Department of Radiology, Second Xiangya Hospital, Central South University, Changsha, Hunan, 410011, China;

2 Center of Radiation Therapy, Tongji Hospital of Tongji Medical College, Wuhan, Hunan, 430030, China)

ABSTRACT Objective: To discuss the clinical efficacy and safety of transcatheter arterial chemoembolization (TACE) combined with stereotactic X- knife in the treatment of liver cancer. **Methods:** 120 patients with primary liver cancer were selected from December 2015 to August 2017 in our hospital. The patients were randomly divided into X- group, TACE group and combined group, each group had a total of 40 patients. X- knife group patients were treated with X- knife, TACE group was treated with TACE alone, and the combination group was treated with X- knife combined with TACE. The clinical effect, survival time, liver function before and after treatment and the occurrence of toxic side effects were compared among the three groups. **Results:** The total effective rate of combined group was 47.5%, which was significantly higher than that of the X-knife group and the TACE group ($P<0.05$). The total effective rate of X- knife group was 27.5%, which was significantly higher than that of TACE group ($P<0.05$). The survival time of the combined group was (0.73 ± 0.18) years, (0.48 ± 0.18) years, (1.10 ± 0.22) years, and the survival time of the combined group was significantly longer than that in the X- knife group and TACE group ($P<0.05$), the survival time of the X-knife group was longer than that in TACE group ($P<0.05$). The level of Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), Gamma - glutamyl transpeptidase (γ -GT) and total bilirubin (TBil) were significantly lower than those before treatment ($P<0.05$). The level of serum ALT and AST after treatment in the combined group were no significant difference with TACE group or X-knife group ($P>0.05$), but the level of serum γ -GT and TBil was significantly lower than that of TACE group and X-knife group ($P<0.05$). There was no significant difference in the toxic and side effects among the three groups ($P>0.05$). **Conclusion:** The clinical efficacy of TACE combined with stereotactic X- knife is superior to TACE or X- knife alone in the treatment of liver cancer, and the safety of three treatments is equal.

Key word: Primary liver cancer; X- knife; TACE; Clinical efficacy

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作者简介:曾俊(1980-),男,硕士研究生,主治医师,研究方向:影像诊断及介入,电话:13574112406, E-mail:xyzengxyz@163.com

Δ 通讯作者:谭利华,主任医师,教授,硕士研究生导师,研究方向:骨肌系统和中枢神经系统影像诊断,电话:18670701597

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原发性肝癌是临床常见的恶性肿瘤,以肝细胞癌较多见,具有恶性程度高、病情进展迅速、死亡率高的特点^[1]。手术是治疗原发性肝癌的首选方法,但由于本病起病隐匿,大部分患者确诊时已是晚期肝癌,丧失最佳手术时机^[2]。目前,临床对于不具备手术条件的原发性肝癌患者多采用经肝动脉化疗栓塞术(transarterial chemoembolization, TACE)、射频消融、微波消融、放疗、生物治疗等治疗^[3-5]。近年来,随着介入放射学的迅速发展,立体定向体部 X-刀治疗应运而生。由于肝脏是放射敏感器官,因此立体定向体部 X-刀对不具备手术条件的原发性肝癌患者可起到良好的效果^[6]。而将 TACE 和立体定向体部 X-刀两种方法结合应用的国内相关报道较少。本研究主要探讨了 TACE 结合立体定向体部 X-刀治疗肝癌对患者肝功能影响情况,现报道如下。

1 资料与方法

1.1 临床资料

回顾性分析 2015 年 12 月至 2017 年 8 月在中南大学湘雅二医院(以下简称“我院”)治疗原发性肝癌患者的临床资料。纳入标准:经病理学诊断或临床诊断证实为原发性肝癌;预计生存期大于 3 个月,无明显腹水及远处转移;因患者自身因素或技术因素不能手术者,或患者、家属拒绝手术者;KPS 评分大于或等于 60 分;患者知情同意,依从性好,本研究通过医学委员会同意。排除标准:合并严重全身感染者;资料不全者。根据纳入排除标准共纳入 120 例研究对象,随机分成随机 X-刀组、TACE 组和联合组,每组患者各 40 例。X-刀组男 25 例,女 15 例,年龄 20~75 岁,平均 46.24 ± 15.53 岁,肝功能 Child-Pugh 分级 A 级 21 例, B 级 19 例;TACE 组男 22 例,女 18 例,年龄 21~76 岁,平均 47.64 ± 14.59 岁,肝功能 Child-Pugh 分级 A 级 22 例, B 级 18 例;联合组男 17 例,女 23 例,年龄 20~76 岁,平均 45.34 ± 13.52 岁,肝功能 Child-Pugh 分级 A 级 24 例, B 级 16 例。三组患者在性别、年龄、肝功能分级等一般资料比较差异无统计学意义,具有可比性($P > 0.05$)。

1.2 治疗方法

TACE 组采用 Seldinger 法经皮穿刺股动脉,选择性肝动脉插管灌注化疗药物。化疗药物为丝裂霉素 20 mg、顺铂 80 mg、氟尿嘧啶 1000 mg,栓塞剂为 40%碘化油。每隔 3 周治疗 1 次。

