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Surgical management of liver metastases from colorectal cancer

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Abstract: With the persistent rise in colorectal cancer incidence, approximately 50% of patients develop liver metastases during the disease course. According to international staging systems, colorectal cancer liver metastases (CRLM) are classified as advanced-stage malignancies, typically associated with poor clinical prognoses. In recent years, the CRLM treatment paradigm has undergone multidimensional evolution. Against the backdrop of continuously evolving therapeutic concepts, comprehensive treatment strategies centered on surgical intervention have demonstrated substantial survival benefits. Notably, the integration of novel therapies—including targeted agents and immunotherapy—has not only significantly extended overall survival in advanced cases but also markedly improved the resectability of hepatic metastatic lesions. From a technical perspective, innovations such as intraoperative ultrasound navigation, radio frequency ablation combined with resection techniques, and fluorescence laparoscopy-guided precise hepatectomy have achieved breakthroughs in surgical safety and accuracy. Nevertheless, critical controversies persist in the surgical management of CRLM, particularly regarding the refinement of surgical indications, optimization of surgical timing within multidisciplinary frameworks, and evidence-based selection of local treatment modalities, all of which remain subjects of ongoing debate. This review synthesizes recent high-impact literature with our institutional expertise in CRLM management to summarize contemporary advancements and share practical insights, aiming to inform clinical decision-making and enhance surgical outcomes in CRLM treatment.

Keywords: Colorectal cancer; Liver metastasis; Surgical treatment; Intraoperative ultrasound navigation; Radiofrequency ablation; Precise hepatectomy; Laparoscopic liver resection

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Colorectal cancer is a type of common digestive tract tumor. According to the latest data from the National Cancer Center in 2024, there were 517,200 new cases of colorectal cancer in China in 2022, ranking second in incidence, and 240,000 deaths, ranking 4th in mortality. Meanwhile, both incidence and mortality are still gradually increasing [1]. It is reported that approximately 50% of colorectal cancer patients develop liver metastases, with about 15% presenting with synchronous liver metastases [2-3]. The median survival time of patients undergoing surgical treatment is 43.2 months, with a 5-year overall survival rate of 42%, while the 5-year overall survival rate of patients receiving systemic therapy alone is merely 9%. For synchronous liver metastases, synchronous or staged surgical treatment of colorectal cancer liver metastases (CRLM) is the primary means to prolong patient survival. Compared with staged surgery, synchronous resection of the primary tumor and metastatic lesions has certain advantages, such as removing both lesions in a single operation, lower cost, similar complication rates, and better prognosis. Thus, synchronous resection is increasingly recommended by

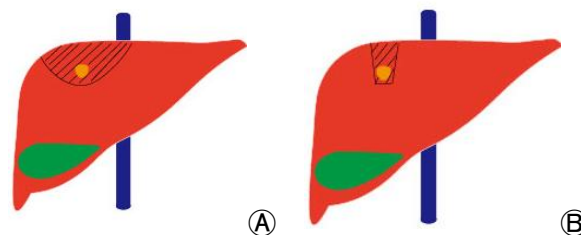
physicians [4]. However, there remains controversy regarding the timing of surgery for initially resectable patients [5-6]. Risk factors affecting the prognosis of surgical treatment for CRLM are also being continuously explored. Approximately 75% of patients experience recurrence after surgical treatment, with 5-year progression-free survival and overall survival rates of 21.2% and 46.4% respectively [7-8]. A study by Wicherts *et al.* [9] showed that patients undergoing repeat liver resection after recurrence achieved 3-year and 5-year survival rates of 76% and 54% respectively, indicating that patients with CRLM can still benefit from reoperation after initial liver resection. Therefore, the concept of preserving liver parenchyma has emerged to ensure sufficient hepatic volume for potential secondary surgery by maximizing the preservation of liver parenchyma during the initial liver resection [10]. For initially unresectable CRLM, surgical resection after successful conversion therapy is also feasible. Additionally, patients with unresectable intrahepatic lesions can benefit from local treatments such as radiofrequency ablation (RFA), microwave ablation

(MWA), stereotactic radiotherapy (SRT), and interventional therapy [11]. This article reviews the progress in surgical and local treatments for CRLM and shares clinical experiences, aiming to improve the level of treating CRLM.

1 Surgical resection for CRLM

Scholars believe that the evaluation of resectability for CRLM should consider both technical resectability and oncological resectability. For example, if a tumor is technically resectable but oncologically unresectable, surgical resection is not recommended, as even if the surgery is performed, patients will not benefit due to short-term recurrence of the tumor postoperatively. There is no clear standard for evaluating oncological resectability, and guidelines recommend evaluation referring to the CRS score. Sasaki *et al.* [12] introduced the tumor burden score (TBS), and studies have shown that CRLM with RAS, BRAF, TP53, and SMAD4 mutations show worse prognoses. A Japanese study in 2021 found that patients with V600E BRAF-mutated CRLM who are technically resectable have survival outcomes as poor as those with unresectable disease. Thus, the authors argue that the presence of V600E BRAF mutations alone should be an absolute contraindication for surgery in technically resectable CRLM patients [13-14]. CRLM combined with hepatic lymph node (HLN) metastasis is also a key factor for poor postoperative prognosis. Most researchers consider HLN metastasis as either a recurrence of CRLM or regional lymph node metastasis of CRLM. Therefore, during hepatic resection, HLN dissection is required for cases with suspected HLN metastasis. Studies show that 10%–30% of CRLM cases develop HLN metastasis. Even if both hepatic metastatic lesions and HLN are completely resected, the 5-year postoperative survival rate is still only 10%–20%, leading some scholars to view CRLM with HLN metastasis as a contraindication for surgery [15-17]. The team of Hepato-Biliary-Pancreatic Surgical Oncology, Peking University Cancer Hospital, Inner Mongolia Campus believes that for initially resectable CRLM with high recurrence risk, the efficacy of neoadjuvant therapy can predict the prognosis of surgical treatment. Previous experience shows that patients with CRLM who respond well to neoadjuvant therapy in tumor shrinkage and have a longer duration of response (DOR) show better prognoses, and vice versa. There remains debate regarding whether to continue chemotherapy with a second-line regimen or proceed directly to surgery in cases where tumors progress after neoadjuvant therapy [18]. Active surgical resection for CRLM with extrahepatic metastasis still enables some patients to achieve long-term survival or even cure. For initially unresectable CRLM, patients who undergo resection after successful conversion therapy can still benefit [19]. There is no unified standard for the timing and duration of conversion therapy. Our team's experience is to evaluate efficacy every 2 cycles, actively proceeding to surgery for cases with significant efficacy

