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·专题报道·

原发性肝癌切除术后复发患者的补救性肝移植治疗疗效分析

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[摘要] 目的:比较原发性肝癌切除术后复发患者与初次发生肝癌患者肝移植术后生存率的差异,筛选肝移植术后病死率相关的危险因素。方法:回顾性分析2003年7月至2005年8月收治的77例原发性肝癌患者,其中15例为术后复发肿瘤患者(复发组),62例为初发肿瘤患者(对照组),比较两组患者术后生存率。对所有患者的临床数据进行分析,并通过Cox风险比例模型筛选患者移植术后生存率的影响因素。结果:患者平均年龄为(48.6±4.3)岁,术后随访(20±3.7)个月,复发组和对照组分别有3例(20%)和15例(24.2%)患者死亡,移植术后30 d内病死率分别为6.7%和1.6%。Cox风险比例模型提示,术前高胆红素、最大肿瘤直径较大、肉眼癌栓、术后输血以及肿瘤家族史是术后死亡的危险因素。结论:复发和初发肝移植患者术后生存率无显著差异;术前高胆红素、最大肿瘤直径较大、肉眼癌栓、术后输血以及肿瘤家族史是移植术后病死的危险因素。

[关键词] 肝肿瘤;肝移植;肝切除术;复发;生存率
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Orthotopic liver transplantation as a rescue operation for recurrent hepatocellular carcinoma after partial hepatectomy

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[**ABSTRACT**] **Objective**: To compare post-orthotopic liver transplantation(OLT) survival rates between patients with recurrent HCC after partial hepatectomy and those with de novo OLT for HCC, and to screen for the risk factors associated with post-OLT mortality. **Methods**: From July 2003 to August 2005, 77 consecutive HCC patients underwent OLT, including 15 patients with recurrent HCC after partial hepatectomy for tumor resection(the rescue OLT group) and 62 patients with de novo OLT for HCC(the de novo OLT group); the post-operation survival rates were compared between the 2 groups. Thirty-three demographic, clinical, histological, laboratory and intra- and post-operative variables were analyzed. Cox proportional hazards regression model were used to screen for the factors associated with the survival rate. **Results**: The median age of the patients was 48.6 years and the median follow-up period was 20 months. Three patients(20.0%) in the rescue OLT group and 15 patients (24.2%) in the de novo OLT group died during follow-up($P=0.73$). The 30 day-mortality of OLT was 6.7% for the rescue OLT group *vs.* 1.6% for the de novo OLT group($P=0.27$). Cox proportional hazards model showed that the presence of pre-OLT hyperbilirubinemia, requirement of post-OLT transfusion, size of the largest tumor, tumor macroembolism and family history of HCC were significantly associated with a higher hazard for mortality. **Conclusion**: No significant difference is found in the survival rates between OLT as de novo therapy and OLT as a rescue therapy for patients with HCC. Pre-OLT hyperbilirubinemia, post-OLT requirement of transfusion, size of the largest tumor, tumor macroembolism, and family history of HCC are associated with a poor survival outcome.

[**KEY WORDS**] liver neoplasms; liver transplantation; hepatectomy; recurrence; survival rate
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原发性肝癌(hepatocelluar carcinoma,HCC)是世界范围内最常见的恶性肿瘤之一,每年大约有37.2 万新发患者,占所有恶性肿瘤的 4.6%(男性6.3%,女性 2.7%)[1-2],其中以东亚与非洲的发病率最高。中国的 HCC 患者占全球患者总数的40%～50%,病死率居于所有恶性肿瘤的第二位[3]。其发病机制尚不完全清楚,目前认为与其发病有关的因素主要为继发于 HBV 和 HCV 感染的肝炎后肝硬化、饮食中黄曲霉毒素的污染以及酒精性肝硬化等[4]。

肝切除术是目前 HCC 最主要的治疗方法,但患者术后复发率较高,目前复发后治疗手段主要包括经皮无水乙醇注射(PEI)、经动脉化疗栓塞(TACE)以及复发肿瘤的再次手术切除[5-6],而随着技术上的不断成熟,肝移植也逐渐成为肝癌复发患者的补救性治疗方式之一[7]。Poon 等[7]对肝功能良好的切除术后复发性小肝癌患者(单个肿瘤不超过 5 cm,或不超过 3 个肿瘤且直径之和不超过 3 cm)进行补救性肝移植,获得较好的疗效。尽管如此,肝移植仍未成为晚期复发性肝癌患者的常规治疗方式[8]。本研究的目的在于比较复发性肝癌患者与初发性肝癌患者移植术后的生存率差异,并评估影响患者术后生存率的危险因素。

