·指南与共识·

中国肝癌肝移植临床实践指南(2014 版)

中华医学会器官移植学分会　中华医学会外科学分会移植学组
中国医师协会器官移植医师分会

【摘要】 肝移植是被全世界认可的治疗终末期肝病的有效手段之一。目前,肝移植在全国范围内已得到广泛开展,亟待相关临床实践指南来指导全国肝移植工作更规范、有效、安全地开展。中华医学会器官移植学分会、中华医学会外科学分会移植学组及中国医师协会器官移植医师分会组织专家制订了《中国肝癌肝移植临床实践指南(2014 版)》,重点阐述肝移植受者选择标准、术前降期治疗、受者抗病毒治疗、受者免疫抑制剂应用、术后肿瘤复发的防治 5 部分内容。米兰标准是肝癌肝移植受者选择的参考基准,而杭州标准是对米兰标准局限于肿瘤形态学的巨大突破。肝癌肝移植术前肿瘤降期治疗可使不满足肝癌肝移植受者选择标准的患者能够被纳入移植标准,获得肝移植机会。对于乙型病毒性肝炎肝癌肝移植受者行抗病毒治疗,有助于降低移植术后乙型病毒性肝炎复发率,提高受者长期生存率。目前主张个体化的低剂量免疫抑制方案以达到最大限度保护移植肝脏功能,同时减轻其毒副作用,减少移植后肝癌复发。肝癌肝移植术后复发的防治可采用手术、TACE、局部消融以及放射免疫、靶向治疗、系统性化疗等手段,为受者制订个体化治疗方案。

【关键词】 肝移植;　肝肿瘤;　指南

The Chinese clinical practice guideline on liver transplantation for hepatocellular carcinoma (2014 edition)

Chinese Society of Organ Transplantation; Section of Organ Transplantation, Chinese Society of Surgery; Chinese College of Transplant Doctors

Corresponding author: Zheng Shusen, Department of Hepatopancreatobiliary Surgery, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China, Email: zyzss@zju.edu.cn

【**Abstract**】 Liver transplantation is still one of the most effective treatments for end-stage liver diseases. Presently, liver transplantation has been widely carried out around China, and a clinical practice guideline is necessary for more standard, effective and safer application of liver transplantation. Therefore, *the Chinese clinical practice guideline on liver transplantation for hepatocellular carcinoma* (*HCC*) was developed by the experts from Chinese Society of Organ Transplantation; Section of Organ Transplantation, Chinese Society of Surgery; Chinese College of Transplant Doctors. *The Chinese clinical practice guideline on liver transplantation for HCC* mainly focused on the following 5 parts: recipients selection criteria for liver transplantation, preoperative down-staging treatments, antiviral therapies, applications of immunosuppressant and postoperative treatment for prevention of HCC recurrence. Milan criteria are regarded as the international standard for selecting recipients, while the Hangzhou criteria are a breakthrough for the Milan criteria which is limited to tumor morphology. For patients who are not candidates for liver transplantation or resection, a variety of down-staging treatments can be offered to help them get the chance for liver transplantation. For recipients with hepatitis B virus (HBV) infection, the antiviral treatment should be initiated with the aim to reduce the rate of HBV recurrence after liver transplantation and improve the long-term survival of recipients. Meanwhile, tailored immunosuppression is recommended with the aim of achieving optimal graft function while avoiding undesirable side effects and the recurrence of HCC. For the treatment of HCC recurrence after liver transplantation, several methods including surgery, transcatheter arterial chemoembolization, regional ablation, radioimmunotherapy, target therapy and systemic chemotherapy could be selected for designing the individualized treatment.

【**Key words**】 Liver transplantation;　Liver neoplasms;　Guideline

据统计中国每年超过 30 万人死于肝细胞癌(以下简称肝癌),占全球肝癌死亡人数的一半左右。而肝移植是被全世界认可的治疗终末期肝病的有效手段之一。我国自 20 世纪 90 年代掀起第 2 次肝移植热潮以来,肝移植事业发展迅猛,呈专业化和规模化发展态势,在移植数量和质量方面已接近或达到西方发达国家水平。截至 2014 年 4 月,中国肝移植注册网站登记肝移植 26 751 例。目前,肝移植在全国范围内已得到广泛开展,亟待相关临床实践指南来指导全国肝移植工作更规范、安全、有效地开展。中华医学会器官移植学分会、中华医学会外科学分会移植学组及中国医师协会器官移植医师分会组织专家制订了《中国肝癌肝移植临床实践指南(2014 版)》(以下简称"指南"),重点阐述肝移植受者选择标准、术前降期治疗、受者抗病毒治疗、受者免疫抑制剂应用、术后肿瘤复发的防治 5 部分内容。

