Annals of Gastroenterology (2019) **32,** 147-155

The role of interventional oncology in the treatment of colorectal cancer liver metastases

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Abstract

Colorectal cancer is a leading cause of death both in Europe and worldwide. Unfortunately, 20-25% of patients with colorectal cancer already have metastases at the time of diagnosis, while 50-60% of the remainder will develop metastases later during the course of the disease. Although hepatic excision is the first-line treatment for patients with liver-limited colorectal metastases and is reported to prolong the survival of these patients, few patients are candidates. Locoregional therapy encompasses minimally invasive techniques practiced by interventional radiology. Most widely used locoregional therapies include ablative treatments (radiofrequency ablation, microwave ablation) and transcatheter intra-arterial therapies (transarterial chemoembolization, and radioembolization with yttrium-90).

Keywords Colorectal cancer, treatment, thermal ablation, intra-arterial therapies

Ann Gastroenterol 2019; 32 (2): 147-155

Introduction

Colon cancer is the third most common type of cancer diagnosed in patients worldwide and is a leading cause of death both in Europe and worldwide [1,2]. Researchers have recognized several lifestyle behaviors that heighten the risk of this cancer among men and women: poor diet, smoking, physical inactivity, obesity, and use of carcinogens in processed foods [3]. However, over the past decade, the incidence and mortality of colorectal cancer have decreased in both men and women and the clinical outcome of metastatic colorectal cancer patients has improved. This was made possible by strategic improvements and the development of innovative and sophisticated diagnostic and therapeutic tools, which include both invasive procedures and noninvasive techniques [4].

Unfortunately, 20-25% of patients with colorectal cancer already have metastases at the time of diagnosis, while 50-60% of the remainder will develop metastases later during the course of the disease [5,6]. During the metastatic stage, colon or rectal cancer often spreads systemically to the liver followed by lungs, bones or any other part of the body. Surgical resection is widely accepted as the first-line treatment for patients with liver-limited colorectal metastases and is reported to prolong the survival of these patients. Studies have shown that the 5-year survival rate is over 50% in patients with hepatic metastases treated successfully with resection [5,7,8]. Regrettably, about 80-90% of colorectal liver metastases (CRLM) are deemed not suitable for resection because of complex tumor anatomy (metastasis site, number, and size), extrahepatic disease and the patient's deteriorating health condition [9]. Moreover, up to 80% of patients develop liver recurrence up to 10 years post surgery, the majority within the first 2 years [10]. However, with the evolution of new chemotherapeutic agents, the advent of immunotherapy and targeted minimally invasive therapies, clinicians are now incorporating a multidisciplinary approach to treat patients with unresectable disease or potentially resectable disease, to treat recurrences and prolong these patients' survival [11].

Additionally the role of imaging in colon cancer has evolved significantly, with the development of techniques that provide high accuracy in establishing localized invasive treatments. Consequently, new therapeutic techniques have been exploited by clinicians to incorporate hi-tech imaging modalities for targeted removal of malignant tissues and cells [12]. Various interventional radiology procedures are considered as either alternatives to surgery or ancillary treatment methods in the interdisciplinary therapy management of metastatic colorectal patients. Most widely used treatment methods include percutaneous ablation (radiofrequency, microwave), transarterial chemoembolization (TACE), and selective internal radiation therapy [13]. For some patients, locoregional

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Conflict of Interest: None

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Received 10 July 2018; accepted 20 November 2018; published online 14 December 2018

DOI: https://doi.org/10.20524/aog.2018.0338

therapies can alternatively be used as symptomatic or palliative treatments.

Given the wide spectrum of alternative or ancillary therapies to resection, this paper will focus on the energy-based ablation techniques, specifically the utilization of radiofrequency ablation (RFA) and microwave ablation (MWA), as well as intra-arterial therapies, chemoembolization and radioembolization, and will discuss the extent to which each of these techniques is effective for the treatment of colorectal metastases.

Thermal ablation

In recent years, there has been growing interest in minimally invasive local ablative therapies to treat lesions not amenable to surgery as well as resectable lesions in poor surgical candidates [14].

