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# Local Treatment Options for Unresectable Liver Metastases in Colorectal Cancer

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.73014>

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## Abstract

Despite the increase in effectiveness of systemic therapy, cure for colorectal cancer with liver metastases (CRLM) is rarely achieved without surgical resection, with less than 20% of patients initially suitable for surgery. Liver-directed therapies are continually being investigated in the hope of improving cure rates in patients with unresectable liver metastases. These modalities include selective internal radiation therapy (SIRT), radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and hepatic artery infusion (HAI) chemotherapy. While there is evidence of activity for all these treatments, they are somewhat lacking in high level randomized, controlled trial evidence (RCT) with appropriate control arms relevant to current standard of care. This review examines the efficacy and safety of these treatments in unresectable CRLM.

**Keywords:** colorectal cancer, SIRT, RFA, HAI, TACE, liver metastases

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## 1. Introduction

Colorectal cancer is the fourth most common cancer and third leading cause of cancer death worldwide [1]. Approximately 20% of patients have stage 4 disease at diagnosis with 5 year overall survival rate traditionally not exceeding 13% [2, 3] or 20% in more recent clinical trial populations on multi-agent chemotherapy [4]. The venous drainage of the intestinal tract is through the portal system and hence the first site of dissemination is usually the liver. Up to 25% of patients present with synchronous hepatic metastases with a further 50% developing liver metastases during the course of their illness [5]. This is the most common site for metastases in colorectal cancer and the leading cause of death [6].

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Surgical resection of liver metastases remains the only potentially curative treatment modality in patients with colorectal liver metastases (CRLM). Resection of liver metastases can result in 3 year survival rates of 76% [7] and an average 5 year overall survival of 40–45% [8, 9]. At the time of diagnosis, fewer than 20% of patients are considered suitable for resection due to tumor size and location, inadequate hepatic reserve or presence of extra-hepatic metastases [5, 10, 11].

Patients with unresectable disease and best supportive care alone have a median overall survival of less than 10 months [10]. This significantly increases with the use of multiagent chemotherapy of fluoropyrimidine and oxaliplatin or irinotecan [12–14]. The additional use of biological agents such as bevacizumab (VEGF inhibitor) or cetuximab and pantimumab (EGFR inhibitors) have further improved response rates and duration of survival. Further discovery of predictive and prognostic biomarkers such as activating RAS mutation and BRAF mutations are also helping to assist in personalizing treatment decisions and improve survival (EGFR inhibitors in RAS wild type). More recently, the location (left versus right) of the primary colorectal tumor has been found to have prognostic and predictive significance with left sided tumors having an improved prognosis versus right side, as well as predicting for improved efficacy of first-line cetuximab [15]. Despite these advances, systemic therapy alone still does not offer a meaningful chance of cure.

The use of systemic therapy including chemotherapy and biological agents (VEGF and EGFR inhibitors) can be used to downstage liver metastases to allow for subsequent resection in a small proportion of patients, with 5 year survival rates of these patients 33% [16–19].

The low rates of resectable liver metastases combined with the limitations of systemic therapy alone has led to multiple trials of a number of different loco-regional therapies to achieve better control of liver metastases and improve long term outcomes for those with unresectable disease. These therapies utilize the predominant hepatic arterial perfusion of liver metastases compared to portal venous supply of non-cancerous liver parenchymal tissue. Locoregional therapies include selective internal radiation therapy (SIRT), radio-frequency ablation (RFA), trans-arterial chemoembolization (TACE) and hepatic artery infusion (HAI) chemotherapy. With multiple treatment options now available for metastatic colorectal cancer, and their potential for sequential use, it is unclear how and when locoregional therapies should be utilized. The magnitude of clinical benefit of these therapies must be weighed against cost, toxicity and inconvenience. This chapter will examine the efficacy and toxicity of some of these therapies, with particular focus on the use of SIRT and concentrating on results from the small number of randomized controlled trials that have been conducted for these treatment modalities.

## 2. Selective internal radiation therapy

Normal liver parenchyma has an inherently low radiation threshold of approximately 30–40 Gy before developing the clinical syndrome of radiation induced liver dysfunction [20].

This has limited the utility and efficacy of external beam radiation in those with liver metastases.

SIRT involves the embolization of radiolabelled spheres into the hepatic artery, preferentially lodging in vasculature surrounding tumor deposits and delivering high doses of radiation to these specific sites. Yttrium-90 (Y90) is a high energy beta emitting radioisotope which can be incorporated into glass or resin microspheres. The mean and maximum tissue penetration of radiation from Y90 is 2.5 and 11 mm respectively, resulting in delivery of effective doses of radiation (200–300 Gy) to tumor tissue without significant toxicity to surrounding normal liver tissue [21–23].

The commercially available product for use in colorectal cancer with liver metastases is the SIR-Sphere (SIRTex Medical, Sydney, Australia), which is a resin microsphere of 32  $\mu\text{m}$  diameter, embedded with Y90. Given the small mean diameter, absolute contraindications include excessive (>20%) hepatopulmonary shunting or shunting to the gastrointestinal tract due to the risks of radiation pneumonitis and gastrointestinal ulceration. Prior to the use of SIRT, angiography is performed to ensure arterial anatomy is favorable to proceed. Macroaggregated albumin labeled Technetium 99 m is subsequently injected into the hepatic artery to determine the degree of shunting with the option of occlusion of potential enteric channels such as the gastroduodenal artery. Further adverse effects include abdominal pain, liver function abnormalities and fatigue [22, 24, 25]. As well as excessive shunting, other relative contraindications include significant synthetic liver dysfunction, high extrahepatic burden predicting short-term mortality and extensive portal vein thrombosis [26].

### 2.1. Efficacy

A phase 3 randomized, controlled trial from Gray et al. [27], demonstrating the activity of SIRT in combination with HAI chemotherapy, led to SIR-Spheres obtaining FDA approval in treatment of colorectal cancer liver metastases in 2002. In this trial, 74 patients with unresectable liver metastases from colorectal cancer were randomized to HAI chemotherapy using floxuridine alone versus HAI floxuridine with the addition of SIRT. Treatment protocol excluded those with extra-hepatic metastases at time of trial entry; however, 41 patients were found to have extra-hepatic disease post randomization. Patients were treatment naïve, except for 11 patients (15%) who had previously received chemotherapy, with trial treatment either commencing for progressive disease after first-line chemotherapy or post a short course of bridging chemotherapy. For the total study population, the addition of SIRT resulted in a higher response rate (44 versus 18%) and time to progression of disease in the liver (12.0 versus 7.6 months) compared to HAI alone. No statistically significant difference was found in median overall survival (OS) between the two groups (17 months versus 15.9 months,  $p = 0.18$ ). Five-year OS was 6% in SIRT + HAI group and 0% in HAI alone group. Those receiving HAI alone were 3.1 times more likely to die from progression of liver metastases. Exploratory Cox regression analysis found a survival advantage for SIRT + HAI in those patients who survived at least 15 months, with a possible explanation that those who did not rapidly develop extra-hepatic metastases benefited more from the improved locoregional control of additional

SIRT. Only two patients had liver metastases resected after treatment, one from each group. Significant numbers of patients in both groups received extra off-protocol chemotherapy, adding further limitation to the analysis.

