ISSN 1009-3079 (print)
ISSN 2219-2859 (online)

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

Shijie Huaren Xiaohua Zazhi

2021 年 5 月 28 日　　第 29 卷　　第 10 期　　(Volume 29 Number 10)

10/2021

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

ISSN 1009-3079

世界华人消化杂志 https://www.wjgnet.com 二零二一年五月二十八日 第二十九卷 第十期

WCJD 世界华人消化杂志®

目　次

2021年5月28日 第29卷 第10期 (总第678期)

述评

501 原发性肝癌转化治疗指征与选择策略

秦建民

临床研究

511 肝癌组织中IL-26水平对乙肝相关肝癌术后患者的预后判断价值

鲍建亨, 尚海涛, 郝成飞, 刘军舰, 韩树旺, 张德林, 李忠廉

517 复发性急性胰腺炎危险因素的Meta分析

周露, 高一雯, 许松欣, 路国涛, 肖炜明

526 miR-128-3p靶向xCT基因在结直肠癌中的分子机制及其与肠癌患者临床病理特征的相关性

吴珺, 廖旭慧, 吴勤丽, 余伟

文献综述

537 胃黄斑瘤的研究进展

陈鸿鑫, 易芳芳, 吴艳艳, 祁兴顺

543 以超声检测为基础的NALFD肝脏脂肪变性的无创诊断

刘芳

临床实践

550 扬州农村地区人群幽门螺杆菌感染现状及其与胃黏膜病理变化的关系

张云, 冯心怡, 李贵庆, 许菲, 刘芳, 李瑶瑶, 邓彬

557 孕前及孕早期母体风险因素与早产儿坏死性小肠结肠炎的相关性研究

马小江, 郑彤彤

消　　息

525　《腹痛的诊断、鉴别诊断与治疗》书讯
549　《世界华人消化杂志》正文要求
556　《世界华人消化杂志》参考文献要求
562　《世界华人消化杂志》外文字符标准

封面故事

颜学兵, 医学博士, 教授, 主任医师, 博士研究生导师. 徐州医科大学附属医院感染性疾病科主任及教研室主任. 江苏省医学会感染病分会候任主委, 江苏省医学会肝脏病学分会副主任委员, 江苏省医师协会感染病分会副会长, 亚太肝病诊疗技术联盟江苏省联盟副理事长, 江苏省中西医结合学会感染病专业委员副主任委员, 江苏省研究型医院学会感染检验与合理用药专委会副主任委员, 国家《抗菌药物专委会》委员, 中华医学会肝病学会药物性肝病学组委员, 全国疑难及重症肝病攻关协作组委员. 主持国家自然科学基金、“十三五、十二五”、省、市各级课题多项, 获科技进步奖多项. 在国内外发表含SCI及EI论文多篇. 擅长感染性疾病及肝病等疑难杂症的救治.

本期责任人

编务 张砚梁; 送审编辑 张砚梁; 组版编辑 张砚梁; 英文编辑 王天奇;
形式规范审核编辑部主任 吴云晓健; 最终清样审核总编辑 马连生

世界华人消化杂志

Shijie Huaren Xiaohua Zazhi

吴阶平　题写封面刊名
陈可冀　题写版权刊名

(半月刊)

创　刊 1993-01-15
改　刊 1998-01-25
出　版 2021-05-28
原刊名 新消化病学杂志

期刊名称
世界华人消化杂志

国际标准连续出版物号
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

编辑部
王金磊, 主任
《世界华人消化杂志》编辑部
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
http://www.wjgnet.com

出版
百世登出版集团有限公司
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

制作
北京百世登生物医学科技有限公司
100025, 北京市朝阳区东四环中路62号, 远洋国际中心D座903室
电话: +86-10-85381892

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

《世界华人消化杂志》正式开通了在线办公系统(https://www.baishideng.com), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

特别声明
本刊刊出的所有文章不代表本刊编辑部和本刊编委会的观点, 除非特别声明. 本刊如有印装质量问题, 请向本刊编辑部调换.

定价
每期136.00元 全年24期3264.00元

WCJD 世界华人消化杂志®

Contents

Volume 29 Number 10 May 28, 2021

EDITORIAL

501 Conversion therapy for primary liver cancer: Indications and selective strategies
Qin JM

CLINICAL RESEARCH

511 Prognostic value of IL-26 level in hepatocellular carcinoma tissue in postoperative patients with hepatitis B related hepatocellular carcinoma
Bao JH, Shang HT, Hao CF, Liu JJ, Han SW, Zhang DL, Li ZL
517 Meta-analysis of risk factors for recurrent acute pancreatitis
Zhou L, Gao YW, Xu SX, Lu GT, Xiao WM
526 MiR-128-3p targets *xCT* gene in colorectal cancer: Molecular mechanism and correlation with patients' clinicopathological features
Wu J, Liao XH, Wu QL, Yu W

REVIEW

537 Recent advances in research of gastric xanthelasma
Chen HX, Yi FF, Wu YY, Qi XS
543 Ultrasound-based techniques for noninvasive diagnosis of liver steatosis in nonalcoholic fatty liver disease
Liu F

CLINICAL PRACTICE

550 Epidemiological study of *Helicobacter pylori* infection and its relationship with pathologic changes of the antral mucosa in rural areas of Yangzhou
Zhang Y, Feng XY, Li GQ, Xu F, Liu F, Li YY, Deng B
557 Relationship between maternal risk factors and occurrence of necrotizing enterocolitis in premature infants before and during the first trimester
Ma XJ, Zheng TT

Contents

World Chinese Journal of Digestology
Volume 29 Number 10 May 28, 2021

COVER Editorial Board Member of *World Chinese Journal of Digestology*, Xue-Bing Yan, Ph.D, Professor, Chief Physician, Department of Infectious Disease, The First Affiliated Hospital of Xuzhou Medical University, No. 99 Kunpeng North Road, Xuzhou 221002, Jiangsu Province, China. yxbxuzhou@126.com

Indexed/Abstracted by Chemical Abstracts, EMBASE/Excerpta Medica, Abstract Journals, Scopus, CNKI, CSTJ and Superstar Journals Database.

Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993
Renamed on January 25, 1998
Publication date May 28, 2021

NAME OF JOURNAL
World Chinese Journal of Digestology

ISSN
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Chinese Journal of Digestology
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
https://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PRODUCTION CENTER
Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381892

PRINT SUBSCRIPTION
RMB 136 Yuan for each issue
RMB 3264 Yuan for one year

INSTRUCTIONS TO AUTHORS
Full instructions are available online at https://www.wjgnet.com/1009-3079/Nav/36. If you do not have web access, please contact the editorial office.

WCJD 世界华人消化杂志®

在线投稿: https://www.baishideng.com

世界华人消化杂志 2021年5月28日; 29(10): 501-510

DOI: 10.11569/wcjd.v29.i10.501

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

原发性肝癌转化治疗指征与选择策略

秦建民

秦建民, 海军军医大学第三附属医院普外科 上海市 201805

秦建民, 教授, 主任医师, 研究方向为肝癌复发、转移机制与纳米靶向药物治疗.

作者贡献分布: 本文由秦建民单独完成.

通讯作者: 秦建民, 教授, 主任医师, 201805, 上海市嘉定区墨玉北路700号, 海军军医大学第三附属医院普外科. jianminqin@yahoo.com

收稿日期: 2021-02-04
修回日期: 2021-03-30
接受日期: 2021-04-23
在线出版日期: 2021-05-28

Conversion therapy for primary liver cancer: Indications and selective strategies

Jian-Min Qin

Jian-Min Qin, Department of General Surgery, the Third Hospital Affiliated to Naval Military Medical University, Shanghai 201805, China

Corresponding author: Jian-Min Qin, Professor, Chief Physician, Department of General Surgery, the Third Hospital Affiliated to Naval Military Medical University, No. 700 North Moyu Road, Shanghai 201805, China. jianminqin@yahoo.com

Received: 2021-02-04
Revised: 2021-03-30
Accepted: 2021-04-23
Published online: 2021-05-28

Abstract

Primary liver cancer has an insidious onset and no specific symptoms at early stage. Most patients are in the middle or advanced stage when diagnosed, and only 20%-40% of patients meet the criteria for radical resection. At present, surgical resection is still the main radical treatment for primary liver cancer, but factors such as liver function decompensation, too large tumor volume, too small future liver remnant, intrahepatic multiple metastasis, tumor thrombus invading the large vessels or bile duct, and distant metastasis limit the application of surgical resection or liver transplantation. In recent years, with the advances of basic research of primary liver cancer, the development of surgical techniques and equipment, as well as the development of new molecular targeted drugs and immunotherapy drugs, a part of unresectable patients with primary liver cancer can receive conversion therapy to improve liver function, minimize tumor volume, minimize or inactivate tumor thrombus, and increase the residual liver volume. Following conversion therapy, patients with primary liver cancer can undergo surgical resection or liver transplantation, which greatly improve the therapeutic efficacy and patient survival.