Indications

The indications for ablation of CRLM are in line with the accepted definition of oligometastatic disease. Patients with a limited number (<4) of small-sized (<5 cm in largest diameter) metastases that are not amenable to surgery (or the patient refuses) and can be treated with a curative intent are good candidates for percutaneous image-guided ablation therapy. Image-guided ablative therapies, percutaneous or intraoperative, can also be applied in combination with surgical treatment strategies to improve resectability in patients who fail to meet the resection criteria.

RFA

RFA induces thermal damage through frictional heating due to ionic oscillation by a high-frequency alternating current (375-500 kHz) from monopolar or bipolar radiofrequency systems. The positive attributes of RFA are that it is a simple, repeatable, standardized and low-risk therapy. However, it is limited by an active heating zone of a few millimeters, while its impedance increases as the tissue boils and char residue is produced, since char insulates against electrical signals. The exposure of tumor cells to a temperature of approx. 50°C for 4-6 min induces cytotoxicity, while between 60-100°C the proteins in the cells start to coagulate irreversibly [15]. At 100°C, water evaporates from the tissues, causing desiccation, and the resultant electrical impedance limits the volume of thermal transmission. In addition, especially near large blood vessels, heating facilitates a heat sink effect to reduce the efficacy of cell death by RFA [16].

There are several studies reporting the safety and efficacy of RFA for the treatment of unresectable CRLM (Table 1). Solbiati *et al* reported 3-, 5- and 10-year survival rates of 69%, 48% and 18%, respectively, in a series of 202 CRLM treated with percutaneous ablation; the major complication rate was 1.3% and there were no procedure-related deaths [17]. Gillams & Lees also reported the results of ablation guided by computed tomography or ultrasound, with single or clustered water-cooled electrodes, in 167 patients with CRLM; the 5-year survival rate was 30% and the major complication rate 4% [18]. These results are close to the 5-year survival rates of surgical resection (33-58%) [8,19].

Factors that limit RFA success rates include lesion location, size, tumor-free margin and number of lesions. Wang *et al* in

Table 1 Literature highlights of thermal (RFA and MWA) ablation for colorectal liver metastases

Study [Ref]	Year	Study details	OS
Gillams *et al* [18]	2004	Prospective, 167 patients RFA Mean 4 lesions Mean 4 cm max diameter	Median OS 38 months
Hildebrand *et al* [72]	2006	Prospective, 88 pts/420 lesions RFA Mean 3.5 lesions Median 2.7 cm max diameter	Median OS 28 months
Gillams and Lees [73]	2009	Prospective, 309 pts/617 lesions RFA Mean 4 lesions Median 2.3 cm max diameter	Median OS 36 months
Sofocleous *et al* [74]	2011	Prospective, 56 pts/71 lesions RFA Mean 1.4 lesions Median 1.9 cm max diameter	Median OS 31 months
Solbiati *et al* [17]	2012	Retrospective, 99 pts/202 lesions RFA Mean 2 lesions Mean 2.1 cm diameter	Median OS 53.2 months
Wang *et al* [46]	2014	Retrospective, 115 pts/165 lesions MWA Mean lesion diameter 3.1cm	3-year OS 78.7%
Bonne *et al* [75]	2018	Retrospective, 193 pts, 456 ablations (343 RFA, 113 MWA), Median lesion size 17 mm	2- and 5-year OS: 88% and 35% for RFA and 89% and 66% for MWA

RFA, radiofrequency ablation; MWA, microwave ablation; OS, overall survival

2013 emphasized the presence of an irregular ablation defect and the need for at least a 5 mm margin surrounding the tumor homogeneously to attain good local tumor control [20]. It is generally advocated that the ideal lesions for consistently successful ablation are those <3 cm in maximum diameter. Accordingly, Shady *et al* have suggested that RFA may not be as effective for tumor size >3 cm [21]. Van Tilborg *et al* reported the results of RFA ablation in 237 treated lesions in 100 patients; local RFA site recurrence was 5.6%, 19.5% and 41.2% for tumor diameters <3 cm, 3-5 cm and >5 cm, respectively [22]. In addition, centrally located lesions recurred more often than peripheral ones: 21.4% (21/98) vs. 6.5% (9/139) [21]. However, with more experience and more sophisticated tools of ablation there is a tendency to increase the cutoff point for potential complete ablation. So there are authors who suggest that, depending on their location, accessibility and the ablation protocol used, lesions up to 5 cm can also be treated effectively with low local recurrence rates. Hammil *et al* reported a 3% local recurrence rate for tumors <3 cm and a 4% recurrence rate for 3-5 cm tumors [23].

