

## Colorectal liver metastases: An update on multidisciplinary approach

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**Author contributions:** Chok KSH conceptualized and supervised the study; Chow FCL did the literature review and wrote the manuscript; both authors approved the submitted version of manuscript.

**Conflict-of-interest statement:** None of the authors has any conflict of interest.

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**Manuscript source:** Invited manuscript

**Received:** October 5, 2018

**Peer-review started:** October 6, 2018

**First decision:** November 15, 2018

**Revised:** November 24, 2018

**Accepted:** December 4, 2018

**Article in press:** December 5, 2018

**Published online:** February 27, 2019

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### Abstract

Liver metastasis is the commonest form of distant metastasis in colorectal cancer. Selection criteria for surgery and liver-directed therapies have recently been extended. However, resectability remains poorly defined. Tumour biology is increasingly recognized as an important prognostic factor; hence molecular profiling has a growing role in risk stratification and management planning. Surgical resection is the only treatment modality for curative intent. The most appropriate surgical approach is yet to be established. The primary cancer and the hepatic metastasis can be removed simultaneously or in a two-step approach; these two strategies have comparable long-term outcomes. For patients with a limited future liver remnant, portal vein embolization, combined ablation and resection, and associating liver partition and portal vein ligation for staged hepatectomy have been advocated, and each has their pros and cons. The role of neoadjuvant and adjuvant chemotherapy is still debated. Targeted biological agents and loco-regional therapies (thermal ablation, intra-arterial chemo- or radio-embolization, and stereotactic radiotherapy) further improve the already favourable results. The recent debate about offering liver transplantation to highly selected patients needs validation from large clinical trials. Evidence-based protocols are missing, and therefore optimal management of hepatic metastasis should be personalized and determined by a multi-disciplinary team.

**Key words:** Colorectal cancer; Liver metastases; Hepatic resection; Neoadjuvant therapy; Adjuvant chemotherapy; Intra-arterial therapy; Precision medicine; Multidisciplinary approach

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**Core tip:** Surgery offers the only hope of cure in colorectal liver metastasis. It can be

performed if complete metastasectomy is attainable. There is no consensus on the ideal management strategy for synchronous disease. A subset of patients presenting with unresectable disease may become eligible for resection after liver remnant augmentation or conversion therapy (chemo-therapeutics +/- biological agents). Amid increasing application of loco-regional therapies to colorectal liver metastasis, their role in the treatment paradigm remains to be defined. Refined patient selection – with greater emphasis on tumour biology – is essential to improving treatment outcome. The multidisciplinary approach helps determine the optimal treatment strategy from an expanding armamentarium of therapeutic options for each patient.

**Citation:** Chow FCL, Chok KSH. Colorectal liver metastases: An update on multidisciplinary approach. *World J Hepatol* 2019; 11(2): 150-172

**URL:** <https://www.wjgnet.com/1948-5182/full/v11/i2/150.htm>

**DOI:** <https://dx.doi.org/10.4254/wjh.v11.i2.150>

## INTRODUCTION

Colorectal cancer (CRC) is a leading cause of tumour-related morbidity and mortality worldwide<sup>[1]</sup>. Approximately 50% of patients develop liver metastases (LM) in their course of disease<sup>[2]</sup>. Surgical resection is the only treatment that offers a chance of cure and long-term survival, with 5- and 10-year survival rates at around 40% and 25% respectively<sup>[3]</sup>. In selected cohorts, up to 97% of ten-year survivors remained disease-free after resection of colorectal LM (CRLM)<sup>[4]</sup>. However, only a minority of patients is suitable for upfront surgery. While improving surgical techniques and better adjuvant therapies are pushing forward the frontiers of resection, the importance of careful patient selection should not be overlooked. Not all patients undergoing resection enjoy long-term benefit – around 30% developed recurrence and 15% succumbed to their disease within a year after surgery<sup>[5]</sup>. A personalized treatment approach – taking tumour biology, disease staging and patient condition into consideration – is the key to improving outcomes.

Management of stage IV CRC is optimized by grouping relevant specialists together under a multidisciplinary team (MDT) setting<sup>[6]</sup>. A proficient MDT consists of at least a colorectal surgeon, a liver surgeon, medical and radiation oncologists, a radiologist, a pathologist and a case nurse<sup>[7]</sup>. Better patient and disease evaluation, joint decision-making and optimization of multimodal therapy not only improve patient outcome, but also enhance consistency and coordination of care. The value of multidisciplinary approach in the management of gastrointestinal malignancies has been demonstrated in a prospective study. Despite 84% of clinicians being certain of their original plan before discussion, a change was recommended in 36% of cases, 72% of which were major<sup>[8]</sup>. This review highlights current controversies and relevant evidence in the management of CRLM.

## PATIENT AND TUMOUR EVALUATION

Accurate assessment of a patient's general health condition (comorbidities, performance status and liver function) and the extent of disease is important for treatment planning.

### **Radiological assessment**

Guidelines recommend CT scan of thorax, abdomen and pelvis for initial workup. It is adequate for determining resectability in most cases. In cases of doubt, a second imaging modality such as MRI could be added<sup>[9,10]</sup>. In patients planning for upfront resection, sensitivity of MRI and CT were similar (94% *vs* 91%)<sup>[11]</sup>. However, in general, MRI was more sensitive than CT in detecting CRLM (91% *vs* 82%), particularly for sub-centimetre lesions or reassessment after neoadjuvant chemotherapy (when the sensitivity of CT dropped to 77%)<sup>[12]</sup>. Gadoteric contrast further increased the diagnostic confidence of MRI to 98.3%, compared with 85.7% and 65.2% in conventional contrast MRI and CT<sup>[13]</sup>. High-quality baseline imaging is essential before any chemotherapy, when lesions are more readily detectable; whereas comparison with post-chemotherapy films gauges treatment response and delineates tumour biology. MRI is useful when characterization is difficult *e.g.*, underlying fatty

liver, or multiple small nodules with uncertain nature.

**Controversy 1: Role of positron emission tomography - computed tomography:** Whether positron emission tomography - computed tomography (PET-CT) offers additional information to CT and/ or magnetic resonance imaging (MRI) is controversial. An early randomized study showed PET (without CT) significantly reduced the number of futile operations (28% *vs* 45% in control) and prevented an unnecessary surgery in every 6 patients<sup>[14]</sup>. In another randomized trial, however, PET-CT did not influence decision-making in patients with resectable CRLM – the PET-CT group had similar hepatic resection rate and survival as the controls; it only altered surgical management in 8% patients (2.7% did not undergo surgery and 3.4% underwent additional organ surgery)<sup>[15]</sup>. Long-term follow-up of this trial concluded PET-CT did not improve disease-free or overall survival<sup>[16]</sup>. According to a meta-analysis, PET-CT was less sensitive but more specific than CT or MRI in detecting CRLM – sensitivity 66% *vs* 79% *vs* 89%; specificity 86% *vs* 67 *vs* 81%<sup>[17]</sup>. In our practice, we still perform PET-CT in the majority of patients to assess for extra-hepatic disease (EHD). As an adjunct to CT, its value in staging EHD was evident in 20% patients – preventing futile operations, guiding resection of loco-regional nodal disease, or clarifying indeterminate CT findings<sup>[18]</sup>.