Key Words: Primary liver cancer; Conversion therapy; Indication; Strategy

Citation: Qin JM. Conversion therapy for primary liver cancer: Indications and selective strategies. Shijie Huaren Xiaohua Zazhi 2021; 29(10): 501-510
URL: https://www.wjgnet.com/1009-3079/full/v29/i10/501.htm
DOI: https://dx.doi.org/10.11569/wcjd.v29.i10.501

摘要

原发性肝癌发病隐匿, 早期无特异性症状, 多数患者确诊时已属中晚期, 符合根治性切除术的患者20%-40%. 目前外科切除仍是原发性肝癌主要根治性治疗手段, 但由于肝功能失代偿、肿瘤体积过大、剩余肝体积过小、肝内多发转移、癌栓侵及大血管或胆管、远处转移等因素限制手术切除或肝移植. 近年来, 随着原发性肝癌发生、发展机制研究的不断深

入, 外科技术和器械发展, 以及新的分子靶向药物、免疫治疗药物的研制, 使得一部分无法手术切除或肝移植的原发性肝癌患者经过转化治疗, 改善肝功能、缩小肿瘤体积、使脉管癌栓缩小或消失、促进剩余肝脏体积代偿性增大, 最终得以手术切除或肝移植, 极大提高了原发性肝癌治疗效果和患者生存期.

关键词: 原发性肝癌; 转化治疗; 指征; 策略

核心提要: 由于剩余肝体积过小、肝内多发转移、肿瘤侵及大血管或胆管、远处转移等因素限制原发性肝癌手术切除或肝移植.转化治疗使一部分无法手术的原发性肝癌患者最终实施手术切除或肝移植,提高了原发性肝癌疗效和患者生存期.

文献来源: 秦建民. 原发性肝癌转化治疗指征与选择策略. 世界华人消化杂志 2021; 29(10): 501-510
URL: https://www.wjgnet.com/1009-3079/full/v29/i10/501.htm
DOI: https://dx.doi.org/10.11569/wcjd.v29.i10.501

0 引言

原发性肝癌(primary liver cancer, PLC)是常见的肝脏恶性肿瘤, 其发病率和死亡率在全球癌症排名第7位和第3位, 其中, 肝细胞癌(hepatocellular carcinoma, HCC)占75%-85%, 肝内胆管细胞癌(intrahepatic cholangiocarcinoma, ICC)占10%-15%, 发病隐匿, 早期无特异性症状, 多数患者虽然确诊时已属中晚期, 随着外科技术的进步, 手术切除率显著提高20%-40%, 但术后复发率仍然较高为40%-80%[1,2]. 目前外科切除仍是PLC主要根治性治疗手段, 但由于肿瘤体积过大、剩余肝体积过小、肝内多发转移、癌栓侵及大血管或胆管、远处转移等因素限制手术切除或肝移植, 若强行肝切除或肝移植, 极大增加术后高复发、转移与肝衰竭发生风险[3]. 近年来, 随着PLC发生、发展机制研究的不断深入, 外科技术和器械发展, 以及新的分子靶向药物、免疫治疗药物的研制, 使得一部分无法手术切除或肝移植的肝脏肿瘤经过个体化的治疗得以手术切除或肝移植, 极大提高了PLC治疗效果和生存期. 转化治疗(conversion therapy)是因肝功能差(Child-Pugh C级)、肺转移、门静脉癌栓、肿瘤播散或多发、肿瘤巨大等因素不能行根治性手术切除或肝移植, 但具有潜在手术切除或肝移植的PLC患者, 经积极内科治疗(保肝、分子靶向、免疫、化疗等)联合局部介入、放疗等治疗后, 使患者肝功能转为Child-Pugh A或B级, 控制肿瘤进展, 降低临床分期, 从而获得手术切除或肝移植机会[4,5]. 转化治疗不同于术前新辅助治疗, 前者治疗的目的在于改善肝功能、缩小肿瘤体积、促使脉管癌栓缩小或消失、促进剩余肝脏体积代偿性增大, 为PLC患者创造手术切除或肝移植机会. 后者是指有手术指征的PLC患者, 经术前治疗后减小肿瘤, 增加R0切除率, 降低远处转移和复发率, 提高PLC患者的生存. 本文结合相关文献, 探讨PLC转化治疗指征与选择策略.

1 原发性肝癌转化治疗指征

依据患者肝功能、肿瘤体积、脉管癌栓、未受累肝脏体积等情况, 确定PLC转化治疗的指征[3]: (1)肝功能损害, Child-Pugh C级; (2)肿瘤巨大, 根治性切除后剩余肝体积不足(无肝硬化者, 剩余肝体积/标准肝体积＜20%-30%, 合并肝硬化、重度脂肪肝和化疗或梗阻性黄疸引起的肝损伤者, 剩余肝体积/标准肝体积＜40%); (3)肿瘤合并大血管癌栓, 如门静脉主干或一级分支癌栓、合并下腔静脉癌栓, 难以完全取净癌栓, 具有肝内外播散风险; (4)肿瘤多发, 分布在多个肝叶, 难以根治性切除; (5)肿瘤合并肺、局部淋巴结多发转移, 无全身广泛肿瘤转移; (6)肿瘤侵犯3支肝静脉或左右门静脉主干, 难以完成肿瘤根治性切除. 因此原发性肝癌转化治疗期间, 需要采用超声、超声造影、增强CT和/MRI、PET-CT/MRI等合适的影像技术, 结合血肝功能、肿瘤标记物(AFP、DCP、CA19-9)、病理学检查等进行综合评估, 评价ECOG评分、剩余肝体积、肿瘤大小、数目、坏死、癌栓大小与分布、血肿瘤标记物水平等, 监测肿瘤对转化治疗的反应率, 适时评估肿瘤临床分期及转化治疗效果.

转化治疗后手术切除或肝移植指征[6-8]: (1)无肝硬化背景肝病患者功能性剩余肝体积≥标准肝体积的35%, 具有肝硬化背景的患者功能性剩余肝体积≥标准肝体积的45% , 肿瘤切缘＞2 cm; (2)肝功能储备吲哚菁绿15 min滞留率≤20% ; (3)肝功能Child-Pugh分级为A/B级; (4)ECOG评分为0-1分; (5)MRI与PET-CT提示大血管内癌栓失活, 累积3支肝静脉或左右门静脉主干的肿瘤退缩, 能够完成肿瘤根治性切除; (6)符合米兰或UCSF标准. 原发性肝癌转化治疗后增加机体接触肿瘤新抗原的时间可能会导致通过免疫治疗激活的T细胞重新进入功能障碍状态, 从而增加肿瘤再次进展的可能[6,9], 因此不可手术切除或肝移植的原发性肝癌经转化治疗达到部分或完全缓解符合上述手术指征时均需适时进行手术切除或肝移植治疗, 以免错过最佳的手术治疗时机. 成功转化治疗的最终目标是降低肿瘤分期, 增加剩余肝体积, 提高挽救性手术率, 但不增加手术并发症、

死亡率.

2 原发性肝癌转化治疗策略

原发性肝癌转化治疗的目的是使肝内、外部分肿瘤消失、巨大肿瘤体积缩小、静脉或胆管癌栓缩小、消失或灭活、未受肿瘤累及的肝脏代偿性增大, 增加患者手术切除或肝移植机会. 目前转化治疗的方法包括: (1)肝功能维护; (2)未受累肝脏体积代偿性增大(联合肝脏分割和门静脉结扎的分阶段肝切除术、门静脉栓塞术等); (3)肿瘤体积缩小、脉管癌栓缩小或灭活(包括介入治疗、放疗、分子靶向药物、免疫治疗等), 转化治疗方法的选择取决于患者肝功能、肝脏肿瘤的位置、大小、数目、血供、血管或胆管癌栓分布、未受累肝脏体积等情况, 制定合适的转化治疗方案.

2.1 改善肝功能 HCC患者多数合并乙型或/和丙型肝炎病毒感染, 或长期饮酒引起肝硬变, ICC患者多合并肝内胆管结石、肿瘤累及胆管致胆汁淤积引起肝功能损害, 均导致肝功能失代偿(Child-Pugh评分C级), 使患者出现低蛋白血症、凝血功能紊乱、高胆红素血症、骨髓造血功能障碍(贫血、中性粒细胞减少、血小板减少等), 不能耐受手术切除、介入治疗及放疗等治疗. 因此维护和改善患者肝功能, 是原发性肝癌转化治疗的重要一环, 需要戒烟酒, 停止接触肝毒性药物, 给予高热量、高蛋白质、低脂肪饮食, 静脉补充葡萄糖、维生素、氨基酸等, 肝内胆汁淤积给予熊去氧胆酸, 肝细胞炎症应用甘草酸二胺、多烯磷脂酰胆碱等保肝药物. 乙肝病毒相关肝癌患者即使HBV-DNA浓度＜2×10^3/L, 处于低水平状态, 亦应给予抗病毒治疗, 若合并TBil或ALT升高, 同时给予保肝和利胆治疗, 改善肝功能, 以减少术后肝功能失代偿和肿瘤复发[10]. 胆管梗阻患者血总胆红素＞200 μmol/L需要及时给予胆汁内/外引流, 严重低蛋白血症者给予输新鲜血浆或人血白蛋白, 辅助肝细胞修复和再生, 补充维生素K1, 纠正凝血功能紊乱; 合并食管胃底静脉曲张者口服卡维地洛降门静脉压力, 腹腔积液引起腹内压增高者适当引流腹水、利尿剂治疗. 经过内科转化治疗适时评估肝功能、肝脏储备功能, 一旦肝功能达到Child-Pugh评分A或B级, 及时行手术切除、介入治疗或放疗等治疗.

