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· 专题研究 ·

肝切除联合血管切除重建治疗肝内胆管癌并血管侵犯疗效与安全性的多中心回顾性研究

于小鹏^{1,2}, 陈家璐¹, 唐玥¹, 陈晨³, 邱应和⁴, 吴泓⁵, 宋天强⁶, 何宇⁷, 毛先海⁸, 翟文龙⁹, 程张军¹⁰, 梁霄¹¹, 李敬东¹², 孙传东¹³, 马凯¹³, 耿智敏³, 汤朝晖¹, 全志伟¹

(1.上海交通大学医学院附属新华医院 普通外科, 上海 200092; 2.上海市第六人民医院 肿瘤科, 上海 200030; 3.西安交通大学第一附属医院 肝胆外科, 陕西 西安 710061; 4.中国人民解放军海军军医大学东方肝胆外科医院 胆道外科, 上海 200433; 5.四川大学华西医院 肝脏外科, 四川 成都 610041; 6.天津医科大学肿瘤医院 肝胆肿瘤科, 天津 300060; 7.中国人民解放军陆军军医大学西南医院 肝胆外科, 重庆 400038; 8.湖南省人民医院 肝胆外科, 湖南 长沙 410005; 9.郑州大学附属第一医院 肝胆胰与肝移植外科, 河南 郑州 450052; 10.东南大学附属中大医院 肝胆外科, 江苏 南京 210009; 11.浙江大学医学院附属邵逸夫医院 肝胆胰外科, 浙江 杭州 310020; 12.川北医学院附属医院 肝胆外科, 四川 南充 637000; 13.青岛大学附属医院 肝胆胰外科, 山东 青岛 266003)

摘要

背景与目的: 在过去, 大血管(门静脉、下腔静脉等)侵犯被认为是肝内胆管癌(ICC)根治性切除的禁忌证, 随着手术技术的进步, 目前肝切除联合血管切除重建的安全性逐渐被认可, 但其疗效如何尚无定论。因此, 本研究通过国内多中心数据探讨ICC并血管侵犯患者肝切除联合血管切除重建的安全性和疗效, 以及术后辅助治疗的价值。

方法: 回顾性收集2010年1月—2021年6月国内12家三甲医院收治的1 040例行根治性切除术的ICC患者临床病理资料, 包括未发生血管侵犯872例, 血管侵犯168例(其中行联合血管切除重建35例, 行常规ICC根治术未行血管切除133例)。分析全组及不同类型患者的总生存(OS)时间; 在血管侵犯的患者中, 分析血管切除重建对患者的主要临床指标与OS时间的影响, 以及术后辅助治疗对患者OS时间的影响。

结果: 全组患者中位OS时间为18(9.4~30.6)个月, 无血管侵犯患者中位OS时间为18.51(10~32)个月, 血管侵犯患者中, 未血管切除患者中位OS时间为16.3(9.4~28)个月, 血管切除患者中位OS时间为10(5.5~21.6)个月。生存分析结果显示, 血管侵犯患者无论是否行血管切除, OS时间均低于无血管侵犯患者(均 $P<0.05$), 血管切除重建对血管侵犯患者的OS无明显改善作用($P=0.662$); 两两1:1倾向评分匹配后分析显示, 血管侵犯患者无论是否行血管切除, 中位OS时间均低于无血管侵犯患者, 但差异无统计学意义(无血管侵犯 vs. 血管切除: 26个月 vs. 21.8个月, $P=0.087$; 无血管侵犯 vs. 未血管切除: 27个月 vs. 16个月, $P=0.068$), 血管切除重建对血管侵犯患者的OS无明显改善作用($P=0.293$)。在血管侵犯的患者中, 血管切除重建患者手术时间及术后住院时间均长于未血管切除患者(均 $P<0.05$), 而术后并发症等其他临床指标均无明显差异(均 $P>0.05$); 同种类型血管侵犯患者的亚组分析结果显示, 血管切除重建对不同类型的血管侵犯患者的OS均无改善作用(均 $P>0.05$); 无论是否行血管切除重建, 术后辅助治疗对患者的OS均有一定的改善作用, 但差异均无统计学意义(均 $P>0.05$)。

结论: 血管侵犯是ICC患者预后的危险因素, 血管切除重建不能明显改善患者预后, 且可能增加患者手术时间及术后住院时间。对血管侵犯是ICC患者术后进行辅助治疗可能有助于改善预后。

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作者简介: 于小鹏, 上海交通大学医学院附属新华医院硕士研究生, 主要从事胆道系统肿瘤方面的研究。

通信作者: 汤朝晖, Email: tzh1236@163.com

关键词 胆管肿瘤;胆管,肝内;血管侵犯;血管切除;辅助治疗
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Analysis of the efficacy of hepatectomy combined with vascular resection and reconstruction in treatment of intrahepatic cholangiocarcinoma with vascular invasion: a multi-center retrospective analysis