Using individual patient data, analysis was performed on only those patients who had not had any prior chemotherapy (excluding 11 patients). In the 63 first-line therapy patients, response rate was 37 versus 14% ( $p = 0.051$ ). There was no significant improvement in median progression free survival (PFS) when SIRT was added to HAI (7.3 months versus 5.9 months, HR 0.72,  $p = 0.21$ ). Median OS also was not significantly different (17.6 months versus 15.9 months, HR 0.62,  $p = 0.07$ ). In the 22 patients with no extra-hepatic disease, there was also no significant benefit on median progression free or overall survival although 2 year overall survival was 50% with SIRT + HAI versus 21% with HAI alone.

How generalizable these findings are in today's treatment of colorectal cancer is debateable given the more widespread use of systemic rather than regional chemotherapy, particularly in the first-line setting. Since this trial, there have been numerous trials demonstrating activity in various lines of treatment, with and without the use of systemic therapy.

#### *2.1.1. Refractory setting*

In the setting of colorectal cancer with liver metastases refractory to systemic chemotherapy, SIRT has shown significant activity in numerous single arm trials. Kennedy et al. treated 208 patients with liver metastases, refractory to oxaliplatin and irinotecan, with unimodality SIRT achieving response rates (RR) of 35% by RECIST, 91% RR by PET scanning and 70% RR by CEA. Response was a predictor of survival with median OS 10.5 months in RECIST responders and only 4.5 months in non-responders [28]. Mulcahy et al. administered SIRT to 72 pretreated patients with liver metastases and minimal extra-hepatic disease with a response rate of 40.3% and median overall survival of 14.5 months, with significant differences in survival in those with and without extra-hepatic disease (7.9 versus 21 months) [29]. A phase 2 trial by Cosimelli et al. used SIRT also in the population with disease refractory to oxaliplatin and irinotecan, with most having at least 4 lines of prior treatment and high volume liver metastases. Response rate was 24 with 2% complete response (CR) and 24% stable disease. Once again, response predicted improvement in overall survival with a median OS of 16 months in responders versus 8 months in non-responders. Two year OS for all participants was 19.6% [30]. Further phase 1 and 2 trials of SIRT alone or with chemotherapy in second line or later settings, achieved response rates of 17–32% with consistent findings of improved survival being associated with radiological and CEA response and lack of extrahepatic disease [31–33].

The only prospective randomized controlled trial of the use of SIRT in chemotherapy refractory CRLM was from Hendlisz et al., who enrolled 44 patients progressing on standard chemotherapy of fluorouracil (5FU), oxaliplatin and irinotecan and randomized them to protracted 5FU infusion alone versus SIRT + protracted 5FU infusion. All patients had no extrahepatic disease at randomization. Response rate was low with no significant difference found between groups (10 versus 0%,  $p = 0.22$ ) although stabilization rate (PR + stable disease)

was significantly higher in the SIRT +5FU group (86 versus 35%,  $p = 0.001$ ). One patient who gained a response underwent resection of hepatic metastasis. PFS was significantly increased in the SIRT +5FU group compared to 5FU alone, with median PFS of 4.5 versus 2.1 months (HR 0.51,  $p = 0.03$ ). Median time to progression in liver was similar at 5.5 versus 2.1 months, suggesting systemic control was not a major factor in this population of liver limited disease. Despite the PFS benefit, there was no significant overall survival benefit with the addition of SIRT (median OS 10 months versus 7.3 months,  $p = 0.80$ ). Potential reasons for this include small study numbers as well as the high number of subsequent treatments in chemotherapy alone arm with 70% (16/23) of patients in chemotherapy alone arm treated with further therapies, and 10 of those 16 treated with radioembolization. This compared to only 39% of the SIRT group receiving further lines of treatment [34].

Although this randomized trial examined only a small number of participants, PFS and OS figures of the experimental arm were similar to some of the single arm trials of SIRT in refractory disease previously described [29, 30, 33], suggesting there is activity in selected patients with CRLM refractory to standard treatments. A meta-analysis of patients with unresectable, chemorefractory CRLM patients, including 20 studies of 979 patients prior to 2012, showed an average response rate of 31% and disease control rate of 71.5% with median time to intra-hepatic progression at 9 months. Median overall survival was 12 months [35]. Poorer overall survival was associated with multiple previous lines of chemotherapy, lack of radiological response, extra-hepatic disease and extensive liver disease >25%. There was a very wide range of delivered radioactivity, treatment volume, extrahepatic disease and concurrent use of chemotherapy between included trials, compromising the ability to interpret results to a wider population.

There is still no definitive evidence that the activity described in this refractory group of patients results in an overall survival benefit compared to other available systemic treatments. Although EGFR antagonists were used in a number of patients prior to randomization and post progression, they were not routinely available and RAS testing was not commonplace as part of patient selection for these agents. With EGFR antagonists now used much more frequently in RAS wild-type disease, including as single agents in refractory disease, further randomized, controlled trials assessing the benefit of SIRT in those refractory to all standard treatments, including EGFR inhibitors and bevacizumab, are required to better understand the efficacy, patient selection and sequence of use of SIRT. These potential trials may be inhibited by poor recruitment given the development and study of newer systemic agents such as TAS-102 and regorafenib in the refractory setting [36, 37].

### *2.1.2. First-line combination with chemotherapy*

After Gray et al. showed improved response rate and time to progression in the liver when SIRT was used with HAI chemotherapy as first-line treatment [27], numerous studies have been conducted to assess the benefit of SIRT in combination with systemic chemotherapy in the first-line setting.

A small randomized, controlled phase 2 study by van Hazel et al. compared SIRT in addition to fluorouracil and leucovorin (5FU/LV) with 5FU/LV alone in 21 patients with unresectable liver metastases and no previous treatment [38]. Six of the twenty-one patients had extrahepatic disease present at randomization and the data for these patients were not reported separately. Response rate was significantly increased with the addition of SIRT (73 versus 0%) as well as median time to progression (18.6 months versus 3.6 months,  $p = 0.004$ ). Median overall survival was also significantly increased with SIRT (29.4 months versus 12.8 months). Similar to Gray's earlier trial in 2001 [27], the application of these results to standard clinical practice is limited by small numbers as well as the superseded nature of the control arm of 5FU/LV alone as a standard chemotherapy regime in first-line metastatic colorectal cancer. For that reason, a planned phase 3 trial of these groups was abandoned with further trials set up to examine the addition of SIRT to combination chemotherapy such as FOLFOX.

