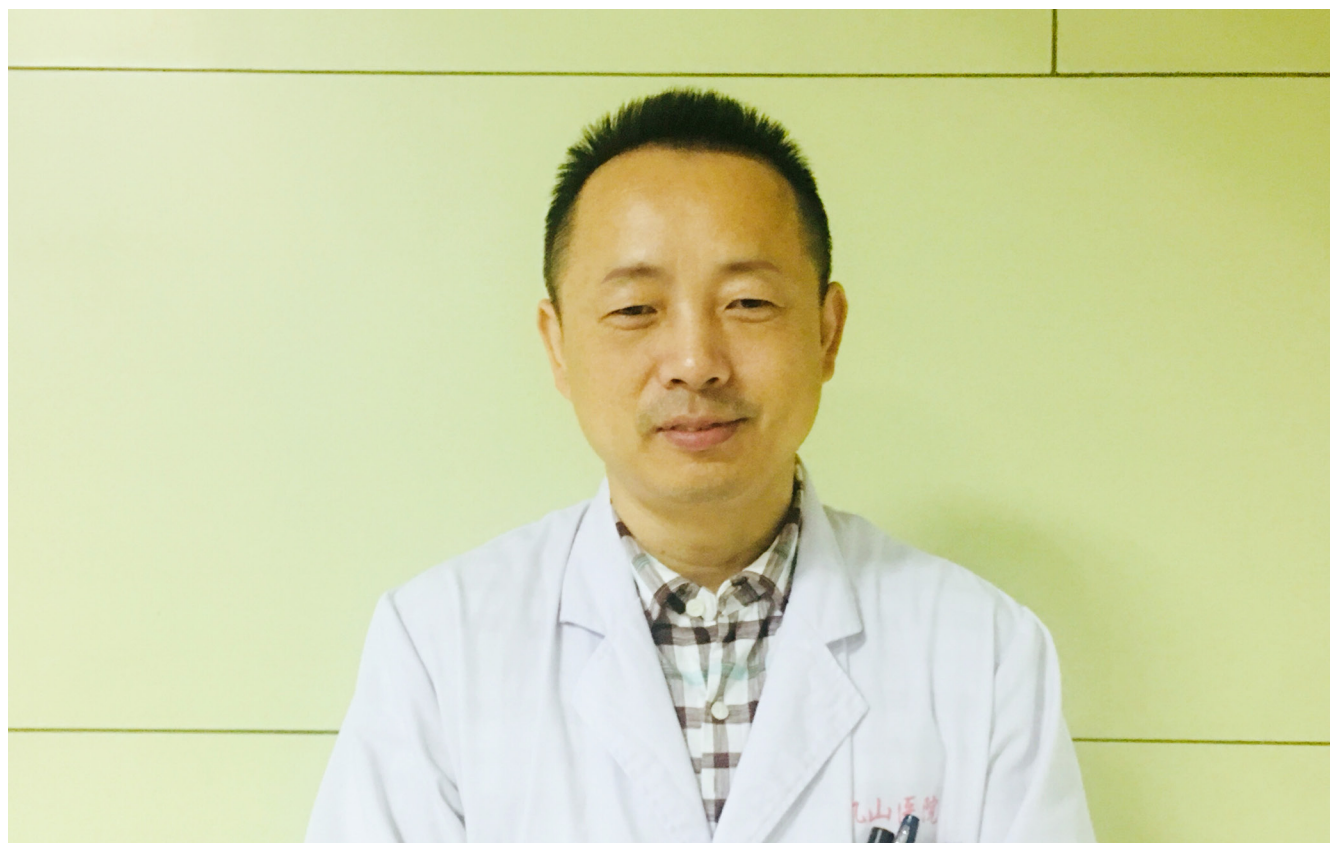


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结直肠癌肝转移的外科治疗

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Surgical treatment of colorectal liver metastasis

