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联合肝脏分隔和门静脉结扎的二步肝切除术（ALPPS）与肝癌

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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）是肝脏外科突破性的创新技术，提高了Ⅰ期无法手术切除巨大/多发肝癌的手术切除率。ALPPS手术方式的不断改进，进一步提高了手术的安全性。与系统治疗、局部治疗导致的肿瘤学转化相比，在手术切除成功率、间隔时间方面，ALPPS具有显著优势。未来研究应重点关注ALPPS术后患者的长期肿瘤学预后和生活质量评估。

关键词：肝肿瘤；联合肝脏分隔和门静脉结扎的二步肝切除术；治疗学

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Associating liver partition and portal vein ligation for staged hepatectomy and liver cancer

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Abstract: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a groundbreaking and innovative technique in the field of liver surgery, and it has significantly increased the resection rate of large or multifocal liver cancer that cannot be resected in stage Ⅰ surgery. Continuous improvements in the ALPPS surgical procedure have further enhanced surgical safety. Compared with systemic therapy and local treatment for oncological conversion, ALPPS has notable advantages in the success rate of surgical resection and the time interval required for the procedure. Future research will focus on the long-term oncological outcomes and quality of life of patients after ALPPS.

Key words: Liver Neoplasms; Associating Liver Partition And Portal Vein Ligation For Staged Hepatectomy; Therapeutics

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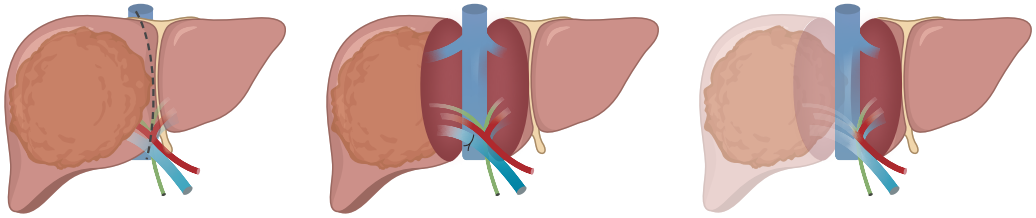
2007年，德国Schlitt教授团队成功开展了首例联合肝脏分隔和门静脉结扎的二步肝切除术（associating liver partition and portal vein ligation for staged hepatectomy，ALPPS），2012年，de Santibañes和Clavien教授正式将该术式命名为ALPPS[1]。此后，ALPPS获得广泛关注，并迅速地得到推广应用[2-5]。ALPPS是肝脏外科近半个世纪以来继肝移植、腹腔镜技术后，又一突破性的创新技术，为剩余肝体积（future liver volume，FLR）不足而不能行手术切除的肝肿瘤患者，提供了通过单次住院即可获得根治性治愈的机会。ALPPS的基本原理是通过结扎肿瘤侧肝脏的主要门静脉分支，同时通过肝实质离断等方式在肿瘤侧肝脏与剩余肝脏之间形成分隔，诱导剩余肝脏增生，待FLR增生达到安全标准后行再次手术、切除肿瘤（图1）。

1　ALPPS的一般适应证及禁忌证

ALPPS主要适用于：（1）FLR不足的原发性或转移性肝恶性肿瘤，即对于正常肝脏，术前影像学评估的FLR<30%标准肝体积；（2）病变肝脏（如梗阻性黄疸、肝纤维化、中重度脂肪肝或化疗导致的肝脏病变等）的



注：Ⅰ期手术，结扎门静脉右支，同时行肝实质离断；Ⅱ期手术，在FLR增生达到安全标准后行再次手术，切除肿瘤。

图1　ALPPS手术示意图

Figure 1　Schematic diagram of liver partition and portal vein ligation for staged hepatectomy