2.2 增大剩余肝体积的转化治疗 许多原发性肝癌患者因肿瘤巨大毗邻重要脉管结构需行大范围肝切除, 导致剩余肝脏体积(future 1iver remnant, FLR)不足而无法行一期根治性切除, FLR不足是影响肝切除术后肝功能衰竭和围手术期死亡的决定性因素[11]. 保证足够的FLR是决定肝肿瘤切除手术的关键因素之一, 目前主要用于增大FLR体积方法包括联合肝脏分割和门静脉结扎的分阶段肝切除术(associating liver partition and portal vein ligation for staged hepatectomy, ALPPS)和门静脉栓塞术(portal vein embolization, PVE), ALPPS术通过阻断患侧肝脏的门静脉主干及健侧肝脏来源的交通支, 使健侧肝脏获得足够的门静脉血流和营养物质, 术后1-2 wk左右诱导FLR增生率高达47%-192%, 日增生体积高于PVE(4.4 mL/d±4.8 mL/d *vs* 3.66 mL/d±2.2 mL/d), 且两期手术间隔时间短(术后2 wk左右), 能最大程度减少肿瘤进展风险, 肿瘤切除率达95%-100%, 高于PVE(66%)[12-14]. Wang等[15]计划实施ALPPS治疗初期不可切除的原发性肝癌, 第一期手术使残余肝体积增加了56.8%, 82%患者成功完成了第二期手术, 1年、3年总生存率分别为64.2%和60.2%, 但ALPPS属于创伤较大手术, 且短时间内需要进行两次手术, 术后胆漏发生率为20%-24%, 术后感染发生率为20%-23% , 术后肝功能衰竭发生率高达15%-22%[16,17], 虽然目前有一些改良的ALPPS技术(如绕肝提拉带、射频或微波辅助ALPPS, 腹腔镜或机器人辅助ALPPS等)在一定程度上减少了ALPPS术创伤和围手术期并发症[18-21], 但对肝癌患者仍然带来较大的创伤, 因此应严格限制原发性肝癌患者ALPPS术应用指征: 年龄＜60岁, 肝功能正常(Child-Pugh A级, ICG-R15＜10%), FLR不足(正常肝脏, FLR/SLV＜30%; 伴有慢性肝病和肝损伤, FLR/SLV＜40%), 一般状态良好, 无严重肝硬化、脂肪肝和门静脉高压症[22-24], 在实施ALPPS时, 如果二期术前患者MELD评分＞10分者建议延迟第二步手术[25], 加强围手术期机体脏器功能维护, 积极处理并发症, 降低围手术期死亡率.

PVE技术采用经皮穿刺应用钢圈或a-氰基丙烯酸正丁酯(N-butyl a-cyanoacrylate, NBCA)胶等栓塞剂栓塞患侧门静脉, 诱导健侧肝脏组织增生, PVE治疗4 周后患者肝脏体积总体增加10%-12%, 二期肝切除成功率为60%-80%, 并发症发生率约10%-20%[26-28]. 与ALPPS相比, PVE后栓塞对侧肝脏增生时间相对较长(4-6 wk), 在此期间20%以上患者因肿瘤进展或FLR增生体积不足而失去手术机会[29,30]. 为克服PVE缺点, Peng等[31]采用NBCA胶栓塞患侧门静脉及末梢分支, 使其兼具ALPPS肝脏快速增生和PVE的微创效应, 二期肝切除率提高至84%左右, 平均等待时间缩短至2-3 wk. PVE联合肝动脉栓塞化疗(transarterial chemoembolization, TACE)能进一步促进FLR增生率(12%), 显著高于单用PVE(8%), 能够更好地控制肿瘤进展, 提高肿瘤切除率(97%), 显著提高5年存活率(43%-72%), 降低5年肿瘤复发率(37%-61%)[32,33]. PVE联合肝静脉栓塞(hepatic vein embolization, HVE)显著诱导FLR增生(28.9%), 优于单独PVE增生率(13.3%), 3年存活率为45.1%[28,34]. 与ALPPS相比, PVE具有较小

创伤, 但并非适合于任何原发性肝癌患者, 对于栓塞侧门静脉有癌栓, 肿瘤广泛转移, 合并严重的门静脉高压症和凝血功能障碍等肝癌患者禁忌[35]. 当剩余肝脏体积＜30%时宜行ALPPS, 当剩余肝脏体积＞30%且＜40%时宜行PVE[36]. 因此对于FLR不足的原发性肝癌患者, 应结合患者年龄、肿瘤、机体脏器功能等情况, 选择合适的增加FLR体积的方法, 适时进行影像学评估, 及时进行肝肿瘤切除.

2.3 缩小肿瘤体积、灭活大血管或胆管癌栓的转化治疗 对于肿瘤负荷大或大血管、胆管癌栓无法根治性切除/肝移植的PLC患者, 如果不进行积极地治疗, 患者预后极差, 晚期HCC患者门静脉癌栓(portal vein tumor thrombus, PVTT)发生率高达44%-62.2%, 胆管癌栓为1.2%-9%[37,38], 合并PVTT, 中位生存时间为2-4 mo, 合并肝静脉或下腔静脉癌栓, 自然病程1-8 mo, 合并胆管癌栓, 中位生存4.3 mo[39-41]. 因此对于此类肝癌患者需要采取积极的治疗方法, 争取手术切除或肝移植机会, 延长患者生存期.

2.3.1 全身化疗: 不可手术切除的晚期HCC患者应用FOLFOX4方案全身化疗, 与单用阿霉素相比, 患者中位无进展生存期(median progression-free survival , mPFS)分别为2.93 mo和1.77 mo, 客观反应率(objective response rate, ORR)分别为8.15%和2.67%, 总生存期(overall survival, OS)分别为6.47 mo和4.9 mo[42]. Kaseb等[43]对84例不可切除性HCC患者采用顺铂、阿霉素、5-氟尿嘧啶和IFNα-2b联合治疗方案, 其中33%患者转化治疗后行根治性肝肿瘤切除. 雷替曲塞联合奥沙利铂方案较FOLFOX4方案对晚期原发性肝癌的疾病控制率(disease control rate, DCR)显著提高(56.76% *vs* 40.54%)[44]. Zaanan等[45]采用GEMOX化疗方案(吉西他滨联合奥沙利铂)治疗进展期HCC, 8.5%患者成功降期后行肝肿瘤根治性切除. Le等[46]采用吉西他滨联合奥沙利铂治疗74例不可切除的ICC, 6个疗程后39例(53%)患者成功转化手术切除. 表明随着高效化疗药物的研制和联合临床应用, 在晚期原发性肝癌转化治疗中发挥重要的治疗作用.

2.3.2 介入治疗: TACE通过破坏肿瘤血供从而诱导肿瘤缺血, 化疗药物通过肿瘤血管直接注入肿瘤组织, 形成肿瘤组织局部高浓度药物环境, 碘油栓塞肿瘤滋养末梢血管, 协同抑制肿瘤生长, 已成为进展期肝癌治疗的主要方法之一. 但由于碘油清除过快, 达不到长久栓塞的目的, 同时药物在碘化油中迅速释放, 不能在肿瘤组织内长时间保持较高浓度, 导致TACE术后肿瘤完全坏死比例相对较低(1.7%-6.6%)[47]. Fan等[48]采用TACE治疗不可手术切除HCC患者转化为肝脏肿瘤切除率为18.1%. 药微球能够吸附化疗药物, 使化疗药物持续地作用于肿瘤内部, 而且微球在体内不降解, 能长久栓塞肿瘤血管, 进一步提高TACE的疗效, 王浩等[49]术前应用携载表柔比星药物洗脱微球肝动脉栓塞治疗进展期肝癌, 76.7%患者降期至符合UCSF标准, 53.3%患者降期至符合米兰标准, 成功降期后进行了肝移植. Affonso等[50]术前采用载药微球肝动脉栓塞治疗超过米兰标准肝癌患者, 34.4%患者成功降期后行肝移植, 与符合米兰标准的肝癌患者相比, 肝移植术后OS(73.5% *vs* 72.3%)和无瘤生存率(62.1% *vs* 74.8%)无显著性差异. TACE治疗的局限性在于栓塞术后肿瘤微环境改变, 缺氧诱导因子上调, 使血管内皮细胞和血小板源生长因子增加, 诱导肿瘤新生血管的形成, 导致肿瘤生长、肝外转移等不良结果而影响疗效[51,52]. 因此TACE联合酪氨酸激酶受体抑制剂索拉非尼能够抑制肿瘤细胞增殖和血管新生, 14.8%患者成功转化实施肝肿瘤切除, 术后1、2、3年的无瘤存活率分别为76.2% 、52.4% 、43.6%[53]. 肝动脉灌注化疗(hepatic arterial infusion chemotherapy, HAIC)与传统的TACE不同, HAIC以肿瘤滋养动脉持续灌注以奥沙利铂为主的化疗药物(如FOLFOX方案、GEMOX方案等)48-72 h, 使局部肿瘤组织持续维持高浓度化疗药物, 提高化疗药物杀灭肿瘤效果. Lee等[54]应用HAIC治疗进展期HCC患者, 11.7%患者转化后行肝肿瘤切除, 中位OS为(37±6.6) h. HAIC 联合索拉非尼治疗合并有门静脉分支或主干癌栓的HCC患者, 6.48%患者转化成外科手术切除, 优于单用索拉非尼治疗(0.4%), 且联合治疗患者中位OS 为13.37 mo, PFS为7.03 mo, 优于单纯索拉非尼治疗中位OS(7.13 mo), PFS为2.6 mo[55]. HAIC联合三维适形放疗治疗HCC合并门静脉癌栓患者, 有效率为61.5%, 17.3%不能手术切除的HCC患者转化为手术切除, 术后1、2、3年OS分别为100%、100%、71%, 优于非手术患者(50%、20%、18%)[56]. Chong等[57]采用放疗联合肝动脉灌注5-氟尿嘧啶治疗HCC合并门静脉一级分支或二级分支癌栓的患者, 26.5%患者降期转化后再手术切除, 术后中位生存期显著优于直接手术的患者(62 mo *vs* 15 mo). Massani等[58]应用HAIC(5-FU+奥沙利铂)治疗11例不可切除ICC患者, 4-12个周期(平均8个周期)后3例(27.3%)进行肝肿瘤切除, 术后病理证实70%肿瘤发生坏死. 经肝动脉放疗栓塞(transarterial radioembolization, TARE)是将载有发射β射线的钇-90(^{90}Y)玻璃微球选择性注入肝动脉, 放射性微球因无法通过肿瘤的毛细血管床而聚集在肿瘤组织, 其发出的β射线对靶肿瘤具有细胞毒性作用, 由于β射线在肝组织内的穿透能力只有2.5 mm, 在杀伤肿瘤细胞的同时对正常肝脏组织损伤较小[59]. TARE后57% HCC患者肿瘤缩小, 因门静脉癌栓对放疗较为敏感, 癌栓内的癌细胞能被β射线迅速杀灭, 即

