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手术切除联合预防性介入对降低肝癌复发率、提高个体生存率的可行性分析 *

张龙虎[1] 郭平学[2] 李 超[3] 何 莹[4] 张旭锋[5] 庞卫东[6] 罗春海[7△]

(1 西安交通大学第一附属医院东院医学影像科 陕西 西安 710089;2 西安医学院第二附属医院肝胆外科 陕西 西安 710038;
3 空军军医大学唐都医院疼痛微创治疗中心 陕西 西安 710038;4 西安交通大学第二附属医院影像科 陕西 西安 710004;
5 咸阳彩虹医院影像科 陕西 咸阳 712021;6 西安交通大学第一附属医院东院普外科 陕西 阎良 710089;
7 西安医学院第二附属医院医学影像科 陕西 西安 710038)

摘要 目的:探究手术切除联合预防性介入对降低肝癌复发率及提高个体生存率方面的可行性。**方法:**选择 2011 年 2 月至 2014 年 2 月于我院接受治疗的 76 例肝癌患者，单纯接受根治术的 31 例患者为对照组，接受根治术后 6 个月内应用预防性介入治疗的 45 例患者为研究组,对全部病例实施最多 48 个月的随访,对比两组患者术后 1 年、2 年及 3 年肝癌复发率、生存率及中位生存期。将研究组患者按照接受介入治疗时间分为 A 组(1 个月内接受介入治疗)、B 组(1-2 个月接受介入治疗)、C 组(2-3 个月接受介入治疗)、D 组(3-6 个月接受介入治疗)4 个亚组,对比各组患者 1 年内复发率。最后分析影响肝癌复发的独立危险因素。**结果:**(1)研究组患者术后 1 年、2 年及 3 年复发率均低于对照组(P<0.05),而 1 年、2 年及 3 年生存率均高于对照组(P<0.05),中位生存期长于对照组(P>0.05);(2)术后 2 个月内接受预防性介入治疗的 A、B 亚组患者 1 年复发率明显低于 C、D 两组(P<0.05);(3)包膜不完整、肿瘤直径≥ 5 cm、合并肝硬化与肝癌复发有相关性(P<0.05),将肿瘤包膜是否完整、肿瘤直径、肝硬化 3 个变量采用多因素 Logistic 回归分析肝癌术后复发的危险因素,显示肿瘤包膜是否完整与合并肝硬化是肝癌复发的独立危险因素(P<0.05)。**结论:**肝癌切除术后预防性应用介入治疗能够显著降低肝癌患者术后复发率,提高其生存率,且术后 1-2 个月实施介入治疗效果最好,包膜不完整、合并肝硬化是导致肝癌复发的独立危险因素。

关键词:手术切除;肝癌;介入治疗;复发率;生存率

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Feasibility Analysis of Surgical Resection Combined with Preventive Interventions in Reducing the Recurrence Rate and Improving the Individual Survival Rate of patients with Hepatocellular Carcinoma*

ZHANG Long-hu[1], GUO Ping-xue[2], LI Chao[3], HE Ying[4], ZHANG Xu-feng[5], PANG Wei-dong[6], LUO Chun-hai[7△]

(1 Department of Medical Imaging, East Hospital, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710089, China; 2 Department of Hepatobiliary Surgery, the Second Affiliated Hospital of Xi'an Medical College, Xi'an, Shaanxi, 710038, China; 3 Minimally invasive pain treatment Center, Tangdu Hospital, Air Force military Medical University, Xi'an, Shaanxi, 710038, China; 4 Department of Imaging, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710004, China; 5 Department of Imaging, Xianyang Rainbow Hospital, Xianyang, Shaanxi, 712021, China; 6 General Surgery Department, Eastern Hospital, the First Affiliated Hospital of Xi'an Jiaotong University, Yanliang, Shaanxi, 710089, China; 7 Medical Imaging Department, the Second Affiliated Hospital of Xi'an Medical College, Xi'an, Shaanxi, 710038, China)