A phase 1 trial from Sharma et al. combined SIRT with FOLFOX4 systemic therapy in 20 treatment-naïve patients with unresectable CRLM. Overall response rate was 90% with stable disease in the remaining 10%. Median PFS was 9.3 months and median time to progression in the liver was 12.3 months. Two patients underwent resection of liver metastases at completion of protocol treatment [39].

Larger phase 3 trials have since been carried out adding SIRT to more modern conventional chemotherapy regimes, first in the SIRFLOX trial by van Hazel et al. published in 2016 [40], followed by a combined analysis of SIRFLOX, FOXFIRE and FOXFIRE-Global from Wasan et al. published in 2017 [41].

The SIRFLOX trial enrolled 530 patients with colorectal cancer with unresectable liver metastases who had no prior systemic treatment [40]. Liver only metastases or limited extrahepatic metastases (fewer than 5 lung nodules of  $\leq 1$  cm diameter or a single nodule of  $\leq 1.7$  cm diameter, and/or lymph node involvement with a single anatomic area of  $< 2$  cm diameter) were included. Patients were randomized to receive mFOLFOX6  $\pm$  bevacizumab (physician's choice) and SIRT (with cycle 1) or mFOLFOX6  $\pm$  bevacizumab alone. The SIRT arm received lower doses of oxaliplatin and no bevacizumab for the first 3 cycles based on toxicity seen in the previous phase 1 trial [39]. Primary end point was progression free survival and secondary endpoints included PFS in liver, response rate at any site, response rate in liver, liver resection rate and overall survival. Both arms had 40% of participants with extrahepatic metastases. There was no difference between the groups in primary endpoint with median PFS 10.7 months in SIRT + chemotherapy versus 10.2 months in chemotherapy alone ( $p = 0.43$ ). Difference in overall response rate did not reach statistical significance (76.4 versus 68.0%,  $p = 0.113$ ). Despite lack of overall response or PFS benefit when including all sites of metastases, SIRT did lead to an improvement in response rates in liver (78.7 versus 68.8%,  $p = 0.042$ ) as well as liver-specific progression free survival (20.5 months versus 12.6 months). This did not lead to a significant difference in liver resection rates (13.7 versus 14.2%). This trial was underpowered to meaningfully assess overall survival and thus was not published in this original paper, with survival data reported and published in the combined analysis of SIRFLOX with FOXFIRE and FOXFIRE-Global. The site of first disease progression appeared to explain the discrepancy between PFS at all sites and PFS in the liver with 77% of the control arm progressing first in the liver compared to 52.4% of SIRT arm, while the SIRT arm had a

higher rate of first progression at non-liver sites (27.7 versus 7.9%). Other proposed factors for lack of PFS benefit were the 8% of patients assigned SIRT who did not undergo the procedure, 8% of patients with bilobar liver disease who received SIRT to only one lobe and the large proportion (45%) of patients who had an intact primary tumor.

Prior to publication of the combined analysis, the authors postulated that liver-specific PFS and response could translate into an overall survival benefit in this population of patients. Liver PFS was a new endpoint used in this trial and interpreting across trials was difficult. If the extra-hepatic disease at diagnosis and progression was more indolent in nature, such as is often seen in lung metastases in colorectal cancer [42], then liver PFS may be more important to survival in the liver-dominant metastatic colorectal cancer setting. This hypothesis is also the premise behind increasing rates of hepatic resection in the setting of coexistent low volume lung metastases [43]. A similar hypothesis was used in explaining the improved overall survival of RFA when combined with chemotherapy in metastatic colorectal cancer with metastases confined to liver in the CLOCC study [44]. The authors of that trial postulated the lower incidence of liver metastases as the first site of recurrence (45 versus 76%) contributed to the median overall survival benefit (45.6 months in RFA + chemotherapy versus 40.5 months in chemotherapy alone). However, that population also had an improved overall PFS with the addition of RFA as well as an increased hepatic resection rate of 45 versus 10% with RFA, limiting the ability to directly compare these studies and assign meaningful benefit to liver-specific PFS as an endpoint.

Wasan et al. published a combined analysis of three multicentre, randomized phase 3 trials evaluating the addition of SIRT to standard chemotherapy in the first-line setting for patients with unresectable colorectal liver metastases [41]. Limited extra-hepatic metastases were permitted. 1103 patients were recruited in total across 14 countries. The three individual trials each had very similar designs to allow for this pre-planned combined analysis, randomizing patients to FOLFOX chemotherapy with SIRT or FOLFOX chemotherapy alone. Use of bevacizumab or cetuximab (in RAS wild-type tumors) was permitted and overall survival was the primary endpoint. There was no significant difference in patient characteristics between the two groups with 35.9% of SIRT group and 34.8% of control arm having extra-hepatic metastases; 50.2 versus 55% having primary tumor in situ and 32.3 versus 30.6% having >25% liver involvement of metastatic disease. There was a significant difference in the number of patients receiving bevacizumab with 35.6% receiving bevacizumab in the SIRT group compared to 46.6% in the control arm. Only 0.6 versus 1.7% received cetuximab.

There was no difference in overall survival between those receiving SIRT + chemotherapy versus those receiving chemotherapy alone (median OS 22.6 versus 23.3 months,  $p = 0.61$ ) with no difference found in the liver-metastasis only subgroup. Median PFS was also not significantly impacted (11.0 versus 10.3 months,  $p = 0.11$ ). Compared to the SIRFLOX trial, increase in overall response rate reached statistical significance in the SIRT group (72 versus 63%,  $p = 0.001$ ) with no impact on hepatic resection rate (17 versus 16%). Liver specific progression free survival was increased in the SIRT + FOLFOX group with first progression in the liver occurring in 31 versus 49% in FOLFOX alone (HR 0.51,  $p < 0.0001$ ). Non-liver progression and death without liver progression occurred in 54% of SIRT + FOLFOX group versus 36% in FOLFOX alone (HR 1.76,  $p < 0.0001$ ).