DOI: 10.3760/cma.j.issn.1673-9752.2014.07.001

通信作者:郑树森,310003 杭州,浙江大学医学院附属第一医院肝胆胰外科 卫生部多器官联合移植研究重点实验室,Email: zyzss@zju.edu.cn

1　循证医学证据

本指南采用的循证医学证据分级主要参考 2001 牛津大学循证医学中心证据分级标准(表 1),推荐意见强度主要参考 GRADE 系统推荐分级等[1-2]。

表 1　循证医学证据分级标准

证据级别	定　义
Ⅰ	同质随机对照试验(randomized controlled trial, RCT)的系统评价
	单个 RCT(可信区间窄)
	全或无病案系列研究
Ⅱ	同质队列研究的系统评价
	单个队列研究(包括低质量 RCT,如随访率 <80%)
	结果研究,生态学研究
Ⅲ	同质病例对照研究的系统评价
	单个病例对照研究
Ⅳ	病例系列研究(包括低质量队列及病例对照研究)
Ⅴ	基于经验未严格论证的专家意见

2　肝癌肝移植受者选择标准(表 2)

供肝短缺是世界性难题,故应将宝贵的供肝资源优先分配给肝移植的最大获益者。心脏死亡器官捐献是中国目前拓展供肝来源的主要方向,而活体肝移植在有丰富移植经验的医疗单位已成为一项成熟技术[3]。1996 年,Mazzaferro 等提出米兰标准后,符合米兰标准的肝癌肝移植受者获得了长期生存[4-7]。但米兰标准对肝癌大小和数目的限制过于严格,更重要的是忽略了肿瘤的生物学特性。如果根据米兰标准,中国大多数肝癌患者将失去肝移植机会。近年来国际上涌现出一些新的肝癌肝移植受者选择标准,如加州大学旧金山分校(UCSF)标准、Up-to-Seven 标准等,这些新标准提出的共同目的是扩大受者人群并取得与米兰标准相似的移植生存率[8-9]。2008 年,中国提出的杭州标准是国际上率先引入肿瘤生物学特性和病理学特征的肝移植标准,这是对以往局限于肿瘤形态学标准的巨大突破。研究结果证实:无论是尸体肝移植还是活体肝移植,符合杭州标准的肝移植受者均获得满意的术后生存率[10-15]。近年来,对于肝癌切除术后复发者,如符合肝移植准入标准,多数专家主张行抢救性肝移植;对于肝癌肝移植术后移植物失功能者,再次肝移植应审慎考虑[16-17]。

3　肝癌肝移植术前降期治疗(表 3)

肝癌肝移植术前肿瘤降期治疗是通过一系列治疗手段,减轻肿瘤负荷,降低分期,使不满足肝癌肝移植受者选择标准的患者能够被纳入移植标准,获得肝移植机会。降期治疗主要适用于不符合现有肝癌肝移植标准,且无门静脉主干或下腔静脉等大血管侵犯、无远处转移的肝癌患者[18-21]。降期治疗的方法主要有局部消融治疗和 TACE 等[18-19,22]。局部消融治疗包括 RFA、微波消融、冷冻消融和经皮无水乙醇注射等方法。降期治疗的疗效采用增强 CT 和 MRI 检查结合 AFP 进行评估,评价指标包括肿瘤大小、数目和 AFP 水平等[22-28]。目前有研究结果显示:多种治疗方法的联合应用可达到更好的降期疗效[29]。