ABSTRACT Objective: To explore the feasibility of surgical resection combined with preventive intervention in reducing the recurrence rate of hepatocellular carcinoma and improving individual survival rate. **Methods:** 76 patients with hepatocellular carcinoma treated in our hospital from February 2011 to February 2014 were selected. 31 patients who underwent radical surgery were selected as the control group, and 45 patients who underwent prophylactic interventional therapy within 6 months after radical surgery were selected as the study group. All patients were followed up for up to 48 months. The recurrence rate, survival rate and median survival time of hepatocellular carcinoma at 1, 2 and 3 years after operation were compared between the two groups. Patients in the study group were divided into 4 subgroups: group A (1 month for interventional therapy), group B (1-2 months for interventional therapy), group C (2-3 months for interventional therapy), and group D (3-6 months for interventional therapy), the recurrence rate of four subgroups within 1 year was compared. Finally, analyze the independent risk factors affecting the recurrence of liver cancer. **Results:** (1) The recurrence rate

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作者简介:张龙虎(1970-),男,大专,主治医师,研究方向:影像诊断,介入治疗,电话:13709260703,E-mail:sxzhanglonghu@163.com

△ 通讯作者:罗春海(1971-),男,本科,主任医师,研究方向:影像诊断,介入治疗,电话:18161802371,E-mail:773596555@qq.com

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of 1, 2 and 3 years after operation in the study group was lower than that in the control group (P<0.05), and the 1, 2, and 3 year survival rates were higher than the control group (P<0.05). The median survival time was longer than that of the control group (P>0.05). (2) The 1-year recurrence rate of patients in group A and B who received preventive intervention within 2 months after operation was significantly lower than that in group C and D (P<0.05). (3) Incomplete capsule, tumor diameter ≥ 5 cm, cirrhosis and liver cancer recurrence were associated (P<0.05). Multivariate Logistic regression analysis was used to determine whether the tumor capsule was intact, tumor diameter and cirrhosis. The risk factors for postoperative recurrence of liver cancer showed that the integrity of the tumor capsule and cirrhosis were independent risk factors for liver cancer recurrence (P<0.05). **Conclusion:** Preventive interventional therapy after hepatectomy can significantly reduce the recurrence rate and improve the survival rate of patients with hepatocellular carcinoma, and the best interventional therapy is performed 1-2 months after operation. Incomplete capsule and cirrhosis are liver cancer. Independent risk factors for recurrence.

Key words: Surgical resection; Hepatocellular carcinoma; Interventional therapy; Recurrence rate; Survival rate

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前言

肝癌是指发生于肝脏部位的癌症，按照其发病来源可分为原发性肝癌和转移性肝癌两种，以原发性肝癌较为普遍。据统计，肝癌发病率位居恶性肿瘤第 5 位，致死人数在肿瘤中位居第三位[1]。流行病学调查显示全球每年肝癌新发病人数可达 60 多万，占同期癌症发病数的 5.6 %，我国是肝癌新发病人数约占全世界的 55 %左右，约占亚洲地区的 80 %左右。我国的一项调研结果显示国内现有肝癌例数约 35 万，占同期癌症发病例数的 11.6 %[2,3]。近些年，随着居民生活方式和饮食习惯的改变，肝癌的发病率呈现逐年递增趋势，其发病原因主要包括病毒感染、酒精刺激、水源污染、疾病影响、免疫疾病等，患者临床表现主要有肝区疼痛、发热、消瘦等，晚期肝癌患者常伴发肝性脑病、肝肾功能衰竭等[4]。

现阶段对肝癌的治疗方式包括生物修复、外科治疗、系统治疗等，其中肝癌根治术是外科治疗中常用的手段，对各类肝癌均有较好的效果[5]。但临床实践显示受肝癌分子病理学特征影响，多数肝癌患者接受根治切除术后复发率较高，导致治疗效果欠佳[6]。有研究指出肝癌术后预防性介入治疗有助于杀灭扩散的肿瘤细胞以及残存的肿瘤细胞，从而降低复发率[7,8]。本研究结果肝癌切除术后预防性应用介入治疗能够显著降低肝癌患者术后复发率，提高其生存率，且术后 1-2 个月实施介入治疗效果最好，包膜不完整、合并肝硬化是导致肝癌复发的独立危险因素，现详述如下。

1 资料与方法

1.1 一般资料

选择 2011 年 2 月至 2014 年 2 月于我院接受治疗的 76 例肝癌患者为研究对象，筛选出其中单纯接受根治术的 31 例患者设置为对照组，筛选出接受根治术后 6 个月内应用预防性介入治疗的 45 例患者为研究组。对照组中，男性 16 例，女性 15 例，年龄 27-69 岁，平均年龄(43.26±3.26)岁；研究组中，男性 26 例，女性 19 例，年龄 26-70 岁，平均年龄(43.01±3.66)岁。两组患者一般资料如性别、年龄等对比差异无统计学意义(P>0.05)，具有可比性。

