Abstract
Selection of the optimal surgical and interventional therapies for advanced colorectal cancer liver metastases (CRLM) requires multidisciplinary discussion of treatment strategies early in the trajectory of the individual patient’s care. This paper reports on expert consensus on locoregional and interventional therapies for the treatment of advanced CRLM. Resection remains the reference treatment for patients with bilateral CRLM and synchronous presentation of primary and metastatic cancer. Patients with oligonodular bilateral CRLM may be candidates for one-stage multiple segmentectomies; two-stage resection with or without portal vein embolization may allow complete resection in patients with more advanced disease. After downsizing with preoperative systemic and/or regional therapy, curative-intent hepatectomy requires resection of all initial and currently known sites of disease; debulking procedures are not recommended. Many patients with synchronous primary disease and CRLM can safely undergo simultaneous resection of all disease. Staged resections should be considered for patients in whom the volume of the future liver remnant is anticipated to be marginal or inadequate, who have significant medical comorbid condition(s), or in whom extensive resections are required for the primary cancer and/or CRLM. Priority for liver-first or primary-first resection should depend on primary tumour-related symptoms or concern for the progression of marginally resectable CRLM during treatment of the primary disease. Chemotherapy delivered by hepatic arterial infusion represents a valid option in patients with liver-only disease, although it is best delivered in experienced centres. Ablation strategies are not recommended as first-line treatments for resectable CRLM alone or in combination with resection because of high local failure rates and limitations related to tumour size, multiplicity and intrahepatic location.

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Approaches to bilateral colorectal cancer liver metastases
Historically, criteria for the resectability of colorectal cancer liver metastases (CRLM) included factors such as a tumour size of <5 cm, the presence of fewer than four lesions, and unilateral distribution.1–3 However, contemporary studies show that the bilateral distribution of CRLM is not an independent predictor of poor oncologic outcome, but, rather, presents a technical challenge to the achievement of a margin-negative resection and the simultaneous preservation of sufficient functional liver parenchyma.4 Contemporary consensus supports the suggestion that ability to remove all metastatic deposits leaving an adequate liver remnant is key to the definition of resectability.5 Modern chemotherapy and biologic agents have further expanded the proportion of patients with bilateral CRLM eligible for resection by downsizing tumours; response to chemotherapy is used by many investigators as a surrogate marker of tumour biologic behaviour and...
may have the potential to contribute to selection for hepatectomy in some patients.6-8

For patients with multiple bilateral CRLM that cannot be safely or completely resected in a single procedure, two-stage hepatectomy is a technical approach that has been shown to accomplish the complete resection of disease that is otherwise considered unresectable to facilitate longterm survival comparable with that in patients who undergo initial resection.6 These favourable results are likely, in large part, to reflect selection because all patients who completed two-stage hepatectomy demonstrated a radiographic and significant histologic response to chemotherapy. It should be emphasized that an intention-to-treat analysis which included patients who did not complete all stages of therapy showed impressive 5-year overall survival superior to that of matched patients who did respond to chemotherapy but did not undergo surgery, further emphasizing the potential benefit of liver resection in this setting.6 This approach typically entails initial treatment with systemic chemotherapy with or without a biologic agent, with reassessment after four to six chemotherapy cycles. The first-stage resection is typically performed when cross-sectional imaging demonstrates response to treatment or stable disease. Most commonly, first-stage hepatectomy includes the complete resection of all metastases from the future liver remnant (FLR) in the form of minor resections that avoid hepatic pedicle dissection or mobilization of the liver to be resected in the second stage.9 Portal vein embolization (PVE) may be required if the FLR volume is insufficient. After 4–6 weeks (without interval chemotherapy), or later (with chemotherapy); re-imaging is performed to assess liver regeneration and second-stage major hepatectomy may be performed, possibly followed by additional chemotherapy.6

Neither cytotoxic agents nor bevacizumab impair liver regeneration after PVE.10,11 In a study by Mentha et al, evaluating patients undergoing two-stage hepatectomy, mostly without interval chemotherapy, histologic examination demonstrated the increased proliferation of tumour cells at the periphery of lesions after second-stage resection.12 Some investigators therefore recommend interval chemotherapy, whereas others do not in order to mitigate chemotherapy-associated hepatotoxicity.6,3 If chemotherapy is selected, PVE may also be performed during this time without fear of reduced efficacy.

The in situ split procedure is a recently reported, novel method for inducing rapid remnant liver hypertrophy by ligating and dividing the portal vein, and splitting the liver parenchyma along the intended transection line; a second procedure, to be conducted during the same hospitalization, is required to remove the specimen once hypertrophy of the liver remnant has occurred. Recently, Schnitzbauer et al described this procedure in 25 patients with various malignancies, including 14 with CRLM.13 Although this technique may have a role in selected patients, enthusiasm must be tempered by the high perioperative mortality rate of 12% (mainly related to liver failure and infection) and absence of large studies or longterm results.