YU Xiaopeng^{1,2}, CHEN Jialu¹, TANG Yue¹, CHEN Chen³, QIU Yinghe⁴, WU Hong⁵, SONG Tianqiang⁶, HE Yu⁷, MAO Xianhai⁸, ZHAI Wenlong⁹, CHENG Zhangjun¹⁰, LIANG Xiao¹¹, LI Jingdong¹², SUN Chuandong¹³, MA Kai¹³, GENG Zhimin³, TANG Zhaohui¹, QUAN Zhiwei¹

(1. Department of General Surgery, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200092, China; 2. Department of Oncology, Shanghai Sixth People's Hospital, Shanghai 200030, China; 3. Department of Hepatobiliary Surgery, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China; 4. Department of Biliary Surgery, Oriental Hepatobiliary Hospital Affiliated to Naval Medical University, Shanghai 200433, China; 5. Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu 610041, China; 6. Department of Hepatobiliary Oncology, Tianjin Medical University Cancer Hospital, Tianjin 300060, China; 7. Department of Hepatobiliary Surgery, the Southwest Hospital of Army Medical University, Chongqing 400038, China; 8. Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital, Changsha 410005, China; 9. Department of Hepatopancreatobiliary and Liver Transplantation Surgery, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China; 10. Department of Hepatobiliary Surgery, Zhongda Hospital of Southeast University, Nanjing 210009, China; 11. Department of Hepatobiliary and Pancreatic Surgery, Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine, Hangzhou 310020, China; 12. Department of Hepatobiliary Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan 637000, China; 13. Department of Hepatobiliary and Pancreatic Surgery, the Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, China)

Abstract

Background and Aims: In the past, the invasion of major vessels (such as the portal vein and inferior vena cava) was considered a contraindication for radical resection of intrahepatic cholangiocarcinoma (ICC). With advancements in surgical techniques, the safety of liver resection combined with vascular resection and reconstruction is gradually being recognized, but its efficacy remains inconclusive. Therefore, this study was conducted to investigate the safety and efficacy of liver resection with vascular resection and reconstruction for ICC patients with vascular invasion and the value of postoperative adjuvant therapy using multi-center data from domestic institutions.

Methods: The clinicopathologic data of 1 040 ICC patients who underwent radical resection between January 2010 and June 2021 in 12 grade A tertiary hospitals in China were retrospectively collected. This cohort included 872 patients without vascular invasion and 168 patients with vascular invasion (among whom 35 underwent combined vascular resection and reconstruction, and 133 underwent conventional radical ICC resection without vascular resection). Overall survival (OS) was analyzed for the entire cohort and patient subgroups. The impact of vascular resection and reconstruction on major clinical variables and OS of patients with vascular invasion and the influence of postoperative adjuvant therapy on OS were analyzed.

Results: The median OS for the entire cohort was 18 (9.4–30.6) months. The median OS for patients without vascular invasion was 18.51 (10–32) months, while for patients with vascular invasion, the median OS was 16.3 (9.4–28) months for those without vascular resection and 10 (5.5–21.6) months for

those with vascular resection and reconstruction. Survival analysis indicated that patients with vascular invasion had lower OS than those without vascular invasion, regardless of whether vascular resection was performed (all $P < 0.05$). Vascular resection and reconstruction did not significantly improve OS for patients with vascular invasion ($P = 0.662$). After 1:1 propensity score matching, the median OS for patients with vascular invasion remained lower than those without vascular invasion, but the differences were not statistically significant (non-vascular invasion vs. vascular resection: 26 months vs. 21.8 months, $P = 0.087$; non-vascular invasion vs. non-vascular resection: 27 months vs. 16 months, $P = 0.068$), and vascular resection and reconstruction did not significantly improve OS ($P = 0.293$). Among patients with vascular invasion, vascular reconstruction led to longer operative time and length of postoperative hospitalization than those without vascular resection (all $P < 0.05$). In contrast, other clinical variables, such as postoperative complications, showed no significant differences (all $P > 0.05$). Subgroup analysis of patients with similar types of vascular invasion indicated that vascular resection and reconstruction did not improve OS for patients with different kinds of vascular invasion (all $P > 0.05$). Regardless of whether vascular resection and reconstruction were performed, postoperative adjuvant therapy positively impacted OS, but the differences were not statistically significant (both $P > 0.05$).

Conclusion: Vascular invasion is a prognostic risk factor for ICC patients, and vascular resection plus reconstruction does not significantly improve patients' prognosis, possibly leading to longer operative time and length of postoperative hospitalization. Postoperative adjuvant therapy for ICC patients with vascular invasion may help improve prognosis.

