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腹腔镜肝切除术对左外叶肝细胞癌患者免疫功能的影响及其远期疗效 *

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摘要 目的:比较腹腔镜左肝外切除术(LLLR)和开腹左肝外切除术(OLLR)治疗左外叶肝细胞癌(HCC)的临床效果及生存期。**方法:**选取我院 2013 年 6 月 -2014 年 8 月收治的左外叶 HCC 患者 82 例,随机分为对照组和观察组,每组 41 例。对照组患者行 OLLR 治疗,观察组患者行 LLLR。观察并比较两组患者的手术时间、术中出血量、首次进食时间、住院时间、并发症发生率、术后一年和两年生存率,以及治疗前后血清 ICAM-1,MMP-13,PCT,IL-6,IgA,IgM 及 IgG 水平的变化情况。**结果:**观察组患者术中出血量、首次进食时间及住院时间均短于对照组 (P<0.01);手术后,观察组患者血清 ICAM-1,MMP-13,PCT 及 IL-6 水平均低于对照组,而血清 IgA,IgM 及 IgG 水平均高于对照组 (P<0.01);观察组并发症发生率(17.08%)低于对照组(41.47%) (x^2=5.89, P=0.01);两组患者术后 1 年和 2 年的生存率比较,差异无统计学意义 (P>0.05)。**结论:**LLLR 治疗 HCC 具有创伤小、并发症低及预后快等优点,能有效抑制术后炎症反应,对患者免疫功能影响低,可显著降低肿瘤侵袭力,远期生存率较高,值得在临床推广。

关键词:腹腔镜左肝外切除术;开腹左肝外切除术;肝细胞癌;生存期

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Effects of Laparoscopic Hepatectomy on Immune Function of Patients with Left External Lobe Hepatocellular Carcinoma and Its Long-term Efficacy*

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ABSTRACT Objective: To compare the clinical efficacy and survival rate of laparoscopic left hepatic resection (LLLR) and laparoscopic left hepatic resection (OLLR) on the treatment of left lateral lobe hepatocellular carcinoma (HCC). **Methods:** 84 patients with left lateral lobe HCC who were treated in our hospital from June 2013 to August 2014 were selected and randomly divided into the control group and the observation group, with 41 cases in each group. The patients in the control group were treated with OLLR, while the patients in the observation group were treated with LLLR. Then the blood loss, the first time for diet, the hospitalization, the incidence of complications and the survival rate of operation for one and two yeas, and the serum levels of ICAM-1, MMP-13, PCT, IL-6, IgA, IgM and IgG between the two groups were observed and compared. **Results:** The blood loss, the first time for diet and the hospitalization in the observation group were significantly lower than those of the control group (P<0.01); After operation, the serum levels of ICAM-1, PCT, MMP-13 and IL-6 in the observation group were significantly lower than those of the control group, while the serum levels of IgA, IgM and IgG were significantly higher (P<0.01); The incidence of complications in the observation group was 17.08%, which was significantly lower than 41.47% of the control group (x^2=5.89, P=0.01); There was no statistically significant difference about the survival rate of operation for one year and two years between the two groups (P>0.05). **Conclusions:** LLLR has obvious clinical efficacy on the treatment of HCC with small trauma, low complication and better prognosis, which can effectively inhibit the inflammatory reactions of patients, reduce the tumor invasive, and improve the survival rate, and it is worthy of clinical application.

Key words: LLLR; OLLR; HCC; Survival rate

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前言

肝癌是临床常见的恶性肿瘤，发病率及病死率均较高,分别占恶性肿瘤的第六位和第三位[1]。肝癌早期临床表现较隐匿，具有多中心发病倾向，当患者就诊时往往已发展为中晚期,临床预后较差。据统计显示,全球每年因肝癌死亡患者达 100 万以上,既往肝癌病的死率极高,五年生存率不足 5.0%[2]。肝癌可分为原发性和转移性肝癌两类,其中原发性肝癌根据其细胞分型又可分为肝细胞癌(HCC)、胆管细胞癌(CC)及混合型肝癌(cHCC-CC)，而 HCC 占到原发性肝癌的 90.0%以上 [3]。由于 HCC 对放化疗敏感度较低,因此临床治疗多采用肝移植、肝细胞移植、射频消融、手术切除等手段[4],其中手术切除被认为是

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可能治愈 HCC 的唯一手段，既往临床多采用开腹肝切除术，可明显提高患者的生存期，但研究发现[5]，由于肝脏血供丰富，且多数合并有肝硬化，开腹切除对机体的创伤较大，术中出血量较高，存在手术失败及并发症风险。近年来腹腔镜手术因其创伤小、术后恢复快、并发症低等独特优点[6]，在肝癌的治疗中具有明显的效果。因此，本研究对两种术式在 HCC 中应用效果进行比较，旨在为临床提供指导。