One-stage hepatectomy with multiple parenchyma-sparing resections is widely practised and, when technically feasible, can be considered a standard approach.14 One-stage hepatectomy requires high-quality preoperative imaging and mastery of intraoperative ultrasound and segmental hepatic resections.15 Advantages of one-stage resection include low published morbidity and mortality rates and the avoidance of a second laparotomy.14 The selection of a one- or two-stage approach in a patient with bilateral CRLM is challenging and should be individualized based on disease burden, potential for positive margins, the anatomic distribution of disease and the nature of any extrahepatic resections that will be performed. A greater disease burden targeted using the multiple-wedge approach carries the risk for narrow resection margins and higher recurrence rates. In a report by Kokudo et al., 57% of patients with four or more metastases preferentially treated with one-stage multiple sub-segmentectomies developed recurrence in the remnant liver.15 However, many patients were amenable to repeat resection and, in patients with five or more metastases resected in one to three hepatectomies, 5-year overall survival after the first hepatectomy was 45%.

The role of ablation as an adjunct to resection in patients with bilateral CRLM remains controversial.17 Studies combining ablation with resection usually reflect outcomes in patients with more advanced intrahepatic disease burdens and profiles that many would consider unresectable, and show 3-year overall survival rates of 47–51%.18-19 A multi-institution study of 125 patients who underwent resection with ablation demonstrated median disease-free and overall survival of 14.7 months and 34.8 months, respectively, which were shorter than those of patients undergoing resection alone (median overall survival: 50.5 months).20 However, the two groups were not comparable because patients in the former were more frequently associated with adverse prognostic factors, including synchronous multinodular bilateral disease. Intraoperative ablation combined with resection may expand the number of patients eligible for liver-directed therapy because normal liver parenchyma can be spared, allowing for contralateral major resections. Selection for the use of intraoperative ablation is critical and should be limited to small (<3 cm, preferably ≤1 cm) tumours away from major vessels.20 The short-term benefits of ablation should thus be balanced with the high longterm risk for recurrence.

When the disease is refractory to contemporary chemotherapeutic agents, intra-arterial therapies may downsize metastases sufficiently to allow resection in some patients.21 However, data are limited on the safety of hepatectomy after yttrium-90 radioembolization, which may induce portal hypertension, parenchymal fibrosis and liver atrophy. Chemotherapy delivered by hepatic arterial infusion (HAI) has also been used successfully to convert unresectable disease to resectable disease.22,23 Very advanced disease is the norm in these patients, who often require ablation combined with resection, and in whom disease recurrence rates are as high as 90%.24 In patients in whom bilateral CRLM is sufficiently downsized to allow operative therapy after systemic or intra-arterial therapies,
resection should encompass all initial sites of disease if possible. ‘Adjutant hepatectomy’ or incomplete removal of just some CRLM should be avoided because the currently available data do not demonstrate any oncologic benefit of such an approach.

Consensus statements

1. Resection is the reference standard treatment for bilateral CRLM.
2. One-stage surgery with multiple resections of multiple bilobar lesions is an effective strategy with which to treat appropriately selected patients with bilateral metastases.
3. Two-stage hepatectomy with perioperative chemotherapy ± PVE (or portal vein ligation) may allow the complete resection of disease in patients who are otherwise considered unresectable.
4. Ablation may be a useful adjunct for managing extensive bilateral CRLM not amenable to complete resection, but proper selection is critical and higher local recurrence rates must be recognized.
5. After downsizing with preoperative systemic or intra-arterial therapy, the goal of a curative-intent hepatectomy remains to remove all initial and currently known sites of disease if possible. Incomplete removal of CRLM is not recommended.

Approaches to the synchronous presentation of colorectal cancer and CRLM

Of the 50% of patients with colorectal cancer (CRC) who develop liver metastases, a large proportion present with synchronous disease. Many studies have found that synchronous CRLM is associated with worse survival than metachronous disease, although others have shown no difference. Patients with synchronous CRLM often have advanced disease and decisions on their management can be complex, mandating a multidisciplinary approach that includes the expertise of colorectal and hepatic surgeons and medical oncologists. Because the timing of chemotherapy, hepatic resection and colorectal resection must be carefully planned and sequenced, it is imperative that all relevant specialties participate in clinical decision making from the beginning.