表 2　肝癌肝移植受者选择标准

序号	建　议	证据级别	推荐强度
1	米兰标准是肝癌肝移植受者选择的参考基准。	Ⅱ	强
2	杭州标准是可靠的肝癌肝移植受者选择标准,符合杭州标准者接受肝移植可获得满意的术后生存率。	Ⅱ	强
3	某项肝移植标准如经多中心大样本研究证实,能取得与米兰标准相似的效果,则可应用于临床。	Ⅱ	弱
4	肝癌切除术后肝内肿瘤复发且无法再次手术切除者,如无肝外播散及大血管侵犯,可行抢救性肝移植。	Ⅱ	弱
5	符合肝癌肝移植选择标准的患者可接受活体肝移植,术前须严格评估供者与受者的社会心理学状态。	Ⅲ	弱
6	对于符合肝癌肝移植选择标准的患者,实施活体肝移植后如出现移植物失功能,可行尸体肝移植。	Ⅲ	弱
7	对于超越肝癌肝移植选择标准的患者,实施活体肝移植后如出现肝癌复发导致的移植物失功能,不建议行尸体肝移植。	Ⅴ	强
8	为了最小化供者风险及最优化受者预后,活体肝移植的开展仅限于具有成熟肝移植技术的医疗单位。	Ⅴ	强

表 3　肝癌肝移植术前降期治疗

序号	建　议	证据级别	推荐强度
9	降期治疗的方法主要有局部消融治疗和 TACE 等。局部消融治疗包括 RFA、微波消融、冷冻消融和经皮注射无水乙醇等方法,需根据个体病情选择适合的降期治疗方法。	Ⅱ	强
10	多种降期治疗方法的联合应用可达到更好的降期疗效。	Ⅱ	强
11	降期治疗效果的评价指标包括肿瘤大小、数目和 AFP 水平等。	Ⅱ	强

4　肝癌肝移植受者抗病毒治疗(表 4)

中国肝癌肝移植受者 90% 以上与 HBV 感染相关。肝移植前 HBV 载量高以及肝移植后乙型病毒

性肝炎(以下简称乙肝)复发的受者,肝癌复发的风险增加,因此,对乙肝肝移植受者尽早行抗病毒治疗,尽快降低 HBV 水平,有助于降低肝移植术后乙型肝炎复发率,提高受者长期生存率[30-32]。HBV 载量高的等待肝移植患者应采用恩替卡韦等强效、高耐药屏障核苷类似物(nucleostide analogues, NAs)。肝移植术中无肝期应给予乙肝免疫球蛋白(hepatitis B immunoglobulin, HBIG)。肝移植术后的主要抗病毒治疗方案为 NAs 联合低剂量 HBIG,其中恩替卡韦或替诺福韦的联合方案能更好地预防移植术后乙肝复发[33-38]。应用无激素免疫抑制方案可降低移植术后乙肝复发率[39]。此外也有肝移植患者术后接种乙肝疫苗预防乙肝复发的报道,其临床应用尚有争议[40-42]。中国 HCV 感染患者呈增多趋势,HCV RNA 阳性患者如肝功能 Child-Pugh 评分≤7 分,术前宜进行抗病毒治疗,移植术后须经病理检查确认丙型病毒性肝炎复发后方可给予抗 HCV 治疗[43]。

表 4　肝癌肝移植受者抗病毒治疗

序号	建　　议	证据级别	推荐强度
12	HBV 相关性肝癌肝移植患者,如移植前 HBV DNA 阳性,应于术前尽早给予 NAs,尽可能降低 HBV DNA 水平。	Ⅰ	强
13	如术前 HBV 高载量,应优先选择强效、高耐药屏障药物;耐药者应根据耐药位点检测结果选择相应药物,如发生拉米夫定耐药,可加用阿德福韦酯或改用替诺福韦治疗。	Ⅱ	强
14	HBV 相关性肝癌肝移植受者术中无肝期应给予 HBIG,术后长期使用 NAs 和 HBIG 预防乙肝复发。	Ⅱ	强
15	恩替卡韦或替诺福韦联合低剂量 HBIG 相比拉米夫定联合低剂量 HBIG,可更好地预防移植术后乙肝复发。	Ⅱ	强
16	无激素免疫抑制方案可降低肝移植术后乙肝复发率。	Ⅳ	弱

注:NAs:高耐药屏障核苷类似物; HBIG:乙肝免疫球蛋白

5　肝癌肝移植受者免疫抑制剂应用(表 5)

