

· 综述 ·

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## 剩余肝体积不足的二期肝切除技术的应用现状与展望

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**摘要:** 剩余肝体积不足是限制肝脏恶性肿瘤患者接受一期手术的关键因素。促进剩余肝体积增生以实现二期肝切除的技术包括门静脉栓塞术、联合肝脏分隔和门静脉结扎的二步肝切除术及肝静脉剥夺术。近年来,辅助性肝移植的应用进一步实现二期全肝切除。本文系统综述了上述技术的临床应用现状,并分析其优劣势,旨在为优化临床决策提供参考。

**关键词:** 肝切除术; 肝肿瘤; 治疗学

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### Current status and perspectives of the application of two-stage hepatectomy for insufficient future liver remnant volume

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**Abstract:** Insufficient future liver remnant volume remains a critical limitation for single-stage resection in patients with hepatic malignancies. The techniques for promoting future liver remnant hypertrophy to realize two-stage hepatectomy include portal vein embolization, associating liver partition and portal vein ligation for staged hepatectomy, and portal vein ligation. In recent years, the application of auxiliary liver transplantation has further facilitated two-stage total hepatectomy. This article systematically reviews the clinical applications of these techniques and analyzes their advantages and limitations, so as to provide a reference for optimizing clinical decision-making.

**Key words:** Hepatectomy; Liver Neoplasms; Therapeutics

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肝切除术是肝细胞癌(hepatocellular carcinoma, HCC)、结直肠癌肝转移(colorectal liver metastasis, CRLM)和肝门部胆管癌(hilar cholangiocarcinoma, HCCA)等肝脏相关恶性肿瘤的核心治疗手段<sup>[1-2]</sup>,手术安全性高度依赖于对剩余肝体积(future liver remnant volume, FLR)的评估。对于肝硬化或胆汁淤积患者,建议FLR至少保留40%;无肝脏基础病变者,FLR可放宽至20%~30%<sup>[3-4]</sup>。FLR不足可能引发肝切除术后肝衰竭(post-hepatectomy liver failure, PHLF),

其发病率达1%~35%,围手术期病死率高达60%<sup>[5]</sup>。为降低PHLF风险,临床针对FLR不足患者可采用多种技术,包括门静脉栓塞术(portal vein embolization, PVE)、联合肝脏分隔和门静脉结扎的二步肝切除术(associating liver partition and portal vein ligation for staged hepatectomy, ALPPS)以及肝静脉剥夺术(liver venous deprivation, LVD),在诱导残肝增生后行二期肝切除<sup>[6]</sup>。近年来,辅助性肝移植(auxiliary liver transplantation, ALT)的应用进一步实现

了二期全肝切除<sup>[7]</sup>。本文系统综述了上述技术的临床应用现状,分析其优劣势并探讨优化治疗策略的方向。

## 1 PVE

PVE通过介入手段栓塞、阻断目标门静脉血流,从而诱导非栓塞侧肝脏的代偿性增生<sup>[8]</sup>。自20世纪80年代日本Makuuchi教授将PVE用于HCCA切除术以来,其安全性和促进残肝增生的有效性得到学术界的广泛认可<sup>[9-10]</sup>。目前,PVE已被广泛应用于FLR不足的肝脏相关恶性肿瘤切除术前,以增加FLR、避免PHLF发生。门静脉结扎术(portal vein ligation, PVL)原理与PVE类似,因涉及外科操作,常应用于ALPPS手术中而不单独使用,本节不做过多讨论。

PVE后肝脏再生相对缓慢,通常在术后1周启动,3周后达到平台期<sup>[11]</sup>。PVE术后21~30 d可观察到FLR增大12%~48%,且术后肿瘤可切除性达75%<sup>[12]</sup>。然而,约20%的患者因行PVE后FLR生长仍达不到肝切除标准或期间肿瘤进展导致未能接受二期手术<sup>[13]</sup>。从另一角度分析,PVE诱导肝脏缓慢增生的过程可甄别出那些高度恶性、快速进展的肿瘤,从而使患者避免了获益有限的手术。有关PVE的研究主要集中于手术路径、栓塞材料及PVE联合经导管肝动脉栓塞化疗(transcatheter arterial chemoembolization, TACE)。