Role and timing of colon and liver resection

One of the main considerations in the management of patients with synchronous CRLM concerns the roles and timings of resections of the primary tumour and liver metastases. Resection of the primary tumour does not improve survival in patients in whom liver metastases are not resected. Therefore, among patients with unresectable CRLM, primary tumour resection is reserved for patients with symptoms that cannot be controlled with less invasive techniques such as endoscopic stenting. The reported 5-year survival rates of 40–58% following CRLM resection have made resection the standard of care in patients who can be rendered disease-free. For patients with initially unresectable CRLM, systemic chemotherapy is the primary therapy, but the possibility of reducing the tumour burden sufficiently to allow resection should always be considered. Adam et al. demonstrated that treatment with FOLFOX [folinic acid (leucovorin), fluorouracil (5-FU), oxaliplatin] or FOLFIRI [folinic acid (leucovorin), 5-FU, irinotecan] converted 12.5% of patients with unresectable CRLM to resectable status. In selected patients, higher rates of conversion to resectable intrahepatic disease have been reported after HAI treatment combined with systemic chemotherapy than after systemic chemotherapy alone.

For patients with a resectable primary tumour and resectable synchronous CRLM, there are three options in regard to sequencing the operative components: (i) staged resection with colon resection first; (ii) staged resection with liver resection first, and (iii) simultaneous resection of the primary tumour and CRLM. Regardless of the sequencing of the procedures, in all patients it is critically important that an adequate oncologic resection at both sites (liver and primary disease) be performed.

Historically, simultaneous resection was associated with higher rates of morbidity and mortality and therefore was not advocated. As a result of continued improvements in anaesthetic and surgical management, mortality in even major hepatic resections has decreased to very low rates, prompting many centres to revisit the safety of simultaneous resection. Thelen and colleagues reported higher operative mortality after simultaneous (10%) versus staged (1.1%) resections; all of the lethal events in the former group occurred after major hepatic resections. By contrast, several recent series have reported equal rates of mortality in simultaneous and staged resections. Van et al. compared outcomes in 73 patients undergoing simultaneous resection with those in 30 patients undergoing staged resection and found mortality rates of 0% in both groups, although about three quarters of patients in both groups were submitted to major hepatic resection. Martin and colleagues reported results in 230 patients in a contemporary series who underwent resection for synchronous CRLM (70 simultaneous, 160 staged resections), in whom the decision on type of resection was based upon the complexity of the two resections and the overall comorbidity of the patient. The two groups were equivalent in age and comorbid conditions, lesion numbers and sizes, and extent of liver resection. The mortality rate was 2% in both groups and complication rates (56% versus 55%) and the severity of complications were equivalent in both groups. The simultaneous resection group had a significantly shorter length of stay (LoS) in hospital compared with the combined lengths of both hospitalizations in the staged resection group (LoS: 10 days versus 18 days; P = 0.001). Furthermore, Turrini et al. reported that patients submitted to simultaneous resection were able to start chemotherapy sooner after surgery and were more likely to complete the treatment course.

In a recent meta-analysis of 14 published reports on 2204 patients, Chen et al. showed that simultaneous resection was associated with a shorter hospital LoS [weighted mean difference −4.77 days, 95% confidence interval (CI) −7.26 to −2.28; P < 0.01] and lower morbidity (odds ratio 0.71, 95% CI 0.57–0.88; P = 0.002) compared
with staged resections, with no difference in long-term survival. A recent non-randomized study comparing simultaneous versus staged resection in synchronous CRLM demonstrated equivalent (or lower) morbidity, equivalent mortality rates, and shorter hospital LoS for simultaneous resection.49

Unfortunately, the studies addressing this particular issue are limited by a high degree of selection bias arising from the fact that patients in whom complication rates were expected to be higher (as a result of greater comorbidity, marginal FLR volume, etc.) are generally selected for staged resections. The most that can be concluded from this body of work is that, with careful patient selection and selective use of PVE, simultaneous colon and liver resections appear to result in a shorter LoS and equivalent morbidity and mortality rates compared with staged resections. It appears to be safe to combine a straightforward colon resection (segmental or hemi-colectomy) with a hepatectomy in which up to four segments are removed, or minor hepatectomy with any colorectal resection; in combinations of extended intestinal resections (i.e. rectal resections, total abdominal colectomy) with major hepatectomy, morbidity risks are significantly greater.50 From a technical perspective, in patients undergoing simultaneous resection, liver resection is generally performed first under low central venous pressure conditions, followed by the colon resection.

In patients who are deemed unsuitable for synchronous resection, the ‘colorectal-first’ approach has historically been favoured because of the perceived risks for bleeding, obstruction, perforation or progression of the primary tumour.44,46,47,48,51 In patients with haemorrhage or obstruction, resection of the primary disease should, in nearly all cases, be performed without considering a simultaneous resection. Likewise, patients who present with a perforation require urgent surgical intervention, should almost never undergo simultaneous treatment of the liver disease, and are at significant risk for peritoneal carcinomatosis that will mitigate any anticipated benefit of CRLM resection.