The number of lesions to be treated can also adversely affect the result. Ablation of solitary metastases, similarly to the resection literature, has been related with high local tumor control. Kim *et al* reported 5-year survival of 51%, while Gilliams *et al* reported a 5-year survival rate of 54% in 40 patients with solitary lesions up to 4 cm [24,25].

Some authors claim that RFA can be used as first-line treatment instead of resection, since it is equally safe and effective, with comparative median disease-free survival, minimal invasiveness and shorter hospital stays, especially for small and medium size lesions [18,22,24,26,27]. To date, there are several retrospective studies but no prospective randomised trials regarding RFA ablation vs. surgical resection for CRLM. Most of these studies report a lower recurrence rate after hepatic resection; however, it should be noted that the selection of the ablation and resection groups was not randomized. In the majority of these studies ablation was performed for lesions not amenable to surgical resection, or for resectable lesions in patients with poor general condition and multiple comorbidities. Nevertheless, subgroup analysis showed similar survival outcomes for RFA and hepatic resection in patients with tumor size <3 cm [28]. Lee *et al* [29] and other authors claim that, while RFA may be a better therapeutic approach for unresectable single and small (≤2 cm) lesions and the survival rates are comparable to hepatectomy and chemotherapy, it cannot replace resection, particularly in cases with tumor diameters >3 cm [24,30-34].

Other researchers have outlined the value of combination therapies, so that resection and RFA complement each other for better results in terms of reducing recurrence, as opposed to utilizing them independently [19,35]. Likewise, other researchers have suggested the combined use of chemotherapy and RFA [36,37] to prolong survival and decrease local recurrence rates in patients with CRLM. The CLOCC study was the first to prospectively evaluate RFA plus chemotherapy [38]. This study showed that radiofrequency plus chemotherapy is clearly superior to systemic chemotherapy in terms of progression-free survival (PFS) and overall survival (OS) in colorectal cancer patients with inoperable liver metastases. Median OS was 45.3 months in the RFA arm vs. 40.5 months in the chemotherapy-alone arm, while the 8-year OS was 35.9% vs. 8.9% in the RFA arm and the 8-year PFS was 22% vs. 2% [38].

MWA

During the past several years MWA has gained acceptance as a favorable alternative to RFA and in some cases a preferred choice of ablation modality. Microwave systems use an electromagnetic signal to generate heat. Current microwave manufactures operate at frequencies between 900-2450 MHz. At this frequency range, electromagnetic microwaves heat matter by vigorous agitation of water molecules in the tissues, producing friction and heat. This results in cellular death via coagulation necrosis [38]. MWA features several advantages compared with RFA ablation, such as higher intratumoral temperatures, faster heating over a larger volume of tissues, incorporation of multiple applicators simultaneously and less procedural pain (Fig. 1). In contrast to RFA, MWA generates electromagnetic waves that produce thermal necrosis via molecular friction. As a result, resistance to heat sink effect, high impedance, low thermal conductivity and low penetrability are less of an issue in this treatment modality [39,40].

Ierardi *et al* [41] published a study highlighting the advantages of MWA. The authors evaluated the technical success, safety and efficacy of MWA for the treatment of hepatic malignancies in a series of 31 hepatic lesions, with 21 being CRLM. Characteristically, all metastases were >3 cm in diameter or were located in close proximity to hepatic vessels, rendering them ineligible for RFA. Overall disease-free survival was 20.5 months and local recurrence rate was 12.9%, endpoints similar to those of RFA treatment. There were no major complications and no procedure-related deaths.