Key words

Bile Duct Neoplasms; Bile Ducts, Intrahepatic; Vascular Invasion; Vascular Resection; Adjuvant Therapy

CLC number: R735.8

肝内胆管癌 (intrahepatic cholangiocarcinoma, ICC) 是肝脏第二大原发性恶性肿瘤, 约占 10%~20%, 近年来其全球发病率呈上升趋势^[1-3]。ICC 恶性程度高, 不可切除 ICC 患者的 5 年生存率仅为 5%~10%, 而根治性手术后患者的 5 年生存率约为 35%~50%^[4-5]。血管侵犯是 ICC 预后的危险因素之一^[6-8], 但肝切除联合血管切除能否使患者获益尚不明确。《肝内胆管癌外科治疗中国专家共识 (2020 版)》^[9]认为大血管侵犯并非 ICC 肝切除术禁忌证, 推荐侵犯大血管的 ICC 行肝切除联合血管切除和重建术, 但缺乏证据表明其能够改善远期生存情况。最近一项研究^[10]表明血管切除患者有更好的生存结局, 然而, 这项研究和先前的研究^[11-13]都受到了来自单一机构、小样本量的限制。因此, 本研究的目的是利用国内多中心数据库, 确定 ICC 患者行肝切除联合血管切除术的安全性和有效性, 并探讨其与辅助治疗效果的关系。

1 资料与方法

1.1 基线资料

采用回顾性队列研究方法, 收集 2010 年 1 月—2021 年 6 月国内 12 家三甲医院收治 ICC 患者的临床病理资料。共回收 1 473 份病例报告表, 根据纳入及排除标准, 本研究最终纳入 1 040 例患者 (图 1), 其中西安交通大学第一附属医院 192 例、天津医科大学附属肿瘤医院 155 例、浙江大学医学院附属邵逸夫医院 148 例、中国人民解放军海军军医大学东方肝胆外科医院 125 例、四川大学华西医院 114 例、湖南省人民医院 110 例、中国人民解放军陆军军医大学西南医院 56 例、东南大学附属中大医院 46 例、郑州大学第一附属医院 35 例、川北医学院附属医院 27 例、上海交通大学医学院附属新华医院 23 例、青岛大学附属医院 9 例; 男性 548 例, 女性 492 例; 中位年龄 60 (52~66) 岁。

本研究通过上海交通大学医学院附属新华医院伦理委员会审批 (批号: XHEC-JDYXY-2018-002), 所有患者签署手术治疗知情同意书。

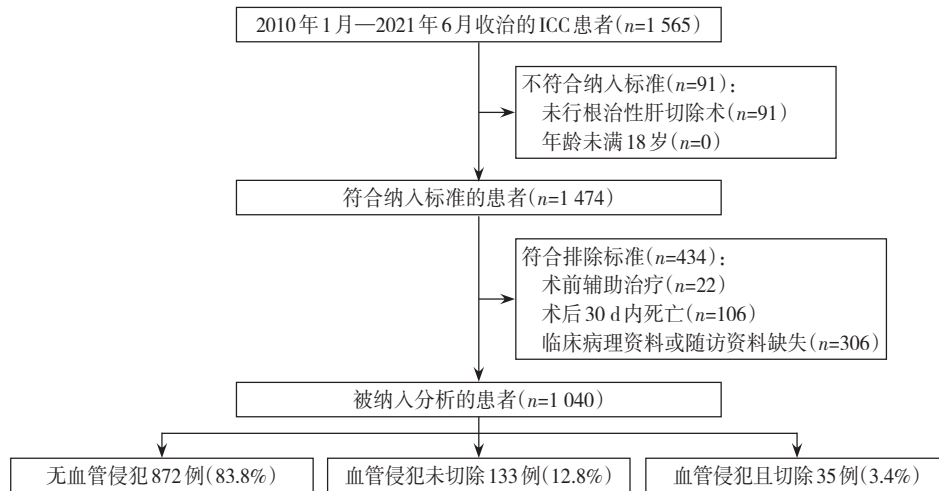


图1 患者纳入排除流程图

Figure 1 Flowchart of patient inclusion and exclusion

1.2 纳入与排除标准

纳入标准：(1) 年龄 ≥ 18 岁；(2) 行根治性肝切除术；(3) 术后经病理检查确诊为 ICC^[14]；(4) 随访资料完整。排除标准：(1) 姑息切除；(2) 术后 30 d 内死亡；(3) 术前辅助治疗；(4) 临床资料不完整。