and resectability to avoid over-treatment which may lead to lesion disappearance and uncertain resection, and chemotherapy-related liver injury. For disappeared lesions, there are two management approaches: (1) performing intraoperative ultrasound tools to detect and address lesions which were not found preoperatively; (2) rechecking with enhanced liver MRI 3–4 weeks after stopping chemotherapy, as disappeared lesions may reappear, allowing subsequent resection. Our team believes that disappeared lesions may still be active and pose a potential risk of local recurrence. Additionally, if all resected intrahepatic lesions have a TRG score of 0 (i.e., pathological complete response), preoperatively disappeared lesions or lesions which are not addressed intraoperatively (e.g., unsuitable for resection or local treatment) will behave likely inactive, and no further postoperative management is required. The necessity of neoadjuvant therapy for initially resectable CRLM remains controversial [20]. Surgical resections of synchronous CRLM are divided into simultaneous resection and staged resection. The staged resection is further categorized into liver-first and primary-first approaches. There is no difference in overall survival or disease-free survival between the two approaches, but the liver-first approach is currently more widely accepted, particularly for patients with multiple liver lesions and high tumor burden [21-22]. Simultaneous resection confers more significant survival benefits for synchronous CRLM patients with wild-type KRAS, whereas for those with KRAS-mutated CRLM, survival outcomes are similar between simultaneous and staged resection [23]. Additionally, there is no uniform standard for the order of primary and metastatic lesion resection in simultaneous resection. Our team's experience suggests prioritizing liver lesion resection and there are two reasons: (1) avoiding gastrointestinal congestion caused by hepatic hilar inflow occlusion during liver resection adversely affecting anastomotic healing, thereby reducing the risk of anastomotic fistula; (2) adhering to aseptic principles. Notably, the liver-first approach is premised on the resectability of the primary lesion. Furthermore, implementing hepatic resection with the principle of preserving liver parenchyma is crucial, with a 1 mm margin being a widely recognized standard and a concrete manifestation of this principle. For local resection of hepatic lesions, our team's technique involves "bowl-shaped" rather than "well-shaped" resection to ensure no tumor cells are observed at the incision margin and effective hemostasis [Figure 1].



Note: A is the "bowl-shaped" hepatic wound surface; B is the "well-shaped" hepatic wound surface.

Fig.1 Local resected wound of liver disease lesion

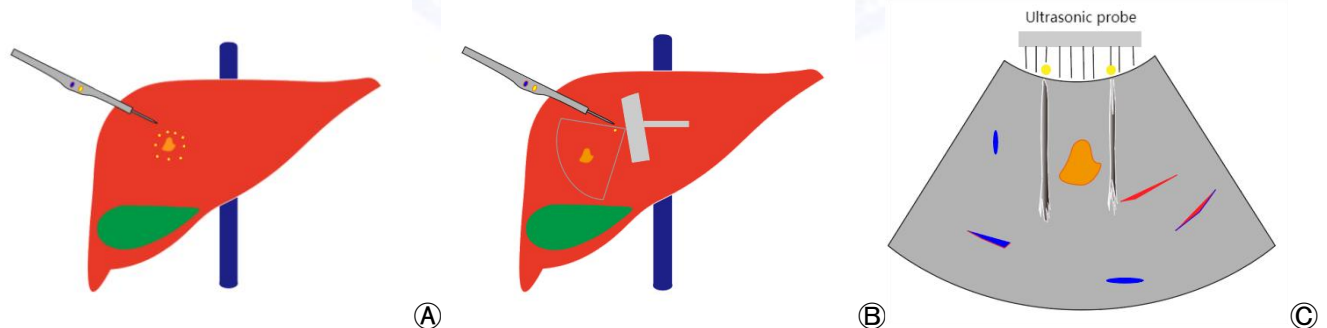
For patients with extensive hepatectomy and insufficient remaining liver volume, particularly those with colorectal liver metastases complicated by chemotherapy-associated steatosis and liver dysfunction, preserving more remaining liver tissue can significantly reduce the incidence of postoperative liver failure. Studies have shown that the 5-year survival rate is 51% in patients undergoing two-step hepatectomy, compared to 15% in non-surgical patients with inadequate remaining liver tissue. Current conventional two-step hepatectomy methods include portal vein embolization, hepatic vein embolization, and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) [24].