In a recent systematic review, 75 studies were identified that reported outcomes on thermal ablation for CRLM between

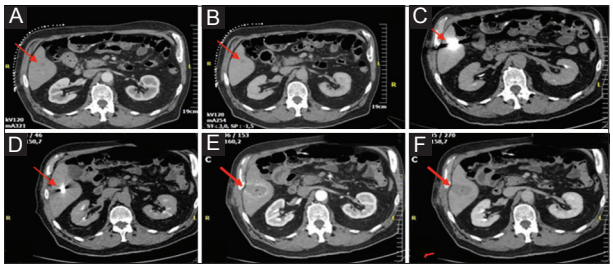

Figure 1 Patient with a small metastatic lesion from colorectal cancer, measuring 1 cm in maximum diameter, treated with microwave ablation under computed tomographic (CT) guidance. (A) CT scan in arterial phase depicting a hypodense hypovascular lesion in segment VI (red arrow) (B) CT scan in portal venous phase depicting a hypodense lesion with rim enhancement in segment VI (red arrow). (C, D) CT scan during the procedure, note the tip of the microwave antenna within the lesion (red arrow). CT scan immediately post-ablation during arterial (E) and venous (F) phase, depicting the necrotic zone of ablation; note the presence of a peripheral rim of enhancement representing a hypervascular rim of inflammation immediate post ablation (red arrows)

1994 and 2010. Most studies reported results with RFA (36 studies), with local recurrence rates ranging between 10% and 31%, whereas studies reporting outcomes of MWA (13 studies) had much lower recurrence (5-13%) [42].

In a retrospective cohort analysis, Correa-Gallego *et al* compared the difference in ablation site recurrence between intraoperative MWA and RFA, specifically for CRLM. For MWA the local recurrence rate was 6%, whereas for RFA it was 20%, a statistically significant difference [43]. Additionally, there are several studies that show no significant difference in OS. In 2015, Huo & Eslick published the results of a meta-analysis comparing the efficacy and safety of MWA vs. RFA ablation for the treatment of hepatic lesions; overall, 16 studies involving 2062 patients were included. MWA was found to have significantly better 6-year OS than RFA, but this was based on only a few articles (3 of 16). MWA and RFA had similar 1-5-year OS, disease-free survival, local recurrence rate and adverse events [44].

Nevertheless, the safety and efficacy of MWA for the treatment of CRLM is widely supported in the current literature (Table 1). Eng *et al* presented outcomes and recurrence patterns after intraoperative MWA for CRLM. Thirty-three patients were retrospectively analyzed. The maximum size of tumors treated in this study was 5.5 cm. There was only one liver recurrence, while approx. 23% of patients presented with distant disease alone. OS in this cohort was 35.2% at 4 years [45]. Wang *et al* studied the clinical outcomes after ultrasound-guided percutaneous MWA for colorectal metastases. They reported a 3-year survival rate of 78.7% for colon cancer and 78.6% for rectal cancer patients. Cumulative recurrence rates in this population were reported as 1-year 27.8%, 2-year 48.4% and 3-year recurrence rate of 59.3% post ablation [46].

Both thermal ablative techniques have been shown in several studies to have high local tumor control with a low recurrence rate, though in the majority of these studies neither method showed a clear benefit in terms of survival outcome. The ease of use, the absence of a need for grounding pads, the shorter overall average ablation time and the theoretical technical advantages over RFA has fueled the shift towards the routine use of MWA. In a recent clinical study by Shady *et al* concerning ablation with clear margins, the authors concluded that margins >5 mm are critical for local tumor control, regardless of the thermal ablation modality used; furthermore, no local tumor progression was noted for margins over 10 mm [47]. In the same study the authors concluded that, unlike RFA, the efficacy of MWA is not affected in perivascular tumors, suggesting that this type of ablation could be ideal for metastatic lesions close to vessels [47].

Intra-arterial therapies

Contemporary intra-arterial treatment options for CRLM include TACE, using either emulsions of ethiodized oil and chemotherapy solution (conventional TACE) or drug-eluting beads and chemotherapy solution (DEB-TACE); transarterial radioembolization (TARE), with microspheres labeled with the β emitter yttrium-90 (^{90}Y); hepatic arterial infusion (HAI) of chemotherapy; and percutaneous hepatic perfusion (PHP, also termed chemosaturation) using an organ isolation perfusion system with melphalan. Since the availability of HAI and PHP is limited to only a few centers, in this paper we will focus only on TACE, DEB-TACE and TARE [48].