There are a number of potential factors to explain the improved response and liver specific PFS not translating to an overall survival or PFS benefit, even in liver only metastatic disease. These include reduced oxaliplatin dose and reduced and delayed bevacizumab usage in SIRT patients, as well as fewer patients from SIRT group receiving subsequent systemic therapy compared to chemotherapy alone group (67.9 versus 74%). Eight percent of patients assigned to SIRT did not receive the treatment while 3% of patients in FOLFOX alone group crossed over to SIRT, and 12% received it as a later line of therapy. Likely to be of more significance is the high proportion of patients developing extra-hepatic progression in the SIRT group and the impact this may have had on liver resection rates, which was equal between groups despite a higher liver response rate with SIRT. The low overall survival rates in both groups compared to other more recent trials likely reflects the relative lack of use of bevacizumab and EGFR inhibitors [4].

An unplanned subgroup analysis did show a significant PFS and OS advantage for SIRT + FOLFOX versus FOLFOX alone in those with right sided primary tumors (overall survival HR 0.67,  $p = 0.007$ ) [45]. Right sided tumors have recently been shown to be predictive of poorer response and prognosis compared to left sided tumors when systemic chemotherapy is used [15]. The use of SIRT in this population appears to overcome this intrinsic resistance to chemotherapy, although this is hypothesis generating only given the unplanned, post-hoc nature of this subgroup analysis. Further research into this patient group and analysis of various other biological subtypes (RAS and BRAF mutant disease) is required to aid patient selection.

The results of these large phase 3 trials do not currently support the use of SIRT in combination with chemotherapy for liver-only or liver-dominant unresectable metastatic colorectal cancer in the first-line setting.

A summary of the completed RCT's in SIRT is provided in **Table 1**.

## 2.2. Toxicity and quality of life

SIRT has been demonstrated to be a relatively safe procedure when the appropriate pre-treatment investigations are carried out correctly. Recognized toxicities include post-radioembolization syndrome with transient liver toxicity characterized by elevation of ALP, ALT and bilirubin [46], although the severity of this syndrome in SIRT is milder than the post-embolization syndrome in TACE [47]. Other radioembolization specific complications include gastric ulceration, pancreatitis, portal hypertension from liver fibrosis, radiation induced liver disease and radiation pneumonitis. In meta-analysis in 2009, the rates of all of these complications were <1% with the exception of gastric ulceration which was <5% [46]. There is a lack of reporting of delayed radiation toxicity such as liver dysfunction and gastric ulceration with rates reported in the range of 4–10% in a small number of phase 2 and observational trials [30, 33, 48, 49] and interpreting etiology of liver dysfunction (treatment related versus disease related) is difficult.

There is increased toxicity with the addition of SIRT to systemic chemotherapy compared to chemotherapy alone in the first-line setting. The addition of SIRT to 5FU/LV in the small trial of 21 patients by Van hazel [38] led to increase in grade 3/4 toxicities compared to

Study	Response rate	Liver resection rate	Median progression free survival	Median overall survival
<b>Gray [27]</b>	<i>All patients (n = 74)</i>	<i>All patients (n = 74)</i>	<i>All patients (n = 74)</i>	<i>All patients (n = 74)</i>
HAI floxuridine + SIRT versus HAI floxuridine	44 versus 17.6% (p = 0.01)	2.9 versus 2.8%	12 versus 7.6 months (p = 0.04)	17 versus 15.9 months (p = 0.18)
74 patients, 11 with prior systemic treatment	<i>First line (n = 63)</i>	(1 in each group)	<i>First line (n = 63)</i>	<i>First line (n = 63)</i>
	37 versus 14% (p = 0.051)		7.3 versus 5.9 months (p = 0.21)	17.6 versus 15.6 months (p = 0.07)
	<i>Liver only disease (n = 22)</i>		<i>Liver only disease (n = 22)</i>	<i>Liver only disease (n = 22)</i>
	25 versus 14% (p = 0.60)		2.7 versus 4.3 months HR 0.72 (CI 0.27–1.90)	14.2 versus 15.6 months HR 0.54 (CI 0.20–1.44)
<b>van Hazel [38]</b>	<i>All patients (n = 21)</i>	<i>All patients (n = 21)</i>	<i>All patients (n = 21)</i>	<i>All patients (n = 21)</i>
FU/LV + SIRT versus FU/LV	73 versus 0% (p = 0.001)	0 versus 0%	11.5 versus 4.6 months HR 0.23 (CI 0.08–0.68)	29.4 versus 11.8 months HR 0.22 (CI 0.07–0.74)
21 patients, previously untreated	<i>Liver only disease (n = 15)</i>		<i>Liver only disease (n = 15)</i>	<i>Liver only disease (n = 15)</i>
	78 versus 0% (p = 0.007)		19.1 versus 4.9 months HR 0.23 (CI 0.06–0.96)	31.9 versus 13.8 months HR 0.24 (CI 0.06–0.99)
<b>Hendlisz [34]</b>	<i>All patients (n = 44)</i>	<i>All patients (n = 44)</i>	<i>All patients (n = 44)</i>	<i>All patients (n = 44)</i>
5FU infusion + SIRT versus 5FU infusion	10 versus 0% (p = 0.22)	0 versus 4.7% (1 patient)	4.5 versus 2.1 months (p = 0.03)	10.0 versus 7.3 months (p = 0.80)
44 patients, refractory to chemotherapy, liver only disease				
<b>van Hazel [40]</b>	<i>All patients (n = 530)</i>	<i>All patients (n = 530)</i>	<i>All patients (n = 530)</i>	Not published
mFOLFOX6 + SIRT versus mFOLFOX6	76.4 versus 68.1% (p = 0.113)	14.2 versus 13.7% (p = 0.86)	10.7 versus 10.2 months HR 0.93; (CI 0.77–1.12)	
530 patients, previously untreated, liver dominant disease	<i>Liver specific response</i>		<i>Liver only disease (n = 318)</i>	
	78.7 versus 68.8% (p = 0.042)		Not published HR 0.9 (0.70–1.15)	
<b>Wasan [41]</b>	<i>All patients (n = 1103)</i>	<i>All patients (n = 530)</i>	<i>All patients (n = 1103)</i>	<i>All patients (n = 1103)</i>
mFOLFOX6 ± bev + SIRT versus mFOLFOX6 ± bev	72.4 versus 62.8% (p = 0.0012)	17 versus 16% (p = 0.67)	11.0 v 10.3 months HR 0.90; (CI 0.79–1.02)	22.6 versus 23.3 months HR 1.04; (CI, 0.90–1.19)
1103 patients from three trials, previously untreated, liver dominant disease	<i>Liver specific response</i>		<i>No extrahepatic disease (n = 713)</i>	<i>No extrahepatic disease (n = 713)</i>
	Not available		Not reported	24.5 versus 24.6 months HR 1.00; (CI 0.85–1.19)