Liver transplantation can serve as one of the treatment options for patients with colorectal liver metastases confined to the liver who are not candidates for surgical resection. However, strict criteria exist for patient selection, such as excluding those with primary right-sided colon tumors, BRAF gene mutations, N2 stage, or poorly differentiated tumors. The Oslo Liver Transplant Score for Colorectal Liver Metastases has been proposed, comprising four components: (1) maximum diameter of liver metastatic tumors >5.5 cm; (2) tumor progression after chemotherapy; (3) interval between colorectal cancer resection and liver transplantation <24 months; (4) carcinoembryonic antigen (CEA) >80 $\mu\text{g/mL}$ (1 point per component, total 4 points). Patients with an Oslo score of 0-1 have a 10-year survival rate of 50%, while those with a score of 2 have a 10-year survival rate of 33% [25-26].

2 Application of intraoperative ultrasound in hepatectomy for CRLM

In recent years, intraoperative ultrasound has been widely used in hepatic surgery, particularly valuable in CRLM [27]. Studies have found that intraoperative ultrasound can detect additional intrahepatic lesions in CRLM patients, thereby altering preoperatively planned surgical strategies. Meanwhile, contrast-enhanced intraoperative ultrasound (CE-IIOUS) not only clarifies lesion characteristics but also significantly increases the

detection rate of additional lesions, particularly demonstrating higher sensitivity in detecting intrahepatic lesions that were undetectable by preoperative imaging after chemotherapy [28-29]. However, intraoperative ultrasound or CE-IIOUS sometimes struggles to determine the nature of newly detected lesions, especially when severe post-chemotherapy liver injury, necrotic liquefaction, or calcification of metastatic lesions occurs. Our team's experience is to decisively manage such lesions (e.g., resection or ablation) without compromising surgical safety, maximizing the avoidance of missed metastatic lesions. CE-IIOUS should be routinely performed during surgery, with careful scanning of the left lateral lobe, left medial lobe, right anterior lobe, and right posterior lobe in sequence, followed by comparison with lesions identified by preoperative imaging to strictly prevent missed lesions. Additionally, intraoperative ultrasound examination can assist in planning surgical margins and improving the R0 resection rate [30-31]. For margin planning, lesions are categorized into two types based on their intrahepatic location: "liver surface type" and "superficial intrahepatic type," with tailored designs for each. The "liver surface type" refers to lesions visible on the liver surface. For these, an electric scalpel is used to mark a circumferential surface margin, and the lesion is resected after intraoperative ultrasound determines its depth [Figure 2A]. The "superficial intrahepatic type" refers to non-visible, superficially located intrahepatic lesions that can be locally resected. The surgical margins for this type requires the full use of intraoperative ultrasound. Our team's approach involves: first, using intraoperative ultrasound to roughly determine the projection of the lesion on the liver surface; then, marking the surface with electrocautery [Figure 2B]; rechecking with ultrasound to ensure the acoustic shadow of the cauterized site aligns with the outer margin of the intrahepatic lesion [Figure 2C]; and repeating the process if adjustments are needed. Finally, the circumferential margin is designed on the liver surface, and palpation of the lesion during resection aids in assessing the intrahepatic margin.



Note: A: surgical margin for the liver surface type; B: surgical margin for the superficial intrahepatic type; C: intraoperative ultrasound for the superficial intrahepatic type.

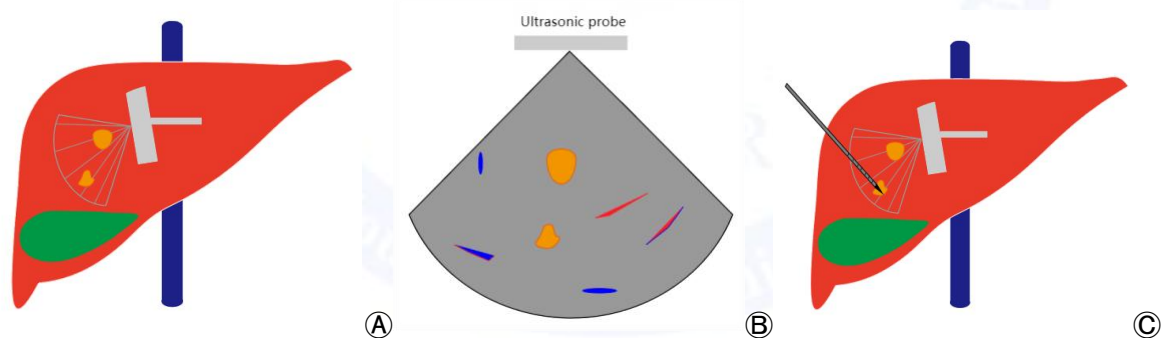
Fig.2 Planning of the resection margin of the lesion and Schematic diagram of intraoperative ultrasound

3 Application of intraoperative ablation in CRLM

Ablation techniques are increasingly used in CRLM, aiming to completely destroy tumors through thermal injury while preserving adjacent healthy liver tissue. Common thermal ablation techniques include microwave ablation (MWA) and radiofrequency ablation (RFA), which can be categorized into percutaneous ablation and intraoperative ablation based on the approach. For intrahepatic lesions that are multiple, small, deeply located, in special positions (e.g., adjacent to major blood vessels), or unsuitable for surgical resection, MWA or RFA represents an excellent option, with some lesions achieving outcomes comparable to surgical resection. The latest phase III international multicenter randomized controlled study demonstrates that for CRLM patients with ≤ 10 liver metastases and a maximum lesion diameter < 3 cm, thermal ablation is non-inferior to surgical resection. Studies indicate that lesion size is the most critical factor affecting ablation efficacy, with the maximum diameter of a single ablated lesion generally not exceeding 3–4 cm. Compared to percutaneous ablation, intraoperative ablation is safer for managing intrahepatic lesions in special locations, such as deeply seated lesions without a suitable puncture path or those adjacent to hollow organs like the gallbladder or gastrointestinal tract. Lesions located < 1 cm from the main bile duct are contraindications for ablation, as they may lead to bile duct injury, stricture, or abscess formation[32].