**1.1 手术路径** 在介入路径方面,多数PVE临床研究通常选择(同侧/对侧)经皮经肝入路。同侧入路可最大限度降低PVE意外损伤残肝的风险,若计划进行扩大的右半肝切除术,则可更轻松地进入第IV段门静脉<sup>[14]</sup>。对侧入路的优点是有益于右门静脉分支的插管和顺行栓塞,但应注意对残肝的损伤和进入第IV段门静脉难度增加的问题。经回肠结肠门静脉栓塞(transileocolic portal vein embolization, TIPE)采用开腹手术入路,经肠系膜静脉分支插入导管,顺行直达门静脉实施栓塞<sup>[15-16]</sup>。TIPE在直视下进行血管穿刺,操作难度较低,可避免经皮经肝入路的胆漏等并发症,同时可在术前明确有无腹腔转移。尽管有研究认为,无论是经皮经肝穿刺入路还是开腹手术入路,均可增加FLR且差异无统计学意义,但TIPE开腹需全身麻醉支持,整体手术时间更长,将其作为开腹探查术时的补充治疗可能更为合理<sup>[16]</sup>。关于二期手术的入路选择,腹腔镜和开放手术的肿瘤R0切除率(71% vs 60%,  $P=0.230$ )和中位总生存期(28个月 vs 42个月,  $P=0.614$ )均无明显的统计学差异,表明腹腔镜手术在预后并未显著优于开放手术,但腹腔镜的微创性和潜在的术后

恢复优势仍使其在临床实践中具有一定选择价值<sup>[17]</sup>。

**1.2 栓塞材料** 在栓塞材料选择方面,无水乙醇、钢线圈、明胶海绵、 $\alpha$ -氰基丙烯酸正丁酯(*n*-butyl cyanoacrylate copolymer, NBCA)凝胶及微粒均为PVE常用栓塞材料<sup>[14,18]</sup>。研究显示,对于初始不可切除的HCC患者,以NBCA与明胶海绵作为栓塞材料的PVE疗效较好,其中选用NBCA作为栓塞材料的患者在FLR生长速率(9.03 mL/d vs 3.76 mL/d,  $P<0.001$ )及二期可切除率(80% vs 60%,  $P=0.043$ )方面更具优势<sup>[19]</sup>。相较于微粒组,采用NBCA仍能得到相似的结果<sup>[20]</sup>。由此可见,NBCA作为PVE栓塞剂具有良好的应用前景。近期,Cevik等<sup>[21]</sup>研发了一种用于药物输送的液体栓塞和消融剂,不仅可在PVE期间阻塞血流,还能消融肝实质和邻近胆管,并促进治疗药物(顺铂、纳武利尤单抗)的局部递送。这有助于在FLR增生期间降低肿瘤进展的风险,避免患者因肿瘤进展丧失手术机会<sup>[13]</sup>。该材料还具备一定的抗菌特性,有望减少甚至消除传统栓塞剂相关的感染并发症。栓塞材料研究的突破可能进一步提高PVE疗效,并推动其临床应用。

**1.3 PVE联合TACE** 鉴于HCC为富血供肿瘤(主要由肝动脉供血),PVE联合TACE可在等待二期手术期间控制肿瘤进展。研究显示,PVE+TACE组与PVE组相比,患者的二期手术切除率(72.2% vs 53.3%)无统计学差异( $P>0.05$ ),但PVE+TACE组患者二期手术后的1、3、5年无复发生存率(73.0%、53.3%、35.4%)均高于PVE组(62.5%、37.5%、18.8%),差异具有统计学意义( $P<0.05$ )<sup>[22]</sup>。这可能与PVE联合TACE的作用机制有关:通过促进肿瘤侧肝组织坏死并降低微血管侵犯风险,从而改善患者的预后。Yan等<sup>[23]</sup>在PVE联合TACE的基础上加入腹腔镜PVL,结果显示一期术后28 d患者FLR平均增加183.4 cm<sup>3</sup>(相当于增加49%),所有患者( $n=13$ )均接受二期肝切除术,且无死亡病例。PVE+TACE方案在改善HCC患者预后方面展现出较好的前景,但还需多中心、大样本研究进一步评估其安全性与有效性。