X-刀组患者取仰卧位或俯卧位做真空体模,螺旋 CT 扫描层厚度为 5 mm,利用剂量体积直方图确保 90%的剂量曲线环绕计划靶区。埋置金属标记物于后体中线 T9-L1 水平,使金属标记物与肿瘤病灶的相对空间关系固定。植入金属标记物后 1 周在特定框架中行 CT 扫描,描画肿瘤靶区,使计划系统数值化地确定空间关系。根据病灶体积确定治疗计划,包括限光筒、机架起始终止角度、放射剂量,尽可能使放射剂量集中于靶区,区域淋巴结不进行预防性照射,避免照射周围正常肝组织、肾脏、脊髓等。在加速器上进行在线验证,矫正体位差异。制定出治疗计划后使用 X-刀治疗,患者平躺于治疗床,由 Cyberknife 系统机器人完成治疗。

联合组在 TACE 治疗结束后休息 6 周,再接受 X-刀立体定向放疗。治疗方法同上。

1.3 观察指标

观察并比较三组患者临床疗效、生存期、治疗前后肝功能的变化及治疗过程中毒副反应的发生情况。临床总有效率 = 完全缓解 + 部分缓解。肝功能包括血清谷丙转氨酶(alanine aminotransferase, ALT)、谷草转氨酶(aspartate aminotransferase, AST)、 γ -谷氨酰转肽酶(Glutamyl transpeptidase, γ -GT)、总胆红素(total bilirubin, TBil)。

1.4 统计学方法

采用 SPSS19.0 统计软件处理数据,计量指标采用($\bar{x} \pm s$)描述,组间比较采用 t 检验,计数资料的组间比较采用 χ^2 检验,以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 三组患者临床疗效的比较

联合组患者临床总有效率为 47.5%,显著高于 X-刀组和 TACE 组(27.5%, 22.5%, $P < 0.05$);X-刀组患者临床总有效率位 27.5%,显著高于 TACE 组($P < 0.05$)。见表 1。

表 1 三组患者临床疗效的比较【例(%)】

Table 1 Comparison of the clinical efficacy among three groups of patients[n(%)]

Groups	n	Complete remission	Partial remission	Disease progression	Total effective rate
X- knife group	40	5(12.5)	6(15.0)	29(72.5)	11(27.5)
TACE group	40	4(10.0)	5(12.5)	31(77.5)	9(22.5)
Combination group	40	8(20.0)	11(27.5)	21(52.5)	19(47.5)
P					<0.05

2.2 三组患者生存期比较

X-刀组、TACE 组、联合组患者生存时间分别为 0.73 ± 0.18 年、 0.48 ± 0.18 年、 1.10 ± 0.22 年。联合组患者生存时间显著长于 X-刀组和 TACE 组 ($P < 0.05$),X-刀组患者生存时间长于 TACE 组($P < 0.05$),见表 2。

2.3 三组患者治疗后肝功能的比较

治疗前,三组患者肝功能指标比较差异无显著统计学意义($P > 0.05$);三组患者治疗后血清 ALT、AST、 γ -GT、TBil 水平与

表 2 三组患者生存期比较($\bar{x} \pm s$)

Table 2 Comparison of the survival time among three groups of patients($\bar{x} \pm s$)

Group	n	life period(year)
X- knife group	40	0.73 ± 0.18
TACE group	40	$0.48 \pm 0.18^*$
Combination group	40	$1.10 \pm 0.22^{**}$

Note: compared with X- knife group, * $P < 0.05$; compared with TACE group, ** $P < 0.05$.

本组治疗前比较均显著降低($P<0.05$),联合组患者治疗后血清 ALT、AST 水平与 TACE 组和 X- 刀组比较差异均无统计学意义 ($P<0.05$), 联合组治疗后血清 γ -GT、TBil 水平显著低于 TACE 组和 X- 刀组($P<0.05$),见表 3。

表 3 三组患者治疗前后肝功能的比较($\bar{x}\pm s$)Table 3 Comparison of the liver function among three groups of patients before and after treatment($\bar{x}\pm s$)

Index	Time	X- knife group	TACE group	Combination group
ALT(U/L)	Before treatment	114.1 $\pm$ 84.6	110.6 $\pm$ 81.4	113.8 $\pm$ 82.6
	After treatment	66.8 $\pm$ 46.2*	53.1 $\pm$ 48.0*	61.3 $\pm$ 47.1*
AST(U/L)	Before treatment	123.5 $\pm$ 81.9	127.6 $\pm$ 72.2	129.3 $\pm$ 86.0
	After treatment	81.6 $\pm$ 51.4*	74.3 $\pm$ 49.1*	74.1 $\pm$ 48.8*
γ -GT(U/L)	Before treatment	106.3 $\pm$ 3.2	107.5 $\pm$ 3.4	104.9 $\pm$ 3.5
	After treatment	98.2 $\pm$ 3.2*	95.6 $\pm$ 2.3*	89.2 $\pm$ 3.1* [△]
TBil(μ mol/L)	Before treatment	26.3 $\pm$ 2.1	27.1 $\pm$ 2.0	26.8 $\pm$ 2.2
	After treatment	19.6 $\pm$ 2.1*	18.3 $\pm$ 2.4*	14.8 $\pm$ 1.9* [△]

Note: compared with the group before treatment, * $P<0.05$; compared with X- knife group after treatment, [△] $P<0.05$; compared with TACE group after treatment, [△] $P<0.05$.