1 资料与方法

1.1 一般资料

选取我院 2013 年 6 月到 2014 年 8 月间收治的 HCC 患者 82 例，纳入标准[7]：① 均符合临床 HCC 诊断标准，并经病理活检证实；② 肿瘤直径≤ 8 cm 并仅局限于左肝外叶；③ Child-pugh 分级为 A 级或 B 级；④ 无合并严重的心脑血管、肝肾肺等脏器组织疾病；⑤ 预计生存期均在 6 个月以上；⑥ 均自愿参加并签署知情同意书。排除标准：① 肝癌已侵犯至邻近器官组织或淋巴结；② 合并左肝外叶以外部分肝癌或转移性肝癌；③ 合并严重的血液系统、免疫系统疾病或其他部分恶性肿瘤；④ 合并活动性肝炎、失代偿肝硬化等严重肝脏疾病者。采用随机数字法将其分为对照组和观察组，每组各 41 例。两组患者在性别、年龄、病情、肿瘤直径等一般资料比较，差异均无统计学意义(P>0.05)，故具可比性，详情见表 1。且本研究经院内伦理委员会审核批准。

表 1 两组患者的一般资料比较

Table 1 Comparison of the general data between the two groups

General data	Control group (n=41)	Observation group (n=41)	P
Sex (Male / Female)	27/14	26/15	>0.05
Average age (Years)	55.82± 10.17	56.04± 11.42	>0.05
HBsAg (Positive / Negative)	25/16	24/17	>0.05
Liver cirrhosis (Yes / No)	22/19	23/18	>0.05
Child-pugh classification (A/B)	30/11	28/13	>0.05
AFP(>400 ng/mL/≤ 400 ng/mL)	18/23	19/22	>0.05
Tumor diameter (cm)	4.87± 0.59	4.94± 0.62	>0.05

1.2 方法

1.2.1 **LLLR** 观察组行 LLLR 治疗，取头高脚底式仰卧位，术中根据手术需要对体位进行调整，给予全麻并气管插管，常规消毒铺巾后，充入 CO_2 建立 14 mmHg 左右腹压。观察孔位置选取在脐下处，操作孔位置选取剑突下 3~5 cm，进入腹腔后首选观察肿瘤的大小、位置、腹腔粘连等情况，评估完全后，采用超声刀依次切断肝圆韧、镰状韧带、左侧冠状韧带、左三角韧带以及肝胃韧带，使左肝完全游离出。同时分离至左肝静脉左侧缘，注意避免过度游离，随后使用超声刀在肝脏表面画出预切线，维持中心静脉压至 3~5 cmH_2O 后，使用超声刀逐层对肝实质进行断离，同时游离出肝左外叶血管蒂，采用 Hem-O-Lock 急性夹闭处理后切断。随后再次使用超声刀离断肝实质，并使用直线切割闭合器将左肝静脉及周围部分肝组织进行闭合，主刀经操作孔离断左肝静脉，并将气腹压降至 11 mmHg。手术完成后立即将标本放入标本袋中，并送病理活检。肝脏创面经冲洗后，使用氩气刀止血处理，并于肝断面留置引流管，术后密切观察引流液。确定手术器械无误后关腹。

1.2.2 **OLLR** 对照组患者行 OLLR 治疗，在全麻下做腹正中 L 型切口，其他步骤及策略同 LLLR 治疗组。

1.3 观察指标

① 比较两组患者的手术时间、术中出血量、首次进食时间、住院时间；② 比较两组患者的胸腔积液、肺部感染、创面渗血、胆瘘、肝腹水、全身感染等并发症发生率；③ 比较两组患者手术前后的血清细胞间黏附分子(ICAM)-1、基质金属蛋白酶(MMP)-13、降钙素原(PCT)、白细胞介素(IL)-6、免疫球蛋白(Ig) A、IgM、IgG 水平；④ 随后随访 2 年，比较两组患者术后 1 年和术后 2 年的生存率。

1.4 检测方法

于手术前后抽取患者空腹静脉血 5 mL，禁止后置入离心机中分离出血清，采用酶联免疫吸附试验(ELISA)测定血清 I-CAM-1、MMP-13、PCT、IL-6、IgA、IgM、IgG 水平，试剂盒由上海酶研生物科技有限公司提供，严格按照试剂盒操作说明书进行操作[8]。