An alternative to the synchronous approach and classic ‘colorectal-first’ approach is the ‘liver-first’ approach (or ‘reverse’ approach), initially described by Mentha et al.52 This approach is useful in patients with a rectal primary tumour, in whom possible treatments can be sequenced as follows: systemic chemotherapy first, followed by liver resection, followed by chemoradiation to the rectal primary tumour, followed by resection of the rectal primary tumour. The radiation component may be individualized as the resulting reduction in risk for local recurrence may be considerably smaller than the risk for distant recurrence.53 The benefit of this approach is that treatment of the metastatic disease is not delayed by chemoradiation.54 The ‘liver-first’ approach may also be useful in advanced CRLM that may progress to become unresectable while off chemotherapy, although this possibility should not drive clinical decision making in most patients. Brouquet et al. analysed outcomes in 156 patients with synchronous CRLM who underwent resection via ‘combined’, ‘colorectal-first’ or ‘liver-first’ approaches49 and found that the last of these was associated with morbidity, mortality and overall survival rates similar to those of the other strategies. A total of 5% of patients in the ‘liver-first’ group developed primary tumour-related complications; all of these patients had demonstrated nearly obstructing primary tumours prior to chemotherapy. This study showed that outcomes in patients with colon and rectal primary tumours were similar regardless of treatment sequence.

The ‘simultaneous’, ‘colorectal-first’ and ‘liver-first’ approaches all have roles in the treatment of patients with synchronous CRLM. The particular approach used must be tailored to the patient through multidisciplinary discussion that prioritizes therapy for the most pressing disease component, minimizes the risk for complications and expedites the use of systemic therapy.

**Consensus statements**

1. Patients with synchronous CRLM should undergo formal multidisciplinary evaluation by colorectal and hepatic surgeons and medical oncologists prior to the initiation of any treatment.

2. In many patients with synchronous CRLM, simultaneous resection by experienced surgeons is feasible, safe and effective; however, staged resection should be considered for patients with a marginal or inadequate FLR volume, those with significant morbidity-related risks, or when extensive operations are anticipated at both sites.

3. Priority in staged resections may be given to colorectal-first or liver-first strategies based on concern for complications related to the primary tumour or the progression of marginally resectable CRLM during treatment of the primary tumour.

**Role and timing of chemotherapy in synchronous CRLM**

A more detailed discussion of the timing of chemotherapy and liver resection (preoperative/neoadjuvant, perioperative, postoperative/adjuvant) is included in the accompanying third Expert Consensus Statement presented by Schwarz et al. in this issue of HPB. However, several issues relevant to the treatment of patients with synchronous CRLM warrant specific discussion.

The concept of selection for resection based on response to chemotherapy has gained popularity in this group of patients with CRLM. In the great majority of patients, tumours either decrease in size or remain stable following treatment with systemic chemotherapy, a finding reported in virtually every prospective study completed using modern chemotherapy.55–58 Response to chemotherapy is associated with a lower incidence of non-therapeutic laparotomy in the prospective European Organization for Research and Treatment of Cancer (EORTC) study (95% resected in the chemotherapy arm versus 89% resected in the no-chemotherapy arm),55 and in multivariate analyses of retrospective data.59 Conversely, in patients with extensive disease (e.g. four or more CRLM), progression on chemotherapy is associated with shorter long-term survival compared with patients with stable or responding disease (5-year overall survival: 37% in responders, 30% in patients with stable disease, 8% in patients...
with progression).\textsuperscript{41} Progression, however, is rare (7% in the EORTC trial) and progression that precludes resection is even less common (4%)\textsuperscript{35} and thus few patients will be denied resection based on response to chemotherapy.

If chemotherapy is to be given preoperatively, a short course (four to six cycles) is recommended in view of considerations of hepatotoxicity.\textsuperscript{50} Chemotherapy can be safely delivered to patients with intact primary tumours.\textsuperscript{49,61} A series of 233 patients [of whom 78 (33\%) had rectal primary lesions] with stage IV CRC and intact primary tumours treated by systemic chemotherapy revealed that 11\% developed primary tumour-related complications and 3.5\% required a bypass or stoma as a result (other primary disease-related complications were managed with resection, stent or radiation).\textsuperscript{62} When symptoms are minimal or absent, and when the colonoscope can traverse the lesion, systemic chemotherapy for synchronous CRLM and untreated primary tumours can be safely delivered.\textsuperscript{49,61}

Given that the majority of patients respond to chemotherapy (in both the primary tumour and CRLM), consideration must be given to marking lesions that might be difficult to locate after a major chemotherapy response. India ink tattoo of small primary tumours is recommended to facilitate localization at the time of resection as some lesions will nearly disappear following short-course treatment. Similarly, small non-subcapsular liver metastases that would otherwise be amenable to limited liver resection should be considered for marking (e.g. with a metallic coil by the interventional radiologist) in case they disappear or become difficult to localize after systemic therapy.\textsuperscript{63}