2.4 三组毒副反应发生情况的比较

肝癌患者的毒副反应主要是发热、胃肠道反应、乏力等,经临床对症治疗后毒副反应均得以缓解,骨髓抑制全部是 I ~ II 级,肝功能损伤主要是 I 级,无死亡病例。联合组副反应发生率略高于 TACE 组和 X- 刀组, 但三组患者比较差异无统计学意义($P>0.05$)。

3 讨论

我国是原发性肝癌的高发国家,每年新发病例数和死亡率均处于较高水平。原发性肝癌的治疗也给患者家庭和社会医疗资源造成较大的负担^[7]。由于原发性肝癌具有起病隐匿的特点,早期往往无明显的特异性症状,在确诊时多数患者已处于病情的晚期阶段,不具备手术治疗的条件^[8,9]。近年来,临床对晚期肝癌患者多采用综合治疗,放疗、化疗、经肝动脉化疗栓塞、射频消融、微波消融、中医药、生物治疗等在提高肿瘤局部控制率、生存率方面具有一定的效果^[10,11]。

现阶段临床治疗晚期肝癌的方法较多,以经肝动脉化疗栓塞最常见。该技术在数字减影技术的辅助下,精确地超选择肝脏肿瘤的供血血管,通过导管置入化疗药物进行栓塞,可获得令人满意的治疗效果^[12-15]。但由于肝脏局部供血丰富,对原发性肝脏肿瘤的供血血管进行栓塞后,会逐渐形成侧支循环。而在经肝动脉化疗栓塞治疗后,仍有部分肿瘤细胞残存,尤其是在肿瘤病灶的边缘区细胞由门静脉供血,血流丰富^[16]。因此,单纯的经肝动脉化疗栓塞治疗并不能彻底清除病灶,往往需要重复多次治疗,远期局部复发风险大^[17]。

肝脏是对放射线敏感的器官,因此原发性肝癌采用放射治疗可以获得满意的疗效。但放射治疗的操作一直是一个难题,正常肝脏组织的放射性照射的耐受性差,常规放疗可能引发肝脏纤维化、肝功能损害等副作用^[18,19]。放疗剂量在肿瘤靶区无法得到有效提高^[20]。立体定向体部 X- 刀是近年来发展起来的一种放射外科治疗新技术,具有在线校位、同步实时呼吸跟踪、图像引导放疗等特点,集合等中心、多中心、适形照射等多种治疗计划,能有效提高靶区放射剂量,并可尽量避免正常组织,对肿

瘤边缘的正常组织照射剂量极其微小,其治疗周期短、治疗增益比高,在治疗过程中无需患者进行特殊配合,接受度和依从性好^[21,22]。本研究中,X- 刀组患者临床总有效率高于经肝动脉化疗栓塞组,生存时间长于经肝动脉化疗栓塞组,这一结果提示立体定向体部 X- 刀对原发性肝癌的疗效优于经肝动脉化疗栓塞,更有利于延长患者的生存时间。

本研究将经肝动脉化疗栓塞和立体定向体部 X- 刀联合治疗原发性肝癌,结果显示联合组患者临床总有效率高于单纯 X- 刀组和经肝动脉化疗栓塞组,生存时间长于单纯 X- 刀组和经肝动脉化疗栓塞组。这是由于放射治疗可巩固经肝动脉化疗栓塞的治疗成果,进一步杀灭残存的肿瘤细胞,使机体的肿瘤负荷减少,病情得到控制^[23,24]。而经肝动脉化疗栓塞术中使用的化疗药物具有放疗增敏效应,提高放射治疗的效果^[25,26]。此外,三组患者治疗后 ALT、AST、 γ -GT、TBil 等肝功能指标水平与本组治疗前比较均显著降低,提示不管是经肝动脉化疗栓塞、立体定向体部 X- 刀还是二者联合治疗,均对原发性肝癌患者的肝功能起到一定的改善作用。联合组患者治疗后血清 γ -GT、TBil 水平显著低于单纯经肝动脉化疗栓塞组和 X- 刀组,这可能是由于经肝动脉化疗栓塞治疗后肿瘤体积大大缩小,再接受放疗时放射野缩小,在提高靶区剂量的同时可保护好病灶周围的正常组织和器官,对肝脏功能起到一定的保护作用。

综上所述,TACE 结合立体定向体部 X- 刀治疗肝癌的临床疗效明显优于单用 TACE 或 X- 刀治疗,且三种治疗方法的安全性相当,值得临床推广运用。

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