使术中癌栓内癌细胞脱落到正常肝脏, 由于癌细胞活性降低, 难以增殖存活, 对门静脉癌栓具有显著的治疗作用[60]. Lau等[61]采用^{90}Y微球联合PIAF化疗方案(顺铂+密拓蒽醌+5-氟尿嘧啶+干扰素)治疗不能切除HCC, 17.8%患者成功降期接受手术切除, 5年生存率为57%. 不可切除的ICC, 10.8%-21.6%患者经^{90}Y 微球TARE转化治疗后接受肝肿瘤切除[62,63]. 由于放疗对肿瘤细胞杀伤作用的滞后性, TARE治疗3-6 mo后肿瘤坏死范围仍会增加, 因此中晚期原发性肝癌患者行TARE后肿瘤对TARE的应答率高于TACE(61% *vs* 37%), TARE治疗后降期接受手术成功率高于TACE(58% *vs* 31%)[64]. Tabone等[65]应用^{90}Y微球TARE治疗24例合并门静脉癌栓不可手术HCC患者, 5例(20%)转化后接受肝肿瘤切除, 术后中位OS为30个月. Riby等[66]应用^{90}Y微球TARE治疗19例不可切除ICC, 100%成功降期接受肝肿瘤切除, 术后中位OS与I期手术切除ICC相似(32.3 mo *vs* 45.9 mo). Labgaa等[67]应用TARE治疗319例不能手术切除HCC, 10.03%患者降期成功后行根治性手术, 其中22例行肝移植术, 10例行肝肿瘤切除, 术后中位OS超过41.5 mo. 临床研究表明针对不同患者选择TACE、HAIC、TARE等局部介入治疗是进展期原发性肝癌降期转化治疗的重要治疗方法之一.

2.3.3 *放疗*: 三维适形放疗采用精准定位肿瘤靶区发射X射线使癌细胞核的DNA 链发生断裂, 抑制癌细胞增殖分裂、杀灭癌细胞, 不能手术切除的HCC患者经体外放疗后, 23%患者转化为二期手术切除[68]. Assalino等[69]对侵犯大血管的HCC进行治疗, 局部放疗能够控制肿瘤负荷、缩小肿瘤体积, 66.7%患者经局部放疗后血管浸润完全消退, 成功接受肝移植术. 立体定向放射治疗(stereotactic body radiation therapy, SBRT)治疗HCC合并PVTT侵犯门静脉右支、左支或主干, 12例患者获得PVTT降期(PVTT从程式分型的Ⅲ型降至Ⅱ型或从Ⅱ型降至Ⅰ型), 新辅助放疗联合肝肿瘤切除术后1年、1.5年和2年的OS分别为75.2%、43.9%和27.4% , 优于单纯手术切除43.1%、16.7%和9.4%[70]. Yeh等[71]回顾性分析106例合并PVTT的HCC患者接受调强放疗, 其中癌栓位于门静脉主干30例次, 门静脉右支71例次, 门静脉左支37例次, 12例(11.3%)患者成功降期接受手术切除, 2年总生存率为66.7%, 中位OS为30 mo, 显著优于未能手术切除的患者. 提示门静脉癌栓对放疗较为敏感, 癌栓内癌细胞能迅速被X射线杀伤或灭活, 即使术中癌栓内癌细胞脱落到剩余肝脏, 由于癌细胞活性降低使其难以增殖存活, 降低了术后复发风险. Shui等[72]对门静脉广泛癌栓无法手术的HCC患者行SBRT治疗, 5.7%患者成功降期转化接受肝肿瘤切除. 采用放疗联合肝动脉灌注5-氟尿嘧啶化疗治疗合并PVTT的HCC, 放疗靶区包含门静脉癌栓和肝脏肿瘤, 13.2%患者成功降期接受肝肿瘤切除, 术后5年生存率为49.6%, 未切除患者仅为9.8%[73]. TACE联合放疗不可切除HCC患者, 11.1%患者成功转化接受肝肿瘤切除[74]. Sumiyoshi等[75]应用调强放疗联合S-1治疗7例不可手术的ICC患者, 5例患者(71.4%)进行肝肿瘤切除, 术后生存6-58 mo(平均28.8 mo). 肝脏肿瘤及血管/胆管癌栓进行局部放射治疗, 不仅能够控制肿瘤生长, 而且能够缩小或灭活癌栓, 提高进展期原发性肝癌患者的手术切除率或肝移植机会, 尤其联合介入治疗、分子靶向药物等方法能够显著提高转化治疗效率.

2.3.4 *分子靶向药物治疗*: Ras/Raf/Mek/ERK、Pl3K/Akt/雷帕霉素靶蛋白(mTOR)等信号通路相关分子、血管内皮生长因子受体(vascular endothelial growth factor receptor, VEGFR)、血小板源性生长因子受体(platelet-derived growth factor receptor, PDGFR)和表皮生长因子受体(epithelial growth factor receptor, EGFR)等在肝癌组织中过表达, 参与肿瘤细胞增殖、侵袭, 在原发性肝癌发生、发展过程中具有重要生物学作用, 亦是原发性肝癌分子靶向药物治疗的分子基础[76,77]. 分子靶向药物是针对肿瘤的特异性分子靶点设计的有针对性地抗肿瘤治疗, 具有特异性强、正常组织细胞损伤小等优点, 近年来研制的分子靶向药物(如索拉非尼、乐伐替尼、瑞戈非尼、卡博替、雷莫芦单抗等)在原发性肝癌治疗中发挥重要的作用, 并取得了较好的疗效. 研究表明成纤维细胞生长受体4(fibroblast growth factor receptor 4, FGF4)是索拉非尼治疗反应的一个新的候选生物学标志物, FGF4阳性的HCC患者应用索拉非尼治疗具有显著的病理反应, 治疗前肿瘤FGFR4水平是索拉非尼、仑伐替尼等分子靶向药物治疗反应的预测因子[78,79]. Yoshimoto等[78]应用索拉非尼治疗2例FGFR4阳性不可切除HCC患者, 治疗3 mo后, 成功实施肝肿瘤切除, 术后随访4.5年无肿瘤复发. Barbier等[80]应用索拉非尼治疗2例HCC合并PVTT患者经9 mo转化治疗后成功行肝肿瘤切除. Tanaka等[81]应用仑伐替尼治疗3例不可切除的HCC, 6 mo后2例行肝肿瘤切除术, 1例行微波消融肝肿瘤治疗, 术后随访10 mo未见肿瘤复发. 单一分子靶向药物治疗进展期HCC的ORR较低, 索拉非尼为2%, 仑伐替尼为24.1%[82,83], 因此需要与其它治疗方法(介入治疗、化疗、放疗等)结合, 以提高转化治疗效果. Vagefi等[84]应用索拉非尼联合局部肿瘤射频消融治疗超过米兰标准的HCC患者, 转化治疗后评估患者符合米兰标准成功进行了肝移植术. Gruenberger等[85]应用靶向EGFR的西妥昔单抗联合吉西他滨和奥沙利铂三药联合治疗不能切除的30例胆管癌患者, 5例ICC患者(16.7%)降期后接受手术切除肝肿瘤, 中位PFS为21.2个月. 分子靶向药物

在进展期原发性肝癌治疗中发挥重要的作用, 依据高通量测序技术等检测肝癌组织和血液基因表达变化, 选择合适的分子靶向药物, 尤其联合介入治疗、放疗、化疗等治疗方法, 具有协同增效作用.