Our team believes that the location of ablation needles, ablation power (energy), and ablation sequence

are also key factors influencing efficacy. A shorter ablation path can improve puncture accuracy and reduce complications. Before needle placement, the ultrasound probe should be used to carefully scan the lesion size and morphology in 360° , with the long axis of the lesion serving as the needle placement plane. A suitable puncture path is selected for needle insertion. Since metastatic tumors are firmer than normal liver tissue, resistance at the needle tip upon reaching the lesion helps confirm accurate targeting. After ablation, ultrasound should recheck for complete ablation, with secondary ablation performed if necessary. Attention should be paid to ablation of the needle tract and hemostasis at the puncture site. The settings for ablation power and duration depend on lesion size and location, with no uniform standard. Compared with hepatocellular carcinoma, metastatic liver tumors lack a capsule, leading to easier diffusion and dissipation of local thermal energy. Thus, theoretically, larger energy and longer ablation time are required for metastatic lesions of the same size. Our team uses MWA, with typical parameter settings as follows: < 1.0 cm lesions—power 50 W, duration 1 min; 1.0–1.5 cm lesions—power 50 W, duration 1.5 min; 1.5–2.0 cm lesions—power 60 W, duration 1.5 min. Ablation for lesions > 2.0 cm is approached conservatively. For lesions adjacent to blood vessels, increased energy or longer ablation time is needed to achieve satisfactory results due to energy dissipation via blood flow. For multiple lesions within the same ablation plane, our team recommends ablating deeper lesions first, followed by superficial ones, to avoid acoustic interference from superficial ablation affecting the localization and efficacy of deeper lesions [Figure 3].



Note: A: Ultrasound examination; B: Two lesions within the ablation plane; C: Ablating deeply seated lesions and the white part is ultrasonic probe.

Fig.3 Schematic diagram of ablation methods for multiple lesions on the same plane

4 Application of laparoscopic liver resection (LLR) in CRLM

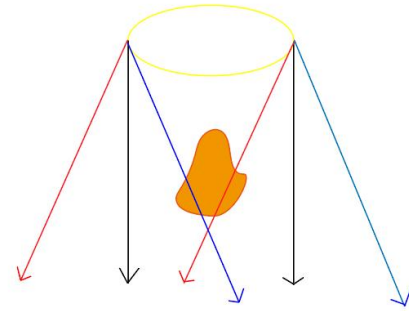
LLR has been widely applied in the management of CRLM, offering multiple advantages over open surgery. However, the number of intrahepatic lesions remains a primary limitation to the use of LLR. Despite over two decades of development, most surgeons perform LLR for CRLM with ≤ 5 lesions (typically 1–2), as there is

currently no evidence supporting the feasibility of LLR for multi-lesion resection. Nassar *et al.*[33] suggested that LLR is not restricted by the number of intrahepatic lesions and is safe and feasible for managing multiple CRLM. Additionally, LLR for multi-lesion CRLM appears feasible under the guidance of the parenchymal-sparing principle, particularly with advancements in intraoperative navigation technologies such as intraoperative ultrasound and fluorescence laparoscopy, which significantly enhance the safety and

feasibility of LLR.

Studies have found that approximately 80% of CRLM patients have multiple intrahepatic lesions, and the number of lesions affects the R0 resection rate. Thus, ensuring margin safety and improving the R0 resection rate are critical in LLR. When ablating deeply seated intrahepatic lesions using LLR, resection along the liver surface margin guided by intraoperative ultrasound often results in incorrect resection planes, incising into the lesion, risky margins or tumor residue [Figure 4]. This challenge can be effectively addressed by fluorescence laparoscopy. Indocyanine green (ICG) is excited by near-infrared light (wavelength: 750–810 nm) to emit fluorescence at 840 nm, with a tissue penetration depth of 5–10 mm. ICG fluorescence imaging demonstrates an overall sensitivity of 83% for identifying CRLM lesions, reaching 100% sensitivity for lesions <8 mm from the liver capsule[34]. There is currently no uniform standard for ICG dosage and administration in CRLM. Our team's experience indicates that intravenous injection of 0.5 mg/kg ICG 3 days preoperatively yields optimal staining. Notably, the same 0.5 mg/kg dosage is used for the ICG 15-minute retention test (ICG-R15) to assess liver function, allowing a single ICG injection to serve both purposes: evaluating liver function and facilitating intraoperative fluorescence imaging. CRLM lesions exhibit unique ICG staining characteristics: tumors do not

uptake ICG, but compression of surrounding bile ducts by the tumor causes ICG retention, resulting in a circumferential fluorescent ring around the tumor [Figure 5A]. Given the 5–10 mm tissue penetration depth of ICG fluorescence, the safety margin for deeply seated lesions is defined by the absence of fluorescence on the preserved liver surface, ensuring at least a 5 mm effective margin. This approach achieves R0 resection while maximizing parenchymal preservation [Figure 5B, 5C]. Additionally, ICG plays a crucial role in detecting small metastatic lesions on the liver surface.



Note: Yellow represents the resection line on the liver surface, black is the correct plane (safe resection margin), and red and blue are the incorrect planes.

Fig.4 Schematic diagram of laparoscopic liver resection



Note: A: the circumferential staining of the tumor margin induced by ICG; B: the staining of the tumor by ICG; C: the appearance after lesion resection.