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Abstract

Liver metastasis is the most common form of distant metastasis in colorectal cancer and is a key factor for prognosis in patients with colorectal cancer. Surgery may be the only way to cure colorectal liver metastases. This paper mainly summarizes the latest progress in surgical treatment of colorectal liver metastases, including how to increase

resection rate of liver metastases with neoadjuvant therapy or staged hepatectomy, the effect of surgical margin on the prognosis of patients, the timing of surgery in patients with synchronous colorectal liver metastasis, the impact of laparoscopic hepatectomy of liver metastases, the application of liver transplantation in patients with colorectal liver metastases, etc, with an aim to help develop an optimal treatment for patients with colorectal liver metastases through combination of surgical innovations with individualized treatment, thereby improving patients' disease-free survival and overall survival.

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Key Words: Colorectal liver metastasis; Surgery; Prognosis

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摘要

结直肠癌患者容易出现肝转移, 肝转移是影响结直肠癌患者预后的主要原因之一. 手术是目前治愈结直肠癌肝转移的唯一方法. 本文主要总结了近年来结直肠癌肝转移患者肝转移病灶的手术进展情况: 包括通过新辅助化疗或分阶段肝切除等方法提高肝转移病灶的手术切除率、肝转移灶切缘对患者预后的影响、同时性结直肠癌肝转移患者手术时机的选择、腹腔镜下肝转移灶切除的影响及优势, 肝移植在结直肠癌肝转移患者中的应用等. 本文旨在结合结直肠癌肝转移的手术进展和患者的实际情况, 为患者选择最佳的治疗方案, 从而提高患者的生存时间.

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关键词: 结直肠癌肝转移; 手术; 预后

核心提要: 手术是结直肠癌肝转移患者的治疗的唯一治愈的方式, 要根据患者实际情况、多学科讨论, 选择最佳的手术方案, 从而提高患者的生存率。

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0 引言

世界范围内, 结直肠癌发病率在各种癌症中排名第三, 死亡率排名第二, 而其在中国, 发病率上升为第二, 死亡率排名第五^[1]. 近50%的结直肠癌患者在病程中会发生肝脏转移, 约25%患者发生同时性肝转移, 即在初诊时便发现存在肝转移, 另25%患者会出现异时性肝转移, 即在原发病灶根治性手术后出现肝转移^[2]. 肝转移是影响结直肠癌患者预后的主要原因之一, 未及时治疗肝转移的结直肠癌肝转移(colorectal liver metastasis, CRLM)患者的平均寿命只有6-12 mo, 5年生存率小于10%^[3].

迄今, 手术仍是治愈CRLM的唯一方法, 其可将CRLM患者术后5年和10年生存率分别提高至35%-60%和20%^[4,5]. 通过影像学评估肝转移灶R0可切除性及术后残余肝体积可将CRLM分为初始可切除、潜在可切除以及不可切除肝转移灶三类^[6], 仅约20%的CRLM为初始可切除^[7], 转化治疗能把CRLM可切除比例提高至50%左右^[8]. CRLM患者的肝转移灶切除术后复发率高, 超过50%的CRLM患者在肝转移灶切除后出现复发, 其中约92%患者在术后2年内出现复发^[9,10], 复发后再次肝切除术被证明可提高患者生存率^[11]. 相比之下, 具不可切除的复发肝转移灶的CRLM患者预后较差, 即使进行化疗, 其5年生存率仍低于10%^[12].

随着医疗技术、药物研发的进步, CRLM患者的诊疗过程逐渐发展为MDT模式, 即在多学科诊疗团队的综合评估决策下, 以患者为中心, 联合手术为主, 辅助化疗、免疫靶向治疗、介入治疗等为辅的相互补充的个体化综合性治疗. 参与MDT的科室主要包括: 外科、肿瘤科、放射科、病理科, 有时还需要麻醉、护理等相关科室. 通过多名专家共同商议讨论, 为患者明确诊断与分期, 制定最为适宜的治疗方案. MDT诊疗模式明显的提高了CRLM患者的手术的切除率, 降低了其术后的复发率, 进而延长其无病生存与总存活时间^[13,14].

