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·述评·

联合肝脏分隔和门静脉结扎的二步肝切除术临床与基础研究进展

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摘　　要　联合肝脏分隔和门静脉结扎的二步肝切除术（ALPPS）由德国 Hans Schlitt 教授在 2007 年首创，即通过I期手术时结扎肝脏荷瘤侧肝叶的门静脉分支，同时分隔荷瘤侧和健侧肝组织，使健侧肝脏在 1~2 周内快速再生，待健侧肝脏增生足够时，II期手术切除荷瘤侧肝脏，可使相当一部分原本不能手术切除的肝癌患者重新获得根治性切除的机会。ALPPS 效果显著，相对于门静脉栓塞可更快速地诱导肝脏再生，并且随着手术经验的积累和外科技术的改良，ALPPS 术后并发症率明显降低，越来越多地应用于原发性和继发性肝脏肿瘤的治疗，包括结直肠癌肝转移、肝细胞癌和肝内胆管癌等。ALPPS 自创立以来，其临床改良术式不断涌现，包括基本手术技术和技巧的改进、肝脏分隔的微创改进、门静脉结扎的微创改进、手术入路的微创改进和经导管动脉栓塞术补救性 ALPPS 等。ALPPS 诱导肝再生过程中肝脏免疫微环境可发生明显的变化，但关键免疫组分的作用、肝再生的空间起源、分布及其亚群特征等仍有待明确。目前，ALPPS 对肝脏肿瘤的具体影响及其机制并不完善，仍需进一步探索和证实。ALPPS 的临床应用前景广阔，相关机制研究的转化也有望为临床主动诱导肝再生和肝功能衰竭的防治提供新的思路。

关键词　肝肿瘤；肝切除术；ALPPS；肝再生；转化科学，生物医学

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Advances in clinical and basic research of associating liver partition and portal vein ligation for staged hepatectomy

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Abstract　The Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), first developed

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by Professor Hans Schlitt from Germany in 2007, combines the ligation of the portal vein branches of the tumor-bearing lobe and separation of the tumor-bearing lobe from the healthy lobe at the same time during the first stage, allows for rapid regeneration of the healthy lobe within 1–2 weeks. Once the healthy liver lobe has grown sufficiently, the tumor-bearing lobe is removed in the second stage of operation, which provides an opportunity for radical resection for a significant portion of patients with liver cancer initially considered unresectable. ALPPS has remarkable efficacy inducing more rapid liver regeneration than traditional portal vein embolization. Furthermore, with the accumulation of surgical experience and refinements in surgical techniques, the postoperative complication rate of ALPPS has significantly decreased. As a result, it is increasingly being applied in the treatment of primary and secondary liver tumors, including colorectal liver metastases, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma. Since its inception, ALPPS has undergone continuous clinical modifications, such as advancements in basic surgical techniques and skills, minimally invasive hepatic partition, minimally invasive portal vein ligation, minimally invasive surgical approaches, and rescue ALPPS using transcatheter arterial embolization. During the liver regeneration induced by ALPPS, significant changes can occur in the hepatic immune microenvironment. However, the roles of key immune components, spatial origin, distribution, and subpopulation characteristics during liver regeneration remain to be clarified. The specific effects and mechanisms of ALPPS on liver tumors are not fully understood and require further exploration and confirmation. The clinical application prospects of ALPPS are promising, and research on related mechanisms may offer new insights into the active induction of liver regeneration and the prevention and treatment of liver function failure.

Key words Liver Neoplasms; Hepatectomy; ALPPS; Liver Regeneration; Translational Science, Biomedical

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原发性肝癌是最常见的恶性肿瘤之一，我国每年新发肝癌占全球50%左右，目前是我国发病率第5位的常见恶性肿瘤及第2位肿瘤致死病因，患者总体5年生存率仅14%[1-3]。在我国，由于肝癌早期诊断率低，仅有15%~30%的患者能够接受根治性手术切除，如何提高肝癌的手术切除率，是进一步提升肝癌患者总体生存时间和生活质量的关键[4]。其中，限制肝肿瘤切除的一个关键因素是剩余肝脏体积（future liver remnant，FLR）不足[5-6]。作为21世纪以来肝脏外科革命性的创新手术方式，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）是通过I期手术时结扎肝脏荷瘤侧肝叶的门静脉分支，保留肝动脉和胆道，同时分隔荷瘤侧和健侧肝组织，促使健侧肝脏在1~2周内快速再生；待健侧肝脏增生足够时，在II期手术切除荷瘤侧肝脏，可使一部分原本不可手术切除的肝癌患者重新获得根治性切除[7-8]。ALPPS术的临床应用日益广泛，其临床术式的发展和探索不断，关于其基础研究探索目前并不完善。本文就ALPPS术式的起源与发展、临床应用现状、未来方向、其诱导肝再生的机制及其对肿瘤进展的影响等方面进行分析和总结，以期深化对ALPPS术式临床应用和机制探索的认知，最终更好地发挥其应用价值。