钙调磷酸酶抑制剂(calcineurin inhibitor, CNI)的应用是肝移植后肝癌复发的独立危险因素[44]。对于肝癌肝移植受者,肿瘤的复发风险与其侵袭性及机体的免疫功能有关,受者处于强免疫抑制状态时其免疫监视系统受到破坏,促进肿瘤复发、转移,而免疫抑制剂量不足则容易诱发排斥反应。如何维持这一平衡,目前尚无定论[45-47]。肝癌肝移植受者目前尚不建议将免疫抑制剂全线撤除,但主张个体化的低剂量免疫抑制方案[45]。近年来临床上有糖皮质激素早期撤除、无糖皮质激素及使用具有肿瘤抑制作用的 mTOR 抑制剂(西罗莫司为代表)的成功应用方案[44,48-50]。目前临床上主要的免疫抑制方案为:(1)他克莫司或环孢素 + 吗替麦考酚酯 + 糖皮质激素;(2)IL-2 受体阻滞剂 + 西罗莫司 + 吗替麦考酚酯 + 糖皮质激素;(3)IL-2 受体阻滞剂 + 吗替麦考酚酯 + 他克莫司/西罗莫司[51-54]。

表 5　肝癌肝移植受者免疫抑制剂应用

序号	建　　议	证据级别	推荐强度
17	CNI 的应用是肝移植术后肝癌复发的独立危险因素。	Ⅰ	强
18	对合并肝肾综合征或肾功能不全受者应避免应用 CNI,采用 IL-2 受体阻滞剂、吗替麦考酚酯和西罗莫司治疗。	Ⅰ	强
19	肝癌肝移植受者,应采用低剂量 CNI 及糖皮质激素早期撤除方案。	Ⅱ	强
20	肝癌肝移植受者应用 mTOR 抑制剂(西罗莫司为代表)可减少术后肿瘤复发和转移。	Ⅱ	强
21	肝癌肝移植受者,可采用无糖皮质激素免疫抑制方案。	Ⅱ	弱

注:CNI:钙调磷酸酶抑制剂

6　肝癌肝移植术后肿瘤复发的防治(表 6)

肝癌肝移植术后 5 年肝癌复发率可达 20.0%~57.8%,故复发、转移的防治十分重要[9,55]。肝癌的形态学特征(大小、数目等)、分期、组织学分级以及生物学特性等应作为术后用药的重要参考,制订个体化治疗方案。

肝癌肝移植术后可能存在针对肿瘤的免疫逃逸,故应给予受者一定疗程的术后治疗,以期尽可能地减少微小转移灶,降低术后复发率。选用碘^{131}美妥昔单抗放射免疫治疗、索拉非尼治疗以及系统性化疗(如奥沙利铂或阿霉素分别与氟尿嘧啶联合使用),均可为部分受者提供一定的生存获益[56-59]。

对于肝移植术后肝癌复发转移者,应用索拉非尼治疗,可延长受者生存时间[18,60-62]。肺转移灶如可切除,首选手术切除[63]。移植肝内复发病灶的局部治疗包括手术切除、TACE、局部消融等[64-66]。有专家提出放疗、再次肝移植等可作为治疗的选择。对于晚期患者,可考虑减少或停止免疫抑制剂的使用。

表 6　肝癌肝移植术后复发的防治

序号	建　　议	证据级别	推荐强度
22	超越米兰标准的肝癌肝移植受者，术后应用放射免疫治疗可降低肝癌复发率。	Ⅱ	弱
23	超越米兰标准的肝癌肝移植受者，术后应用索拉非尼治疗或系统性化疗，可提高生存率。	Ⅲ	弱
24	对于可切除的肺转移癌，手术治疗可提供长期生存的机会。	Ⅲ	强
25	局限于移植肝内的复发癌，可采用手术切除、TACE、局部消融治疗。	Ⅳ	强
26	肝癌肝移植术后不可切除的复发转移癌，应用索拉非尼治疗，可延长受者生存时间。	Ⅳ	强

《中国肝癌肝移植临床实践指南(2014 版)》编审委员会成员名单

编审专家组组长：郑树森

编审专家组成员(按姓氏拼音排序)：

陈规划　陈　实　陈孝平　陈燕凌　陈知水　陈忠华
丁义涛　董家鸿　窦　剑　窦科峰　杜国盛　段伟东
傅志仁　高　杰　高良辉　何晓顺　贺　强　景鸿恩
李　波　李　立　李　宁　李玉民　刘景丰　刘　军
卢实春　吕国悦　明英姿　彭承宏　彭贵主　彭志海
钱建民　沈　岩　沈中阳　石承先　时　军　孙军辉
孙玉岭　王伟林　温　浩　吴　健　吴忠钧　夏　强
徐　骁　严律南　杨广顺　杨家印　杨　扬　杨占宇
叶啟发　臧运金　张　峰　张　珉　张水军　郑树森
周　琳　朱继业　朱志军