1.3 结局及观察指标

以患者总生存 (overall survival, OS) 时间为主要结局指标，以围术期及术后切缘资料为次要结局指标。围术期资料包括术中失血量、术后并发症 (包括大量腹水、腹腔感染、胆汁漏、肝衰竭、出血、胸腔积液、肺部感染、切口感染)、手术时间、术后住院时间。基线资料观察指标包括性别、年龄、肿瘤直径、合并结石、合并肝炎、血管侵犯、术前最后 1 次 CA19-9、总胆红素 (TBIL)、丙氨酸氨基转移酶 (ALT) 水平及卫星灶。辅助治疗组包括接受术后预防性经导管动脉栓塞化疗、辅助化疗、辅助放疗患者。

1.4 统计学处理

采用 SPSS 26.0 软件进行统计学分析。非正态分布的计量资料以中位数 (四分位间距) [M (IQR)] 表示，分类资料以频数 (百分数) [n (%)] 表示，倾向评分匹配 (propensity score matching, PSM) 卡钳值为 0.02。采用 R 4.2.2 绘制 Kaplan-Meier 曲线，Log-rank 检验比较组间 OS 时间差异， $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 纳入患者基线资料

1 040 例 ICC 患者中，无血管侵犯 872 例 (83.8%)、血管侵犯 168 例 (16.2%)，后者中 35 例 (3.4%) 行血管切除重建，133 例 (12.8%) 未行血管切除。患者的详细基线资料见表 1。

2.2 血管切除的疗效与安全性

全组 1 040 例患者中位 OS 时间为 18 (9.4~30.6) 个月，其中无血管侵犯患者中位 OS 时间为 18.51 (10~32) 个月；血管侵犯患者中，未血管切除患者为 16.3 (9.4~28) 个月，血管切除患者为 10 (5.5~21.6) 个月。对三组患者绘制 Kaplan-Meier 曲线并进行 Log-rank 检验，结果表明，血管侵犯患者无论是否行血管切除，OS 时间均低于无血管侵犯患者 (无血管侵犯 vs. 血管切除， $P=0.012$ ；无血管侵犯 vs. 未血管切除， $P=0.002$)，而血管侵犯患者行血管切除不能改善患者预后 ($P=0.662$) (图 2A)。对三组患者进行两两 1:1 PSM 后，绘制 Kaplan-Meier 曲线并进行 Log-rank 检验，结果表明，血管侵犯患者无论是否行血管切除，中位 OS 时间均低于无血管侵犯患者，但差异无统计学意义 (无血管侵犯 vs. 血管切除：26 个月 vs. 21.8 个月， $P=0.087$ ；无血管侵犯 vs. 未血管切除：27 个月 vs. 16 个月， $P=0.068$) (图 2B-C)，而血管侵犯患者行血管切除不能改善患者预后 ($P=0.293$) (图 2D)。

血管切除的安全性分析显示，血管切除患者手术时间及术后住院时间均长于未切除患者，差

异有统计学意义 (均 $P < 0.05$), 而血管切除与未切除患者在术中失血量 ($P = 0.053$)、术后并发症 ($P = 0.843$)、切缘 ($P = 0.052$) 方面差异均无统计学意义 (表2)。

2.3 切除重建血管类型对预后的影响

35例血管切除患者中, 肝动脉切除1例、肝静脉切除2例、门静脉切除19例, 联合肝动脉静脉切除4例、联合肝动脉门静脉切除8例、联合肝动脉及门静脉切除1例。进一步对同种类型血管侵

犯患者的预后进行亚组 (血管切除重建 vs. 未血管切除) 比较, 结果显示, 单纯门静脉侵犯时, 门静脉切除重建不能改善患者预后 (中位 OS 时间: 16.3个月 vs. 21.2个月, $P = 0.797$) (图3A); 门静脉联合其他血管切除重建及肝动脉和 (或) 肝静脉切除重建也不能改善预后, 且切除重建后中位 OS 时间缩短 (8.97个月 vs. 28个月, $P = 0.225$; 10.08个月 vs. 22个月, $P = 0.365$) (图3B-C)。