Indications

Locoregional intra-arterial therapies are generally indicated for patients with oligometastatic disease, who are not candidates for surgery or other curative locoregional therapies, showing no response, disease progression or toxicity to systemic chemotherapy (Fig. 2). The goal in this group of patients is to achieve long-term disease control, potentially contributing to OS, with well-controlled sites of metastases.

TACE

The concept of TACE is to infuse chemotherapeutic agents followed by embolic particles into the hepatic arteries supplying the liver tumors, while sparing the surrounding normal hepatic parenchyma. Conventional TACE (c-TACE) has traditionally been performed; it was a common practice to deliver chemotherapeutic agents emulsified with lipiodol, followed by delivery of an embolic agent, often polyvinyl alcohol (PVA) or gelfoam. During the past decades, with the advent of calibrated embolic agents, there was a surge of the use of drug-eluting beads as embolic agents for delivery of the chemotherapeutic solution. The introduction of drug-eluting beads with TACE (DEB-TACE) has been proposed to improve the ability of c-TACE to enhance drug delivery to the tumor,

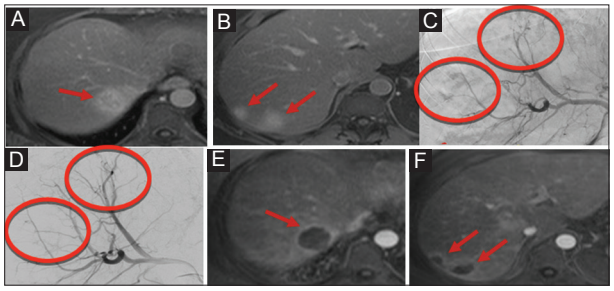

Figure 2 Patient with oligometastatic disease from colorectal cancer treated with liver chemoembolization after failed second line chemotherapy. (A, B) Magnetic resonance (MRI) images after i.v. gadolinium administration depicting 3 hypervascular hepatic lesions in the right lobe (red arrows). (C) Selective hepatic angiogram, depicting the hypervascular lesions in the right liver lobe (red circles). (D) Final selective hepatic angiography after chemoembolization with drug-eluting beads and chemotherapy solution, revealing absence of the pathologic tumor blush (red circles). (E, F) MRI images after i.v. gadolinium administration 1 month after chemoembolization, depicting central necrosis of the lesions with residual minimal peripheral enhancement representing response to the treatment (red arrows)

theoretically mitigating the systemic drug exposure and thus minimizing side-effects [48].

The safety and efficacy of both c-TACE and DEB-TACE have been studied extensively for the treatment of hepatocellular carcinoma (HCC). The Barcelona criteria include TACE as the standard of care for intermediate stage HCC with level of evidence 1A [48]. Because of the proven survival benefit in HCC patients, several series have analyzed the role of TACE in the treatment of secondary hepatic lesions, focusing mainly on colorectal metastases (Table 2). Nowadays it is considered a good therapeutic approach for patients with colorectal cancer and liver-limited disease who fail the available chemotherapeutic options [49-53].

c-TACE

In 1998, in a phase II trial, Tellez *et al* evaluated chemoembolization treatment in 30 patients with CRLM who had failed standard-of-care systemic chemotherapy. Radiological responses were seen in 63% of patients and 95% experienced a decrease of at least 25% in their baseline carcinoembryonic antigen level. Median OS for all patients was 8.6 months. The most common toxicity was postembolization syndrome, including fever, nausea, vomiting, and right upper quadrant pain. The authors concluded that c-TACE is a feasible treatment that results in high response rates, with mild-to-moderate toxicity, for patients with CRLM in a salvage setting [54].