Fig.5 Application of indocyanine green fluorescence imaging in CRLM

5 Summary

In recent years, the concept of surgical treatment of CRLM has been constantly updated. Although CRLM is advanced-stage malignancy, due to its special oncological characteristics, surgical resection combined with other local treatments, such as ablation, stereotactic radiotherapy, and interventions can significantly prolong the survival, and some patients can even be cured. In addition, with the development of intraoperative ultrasonography, ICG imaging, and intraoperative 3D navigation techniques have further improved the safety and feasibility of CRLM surgical treatment.

Conflict of interest None

Reference

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· 研究进展 ·

结直肠癌肝转移外科治疗

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摘要: 随着结直肠癌发病率的持续攀升,约 50% 的患者在病程中会出现肝转移。根据国际分期标准,结直肠癌肝转移(CRLM)已属晚期病变,其临床预后普遍不良。近年来,CRLM 治疗体系呈现多维度发展态势,在治疗理念持续革新的背景下,基于外科手术的综合治疗方案已被证实可为患者带来显著生存获益。值得关注的是,靶向药物及免疫治疗等新型治疗手段的应用,不仅明显延长了晚期患者的总体生存期,同时使肝转移病灶的可切除率显著提升。在手术技术层面,术中超声导航、射频消融联合切除技术以及荧光腹腔镜引导下的精准肝切除等创新方法,已使手术安全性和精准度获得突破性提升。然而,目前 CRLM 在外科治疗领域仍存在诸多争议,包括手术指征的把握、多学科协作模式下的手术时机选择、不同局部治疗手段的适应证界定等关键问题尚未形成统一共识。本文通过对 CRLM 外科治疗进展进行总结和经验分享,以期提升 CRLM 外科治疗水平提供实践参考。

关键词: 结直肠癌; 肝转移; 外科治疗; 术中超声导航; 射频消融; 精准肝切除; 腹腔镜肝切除

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Keywords: Colorectal cancer; Liver metastasis; Surgical treatment; Intraoperative ultrasound navigation; Radiofrequency ablation; Precise hepatectomy; Laparoscopic liver resection

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结直肠癌是常见的消化道肿瘤,2024年国家癌症中心发布的最新数据显示,2022年我国结直肠癌发病例数为51.72万人,发病率位居第2位,死亡病例数为24万人,死亡率位居第4位,

发病率和死亡率逐渐上升^[1]。据报道,约50%的结直肠癌患者会出现肝转移,其中约15%的患者出现同时性肝转移^[2-3]。接受手术治疗患者的中位生存时间为43.2个月,5年总生存率

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为42%,而接受单纯系统治疗的患者的5年总生存率仅为9%。对于同时性肝转移而言,同期或分期手术治疗结直肠癌肝转移(colorectal cancer liver metastases, CRLM)是延长患者生存的最主要手段,与分期手术相比,原发灶和转移灶同期切除具有一定优势,如一次手术可切除两处病变、花费低、有相近的并发症发生率、更好的预后等,故同期切除被越来越多的医生所推荐^[4],但对于初始可切除的患者,手术时机的把握仍存在争议^[5-6]。影响CRLM手术治疗预后的危险因素也在不断探索。手术治疗后约75%的患者出现复发,5年无进展生存率及总生存率分别为21.2%、46.4%^[7-8]。Wichert等^[9]研究显示,复发后再行肝切除的患者3年和5年生存率分别达到76%和54%,说明CRLM术后再次手术患者仍然可获益,故首次肝切除需尽可能保留足够的肝实质,为接受二次手术提供足够的肝体积,故保留肝脏实质的概念应运而生^[10]。对于初始不可切除的CRLM,转化成功后再行手术切除也是可行的,此外,对于不可切除的肝内病灶,行射频消融(radiofrequency ablation, RFA)、微波消融(microwave ablation, MWA)、立体定向放疗(stereotactic radiotherapy, SRT)及介入治疗等局部治疗患者仍可获益^[11]。本文就CRLM的外科及局部治疗进展进行文献复习及经验分享,旨在提高CRLM的治疗水平。

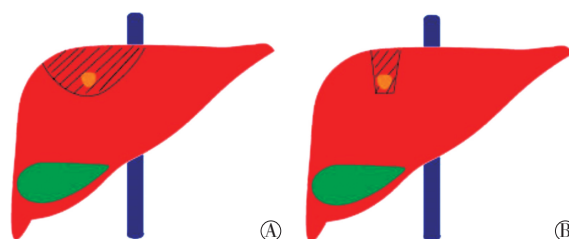
1 手术切除治疗CRLM

学者们认为CRLM可切除性的评价应该从技术可切除性和肿瘤学可切除性两方面考虑。如技术上可切除,但肿瘤学不可切除是不推荐手术切除的,因为即使手术切除,术后肿瘤短期内复发患者并不获益。对肿瘤学可切除性的评价尚无明确标准,指南推荐参考CRS评分,Sasaki等^[12]引入了肿瘤负荷评分(tumor burden score, TBS),也有研究显示RAS、BRAF、TP53及SMAD4突变的CRLM预后更差,日本2021年的一项研究发现,技术上可切除的V600E、BRAF突变CRLM患者的生存结果与不可切除的患者一样差,因此该作者认为对于技术上可切除的CRLM患者,仅存在V600E、BRAF突变就应该是手术的绝对禁忌证^[13-14]。CRLM合并肝门周围淋巴结(hepatic lymph node, HLN)转移也是手术后预后不良的关键因素至之一,多数研究者认为HLN转移是CRLM再转移,也可以认为是CRLM的区域淋巴结转移,故手术肝切除时对于HLN可疑转移者需清扫HLN。研究表明10%~30%的CRLM会发生HLN转移,即使将肝转移病灶和HLN一并完整切除,术后5年生存率仅10%~20%,故也有学者认为合并HLN转移的CRLM是手术禁忌证^[15-17]。北京大学肿瘤医院内蒙古医院肝胆胰肿瘤外科团队(以下简称本团队)认为,对于高危复发风险的初始可切除CRLM,新辅助治疗的疗效可预测手术治疗的预后情况,经验表明,新辅助治疗缩瘤效果好且有较长缓解持续时间(duration of response, DOR)的CRLM患者预后更好,反之亦然。研究认为,新辅助治疗后肿瘤进展,选择二线方案继续化疗还是直接手术仍然存在争议^[18]。CRLM合并肝外转移积极手术切除,仍然有部分患者获得长期生存甚至治愈。针对初始不可切除的CRLM,转化治疗成功后再行手术切除