表1 1 040例ICC患者术前临床资料

Table 1 Preoperative clinical data of the 1 040 ICC patients

| 资料 | 血管侵犯($n=168$) | | 无血管侵犯($n=872$) | 合计($n=1\ 040$) |
|--------------------------------------|-----------------|------------------|------------------|------------------|
| | 血管切除($n=35$) | 未血管切除($n=133$) | | |
| 合并结石[n(%)] | | | | |
| 否 | 30(85.7) | 98(73.7) | 692(79.4) | 820(78.8) |
| 是 | 5(14.3) | 35(26.3) | 180(20.6) | 220(21.2) |
| 性别 | | | | |
| 男 | 19(54.3) | 68(51.1) | 461(52.9) | 548(52.7) |
| 女 | 16(45.7) | 65(48.9) | 411(47.1) | 492(47.3) |
| 年龄[岁, $M(IQR)$] | 57(49.5~62.5) | 59(51~64) | 60(52~66) | 60(52~66) |
| 合并肝炎[n(%)] | | | | |
| 是 | 3(8.6) | 36(27.1) | 241(27.6) | 280(26.9) |
| 否 | 32(91.4) | 97(72.9) | 631(72.4) | 760(73.1) |
| CA19-9 [kU/L, $n(\%)$] | | | | |
| ≤ 37 | 14(40.0) | 43(32.3) | 341(39.1) | 398(38.3) |
| > 37 | 21(60.0) | 90(67.7) | 531(60.9) | 642(61.7) |
| ALT [U/L, $n(\%)$] | | | | |
| ≤ 40 | 24(68.6) | 89(66.9) | 663(76.0) | 776(74.6) |
| > 40 | 11(31.4) | 44(33.1) | 209(24.0) | 264(25.4) |
| TBIL [$\mu\text{mol/L}$, $n(\%)$] | | | | |
| ≤ 17.1 | 18(51.4) | 44(33.1) | 267(30.6) | 329(31.6) |
| > 17.1 | 17(48.6) | 89(66.9) | 605(69.4) | 711(68.4) |
| 肿瘤直径[cm, $n(\%)$] | | | | |
| ≤ 5 | 18(51.4) | 61(45.9) | 375(43.0) | 454(43.7) |
| > 5 | 17(48.6) | 72(54.1) | 497(57.0) | 586(56.3) |
| 卫星灶[n(%)] | | | | |
| 无 | 27(77.1) | 110(82.7) | 695(79.7) | 832(80.0) |
| 有 | 8(22.9) | 23(17.3) | 177(20.3) | 208(20.0) |
| OS[月, $M(IQR)$] | 10(5.5~21.6) | 16.3(9.4~28) | 18.51(10~32) | 18(9.4~30.6) |