### **Evaluation of future liver remnant (before major hepatectomy)**

Accurate preoperative estimation of liver functional reserve is essential to prevent post-hepatectomy liver failure, especially in patients with extensive tumour load or highly compromised livers. CT volumetry is routinely used before major hepatectomy. In most centres, future liver remnant (FLR) volumes of 25% and 40% are accepted as adequate for normal and diseased liver respectively. However, FLR volume does not necessarily reflect its function, particularly as quality of liver tissue can be affected by pre-operative chemotherapy<sup>[19]</sup>.

Indocyanine green (ICG) clearance is a long-established functional test for selecting surgical candidates with adequate liver reserve; its determination by pulse dye densitometry and intra-operative application have attracted great interest<sup>[20,21]</sup>. The use of ICG has limitations though: its uptake by hepatocytes can be impaired by hyperbilirubinemia, and it reflects the total liver function rather than specifically the FLR performance, failing to address regional variations within the liver<sup>[19]</sup>. Segmental hepatic function can be measured by hepatobiliary scintigraphy; the commonest used agent being Technetium-99m (99mTc) labelled mebrofenin, which is taken up by hepatocytes and directly excreted into the biliary tree. Using a single cut-off value of 2.7%/min m<sup>2</sup> irrespective of the liver tissue quality, 99mTc-mebrofenin hepatobiliary scintigraphy has been shown to outperform CT volumetry in predicting the risk of post-hepatectomy liver failure<sup>[22]</sup>. Nonetheless, further evidence is required to support its widespread use in clinical practice.

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## **PATIENT SELECTION AND PROGNOSTIC PREDICTION**

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Although hepatic resection gives the best results on a population level, not everyone with technically operable disease benefits from surgery<sup>[5]</sup>. Appropriate patient selection ensures the offered intervention, surgical or systemic, is optimal to each particular patient.

Resectability of a particular CRLM should be determined in a multidisciplinary setting, with input from hepatobiliary surgeons, oncologists, radiologists and pathologists. Apart from pure technical considerations, there is a growing emphasis placed on oncological resectability<sup>[23]</sup>. The former focuses on whether a margin-negative (R0) resection can be achieved while preserving a liver remnant comprised of two contiguous segments with adequate volume, function, vascular inflow and outflow, as well as biliary drainage. Oncological/prognostic evaluation aims to select patients with higher likelihood of cure or sustained disease remission; taking tumour biology (in particular disease progression/remission during neoadjuvant therapy), mutation status, intra-hepatic tumour burden and extent of EHD into consideration. Resection criteria based on the number, maximal size and distribution of tumours no longer apply; instead resectability should be defined case-by-case based on different prognostic factors. With continued advancement in surgical technology, systemic therapies and multimodality treatment, the definition of resectability will continue to evolve and expand to cover advanced diseases once deemed non-resectable.

Traditional clinico-pathological prognostic factors include<sup>[24-26]</sup>: (1) Characteristics of primary CRC, *e.g.*, advanced T stage, nodal status, location of tumour (right sided tumour associated with poorer outcome); (2) Factors related to CRLM *e.g.*, size of largest liver metastasis, number of lesions, grade of differentiation, margin status; (3)

Presence of extrahepatic disease; (4) Elevated serum carcinoembryonic antigen (CEA) level; and (5) Disease-free interval between primary CRC and metachronous CRLM

In clinical practice, the predictive value of each individual factor is limited. Several scoring systems were devised aiming to provide an overall risk assessment; the most widely quoted one is the Fong clinical risk score (assigning points to positive margin, EHD, node-positive primary, disease-free interval from primary to CRLM, more than one solitary LM, largest LM > 5 cm, and CEA > 200 ng/mL)<sup>[27]</sup>. These systems, however, failed to demonstrate predictive accuracy for long-term survival or in the neoadjuvant setting across institutions<sup>[28,29]</sup>. Their clinical utility remained uncertain.

Both radiological and pathological response to preoperative chemotherapy predict better survival after resection of CRLM<sup>[30,31]</sup>. On CT or MRI scans, treatment response can be judged by degree of tumour shrinkage and morphological changes unrelated to size (*e.g.*, tumour density, tumour-liver interface). Due to the limitations of the Response Evaluation Criteria in Solid Tumours (RECIST), new parameters like early tumour shrinkage and depth of response have been proposed to aid in prognostication<sup>[32,33]</sup>. 18-fluorodeoxyglucose (<sup>18</sup>FDG) PET/CT also has a role in prognostication-LM with high glucose metabolism [high pre-treatment standardized uptake value (SUV)] and poor metabolic response to systemic therapy had poorer overall and disease-free survivals<sup>[34]</sup>. Complete pathological response, on the other hand, has been associated with an excellent 5-year survival of 76%<sup>[35]</sup>.

All these clinical, radiological and pathological characteristics are considered surrogate markers of the underlying tumour biology. There is growing interest in directly assessing tumour biology by molecular profiling and integrating biomarkers into prognostication systems. *KRAS* gene has been extensively studied. As there was a high concordance of *KRAS* status between primary CRC and CRLM, it can be evaluated on biopsy or resected specimens of the primary tumour<sup>[36]</sup>. Apart from predicting poor response to anti-epidermal growth factor receptor (EGFR) therapies, *KRAS* mutation has been associated with higher rates of EHD, adverse response to chemotherapy, positive resection margin, worse overall and recurrence-free survivals after surgery irrespective of the chemotherapy regimen, and poorer survival after re-resection for recurrence<sup>[25,37,38]</sup>. In view of the poor prognosis, some suggested aggressive treatment might not be worthwhile for *KRAS* mutant tumours with multiple risk factors (*e.g.*, node-positive primary, individual CRLM > 3 cm, more than 7 cycles of systemic chemotherapy given)<sup>[39]</sup>. Incorporating *KRAS* mutation status to traditional risk scores might improve survival prediction<sup>[40]</sup>. *BRAF*, another commonly tested gene in CRC, also predicted survival outcome in CRLM. *BRAF* mutated tumours were refractory to standard chemotherapy and anti-EGFR agents and had far inferior survival; resection should only be offered to those with limited disease, taking note of the high risk of recurrence<sup>[41,42]</sup>. By using gene expression microarray on resected CRLM, a 20-gene molecular risk score was externally validated to be an independent prognosticator of overall and recurrence-free survival after liver metastasectomy; it was more accurate than traditional clinical risk scores<sup>[43]</sup>. With further research, risk stratification and individualized therapy based on molecular profiling could be realized in the foreseeable future.