患者仍然可获益^[19]。对于转化治疗的时间及疗程目前无统一标准,本团队的经验是每2个周期评效1次,对疗效显著且可切除的病例积极手术,避免过度转化治疗导致病灶消失而无法确切切除,同时也可避免化疗相关的肝损伤。对于消失的病灶有两种处理方式,其一,行术中超声检查,发现术前未发现的病灶并处理;其二,停止化疗3~4周后再复查肝脏增强核磁,此时消失的病灶可能再现,然后再行手术切除。因为本团队认为消失的病灶可能仍有活性,是术后局部复发的潜在风险,另外,当切除的肝内所有病灶TRG评分均为0分,即病理学完全反应(pCR),那么术前消失的病灶或术中无法处理的病灶(如不适合切除或局部治疗)很大可能也无活性,术后可不做进一步处理。对于初始可切除的CRLM,新辅助治疗的必要性仍存在争议^[20]。同时性CRLM手术切除分为同期切除和分期切除,分期切除又分为肝脏优先和原发灶优先,二者总生存期和无病生存期无差异,但目前肝脏优先被广大学者所接受,尤其适合肝脏病灶多、肿瘤负荷重的患者^[21-22]。研究表明,对于KRAS基因野生型的同时性CRLM患者,同期切除的患者生存获益更加显著,而对于KRAS突变型的同时性CRLM患者,同期或分期切除二者的生存期相似^[23]。另外,在同期切除中,原发灶与转移灶的切除顺序尚无统一标准。本团队经验显示,优先切除肝脏病灶更为适宜,原因如下:一方面,可避免肝切除时肝门血流阻断导致的胃肠道淤血对吻合口的不良影响,从而降低吻合口漏的风险;另一方面,从无菌原则考量,亦推荐推荐肝脏优先。需注意的是,肝脏优先切除的前提是原发灶具备可切除性。此外,以保留肝实质的理念实施肝切除至关重要,确保1 mm切缘是被广泛认可的标准,也是保留肝实质理念的具体体现。肝病灶局部切除时,为了保证切缘阴性和有效的止血,本团队的技巧是做“碗状”切除,而非“水井状”切除(图1)。

对于肝切除范围广泛,残余肝体积不足的患者,尤其存在化疗相关性脂肪肝和肝功能障碍的肠癌肝转移,保留更多的剩余肝组织可显著降低术后肝衰的发生率。有研究显示,二步肝切除组患者的5年生存率为51%,而因剩余肝组织不够的非手术治疗患者为15%。目前常规的二步肝切除手术方法包括门静脉栓塞、肝静脉栓塞术和肝分隔联合肝门静脉栓塞术^[24]。

肝移植可作为治疗局限于肝脏、无法手术切除的结直肠癌肝转移瘤患者的治疗选择之一,但对肝移植患者的选择方面



注:A为“碗状”肝创面;B为“水井状”肝创面。

图1 肝病灶局部切除创面

Fig.1 Local resected wound of liver disease lesion

有严格的标准,如避免选择右半结肠原发肿瘤、*BRAF*基因突变、N2分期和低分化肿瘤等。有学者提出Oslo肠癌肝转移肝移植评分,主要包括4项内容:(1)肝转移肿瘤的最大直径>5.5 cm;(2)化疗后肿瘤有进展;(3)肠癌切除至肝移植的时间间隔<24个月;(4)癌胚抗原(CEA)>80 $\mu\text{g/mL}$;每项1分,共4分。Oslo评分为0~1的患者10年生存率为50%,Oslo评分为2的患者10年生存率为33%^[25-26]。

2 术中超声在CRLM肝切除的应用

近年来术中超声在肝脏外科的应用十分广泛,尤其在CRLM中的应用价值很大^[27]。研究发现,术中超声可发现CRLM患者中额外的肝内病灶而改变术前制定的手术策略,而术中超声造影(contrast-enhanced intraoperative ultrasound, CE-IIOUS)在明确病灶特征的同时也大大增加额外病灶的检出率,特别对于化疗后手术前影像检查消失的肝内病灶的检出有更高的敏感性^[28-29]。但有时术中超声或CE-IIOUS难以对发现的额外病灶性质进行判断,尤其在出现严重化疗后肝损伤、转移灶坏死液化或钙化时。本团队的经验是在不影响手术安全性的前提下果断处理上述病灶,包括切除或消融,最大可能避免转移病灶的遗漏。术中应常规行CE-IIOUS,按照肝左外叶、左内叶、右前叶和右后叶的顺序仔细扫查并与术前影像确定的病灶比对再确认,严格避免病灶遗漏。此外,术中超声检查可以帮助规划手术切缘,提高R0切除率^[30-31]。针对切缘的规划,应根据肝内病灶的位置分为“肝脏表面型”和“肝内浅表型”两种分别设计。肝脏表面型指病灶位于肝脏表面,肉眼可见,电刀辅助划出表面环形切缘,术中超声检查判断病灶深度后进行病灶切除(图2A)。肝内浅表型指病灶位于肝内浅表位置,肉眼不可见,但可局部切除的病灶类型,这种类型病灶切缘的规划需要充分利用术中超声,本团队的经验是先做术中超声检查,大概判断病灶在肝表面投影的位置,用电刀在肝表面点烫(图2B),再次超声检查,确保肝表面点烫损伤部位的声影在肝内病灶的外缘(图2C),否则需重新设计点烫位置,反复上述步骤,最终在肝表面设计出环周切缘,进行病灶切除时要对病灶进行触诊有助于对病灶肝内切缘的判断。