1 ALPPS术式的起源、演变及微创改良

上个世纪末开始，国内外专家尝试采取多种措施主动诱导肝再生，以提高肝肿瘤的手术切除率。20世纪80年代，日本外科专家Makuuchi等[9]和Kinoshita等[10]率先利用门静脉栓塞（portal venous embolization，PVE）阻断荷瘤侧肝脏对应的门静脉分支，诱导健侧肝再生，降低了大范围肝切除术后肝功能衰竭的风险，使胆管癌或肝细胞癌（hepatocelluar carcinoma，HCC）患者获得根治性切除的机会。2000年，Adam等[11]提出“二步肝切除”的概念：针对肝脏多发转移瘤的结直肠癌患者，

可以通过2次手术完成，即第1次手术尽量清除肿瘤灶，同时行PVE手术，经过一段时间待肝叶再生后，再切除剩余肿瘤。联合PVE的二期肝切除术，也存在明显不足即诱导FLR增生效率并不高（增长比例常小于40%），诱导时间常需4~8周[12-15]。对于合并肝纤维化或肝硬化背景的肝癌患者，FLR的增长速度更慢，一定程度限制了联合PVE的二期肝切除术的应用[16]。

ALPPS术最早在2007年9月由德国雷根斯堡大学医学中心的Schlitt等在对1例肝门部胆管癌患者行手术治疗时偶然创立，随着后续报道，2012年3月该技术被正式命名为“associating liver partition and portal vein ligation for staged hepatectomy”，按照首字母缩写简称为“ALPPS”[7-8]。2013年4月笔者团队[17]为1例巨大HCC患者成功施行ALPPS术，香港中文大学刘允怡院士在对此的述评中指出：“这是亚洲报道的首例ALPPS术。这例手术的成功施行，亦代表我国的肝脏手术达到国际前列水平”。

在肝胆外科日益微创化和精准化的趋势下，如何在不影响ALPPS术手术效果的前提下尽量减少手术创伤，是肝胆外科医生不断探索的临床课题。近十余年，许多医生对ALPPS术提出改良策略，主要包括：基本手术技术和技巧的改进、肝脏分隔的微创改进、门静脉结扎的微创改进、手术入路的微创改进和经导管动脉栓塞术（transcatheter arterial embolization，TAE）补救性ALPPS。

1.1　基本手术技术和技巧的改进

早期报道的ALPPS术后的高并发症和病死率与胆汁漏、腹腔感染、肝切除术后肝功能衰竭（posthepatectomy liver failure，PHLF）等相关，2014年ALPPS协作组首份安全性分析报告[18]显示，ALPPS术后主要的并发症是胆汁漏及腹腔内感染。早期ALPPS术后胆汁漏发生率较高，I期手术时结扎胆管可使胆汁漏发生率逐渐减少，同时严格的术中胆汁漏排查也是预防术后并发症的可靠手段[19-24]。笔者中心团队[17, 25]常规使用稀释的脂肪乳剂通过胆囊管注射以排查胆汁漏，可明显降低ALPPS术后胆汁漏的发生。早期ALPPS I期手术通常使用塑料袋包裹荷瘤侧肝脏，以防止术后粘连的形成和局限胆汁漏，后续的ALPPS I期手术逐渐摒弃使用塑料袋[22, 26]。

1.2　肝脏分隔的微创改良

经典ALPPS I期手术需完全分隔荷瘤侧和保留侧肝脏，肝实质分隔至下腔静脉前壁，但可能会引起包括胆汁漏、粘连和肝IV段缺血坏死等并发症，因而后续出现了针对肝实质分隔的多种微创改良方式如部分肝实质分隔、绕带结扎分隔和射频/微波消融替代肝实质分隔等。