纳入标准：(1)经病理组织或细胞学诊断确诊为肝癌；(2)影像学检查存在肝癌影像学特征；(3) 意识清晰能够配合进行调研；(4)病历资料齐全；(5)调研经医院伦理学会批准实施；(6)患者及其家属对本次调研过程、方法、原理清楚明白并签署知情同意书。

排除标准：(1)合并精神疾患者；(2)合并全身性感染患者；(3)预计生存期≤ 6 个月者；(4)合并其他恶性肿瘤者；(5)对调研应用药物过敏者；(6)合并严重脏器功能障碍者。

1.2 治疗方法

两组患者施术前均接受各项常规检查及心肺功能评估，常规实施术前准备，对照组患者实施开腹肝肿瘤切除术，术前实施全麻，施术者探查腹腔并寻找肿瘤，而后规则肝叶、肝段切除或不规则肝切除，手术均由我院肝胆外科医师完成，研究组患者肝癌根治术与对照组患者方法一致，施术后采用 seldinger 法实施预防性介入治疗，经股动脉至肝固有动脉或肝左、肝右动脉，注入化疗药物或栓塞剂，化疗药物根据患者具体情况可选择阿霉素、顺铂等，栓塞剂可选择碘油、明胶海绵等；两组患者术后均实施随访，定期复检，检查其肝功能、血样、胸部 X 片、CT 等，重点对有无复发或转移病灶进行排查。

1.3 观察指标及评估标准

1.3.1 介入治疗对肝癌复发率及生存率影响 对研究组及对照组患者术后肝癌复发率及生存率进行统计，并实施组间对比，同时统计计算两组患者中位生存期并对比。

1.3.2 不同时间接受介入治疗对复发率影响 将研究组患者按照接受预防性介入治疗的时间区分为 A 组(1 个月内接受介入治疗，11 例)、B 组 (1-2 个月接受介入治疗，10 例)、C 组(2-3 个月接受介入治疗，12 例)、D 组(3-6 个月接受介入治疗，11 例) 4 个亚组，对比 4 个亚组患者术后 1 年复发率。

1.3.3 分析肝癌复发的影响因素 统计入组的 75 例肝癌患者年龄、性别、肝功能分级、是否存在肝硬化、肿瘤大小、包膜是否完整等各项临床指标，并就上述指标与肝癌复发之间的相关性进行分析。

1.4 统计学方法

使用 SPSS22.0 对采集的数据实施分析，计数资料以率(%)的形式表示，组间比较采用卡方检验。采用卡方检验进行单因素分析，筛选肝癌术后复发的影响因素，对于单因素分析中有统计意义的因素采用 Logistic 回归分析肝癌术后复发的危险

因素，以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者复发率的对比

经随访对比，研究组患者术后 1 年、2 年及 3 年复发率均低于对照组患者($P<0.05$)，具体数据如表 1 所示。

表 1 两组患者术后 1 年、2 年及 3 年复发率对比[例(%)]

Table 1 Comparison of the recurrence rates in 1, 2 and 3 years after operation between two groups[n(%)]

Groups	Case	One year after operation	Two years after operation	Three years after operation
Research group	45	2(4.44)*	6(13.33)*	10(22.22)*
Control group	31	6(19.35)	10(32.26)	14(45.16)

Note: Compare with the control gruop,* $P<0.05$.

2.2 两组患者术后 1 年、2 年及 3 年生存率的对比

经随访，研究组患者术后 1 年、2 年及 3 年生存率明显高于对照组($P<0.05$)，具体数据如表 2 所示。

表 2 两组患者术后 1 年、2 年及 3 年生存率的对比[例(%)]

Table 2 Comparison of the survival rates of 1, 2 and 3 years after operation between two groups[n(%)]

Groups	Case	One year after operation	Two years after operation	Three years after operation
Research group	45	44(97.78)*	40(88.89)*	35(77.78)*
Control group	31	26(83.87)	21(67.74)	13(41.94)

Note: Compare with the control gruop,* $P<0.05$.