1　资料和方法

1.1　*一般资料*　本研究为历史队列研究,经院伦理委员会研究通过。2003 年 7 月至 2005 年 8 月在我院接受肝移植治疗的 77 例原发性肝癌患者,其中男65 例(84.4%)、女 12 例(15.6%),年龄 20～72 岁,平均(48.6±4.3)岁,所有患者按术前肿瘤复发情况分为 2 组,其中复发组为原发性肝癌切除术后复发患者(n=15),对照组为初次发现肿瘤患者(n=62)。

1.2　*纳入与排除标准*　本次研究纳入标准为年满18 周岁,接受肝移植的原发性肝癌患者。排除标准为由于原发性肝癌以外原因接受移植治疗,或合并其他器官移植的患者。

1.3　*诊断与筛选标准*　原发性肝癌的诊断依据为患者临床表现、乙肝感染及肝硬化病史、影像学指标(B 超、CT、MRI),术前实验室检查(AFP)以及术后病理学检查。患者接受肝移植的筛选标准主要包括:(1)原发性或复发性肿瘤性质符合“三亚共识”[9],即单发肿瘤直径≤9 cm;或多发性肿瘤数目≤3 个,最大直径≤5 cm,所有肿瘤直径总和≤9 cm;肝脏无大血管癌栓,包括门静脉主干或主要分支癌栓、肝静脉主干癌栓、下腔静脉癌栓;肝脏无肝外肿瘤转移证据(包括肝门部淋巴结转移、远处转移和其他系统肿瘤)。(2)术后有负担长期抗排斥治疗的经济能力。(3)无明显的全身心肺等禁忌证。

1.4　*临床及实验室统计指标*　主要包括年龄,性别,酗酒情况,吸烟情况,肝癌家族史,乙肝和(或)丙肝感染,肝硬化,糖尿病,心肺疾病,肾功能不全,移植前等待时间,供肝来源,术前血生化指标,术前 Child-Pugh 分级[10],术后 pTNM 肿瘤分级(UICC,国际抗癌联盟,1953),术中情况,术后组织病理学数据以及术后病程等。

1.5　*临床效果评估*　主要包括两部分:术后 30 d 病死率,总体病死率以及无瘤生存期;与病死率相关的风险因素。

1.6　*统计学处理*　统计处理采用 SPSS 13.0 数据包。采用 Kaplan-Meier 生存率分析法统计术后总体生存率及无瘤生存率,Log-rank 法检验组间差异。P<0.05 表示差异具有统计学意义。使用 Cox 风险比例模型来评估与病死率相关的风险因素。

2　结　果

2.1　*围手术期处理*　两组患者临床资料见表 1。经过平均(2.0±1.1)个月的等待后,所有 77 例患者均接受了尸肝移植,其中复发组和对照组分别有 2 例(13.3%)和 11 例(17.7%)患者在移植术前接受了 TACE 或 PEI 等辅助性治疗。术中使用常规的经典式原位肝移植(73 例)或背驮式原位肝移植(4 例),所有血管及胆管均采用端-端方式进行吻合。术中无肝期内肌内注射 4 000 IU 人乙肝免疫球蛋白(HBIG),并在无肝期结束时静脉推注甲泼尼龙 500 mg。术后所有患者均采用他克莫司＋霉酚酸酯＋糖皮质激素抗排斥方案,其中他克莫司血药浓度在术后 3 个月内保持在 10～15 ng/ml,此后保持在 5～10 ng/ml,同时,采用激素减量的方法,在术后 1 个月内改为口服泼尼松 15 mg/d 并停用。此外,74 例(96.1%)患者术后至少接受过 1 个疗程 5-氟尿嘧啶 500 mg＋丝裂霉素 2 mg＋卡铂 100 mg 的“6 d 化疗”。

2.2　*复发组患者一般资料*　所有复发组患者移植前均接受根治性切除术,并经术后病理学检查证实肿瘤边缘距切缘超过 1.5 cm,大多数患者术前接受过辅助性治疗,其中 12 例(80.0%)接受了 TACE 治疗,2 例(13.3%)接受了 PEI 治疗(表 2)。