1.5 统计学方法

所有统计学资料都采用 SPSS21.0 专业统计学软件进行数据分析，计量资料以均数± 标准差表示，进行 t 检验。而所有的计数资料以率(n%)表示，用 x^2 检验，P<0.05 评价为差异具有显著性。

2 结果

2.1 两组患者的手术效果比较

两组患者的手术时间比较无明显差异(P>0.05)；观察组患者的术中出血量、首次进食时间及住院时间均明显低于对照组(P<0.01)，见表 2。

2.2 两组患者的手术前后的血液恶性指标、炎症指标及免疫功能指标比较

两组患者手术前的血清 ICAM-1、MMP-13、PCT、IL-6、IgA、IgM、IgG 水平比较均无明显差异(P>0.05)；手术后，观察组

表 2 两组患者的手术效果比较($\bar{x}\pm s$)

Table 2 Comparison of the surgical effects between the two groups ($\bar{x}\pm s$)

Groups	Operation time (min)	Blood loss (mL)	First diet time (d)	Hospitalization (d)
Control group (n=41)	139.43± 24.31	281.64± 41.76	3.76± 0.83	11.57± 3.14
Observation group (n=41)	146.52± 22.85	136.58± 23.54	2.37± 0.49	7.46± 2.42
P	0.18	0.00	0.00	0.00
t	1.36	19.38	9.00	6.64

患者的血清 ICAM-1、MMP-13、PCT、IL-6 水平均明显低于对照组 (P<0.01)，血清 IgA、IgM、IgG 水平均明显高于对照组(P<0.01)，见表 3。

表 3 两组患者的手术前后的血液恶性指标、炎症指标及免疫功能指标比较($\bar{x}\pm s$)

Table 3 Comparison of hematological malignant markers, inflammatory markers and immune function indexes before and after operation between two groups($\bar{x}\pm s$)

Time	Groups	ICAM-1 (ng/mL)	MMP-13 (ng/mL)	PCT(μg/L)	IL-6(pg/L)	IgA(g/L)	IgM(g/L)	IgG(g/L)
Before operation	Control group (n=41)	22.06± 3.25	250.72± 21.36	3.31± 0.46	8.71± 1.52	4.10± 0.49	2.81± 0.34	13.14± 1.72
	Observation group (n=41)	21.78± 3.19	247.94± 20.83	3.28± 0.44	8.80± 1.48	4.12± 0.51	2.76± 0.35	12.98± 1.69
	P	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
After operation	Control group (n=41)	13.04± 1.58◊	169.27± 18.41◊	10.05± 1.47◊	18.74± 2.30◊	1.53± 0.38◊	1.43± 0.25◊	6.37± 0.83◊
	Observation group (n=41)	6.12± 0.97◊	114.63± 12.50◊	6.29± 0.71◊	11.95± 1.82◊	2.56± 0.44◊	1.89± 0.31◊	9.65± 1.51◊
	P	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	t	25.17	14.67	14.90	14.82	11.34	7.40	12.19

Note: compared with before operation, ◊ P<0.05.

2.3 两组患者的并发症发生率比较

观察组患者的胸腔积液、肺部感染、创面渗血、胆瘘、肝腹水、全身感染等并发症发生率为 17.08%，对照组患者的总并发症发生率为 41.47%，观察组明显低于对照组(x^2=5.89,P=0.01)，见表 4。

表 4 两组患者的并发症发生率比较[n(%)]

Table 4 Comparison of complications between the two groups[n(%)]

Groups	Pleural effusion	Capillary hemorrhage	Pulmonary infection	Biliary fistula	Liver ascites	Systemic infection	Total incidence rate(%)
Control group (n=41)	6(14.63)	3(7.32)	2(4.88)	2(4.88)	3(7.32)	1(2.44)	41.47
Observation group (n=41)	2(4.88)	2(4.88)	1(2.44)	1(2.44)	1(2.44)	0(0.00)	17.08
P				-			0.01
x^2				-			5.89

2.4 两组患者术后 1 年和 2 年生存率比较

随访结果显示，观察组患者术后 1 年内共 6 例患者死亡，术后 1 年生存率为 85.37%；对照组患者术后 1 年内共 5 例患者死亡，术后 1 年生存率为 87.80%，两组患者术后 1 年生存率比较无明显差异 (x^2=0.09, P=0.76)。观察组患者术后 2 年内共 15 例患者死亡，术后 1 年生存率为 63.41%；对照组患者术后 1 年内共 13 例患者死亡，术后 1 年生存率为 68.29%，两组患者术后 1 年生存率比较无明显差异(x^2=0.65,P=0.21)。