1.2.1　部分分隔ALPPS（partial ALPPS）

2013年，Petrowsky等[27]在ALPPS I期手术时，将完全分隔肝实质转换为部分分隔，达到的FLR增生效果与完全分隔相当，而术后并发症和短期病死率大大下降，手术安全性明显改善，因而建立了部分分隔ALPPS并命名为partial ALPPS[27]。

1.2.2　联合绕肝带和门静脉结扎二步肝切除术（associating liver tourniquet and portal ligation for staged hepatectomy，ALTPS）

2011年，Campos等[28]尝试使用绕肝结扎法阻断荷瘤侧和保留侧肝脏之间的交通支替代分隔肝实质诱导FLR再生，术后7 d FLR增生率达150%，术后10 d切除肿瘤，且随访20个月肿瘤无复发，该技术被命名为ALTPS，后续又出现了序贯ALTPS（sequential ALTPS），即将ALTPS与延迟PVE结合[28]，ALTPS可达到与传统的二步肝切除术类似的诱导肝再生效果[29]。2014年，国内学者Cai等[30-32]开展了首例全腹腔镜绕肝带ALPPS，使用内部带有导丝的Flocare鼻胃管作为结扎带进行绕肝结扎。

1.2.3　射频辅助ALPPS（radiofrequency assisted liver partition with portal vein ligation，RALPP）/腔镜微波消融ALPPS（laparoscopic microwave ablation and portal vein ligation for staged hepatectomy，LAPS）

2014年，Jiao等[33]在I期尝试使用射频消融形成凝固无血带分隔荷瘤侧和保留侧肝脏，该技术被命名为RALPP。同时，研究[34-37]表明，LAPS与传统的ALPPS术相比，技术操作难度更小和速度更快，可减少胆汁漏和腹腔感染，术后恢复更快和手术更安全。

1.3　门静脉结扎的微创改良

经典的ALPPS术通常需要进行肝门部的解剖分离以进行门静脉结扎，但容易造成I期术后粘连。这促使一些学者[23, 38]尝试使用PVE替代门静脉结扎阻塞荷瘤侧门静脉分支PVE-ALPPS（hybrid ALPPS、mini ALPPS等），最大限度地减少了I期手术门静脉结扎的不良影响。

1.4 手术入路的微创改进

1.4.1 前入路实施ALPPS 2014年，Chan等[24]首次采用“前入路”（anterior approach）开展ALPPS术，I期仅对肝门作适度解剖分离后结扎门静脉右支，随后使用超吸刀（CUSA）进行原位肝实质分隔，肿瘤侧肝脏韧带不做游离操作。目前，前入路ALPPS已获得广泛应用，成为ALPPS联合改良技术中的重要手段[39-40]。

1.4.2 腹腔镜/机器人辅助ALPPS（laparoscopic/robotic ALPPS） 2012年，Machado等[41]首次报道了腹腔镜下ALPPS治疗结直肠癌肝转移（colorectal liver metastases，CRLM）的病例，结果显示腹腔镜下I期术后腹腔粘连轻微，可降低II期手术难度，提高手术安全性。该技术随之被全球其他各大肝脏中心广泛采用[42-43]。近些年来，机器辅助ALPPS报道逐渐增多，临床应用于CRLM、HCC、肝内胆管癌（intrahepatic cholangiocarcinoma，ICC）和肝门部胆管癌等，但总体应用比例仍较少[44-50]。

1.5 TAE补救性ALPPS

研究[25, 51-53]表明，FLR的增生速率与肝脏纤维化或肝硬化程度呈负相关，合并严重肝纤维化或肝硬化的患者FLR增生能力有限可能导致ALPPS术失败。笔者团队[54-55]2017年创立的TAE补救性ALPPS（周氏ALPPS），2022年，笔者团队回顾性报道了10例TAE补救性ALPPS的成功经验，表明TAE补救性ALPPS可使合并严重肝纤维化或肝硬化患者的R_0切除率达到100%，明显高于前期未使用该技术的合并肝硬化的ALPPS患者的肿瘤切除率（75%，12/16）[55]。TAE挽救性ALPPS可以成为合并严重肝纤维化或肝硬化的HCC患者行传统ALPPS术诱导肝再生不足的新策略。