Nowadays we realize tumour heterogeneity exists not only amongst different patients, but also within individual tumours and among metastatic sites. Multiple cancer subclones coexist and evolve simultaneously, with treatment acting as selection pressure. Tumour biopsy at a single site at a particular time cannot reflect the entire disease throughout the treatment period<sup>[25]</sup>. Serial imaging has the advantage of assessing multiple tumour locations in a longitudinal fashion, but is frequently limited by spatial resolution. The role of circulating liquid biomarkers is under investigation; its collection at several time points (*e.g.*, pre-treatment, after each cycle of chemotherapy, before and after resection) can offer insight into the evolving tumour biology. Presence of circulating tumour cells (CTCs) predicted impaired survival in CRLM; it could also be a source to detect *KRAS* and *BRAF* mutations to guide choice of targeted therapy<sup>[44,45]</sup>. Plasma level of circulating cell-free DNA (cfDNA) has been proven a predictor of survival in metastatic CRC<sup>[46]</sup>. Early work showed cfDNA sequencing allowed identification of gene mutation or micro-satellite instability<sup>[47]</sup>. Its detection and analysis may improve diagnostic efficiency in both screening and surveillance settings<sup>[48]</sup>. MicroRNA provides a molecular snapshot of intracellular activity within cancer; its signature has been shown to predict metastasis and prognosis in CRC<sup>[49]</sup>. If microRNA profiling can be obtained from serum samples, tumour prognostication from blood tests is distinctly feasible.

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## NEOADJUVANT TREATMENT

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### **Controversy 2: Role of neoadjuvant therapy in clearly R0 resectable CRLM**

Theoretically, neoadjuvant therapy allows assessment of the natural history of disease before embarking on metastasectomy. It potentially shrinks the tumour and reduces the extent of liver resection, treats micro-metastases thereby lowering recurrence rate, as well as guides further therapeutic plan based on disease response to treatment. Its benefit is not proven from an evidenced-based point of view though.

Earlier studies confirmed an objective radiological response could be expected in two-thirds of treated patients<sup>[50]</sup>. However, the majority of retrospective studies failed to demonstrate any overall survival (OS) benefits from neoadjuvant therapy – five-year OS rates ranged from 38.9% to 74% in patients who had pre-operative chemotherapy before liver resection, compared with 20.7 to 56% in patients who underwent upfront surgery<sup>[51]</sup>. A landmark randomized controlled trial (the EORTC intergroup trial 40983) showed perioperative FOLFOX (folinic acid, fluorouracil, and oxaliplatin; 6 cycles before and 6 cycles after surgery) improved 3-year progression-free survival (PFS) modestly – 42.4% compared with 33.2% in surgery-only patients, an absolute 9.2% increase – at the cost of higher peri-operative morbidity (25% *vs* 16%). This did not translate into any overall survival benefit at a median follow-up of 8.5 years<sup>[52,53]</sup>. A meta-analysis including 18 studies concurred neoadjuvant treatment, in general, did not offer PFS or OS advantage; however, it could improve survival in patients considered high risk of recurrence (pooled hazard ratio for 5-year OS = 0.69)<sup>[54]</sup>. The CHARISMA randomized trial is underway to investigate whether neoadjuvant XELOX improves survival in high-risk CRLM patients<sup>[55]</sup>.

Based on current evidence, the European Society for Medical Oncology (ESMO) guidelines suggested the need for perioperative systemic therapy is defined by “technical criteria for resection and prognostic considerations”. Upfront surgery is justified in patients with clearly resectable disease and favourable prognosis; while peri-operative FOLFOX or XELOX should be considered when resectability or prognostic criteria is unclear or “not excellent”<sup>[9]</sup>. In our centre, we favour the surgery-first approach as long as R0 resection can be attained, because the unclear survival benefit of neoadjuvant treatment carries with it the risk of chemotherapy-associated liver injury (discussed below). Future research should focus on accurately defining “high-risk” patients who will benefit most from preoperative therapy.

### **Regimens and potential risks**

Current guidelines suggest oxaliplatin-based doublet chemotherapy (FOLFOX/XELOX) as the neoadjuvant treatment-of-choice for resectable CRLM, while FOLFIRI or FOLFOXIRI are alternatives<sup>[9,10]</sup>. A meta-analysis showed the addition of molecular targeted therapy conferred a higher overall response rate than chemotherapy alone (68% *vs* 43%), but did not improve survival<sup>[56]</sup>. A lack of PFS benefit was also observed in the New EPOC trial, which studied the effect of combining EGFR-inhibitor (cetuximab) to perioperative systemic chemotherapy; patients who received cetuximab actually experienced worse PFS (14.1 *vs* 20.5 months in control)<sup>[57]</sup>. Given these results, cetuximab should not be added to standard perioperative chemotherapy regimens. Bevacizumab, an anti-vascular endothelial growth factor (VEGF), plus FOLFIRI in the neoadjuvant setting yielded a response rate of 66.7% in resectable CRLMs<sup>[58]</sup>; whether this translates into any survival benefit remains to be investigated. The ongoing PERIMAX trial compares perioperative bevacizumab plus FOLFOXIRI with adjuvant FOLFOX; with the primary endpoint being failure-free survival<sup>[59]</sup>.

The potential risks of perioperative chemotherapy include disease progression during treatment and hepatotoxicity. Initially resectable CRLM may progress despite using the best available chemotherapeutics, and become unresectable or require a more extensive surgical approach; the rate was 7% in the EORTC trial<sup>[52]</sup>. From another perspective, this small group of patients have very aggressive tumour and their disease would progress despite any treatment given; some argue neoadjuvant treatment only selects them out and prevents futile operations.

Chemotherapy-associated liver injury (CALI) can occur with commonly used regimens. Oxaliplatin was associated with sinusoidal obstruction syndrome in up to 38% patients, while steatosis and steatohepatitis complicated 9.3% patients receiving irinotecan<sup>[60]</sup>. Patients with severe sinusoidal dilation (OR 1.73) or steatohepatitis (OR 2.08) were more likely to suffer from postoperative major morbidity and liver surgery-specific complications<sup>[61]</sup>. It has been shown postoperative complication rate increases if the interval between chemotherapy completion and surgery is too short (< 4 wk) or too many cycles (>9) of preoperative chemotherapy are given<sup>[62,63]</sup>; limiting the duration of neoadjuvant therapy and ensuring recovery of liver function before operation can reduce the impact of CALI. Future research should focus on identifying patients at risk of CALI and devising liver protective strategies for such patients.

### **Disappearing LM**

A subset of CRLMs can totally vanish on imaging after neoadjuvant treatment; they were referred as disappearing LMs (DLMs). This phenomenon is related to the quality of imaging, particularly as chemotherapy can compromise radiological detection of CRLM<sup>[64]</sup>. The key question is whether the lesions have been truly cured or just being missed by suboptimal post-neoadjuvant scans.

MRI has the highest sensitivity and is the preferred imaging modality in this setting<sup>[65]</sup>. In existing literature, the percentage of patients with one or more DLMs ranged widely from 7% to 37%; however, this phenomenon may be over-reported as most studies only utilized CT and intraoperative ultrasound for reassessment<sup>[66]</sup>. Complete disappearance of all initial CRLMs is rare, with an incidence of 0%-6%; therefore, most patients still undergo surgery. In laparotomy, macroscopic residual disease could be detected at 11%-67% DLM areas, highlighting the inadequacy of current post-neoadjuvant imaging. Importantly, there was clear difference between complete radiological and pathological responses – when areas of DLM were resected, microscopic residual disease was found in up to 80% of specimens<sup>[67]</sup>.