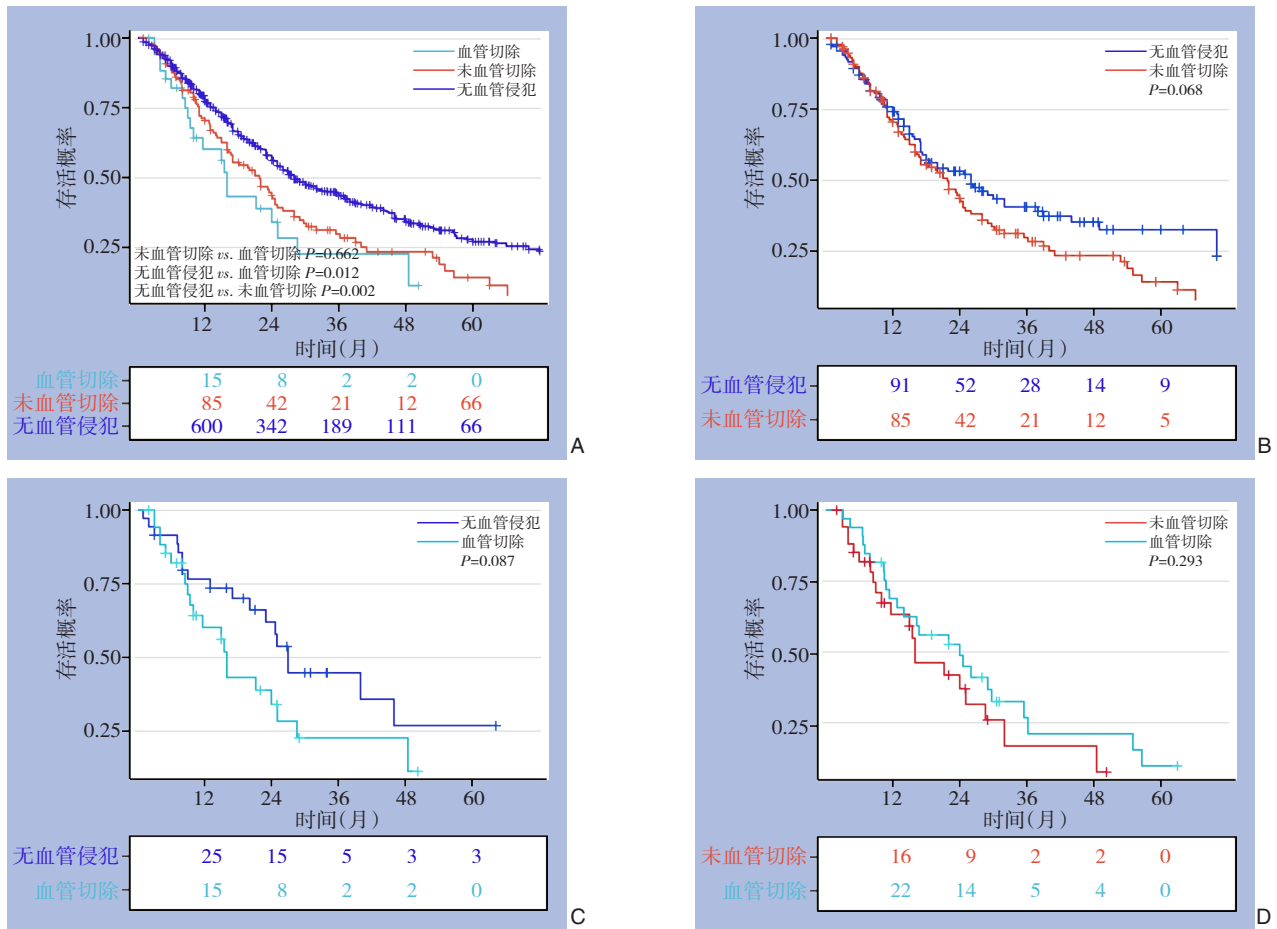


图2 不同类型ICC患者预后分析 A: PSM前血管切除、未血管切除及无血管侵犯患者OS曲线; B: PSM后未血管切除与无血管侵犯患者OS曲线; C: PSM后血管切除与无血管侵犯患者OS曲线; D: PSM后血管切除与未血管切除患者OS曲线

Figure 2 Prognostic analysis of different types of ICC patients A: OS curves of patients with or without vascular resection, and those without vascular invasion before PSM; B: OS curves of patients without vascular resection and those without vascular invasion after PSM; C: OS curves of patients undergoing vascular resection and those without vascular invasion after PSM; D: OS curves of patients with vascular resection and those without vascular resection after PSM

表2 血管切除与未切除患者围术期及术后病理资料比较

Table 2 Comparison of perioperative and postoperative pathological data between patients with and without vascular resection

| 特征 | 血管切除(n=35) | 未血管切除(n=133) | P |
|-------------------|----------------|--------------|-------|
| 术中失血量[mL, M(IQR)] | 600(300~1 000) | 400(200~700) | 0.053 |
| 术后并发症[n(%)] | | | |
| 无 | 22(62.9) | 86(64.7) | 0.843 |
| 有 | 13(37.1) | 47(35.3) | |
| 手术时间[h, M(IQR)] | 5(3.6~7.5) | 3.67(2~6) | 0.012 |
| 术后住院时间[d, M(IQR)] | 13(11~17.5) | 11(8~16) | 0.036 |
| 切缘[n(%)] | | | |
| R ₁ | 5(14.3) | 10(7.5) | 0.052 |
| R ₀ | 30(85.7) | 123(92.5) | |

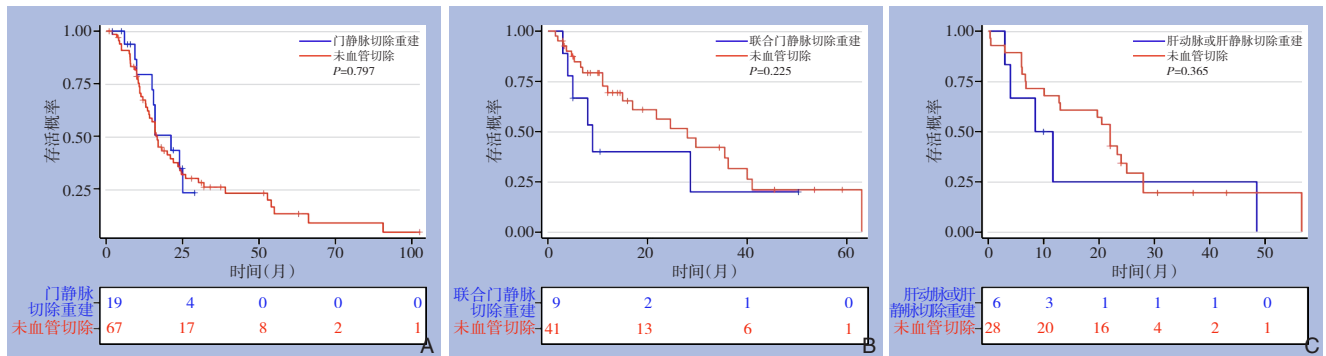


图3 各类型血管侵犯切除重建的亚组预后分析 A: 门静脉侵犯患者血管切除重建对OS时间的影响; B: 门静脉联合其他血管切除重建对OS时间的影响; C: 肝动脉和/或肝静脉切除重建对OS时间的影响