3 讨论

相关研究显示[9]，病毒性肝炎、食用黄曲霉毒素污染食物、长期嗜酒等因素均可导致 HCC 的发生，但其具体病因及发病

机制仍未明确定论。早期 HCC 并无典型临床症状，随机病情进展可出现肝区疼痛、肝大、消化道出血等症状，严重可导致肝癌破裂出血、肝肾功能衰竭等严重并发症[10]，无法实施手术根治，患者预后极差。目前肝癌的手术切除率已由既往的 10.0%左右提升至现在的 60.0%左右[11]。外科手术被认为是可能治愈肝癌的唯一手段，包括手术切除和肝脏移植，均可显著提高患者的生存期，国外资料显示[12]，经肝脏移植术和手术切除术的早期 HCC 患者，五年平均生存率可分别达到 63.0%、53.0%[13]。但肝脏移植术禁忌症多、操作难度高，且肝源及其稀少，极大限制其临床开展，因此手术切除成为早期 HCC 的首选治疗手段。腹腔镜和开腹切除术是临床最常见的两种术式，开腹切除术作为传统的术式，其临床效果已被临床广泛证实。腹腔镜切除术是随着微创外科发展出的术式，具有创伤小、粘连少、术后康复快、并发症低、美观度高等独特优势[14]，目前在肝癌中已有广泛应用。

近年来有关腹腔镜与开腹切除术在肝癌中的报道较多，均显示腹腔镜切除术治疗手术安全性和近期疗效均明显优于开腹切除术，并可实现与开腹切除术相当的远期疗效。Li N 等[15]一项 META 分析显示，腹腔镜肝切除术治疗 HCC 较开腹手术，具有创伤更小、出血量更低、住院时间更少及并发症更低等优点，且 3~5 年生存率可达到开腹肝切除术效果。本研究结果同样显示，LLLR 治疗 HCC 的术中出血量、并发症、住院时间、胃肠恢复时间较 OLLR 治疗患者低，与目前报道基本一致[16]。其中 LLLR 治疗时所建立的 CO_2 气腹，形成的高腹腔压力具止血作用，而 LLLR 治疗应用的小切口，有效保留了腹壁肌肉的强度，这与减少术中出血量和肝腹水、渗血等并发症有关[17]。本研究结果显示，两组患者在术后 1 年和 2 年的生存率比较无明显差异，表明两种术式的远期疗效相当，均有较高临床价值，与国内外报道基本一致。但目前有关两种术式对机体炎症反应、免疫功能和肿瘤预后等方面影响的报道开展极少，本研究就对血清 ICAM-1、MMP-13、PCT、IL-6、IgA、IgM、IgG 等指标开展比较，研究证实[18]，ICAM-1 可通过讲解聚合素、水骨胶、胶原等破坏细胞外基质，提高恶性肿瘤的转移及侵袭能力。MMP-13 在多种恶性肿瘤中均证实有高水平表达，被认为是评估肿瘤恶性程度及预后的重要指标。本研究结果显示，LLLR 治疗后的血清 ICAM-1、MMP-13 均明显低于 OLLR 治疗者，表明 LLLR 对肝癌的预后效果更佳。研究证实，当机体受到手术、外伤等创伤时，可出现严重的应激反应，导致血清 PCT、IL-6 显著提升，因此其常被用于评价机体创伤程度的指标[19]。本研究结果显示，LLLR 治疗后的血清 PCT、IL-6 均明显低于 OLLR 治疗者，表明 LLLR 治疗的对机体创伤更小。大量研究显示[20]，无论是腹腔镜还是开腹切除术，均可一定程度抑制机体免疫功能，本研究对 IgA、IgM、IgG 等免疫效应因子比较发现，HCC 在 LLLR 和 OLLR 治疗后的血清 IgA、IgM、IgG 水平均明显降低，但 LLLR 治疗的降低程度更小，表明 LLLR 对 HCC 患者免疫功能损伤更低，有利于提高术后恢复质量。

综上所述，LLLR 治疗 HCC 具有创伤小、并发症低及预后快等优点，能有效抑制术后炎症反应，对患者免疫功能影响低，可显著降低肿瘤侵袭力，远期生存率较高，值得在临床推广应用。

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患者血清 IL-8 水平,同时缩短临床症状时间,减少炎症反应发生,促进受损组织恢复。

综上所述,八正颗粒联合左氧氟沙星治疗单纯性急性尿路感染效果显著，能降低患者血清 PCT、IL-8 水平，减少尿路疼痛、腰痛、尿频、尿急等症状改善所需的时间。

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