Only surgery potentially offers cure; the phenomenon of DLM should be prevented, albeit complete pathological response has been associated with good prognosis<sup>[35]</sup>. To reduce the risks of DLMs, preoperative over-treatment has to be avoided – some proposed restaging after every 3 cycles of neoadjuvant therapy to enable earlier decision of surgery, and limiting the entire course of chemotherapy to 4 to 6 cycles<sup>[66,68]</sup>. Using a combination of imaging modalities enhances the detection of residual metastases and lowers the incidence of false DLMs. As conservative management i.e. leaving DLMs in-situ resulted in a local recurrence rate of 19% to 74%<sup>[66]</sup>, DLMs should be resected whenever feasible. Some proposed even in patients with complete radiological resolution of all CRLMs, surgical exploration may be warranted for meticulous intra-operative assessment. Whether resection offers survival benefit is unclear though; patients with untreated DLMs could have comparable OS to those who underwent complete surgical treatment, in spite of a higher intrahepatic recurrence rate<sup>[69]</sup>. In selected patients, leaving certain DLMs untreated may be reasonable but this decision should only be made in a multi-disciplinary setting<sup>[23,68,70]</sup>. Ablation of DLM sites is an appealing alternative, but there is no evidence proving its efficacy to date. Initial experience with computer-guided resection of DLMs showed promising results. Augmented reality is a technology fusing reconstructed pre-treatment CT images with real-time patient images, thereby facilitates DLM localization and ensures clear resection<sup>[71]</sup>.

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## SYNCHRONOUS DISEASE

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About one sixth of CRC patients had LM at presentation<sup>[72]</sup>. Defined as CRLM detected concurrently or before the primary CRC, synchronous disease has been shown to have less favourable cancer biology and post-resection survival – 5-year survival was 39%, compared with 48% in metachronous CRLM<sup>[7]</sup>. Western guidelines and expert consensus recommend neoadjuvant chemotherapy in this higher-risk setting, unless resection at both sites are considered easy<sup>[7,9]</sup>. However, an analysis based on the Liver Met Survey International Registry showed neoadjuvant therapy offered no survival advantage in resectable synchronous CRLM, with a 5-year OS of 42% similar to 47% in the upfront surgery group<sup>[73]</sup>. In Asian countries, preoperative chemotherapy is not a standard in resectable synchronous disease.

### **Controversy 3: Optimal surgical sequencing for resectable synchronous disease**

To date, there has been no randomized trial on the surgical approach to synchronous disease. The optimal strategy remains controversial. Decision should be individualized taking into consideration of patient's fitness and tumour status – whether the primary CRC is symptomatic or obstructive (CRC needs to be resected first under these circumstances), as well as the extent of CRLM and magnitude of liver resection required. Treatment strategy is best determined in multi-disciplinary setting, which has been associated with greater likelihood of simultaneous resection<sup>[74]</sup>.

The conventional approach comprises of resection of the primary CRC followed by liver metastasectomy, commonly with chemotherapy applied between the two surgeries. This avoids potential complications of the primary tumour, but carries significant risk of CRLM progression beyond resectability; less than 30% patients completed the whole treatment and underwent liver resection<sup>[75]</sup>.

The liver-first approach, also known as the reversed strategy, may be more appropriate if an asymptomatic colon primary coexists with extensive CRLM or the primary tumour is a locally advanced rectal cancer (which needs neoadjuvant chemoirradiation). After systemic chemotherapy, patients underwent liver

metastasectomy prior to removal of primary CRC. Given hepatic metastases rather than the primary tumour dictates these patients' prognosis, early administration of chemotherapy to control liver and systemic diseases optimizes the chance of potentially curative hepatic resection and long-standing survival<sup>[76]</sup>. Compared to the classical approach, more patients (around three quarters) could complete the whole paradigm and underwent both liver and colorectal resection<sup>[77]</sup>. In spite of a respectable 5-year OS of 33.1% and acceptable perioperative morbidity and mortality rates of 31.5% and 3.3%, a recent single-centre study reported a high recurrence rate of 51.4% after a median follow-up of 20.9 mo<sup>[78]</sup>. Whether liver-first approach confers survival benefit remains undetermined.

Combined colorectal and liver resection in one single operation is generally reserved for patients with easy-to-resect primary tumours and limited hepatic disease<sup>[7]</sup>. Traditionally this approach was associated with increased morbidity, including infectious liver and anastomotic complications. With technological advancement, outcomes of combined resection have improved. Provided resection at the other site is minor, incorporating a major liver or rectal resection into this approach is deemed safe<sup>[79,80]</sup>. Cumulative morbidity and mortality rates were comparable to, or even better than, staged procedures; long-term oncological outcomes were similar – 1- and 5-year OS rates for one-stage operation were 90.5% and 38.5% respectively, while 5-year DFS was 25.3%<sup>[81,82]</sup>. A recent meta-analysis of 30 studies confirmed simultaneous liver and colorectal resection was associated with shorter hospital stay compared with staged procedure, without adversely affecting perioperative morbidity or long-term survival<sup>[83]</sup>. This approach is gaining popularity as more evidence proved its safety and efficacy.

A meta-analysis comparing the classical, synchronous and liver-first approaches did not show any difference in surgical outcomes or survival advantage<sup>[84]</sup>. Because of the limited evidence available, the optimal treatment strategy is unclear. Choice of procedure should be personalized and based on expertise available in different institutions.

In the presence of unresectable metastases, the benefit of resecting an asymptomatic primary without liver surgery is debatable. A meta-analysis showed primary tumour resection conferred a survival benefit of 6.4 months compared with chemotherapy alone, however the result is questionable given the significant selection bias<sup>[85]</sup>. To date, no randomized trial was completed to clarify this issue.

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## HEPATIC RESECTION

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CRLM resection offered an overall median survival of 3.6 years; five- and 10-year survival ranged from 16% to 74% (median 38%) and 9% to 69% (median 26%) respectively<sup>[3]</sup>. Following major hepatectomy for CRLM, large contemporary series reported perioperative mortality and major morbidity rates of 1%-5% and approximately 20% respectively.

### **Surgical approach**

Despite the addition of systemic chemotherapy, intra-hepatic recurrence is common after surgery of curative intent and occurred in two-thirds of patients within 3 years<sup>[5]</sup>. Increasing evidence showed re-resection of liver-limited recurrence is safe and can produce good long-term outcomes in selected patients<sup>[86]</sup>. Compared with anatomical resection, parenchymal-sparing hepatectomy (PSH) enhances the likelihood of repeated resection in the event of intra-hepatic recurrence. Both approaches have equivalent safety profile and oncological outcomes (R0 resection rate, liver recurrence-free survival and OS) after the index operation. However, in case of recurrence, PSH has been associated with a better 5-year survival since more patients could undergo salvage surgery<sup>[87,88]</sup>. Nowadays, PSH is considered the standard approach to CRLM unless it is precluded by the anatomy of the disease.

Amid growing interest in laparoscopic liver resection (LLR), the recently published OSLO-COMET randomized controlled trial demonstrated the safety and short-term efficacy of laparoscopic minor PSH for CRLM. Compared with the open-surgery group, the LLR group had less postoperative complications and a shorter hospital stay, while 90-d mortality and percentage of involved resection margins were similar<sup>[89]</sup>. For oncological outcomes, both approaches had comparable tumour recurrence rate, DFS, and 5-year OS in a meta-analysis of propensity-score matched studies; the LLR group even had better 3-year OS<sup>[90]</sup>. While there were evidence supporting the use of minimally invasive techniques for minor CRLM resection, its role in major liver surgery and challenging tumour locations needs further clarification. The advanced laparoscopic skills required can limit its widespread

application. There are ongoing efforts to facilitate the education and implementation of LLR worldwide<sup>[91]</sup>.