综上所述,PVE能在保证较高安全性的前提下增加FLR,但肝脏增生相对缓慢。选择合适的手术路径和栓塞材料以及联合TACE治疗,有望进一步提升其疗效。

## 2 ALPPS

早在2007年,Schlitt已开展首例ALPPS<sup>[24]</sup>,而完整的ALPPS则由Schnitzbauer等<sup>[25]</sup>于2012年报道。ALPPS分为两个阶段实施<sup>[26]</sup>:第1阶段先切除肝左外叶(即肝II~III段)肿瘤,结扎右门静脉,沿镰状韧带右侧离断肝实质,

切除胆囊,并经胆囊管行胆道造影,检查肝断面有无胆漏情况,随后置入引流管;术后6~7 d行计算机断层扫描(CT)造影,若FLR增生达到手术标准,则进行扩大右半肝切除的第2阶段手术。ALPPS可实现FLR短期内(通常1~2周内)快速增大,即使对于PVE失败的病例,也可考虑进一步选择ALPPS<sup>[27]</sup>。该技术的主要缺点是术后并发症发生率较高(可达69.2%)<sup>[28]</sup>,尤其是对于伴有肝硬化的HCC患者,其90 d病死率和总生存期与肝纤维化程度显著相关<sup>[29]</sup>。

后续对ALPPS的改进主要体现在将第1、2阶段的开放手术转变为微创手术,如腹腔镜手术<sup>[30]</sup>、机器人手术<sup>[31]</sup>。近期一项纳入9项研究的荟萃分析显示,相较于开放ALPPS,微创ALPPS可显著降低患者90 d病死率,缩短中位住院时间,同时在肿瘤R0切除率(92% vs 86%)方面与开放手术保持相当疗效<sup>[32]</sup>。经皮微波或射频消融肝实质分隔联合PVE计划性肝切除术(percutaneous microwave/radiofrequency ablation liver partition and PVE for planned hepatectomy, PALPP)是微创ALPPS的典型代表,其在第1阶段通过经皮射频或微波消融分离肝实质,同时进行PVE(而非传统的PVL)<sup>[33-34]</sup>。PALPP可大幅减少手术创伤,降低游离肝脏和解剖肝门时的肿瘤播散风险,同时减少二期肝切除时的粘连。杨鸿国等<sup>[35]</sup>研究发现,与TACE联合PVE相比, PALPP虽能提高FLR增生率(76.5% vs 31.4%,  $P < 0.001$ ),但患者术后并发症发生率显著升高(80.0% vs 27.6%,  $P = 0.009$ ),预后较差。Ye等<sup>[34]</sup>研究则显示, PALPP可在不增加术后并发症的情况下获得更高的二期切除率。这种差异可能与不同手术团队的操作技巧相关, PALPP是否会增加术后并发症仍需进一步研究证实。

总体而言, ALPPS为FLR不足的肝脏恶性肿瘤患者提供又一治疗选择。鉴于其并发症发生率较高,对患者进行改良的微创手术可减少创伤,有望降低并发症发生率并改善患者预后。同时,选择合适的患者接受手术至关重要。HCCA患者常并发黄疸或胆道感染,肝脏再生能力较弱,且ALPPS需解剖肝门,可能增加手术并发症风险和病死率<sup>[36]</sup>。因此,不应将ALPPS作为HCCA的首选治疗方式,需在多学科团队指导下,根据患者的具体情况制定个体化治疗策略。

### 3 LVD

对于PVE后4周FLR增加仍不足的患者,联合肝静脉栓塞(hepatic vein embolization, HVE)已被证实可进一步促进肝脏再生<sup>[37]</sup>,这种序贯治疗策略称为PVE-HVE。