2.3　*术后死亡率*　平均(20±3.7)个月的随访期内共有 18 例(23.4%)患者死亡,复发组和对照组分别为 3 例(20%)和 15 例(24.2%),两组各有 1 例患者

分别因 DIC 和肺部感染在术后 30 d 内死亡(6.7% *vs* 1.6%)。对照组 1 例患者术后 2 个月因移植物抗宿主反应而死亡，其余患者的主要死亡原因为肿瘤复发及远处转移。

两组患者总体生存率和无瘤生存率的 Kaplan-Meier 分析结果(图 1)显示，患者总体生存率和无瘤生存率与随访时间之间均有不成比例的风险关系，但复发组患者与初发患者生存率之间差异并没有统计学意义。

表 1　复发组和对照组患者移植临床指标的比较

Tab 1　Comparison of demographic and clinical data between recurrent group and control group

Factor	Rescue OLT (N=15)	De Novo OLT(N=62)
Age(year)	50.0(46.0-55.0)	49.0(44.0-55.0)
Male n(%)	14(93.3)	51(82.3)
Excessive alcohol use n(%)	5(33.3)	13(21.0)
Tobacco use n(%)	7(46.7)	52(83.9)
Family history of liver cancer n(%)	3(20.0)	8(12.9)
Hepatitis B infection n(%)	15(100.0)	57(91.9)
Diabetes n(%)	2(13.3)	7(11.3)
Liver cirrhosis n(%)	15(100.0)	60(96.8)
Time from tumor detection to OLT t/month	1.0(1.0,3.0)	2.0(1.0,3.0)
Child-Pugh score n(%)		
A	7(46.7)	39(62.9)
B	6(40.0)	23(37.1)
C	2(13.3)	0(0.0)
UICC pTNM tumor staging	3.0(3.0,3.0)	3.0(3.0,3.0)
Total bilirubin c_B/(μmol·L^{-1})	22.8(15.0,54.6)	32.1(23.0,55.4)
Direct bilirubin c_B/(μmol·L^{-1})	10.4(5.8,35.3)	14.4(9.8,29.5)
Albumin ρ_B/(g·L^{-1})	35.3(32.1,42.1)	34.5(32.0,37.6)
Prealbumin ρ_B/(g·L^{-1})	12.7(9.3,15.3)	10.3(6.9,14.5)
Alanine aminotransferase z_B/(U·L^{-1})	90.1(37.7,183.9)	48.9(37.8,91.7)
Aasparate aminotransferase z_B/(U·L^{-1})	85.4(36.5,150.0)	65.5(47.1,99.4)
Prothrombin time t/s	14.5(13.3,17.9)	15.2(13.4,17.8)
Activated partial thromboplastin time t/s	34.7(31.8,38.0)	34.8(30.7,41.3)
OLT operating room time t/h	8.0(7.2,8.1)	6.8(5.7,7.7)
OLT anhepatic time t/min	65.0(60.0,81.0)	62.0(56.0,74.0)
OLT intra-op bleeding V/L	2.0(1.5,2.3)	1.5(1.2,2.0)
OLT intra-op transfusion V/L	1.6(1.0,2.0)	0.8(0.4,1.4)
OLT post-op transfusion V/L	1.2(0.8,2.0)	0.4(0.0,1.4)
Pre-OLT α-fetoprotein z_B/(U·L^{-1})	7.5(4.9,27.1)	362.6(20.4,3480.0)
Post-OLT α-fetoprotein z_B/(U·L^{-1})	5.3(4.1,10.9)	15.7(5.4,120.4)
Change in α-fetoprotein after OLT	4.2(0.8,21.8)	337.9(13.3,3023.5)
Postoperative histopathology		
Size of largest tumor in diameter d/cm	3.0(1.5,6.0)	3.6(2.5,6.0)
Number of tumor	1.0(1.0,4.0)	1.0(1.0,2.0)
Histology differentiation of tumor n(%)		
Moderate	8(53.3)	9(14.5)
Poor	7(46.7)	53(85.5)
Tumor vascular invasion n(%)		
None	5(33.3)	26(41.9)
Microvascular	8(53.3)	33(53.2)
Macrovascular	2(13.3)	3(4.8)
Tumor in right lobe	13(86.7)	53(85.5)
Post-OLT treatment n(%)		
None	1(6.7)	2(3.2)
Chemotherapy	14(93.3)	60(96.8)
Time of follow-up t/month	18.0(12.0,24.0)	21.0(14.0,32.0)