FLR<40%标准肝体积；(3)肝功能正常或轻度可逆性受损；(4)全身状况良好，能耐受大手术。除肝肿瘤情况外，肝实质状态是ALPPS适应证的一个重要考量因素。肝恶性肿瘤患者常合并基础肝病或肝损伤(包括病毒性肝炎、肝纤维化/肝硬化、胆汁淤积、化疗和/或靶向治疗所致肝损伤等)，其实际的功能性肝细胞总量(功能性肝细胞群)低于同等体积的正常肝脏。上述基础性病变可能影响FLR增生，患者或需更多时间才能获得足够的FLR。

ALPPS的禁忌证：麻醉风险高，不能达到R0切除的肝肿瘤患者；肝功能不佳(Child分级为B级或C级，吲哚菁绿15 min清除率>20%)，合并严重门静脉高压症和/或腹水，严重肝硬化以及超过50%的大泡脂肪肝；存在不可切除肝外转移灶；肝动脉灌注不良，一般状况较差不能耐受大手术者。对于年龄>65岁者实施ALPPS须慎重考虑。肝硬化等并非ALPPS的绝对禁忌证，但需要谨慎评估应用。

2　ALPPS在肝癌治疗中的应用

ALPPS可以增加Ⅰ期无法手术切除的巨大/多发肝恶性肿瘤的手术切除率，甚至可扩展至部分伴有大血管侵犯的病例[6-8]。近期研究显示：ALPPS较传统的门静脉栓塞(portal vein embolization，PVE)在诱导FLR增生方面具有显著优势[9]。然而，来自ALPPS临床注册网的早期报告显示，35例中期肝细胞癌(以下简称“肝癌”)患者接受ALPPS治疗后90天病死率达31%[10]。但随着经验的积累、病例选择标准的不断优化，ALPPS已经被广泛接受并被纳入各种标准或指南中[11]。香港大学Chan团队[12]制定了肝癌患者接受ALPPS治疗的入组标准(FLR<30%标准肝体积、Child-Pugh A级、吲哚菁绿15 min清除率<20%、血小板计数>100/nL，无门静脉右支血栓形成)，手术预后得到了明显改善，90天病死率降至7.1%。意大利IGROWtoH的回顾研究也得出类似结果[13]。ALPPS术前风险评估模型，可用于准确预测术后死亡风险[14]。

复旦大学附属中山医院的一项单中心研究，分析了45例肝癌合并乙型肝炎患者接受ALPPS治疗的结果。研究发现，肝硬化程度与肝脏增生的程度、速度呈负相关。接受ALPPS治疗的中晚期肝癌患者1、3年总生存率分别为64%和60%，明显优于无法手术而接受经动脉化疗栓塞术治疗的类似肿瘤患者。迄今该中心已完成超过200例ALPPS，5年总生存率接近50%[15]。

3　ALPPS的改进

为了进一步减少ALPPS的并发症，降低病死率，提高手术的安全性[16]，学者们从多个方面对经典ALPPS术式进行了改进，主要包括：(1)应用微创技术(腹腔镜、机器人辅助)开展ALPPS[17-20]。(2)肝实质分隔方式包括，经典的完全肝实质离断ALPPS、部分离断ALPPS、射频辅助ALPPS、微波辅助ALPPS和绕肝带ALPPS[21-27]。(3)肿瘤部位及肝切除范围：ALPPS起初用于肝右三叶切除，后不再受限于肿瘤部位和切除范围。目前依据肿瘤部位，对于切除范围、相应FLR位置和肝分隔/离断面均无特别限制，具体应用视情况而定[28-31]。反式ALPPS、中叶ALPPS和极限的单段ALPPS等术式显著推进了该技术的发展，将ALPPS的手术原理进行了全新的诠释：剩余肝脏不再局限于肝左外叶或左半肝，任何一个肝叶或肝段，甚至一个具备独立完整脉管结构和功能的肝区域，都可以作为剩余肝脏进行分割、诱导增生，然后进行肿瘤切除。