### **Width of resection margin**

Contrary to the historic “1-cm rule”, several large series showed as long as R0 resection ( $\geq 1$  mm) is achieved, extra margin width does not add DFS/OS advantage<sup>[92-94]</sup>. From observations that (1) survivals were similar between R0 and R1 resections if tumour showed optimal radiological or pathological response to neoadjuvant chemotherapy<sup>[95]</sup>; (2) most recurrences occurred outside the surgical margin in a disseminated manner; and (3) margin re-resection from R1 to R0 did not improve long-term outcomes<sup>[96]</sup>, positive margin status could just be a surrogate of aggressive tumour biology. The latter is increasingly recognized as the most important prognostic determinant. While an expected close margin (especially when tumour is close to vital vessels) is not a contraindication to surgery, surgeons should aim at wider margins to ensure a R0 resection<sup>[97]</sup>.

**Controversy 4: Role of surgery in the presence of extrahepatic disease:** Management of CRLM in this setting remains controversial. Albeit defined as a poor prognostic factor, limited extrahepatic disease (EHD) does not contraindicate liver surgery; the prerequisite is all diseases including the primary CRC, LM and EHD can be completely resected or controlled<sup>[9,98]</sup>. Resection of CRLM together with concurrent EHD significantly improved the 5-year OS from 0% to 28%, with a median survival of 31 mo<sup>[99]</sup>.

The location of EHD matters – lung metastasis carries a more favourable prognosis than peritoneal or portal/para-aortic nodal metastases (5-year OS being 26%, 17% and 15% respectively after complete resection of CRLM and EHD)<sup>[100]</sup>. According to data from the LiverMetSurgery registry, resection of concurrent liver and lung metastases was associated with similar OS as isolated liver metastasectomy<sup>[101]</sup>. The relative indolent nature of most colorectal pulmonary metastases supports CRLM resection in the presence of unresectable lung disease – 5-year OS of 13.1% was better than 1.6% achieved by chemotherapy alone, but as expected much worse than the 56.9% after complete metastasectomy at both sites<sup>[102]</sup>.

Although long-term survival is possible, true definitive cure is rare after resecting concurrent CRLM and EHD. In a retrospective review, disease recurred in 90.2% patients at a median of 8 mo, 85% being systemic recurrence; 5-year recurrence-free survival was 5%<sup>[103]</sup>. Effort was made to identify subgroups who benefit most from radical surgery. For example, in patients with synchronous LM and peritoneal carcinomatosis (PC) of colorectal origin, complete cytoreductive surgery and liver metastasectomy followed by intra-peritoneal chemotherapy achieved a median OS of 40 mo in those with limited PC (peritoneal cancer index, PCI < 12) and 1-2 LM. Outside these criteria, the survival benefit of radical surgery was significantly reduced – patients with PCI  $\geq 12$  or at least 3 LM had a median OS of 27 mo<sup>[104]</sup>. Non-pulmonary EHD, EHD concomitant to LM recurrence, CEA  $\geq 10$  ng/mL, more than 5 LM and right-sided colonic primary all predict poor prognosis after surgery for concurrent CRLM and EHD; no patients with more than 3 factors achieved 5-year survival<sup>[105]</sup>. However, this prognostication system has not been externally validated.

In summary, complete resection of all concurrent metastases can improve disease control and survival in selected patients, although cure is rare and recurrence is expected. Future research can help develop prognostic scores to better select patients for radical surgery.

**Controversy 5 - Ablation or surgical resection?** Thermal ablation involves destruction of cancer by heat, with radiofrequency ablation (RFA) and microwave ablation (MWA) being the most widely employed and studied modalities. Despite showing advantage of fewer complications and better post-procedural quality of life, RFA was inferior to hepatic resection in terms of survival (lower OS and DFS) and recurrence (higher rates of local, intra-hepatic and any recurrences)<sup>[106-108]</sup>. Surgical resection is the choice of treatment in young, fit patients, based on its proven long-term efficacy and lower recurrence rate.

In small tumours less than 3 cm, however, RFA may attain comparable oncological outcomes to resection. Following ablation to complete tumour necrosis with a margin over 5 mm, one-year local disease progression rate as low as 3% has been reported<sup>[109,110]</sup>. In high-risk patients (elderly, or with significant comorbidities), the considerably lower morbidity associated with ablation could justify its use over resection, provided patients accept the trade-off of potentially inferior long-term results. The ongoing LAVA randomized trial is designed to clarify the optimal treatment strategy in these high-risk individuals<sup>[111]</sup>.

**Borderline resectable disease due to insufficient liver remnant:** Patients with



extensive bilobar LM poses a unique challenge. The major limiting factor for a curative resection is the volume and function of the future liver remnant (FLR). Different management strategies and their advantages and disadvantages were listed below.

Portal vein embolization (PVE) is a well-established method for augmentation of small liver remnant, thereby enables extensive curative resection initially deemed high risk of postoperative liver failure. By obliterating portal flow to the liver segments involved by metastases (intended to be resected) and diverting it to the side that will remain, PVE is expected to increase the FLR volume by 43.1% on average. Less than 5% patients had inadequate hypertrophy response precluding them from the planned resection<sup>[112]</sup>. In one study, extended right hepatectomy became feasible after PVE in two thirds of patients who initially had inadequate FLR, yielding a survival similar to those who did not need PVE<sup>[113]</sup>. There were concerns about post-PVE tumour progression leading to unresectable disease, which could occur in up to 20-30% patients; whether PVE itself accelerates tumour growth remained controversial. Continued administration of chemotherapy after PVE has been shown to reduce tumour progression rate, while minimizing the interval between PVE and resection to 4 wk has also been advocated<sup>[114]</sup>. Reassuringly a meta-analysis showed PVE did not adversely affect overall survival or intrahepatic recurrence in patients undergoing major liver resection for CRLM<sup>[115]</sup>. Future research goals include identification of individuals at risk of rapid tumour progression and strategies to reduce progression rate without compromising FLR hypertrophy.

Two-stage hepatectomy (TSH) aims to remove all CRLM in two sequential operations for selected patients with advanced bilobar disease, in whom removing all lesions with safe margin is impossible during a single procedure. Pre-operative chemotherapy was frequently employed to select patients with favourable tumour biology. Following the first stage (for tumour clearance of FLR), a 2- to 3-mo interval allows liver tissue to regenerate (often aided by PVE) before a second stage hepatectomy took place to achieve R0 resection. A systematic review reported three quarters of patients successfully underwent second stage hepatectomy and R0 resection rate was 75%; the main reason for non-completion was interval disease progression (88%). Postoperative morbidity rate was 17% and 40% after first and second stage respectively, and overall mortality was less than 5%. A median OS of 37 mo and a 3-year DFS rate of 20% were encouraging, and comparable to other series of lesser-scale CRLM resections<sup>[116]</sup>.