1 CRLM患者的手术指征

手术是目前CRLM患者获得根治的唯一方法. 只要患者

一般情况可耐受手术, 原发病灶已控制或可控制, 无不可切除的肝外转移病灶, 影像评估肝转移灶可完全切除(R0), 并且术后能保留足够的功能性肝脏, 都可以考虑切除肝转移灶^[15]. 对于肝转移灶体积大或病灶多等需要行扩大肝切除的, 或合并肝硬化等基础肝病的CRLM患者, 术前需准确评估其术后残余肝储备, 这对于预防术后肝功能衰竭至关重要. 正常肝组织的患者极限情况下仅需25%残余肝脏便可以维持术后正常的肝功能, 慢性肝病但无肝硬化的患者通常至少需要30%残余肝脏才能维持, 而肝硬化但无门静脉高压的患者则至少需40%的残余肝脏才能降低术后发生肝功能衰竭的风险^[16,17]. 另外, 对于部分经过放化疗等系统治疗或介入治疗的CRLM患者, 即使既往无肝脏基础疾病, 但仍需考虑前述治疗对于肝脏功能的损伤, 术后也要保留足够比例的残余肝脏, 以防止术后肝功能衰竭的发生.

CRLM患者中可一期完整切除肝转移灶(R0)的比例相对较少. 为提高CRLM的手术切除率, 可通过新辅助治疗、介入治疗、二阶段肝切除等转化治疗使部分不可一期完整切除肝转移灶的CRLM患者的肝转移灶变小或术后残余肝体积增大, 从而达到符合肝转移灶整体切除(R0)的标准.

2 新辅助治疗与CRLM手术

新辅助治疗存在多种选择, 包括单独或联合使用放疗、化疗等, CRLM的新辅助治疗已被证明能够在治疗性手术之前有效地减少肝转移肿瘤负荷^[18,19]. 目前欧洲肿瘤内科学会指南建议联合奥沙利铂、亚叶酸钙及5-氟尿嘧啶方案(FOLFOX)或联合卡培他滨与奥沙利铂方案(XELOX)可作为潜在可切除CRLM的一线新辅助治疗方案, 而联合5-氟尿嘧啶、亚叶酸钙及伊立替康方案(FOLFIRI)或联合5-氟尿嘧啶、亚叶酸、伊立替康及奥沙利铂方案(FOLFOXIRI)等可作为其替代新辅助治疗方案^[20]. 目前临床实践在此基础上衍生出了各种方案, 增加了潜在可切除CRLM的转化效率. D'Angelica等^[21]报道联合肝动脉灌注化疗和系统化疗可使CRLM患者的初始不可切除肝转移灶的完整切除率提高到47%, 将此类CRLM患者3年生存率提高至80%, 而未能转化为可切除肝转移灶的CRLM患者的3年存活率仅为26%. 经过新辅助治疗后, 部分CRLM患者的肝转移灶在影像学上可能会消失, 但其在病理学上并不一定消失, 这不仅影响了手术的切除率, 还提高了术后的复发率^[22,23]; 因此, 在临床上应预防新辅助治疗后出现影像学上病灶消失的现象, 建议每2-3个新辅助治疗周期后重新评估肝转移灶的状态, 以便更早地做出手术决策, 提高手术切除率^[24,25].