For primary tumours that present with minimal bleeding or demonstrate significant mucosal erosion, treatment with bevacizumab is not generally recommended for the first cycle(s) of therapy in view of the risks for bleeding and perforation.\textsuperscript{64} Development of colonic obstruction in the setting of chemotherapy-associated neutropenia is associated with significant risk for morbidity and mortality, and thus resection of the primary tumour prior to chemotherapy should be strongly considered in patients with impending obstruction.\textsuperscript{39}

In conclusion, data from several studies indicate that the administration of up to six cycles of neoadjuvant FOLFOX is a reasonable strategy for use in patients with resectable CRLM. Other data support the safety of chemotherapy in the presence of an intact primary tumour. A key to this approach involves limiting pre-resection chemotherapy to 2–3 months to prevent the occurrence of chemotherapy-induced liver injury. Patients at intermediate or high risk for recurrence (based on the clinical risk score)\textsuperscript{65} may benefit from preoperative chemotherapy.

**Consensus statement**

4 In patients with synchronous CRLM and asymptomatic primary tumours, preoperative chemotherapy (of 2–3 months’ duration) is relatively safe and should be considered in patients at high risk for recurrent disease.

### Intra-arterial therapies

#### Rationale for hepatic arterial therapy

The liver is the sole site of metastatic disease in many patients with CRC. Normal liver parenchyma is perfused predominantly by portal venous blood, whereas metastatic tumours of >1 mm in size are supplied primarily by the hepatic arterial system.\textsuperscript{66,67} The administration of therapy via the hepatic arterial system enhances drug delivery to tumour tissue and substantially reduces the occurrence of systemic side-effects.\textsuperscript{66,67}

#### Hepatic arterial infusion therapy

Hepatic arterial infusion chemotherapy is administered either through surgically placed ports or through an implantable continuous infusion pump, both of which provide more durable delivery than percutaneous catheters.\textsuperscript{68} Arterial infusion catheters are best inserted into the gastroduodenal artery.\textsuperscript{69} Hepatic arterial infusion pumps are best placed at centres with considerable experience in this technique by surgeons who have placed at least 25 pumps.\textsuperscript{70} In this circumstance, complications can be minimized, and pump function preservation can be as high as 91\% at 1 year and 84\% at 2 years.\textsuperscript{70}

Floxuridine is an antimetabolite chemotherapy agent most commonly used in HAI therapy and is the most thoroughly studied drug for this purpose. It has a half-life of <10 min and 95\% of drug is extracted on its first pass through the liver.\textsuperscript{71} Radioactive HAI floxuridine distributes a 15-fold higher concentration of chemotherapy to the tumour than to normal liver parenchyma and a 400-fold higher concentration of chemotherapy to the tumour than is observed with systemic administration.\textsuperscript{72} 5-Fluorouracil (5-FU) has been the preferred agent in Europe (usually delivered via surgically placed ports)\textsuperscript{73,74} and oxaliplatin has been used more recently in HAI therapy with favourable results.\textsuperscript{75,76}

Systemic toxicity is low with HAI-administered floxuridine. Aberrant gut perfusion can result in ulceration and diarrhoea.\textsuperscript{77} Biliary toxicity is the most common treatment-related complication of floxuridine-based HAI chemotherapy and occurs because the biliary system is also perfused by the hepatic artery.\textsuperscript{78} Elevated liver enzymes warrant dose modification.\textsuperscript{79} Simultaneous administration of dexamethasone reduces the biliary toxicity of floxuridine-based HAI.\textsuperscript{80} The addition of concomitant systemic chemotherapy can increase the toxicity of HAI pump therapy.\textsuperscript{81}

#### Efficacy in unresectable disease

Hepatic arterial infusion chemotherapy has been extensively studied as first-line treatment for unresectable CRLM in at least 10 randomized studies.\textsuperscript{82} Although response rates to HAI are higher than those in non-HAI-treated control subjects, improvements in survival have been inconsistent, with the best being a 4.4-month advantage in patients treated with floxuridine-based HAI compared with those receiving systemic 5-FU and
leucovorin in a well-performed trial conducted by the Cancer and Leukaemia Group B (CALGB) reported in 2006. In this trial, quality of life in HAI recipients was superior to that in those treated with systemic therapy only. In the HAI-treated group, median time to hepatic progression was longer than in the non-HAI group (9.8 months versus 7.3 months), whereas time to extrahepatic progression was shorter (7.7 months versus 14.8 months). It is important to note that fluoruridine-based HAI was administered without systemic therapy in this trial, which is not the current standard approach.

An EORTC trial comparing outcomes in 290 patients on either systemic therapy or HAI-administered 5-FU and leucovorin showed no difference in median survival between the groups; 37% of patients in the HAI group received no regional therapy, underscoring the complexity of this modality. A meta-analysis of 10 selected randomized trials demonstrated a greater tumour response to HAI therapy than systemic therapy alone (43% versus 18%; \( P < 0.0001 \)), but no significant overall survival difference (15.9 months versus 12.4 months; \( P = 0.24 \)). There may be an advantage to combining HAI with systemic chemotherapy in patients in whom first-line systemic chemotherapy alone has failed and in a preoperative approach in patients with initially unresectable disease. In the latter scenario, response rates as high as 92% have been reported. A recent French Phase II trial of 26 oxaliplatin-naïve patients with CRLM treated with infusional port oxaliplatin and systemic 5-FU/leucovorin showed median overall and disease-free survival of 27 months each.