2.3 两组患者中位生存期的对比

研究组患者术后中位生存期为(32.09±0.51)个月，对照组患者术后中位生存期为(31.55±0.66)个月，两组对比差异无统计学意义($P>0.05$)。

2.4 不同介入治疗时机对肝癌复发率影响

研究组各亚组间复发率对比总体差异具有统计学意义($P<0.05$)，A 组患者与 B 组患者对比差异不明显($P>0.05$)，但复发率明显低于 C、D 两组($P<0.05$)，具体数据如表 3 所示。

表 3 不同介入时机对肝癌复发率的影响[例(%)]

Table 3 Analysis of the influence of different intervention timing on the recurrence rate of liver cancer[n(%)]

1 year postoperative recurrence	Initial intervention time after surgery			
	Group A Within 1 month	Group B 1-2 months	Group C 2-3 months	Group D 3-6 months
Relapse	1	1	4	5
No recurrence	10	9	8	6
Total	11	10	12	11
Recurrence rate	9.09	10.00#	33.33*	45.45*

Note: Compared with group A and group B, *$P<0.05$, compared with group A, #$P>0.05$.

2.5 肝癌术后复发的影响因素

经统计，患者的年龄、性别、肿瘤部位、肝功能分级与肝癌术后复发不存在模型相关性($P>0.05$)，而包膜不完整、肿瘤直径≥ 5 cm、合并肝硬化与肝癌复发存在相关性($P<0.05$)，具体数据如表 4 所示。将肿瘤包膜是否完整、肿瘤直径、肝硬化 3 个变量采用多因素 Logistic 回归分析肝癌术后复发的危险因素，显示肿瘤包膜是否完整与合并肝硬化是肝癌复发的独立危险因素($P<0.05$)。

3 讨论

肝癌是消化系统常见的恶性肿瘤之一，2013 年全球新发肝癌病例多达 79 万例，为恶性肿瘤新增病例的第 6 位[9,10]，肝癌的发病趋势与地区存在一定关联，我国作为发展中国家，肝癌的发病率一直居高不下[11,12]。另有学者的研究显示肝癌发病率会随着年龄的递增呈现上升趋势[13,14]，随着我国人口老龄化趋势的显现，肝癌可能会成为影响我国经济和社会发展的重要因素。目前，肝癌的治疗手段主要包括如下几种：(1)外科手术根治术，切除病灶；(2)非手术治疗：⓪ 血管内介入治疗，即肝动脉化疗栓塞；⓪ 血管外介入治疗，包括射频消融、微波消融、冷冻治疗、高温治疗等；(3)其他疗法，包括生物治疗、激素治疗、中药疗法等[15]。上述方式中，外科手术根治术仍是目前最优先也是首选治疗方式，但临床实践显示能够实施外科手术根治术的患者仅占全部肝癌患者的 20 %左右，且切除术后患者肝癌复发率较高，分析其原因与切除范围、肿瘤因子、患者免疫机能等多方面因素有关，目前尚无法解释清楚[16,17]。肝癌复发后治疗难度较大，且易对患者身心造成二次伤害，因而如何采取预防性措施降低肝癌复发率成为当前医务工作者研究的重点方向[18,19]。

预防性介入治疗是指在肝癌根治术后，通过阻断肿瘤供血

表 4 肝癌术后复发影响因素分析

Table 4 Analysis of the influencing factors of recurrence of hepatocellular carcinoma after operation

Factor		Case(n=76)	Number of recurrences			χ^2	*P*
			One year	two years	three years		
Gender	Male	42	5	9	14	6.326	>0.05
	Female	34	3	7	10		
Age	≧40 years old	46	5	10	13	5.116	>0.05
	<40 years old	30	3	6	11		
Tumor site	left liver	25	3	11	16	8.021	>0.05
	Right liver	51	5	5	8		
Classification of liver function	A	50	6	11	17	4.551	>0.05
	B	26	2	5	9		
Tumor diameter	<5 cm	26	1	12	20	6.232	<0.05
	≧5 cm	50	7	4	4		
Envelope condition	Complete	30	1	3	5	4.598	<0.05
	Incomplete	46	7	13	19		
Complicated cirrhosis of liver	Yes	51	6	14	20	5.036	<0.05
	No	25	2	2	4		

表 5 Logistic 回归多因素分析

Table 5 Logistic regression multivariate analysis

Index	β	SE	Wold	*P*	Hr
Tumor envelope	1.426	0.651	4.5	0.027	0.24
Tumor diameter	0.521	0.696	0.523	0.412	1.675
Cirrhosis	1.305	0.623	4.152	0.038	0.29