Albert *et al* reported the results of TACE with cisplatin, doxorubicin, mitomycin C, and lipiodol mixture followed by PVA particles in patients with colorectal cancer and unresectable liver dominant disease who had failed systemic chemotherapy. A total of 245 treatments were performed in 121 patients. Patients underwent a mean of two c-TACE sessions. Median time-to-disease progression (TTP) in the treated liver was 5 months, while median TTP anywhere was 3 months. Median survival was 33 months from initial diagnosis and nine months from chemoembolization. OS was significantly better when chemoembolization was performed after first- or second-line systemic therapy than after three to five lines of chemotherapy. Presence of extrahepatic metastases did not adversely affect survival. Albert *et al* concluded that TACE provided local disease control of liver metastases after 43% of treatment cycles [55].

Vogl *et al* reported the results of c-TACE in 463 patients with pretreated unresectable colorectal metastases. Patents were treated with 3 different chemotherapy regimens, including mitomycin C alone, mitomycin C with gemcitabine, or mitomycin C with irinotecan, depending on prior chemotherapy history, mixed with lipiodol and followed by starch microsphere embolization. The 1-year survival rate after chemoembolization was 62% and 2-year survival was 28%. No significant survival difference was observed between c-TACE regimens. As with prior studies, the most commonly experienced toxicities of the procedure were symptoms of post-embolization syndrome [56].

DEB-TACE

DEB-TACE was introduced into clinical trials in 2006, with the rationale of lowering systemic toxicity while increasing the efficacy of chemoembolization through a slower and more sustained release of chemotherapy drugs within the tumor bed. Several studies have been carried out with irinotecan-loaded DEB (DEBIRI) for the treatment of CRLM, reporting promising initial data as regards safety and efficacy, especially in patients who had failed systemic chemotherapy.

Martin *et al* reported the results of DEBIRI in patients with advanced liver metastases from colorectal cancer that failed oxaliplatin- and irinotecan-based systemic chemotherapy and biological agents. The study met its primary endpoints by demonstrating that DEBIRI is safe and well tolerated. Response rate was 66% at 6 months and 75% at 12 months. OS was 19 months, with a PFS of 11 months [57].

Aliberti *et al* reported the results of a phase II study of DEBIRI in 82 patients with CRLM who had failed at least two previous lines of chemotherapy. The response was 78% at three months, with a median duration of response of 6 months. The median OS was 25 months with a PFS of 8 months [58].

Fiorentini *et al* conducted the first randomized trial in patients with unresectable CRLM receiving DEBIRI as a salvage therapy, compared to those who underwent FOLFIRI.

Table 2 Literature highlights of chemoembolization for colorectal liver metastases

Study [Ref]	Year	Study details	Median OS (months)
Vogl *et al* [53]	2009	TACE, mitomycin C alone or with gemcitabine *vs.* irinotecan Prospective cohort, 463 patients	14
Albert *et al* [55]	2011	TACE, cisplatin, doxorubicin, mitomycin C Retrospective cohort, 121 patients	9
Martin *et al* [76]	2011	DEB-TACE (DEBIRI), irinotecan Prospective cohort, 55 patient	19
Fiorentini *et al* [59]	2012	DEB-TACE (DEBIRI), irinotecan Randomized controlled trial, 74 patients, DEBIRI *vs* FOLFIRI	15
Narayanan *et al* [77]	2013	DEB-TACE (DEBIRI) Retrospective cohort, 28 patients	13.3
Iezzi *et al* [78]	2015	DEB-TACE (DEBIRI), irinotecan+Capecitabine Prospective phase II Trial, 20 patients	7.3

TACE, transarterial chemoembolization; DEB, drug-eluting beads; DEBIRI, irinotecan-loaded DEB; OS, overall survival, FOLFIRI, FOLinic acid-Fluorouracil-IRInotecan

All patients had received 2-3 lines of prior chemotherapy. Median OS was longer for patients in the DEBIRI arm (22 vs. 15 months). Compared to patients receiving systemic FOLFIRI, those in the DEBIRI arm also had a greater PFS of 3 months, greater likelihood of objective tumor response (68.6% vs. 20%), and better sustained quality of life (8 vs. 3 months, P<0.001). A major drawback of this study is the omission of oxaliplatin, bevacizumab, cetuximab or panitumumab, as these agents were not part of standard care at the time of the study. When added to FOLFIRI, these agents have demonstrated a greater OS compared with FOLFIRI alone [59].