**Table 1.** Outcomes of randomized trials in SIRT.

chemotherapy alone (13 versus 4 events), including nausea, abdominal pain, radiation hepatitis and hematological abnormalities. In the combination group, there was one death due to neutropenic sepsis, one liver abscess and one episode of radiation induced cirrhosis in a group of only 11 patients. In the much larger and more recent trial population of SIRFLOX, FOXFIRE and FOXFIRE-Global [41], there also was an increase in grade 3/4 adverse effects with the addition of SIRT (74 versus 66.5%) including neutropenia (36.7 versus 24.2%), febrile neutropenia (6.5 versus 2.8%), thrombocytopenia (7.7 versus 1.2%), fatigue (8.5 versus 4.9%) and abdominal pain (6.1 versus 2.3%). Only 0.8% of SIRT patients developed radiation hepatitis. Adverse events leading to treatment discontinuation were higher in the SIRT group in FOXFIRE population (14 versus 8%) with data not fully available for the other two trials. There were eight treatment related deaths in FOLFOX + SIRT group and three treatment related deaths in FOLFOX alone group. Of the eight deaths in the SIRT group, three were due to radiation induced liver disease, two due to complications from surgery, one due to liver failure, one due to radiation pneumonitis and one due to off-target delivery of microspheres. Long-term toxicity data showed two deaths due to hepatic failure after the end of the main safety window. Any potential use of SIRT in the first-line setting where overall survival is often over 2 years, would require close monitoring for long-term toxicity that may not be well described in trials.

Perhaps surprisingly by contrast, there was no significant increase in toxicity in the randomized controlled trial conducted in the chemotherapy refractory setting, albeit with a very small patient population [34]. There was one reported grade 3 event in SIRT + chemotherapy group compared to 6 in chemotherapy alone. Grade 1–2 nausea was more common in the combination group (5 events versus 0). Addition of SIRT to HAI also was not shown to have higher grade 3 or 4 events compared to HAI alone in the trial by Gray et al. [27], with a slight increase in grade 1–2 nausea and diarrhea.

Given the palliative nature of these treatments, quality of life is an important consideration when assessing the utility of SIRT. Despite this, there is a relatively limited amount of data on SIRT's impact on quality of life. The most recent analysis by Wasan et al. [41] incorporated quality of life analysis into their study using a EuroQol-5D three level questionnaire to measure health in five dimensions and summarized as utility score between 0 (death) and 1 (full health). This was done at baseline, 2–3 months, 6 months and 12 months followed by annually. The average unadjusted utility scores were not significantly different between treatment groups at any time except at 2–3 months (0.828 in SIRT + chemotherapy versus 0.846 in chemotherapy alone), although this was by a magnitude that would not be considered clinically meaningful. Lack of analysis during the first six weeks of treatment, the period where SIRT was administered, may have potentially missed a period of time where quality of life suffered due to the invasive nature of the procedure. Van Hazel et al. [38] used a Functional Living Index-Cancer questionnaire which found no change from baseline but did not report the impact of treatment.

In the refractory setting, Cosimelli et al. collected quality of life data, however only 28% of patients completed questionnaires with potentially biased results [30]. Further trials did not report quality of life data [34, 35], an unfortunate omission in a chemotherapy refractory population in whom any measurement of treatment effectiveness should include quality of life.

### 2.3. Summary

The lack of definite PFS and OS benefit and lack of increased hepatic resection rates, as well as increased toxicity and no improvement on quality of life, suggests there is no strong evidence to recommend SIRT's routine use with chemotherapy in the first-line setting in those with unresectable CRLM. Particular subgroups of patients who may be predisposed to resistance to chemotherapy (right sided tumors, BRAF mutant) need further trials exploring any potential benefits specific to them. SIRT has activity and improves PFS in the chemotherapy refractory setting with tolerable toxicity in small trials, although its impact on quality of life is unknown and has no proven benefit on overall survival. The potential benefit of SIRT needs to be weighed against the invasive nature, costs and risks of toxicity of the procedure, with assessment for treatment based on individual patient factors.

## 3. Radiofrequency ablation

Over the recent years, RFA has become a widely accepted liver-directed option for the treatment of hepatocellular carcinomas (HCC) and liver metastases, especially from colorectal cancers. Unlike other liver-targeted modalities for unresectable colorectal liver metastases, such as SIRT or TACE, RFA can be used with curative intent [50, 51].

A high-frequency alternating electric current is delivered through metal probes which are conveniently inserted into the target lesion. These needle electrodes can be placed percutaneously using imaging guidance, via laparoscopy or during abdominal laparotomy. When this electrical current is applied, heat is generated (with temperatures ranging from 60–100°C), which causes localized coagulative necrosis and protein denaturation within the tumor along with a margin of healthy tissue [52, 53].

### 3.1. Efficacy

In current clinical practice, RFA is being used as an alternative to liver resection in patients ineligible for surgery due to comorbidities or poor performance status or for those colorectal cancer patients with unresectable liver metastases. For patients with cirrhosis, poor liver reserve or chemotherapy-associated steatohepatitis or for those with recurrences posthepatectomy with minimal hepatic reserve, RFA may also be beneficial since it minimizes the destruction of the surrounding healthy hepatic tissue [54]. However, all of these theoretical indications are conditioned by the fact that liver metastases have to be limited in number (usually less than 5) and size (generally no more than 5 cm) [55]. Although there are no randomized clinical trials data demonstrating survival equivalence between hepatectomy and RFA for colorectal cancer liver metastases, some retrospective studies have shown that RFA may provide similar outcomes to those of liver surgery when the lesions are completely ablated and clear margins are achieved [56–58]. However there is no consensus on this with other authors suggesting alternate views [59–61]. Therefore prospective trials comparing RFA and liver surgery are necessary to definitively answer this question [62, 63].

Among several cohort studies looking at RFA as primary treatment for liver metastases, the 5-year survival and local tumor recurrence rates reported vary widely, mainly due to variable patient selection, imbalance in the baseline patients' characteristics and different techniques and probes used over time. The 5-year survival reported in the literature ranges from 15–50% after RFA for liver-only metastatic colorectal cancers [55, 63–66]. As mentioned, the local recurrence rates reported also vary widely (2–40%), although there is the suggestion from these studies that the smaller the treated lesion is (<3 cm) and the longer the distance from major vessels, the better the outcome [55, 57, 67].

In order to select the most suitable liver-only metastatic colorectal cancer patients for RFA, as well as systemic chemotherapy, to attempt to achieve long-term disease control, Stang et al. proposed a score based on four clinical variables: response to systemic therapy,  $\leq 3$  liver metastases,  $\leq 3$  cm in size and low carcinoembryonic antigen (CEA) value [68]. In this retrospective study, patients who fulfilled all four criteria (score 4) had significantly higher probabilities for overall survival and recurrence-free survival at 5 years after RFA (39 and 22%, respectively) compared to those patients who scored  $\leq 3$  (0–27 and 0–9%, respectively). As discussed by the authors in the paper, the clinical significance of this proposed score needs to be validated in a prospective manner.