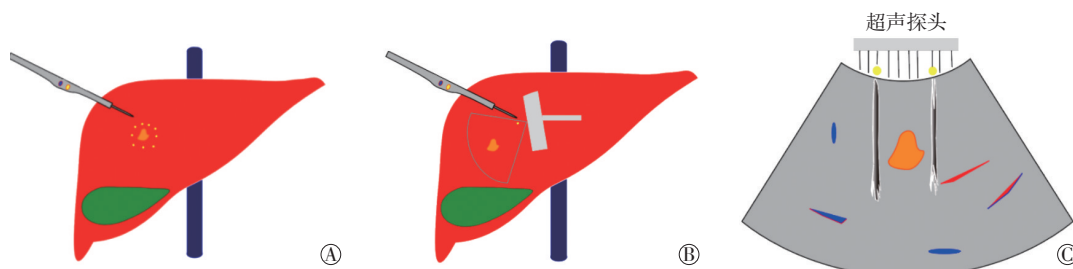
3 术中消融在CRLM中的应用

消融技术在CRLM的应用越来越广泛,目的是通过热损伤完全破坏肿瘤,同时能保留邻近的健康肝组织。常用的热消融技术包括微波消融(microwave ablation, MWA)和射频消融(radiofrequency ablation, RFA),根据消融的方式可分为经皮消融和术中消融。对于肝内多发、较小、位置深在、特殊部位(如邻近重要血管)或不适合手术切除的肝内病灶,MWA或RFA是很好的选择,部分病灶可达到与手术切除同样的效果。最新的III期国际多中心随机对照研究表明,对于肝转移灶<10个、最大病灶<3 cm的CRLM患者,热消融治疗效果非劣效于手术切除。研究显示肝内病灶的大小是影响消融效果的最重要因素,单个消融病灶的最长径线不应超过3~4 cm。与经皮消融相比,

术中消融对肝内特殊部位病灶的处理更具有安全性,如病灶深且无合适的穿刺路径、邻近胆囊或胃肠道等空腔脏器等。对于距离主胆管小于1 cm的病灶是消融的禁忌症,会造成胆管损伤、胆管狭窄或脓肿形成^[32]。本团队认为消融针的布局、消融功率(能量)及消融顺序也是影响效果的重要因素。消融的路径尽可能短,可增加穿刺精度和减少穿刺并发症的发生。布针前应使用超声探头360°仔细扫查病灶的大小及形态,以病灶的长轴作为布针平面,选择合适穿刺路径进针,因转移瘤较正常肝脏组织质地韧,故当针尖达到病灶时会有一定的阻力,这也有助于判断是否准确的穿刺到靶病灶,消融结束后需用超声再次检查消融是否彻底,必要时二次消融,应重视针道的消融和穿刺点的止血。消融功率及时间的设置需结合病灶的大小、部位决定,无统一的标准,与肝细胞癌相比,肝转移瘤无包膜,局部热能易扩散消耗,故理论上对于相同大小的病灶,转移灶消融的能量要更高、消融时间要更长。本团队使用的是MWA,一般<1.0 cm的病灶参数设置为功率50 W,时间1 min;1.0~1.5 cm参数为功率50 W,时间1.5 min;1.5~2.0 cm,参数为功率60 W,时间1.5 min;对于2.0 cm以上病灶的消融是保守的。对于邻近血管在病灶,因能量随血液流动额外消耗,故需较强的能量或较长的消融时间才能达到满意的效果。对于多个病灶位于同一消融平面内,本团队建议先消融深在病灶,后消融浅在病灶,避免浅在病灶消融后形成的声音干扰深在病灶的定位而影响其消融效果(图3)。