2 ALPPS术的手术适应证

ALPPS术可在1~2周内诱导FLR增长49%~84%，效果明显优于PVE [8, 52, 56-58]。目前ALPPS术已广泛应用于原发和继发肝脏肿瘤的治疗，占据ALPPS术应用的90%以上[59]。符合以下条件的患者可以考虑行ALPPS术：(1) 全身情况良好；(2) 使用传统方法不能实现根治性切除，无肿瘤破裂出血、无门静脉主干及胆总管癌栓、无腔静脉侵犯等情况，无肝外及其他脏器转移的证据等；(3) 肝脏存在巨大肿瘤、多发肿瘤或肿瘤位置特殊需行大范围肝切除术才能达到R_0切除，且术前评估肝切除后FLR与标准肝体积之比不足25%的患者（若存在肝硬化或其他肝病背景，不足40%）；(4) 经评估肝功能Child-Pugh分级A级、吲哚菁绿排泄试验15 min滞留率指数（ICG R15）≤20%，无活动性肝炎、肝硬化失代偿期和严重的门静脉高压症存在；(5) 术前6周内未接受射频消融、经导管动脉化疗栓塞等手术治疗，CRLM的患者4周内未接受化疗等[60-63]。

3 ALPPS术诱导快速肝再生的机制

肝再生过程中肝脏免疫微环境可发生明显变化。越来越多的证据[64-66]表明，肝脏也是机体重要的免疫器官，其区域免疫微环境的变化在肝再生中也发挥重要作用。肝切除术后肝脏内中性粒细胞、巨噬细胞和内皮细胞等数量明显扩增，组织潴留的巨噬细胞和募集的巨噬细胞对于肝再生均有重要作用[67]。目前关于ALPPS术的基础研究较少，免疫微环境变化在ALPPS术诱导肝再生中的具体作用及机制还有待进一步明确。

ALPPS术的患者肝脏标本结合动物模型研究[68-71]表明：ALPPS术后，健侧肝脏中白介素6（interleukin 6，IL-6）、肿瘤坏死因子（tumor necrosis factor，TNF）、肝细胞生长因子（hepatocyte growth factor，HGF）、血管内皮生长因子（vascular endothelial growth factor，VEGF）、表皮生长因子（epidermal growth factor，EGF）等因子的转录和蛋白水平明显增高，伴随血清中IL-6、HGF等因子一过性增高。基于接受ALPPS术患者的血清因子检测发现，ALPPS I期后IL-6水平明显提升，而在II期手术后迅速下降；HGF在ALPPS术I期术后明显上升且其升高程度与肝脏增长速度呈正相关[69]。另一项研究[72]表明，ALPPS术与门静脉结扎（portal vein embolization，PVL）联合其他器官消融创伤的肝再生速度相似，研究者认为ALPPS术相对于PVL诱导再生速度更快可能是额外的手术创伤所导致，也可通过诱导其他器官的创伤模拟；进一步的研究[73]表明，ALPPS术后早期数小时内肝星状细胞中的Hedgehog分子的表达和分泌在促进快速肝再生中起重要作用。

肝再生过程被人为粗略地划分为三个阶段：启动阶段、增殖阶段和终止阶段[74]。以部分肝切

除术为例，肝再生过程开始于术后 5 min，到术后 5~7 d 肝再生过程受到明显的抑制而逐渐终止，可恢复至正常的肝脏重量（人类肝脏需要 8~15 d）。从微观角度观察，肝再生也具有一定的空间异质性特征。2/3 肝切除术诱导的肝细胞增殖主要源于肝小叶汇管区域（1 区），其次源于中间区域（2 区）[67, 75]。药物损伤诱导的肝再生与部分肝切除术后肝再生空间区域有所不同，可出现明显的坏死区域，肝细胞增殖通常围绕坏死区域。但 ALPPS 术诱导肝再生的空间起源、分布和亚群特征仍有待明确。