Evrard et al. investigated in a phase II prospective study (EORTC 40004) whether the use of intraoperative RFA in conjunction with hepatic resection could increase the cure rate in colorectal cancer patients with unresectable liver metastases [69]. Fifty-two patients were included in the analysis. The primary endpoint was complete hepatic response at 3 months which was reached in a total of 39 patients. The 5-year overall survival rate was 43%. Karanickolas et al. reached the same conclusion in their study that combining liver resection and ablation may increase the cure for selected patients with bilateral hepatic colorectal metastases [70]. A total of 141 patients were treated with bilateral resection and 95 underwent ablation in this study. Long-term outcome was not significantly different between groups (5-year overall survival rate with ablation was 56% versus resection: 49%;  $p = 0.16$ ).

Another interesting study was conducted by Ruers et al., which prospectively evaluated long-term outcomes of combining RFA plus chemotherapy versus chemotherapy alone. This study was originally designed as a randomized phase III study to detect a difference in survival between both arms; however, due to slow recruitment, the study was downsized to a randomized phase II trial with 10 year overall survival results reported in 2015 [44, 71]. The *EORTC-NCRI-CCSG-ALM Intergroup 40,004 (CLOCC) study* included 119 patients randomized to either chemotherapy alone ( $n = 59$ ) or RFA plus chemotherapy ( $n = 60$ ). At a median follow-up of 9.7 years, the median progression-free survival was 16.8 months for the combined arm compared with 9.9 months for the chemotherapy-only arm (hazard ratio [HR] = 0.57; 95% confidence interval [CI], 0.38–0.85;  $p = 0.005$ ). The median overall survival was 45.6 months for the combined arm compared with 40.54 months for the chemotherapy arm (HR = 0.58; 95% CI, 0.38–0.88;  $p = 0.010$ ). These results suggest that combining RFA with chemotherapy for unresectable liver metastases in colorectal cancer patients can considerably change the outcome for some patients, improving overall survival. However, these results require careful interpretation and indeed, have been questioned on the basis of the imbalance of patient

characteristics between treatment arms, as well as the fact that some of the ablated patients included in the study underwent further liver resection following RFA.

### **3.2. Toxicity and quality of life**

RFA is a minimally invasive liver-targeted modality with a favorable safety profile with low rate of major complications and deaths (around 1–3 and <1%, respectively) [56, 59, 67]. Information regarding tolerability and quality of life is scarce given the retrospective nature of the vast majority of evidence around RFA for liver-only metastatic colorectal cancers. Solbiati et al., for instance, reported major adverse events incidence in 1.3% of the patients (one bowel perforation and one intrahepatic hematoma) although no deaths occurred [72]. Minor adverse event rate was 10% and fever was the most common complication reported (8 of a total of 156 patients). On the other hand, Ruers included in his study health-related quality of life questionnaires (EORTC QLQ-C30) at baseline and every 6 weeks afterwards. Quality of life after RFA showed only a short decline with recovery to baseline levels within 2 months after RFA [44].

### **3.3. Summary**

RFA is a reasonable option for metastatic colorectal cancer patients with unresectable liver metastases or for those with recurrent disease after hepatectomy with small liver metastases providing that adequate margins are thought to be achievable. Given the lack of randomized controlled trial data, liver resection remains the standard treatment for the local treatment of resectable liver metastases. More prospective clinical trials looking at RFA in different settings (for example, RFA + resection, RFA + adjuvant systemic chemotherapy, etc.) are needed.

## **4. Trans-arterial chemo-embolization**

TACE is a locoregional therapy, which uses hepatic artery catheterization to deliver chemotherapy locally followed by embolization with vessel occlusion, delivering high doses of chemotherapy to the target lesion. Combinations of doxorubicin, mitomycin-C and cisplatin are most commonly used as the chemotherapeutic agents in what is known as conventional TACE (cTACE) [73]. For a number of years, TACE has been used in the treatment of unresectable hepatocellular carcinoma (HCC) and is now the standard of care for particular subgroups of HCC after showing survival benefit over best supportive care [74, 75].

### **4.1. Conventional TACE (cTACE)**

In the setting of metastatic colorectal cancer with liver metastases, the use of cTACE has been limited by a paucity of standardized data, with evidence limited to heterogeneous single arm trials, to the extent that consensus guidelines are unable to provide recommendation for its use [50]. Initial non-randomized, single arm trials in the 1990s using cTACE in first and second line of treatment showed modest response rates of 17–25% [76, 77]. Two more recent trials have

examined the effectiveness of cTACE across multiple lines of therapy. Vogl et al. administered repeated cycles of cTACE to 463 patients with unresectable liver metastases not responding to chemotherapy [78]. Response rate was 14.7% with stable disease rate of 48.2% and 12 month survival of 62%. Retrospective analysis of cTACE in patients refractory to 1st–5th line chemotherapy by Albert et al., showed only a 2% response rate and 43% disease stability rate with a 9 month median overall survival from the time of cTACE [79]. The lack of control arms in these trials significantly limits any interpretation of the efficacy of cTACE and its possible role among multiple other locoregional and systemic therapies in colorectal cancer.

Furthermore, toxicity is a significant issue in those undergoing cTACE. Post-embolization syndrome (PES) due to ischaemia induced inflammation occurs in 30–80% of patients with symptoms including abdominal pain, fever, nausea and vomiting and deranged liver function tests [47, 80]. Other complications can include liver abscess, pancreatitis and biliary sclerosis [77, 81].

The lack of evidence showing response or survival rates comparable or superior to current standard treatments, in addition to the toxicity of PES and other complications, leaves cTACE without a clear role in treating colorectal cancer liver metastases.

#### **4.2. Drug-eluting bead TACE (DEB-TACE)**

More recent developments have focused on TACE with the use of drug eluting polyvinyl alcohol beads (DEB-TACE), which allow a sustained release of chemotherapy agents, in particular irinotecan, to the vascular supply of the tumor. Embolization with these beads reduces flow in vessels feeding the tumor, hence increasing dwell time and reducing washout of the active drug [82]. Despite a similar toxicity profile to cTACE, DEB-TACE appears to have fewer drug-related adverse events.

Single arm phase 2 trials showed promising results with response rates between 48 and 75% and downstaging of liver metastases to allow surgical resection or ablation in 7–20% [83, 84].