3 分阶段肝切除技术与CRLM

通过新辅助化疗可使肝转移病灶缩小, 提高CRLM的手术切除率, 但仍有部分CRLM患者, 因肝转移灶切除术后残余肝脏过少而限制了手术的进行。因此, 通过促进残余肝脏体积的生长, 也可以提高CRLM的切除率。增加CRLM患者术后残余肝体积的主要方法包括传统的两步肝切除(two-stage hepatectomy, TSH)、联合肝脏离断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)等^[16,26]。TSH在第一步可行门静脉栓塞(portal vein embolism, PVE)或门静脉结扎(portal vein ligation, PVL)等方法促进残余肝脏体积肥大, 4-8 wk内可使侧侧肝体积增加27%-39%, 进而提高肝转移灶的切除率^[27,28]。广义的TSH, 在第一步可切除部分肝转移灶, 减轻肝脏的肿瘤负荷, 后可根据肝转移病灶及残余肝体积等情况而进行多步肝切除, 直到肝转移肿瘤被完全切除^[27]。显然, TSH存在两步肝切除间隔时间较长及残留肝转移病灶生长速度过快等风险, 可能导致相对肿瘤负荷增加, 使CRLM患者彻底失去手术机会。近年发展起来的ALPPS也能在短时间内促进残余肝体积的生长, 且能在物理上隔绝病灶的肝内播散, 从而提高肝转移灶的切除率^[29]。Andreas等^[30]在2012年首次报道了ALPPS技术, 经历了ALPPS第一步的25名肝肿瘤患者, 在平均9天里肝脏残余体积增加了74%, 降低了等待时间, 增加了二次手术切除率。后ALPPS技术也逐渐用于CRLM患者。Hasselgren等^[31]纳入100名CRLM患者, 将他们随机分到ALPPS组与TSH组, 发现ALPPS组患者的肿瘤切除率与术后完全缓解率分别为92%和77%, 而TSH组的肿瘤切除率及术后完全缓解率为80%和57%; ALPPS组与TSH组患者的中位生存期分别为46 mo与26 mo。故ALPPS比TSH更好地降低了CRLM患者两次手术的等待时间, 并且提高了肿瘤切除率、术后完全缓解率及中位生存期。随着ALPPS技术的成熟, ALPPS将为不可切除肝转移病灶的CRLM患者带来新的希望。

4 CRLM手术切缘与预后

对于CRLM患者, 在残余肝功能足够的前提下, R0切除会获得更好的存活率。Margonis等^[32]纳入34项研究共11477例CRLM手术患者, 分析肝转移病灶R0切除后的边缘状态与患者生存关系, 结果显示>1 cm的肝转移灶切缘能够更好地改善无病生存时间, 且具有更高的3年、5年、10年总存活率。另外, 在切缘<1 cm的CRLM患者中, CRLM手术切缘>1 mm比<1 mm具有更好的预后^[32]。这提示我们应在保证残余肝体积足够的前提下, 尽可能地达到相对宽的切缘。当然, 手术切缘对于

CRLM患者预后的影响可能被肿瘤的生物行为改变。对于RAS野生型CRLM患者, 因其对于系统治疗反应好, 肝转移灶R1切除与R0切除对比, 总生存率无显著性差异^[33]。Georgios等^[34]对332例CRLM患者进行生存分析也发现R0切除与R1切除的中位生存期亦无统计学差异, 考虑患者本身和肿瘤的因素对于CRLM患者预后的影响在一定程度上要超过切缘的影响。随着CRLM患者综合治疗理念的进步, 越来越多的研究发现, 虽然肝转移灶R1切缘与CRLM患者较低的无病生存时间显著相关, 但并不影响其总存活率^[35-37]。