Both PVE and TSH, although proven effective, have a considerable patient drop-out rate due to tumour progression in the waiting interval. A novel surgical technique was introduced in 2012 to treat advanced bilobar liver tumour in a more rapid fashion.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) comprises liver transection and ligation of portal vein in the first operation, followed by resection of the diseased liver segment 7-14 d later. By redistributing total portal blood flow to FLR and triggering an inflammatory response, ALPPS induces rapid hypertrophy of FLR at an estimated growth rate of 22-35 mL/d (compared with 3-5 mL/d after PVE)<sup>[117]</sup>. The benefits of ALPPS include a greater FLR hypertrophy (76% *vs* 37% for PVE) and a higher rate of completion of stage 2 hepatectomy (100% *vs* 77% for PVE)<sup>[118]</sup>. A recent randomized controlled trial confirmed ALPPS had superior resection rate compared with TSH in patients with advanced CRLM, 92% *vs* 57%<sup>[119]</sup>. ALPPS has also been reported as a salvage treatment for failed PVE<sup>[120]</sup>. However, these came at the price of higher morbidity and mortality. The relative risks for overall and major morbidity (*e.g.*, bile leakage and sepsis) were 1.39 and 1.57 compared with TSH<sup>[117]</sup>. As per the international ALPPS Registry, the 90-d mortality rate was high at 8.8%, three quarters were due to postoperative liver failure<sup>[121]</sup>. Oncological outcomes after ALPPS were also unclear; limited data available came from case series only. For CRLM, recurrence rates ranged from 14.3% (after a median follow-up of 9 mo) to 78.3% (after a median of 22.5 mo)<sup>[122,123]</sup>. Patients with "otherwise unresectable" advanced CRLM were identified from the international ALPPS registry, overall survival after ALPPS was not superior to matched controls who received palliative systemic treatment (with median OS of 24.0 mo *vs* 17.6 mo,  $P = 0.88$ )<sup>[124]</sup>. To improve outcomes of this radical surgical strategy, careful patient selection is essential; a consensus on the ideal indications of ALPPS is urgently needed. Recent promising results from high-volume centres suggest that, with surgical advancement, ALPPS can have low perioperative risk (0% mortality and 21% severe complications) and satisfactory survival (3-year OS 50% and 3-year DFS 13%) in experienced hands<sup>[125]</sup>. However, given the unclear long-term outcome and questionable safety profile, currently ALPPS should be limited to high-volume institutes in research setting.

Combining ablation with resection allows potential tumour clearance in extensive

bilobar CRLM. This approach could achieve long-term survivals (5-year OS 37%-56%) comparable to that of TSH, with improved perioperative outcomes – less blood loss and shorter length of stay. The short disease-free interval (median DFS around 9 mo), though, suggested a temporary disease control rather than complete cure<sup>[126-128]</sup>.

## ADJUVANT THERAPY (AFTER POTENTIALLY CURATIVE METASTASECTOMY)

Adjuvant systemic therapy aims to reduce recurrence and prolong survival after curative resection, ideally with minimal treatment-related toxicity. In primary CRC, postoperative oxaliplatin-containing chemotherapy has been shown to offer survival benefit for up to 10 years after curative resection for stage III disease<sup>[129]</sup>.

The role of adjuvant treatment is more controversial for CRLM; according to existing evidence, it only improves DFS but not OS. From pooled analysis of two early randomized trials' results (French FFCD trial and English ENG trial), adjuvant fluorouracil potentially improved OS (median 62.2 mo *vs* 47.3 mo,  $P = 0.095$ ) and PFS (median 27.9 mo *vs* 18.8 mo,  $P = 0.058$ ) compared with surgery alone, but both did not reach statistical significance<sup>[130]</sup>. Adjuvant oral uracil-tegafur and leucovorin also only prolonged recurrence-free survival (from 0.70 to 1.45 years) without improving OS, as demonstrated by a Japanese RCT<sup>[131]</sup>. Current recommendations for oxaliplatin-containing adjuvant regimen (FOLFOX) were based on extrapolation of result of the EORTC intergroup trial 40983, which showed perioperative FOLFOX conferred a PFS benefit but did not affect OS<sup>[53]</sup>. The JCOG0603 trial is now underway to determine if adjuvant mFOLFOX is superior to resection alone<sup>[132]</sup>. Meanwhile, adjuvant FOLFIRI did not improve DFS or OS compared with 5FU alone, but was associated with lower treatment tolerance in a randomized study<sup>[133]</sup>; therefore, FOLFIRI is not commonly used in the adjuvant setting for CRLM. According to the latest ESMO guidelines, there was no strong evidence supporting the use of adjuvant chemotherapy in patients with good oncological and technical criteria who underwent upfront surgery; on the other hand, patients with unfavourable prognostic criteria or have not received any previous chemotherapy for metastatic disease may benefit from adjuvant therapy (*e.g.*, FOLFOX/ XELOX)<sup>[9]</sup>.

To date, no evidence supports the combined use of chemotherapeutics and biological targeted agents in the adjuvant setting after resection of CRLM. Addition of bevacizumab to modern chemotherapy or combination of hepatic arterial chemotherapy infusion (HAI) and systemic chemotherapy did not prolong survival, but appeared to increase biliary toxicity<sup>[134,135]</sup>. A randomized trial is in progress to assess whether bevacizumab gives additional benefit to adjuvant XELOX<sup>[136]</sup>. As the New EPOC trial linked its use in the peri-operative setting to a shorter PFS, cetuximab is generally not recommended in the adjuvant setting after liver metastasectomy<sup>[57]</sup>.

Taking advantage of CRLM's predilection of hepatic artery neovascularization, infusion of cytotoxics via the hepatic artery can deliver high concentration of therapeutic agents to the tumour while minimizing side-effects. An earlier RCT showed adding floxuridine-HAI to systemic fluorouracil (5-FU) chemotherapy improved PFS but not OS after a median follow-up of 10 years<sup>[137]</sup>. In a recent retrospective study, adjuvant HAI offered an OS advantage of approximately 2 years compared to systemic chemotherapy alone, and this benefit was substantiated in patients receiving modern chemotherapy<sup>[138]</sup>; the 5- and 10-year OS reached 78% and 61%<sup>[139]</sup>. The ongoing PACHA-01 trial compares the outcomes of adding oxaliplatin-HAI *vs* systemic oxaliplatin to adjuvant systemic 5-FU after resection or thermal ablation of at least four CRLM<sup>[140]</sup>. More evidence is needed to show whether HAI offers additional benefit to modern doublet or triplet adjuvant chemotherapy. However, the unique expertise required and the need of placing a special port-catheter has limited its use in specialized centres only.

## UNRESECTABLE LIVER-ONLY OR LIVER-DOMINANT METASTASES – A MULTIDISCIPLINARY APPROACH

As mentioned, resectability should be determined by a MDT on a per patient basis, taking into consideration of technical and oncological factors. For unresectable CRLM, the former standard of care is palliative systemic chemotherapy. Although modern doublet or triplet chemotherapy (FOLFOX, FOLFIRI, FOLFOXIRI) have considerably improved the median OS to 15-21 mo and these were further extended by targeted agents, long-term survival remained rare<sup>[141,142]</sup>. In an attempt to obtain durable local

disease control or even cure, two approaches have been employed – (1) conversion therapy followed by potential curative resection; and (2) use of single or a combination of liver-directed therapies. For systemic treatment regimen and local therapy, clinicians can determine the most appropriate strategy from a ‘toolbox’ of ever-expanding options, according to patient and disease factors, treatment goal and its related morbidity<sup>[9]</sup>; again, the decision is best made in a multi-disciplinary setting.