2.3.5 *免疫治疗*: 免疫功能障碍是肝癌发生和转移的重要因素, 免疫治疗通过调节特异性免疫反应抑制或杀死肿瘤细胞, 打破免疫耐受, 增强机体对肿瘤的免疫排斥反应, 延缓肿瘤进展, 降低肿瘤复发和转移的能力. 目前常用的免疫治疗方法如肿瘤疫苗(致敏树突状细胞疫苗和多肽疫苗)、过继性细胞疗法(NK、CIK、CTL、CAR-T细胞等)、免疫检查点抑制剂(immune checkpoint inhibitors, ICIs), CTLA-4抑制剂、PD-1、 PD-L1抑制剂等在肿瘤部位重新激活T细胞或抑制特异性T细胞的活化, 从而抑制肿瘤生长[86]. PD-1抑制剂卡瑞利珠单抗治疗进展期HCC, 中位OS为12.5 mo, ORR为13.8%, 6 mo总生存率为74.4%[87]. 单独使用免疫检查点抑制剂的有效率仅为10%-30%, 因此需要与其它治疗方法(介入治疗、放疗、化疗、分子靶向药物等)联合, 达到协同增效的作用[88]. 分子靶向药物(贝伐单抗)和PD-1抑制剂(阿替利珠单抗)联合应用治疗HCC应答率约为30%[89]. 纳武单抗(nivolumab, PD-1抑制剂)联合伊匹木单抗(ipilimumab, CTLA-4抑制剂)治疗不可手术切除的HCC患者, ORR为80%, DCR为100%[90]. Sun等[91]采用不同酪氨酸激酶抑制剂(阿帕替尼、仑伐替尼)加抗PD-1抗体(帕博利珠单抗、信迪利单抗等)治疗不可手术的HCC患者, 18.3%患者转化为手术切除切除, 5例术后病理证实完全缓解. 免疫治疗尤其免疫检查点抑制剂的研制和临床应用, 为进展期原发性肝癌治疗带来新的曙光, 依据肝癌组织、血液中肿瘤突变负荷(tumor mutation burden, TMB)、微卫星不稳定(microsatellite instability, MSI)、错配修复基因(mismatch repair, MMR)、γ-干扰素、肿瘤浸润淋巴细胞、PD-1和/PD-L1等表达变化, 选择不同免疫治疗方法, 且与分子靶向药物、放疗、化疗、介入治疗等方法的联合应用, 在原发性肝癌转化治疗中发挥越来越重要的作用.

3 原发性肝癌转化治疗手术切除或肝移植术后肿瘤复发与转移的预防

原发性肝癌转化治疗能够缩小肿瘤, 但不能完全杀灭肿瘤细胞, 转化治疗后行手术切除肝肿瘤或肝移植, 术后肿瘤复发率为40%-80%[92,93]. 肿瘤直径>5 cm、多发肿瘤结节无包膜、门静脉/肝静脉癌栓和微血管侵犯(microvascular invasion, MVI)等高危因素是肝癌患者术后肿瘤复发、转移的重要独立危险因素[94]. Wang等[95-97]在肝癌术后应用索拉非尼, 结果发现应用索拉非尼的HCC患者术后复发率明显低于对照组(29.4% *vs* 70.7%), 多因素分析提示索拉非尼是术后肿瘤复发的独立影响因素, 术后应用索拉非尼能够减少肿瘤复发, 显著改善患者PFS及OS. 对超越米兰标准HCC患者肝移植术后应用索拉非尼预后优于吉西他滨[98]. 对于具有高危因素的原发性肝癌患者术后积极序贯TACE治疗, 能够有效降低肿瘤复发率, 提高患者术后OS和无瘤生存率[99]. TACE和放疗对肝癌患者免疫系统部分或完全抑制, 促使HBV大量复制再激活, 再激活率达20%-30%, 尤其血清HBV DNA>1.0×10^4拷贝/mL时, 增加HBV再激活和肿瘤术后复发风险[100,101], 因此转化治疗肝肿瘤切除或肝移植术后需要继续抗乙肝病毒治疗, 降低术后肿瘤复发率. 分子靶向药物、免疫治疗在预防原发性肝癌手术切除或肝移植术后肿瘤复发与转移中作用报道较少, 仍需要多中心、大样本的临床研究, 相信随着基础研究和临床工作的不断深入, 筛选有效的分子标志物作为评估预防复发与转移治疗的预测因子, 未来在预防肝癌术后复发与转移中将发挥重要的生物学作用.

4 结论

转化治疗为部分术前评估不可切除原发性肝癌患者创造了手术切除或肝移植的机会, 而且成功转化并实现手术治疗的肝癌患者与无转化手术切除的患者术后5年生存率(24.9%-57%和30%-60%)相近[48,102]. 但转化治疗仅使8%-18%术前评估不切除肝癌患者成功实现转化接受手术切除[61], 因此根据原发性肝癌患者具体情况, 由放射科、放疗科、病理科、肿瘤内科、肿瘤外科等科室组成多学科诊疗团队(multidisciplinary team, MDT), 制定个体化的联合、序贯转化治疗方案, 以达到最佳的治疗效果. 随着新的化疗药物、分子靶向药物和免疫治疗药物的研制, 以及不同治疗方案的临床实践, 使原发性肝癌转化治疗适应证、方案得到更好的优化, 术后预防肿瘤复发与转移的方案更加完善, 不仅能够显著提高转化治疗后原发性肝癌手术切除或肝移植率, 而且延长患者长期生存期, 改善患者预后, 造福于更多的原发性肝癌患者.

5 参考文献

1 Ransome E, Tong L, Espinosa J, Chou J, Somnay V, Munene G. Trends in surgery and disparities in receipt of surgery for intrahepatic cholangiocarcinoma in the US: 2005-2014. *J Gastrointest Oncol* 2019; 10: 339-347 [PMID: 31032103 DOI: 10.21037/jgo.2018.12.07]

2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

3 Khan AS, Garcia-Aroz S, Ansari MA, Atiq SM, Senter-Zapata

M, Fowler K, Doyle MB, Chapman WC. Assessment and optimization of liver volume before major hepatic resection: Current guidelines and a narrative review. *Int J Surg* 2018; 52: 74-81 [PMID: 29425829 DOI: 10.1016/j.ijsu.2018.01.042]
4 赖俊雄, 刘晓欣, 刘允怡. 原发性肝癌降期手术新进展. 临床外科杂志 2015; 23: 5-7 [DOI: 10.3969/j.issn.1005-6483]
5 中国医师协会器官移植医师分会, 中华医学会器官移植学分会. 中国肝癌肝移植临床实践指南(2018版). 临床肝胆病杂志 2019; 35: 275-280 [DOI: 10.3969/j.issn.1001-5256.2019.02.008]
6 Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, Gores G. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2016; 2: 16018 [PMID: 27158749 DOI: 10.1038/nrdp.2016.18]
7 Bruix J , Sherman M , American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma:an update. *Hepatology* 2011;53:1020-1022.DOI:10.1002/hep.24199.
8 王浩, 陈光, 高海军, 伊正甲, 温连芳, 王鹏辉, 杨颐馨, 张莉, 丁青婵. 载药微球介入栓塞治疗在肝癌肝移植术前降期治疗中的应用. 中华普通外科杂志 2019; 34: 410-412 [DOI: 10.3760/cma.j.issn.1007-631X.2019.05.009]
9 O'Donnell JS, Hoefsmit EP, Smyth MJ, Blank CU, Teng MWL. The Promise of Neoadjuvant Immunotherapy and Surgery for Cancer Treatment. *Clin Cancer Res* 2019; 25: 5743-5751 [PMID: 31040150 DOI: 10.]
10 Huang G, Li PP, Lau WY, Pan ZY, Zhao LH, Wang ZG, Wang MC, Zhou WP. Antiviral Therapy Reduces Hepatocellular Carcinoma Recurrence in Patients With Low HBV-DNA Levels: A Randomized Controlled Trial. *Ann Surg* 2018; 268: 943-954 [PMID: 29521740 DOI: 10.1097/SLA.0000000000002727]
11 Gruttadauria S, Vasta F, Minervini MI, Piazza T, Arcadipane A, Marcos A, Gridelli B. Significance of the effective remnant liver volume in major hepatectomies. *Am Surg* 2005; 71: 235-240 [PMID: 15869140]
12 Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, Fichtner-Feigl S, Lorf T, Goralcyk A, Hörbelt R, Kroemer A, Loss M, Rümmele P, Scherer MN, Padberg W, Königsrainer A, Lang H, Obed A, Schlitt HJ. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012; 255: 405-414 [PMID: 22330038 DOI: 10.1097/SLA.0b013e31824856f5]
13 Lau WY, Lai EC, Lau SH. Associating liver partition and portal vein ligation for staged hepatectomy: the current role and development. *Hepatobiliary Pancreat Dis Int* 2017; 16: 17-26 [PMID: 28119254 DOI: 10.1016/s1499-3872(16)60174-1]
14 Schadde E, Ardiles V, Slankamenac K, Tschuor C, Sergeant G, Amacker N, Baumgart J, Croome K, Hernandez-Alejandro R, Lang H, de Santibañes E, Clavien PA. ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. *World J Surg* 2014; 38: 1510-1519 [PMID: 24748319 DOI: 10.1007/s00268-014-2513-3]
15 Wang Z, Peng Y, Hu J, Wang X, Sun H, Sun J, Shi Y, Xiao Y, Ding Z, Yang X, Tang M, Tang Z, Wang J, Lau WY, Fan J, Zhou J. Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy for Unresectable Hepatitis B Virus-related Hepatocellular Carcinoma: A Single Center Study of 45 Patients. *Ann Surg* 2020; 271: 534-541 [PMID: 29995681]
16 Sala S, Ardiles V, Ulla M, Alvarez F, Pekolj J, de Santibañes E. Our initial experience with ALPPS technique: encouraging results. *Updates Surg* 2012; 64: 167-172 [PMID: 22903531 DOI: 10.1007/s13304-012-0175-y]
17 Nadalin S, Capobianco I, Li J, Girotti P, Königsrainer I, Königsrainer A. Indications and limits for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Lessons Learned from 15 cases at a single centre. *Z Gastroenterol* 2014; 52: 35-42 [PMID: 24420797 DOI: 10.1055/s-0033-1356364]
18 Robles R, Parrilla P, López-Conesa A, Brusadin R, de la Peña J, Fuster M, García-López JA, Hernández E. Tourniquet modification of the associating liver partition and portal ligation for staged hepatectomy procedure. *Br J Surg* 2014; 101: 1129-34; discussion 1134 [PMID: 24947768 DOI: 10.1002/bjs.9547]
19 Gall TM, Sodergren MH, Frampton AE, Fan R, Spalding DR, Habib NA, Pai M, Jackson JE, Tait P, Jiao LR. Radio-frequency-assisted Liver Partition with Portal vein ligation (RALPP) for liver regeneration. *Ann Surg* 2015; 261: e45-e46 [PMID: 24670841 DOI: 10.1097/SLA.0000000000000607]
20 Hong de F, Zhang YB, Peng SY, Huang DS. Percutaneous Microwave Ablation Liver Partition and Portal Vein Embolization for Rapid Liver Regeneration: A Minimally Invasive First Step of ALPPS for Hepatocellular Carcinoma. *Ann Surg* 2016; 264: e1-e2 [PMID: 26967629 DOI: 10.1097/SLA.0000000000001707]
21 Vicente E, Quijano Y, Ielpo B, Fabra I. First ALPPS procedure using a total robotic approach. *Surg Oncol* 2016; 25: 457 [PMID: 26856770 DOI: 10.1016/j.suronc.2015.10.001]
22 Vennarecci G, Laurenzi A, Levi Sandri GB, Busi Rizzi E, Cristofaro M, Montalbano M, Piselli P, Andreoli A, D'Offizi G, Ettorre GM. The ALPPS procedure for hepatocellular carcinoma. *Eur J Surg Oncol* 2014; 40: 982-988 [PMID: 24767805 DOI: 10.1016/j.ejso.2014.04.002]
23 Sun Z, Tang W, Sakamoto Y, Hasegawa K, Kokudo N. A systematic review and meta-analysis of feasibility, safety and efficacy of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH). *Biosci Trends* 2015; 9: 284-288 [PMID: 26559020 DOI: 10.5582/bst.2015.01139]
24 Buac S, Schadde E, Schnitzbauer AA, Vogt K, Hernandez-Alejandro R. The many faces of ALPPS: surgical indications and techniques among surgeons collaborating in the international registry. *HPB (Oxford)* 2016; 18: 442-448 [PMID: 27154808 DOI: 10.1016/j.hpb.2016.01.547]
25 Oldhafer KJ, Stavrou GA, van Gulik TM; Core Group. ALPPS--Where Do We Stand, Where Do We Go?: Eight Recommendations From the First International Expert Meeting. *Ann Surg* 2016; 263: 839-841 [PMID: 26756771 DOI: 10.1097/SLA.0000000000001633]
26 Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, Habib N, Jiao LR. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg* 2008; 247: 49-57 [PMID: 18156923 DOI: 10.1097/SLA.0b013e31815f6e5b]
27 Aloia TA. Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy: Portal Vein Embolization Should Remain the Gold Standard. *JAMA Surg* 2015; 150: 927-928 [PMID: 26308668 DOI: 10.1001/jamasurg.2015.1646]
28 Piron L, Deshayes E, Escal L, Souche R, Herrero A, Pierredon-Foulongne MA, Assenat E, le Lam N, Quenet F, Guiu B. [Portal vein embolization: Present and future]. *Bull Cancer* 2017; 104: 407-416 [PMID: 28477870 DOI: 10.1016/j.bulcan.2017.03.009]
29 Vauthey JN, Dixon E, Abdalla EK, Helton WS, Pawlik TM, Taouli B, Brouquet A, Adams RB; American Hepato-Pancreato-Biliary Association; Society of Surgical Oncology; Society for Surgery of the Alimentary Tract. Pretreatment assessment of hepatocellular carcinoma: expert consensus statement. *HPB (Oxford)* 2010; 12: 289-299 [PMID: 20590901 DOI: 10.1111/j.1477-2574.2010.00181.x]
30 Shindoh J, Vauthey JN, Zimmitti G, Curley SA, Huang SY, Mahvash A, Gupta S, Wallace MJ, Aloia TA. Analysis of the efficacy of portal vein embolization for patients with extensive

liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. *J Am Coll Surg* 2013; 217: 126-33; discussion 133-4 [PMID: 23632095 DOI: 10.1016/j.jamcollsurg.2013.03.004]

31 Peng SY, Wang XA, Huang CY, Zhang YY, Li JT, Hong DF, Cai XJ. Evolution of associating liver partition and portal vein ligation for staged hepatectomy: Simpler, safer and equally effective methods. *World J Gastroenterol* 2017; 23: 4140-4145 [PMID: 28694654 DOI: 10.3748/wjg.v23.i23.4140]

32 Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. *Br J Surg* 2006; 93: 1091-1098 [PMID: 16779884 DOI: 10.1002/bjs.5341]

33 Piardi T, Memeo R, Renard Y, Ammendola M, Bruno O, Habersetzer F, Baumert T, Pessaux P, Sommacale D. Management of large hepatocellular carcinoma by sequential transarterial chemoembolization and portal vein embolization: a systematic review of the literature. *Minerva Chir* 2016; 71: 192-200 [PMID: 26883849]

34 Hwang S, Ha TY, Ko GY, Kwon DI, Song GW, Jung DH, Kim MH, Lee SK, Lee SG. Preoperative Sequential Portal and Hepatic Vein Embolization in Patients with Hepatobiliary Malignancy. *World J Surg* 2015; 39: 2990-2998 [PMID: 26304608 DOI: 10.1007/s00268-015-3194-2]

35 中国抗癌协会. 肝门部胆管癌规范化诊治专家共识(2015). 中华肝胆外科杂志 2015; 21: 505-511 [DOI: 10.3760/cma.j.issn.1007-8118.2015.08.001]

36 Chan A, Zhang WY, Chok K, Dai J, Ji R, Kwan C, Man N, Poon R, Lo CM. ALPPS Versus Portal Vein Embolization for Hepatitis-related Hepatocellular Carcinoma: A Changing Paradigm in Modulation of Future Liver Remnant Before Major Hepatectomy. *Ann Surg* 2019 [PMID: 31305284 DOI: 10.1097/SLA.0000000000003433]

37 Zhang ZM, Lai EC, Zhang C, Yu HW, Liu Z, Wan BJ, Liu LM, Tian ZH, Deng H, Sun QH, Chen XP. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. *Int J Surg* 2015; 20: 8-16 [PMID: 26026424 DOI: 10.1016/j.ijsu.2015.05.009]

38 Zhang R, Xu LB, Zeng H, Yu XH, Wang J, Liu C. Elevated expression of Bmi1 in hepatocellular carcinoma with bile duct tumor thrombi. *Hepatogastroenterology* 2013; 60: 2042-2047 [PMID: 24719948]

39 Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol* 2006; 12: 7561-7567 [PMID: 17171782 DOI: 10.3748/wjg.v12.i47.7561]

40 Wang Y, Yuan L, Ge RL, Sun Y, Wei G. Survival benefit of surgical treatment for hepatocellular carcinoma with inferior vena cava/right atrium tumor thrombus: results of a retrospective cohort study. *Ann Surg Oncol* 2013; 20: 914-922 [PMID: 22956071 DOI: 10.1245/s10434-012-2646-2]

41 Peng BG, Liang LJ, Li SQ, Zhou F, Hua YP, Luo SM. Surgical treatment of hepatocellular carcinoma with bile duct tumor thrombi. *World J Gastroenterol* 2005; 11: 3966-3969 [PMID: 15991304 DOI: 10.3748/wjg.v11.i25.3966]

42 Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, Yang TS, Bhudhisawasdi V, Kang WK, Zhou Y, Lee JH, Sun Y. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol* 2013; 31: 3501-3508 [PMID: 23980077 DOI: 10.1200/JCO.2012.44.5643]

43 Kaseb AO, Shindoh J, Patt YZ, Roses RE, Zimmitti G, Lozano RD, Hassan MM, Hassabo HM, Curley SA, Aloia TA, Abbruzzese JL, Vauthey JN. Modified cisplatin/interferon α-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma. *Cancer* 2013; 119: 3334-3342 [PMID: 23821538 DOI: 10.1002/cncr.28209]

44 鲁文权, 乐凌云, 田炳如, 邢士超, 邵宝儿, 林能明. 雷替曲塞注射剂联合奥沙利铂注射剂治疗晚期原发性肝癌的临床研究. 中国临床药理学杂志 2019; 35: 102-105 [DOI: 10.13699/j.cnki.1001-6821.2019.02.002]

45 Zaanan A, Williet N, Hebbar M, Dabakuyo TS, Fartoux L, Mansourbakht T, Dubreuil O, Rosmorduc O, Cattan S, Bonnetain F, Boige V, Taïeb J. Gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma: a large multicenter AGEO study. *J Hepatol* 2013; 58: 81-88 [PMID: 22989572 DOI: 10.1016/j.jhep.2012.09.006]

46 Le Roy B, Gelli M, Pittau G, Allard MA, Pereira B, Serji B, Vibert E, Castaing D, Adam R, Cherqui D, Sa Cunha A. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg* 2018; 105: 839–847 [PMID: 28858392 DOI: 10.1016/j.currproblcancer.2020.100614]

47 Allard MA, Sebagh M, Ruiz A, Guettier C, Paule B, Vibert E, Cunha AS, Cherqui D, Samuel D, Bismuth H, Castaing D, Adam R. Does pathological response after transarterial chemoembolization for hepatocellular carcinoma in cirrhotic patients with cirrhosis predict outcome after liver resection or transplantation? *J Hepatol* 2015; 63: 83-92 [PMID: 25646884 DOI: 10.1016/j.jhep.2015.01.023]