A small phase 3 trial from Fiorentini et al. has been the only randomized, controlled trial to show a survival benefit from TACE in metastatic colorectal cancer [85]. This study enrolled 74 patients with liver limited disease occupying <50% of parenchyma, having progressed on at least 2 lines of therapy. They were randomized to receive two treatments of TACE with drug eluting beads containing irinotecan (DEBIRI) or FOLFIRI systemic chemotherapy for 4 months. No cross-over was allowed. Primary end point of overall survival was found to be significantly increased in the DEBIRI group compared to FOLFIRI group (median OS 22 versus 15 months,  $p = 0.031$ ). Overall response rates were 69 versus 20%. PFS was also significantly increased in DEBIRI group (7 versus 4 months). Interestingly time to extra-hepatic progression was higher in DEBIRI group (13 versus 9 months) although this did not reach statistical significance, potentially suggesting some activity outside of the liver. Poor prognostic indicators for survival included high percentage of liver involvement, low albumin, high ALP and high LDH. As expected, hematological toxicity and mucositis were higher in the FOLFIRI group, with LFT and bilirubin derangement higher in DEBIRI group and PES occurring in approximately 30% of patients. Quality of life analysis showed significantly higher scores at both 1 and 3 months in those receiving DEBIRI.

Another randomized, controlled phase 2 trial by Martin et al. investigated the use of DEBIRI in combination with chemotherapy in the first-line setting [86]. Seventy patients with liver dominant disease and no prior chemotherapy were randomized to FOLFOX ± bevacizumab + DEBIRI versus FOLFOX ± bevacizumab alone. There were some imbalances in treatment groups with DEBIRI combination arm having a higher proportion of patients ECOG 1–2 and a higher proportion of patients with extra-hepatic disease. Response rate was higher in the DEBIRI combination group compared to chemotherapy alone with 4 month response rate 95 versus 70%. Downstaging of liver metastases to resection occurred in 35% in DEBIRI combination arm versus 16% in chemotherapy alone. Despite the improved response and resection rate in DEBIRI group, it was the chemotherapy alone control arm which showed a trend toward improvement in PFS with median PFS 12 months in DEBIRI arm versus 15 months in control arm ( $p = 0.18$ ). There was significantly higher serious adverse event rate in the DEBIRI combination group. Overall survival data was not published.

### 4.3. Summary

Both trials show promising results, particularly in Fiorentini's trial in the refractory setting, given the overall survival advantage occurred without any crossover of groups and with similar rates of post-progression chemotherapy [85]. Quality of life improvement was also an important endpoint. The first-line trial from Martin et al., was unable to show a significant PFS benefit with overall survival data not yet known [86].

This would suggest that the role of DEB TACE is more likely to be in later lines of therapy based on current evidence. Replication of these results in a larger population, with control arms using more active chemotherapy regimens including bevacizumab or EGFR inhibitors, is required to better define the role of DEB-TACE in the sequence of treatments for CRLM. This is already underway with a recent publication of a prospective single arm trial treating patients with DEBIRI and cetuximab concurrently with encouraging median PFS and OS data (9.8 months and 24 months) [87].

## 5. Hepatic artery infusion chemotherapy

Liver metastases from colorectal cancer generally receive the majority of their blood supply through the hepatic artery, while conversely, the portal vein supplies irrigation to the normal hepatic tissue. Taking advantage of this dual hepatic blood supply, HAI was developed with the aim of delivering high chemotherapy concentrations within hepatic metastases, while minimizing systemic toxicity [88, 89]. HAI can be administered either through a surgically implanted port or via percutaneous catheter connected to a pump. Multiple agents have been tested to be infused via hepatic artery, although Floxuridine (FUDR) is the most widely used drug, thanks to its short half-life and high first-pass metabolism rate which allow the intrametastatic drug concentrations to be increased without significant systemic side effects [88]. On that basis, HAI has been investigated as a treatment for heavily treated metastatic colorectal cancer with liver metastases, as well as in the perioperative liver resection setting [90, 91]. In the following paragraphs, we will review the evidence for HAI in these different categories.



### 5.1. Unresectable liver metastases

In the literature, three meta-analyses [92–94] have undertaken comparisons of FUDR or 5-FU HAI versus systemic chemotherapy for the treatment of unresectable colorectal liver metastases. Their results have been contradictory. In all three, the response rate has universally reported to be in favor of the loco-regional modality comparing to (currently obsolete) systemic chemotherapy regimens. Moreover, while the two earlier meta-analyses [93, 94] detected a survival advantage for HAI, the more recent one by Mocellin et al. failed to demonstrate statistical survival superiority (15.9 versus 12.4 months, HR = 0.90,  $p = 0.24$ ) [92]. However, these results should be interpreted with caution due to limitations in the studies' designs, the use of old-fashioned chemotherapy regimens and selection bias.

Since these initial studies of HAI-FUDR/5-FU alone were reported, other treatment strategies combining HAI and modern systemic chemotherapy have been tested in order to improve long-term outcomes for patients with liver metastases in different settings. Along with the improvement in systemic chemotherapy, HAI in combination with systemic chemotherapy agents has been tested with some success in single-arm single institutional trials [95, 96]. In the refractory setting for instance, Fazio et al. recruited 45 heavily treated colorectal cancer patients with liver-only or liver-dominant metastases who were then exposed to HIA with 5-FU, cisplatin and mitomycin C using a temporary subclavian catheter [97]. Of the 44 patients evaluable, 68% showed response to treatment (35% had a partial response and 33% stable disease). However, this strategy was not exempt from serious complications: grades 3–4 neutropenia and thrombocytopenia were reported in 22 and 15% of patients, respectively, and 20% of the patients developed gastro-duodenal ulcers. Also in the pretreated setting, Boige et al. conducted a retrospective study using HAI-oxaliplatin plus systemic 5-FU/leucovorin (LV) in 44 patients after failure of prior systemic chemotherapy [98]. The authors reported an impressive median overall survival and progression-free survival of 16 and 7 months, respectively. Toxicity included grade 3–4 neutropenia (43%), grade 2–3 neuropathy (43%), and grade 3–4 abdominal pain (14%). Neyns et al. explored the combination of HAI and systemic cetuximab for the treatment of colorectal cancer patients with liver metastases who failed at least one line of treatment [99]. Although theirs' was a very small early study (only eight patients included), it showed that this combination may warrant further investigation.