## CONVERSION CHEMOTHERAPY

A subset of patients with initially unresectable CRLM (around 15%-30% depending on the definition of unresectability) may be rendered resectable after conversion chemo-therapy. In a systematic review of 10 studies using different downsizing regimens, an objective radiological response was achieved in 64% (range 43%-79%) patients; 22.6% underwent macroscopically curative liver resection (most studies reported a range of 12.5%-45%) and R0 resection rate was 87%. The median OS and DFS after liver metastasectomy were 45 and 14 months respectively<sup>[143]</sup>.

The optimal regimen for conversion to operable disease remains unclear. Standard doublet chemotherapy FOLFOX or FOLFIRI had conversion rates between 9% to 33%<sup>[144]</sup>. Compared with FOLFIRI, intensified triplet chemotherapy FOLFOXIRI improved the secondary R0 resection rate from 12% to 36%, median PFS from 6.9 to 9.8 mo, and median OS from 16.7 to 22.6 mo; albeit at the cost of greater but manageable toxicity *e.g.*, peripheral neuropathy and neutropenia<sup>[145]</sup>. Addition of targeted agents is recommended by guidelines, but there is no concrete supporting evidence. In a large RCT, giving bevacizumab together with XELOX/ FOLFOX only moderately improved resectability (from 6.1% to 8.4%) and PFS (from 8 to 9.4 mo), but did not prolong OS<sup>[146]</sup>. According to a recent meta-analysis, the combination of bevacizumab and FOLFOXIRI offers more promising results – the R0 surgery conversion rate was 28.1%, and the median OS and PFS were 30.2 and 12.4 mo respectively<sup>[147]</sup>. Multiple randomized trials have shown the addition of cetuximab to chemotherapy in *KRAS* wild-type (WT) unresectable disease improved the R0 resection rate by 2-3 folds<sup>[144,148]</sup>. An increase in complete resection rate from 11 to 18%, however, did not translate into survival benefit in a meta-analysis<sup>[149]</sup>. Panitumumab, another anti-EGFR agent, has also been linked with greater likelihood of curative resection when added to FOLFOX (29% *vs* 17%) in *KRAS*-WT unresectable CRLM<sup>[150]</sup>.

Adding floxuridine-HAI to best systemic chemotherapy achieved a 47% conversion rate to resectable disease at a median of 6 months; median OS and PFS were 38 and 13 mo<sup>[151]</sup>. Oxaliplatin-HAI, meanwhile, was associated with response rates ranging from 24% to 81% in multiple small-scale studies<sup>[152]</sup>. In the French multicentric OPTILIV trial, triplet-agent-HAI plus systemic cetuximab gave a 30% secondary resection rate in *KRAS*-WT disease<sup>[153]</sup>. Whether HAI strategies offer additional benefit to modern intensive systemic chemotherapy regimens have to be tested by future RCTs.

Of note, patients who required prolonged chemotherapy (> 12 cycles) to achieve resectability had higher perioperative morbidity and inferior oncological outcomes. Conservative strategies rather than radical operation may be more appropriate for this subgroup<sup>[154]</sup>. Nonetheless, in general, conversion therapy followed by curative resection should be attempted whenever possible, as survival in this secondary R0 resected group is similar to those who had curative upfront surgery; early recurrence is not uncommon though.

## LIVER-DIRECTED THERAPIES IN UNRESECTABLE CRLM

Clinicians nowadays can choose from an ever-growing armamentarium of loco-regional therapies to attain hepatic disease control. Yet, there is a lack of high-quality evidence assessing the benefits of each modality and no large-scale trials compared the different treatment strategies. Most of these liver-directed therapies require specific expertise, and should be recommended only in institutions with extensive experience with the procedure; the choice of treatment modality often depends on the availability of expertise. Here we will present an update of the available evidence regarding popular treatment modalities.

### Ablation

Radiofrequency ablation (RFA) produces heat by delivering high-frequency alternating electric current through an electrode. Its widespread application has been limited by the relatively high local recurrence rate (ranged from 5% to 60% across different studies) and associated technical barriers *e.g.*, tissue desiccation (charring)

and heat-sink effect affect energy delivery<sup>[109]</sup>. Five-year survival varies between 17% and 51%<sup>[155]</sup>. According to an international expert panel position paper, thermal ablation is indicated for limited number (five or fewer) of small-sized (preferably < 3 cm) metastases deemed inoperable because of tumour or patient factors (*e.g.*, multiple comorbidities); well-located tumours up to 5 cm or patients with up to nine tumours could also be considered<sup>[155]</sup>. Complete ablation with 10 mm margins in all directions should be attained<sup>[156]</sup>. In the landmark EORTC CLOCC study (40004), on top of systemic chemotherapy, RFA offered PFS benefit (median 16.8 mo *vs* 9.9 mo) and a significant prolongation of OS (median 45.6 mo *vs* 40.5 mo) in unresectable CRLM<sup>[157,158]</sup>.

Producing heat from oscillation of water molecules, microwave ablation (MWA) is less susceptible to charring and heat sink, and could be more efficient in the treatment of large lesions and those near major hepatic vessels. It has been associated with lower local recurrence rate compared to RFA, with similar long-term survival outcomes and safety profiles<sup>[159,160]</sup>.

Irreversible electroporation (IRE) induces cell death by creating permanent nanopores in cellular membranes while preserving tissue architecture. It can be a good ablative modality for tumours adjacent to major vascular or biliary structures. Early series showed encouraging results with PFS and OS rates of 18 and 62% at 2 years, but further evidence is necessary before advocacy for its more widespread use in clinical practice<sup>[109,161]</sup>.

### **Intra-arterial therapies**

Intra-arterial therapies (IATs) are used to palliate symptoms or prolong survival in selected patients with unresectable CRLM refractory to chemotherapy. Selective infusion of tumoricidal and/or embolizing agents into hepatic artery branches enhances their delivery to liver tumours, while minimizes their effect on normal liver parenchyma; thereby avoiding significant hepatic and systemic toxicity.

Trans-arterial chemoembolization (TACE) kills cancer cells by means of high concentration of cytotoxic agents and ischemia. For CRLM, it is mainly used as rescue therapy for chemo-refractory diseases, although evidence for that is lacking. Mitomycin C- and cisplatin/doxorubicin-based conventional TACE (cTACE) offered median survivals of 14 and 11 months from the start of salvage therapy<sup>[162,163]</sup>. Post-embolization syndrome was reported in two-thirds of patients, but most only have nausea, fever, fatigue and mildly deranged liver function; severe complications *e.g.*, liver abscess, hepatic failure and peptic ulcer were rare<sup>[164]</sup>.