4　ALPPS 术对肿瘤转移和复发的影响

Petrowsky 等[76]报道了迄今最大队列的 CRLM 患者行 ALPPS 术的长期生存情况，回顾性地分析了 ALPPS 协作组登记的 2009—2019 年 22 个国际中心行 ALPPS 术治疗 510 例 CRLM 患者生存和复发情况，综合分析显示 ALPPS 术后 3 年内肿瘤复发率约达 80%，肿瘤复发部位依次为肝脏（60%）、肺（43%）、腹膜（19%）和其他器官（6%）。本中心 2018 年报道的 ALPPS 术治疗 HCC 的队列[25]，结果表明 38 例成功完成 ALPPS II期手术的患者中，17 例患者术后发生了复发。香港玛丽医院 Chan 等[52]报道了 46 例行 ALPPS 术的 HCC 患者，其中有 21 例出现了肿瘤复发。Schadde 等[18]报道了 48 例包括各种 CRLM，HCC 等接受 ALPPS 术治疗的队列，1 年内肿瘤复发率为 54%。传统的 ALPPS I 期手术操作对肿瘤产生的挤压和刺激，有可能导致肿瘤细胞播散[77]。I期手术会进一步加重机体的免疫抑制状态，围手术期的多种因素也会影响患者的神经内分泌反应、机体免疫等，从而影响术后的肿瘤转移复发[51, 78–82]。此外，I期手术导致的肝脏血流的重新分布和炎症影响，荷瘤侧肝脏肝动脉灌注代偿性增多，肝脏的免疫微环境可发生显著改变，可能影响肿瘤进展[79, 83–85]。目前关于 ALPPS 术对于肿瘤复发和转移的具体影响尚无明确定论，仍需严谨的随机对照试验及相关基础研究支撑。

5　ALPPS 实验动物模型

ALPPS 实验动物模型是探索其机制和临床转化的重要工具。啮齿类动物、猪和非人灵长类动物等均可用于 ALPPS 动物模型的建立，目前以啮齿类动物的实验应用最为广泛。

啮齿类动物 ALPPS 模型的建立是基于其特殊的肝脏解剖学结构。啮齿类动物肝脏的中叶由门静脉右支和门静脉左支共同汇入，可分为右中叶和左中叶，因而劈离左中叶和右中叶间的肝脏组织可实现肝脏劈离。啮齿类动物 ALPPS（30% FLR）模型中，保留右中叶肝脏（FLR 占比约 30%），结扎其余肝叶门静脉分支，同时用电刀将右中叶和左中叶的肝脏劈离，右中叶体积可在 7 d 内再生至术前的 1.59 倍[86]；ALPPS（10% FLR）模型中，保留左中叶肝脏（FLR 占比约 10%），结扎其余肝叶门静脉分支，劈离右中叶和左中叶之间的肝脏，左中叶体积可在 7 d 内再生至术前的 2 余倍；啮齿类动物 Zurich ALPPS 模型中，切除左外叶同时保留左中叶（FLR 占比约 10%），结扎其余肝叶门静脉分支，劈离右中叶和左中叶之间的肝脏，可能归因于额外部分肝切除术的因素，该模型诱导肝再生速度最快，左中叶体积可在 7 d 内迅速再生至术前的 3.41 倍[72, 87]；此外，还有研究[88–91]在该类模型中引入病理因素如肝硬化、脂肪肝等。为了研究 ALPPS 对肿瘤进展的影响，有研究者[92–94]将肿瘤细胞系或肿瘤组织块提前种植于小鼠保留侧肝脏或剩余肝脏，然后行 ALPPS，观察肿瘤的生长情况。

6　展　望

ALPPS 诱导快速肝再生是源于临床的科学现象，可为临床诱导肝再生和防治肝功能衰竭提供新思路。目前对于 ALPPS 诱导快速肝再生的病理生理学特征描述并不完善、肝再生具体机制探索仍不系统。高通量的单细胞测序技术、空间转录组技术、空间代谢组等多组学技术，可为 ALPPS 诱导快速肝再生的研究提供细胞组分及功能状态变化、空间分布、单细胞水平的通路调节和组织空间转录水平等时空异质性信息和崭新研究视角[95–99]。通过 ALPPS 促进快速肝再生的机制探索，有望鉴定快速诱导肝再生过程中的关键细胞组分和因子并将其转化应用于临床，可进一步提高 ALPPS 的成功率和疗效。同时，ALPPS 促进肝再生相关机制的揭示还可为临床肝切除术后肝功能不全的防治提供新的策略，为急性肝损伤下如何诱

导肝再生和促进肝功能恢复提供新思路[79]。

利益冲突：所有作者均声明不存在利益冲突。

作者贡献声明：闫加艳直接参与文献选题，负责文献资料解读分析和文章初稿撰写；杨欣荣负责文献内容审阅和修改，把控文献中关键性理论要点；周俭负责文献总体选题和设计、文献稿件最终审阅定稿，对学术问题进行解答，并最终同意论文发表。

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