其他一些特殊ALPPS的术式：(1)挽救性ALPPS，专指单纯的门静脉闭塞，包括PVE和门静脉结扎，术后FLR增生不足后行ALPPS。ALPPS已成为门静脉闭塞失败后的重要挽救性治疗措施，治疗成功率高(92.3%～100%)，并发症发生率和病死率与常规ALPPS类似[32]。(2)经导管动脉栓塞(transcatheter arterial embolization，TAE)辅助ALPPS，是一种适用于轻-中度肝硬化或严重肝纤维化患者的术式。轻-中度肝硬化或严重肝纤维化患者在ALPPS Ⅰ期术后，易出现FLR增生不足而导致手术失败或两期间隔时间过长致肿瘤进展。该术式在

ALPPS Ⅰ期术后2周左右、FLR增生不足时行TAE，可再次促进FLR快速增生，挽救濒临失败的ALPPS[33]。（3）肝切除联合部分2/3肝段移植及延迟全肝切除术（resection and partial liver segment 2/3 transplantation with delayed total hepatectomy，RAPID），是ALPPS与活体肝移植的结合，目前主要针对不可切除的结直肠癌肝转移病例[34]。截至2023年，全球报道RAPID治疗病例约50例（主要来自欧洲中心），移植肝叶的中位增生时间为3周，术后1年生存率为70%～80%。近期，本中心完成了首例利用良性肿瘤患者切除的部分废弃肝脏实施的RAPID，废弃的供肝在7天内体积增加70%，成功实施了后续的手术。（4）肝动脉限制联合ALPPS：通过限制肝动脉的血供联合ALPPS，在治疗肝癌患者，尤其是严重纤维化患者中具有一定效果[35]。

4 ALPPS与肿瘤学转化治疗

系统抗肿瘤治疗，特别是靶向药物与免疫检查点抑制剂的联合应用，如阿替利珠单克隆抗体（以下简称单抗）联合贝伐珠单抗（IMbrave 150研究）、信迪利单抗联合贝伐珠单抗类似物IBI305（ORIENT-32研究）、卡瑞利珠单抗联合阿帕替尼（CARES-310研究）等用于晚期或不可切除肝癌可获得20%～30%（基于RECIST v1.1）的客观缓解率，中位生存时间延长至约20个月。另一方面，经动脉化疗栓塞、肝动脉灌注化疗和放射治疗等局部治疗手段也通过技术改进及与其他治疗方式联合应用，在缩小肿瘤、控制癌栓和改善预后等方面较以往取得更好的效果。上述非手术治疗方法已成为肝癌转化治疗的重要手段，转化成功率达15%～70%[36]。与肿瘤学转化治疗相比，ALPPS在手术切除成功率、间隔时间方面具有显著的优势，但其最终的适用人群、远期疗效等还需更多研究验证。当然，局部治疗、系统治疗也可与ALPPS联合应用，共同实现肿瘤切除和延长生存期的目标[37-38]。

5 ALPPS的未来前景

后续研究重点将转移到ALPPS术后的长期肿瘤学预后和生活质量评估。复旦大学附属中山医院自2013年开展亚洲首例ALPPS以来，已有多例患者获得10年以上的长期无瘤体生存。随着新技术、新理念的发展，学者们对胚胎发生、肿瘤生物学和肝脏再生等方面的认知呈指数级增长。越来越多的证据支持，这些复杂的现象背后存在共同的生物学过程和途径。肝脏的再生能力使肝大部切除术成为可能。然而，驱动肝再生的信号也可能促进肿瘤进展，这可能涉及创造一个不同的微环境，以重新激活休眠的癌症细胞。在ALPPS条件下，极限量的肝大部切除术、门静脉血流动力学的改变，可继发导致促进肝再生的大量细胞因子、炎症因子的释放，引起信号通路的改变，使得再生肝脏免疫微环境中免疫细胞、间质细胞的改变，从而可能促进循环肿瘤干细胞或残存肿瘤细胞的激活。当然，ALPPS一般在1～2周内即可完成肝再生和肿瘤的完整切除，与PVE相比，其将肿瘤转移复发可能降至最低限度。深入阐明ALPPS的具体机制将有助于开发相应抗肿瘤干预策略，优化最佳手术适应证病例的选择，从而为未来个性化的外科肿瘤治疗提供依据。

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