The newer drug-eluting bead (DEB)-TACE utilizes microspheres loaded with cytotoxics (doxorubicin or irinotecan); the drug is released in a controlled manner and a higher intra-tumoral dose can be delivered, meanwhile reduced peak plasma concentration may improve patient tolerance. In patients who failed previous chemotherapy, the median OS and PFS after DEB-TACE were 25 and 8 mo respectively<sup>[165]</sup>. In a small RCT, irinotecan-loaded DEB-TACE alone achieved better OS (median 22 mo *vs* 15 mo), PFS (7 mo *vs* 4 mo) and quality of life than systemic FOLFIRI; this needs to be verified in larger studies though<sup>[166]</sup>. Compared with cTACE, fewer patients (30%) experienced drug-related adverse events and most reported only minor symptoms *e.g.*, abdominal pain, vomiting and fever<sup>[164]</sup>. Recent studies explored the combination of DEB-TACE with systemic chemotherapy or other treatment modalities. Concurrent capecitabine administration improved disease control but not survival<sup>[167]</sup>, while adding FOLFOX and bevacizumab increased the conversion rate to resectability<sup>[168]</sup>. In non-surgical candidates, RFA combined with TACE attained local tumour control in 92% and OS at 2 years was 88.0%<sup>[169]</sup>. With better understanding of the properties of drug-eluting microspheres, results of DEB-TACE will improve and it will become a therapeutic option earlier in the course of disease *e.g.*, neoadjuvant therapy, first-line treatment for unresectable disease.

For selective internal radiation therapy (SIRT), instead of cytotoxics, radiolabeled microspheres (Yttrium-90) were infused into the arterial system, delivering an effective dose of radiation to the tumour without causing intolerable toxicity to normal liver. Similar to TACE, it is typically considered in CRLM not amenable to resection or ablation. Earlier data confirmed its role in chemo-refractory disease – when given together with systemic 5-FU as salvage therapy, SIRT prolonged PFS (from 2.1 to 4.5 mo) in spite of no OS advantage<sup>[170]</sup>. However, more recent evidence did not support SIRT as a first-line therapy. Pooled data from 3 randomized trials (FOXFIRE, SIRFLOX and FOXFIRE-Global; including 1103 patients not suitable for curative resection or ablation and have not received any chemotherapy) showed, although associated with a higher objective response rate (72% *vs* 63%), early use of SIRT in combination with FOLFOX did not improve OS, PFS or hepatic resection rate, compared with FOLFOX alone (median OS 22.6 mo *vs* 23.3 mo, median PFS 11.1 *vs* 11.9 mo, hepatic resection rate 17% *vs* 16%). The SIRT group had more grade 3 or



above adverse events (OR 1.42, 74% *vs* 67%). The authors concluded SIRT should not be used in unselected chemotherapy-naïve liver-dominant or liver-only CRLM<sup>[171]</sup>. Further studies can help define patient selection and the role of SIRT in the management of CRLM.

In unresectable CRLM, HAI achieved a better tumour response rate but similar survival compared with standard 5-FU chemotherapy<sup>[172]</sup>; its role in the era of modern chemotherapy and targeted agents is less well-defined. HAI has been associated with relative high rates of technical failure (hepatic artery dissection and thrombosis 21%, catheter occlusion 5%, pump failure and infection 2% and 3%); together with the special equipment and expertise required, its availability is limited to relatively few centres<sup>[164]</sup>.

No randomized trial has compared the efficacy and safety of the above three IAT modalities; evidence supporting one over the other is lacking. A recent systematic review tried to settle this issue - the pooled RECIST response rates for cTACE, DEB-TACE and SIRT were 23%, 36% and 23%, while medians survivals from first therapy were 16, 16 and 12 mo respectively<sup>[173]</sup>. However, significant heterogeneity in terms of patient characteristics, tumour burden, previous and post-IAT therapies exists between the included studies; and this precluded meaningful comparisons between the three therapies. We need higher-quality evidence to properly answer this question.

### **Stereotactic body radiation therapy**

This technique allows delivery of a conformal high dose radiation to the tumour, while sparing normal liver. It is suitable for patients with adequate hepatic function but unresectable CRLM. Precise selection criteria are not well defined; some included good performance status, not more than 3 CRLMs and the largest tumour size less than 3 cm<sup>[174]</sup>. From a systematic review including 18 heterogenous studies with different RT doses and schedules (most patients had 1-2 oligo-metastases), the pooled 1- and 2-year local control rates were 67% and 59.3%, while one- and two-year OS were 67.2% and 56.5% respectively; mild/moderate and severe liver toxicity occurred in 30.7% and 8.7% patients<sup>[175]</sup>. The limited evidence so far showed encouraging results; however, this has to be validated in large prospective trials. Guidelines define stereotactic body radiation therapy as a reasonable treatment option for patients unsuitable for surgery or ablative therapies<sup>[9,10]</sup>.

**Controversy 6: Role of liver transplantation:** Traditionally CRLM was regarded as a contraindication to liver transplantation (LT); this concept was challenged by the pilot SECA study<sup>[176]</sup>. Twenty-one patients with unresectable liver-only CRC metastases underwent deceased donor liver transplantation after at least 6 weeks of chemotherapy. OS rates of 95%, 68% and 60% at 1, 3 and 5 years were comparable to results of LT for other indications, and significantly better than a similar cohort who received first-line chemotherapy (5-year OS 9%). However, only 35% patients remained recurrence-free at 1 year; most of the recurrences were small slow-growing lung metastases. Compared with the chemotherapy group, the equivalent DFS but markedly superior OS attained by LT can be attributed to the different metastatic patterns - progression of non-resected LM carries a much worse prognosis than the post-LT indolent pulmonary metastases<sup>[177]</sup>. Similar OS rates were observed in a small series containing 12 patients - one third remained relapse-free after 4 years, suggesting LT may achieve long-term cure in selected patients with unresectable CRLM<sup>[178]</sup>.

These results have to be interpreted with caution, though. They were small studies and there were no standardized selection criteria for recruiting these patients; it is questionable whether this survival benefit can be reproduced in other patients. Currently, LT remains experimental until better selection criteria help achieve lower recurrence rate, particularly in the setting of limited liver graft availability. A number of trials are underway to address the potential of LT for unresectable CRLM, including clarification of survival advantage by RCTs, the role of living donor LT, and the safety and efficacy of total hepatectomy after transplantation of left lateral section graft<sup>[179-182]</sup>.

## **CONCLUSION**

Recent advances in CRLM management have significantly improved outcome on the one hand while complicating the formulation of treatment strategy on the other. Multi-disciplinary involvement from the outset helps define resectability and devise personalized treatment approach. Refined patient selection, with greater emphasis on tumour biology, ensures patients benefit most from the offered interventions.

Surgical resection remains the cornerstone of treatment for curative intent. Liver augmentation strategies and conversion therapy have expanded the definition of resectability and increased the number of patients getting cured. The role of neoadjuvant therapy in operable disease is still controversial, while the use of adjuvant chemotherapy has gained generalized acceptance. Liver-directed therapies are getting more popular, resulting in better local disease control; however, they are currently not recommended as first-line treatment in unresectable CRLM. Liver transplant remains experimental and needs further evidence to validate its use. In the absence of standardized evidence-based protocols, the optimal management of CRLM should be determined by a multi-disciplinary team.

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