执　笔：徐　骁　李建辉　高　峰　陈　峻　舒哲悦
方维佳　卫　强

参考文献

[1] Oxford Centre for Evidence-based Medicine—Levels of Evidence (March 2009) [DB/OL]. Oxford Centre for Evidence-based Medicine, 2009 [2014-04-15]. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.

[2] Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies[J]. BMJ, 2008, 336(7653): 1106-1110.

[3] Liang WH, Wu LW, Ling XT, et al. Living donor liver transplantation versus deceased donor liver transplantation for hepatocellular carcinoma: a meta-analysis[J]. Liver Transpl, 2012, 18(10): 1226-1236.

[4] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis[J]. N Engl J Med, 1996, 334(11): 693-699.

[5] European Liver Transplant Registry Results[DB/OL]. European Liver Transplant Registry, 2011[2014-04-15]. http://www.eltr.org.

[6] OPTN/SRTR Annual Report[DB/OL]. Organ Procurement and Transplantation Network, 2011 [2014-04-15]. http://www.ustransplant.org.

[7] Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience[J]. Liver Transpl, 2011, 17(Suppl 2): S44-57.

[8] Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival[J]. Hepatology, 2001, 33(6): 1394-1403.

[9] Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis[J]. Lancet Oncol, 2009, 10(1): 35-43.

[10] Zheng SS, Xu X, Wu J, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences[J]. Transplantation, 2008, 85(12): 1726-1732.

[11] Lei JY, Wang WT, Yan LN. Hangzhou criteria for liver transplantation in hepatocellular carcinoma: a single-center experience[J]. Eur J Gastroenterol Hepatol, 2014, 26(2): 200-204.

[12] Audet M, Panaro F, Piardi T, et al. Are the Hangzhou criteria adaptable to hepatocellular carcinoma patients for liver transplantation in Western countries?[J]. Liver Transpl, 2009, 15(7): 822-826.

[13] Chen J, Xu X, Wu J, et al. The stratifying value of hangzhou criteria in liver transplantation for hepatocellular carcinoma[J]. PLoS One, 2014, 9(3): e93128.

[14] 徐骁，杨家印，钟林，等. 肝癌肝移植"杭州标准"多中心应用研究——1163 例报道[J]. 中华器官移植杂志，2013，34(9)：524-527.

[15] 郑树森，汪恺，徐骁，等. 肝移植治疗肝癌的受者选择杭州标准在亲属活体供肝移植中的应用价值[J]. 中华器官移植杂志，2011，32(6)：330-333.

[16] Hu ZH, Wang W, Li ZW, et al. Recipient outcomes of salvage liver transplantation versus primary liver transplantation: a systematic review and meta-analysis[J]. Liver Transpl, 2012, 18(11): 1316-1323.

[17] Olthoff KM, Merion RM, Ghobrial RM, et al. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL Consortium[J]. Ann Surg, 2005, 242(3): 314-325.

[18] Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report[J]. Lancet Oncol, 2012, 13(1): e11-22.

[19] Galuppo R, McCall A, Gedaly R. The role of bridging therapy in hepatocellular carcinoma[J]. Int J Hepatol, 2013: 419302.

[20] European Association for the Study of the Liver. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma[J]. J Hepatol, 2012, 56(4): 908-943.

[21] Washburn K, Edwards E, Harper A, et al. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system[J]. Am J Transplant, 2010, 10(7): 1643-1648.

[22] Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial down staging for hepatocellular carcinoma: chemoembolization versus radioembolization[J]. Am J Transplant, 2009, 9(8): 1920-1928.

[23] Merani S, Majno P, Kneteman NM, et al. The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma[J]. J Hepatol, 2011, 55(4): 814-819.

[24] Mailey B, Artinyan A, Khalili J, et al. Evaluation of absolute serum α-fetoprotein levels in liver transplant for hepatocellular cancer[J]. Arch Surg, 2011, 146(1): 26-33.