48 Fan J, Tang ZY, Yu YQ, Wu ZQ, Ma ZC, Zhou XD, Zhou J, Qiu SJ, Lu JZ. Improved survival with resection after transcatheter arterial chemoembolization (TACE) for unresectable hepatocellular carcinoma. *Dig Surg* 1998; 15: 674-678 [PMID: 9845635 DOI: 10.1159/000018676]

49 王浩, 陈光, 高海军, 温连芳, 王鹏辉, 杨颐馨, 张莉, 丁青婵.载药微球化疗栓塞在肝癌患者肝移植等待期间应用的疗效分析. 中华肝胆外科杂志 2019; 25: 246-248 [DOI: 10.3760/cma.j.issn.1007-8118.2019.04.002]

50 Affonso BB, Galastri FL, da Motta Leal Filho JM, Nasser F, Falsarella PM, Cavalcante RN, de Almeida MD, Felga GEG, Valle LGM, Wolosker N. Long-term outcomes of hepatocellular carcinoma that underwent chemoembolization for bridging or downstaging. *World J Gastroenterol* 2019; 25: 5687-5701 [PMID: 31602168 DOI: 10.3748/wjg.v25.i37.5687]

51 Lin WH, Yeh SH, Yeh KH, Chen KW, Cheng YW, Su TH, Jao P, Ni LC, Chen PJ, Chen DS. Hypoxia-activated cytotoxic agent tirapazamine enhances hepatic artery ligation-induced killing of liver tumor in HBx transgenic mice. *Proc Natl Acad Sci USA* 2016; 113: 11937-11942 [PMID: 27702890]

52 Huang KB, Fan WZ, Zhang YY, Wang Y, Cui W, Li JP. [Transarterial chemoembolization combined with cryoablation for unresectable large hepatocellular carcinoma: a controlled study]. *Zhonghua Yi Xue Za Zhi* 2016; 96: 2978-2982 [PMID: 27760658 DOI: 10.3760/cma.j.issn.0376-2491.2016.37.006]

53 李川江, 周杰. 肝细胞肝癌经肝动脉化疗栓塞联合索拉非尼降期后二期切除的初步报告. 腹部外科杂志 2017; 30: 295-301 [DOI: 10.3969/ j.issn.1003-5591.2017.04.015]

54 Lee BH, Lee DS, Cho CW, Yun SS. Role and limitation of neoadjuvant hepatic arterial infusion chemotherapy in advanced hepatocelluar carcinoma patients with Child-Pugh class A. *World J Surg Oncol* 2019; 17: 143 [PMID: 31416447 DOI: 10.1186/s12957-019-1685-6]

55 He M, Li Q, Zou R, Shen J, Fang W, Tan G, Zhou Y, Wu X, Xu L, Wei W, Le Y, Zhou Z, Zhao M, Guo Y, Guo R, Chen M, Shi M. Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin vs Sorafenib Alone for Hepatocellular Carcinoma With Portal Vein Invasion: A Randomized Clinical Trial. *JAMA Oncol* 2019; 5: 953-960 [PMID:

31070690 DOI: 10.1001/jamaoncol.2019.0250]
56 Hamaoka M, Kobayashi T, Kuroda S, Iwako H, Okimoto S, Kimura T, Aikata H, Nagata Y, Chayama K, Ohdan H. Hepatectomy after down-staging of hepatocellular carcinoma with portal vein tumor thrombus using chemoradiotherapy: A retrospective cohort study. *Int J Surg* 2017; 44: 223-228 [PMID: 28676383 DOI: 10.1016/j.ijsu.2017.06.082]
57 Chong JU, Choi GH, Han DH, Kim KS, Seong J, Han KH, Choi JS. Downstaging with Localized Concurrent Chemoradiotherapy Can Identify Optimal Surgical Candidates in Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Ann Surg Oncol* 2018; 25: 3308-3315 [PMID: 30083834 DOI: 10.1245/s10434-018-6653-9]
58 Massani M, Nistri C, Ruffolo C, Bonariol R, Pauletti B, Bonariol L, Caratozzolo E, Morana G, Bassi N. Intrahepatic chemotherapy for unresectable cholangiocarcinoma: review of literature and personal experience. *Updates Surg* 2015; 67: 389-400 [PMID: 26468142 DOI: 10.1007/s13304-015-0330-3]
59 Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, Mulcahy MF, Baker T, Abecassis M, Miller FH, Yaghmai V, Sato K, Desai K, Thornburg B, Benson AB, Rademaker A, Ganger D, Kulik L, Lewandowski RJ. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. *Gastroenterology* 2016; 151: 1155-1163.e2 [PMID: 27575820 DOI: 10.1053/j.gastro.2016.08.029]
60 Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, Lin XJ, Lau WY. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006; 243: 321-328 [PMID: 16495695 DOI: 10.1097/01.sla.0000201480.65519.b8]
61 Lau WY, Lai EC. Salvage surgery following downstaging of unresectable hepatocellular carcinoma--a strategy to increase resectability. *Ann Surg Oncol* 2007; 14: 3301-3309 [PMID: 17891443 DOI: 10.1245/s10434-007-9549-7]
62 Mouli S, Memon K, Baker T, Benson AB 3rd, Mulcahy MF, Gupta R, Ryu RK, Salem R, Lewandowski RJ. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. *J Vasc Interv Radiol* 2013; 24: 1227-1234 [PMID: 23602420 DOI: 10.1016/j.jvir.2013.02.031]
63 Rayar M, Sulpice L, Edeline J, Garin E, Levi Sandri GB, Meunier B, Boucher E, Boudjema K. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. *Ann Surg Oncol* 2015; 22: 3102-3108 [PMID: 25623598 DOI: 10.1245/s10434-014-4365-3]
64 Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, Ibrahim SM, Sato KT, Baker T, Miller FH, Omary R, Abecassis M, Salem R. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant* 2009; 9: 1920-1928 [PMID: 19552767 DOI: 10.1111/j.1600-6143.2009.02695.x]
65 Tabone M, Calvo A, Russolillo N, Langella S, Carbonatto P, Lo Tesoriere R, Richetta E, Pellerito R, Ferrero A. Downstaging unresectable hepatocellular carcinoma by radioembolization using 90-yttrium resin microspheres: a single center experience. *J Gastrointest Oncol* 2020; 11: 84-90 [PMID: 32175109 DOI: 10.21037/jgo.2019.06.01]
66 Riby D, Mazzotta AD, Bergeat D, Verdure L, Sulpice L, Bourien H, Lièvre A, Rolland Y, Garin E, Boudjema K, Edeline J. Downstaging with Radioembolization or Chemotherapy for Initially Unresectable Intrahepatic Cholangiocarcinoma. *Ann Surg Oncol* 2020; 27: 3729-3737 [PMID: 32472411 DOI: 10.1245/s10434-020-08486-7]
67 Labgaa I, Tabrizian P, Titano J, Kim E, Thung SN, Florman S, Schwartz M, Melloul E. Feasibility and safety of liver transplantation or resection after transarterial radioembolization with Yttrium-90 for unresectable hepatocellular carcinoma. *HPB (Oxford)* 2019; 21: 1497-1504 [PMID: 31005494 DOI: 10.1016/j.hpb.2019.03.360]
68 Zeng ZC, Tang ZY, Yang BH, Liu KD, Wu ZQ, Fan J, Qin LX, Sun HC, Zhou J, Jiang GL. Comparison between radioimmunotherapy and external beam radiation therapy for patients with hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging* 2002; 29: 1657-1668 [PMID: 12458401 DOI: 10.1007/s00259-002-0996-x]
69 Assalino M, Terraz S, Grat M, Lai Q, Vachharajani N, Gringeri E, Bongini MA, Kulik L, Tabrizian P, Agopian V, Mehta N, Brustia R, Vitali GC, Andres A, Berney T, Mazzaferro V, Compagnon P, Majno P, Cillo U, Chapman W, Zieniewicz K, Scatton O, Toso C. Liver transplantation for hepatocellular carcinoma after successful treatment of macrovascular invasion - a multi-center retrospective cohort study. *Transpl Int* 2020; 33: 567-575 [PMID: 31994238 DOI: 10.1111/tri.13586]
70 Wei X, Jiang Y, Zhang X, Feng S, Zhou B, Ye X, Xing H, Xu Y, Shi J, Guo W, Zhou D, Zhang H, Sun H, Huang C, Lu C, Zheng Y, Meng Y, Huang B, Cong W, Lau WY, Cheng S. Neoadjuvant Three-Dimensional Conformal Radiotherapy for Resectable Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Randomized, Open-Label, Multicenter Controlled Study. *J Clin Oncol* 2019; 37: 2141-2151 [PMID: 31283409 DOI: 10.1200/JCO.18.02184]
71 Yeh SA, Chen YS, Perng DS. The role of radiotherapy in the treatment of hepatocellular carcinoma with portal vein tumor thrombus. *J Radiat Res* 2015; 56: 325-331 [PMID: 25411553 DOI: 10.1093/jrr/rru104]
72 Shui Y, Yu W, Ren X, Guo Y, Xu J, Ma T, Zhang B, Wu J, Li Q, Hu Q, Shen L, Bai X, Liang T, Wei Q. Stereotactic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis. *Radiat Oncol* 2018; 13: 188 [PMID: 30253783 DOI: 10.1186/s13014-018-1136-5]
73 Lee HS, Choi GH, Choi JS, Kim KS, Han KH, Seong J, Ahn SH, Kim DY, Park JY, Kim SU, Kim BK. Surgical resection after down-staging of locally advanced hepatocellular carcinoma by localized concurrent chemoradiotherapy. *Ann Surg Oncol* 2014; 21: 3646-3653 [PMID: 24916746 DOI: 10.1245/s10434-014-3652-3]
74 Yoon SM, Ryoo BY, Lee SJ, Kim JH, Shin JH, An JH, Lee HC, Lim YS. Efficacy and Safety of Transarterial Chemoembolization Plus External Beam Radiotherapy vs Sorafenib in Hepatocellular Carcinoma With Macroscopic Vascular Invasion: A Randomized Clinical Trial. *JAMA Oncol* 2018; 4: 661-669 [PMID: 29543938 DOI: 10.1001/jamaoncol.2017.5847]
75 Sumiyoshi T, Shima Y, Okabayashi T, Negoro Y, Shimada Y, Iwata J, Matsumoto M, Hata Y, Noda Y, Sui K, Sueda T. Chemoradiotherapy for Initially Unresectable Locally Advanced Cholangiocarcinoma. *World J Surg* 2018; 42: 2910-2918 [PMID: 29511872 DOI: 10.1007/s00268-018-4558-1]
76 Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De Greve J, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Saltz LB. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; 24: 4293-4300 [PMID: 16908937 DOI: 10.1200/JCO.2005.01.3441]
77 Daveau M, Scotte M, François A, Coulouarn C, Ros G, Tallet Y, Hiron M, Hellot MF, Salier JP. Hepatocyte growth factor, transforming growth factor alpha, and their receptors as combined markers of prognosis in hepatocellular carcinoma. *Mol Carcinog* 2003; 36: 130-141 [PMID: 12619035 DOI: 10.1002/mc.10103]
78 Yoshimoto T, Imura S, Morine Y, Ikemoto T, Arakawa Y, Iwahashi S, Saito YU, Takasu C, Ishikawa D, Teraoku H, Bando Y, Shimada M. The Outcome of Sorafenib Therapy on Unresectable Hepatocellular Carcinoma: Experience of