### Adjuvant approach

Postoperative fluoruridine-based HAI (with systemic 5-FU/leucovorin) following a negative margin hepatic resection has been compared with i.v. 5-FU/leucovorin alone in a randomized controlled trial of 156 patients. At 2 years, the HAI group had improved overall survival (86% versus 72%; \( P = 0.03 \)), but the 10-year follow-up failed to show a sustained, statistically significant survival advantage, despite significantly longer progression-free survival (31.3 months versus 17.2 months; \( P = 0.02 \)) and greater overall survival (41% versus 27%; \( P = 0.10 \)) in the HAI-treated group. No other randomized study to date has shown HAI chemotherapy to result in a significant survival advantage in the adjuvant setting. Although limited by the heterogeneity of the studies it examined, a 2009 Cochrane review of seven randomized trials of adjuvant HAI of fluoruridine or 5-FU therapy for CRLM failed to show a survival benefit for this therapy over adjuvant systemic therapy alone. A recent Phase II trial conducted through the National Surgical Adjuvant Breast and Bowel Project (NSABP) investigated the combination of fluoruridine-based HAI and systemic oxaliplatin and capecitabine in the adjuvant setting and reported a 2-year survival rate of 85%. Studies assessing the role of HAI chemotherapy in association with modern systemic chemotherapy regimens and different infusional agents are ongoing.

### Consensus statements

1. Hepatic arterial infusion therapy is a promising option for the provision of palliative or adjuvant therapy in patients with CRLM, but is best administered in experienced centres.
2. In patients with unresectable CRLM, fluoruridine-based HAI therapy significantly improves tumour response and hepatic progression-free survival, but the survival advantage of fluoruridine-based HAI over contemporary systemic chemotherapy remains questionable.
3. Randomized controlled trials are warranted to examine the potential advantages of and indications for HAI therapy with updated systemic chemotherapy regimens in patients with resectable and unresectable disease.

### Radioembolization

Radiotherapy can induce cytotoxicity in malignant liver tumours; however, the value of standard external beam radiation applied to hepatic malignancies is limited by toxicity to surrounding hepatic parenchyma. Radioembolization is a form of brachytherapy in which a high-energy beta-emitting radiation source (yttrium-90) is coupled with an appropriately sized (~30 μm diameter) embolic particle. This technique allows the delivery of a therapeutic dose to the tumour vasculature and attempts to minimize damage to uninvolved tissue.

SIR-Spheres® (Sirtex Medical Pty Ltd, Sydney, NSW, Australia) are resin-based microspheres approved by the US Food and Drug Administration (FDA) for use in the treatment of CRLM with adjuvant intra-arterial florouridine. The basis of FDA approval was a Phase III trial of fluoruridine-based HAI administered with and without resin microspheres in 72 patients with unresectable CRLM. The combination therapy was associated with an improved time to progression (15.9 months versus 9.7 months; \( P < 0.01 \)) over fluoruridine-based HAI alone. A subsequent multi-centre Phase II trial of yttrium-90 resin microsphere radioembolization was performed in 50 patients refractory to chemotheraphy in whom previous oxaliplatin- and irinotecan-based systemic regimens had failed. Response or stable disease was observed in 48% of patients treated and median overall survival was 12.6 months in these heavily pretreated patients. In this trial yttrium-90 treatment was well tolerated, although longterm hepatic toxicity was not evaluated. An ongoing Phase III trial, SIRFLOX [NCT00724503 (http://www.clinicaltrials.gov)], is evaluating yttrium-90 intra-arterial treatment as first-line therapy for unresectable CRLM treated with FOLFOX6 and SIR-Spheres® versus FOLFOX6 alone, and is expected to complete in 2012.

TheraSpheres® (MDS Nordion, Ottawa, ON, Canada) are glass-based microspheres that have a humanitarian device exemption for the treatment of primary and metastatic liver tumours. There are limited data on the role of this agent in CRLM. A Phase II trial of TheraSpheres® as salvage therapy in patients in whom systemic chemotherapy had failed was performed in 27 patients, with a positron emission tomography response measured at 88% in the first treated hepatic lobe. A randomized Phase III multicentre...
clinical trial, known as the ‘Efficacy Evaluation of TheraSphere following Failed First-Line Chemotherapy in Metastatic Colorectal Cancer’ (EPOCH) trial, will open soon at up to 30 sites worldwide, with a target enrolment of approximately 350 patients (http://clinicaltrials.gov/ct2/show/NCT01483027).