动脉，促进肿瘤坏死的治疗方式，或是经肿瘤供血动脉灌注化疗药物，使药物集中于肿瘤内部，以发挥杀灭癌细胞功能的方式，相比于传统的化疗方式，介入治疗针对性更强，对机体其他器官的损伤更小[20,21]。学者 Vogl T J [22]等通过将 79 例行介入治疗的肝癌患者进行分组对比发现，79 例患者 1 年后复发率为 13.9 %，其中预防性经肝动脉化疗栓塞术患者复发率为 12.2 %，无瘤生存期为(21.6±1.5)个月，经肝动脉化疗灌注术复发率为 15.8 %，无瘤生存期为(17.4±3.0)个月，两组对比差异不大，该学者认为上述两种方式均能够较好的降低肝癌术后复发率，提高患者生存率，效果值得肯定；有研究通过[23]等则通过将 64 例原发性肝癌行手术治疗进行分组干预，发现联合应用介入治疗的观察组患者中位生存期、生存率及平均生存期均高于对照组，由此认为介入治疗能够降低肝癌患者术后并发症的发生率，同时延长患者生存期。

肝脏是机体中血流较丰富的器官，随着癌细胞的增殖，细胞粘附因子分泌量增加并进入血液和周围器官，为恶性肿瘤的再次生长提供了条件。也有研究指出癌细胞在肝脏内呈现侵袭性生长，易形成微卫星病灶，使病灶与周围器官界限不清楚，根治术中一方面难以切除干净，另一方面对病灶的挤压也易使癌栓脱落，出现病灶转移，因而肝癌根治术后复发率较高，患者术后生存率较低[24,25]。而介入治疗能够通过两个途径预防肿瘤细胞的再生，一是利用向病灶血管内灌注化疗药物，来充分杀灭恶变细胞，有研究指出，介入治疗中肝组织中化疗药物浓度高于全身浓度约 400 倍，而病灶内药物浓度又高于肝脏内 10 倍[26,27]，这样能够在杀灭恶变细胞的同时降低全身毒性反应，安全性更高；二是应用碘油等阻断病灶供血，进一步刺激瘤体的纤维化坏死、缩小，有研究指出，肝癌病灶血供有 75 %以上来自肝动脉，通过阻塞肝动脉能够大幅度减少病灶血液供应，加快恶变细胞坏死[28,29]。本研究结果显示预防性应用介入治疗的研究组患者治疗后 1 年、2 年及 3 年复发率均低于单纯实施外科手术治疗的对照组患者，术后 1 年、2 年及 3 年生存率均高于对照组患者，同时中位生存期也高于对照组患者，提示介入治疗可使肝癌术后患者生存获益。本研究还就肝癌根治术后何时实施介入治疗进行了分析，结果显示术后 1-2 个月实施介入治疗的肝癌患者术后 1 年复发率明显低于术后 3-4 个月实施介入治疗的肝癌患者，分析其原因为肝癌术后肝因子分泌增加，导致肝细胞增殖活跃，对化疗药物的敏感性也会随之升高，但术后过早实施介入治疗也会对患者肝功能造成较大的损害，有学者建议于术后 4-6 w 实施介入治疗效果最好，分析其原因为此时患者免疫功能已基本恢复，且残留的癌细胞正处于快速增殖期，药物杀灭作用更明显[30]，这与本研究结果一致。

最后，本文作者还就肝癌复发相关影响因素进行了分析，

结果显示包膜不完整、肿瘤直径≥ 5 cm、合并肝硬化与肝癌复发存在密切相关性，将肿瘤包膜是否完整、肿瘤直径、肝硬化 3 个变量采用多因素 Logistic 回归分析肝癌术后复发的危险因素，显示肿瘤包膜是否完整与合并肝硬化是肝癌复发的独立危险因素。分析其原因如下：(1)包膜不完整或缺如的病灶其细胞增殖扩散几率更大，行病灶切除时难度更高，易出现残留导致复发；(2)一般肝癌常常在肝硬化基础上发生，对已出现肝硬化的患者，虽然病灶被切除了，但肝癌细胞增殖的基础并未消除，肝炎病毒整合的肝细胞仍存在较高的突变几率，因而其复发性更高。

总而言之，肝癌切除术后预防性应用介入治疗能够显著降低肝癌患者术后复发率，提高其生存率，且术后 1-2 个月实施介入治疗效果最好，包膜是否完整、合并肝硬化是导致肝癌复发的独立危险因素。

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