[25] Ravaioli M, Grazi GL, Piscaglia F, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria[J]. Am J Transplant, 2008, 8(12): 2547-2557.

[26] Yao FY, Kerlan RK Jr, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis[J]. Hepatology, 2008, 48(3): 819-827.

[27] Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria[J]. Gastroenterology, 2012, 143(4): 986-994.

[28] Lai Q, Avolio AW, Graziadei I, et al. Alpha-fetoprotein and modified response evaluation criteria in solid tumors progression after locoregional therapy as predictors of hepatocellular cancer recurrence and death after transplantation[J]. Liver Transpl, 2013, 19(10): 1108-1118.

[29] Ashoori N, Bamberg F, Paprottka P, et al. Multimodality treatment for early-stage hepatocellular carcinoma: a bridging therapy for liver transplantation[J]. Digestion, 2012, 86(4): 338-348.
[30] Koda M, Nagahara T, Matono T, et al. Nucleotide analogs for patients with HBV-related hepatocellular carcinoma increase the survival rate through improved liver function[J]. Inter Med, 2009, 48(1): 11-17.
[31] Wong JS1, Wong GL, Tsoi KK, et al. Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma[J]. Aliment Pharmacol Ther, 2011, 33(10): 1104-1112.
[32] Wu JC, Huang YH, Chau GY, et al. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma[J]. J Hepatol, 2009, 51(5): 890-897.
[33] European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection[J]. J Hepatol, 2012, 57(1): 167-185.
[34] Chen CJ, Yang HI, Iloeje UH, et al. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B[J]. Hepatology, 2009, 49(Suppl 5): S72-84.
[35] Lai CL, Yuen MF. Prevention of hepatitis B virus-related hepatocellular carcinoma with antiviral therapy[J]. Hepatology, 2013, 57(1): 399-408.
[36] Yin JH, Li N, Han YF, et al. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study[J]. J Clin Oncol, 2013, 31(29): 3647-3655.
[37] Huang G, Lai EC, Lau WY, et al. Posthepatectomy HBV reactivation in hepatitis B-related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels[J]. Ann Surg, 2013, 257(3): 490-505.
[38] Hu TH, Chen CL, Lin CC, et al. Section 14. Combination of entecavir plus low-dose on-demand hepatitis B immunoglobulin is effective with very low hepatitis B recurrence after liver transplantation[J]. Transplantation, 2014, 97(Suppl 8): S53-59.
[39] Kim JM, Joh JW, Kim SJ, et al. Steroid withdrawal in adult liver transplantation: occurrence at a single center[J]. Transplant Proc, 2010, 42(10): 4132-4136.
[40] Sánchez-Fueyo A, Rimola A, Grande L, et al. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: A new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation[J]. Hepatology, 2000, 31(2): 496-501.
[41] Lo CM, Liu CL, Chan SC, et al. Failure of hepatitis B vaccination in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B[J]. J Hepatol, 2005, 43(2): 283-287.
[42] Lo CM, Lau GK, Chan SC, et al. Efficacy of a pre-S containing vaccine in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B[J]. Am J Transplant, 2007, 7(2): 434-439.
[43] Watt K, Veldt B, Charlton M. A practical guide to the management of HCV infection following liver transplantation[J]. Am J Transplant, 2009, 9(8): 1707-1713.
[44] Vivarelli M, Cucchetti A, La Barba G, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence[J]. Ann Surg, 2008, 248(5): 857-862.
[45] Chen K, Man K, Metselaar HJ, et al. Rationale of personalized immunosuppressive medication for hepatocellular carcinoma patients after liver transplantation[J]. Liver Transpl, 2014, 20(3): 261-269.
[46] Miyagi S, Kawagishi N, Sekiguchi S, et al. The relationship between recurrences and immunosuppression on living donor liver transplantation for hepatocellular carcinoma[J]. Transplant Proc, 2012, 44(3): 797-801.