Consensus statement

4 Yttrium-90 transarterial radioembolization is effective and has shown promising early results in the palliative management of unresectable CRLM, and can be considered for patients with liver-only disease in whom at least one standard line of systemic chemotherapy fails. First-line therapy with yttrium-90 should only be administered in clinical trials; long-term toxicity potential requires further clinical evaluation.

Chemoembolization

The approaches to and reports on traditional transcatheter arterial chemoembolization (TACE) in CRLM are ill-defined and variable. As such, this discussion will focus on drug-eluting beads delivering irinotecan (DEBIRI; Biocompatibles UK Ltd, Farnham, UK), data for which are emerging from ongoing clinical trials.93,94 These are polyvinyl alcohol hydrogel beads loaded with irinotecan.95 The beads are delivered via a selective transcatheter arterial administration and lodge in the interface between the tumour and normal parenchyma. The drug is slowly released into the tumour environment, providing relatively selective drug exposure. Irinotecan was selected because of its chemical properties, charge and ability to be loaded on the beads. An initial experience in 20 patients demonstrated a reduction of >50% in serum carcinoembryonic antigen levels in 12 patients and reduced lesion enhancement on contrasted axial imaging in 80% of patients.96 Right upper quadrant pain has been the main effect of toxicity.97 Subsequently, a multicentre registry of 55 heavily pretreated patients reported rates of hepatic progression-free survival and overall survival at 1 year of 75% for each.98 A Phase II randomized trial of 60 patients comparing treatment with FOLFOX ± bevacizumab plus DEBIRI, with treatment with FOLFOX ± bevacizumab (http://clinicaltrials.gov/ct2/show/NCT00932438) is currently accruing. Although it is too early to speculate on the benefits of this therapy, it appears to be well tolerated and offers the potential for a standardized mode of chemoembolization for CRLM.

Consensus statement

5 Traditional TACE lacks data and standardization as a modality for treatment of CRLM. DEBIRI is a newer form of TACE, which shows promising early results, but requires further study before its use can be recommended.

Ablation strategies including radiofrequency ablation, microwave ablation and external beam radiotherapy

Hepatic resection is associated with 5-year survival rates of up to 58% and cure rates of approximately 20%.27,40,99 Results of this level are not reported with any other therapy. Local failure at the resection margin is uncommon, with most large series reporting rates of significantly <5%.42 Although rates of morbidity in partial hepatectomy for CRLM have remained stable at 30–40%, 90-day mortality has diminished substantially to 1% in high-volume centres.100,101 Furthermore, survival appears to be improving.100 Collectively, these data have established hepatic resection as the reference standard locoregional treatment for CRLM.

The thermal ablation of tumours utilizes image guidance to deliver extreme temperatures to a tumour and its surrounding tissue. The advantages of thermal ablation include its adaptability to minimally invasive approaches, the ability to spare liver parenchyma and a low morbidity rate. Thermal ablation can be performed percutaneously, laparoscopically or at laparotomy. At 60 °C there is immediate cell death; typically, ablation zones are created with temperatures in excess of this threshold. Radiofrequency ablation (RFA) is the most commonly used form of thermal ablation in the treatment of liver tumours. In RFA, needles placed in and around tumours deliver alternating electrical current in the radiofrequency range that generates heat. At high temperatures, tissue desiccates, limiting current flow and impairing further ablation.102–104

In properly selected patients, RFA-associated morbidity is generally <10%, regardless of whether RFA is performed surgically or percutaneously.105 Mortality in RFA is <1%.105 These advantages are balanced by a number of limitations to the use of RFA, which is generally ineffective in tumours of >3 cm in size because of high local recurrence rates.17,102–104 The heat generated by RFA can injure adjacent structures (e.g. the diaphragm, gallbladder, gastrointestinal tract, major bile ducts) and RFA should not be used to treat tumours adjacent to these locations. Lastly, the efficacy of RFA is limited by the presence of large blood vessels as a result of their high flow and the related ‘heat sink’ effect, which protects adjacent cells from thermal ablation.106–108 It is therefore important to note that unresectable tumours are not generally amenable to thermal ablation because the factors that make a tumour unresectable (number, size, proximity to major blood vessels or bile ducts, etc.) also make it unsuitable for ablation.