5 同时性结直肠癌肝转移与手术时机

CRLM存在同时性肝转移和异时性肝转移两大类^[38]。对于异时性肝转移, 可经过MDT讨论来决定先系统治疗还是手术等局部治疗。对于同时性CRLM患者, 其手术时机根据原发灶与肝转移灶手术的先后可以分为分期手术、同期手术以及肝脏优先切除手术。分期手术为CRLM传统的手术方式, 即先切除原发肿瘤, 术后可进行或不进行系统性治疗, 待患者恢复后再切除肝转移^[39]。同期手术是指一期手术将原发病灶及肝转移病灶同时切除^[40], 目前多应用于肝转移灶容易切除的CRLM患者^[41]。肝脏优先手术指先切除肝转移灶, 待患者恢复后再考虑行原发病灶的切除^[42], 这种策略适用于具进展期的肝转移灶且原发肿瘤无症状的CRLM患者。不少研究发现分期、同期和肝脏优先入路三种手术方式对于CRLM患者生存时间的影响并没有显著性差异^[43,44]。但是, 三种手术策略在短期之内的并发症却不尽相同。在开腹手术中, 同期手术因为需要同时切除原发灶及转移灶, 手术创伤大, 术中术后并发症多, 患者难以耐受^[45]。随着腹腔镜微创技术的进步, 这种情况在逐步改善。另外, 有研究发现CRLM患者术后的主要并发症发病率和死亡率与肝切除的程度和高危结肠术式相关, 而不是切除的时机^[46]。

6 CRLM腹腔镜技术与传统开放手术的比较

因为CRLM的多发性, 现阶段开放肝切除术仍然是CRLM主要的手术方式。开放肝切除术的切口包括右肋下及剑突下“人”型切口等, 加上术中长时间对肋缘牵拉, 手术创伤大, 术后早期容易出现伤口疼痛, 腹压的升高还可能导致伤口破裂, 甚至有远期切口疝的风险^[47,48]。近年来, 腹腔镜肝切除术已经越来越多地应用于CRLM患者的肝转移灶切除^[49]。腹腔镜微创技术的应用, 可避免长切口相关并发症, 减轻术后疼痛, 缩短住院时间, 并能促进术后肝功能的恢复。在腹腔镜经验丰富的医疗单位, 部分CRLM患者进行全腹腔镜同期切除原发结直肠癌及肝转移灶也是安全可行的。关于腹腔镜及开腹行

效的比较, Xie等^[50]纳入了32项非随机研究中的4697例CRLM患者, 其中腹腔镜下肝转移灶切除1809人, 开放性肝转移灶切除2888人, 发现腹腔镜肝切除手术时间相对更长, 但术中出血量和输血量更少, 总并发症发病率更低, 术后住院时间更短, 但在围手术期死亡率、疾病复发、3年或5年总体生存和无病生存等方面无明显差异。因此在有条件的医疗单位, 选择合适的CRLM患者, 腹腔镜下肝转移灶切除似乎是开放手术的一种安全可行的替代方案。

7 肝移植术与CRLM

虽然手术是治愈CRLM患者的有效方法, 但可切除肝转移灶的比例低。不可手术的CRLM患者经过全身系统性治疗后获得的中位生存期及5年生存率也相对较低^[51]。因此, 部分无法切除肝转移灶的CRLM患者, 曾被尝试行肝移植手术, 但早期研究中CRLM患者肝移植术后5年生存率仅12%左右^[52], 故这种方式被长期搁置。近年来, 有不少研究者重新开始对CRLM患者肝移植术进行研究, 认为在合理的患者选择后, 通过肝移植提高CRLM患者的生存率是可行的^[53,54]。所有具不可切除肝转移灶且无肝外肿瘤(可切除的肺转移除外)的CRLM患者都是潜在的移植对象^[55]。肝移植涉及供体、费用、术后护理等问题, 需要更多的研究来整体评估肝移植术对CRLM患者的治疗。

8 结论

CRLM患者分期晚, 手术是治愈CRLM的唯一方法。CRLM初始可切除率较低, 通过新辅助治疗、传统TSH、ALPPS等方法能够有效提高CRLM的手术切除率。肝转移灶R0切除是提高CRLM患者术后生存率的重要因素, 但即使是R1切除, 对CRLM患者总生存率的提高也有显著性意义。同时性肝转移病灶的三种手术方式对患者的无病生存率及总生存率的影响均无显著性差异, 需根据患者实际情况选择最佳方案。在手术操作上, 腹腔镜与开放肝转移灶切除对CRLM患者总生存率的影响无显著性差异, 但是腹腔镜技术能够明显减少术后并发症。肝移植在CRLM患者中的应用有待进一步研究。

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