表 2　复发患者相关临床指标

Tab 2　Clinical data of HCC at time of tumor resection in reccurent group

(n=15)

Factor	Statistics*
Years since tumor detection	4.0(3.0,5.0)
Mean diameter of tumor d/cm	4.5(3.0,8.0)
Tumor-free interval after resection t/month	26.0(6.0,38.0)
Microsatellite lesions n(%)	
0	11(73.3)
1	4(26.7)
Number of post-resection trans-catheter arterial chemoembolization n(%)	
0	3(20)
1	4(26.7)
2	5(33.3)
3	2(13.3)
6	1(6.7)
Number of post-resection percutaneous ethanol injection n(%)	
0	13(86.7)
3	1(6.7)
16	1(6.7)
Tumor in the left lobe n(%)	12(80)
Unifocal tumor n(%)	15(100)
Vascular invasion n(%)	
None	10(66.7)
Microvascular	3(20)
Macrovascular	2(13.3)
Non-encapsulated tumor n(%)	9(60)

* Statistics presented are median values (Q25,Q75) or n(%)

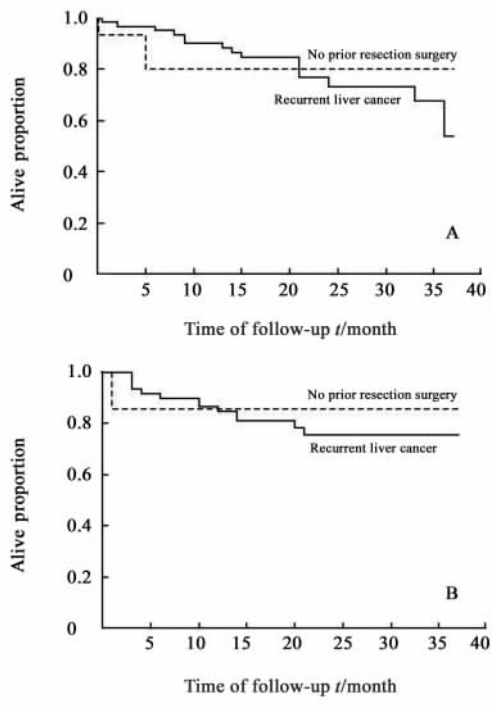

图 1　患者总体生存率和无瘤生存率的 Kaplan-Meier 分析

Fig 1　Kaplan-Meier analysis of total survival rate and tumor-free survival rate of patients

A: Comparison of total survival rates after OLT between recurrent patients and de novo patients; B: Comparison of tumor-free survival rates after OLT between recurrent patients and de novo patients

2.4　**与生存率相关的风险因素**　单变量 Cox 风险比例模型(表 3)分析发现,年龄较小、术前高胆红素、最大肿瘤直径较大、肝癌家族史以及肿瘤肉眼癌栓是影响术后病死率的高危因素。

多变量 Cox 风险比例模型(表 4)仍保留了总胆红素、术后输血、最大肿瘤直径、肝癌家族史以及镜下癌栓等指标。由于其临床重要性,肝癌的复发与否也被保留在这一最终模型中。分析结果表明,总胆红素每升高 1 μmol/L,移植术后病死率就会升高 1%,而术后输血每增加 1 000 ml,病死率就会增加 40%。此外,最大肿瘤直径每增加 1 cm,病死率会增加 30%。最后,有肝癌家族史的患者移植术后病死率是无家族史患者的 7.7 倍。

3　讨　论

肝切除术和肝移植术是合并肝硬化的原发性肝癌患者的最佳治疗方式[11-13],这两种方式的预后效果较为相似,但均有其利弊。对于肝功能较好的 HCC 患者,肝切除术术后病死率较低,但有文献[14-15]提示,其可能在术后短期引起 30%～50%的患者发生肝功能衰竭,并引起 5%～10%的患者死亡,且 80%～100%的患者术后 5 年会发生肿瘤复发[16-19],而肝移植似乎有着更好的生存优势[20-21]。HCC 的肝移植治疗 1 年和 2 年总体生存率已经达到了 90.0%和 65.6%,而无瘤生存率也达到了 77.5%和62.5%[22];3 年生存率为77%～80%[23-24]。HCC 患者移植术后生存率的提高主要归功于以下几个方面,即合适的筛选标准、肿瘤医源性播散的有效控制以及术后辅助性治疗。