Conversion and Salvage Hepatectomy. *Anticancer Res* 2018; 38: 501-507 [PMID: 29277815 DOI: 10.21873/anticanres.12250]
79 Yamauchi M, Ono A, Ishikawa A, Kodama K, Uchikawa S, Hatooka H, Zhang P, Teraoka Y, Morio K, Fujino H, Nakahara T, Murakami E, Miki D, Kawaoka T, Tsuge M, Hiramatsu A, Imamura M, Hayes CN, Fujita M, Nakagawa H, Yasui W, Aikata H, Chayama K. Tumor Fibroblast Growth Factor Receptor 4 Level Predicts the Efficacy of Lenvatinib in Patients With Advanced Hepatocellular Carcinoma. *Clin Transl Gastroenterol* 2020; 11: e00179 [PMID: 32677805 DOI: 10.14309/ctg.0000000000000179]
80 Barbier L, Muscari F, Le Guellec S, Pariente A, Otal P, Suc B. Liver resection after downstaging hepatocellular carcinoma with sorafenib. *Int J Hepatol* 2011; 2011: 791013 [PMID: 22135750 DOI: 10.4061/2011/791013]
81 Tanaka H, Saijo Y, Tomonari T, Tanaka T, Taniguchi T, Yagi S, Okamoto K, Miyamoto H, Sogabe M, Sato Y, Muguruma N, Tsuneyama K, Sata M, Takayama T. An Adult Case of Congenital Extrahepatic Portosystemic Shunt Successfully Treated with Balloon-occluded Retrograde Transvenous Obliteration. *Intern Med* 2021 [PMID: 33456037 DOI: 10.2169/internalmedicine.5914-20]
82 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]
83 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; 391: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]
84 Vagefi PA, Hirose R. Downstaging of hepatocellular carcinoma prior to liver transplant: is there a role for adjuvant sorafenib in locoregional therapy? *J Gastrointest Cancer* 2010; 41: 217-220 [PMID: 20443078 DOI: 10.1007/s12029-010-9163-y]
85 Gruenberger B, Schueller J, Heubrandtner U, Wrba F, Tamandl D, Kaczirek K, Roka R, Freimann-Pircher S, Gruenberger T. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol* 2010; 11: 1142-1148 [PMID: 21071270 DOI: 10.1016/S1470-2045(10)70247-3]
86 Zhu J, Yin T, Xu Y, Lu XJ. Therapeutics for advanced hepatocellular carcinoma: Recent advances, current dilemma, and future directions. *J Cell Physiol* 2019; 234: 12122-12132 [PMID: 30644100 DOI: 10.1002/jcp.28048]
87 Qin S, Ren Z, Meng Z, Chen Z, Chai X, Xiong J, Bai Y, Yang L, Zhu H, Fang W, Lin X, Chen X, Li E, Wang L, Chen C, Zou J. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. *Lancet Oncol* 2020; 21: 571-580 [PMID: 32112738 DOI: 10.1016/S1470-2045(20)30011-5]
88 Dawkins J, Webster RM. The hepatocellular carcinoma market. *Nat Rev Drug Discov* 2019; 18: 13-14 [PMID: 30168534 DOI: 10.1038/nrd.2018.146]
89 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; 382: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]
90 Ziogas IA, Evangeliou AP, Giannis D, Hayat MH, Mylonas KS, Tohme S, Geller DA, Elias N, Goyal L, Tsoulfas G. The Role of Immunotherapy in Hepatocellular Carcinoma: A Systematic Review and Pooled Analysis of 2, 402 Patients. *Oncologist* 2020 [PMID: 33314549 DOI: 10.1002/onco.13638]
91 Sun HC, Zhu XD, Huang C, Shen YH, Yuan J, Ge NL, Tan CJ, Zhou J, Fan J.Initially unresectable hepatocellular carcinoma treated by combination therapy of tyrosine kinase inhibitor and anti-PD-1 antibody followed by resection. *J Clin Oncol* 2020;38:e16690[DOI:10.1200/JCO.2020.38.15_suppl.e16690]
92 Fujiki M, Aucejo F, Kim R. General overview of neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: necessity or option? *Liver Int* 2011; 31: 1081-1089 [PMID: 22008644 DOI: 10.1111/j.1478-3231.2011.02473.x]
93 Lau WY, Lai EC, Lau SH. The current role of neoadjuvant/adjuvant/chemoprevention therapy in partial hepatectomy for hepatocellular carcinoma: a systematic review. *Hepatobiliary Pancreat Dis Int* 2009; 8: 124-133 [PMID: 19357024]
94 Ha SY, Choi M, Lee T, Park CK. The Prognostic Role of Mitotic Index in Hepatocellular Carcinoma Patients after Curative Hepatectomy. *Cancer Res Treat* 2016; 48: 180-189 [PMID: 25797572 DOI: 10.4143/crt.2014.321]
95 Wang SN, Chuang SC, Lee KT. Efficacy of sorafenib as adjuvant therapy to prevent early recurrence of hepatocellular carcinoma after curative surgery: A pilot study. *Hepatol Res* 2014; 44: 523-531 [PMID: 23672310 DOI: 10.1111/hepr.12159]
96 Zhang XP, Chai ZT, Gao YZ, Chen ZH, Wang K, Shi J, Guo WX, Zhou TF, Ding J, Cong WM, Xie D, Lau WY, Cheng SQ. Postoperative adjuvant sorafenib improves survival outcomes in hepatocellular carcinoma patients with microvascular invasion after R0 liver resection: a propensity score matching analysis. *HPB (Oxford)* 2019; 21: 1687-1696 [PMID: 31153833 DOI: 10.1016/j.hpb.2019.04.014]
97 Huang Y, Zhang Z, Zhou Y, Yang J, Hu K, Wang Z. Should we apply sorafenib in hepatocellular carcinoma patients with microvascular invasion after curative hepatectomy? *Onco Targets Ther* 2019; 12: 541-548 [PMID: 30666133 DOI: 10.2147/OTT.S187357]
98 Huang L, Li GM, Zhu JY, Li Z, Li T, Leng XS. Efficacy of sorafenib after liver transplantation in patients with primary hepatic carcinoma exceeding the Milan criteria: a preliminary study. *Onco Targets Ther* 2012; 5: 457-462 [PMID: 23277740 DOI: 10.2147/OTT.S31387]
99 刘臻玉, 武丹, 区锦玲, 曾海峰. 术后TACE对肝癌微血管侵犯治疗效果评估. 肝胆胰外科杂志 2017; 29: 38-372 [DOI: 10.11952/j.issn.1007-1954.2017.05.004]
100 Paul S, Dickstein A, Saxena A, Terrin N, Viveiros K, Balk EM, Wong JB. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: A meta-analysis. *Hepatology* 2017; 66: 379-388 [PMID: 28128861 DOI: 10.1002/hep.29082]
101 张秋明, 钟鉴宏, 游雪梅, 马良, 向邦德, 朱少亮, 龚文锋, 黎乐群. 核苷类似物联合TACE治疗HBV相关性肝细胞癌的预后分析.肿瘤防治研究 2016; 43: 792-795 [DOI: 10.3971/j.issn.1000-8578.2016.09.013]
102 Lau WY, Ho SK, Yu SC, Lai EC, Liew CT, Leung TW. Salvage surgery following downstaging of unresectable hepatocellular carcinoma. *Ann Surg* 2004; 240: 299-305 [PMID: 15273555 DOI: 10.1097/01.sla.0000133123.11932.19]

科学编辑: 张砚梁 制作编辑: 张砚梁

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton,
CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

ISSN 1009-3079