Figure 3 Subgroup prognostic analysis of vascular invasion resection and reconstruction for different types of vascular invasion A: Impact of vascular resection and reconstruction on OS in Patients with portal vein invasion; B: Impact of combined portal vein and other vessel resection and reconstruction on OS; C: Impact of hepatic artery and/or hepatic vein resection and reconstruction on OS

2.4 辅助治疗对血管侵犯患者预后的影响

经过术后辅助治疗的血管切除患者，中位OS时间为25（5.0~25.1）个月；未联合辅助治疗的血管切除患者，中位OS时间为15（6.0~15.5）个月，两者差异无统计学意义（ $P=0.081$ ）（图4A）。经过术

后辅助治疗的血管未切除患者，中位OS时间为23.3（9.7~25.3）个月；未联合辅助治疗的血管未切除患者，中位生存时间为17（7.9~28.0）个月，两者差异无统计学意义（ $P=0.412$ ）（图4B）。

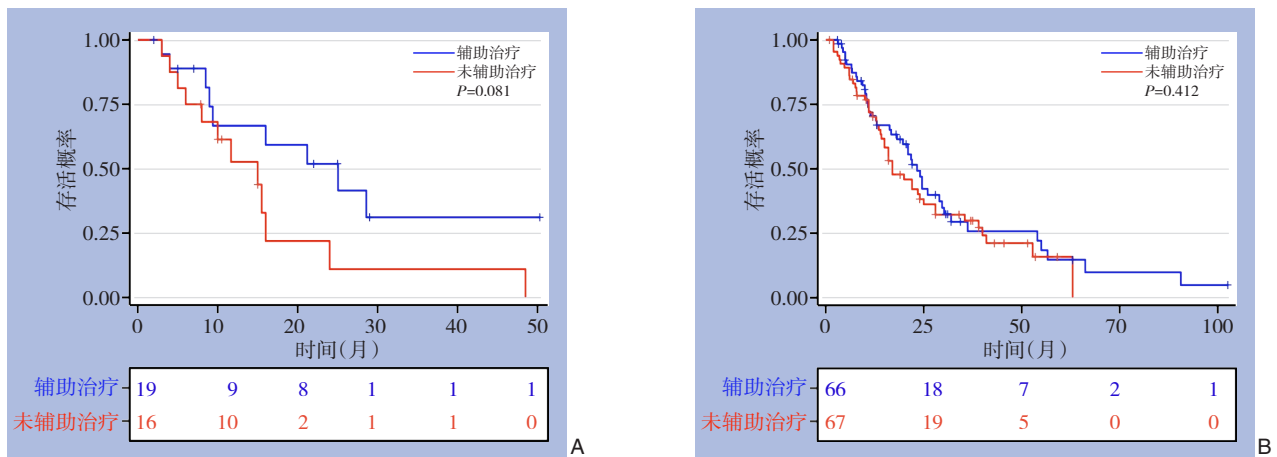


图4 辅助治疗对血管侵犯患者预后的影响 A: 血管切除患者; B: 未血管切除患者

Figure 4 Effect of adjuvant therapy on the prognosis of patients with vascular invasion A: Patients undergoing vascular resection; B: Patients without vascular resection

3 讨论

根治性切除是目前唯一可能治愈ICC的手段，ICC患者的术后预后与手术的根治性、肿块大小、是否淋巴结转移、是否累及血管等相关^[15-17]。手术技术和围手术期护理的进步，极大提高了复杂大范围肝切除术的可行性和安全性^[18-19]。然而，肝切除术联合血管切除和重建的术后及长期预后数据

仍然有限。一些学者^[11,20]报道与标准的ICC根治性切除相比，ICC根治性切除术联合门静脉和/或下腔静脉切除重建的并发症发生率和病死率并无显著增加，中位OS时间亦可与前者相媲美，目前一些专家共识^[9]对联合门静脉和/或下腔静脉切除重建持较为积极的态度。

本研究结果显示，行血管切除重建患者并发症发生率为59%，与未行血管切除重建患者（56%）

相比没有显著增加;在术中出血量方面,尽管行血管切除重建术中出血量较多(中位数:600 mL vs. 400 mL),但两者差异无统计学意义。行血管切除重建患者手术时间和术后住院时间均显著延长,这可能与手术操作难度及术后需要更多观察、护理时间有关。以上说明在本研究12家中心肝切除术联合血管切除重建技术较成熟,大血管侵犯不再是肝切除术禁忌证,在充分术前和术中评估及围术期护理下手术安全性可得到保障。