2016年, Guiu等<sup>[38]</sup>在栓塞荷瘤肝脏门静脉分支的同时栓塞部分肝静脉,并提出LVD概念。LVD通过经皮肝入路栓塞右肝静脉主干,同时采用碘油/胶水混合物栓塞肝静脉末端和小分支。虽然这并未完全阻断肝动脉流入,但有助于减轻PVE后的肝动脉缓冲反应,进一步改变肝脏内血流分布,从而促进FLR增生。2017年, Guiu等<sup>[39]</sup>在LVD基础上进一步栓塞肝中静脉,并将该技术命名为扩大肝静脉剥夺术,接受此技术治疗的患者第21天FLR增加64.3%。此后,基于PVE-HVE的研究陆续开展<sup>[40]</sup>,这些研究仅在HVE的具体方法(如栓塞入路、栓塞分支和栓塞材料)上存在差异,其中以经颈静脉入路行HVE的双栓塞为代表<sup>[41]</sup>。双栓塞仅栓塞肝静脉主干,无需栓塞肝静脉末端和小分支。鉴于不同入路具有相似的安全性和有效性<sup>[42]</sup>,本文将上述技术统称为LVD,不做特别区分。

作为增加FLR的新兴技术, LVD常与PVE和ALPPS比较,以验证其安全性和有效性<sup>[43]</sup>。近期一项纳入10项研究, 588例患者的回顾性分析显示,与PVE相比, LVD在促进FLR肥大( $MD = 1.37$ ,  $95\%CI: 0.31 \sim 2.42$ ,  $P = 0.01$ )和提高肝切除率( $OR = 1.89$ ,  $95\%CI: 1.13 \sim 3.15$ ,  $P = 0.01$ )方面均具有显著优势<sup>[44]</sup>。另一项针对广泛肝转移的CRLM及存在高危因素患者的对比研究也得到类似结论,结果显示,接受LVD的患者FLR肥大程度(16% vs 11%,  $P = 0.017$ )和二期肝切除率(93% vs 55%,  $P = 0.008$ )均更高<sup>[45]</sup>。与ALPPS相比, LVD可改善术中参数(失血量和手术时间),并缩短住院时间,降低并发症发生率<sup>[46]</sup>。Chebaro等<sup>[47]</sup>将124例接受LVD的患者与85例接受ALPPS的患者进行比较,结果显示, LVD后等待二期手术时间显著延长(37 d vs 10 d),切除成功率低于ALPPS组(73% vs 91%),但LVD组90 d病死率(8.4%)略低于ALPPS组(9.4%)。然而,该研究存在选择偏倚: ALPPS组多为CRLM患者, LVD组则以HCCA患者较多,这些患者基础情况较差,可能延长手术前的治疗时间,影响二期手术结果。因此,需进一步研究比较LVD与ALPPS的疗效。

LVD作为一种新兴的FLR增加技术,在兼具PVE安全性的同时,弥补ALPPS并发症发生率高的不足。但目前关于其安全性和有效性的证据多来自回顾性队列研究,结果易受多种偏倚影响<sup>[48]</sup>,需进行更多随机对照试验以收集充足的数据,从而验证其临床实践效果。

### 4 ALT

ALT最初旨在治疗终末期肝病并避免肝移植无肝期,其核心为在不切除或部分切除患者原肝的基础上,

将部分供肝移植于患者体内,主要适用于各种急性肝衰竭和遗传代谢性肝病。2015年,Line等<sup>[49]</sup>结合ALT和ALPPS提出肝切除联合Ⅱ~Ⅲ段部分肝移植的延期全肝切除(resection and partial liver segment 2/3 transplantation with delayed total hepatectomy, RAPID)概念,对1例CRLM患者实施RAPID术:第1阶段切除患者Ⅰ~Ⅲ段肝脏,并将已故供体的Ⅱ~Ⅲ段部分供肝[移植肝与受者体质量比(graft to recipient weight ratio, GRWR)为0.36%]原位移植于切除部位,同时结扎右侧门静脉,促使门静脉血流向移植肝;术后2周移植物的体积增大一倍,术后第23天切除残余右半肝(第2阶段),患者未发生肝功能衰竭,随访期间未见肿瘤复发。在此基础上,Königsrainer等<sup>[50]</sup>开展的活体供体RAPID术进一步拓展供体来源,但该例患者术后随访虽移植肝未见肿瘤复发,但出现肺转移和骨转移。RAPID术不仅拓宽ALT的适应证,还实现小体积供肝(GRWR<0.8%)的临床应用,有效缓解肝移植供体短缺的压力。须注意,为避免移植肝因高灌注引发小肝综合征,应将移植肝门静脉压力控制在<15 mmHg,门静脉血流量维持在 $100 \sim 300 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ <sup>[7,51]</sup>,这可能需联合脾切除、脾动脉结扎等手术调节门静脉血流。此外,肝切除术会诱导残肝再生,RAPID一期肝脏手术操作是否会加速肿瘤进展有待进一步研究。