[47] Saigal S, Shah S. Liver transplantation-economics in the less developed world[J]. Indian J Gastroenterol, 2012, 31(1): 13-14.
[48] Foroncewicz B, Mucha K, Ryszkowska E, et al. Safety and efficacy of steroid-free immunosuppression with tacrolimus and daclizumab in liver transplant recipients: 6-year follow-up in a single center[J]. Transplant Proc, 2009, 41(8): 3103-3106.
[49] Nair S, Eason J, Loss G. Sirolimus monotherapy in nephrotoxicity due to calcineurin inhibitors in liver transplant recipients[J]. Liver Transpl, 2003, 9(2): 126-129.
[50] Menon KV, Hakeem AR, Heaton ND. Meta-analysis: recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma[J]. Aliment Pharmacol Ther, 2013, 37(4): 411-419.
[51] Liang W, Wang D, Ling X, et al. Sirolimus-based immunosuppression in liver transplantation for hepatocellular carcinoma: a meta-analysis[J]. Liver Transpl, 2012, 18(1): 62-69.
[52] Soliman T, Hetz H, Burghuber C, et al. Short-term induction therapy with anti-thymocyte globulin and delayed use of calcineurin inhibitors in orthotopic liver transplantation[J]. Liver Transplant, 2007, 13(7): 1039-1044.
[53] Martin-Mateos RM, Graus J, Albillos A, et al. Initial immunosuppression with or without basiliximab: a comparative study[J]. Transplant Proc, 2012, 44(9): 2570-2572.
[54] Pillai AA, Levitsky J. Overview of immunosuppression in liver transplantation[J]. World J Gastroenterol, 2009, 15(34): 4225-4233.
[55] Zimmerman MA, Ghobrial RM, Tong MJ, et al. Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators[J]. Arch Surg, 2008, 143(2): 182-188.
[56] Xu J, Shen ZY, Chen XG, et al. A randomized controlled trial of Licartin for preventing hepatoma recurrence after liver transplantation[J]. Hematology, 2007, 5(2): 269-276.
[57] Huang L, Li GM, Zhu JY, et al. Efficacy of sorafenib after liver transplantation in patients with primary hepatic carcinoma exceeding the Milan criteria: a preliminary study[J]. Oncol Targets Ther, 2012, 5: 457-462.
[58] Zhang Q, Chen H, Li Q, et al. Combination adjuvant chemotherapy with oxaliplatin, 5-fluorouracil and leucovorin after liver transplantation for hepatocellular carcinoma: a preliminary open-label study[J]. Invest New Drugs, 2011, 29(6): 1360-1369.
[59] 张照辉, 马力文, 宋世兵, 等. 肝癌肝移植术后辅助化疗的临床分析[J]. 中华肿瘤杂志, 2005, 27(1): 45-47.
[60] Waghray A, Balci B, El-Gazzaz G, et al. Safety and efficacy of sorafenib for the treatment of recurrent hepatocellular carcinoma after liver transplantation[J]. Clin transplant, 2013, 27(4): 555-561.
[61] Pfeiffenberger J, Koschny R, Hoffmann K, et al. Sorafenib treatment is save and may affect survival of recurrent hepatocellular carcinoma after liver transplantation[J]. Langenbecks Arch Surg, 2013, 398(8): 1123-1128.
[62] Sposito C, Mariani L, Germini A, et al. Comparative efficacy of sorafenib versus best supportive care in recurrent hepatocellular carcinoma after liver transplantation: a case-control study[J]. J Hepatol, 2013, 59(1): 59-66.
[63] Hwang S, Kim YH, Kim DK, et al. Resection of pulmonary metastases from hepatocellular carcinoma following liver transplantation[J]. World J Surg, 2012, 36(7): 1592-1602.
[64] Taketomi A, Fukuhara T, Morita K, et al. Improved results of a surgical resection for the recurrence of hepatocellular carcinoma after living donor liver transplantation[J]. Ann Surg Oncol, 2010, 17(9): 2283-2289.
[65] Ko HK, Ko GY, Yoon HK, et al. Tumor response to transcatheter arterial chemoembolization in recurrent hepatocellular carcinoma after living donor liver transplantation[J]. Korean J Radiol, 2007, 8(4): 320-327.
[66] Ho CK, Chapman WC, Brown DB. Radiofrequency ablation of recurrent hepatocellular carcinoma in a patient after liver transplantation: two-year follow-up[J]. J Vasc Interv Radiol, 2007, 18(11): 1451-1453.

（收稿日期：2014-06-18）
（本文编辑：张玉琳、陈敏）