与移植术后效果相关的风险因素很多,包括肿瘤直径、脉管浸润、门脉癌栓,以及较差的组织学分化等。而移植术后激素的使用与肿瘤的复发有密切联系,Mazzaferro 等[11]报道了 HCC 术后 3～6 个月内停用激素能有效降低肿瘤复发的可能。同时,术后激素的使用还具有感染和代谢方面的问题,因此,建议移植术后抗排异治疗不使用激素[25]。本研究中所有患者均早期减量使用激素,并在 1 个月内停用。

目前,有关切除术后复发性肝癌患者接受补救性肝移植术后疗效的数据还比较匮乏,通过本次研究,我们发现,切除术后肝癌复发患者与对照组患者相比,总体生存率及无瘤生存率均无统计学差异,这说明肝移植是切除术后肝癌复发患者的有效治疗方法。此外,术前高胆红素、术后输血、最大肿瘤直径以及肝癌家族史是影响移植术后预后的风险因素,而镜下癌栓也可能有不良预后影响。

表 3　单变量 Cox 风险比例模型

Tab 3　Univariable Cox proportional hazards model

Factors	Hazard ratio(95%CI)	*P* value
Demographic		
Age	0.92(0.88,0.97)	<0.001
Gender(Male *vs* Female)	1.6(0.36,6.9)	0.54
Tobacco(Yes *vs* No)	1.7(0.48,5.8)	0.42
Excessive alcohol use(No *vs* Yes)	1.1(0.37,3.4)	0.83
Family history liver cancer (Yes *vs* No)	4.4(1.6,11.9)	0.004
Diabetes(Yes *vs* No)	1.4(0.42,5.0)	0.57
Interval from tumor detection to OLT	0.99(0.91,1.07)	0.74
Disease group		
Recurrent liver cancer (Yes *vs* No)	1.02(0.29,3.5)	0.98
Preoperative laboratory test		
Total bilirubin	1.01(1.004,1.01)	<0.001
Direct bilirubin	1.01(1.01,1.01)	<0.001
Albumin	0.99(0.90,1.10)	0.91
Pre-albumin	0.91(0.82,1.02)	0.11
Alanine aminotransferase	1.00(1.00,1.01)	0.57
Aasparate aminotransferase	1.00(1.00,1.01)	0.15
Prothrombin time	1.04(0.92,1.2)	0.51
Activated partial thromboplastin time	1.01(0.96,1.08)	0.62
Tumor histopathology		
Size of largest tumor	1.1(1.03,1.2)	0.009
Tumor staging	1.6(0.43,6.2)	0.47
Tumor range	1.3(0.90,1.9)	0.16
Tumor location(left *vs* right)	1.2(0.33,4.0)	0.82
Microembolism(micro *vs* none)	2.1(0.67,6.7)	0.2
Macroembolism(macro *vs* none)	10.5(2.3,48.3)	0.003
Preoperative staging		
Child-Pugh Score	1.5(0.67,3.4)	0.31
Intraoperative factors		
OLT operative room time	1.1(0.80,1.6)	0.48
OLT anhepatic time	0.97(0.92,1.01)	0.11
OLT intra-operative bleeding	0.47(0.20,1.1)	0.097
OLT intra-operative transfusion	0.73(0.43,1.2)	0.24
OLT post-operative transfusion	1.1(0.90,1.4)	0.33

表 4　多变量 Cox 风险比例模型

Tab 4　Multivariable Cox proportional hazards model

Factors	Hazard ratio(95%CI)	*P* value
Recurrent liver cancer (Yes *vs* No)	1.7(0.38,7.2)	0.5
Total bilirubin	1.01(1.006,1.02)	<0.000 1
OLT post-operative transfusion	1.4(1.1,1.8)	0.008
Size of largest tumor	1.3(1.1,1.4)	0.000 4
Family history liver cancer (Yes *vs* No)	7.7(2.2,26.9)	0.001
Microembolism (Yes *vs* No)	3.4(0.85,13.5)	0.08

我国的肝移植工作正处于起步阶段，每年接受肝移植的肝癌患者大约 1 400 例左右，如何更好地筛选患者、及时预测患者预后都是研究的重点，对临床工作有着重要的参考意义。通过本次研究，我们认为，切除术后肝癌复发患者与初发肝癌患者的移植术后生存率/病死率均无统计学差异。移植术前高胆红素、术后输血、最大肿瘤直径较大、肉眼癌栓以及肝癌家族史均与移植术后较差的预后有关。当然，这一结果还需要更大样本，更长时间随访来确认和修正。

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