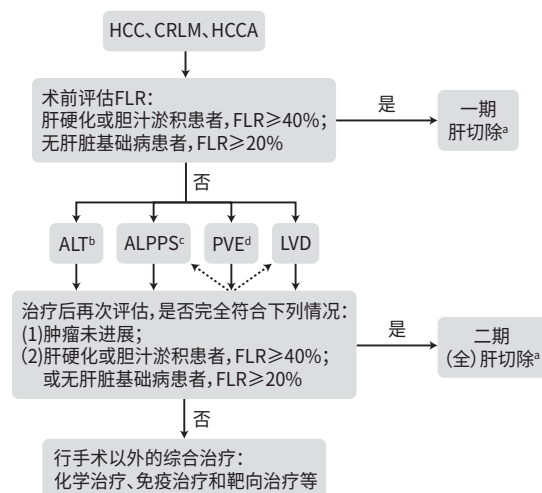
与RAPID手术相比,Ravaioli等<sup>[52-53]</sup>提出的脾切除术后脾动静脉异位肝移植的延期全肝切除术(heterotopic transplantation of segments 2 and 3 using the splenic vein and artery after splenectomy and with delayed total hepatectomy, RAVAS)的主要优势如下:一期无需对自体肝脏进行操作,即使有肝脏手术史的患者也可接受移植;对于伴有肝硬化的患者,RAVAS可同时切除病理性增大的脾脏以缓解门静脉高压。异位肝移植后易出现移植物流出不畅等血管并发症<sup>[54]</sup>,但后续报道显示,接受该手术的患者术后随访未见肝脏流出不畅问题<sup>[55]</sup>,其安全性需更多临床研究验证。

近年来,对于异种肝移植的研究不断开展<sup>[56]</sup>。近期,安徽医科大学第一附属医院团队成功将10基因编辑猪的肝脏以ALT的形式植入HCC患者体内,患者术后状况良好,术后7d已能下地自由活动。这不仅为异种肝移植的临床应用奠定基础,也为ALT在更多肝脏肿瘤治疗中的应用带来可能。ALT的应用可实现肝脏恶性肿瘤的二期全肝切除,但也对外科医生提出更高的技术要求。

## 5 FLR不足的二期肝切除技术决策流程

FLR不足的二期肝切除技术决策流程见图1。须注

意,术前化疗及肝脏基础疾病会导致肝脏再生能力减弱,FLR增大并不等同于肝储备功能提升<sup>[57]</sup>。因此,术前应结合FLR与肝储备检测(吲哚菁绿试验)进行评估。



注:a,术前应结合FLR与肝储备检测(吲哚菁绿试验)进行评估;b,通常HCC及CRLM可选;c,不作为HCCA首选;d,对于术后FLR仍不足的患者可行ALPPS或LVD。

图1 FLR不足的二期肝切除技术决策流程

Figure 1 Decision flowchart of secondary hepatectomy technique with FLR deficiency

## 6 小结与展望

在肝脏切除术实施前,充分评估FLR对确保手术安全性、降低PHLF风险至关重要。PVE、ALPPS、LVD、ALT等策略显著改善FLR不足患者的手术可行性,但需严格评估适应证:PVE安全性较高,但促进FLR增生速度较慢;ALPPS可实现FLR快速增大,但并发症发生率较高;LVD在不增加并发症发生率的前提下可促使FLR快速增生,效果似乎优于PVE和ALPPS,但缺乏大样本前瞻性研究的数据支持。基于ALT的RAPID和RAVAS技术为不可切除性肝脏恶性肿瘤患者提供全肝切除的机会,但手术难度较高,患者选择标准应更加严格。同时,还需考虑移植手术给患者带来的经济负担,且目前肿瘤复发情况缺乏远期观察结果。未来需开展更多前瞻性、多中心的临床研究,以验证这些技术的长期效果和安全性。

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