联合血管切除重建能否改善ICC肝切除术的预后是广受关注的另一焦点。目前对ICC术中联合血管切除重建的研究多为单中心小样本研究,能够检索到的多中心研究仅有一项^[20],共纳入1 087例行根治性切除术患者,联合血管切除重建患者5年生存率为36%,而未联合血管切除重建患者5年生存率为40%,两者差异无统计学意义($P=0.416$),但该研究联合血管切除重建患者未包含血管侵犯及无侵犯患者,不能很好反映血管侵犯患者联合血管切除重建的疗效。本研究将所有纳入病例分为无血管侵犯组、血管切除组和未血管切除组,发现联合血管切除重建并不能改善血管侵犯患者预后,可能与肿瘤一旦侵犯血管内膜便极易形成血行转移有关。Nakagohri等^[21]根据术后病理将胰腺癌根治术中联合门静脉切除患者分为肿瘤侵犯血管壁者和肿瘤未侵犯血管壁者,随访结果发现前者预后更差。进一步亚组分析发现,尽管单纯门静脉切除重建患者中位OS时间与未血管切除患者差异相对较小(16.3个月 vs. 21.2个月),但门静脉联合其他血管切除重建及肝动脉和(或)肝静脉切除重建后中位OS时间明显缩短(8.97个月 vs. 28.00个月、10.08个月 vs. 22.00个月)。这一结果的可能原因一是行血管切除重建患者往往侵犯更加明显,或TNM分期更高,因此即便血管切除重建预后也较差;二是行肝动脉肝静脉切除重建相比门静脉切除重建难度更大,术中更有可能存在切缘阳性、血行或播散转移。

手术的根治性是ICC患者主要的预后因素之一,根治性切除是外科医生的主要目标之一。在过去10年,文献报道ICC的 R_0 切除率为54%~96%不等。尽管在单一机构系列中,可超过90%^[11, 22],但在大量多中心研究中, R_0 切除率范围多在70%~80%之间^[23]。本研究结果显示,联合血管切除重建

患者 R_0 切除率为85.7%,未联合血管切除重建患者 R_0 切除率为92.5%,二者没有显著差异。Torzilli等^[24]证明,在肿块型ICC患者中,与 R_0 患者相比,血管 R_1 切除会导致更高的局部复发风险和更低的生存率。有研究^[25]报道,对于切缘<1 mm患者,其预后与 R_0 切除相似,均相比 R_1 切缘有显著改善。Bartsch等^[13]在最近发表的一项关于102例切除的ICC的单中心研究报告,只有45.7%血管切除的患者有真正的血管浸润,整个队列的 R_0 切除率为85.3%。与一些专家共识^[9]一致,笔者对联合血管切除重建持较为积极的态度,如果ICC与主要血管结构有接触,则更应进行血管切除。

本研究中,血管侵犯是患者不良预后的危险因素,肝切除术无论是否联合血管切除重建,患者预后均较差。辅助治疗是改善患者术后生存的手段之一,对于ICC术后患者,目前支持的证据主要来自BILCAP III期研究^[26-27],卡培他滨用于ICC根治性切除术后辅助化疗可改善患者预后。一项Meta分析^[28]结果显示,辅助放疗和/或化疗均可显著改善胆管癌患者术后总生存情况,其中淋巴结阳性和 R_1 切除患者获益最多。本研究对血管切除重建与辅助治疗效果的关系分析发现,尽管差异没有统计学意义,联合血管切除重建患者行辅助治疗相比未联合血管切除重建患者能够使中位OS时间得到较大提升(分别为:25个月 vs. 15个月、23.3个月 vs. 17个月)。

本研究为多中心大样本研究,其研究结果真实可靠,但本研究仍存在以下局限:(1)本研究为回顾性研究,难以避免出现系统偏倚^[29-30];(2)本研究为多中心研究,各中心的术前评估方式、手术方式尚无统一标准,所以多中心联合、统一管理标准的大样本随机对照试验有待实施;(3)行血管切除重建患者数量较少,尽管能够初步说明一些问题,但的确限制了研究的准确性,特别是在切除重建血管类型的亚组分析中,未来在手术技术进步下,将有更多患者行血管切除重建,进一步验证本研究结论。

综上所述,血管侵犯是ICC患者预后的危险因素,尽管目前研究结果不支持行血管切除重建能够改善患者预后,但在其安全性可保证的前提下,在某些情况下可以减少患者肿瘤负荷,提高患者生存质量,在未来ICC检验、手术技术及综合治疗

发展下,联合血管切除重建结合辅助治疗有望进一步提升患者生活质量,改善患者预后。

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作者贡献声明:于小鹏负责研究设计、实施、数据分析、文章撰写;陈家璐、唐玥负责研究设计、实施、文章审阅;陈晨、邱应和、吴泓、宋天强、何宇、毛先海、翟文龙、程张军、梁霄、李敬东、孙传东、马凯、耿智敏负责数据采集、统计分析;汤朝晖负责研究设计、实施、文章审阅、经费支持;全志伟负责研究指导、支持性贡献。

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