HAI has also been investigated in patients with *a priori* unresectable liver metastases. One of the first randomized studies comparing HAI plus systemic bolus 5-FU/LV ( $n = 40$ ) versus HAI alone ( $n = 36$ ) for patients with non-resectable liver metastases demonstrated an increase in survival in the combined group (20 versus 14 months,  $p = 0.0033$ ), although no significant increase in response rate was seen [100]. With the introduction of better systemic chemotherapy, such as oxaliplatin- or irinotecan-based regimens associated with HAI, the liver metastases conversion rates seem to improve. There are several examples in the literature of prospective (although small) trials combining HAI and systemic oxaliplatin- or irinotecan-based chemotherapy showing encouraging conversion rates of approximately 25–50% [98, 101–103]. Kemeny et al., for instance, achieved a liver metastases conversion rate of 47% (and noted an even higher percentage, 57%, in chemotherapy-naïve patients) in metastatic colorectal cancer patients treated with HAI-FUDR plus systemic oxaliplatin and irinotecan [104]. Ninety-two percent of the total 49 patients had either complete (8%) or partial response (84%) leading to a median overall

survival from the commencement of HAI therapy of 50.8 and 35 months for chemotherapy-naïve and previously treated patients, respectively. Ammori et al. also shared their 10-year experience at the Memorial Sloan-Kettering Cancer Center using HAI and systemic chemotherapy for treating unresectable colorectal liver metastases, focusing on conversion to complete hepatic resection (noted ablation was also permitted) [105]. A total of 373 patients were retrospectively analyzed; 93 of them (25%) subsequently underwent complete liver resection/ablation. Median overall survival for the patients who converted to complete resection was 59 months against 16 months among those who did not undergo surgery ( $p < 0.001$ ).

The literature also reveals several small studies which have combined HAI with systemic chemotherapy and monoclonal antibodies in attempts to further increase the liver metastases conversion rates mentioned above. Although the results of these studies are promising, there is not enough evidence to recommend this approach in current practice. In one such case, D'Angelica et al. found that 47% of their 49 patients treated with HAI-FUDR and systemic therapy (irinotecan, bevacizumab and either oxaliplatin or 5FU/LV depending on existing baseline neuropathy) were able to undergo complete resection [106]. Malka et al. investigated the efficacy and tolerability of HAI-oxaliplatin and 5-FU/LV and cetuximab in patients with unresectable colorectal liver metastases in a phase II trial [107]. Approximately one-third of the patients (11 out of 36) underwent subsequently complete liver resection and/or ablation. More recently, Lévi et al. also examined the role of HAI and systemic cetuximab in unresectable liver metastases from wild-type KRAS colorectal cancer in order to increase the conversion rate of curative liver resection [108]. Almost 30% of the patients in this phase II study were able to undergo R0/R1 resection achieving median overall survival of 35.2 months and survival rate at 4 years of 37.4%.

## 5.2. Post resection of liver metastases

The role of postoperative HAI following complete liver resection has also been tested in several randomized clinical trials comparing adjuvant HAI plus systemic chemotherapy versus chemotherapy alone [109, 110]. A Cochrane review of seven randomized controlled trials did not show significant long-term survival benefit for HAI (either FUDR or 5-FU) and systemic chemotherapy (5-FU/LV) versus 5-FU/LV alone as an adjuvant treatment [111]. Subsequently, the addition of newer (and improved) adjuvant chemotherapy regimens, such as FOLFOX, FOLFIRI or capecitabine–oxaliplatin (CapOx) to a HAI pump has been also examined with some promising results in early phase studies. Alberts et al., in a recent phase II study, investigated the combination of alternating HAI-FUDR and systemic CapOx following hepatic resection for colorectal liver metastases [112]. These authors reported a two-year overall survival rate of 85%. Similarly in another phase I/II study, Kemeny et al. found a 2-year survival rate of 89% among their 96 colon cancer patients treated with HAI-FUDR plus systemic irinotecan following complete hepatic resection [113]. We would like to mention two retrospective comparative studies looking at the efficacy of adjuvant HAI-FUDR and systemic oxaliplatin- or irinotecan-containing-regimens versus systemic chemotherapy alone. These studies suggest that patients who received HAI had better long-term outcomes compared with those patients treated without HAI. With a median follow-up of 43 months, House et al. found a higher 5-year survival among patients treated with HAI compared to patients treated with systemic chemotherapy alone (72 versus 52%, respectively;  $p = 0.004$ ) [114]. The 5-year hepatic

recurrence-free survival was also improved (79 versus 55%, respectively;  $p < 0.001$ ). More recently, Koerkamp et al. reached the same conclusions after analyzing the outcomes of 1442 patients treated with adjuvant HAI in conjunction with oxaliplatin- or irinotecan-containing regimens following liver resection [115]. With a median follow-up of 55 months, the median overall survival was 67 months with HAI versus 47 months without HAI ( $p < .001$ ). It is important to underline that just as in the adjuvant chemotherapy setting, not all chemotherapeutic agents and targeted therapies have shown benefit following liver resection for hepatic metastatic disease. Kemeny et al. tested the adjuvant combination of HAI plus oxaliplatin-based therapy with/without bevacizumab [116]. In terms of efficacy, in this phase II study the results were disappointing. Moreover, this strategy was also associated with an increase in biliary toxicity leading to an early termination of the trial.

Several limitations exist on the use of HAI therapy for liver metastases. These include the lack of standardized systemic chemotherapeutic regimens, the requirement of specific technical expertise, and the potential for complications related either to the catheter (estimated at about 10% of cases in experienced centers) and extrahepatic infusion (5–10%) [117, 118] or to drug-related toxicity (biliary sclerosis 5% with FUDR alone, and 10–20% in polychemotherapy and gastritis and gastroduodenal ulcers in 15–20% of the patients according to some reported studies) [119, 120].

### 5.3. Summary

In summary, although there are prospective single arm studies showing promising results with the combination of HAI and systemic chemotherapy in both postoperative treatment after liver resection and conversion therapy for liver metastases, randomized phase III trials are needed before HAI can feasibly become standard practice in the treatment of colorectal liver metastases. At present, HAI therapy should only be considered as an option for rigorously selected patients and only under the care of physicians and institutions with extensive experience using this technique.

## 6. Conclusion

All treatment modalities have shown activity in different lines of treatment in CRLM. Consistent across all treatments is the heterogenous nature of trials and the relative lack of randomized, controlled trials with control arms which reflect current standard of care. SIRT and DEB-TACE currently only have evidence that would support their use in patients with progression after systemic therapy, with no survival benefit seen in first-line trials. RFA has shown evidence of survival benefit in one RCT, however this has been criticized for imbalances in treatment groups potentially confounding results. HAI has shown evidence of high response rates and conversion of liver metastases to resection, however it lacks comparison to highly active triplet chemotherapy which is current standard of care in this setting. All modalities are also lacking in data on their effects on quality of life, which should always remain a consideration in a mostly palliative population with not insignificant rates of serious toxicities observed for all of these treatments. While further trials are developed to fill these gaps in knowledge, the

use of local therapies needs to continue to be assessed on a case by case basis, weighing up potential efficacy with costs, toxicity and quality of life of the patient.

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