Local recurrence after RFA remains a major problem. Factors associated with higher local recurrence rates include large tumour size, proximity to major blood vessels, diagnosis (CRLM being worse) and percutaneous approach.20,102–104 In a large meta-analysis, tumour size and the percutaneous approach were independently associated with higher recurrence rates. Recurrence rates in tumours of ≥3 cm in size ranged from 25% to 50% regardless of approach. For tumours of <3 cm in size, local recurrence rates in surgical and percutaneous ablation were 4% and 16%, respectively.73 In single-arm percutaneous RFA series, local recurrence rates have ranged from 18% to 50% and are related to tumour size.20,102–108 Recurrence rates in open RFA have typically been <15% with some series reporting rates of <10%.20,102–105 The best local control rates reported for RFA (and other ablation techniques) appear to be achieved at open operation, probably...
because this allows for the mobilization of the liver and the use of direct hepatic intraoperative ultrasound to guide probe placement. Intraoperative ablation is also limited by tumour size, as indicated by recurrence rates of \( \leq 20\% \) for tumours of 1–3 cm in size and \( \leq 50\% \) for tumours of 3–5 cm in size.\cite{126} The utility and limitations of RFA combined with resection are discussed in the section entitled ‘Approaches to bilateral colorectal cancer liver metastases’.

Comparisons between RFA and resection have generally been limited to retrospective series that have attempted to match patients. These retrospective comparative studies have shown substantially higher local recurrence rates for RFA (16–60\% versus 0–24\%) and better long-term survival in resected patients.\cite{102-104} Unfortunately, these comparisons are hampered by tremendous selection bias and confounding factors, and conclusions about survival rates are not possible. One recently published study proposed percutaneous RFA as a ‘test of time’ to manage selected patients with resectable CRLM. In this study, 134 tumours were treated in 88 patients with limited tumour burdens and >40\% of RFA-treated tumours recurred locally. Resection was not performed in two thirds of patients because they either remained free of disease (many with repeat RFA) or had unresectable distant progression.\cite{107} In this study, the avoidance of a surgical procedure was considered the goal of RFA, but whether this should be the desired outcome is disputable. In this series, RFA failed in >40\% of cases and it was unclear whether patients could be effectively salvaged. Therefore, this approach has not been uniformly accepted. Another recent concept refers to the use of laparoscopic RFA in patients with resectable CRLM. A recent example of such an approach was illustrated in a study of 64 patients with resectable metastases who underwent laparoscopic RFA. Local failure occurred in 7\% of patients and median recurrence-free survival was 15 months. Median and 5-year actuarial survival were 4.3 years and 49\%, respectively, which may be considered comparable with outcomes in resection series.\cite{108} Laparoscopic RFA in well-selected patients may be a promising strategy, but has not been sufficiently studied.

Microwave ablation (MWA) is a newer technology that utilizes high-frequency electromagnetic radiation to create thermal damage and coagulation necrosis. This form of ablation carries less risk for charring and a heat sink effect and creates larger ablation zones more rapidly. As MWA is a more powerful energy mediator, there are concerns over injury to adjacent structures. The use of MWA to treat CRLM has not been well studied. Most series reflect outcomes for a large variety of liver tumours. In sum, these studies show complication rates ranging from 6\% to 30\%, with higher rates occurring in patients undergoing laparotomy and other procedures.\cite{102,109,110} Local recurrence rates vary hugely from 3\% to 50\%, but the two largest series reported low rates of 3\% and 6\%, respectively.\cite{109,110} Published MWA series report survival rates, but the heterogeneity of diseases treated in each series precludes the clarification of any conclusions regarding survival data.\cite{102,109,110}

External beam beam radiation therapy (EBRT) has recently been proposed as a potential locoregional therapy in CRLM and other liver tumours. Historically, EBRT was not used in the liver because the therapeutic window between its tumoricidal benefits and liver-specific toxicity was too small. Recent advances in imaging, stereotactic body radiation (SBRT) and corrections for respiratory motion have increased the potential role of EBRT in the treatment of liver tumours. Furthermore, although it has not been well studied, EBRT may be effective and safe when used near major blood vessels; however, the potential for major bile duct toxicity remains a concern. Overall, the use of SBRT for liver tumours has been minimally studied and only a few studies have focused on its use in CRLM. A few well-designed dose-escalation studies have demonstrated that SBRT can be delivered to liver tumours without dose-limiting toxicity in doses of \( \leq 60 \) Gy. Unfortunately, local progression rates at 2 years at the initial lower doses have been high, ranging from 23\% to 43\%;\cite{111-114} higher doses may afford better local control rates. In a recent dose-escalation study, nine patients with malignant liver tumours demonstrated a 90\% response rate and a 2-year local control rate of 100\% at a dose of 60 Gy in five fractions.\cite{114}

**Consensus statements**

1. Ablation strategies are inadequately studied and plagued by high local failure rates, and are limited by tumour size, tumour multiplicity and location, and thus are not recommended as first-line treatments for resectable CRLM.
2. Ablation strategies play a role in highly selected patients with small, appropriately located tumours when resection is not feasible or safe, but should be considered as second-line locoregional therapy to hepatic resection.
3. Prospective trials comparing ablative techniques or comparing resection with ablation in well-defined patients are needed to define the role of ablation in the treatment of CRLM in the future.

**Conflicts of interest**

None declared.

**References**


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