4 腹腔镜肝切除(laparoscopic liver resection, LLR)在CRLM中的应用

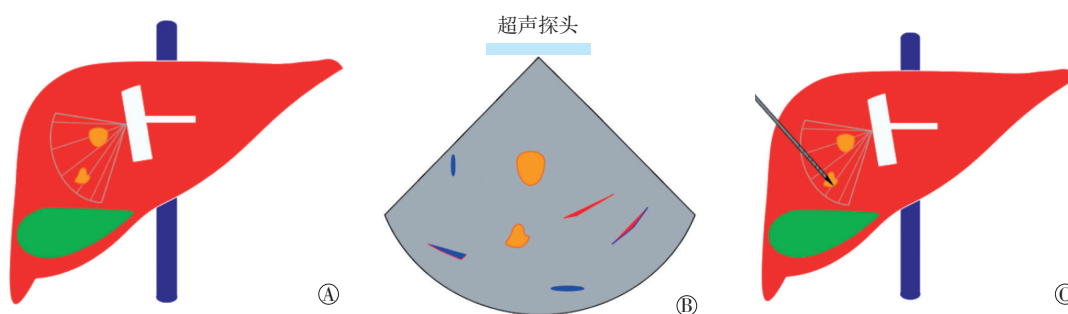
LLR已广泛应用于CRLM,与开腹手术相比具有很多优势。但肝内病灶的数目仍是限制其应用的主要因素,尽管LLR经过二十多年的发展,多数医生切除的CRLM病灶不超过5个,一般为1~2个,因为LLR对于多病灶切除的可行性目前没有证据。Nassar等^[33]表明LLR并不受肝内病灶数目的影响,LLR对肝内多病灶的处理是安全可行的。另外,在保留肝实质理论的支持下,LLR对多灶的CRLM的实施似乎是可行的,尤其是随着术中超声、荧光腹腔镜等术中导航技术的发展,很大程度地提高可LLR的安全性及可行性。研究发现约80%的CRLM患者肝内病灶是多发的,而肝内病灶数目影响R0切除率。故在LLR中确保切缘的安全性、提高R0的切除率至关重要。LLR临床实践中,切除深在肝内病灶时,通过术中超声的辅助,沿着肝表面切除线切除病灶,因不能触诊辅助切除,无法把握正确的切除平面,常切入病灶,导致危险切缘或肿瘤残留(图4)。荧光腹腔镜的应用可有效的解决上述问题。吲哚菁绿可被波长为750~810 nm的近红外光激发,发射840 nm波长的荧光,其组织穿透深度为5~10 mm,吲哚菁绿荧光成像可识别CRLM病灶的总体敏感度为83%,其中,对距离肝被膜<8 mm病灶的敏感度为100%^[34]。CRLM中吲哚菁绿的使用剂量及方法目前无统一标准,本团队的经验是术前3 d,按0.5 mg/kg静脉注射给药有更好的染色效果,同时吲哚菁绿



注: A 为肝脏表面型切缘规划; B 为肝内浅表型切缘规划; C 为肝内浅表型术中超声示意图。

图2 病灶切除的切缘规划和术中超声示意图

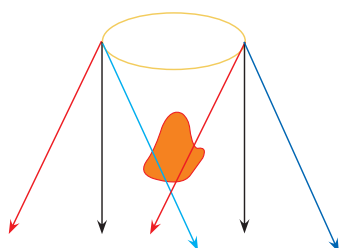
Fig.2 Planning of the resection margin of the lesion and Schematic diagram of intraoperative ultrasound



注: A 为超声检查; B 为 2 个病灶在消融平面; C 为先消融深在病灶, 白色为超声探头。

图3 多个病灶同一平面消融方法示意图

Fig.3 Schematic diagram of ablation methods for multiple lesions on the same plane

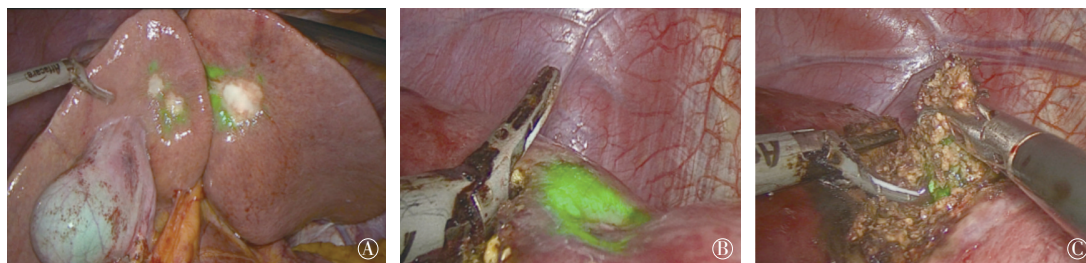


注: 黄色为肝表面切除线, 黑色为正确平面(安全切缘), 红色和蓝色为错误平面。

图4 腹腔镜肝切除示意图

Fig.4 Schematic diagram of laparoscopic liver resection

排泄试验吲哚菁绿 15 min 的使用剂量也是 0.5 mg/kg, 故一次注射吲哚菁绿可以同时达到评估肝功能状态和术中荧光成像两个目的。CRLM 肝内病灶的染色特点是肿瘤不摄取吲哚菁绿, 但由于肿瘤压迫周边胆管而导致吲哚菁绿排泄滞留而显影, 表现为肿瘤边缘环形染色(图 5A)。因为吲哚菁绿荧光的组织穿透深度为 5~10 mm, 故对深在病灶的安全切缘以保留侧肝切面不留荧光为标准, 这样会保证至少 5 mm 有效的安全切缘, 在完全达到 RO 切除标准的同时, 最大程度的保留了肝实质(图 5B、图 5C)。此外, 吲哚菁绿另一重要作用是发现肝脏表面的微小转移病灶。



注: A 为吲哚菁绿引起的肿瘤边缘环形染色; B 为吲哚菁绿对肿瘤的染色; C 为病灶切除后。

图5 吲哚菁绿荧光成像在 CRLM 中的应用

Fig.5 Application of indocyanine green fluorescence imaging in CRLM

5 小结

近年来, CRLM 的外科治疗理念不断更新, CRLM 虽属于晚期, 但由于其具有特殊的肿瘤学特点, 手术切除结合其他局

部治疗手段, 如消融、立体定向放疗、介入等, 可显著延长生存, 部分患者甚至可治愈, 此外, 随着术中超声、吲哚菁绿成像及术中 3D 导航技术的发展, 进一步提高了 CRLM 外科治疗的安全性及可行性。

利益冲突 无

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