Three years later, Martin *et al* published the results of a prospective randomized controlled trial investigating the use of DEBIRI as first-line therapy with simultaneous systemic fluorouracil and oxaliplatin (FOLFOX) and bevacizumab compared with systemic FOLFOX and bevacizumab alone in chemonaïve patients with unresectable CRLM. A significant improvement in overall response rates at 6 months (P=0.05) and liver PFS (P=0.05) was seen in the DEBIRI arm, which did correlate with a significant improvement in downsizing to resection in the FOLFOX-DEBIRI arm (35%) vs. the FOLFOX-alone control arm (6%; P=0.05). It failed, however, to show an improvement in PFS and did not present data on OS. This would suggest that DEBIRI may be better reserved for second-line therapy or later; but more studies are definitely needed to determine its role in the treatment algorithm of patients with CRLM [60].

Recently, the results of a systematic review were published reporting the safety and efficacy of DEBIRI-TACE for the treatment of unresectable CRLM. Overall, 13 studies were included, comprising a total of 850 patients. In all, 6 prospective phase I/II trials, 5 retrospective trials and 2 randomized control trials were evaluated. Authors reported a high toxicity rate of 10.1%, which is to be expected in this heavily pretreated population. The weighted average response rates were 56.2% and 51.1%, according to the RECIST (Response Evaluation Criteria in Solid Tumors) and modified RECIST/EASL (European Association for the Study of the Liver) response criteria, respectively. The weighted average PFS and OS were 8.1 months and 16.8 months, respectively [61].

TARE

TARE is an intra-arterial, catheter-based technique that, like chemoembolization, delivers high doses of internal radiation to liver tumors. In TARE, microspheres loaded with a radioisotope are deployed to the tumor vasculature, the most common agent being ^{90}Y. The most important difference between TACE and TARE is the mechanism of action, i.e. ischemia/chemotherapy vs. irradiation [48].

There is mature and robust evidence that addresses the role of TARE in the treatment of unresectable CRLM. The currently available data have established TARE as a valuable therapeutic salvage option for patients who have failed prior systemic chemotherapy regimens. The literature reports ample data concerning the use of radioembolization in the salvage setting, showing a fairly high response rate of 35-40% based on size criteria, and even higher responses if we consider functional imaging or tumor markers. The median survival is quite consistent, between 8-14.5 months in all these studies, regardless of the radioembolic agent used (Table 3) [62-66].

More recently, registry-type data were published. Kennedy *et al* published the results of a multicenter trial from 11 institutions, including 606 patients with CRLM treated with radioembolization with ^{90}Y resin microspheres. Patients had received a median of 2 (range: 0-6) lines of prior chemotherapy

Table 3 Literature highlights of radioembolization for colorectal liver metastases

Study [Ref]	Year	Study details	Median OS (months)
Kennedy *et al* [63]	2006	Phase II prospective study 208 patients	10.5
Sharma *et al* [79]	2007	Phase I, 20 patients No prior chemotherapy SIRT+FOLFOX4	9.3 (14.2 if had only liver-confined disease)
Lewandowski *et al* [80]	2014	Prospective study 214 patients	10.6
Hickey *et al* [68]	2016	Retrospective multicenter study, 531 patients	10.6
Clinical trials			
Name	Study details		Outcome
Combined FOXFIRE analysis (SIRFLOX, FOXFIRE, FOXFIRE GLOBAL) [81]	Phase III randomized controlled trial, 1103 patients oxaliplatin-based chemotherapy (FOLFOX: leucovorin, fluorouracil, and oxaliplatin) vs. FOLFOX plus single treatment TARE concurrent with cycle 1 or 2 of chemotherapy		No statistically significant difference in OS and overall progression-free survival Statistically significant 4.9 month improvement in median OS in patients with a right-sided primary colon cancer

OS, overall survival; TARE, transarterial radioembolization

and 35.1% had limited extrahepatic metastases. The median OS was 9.6 months from the time of radioembolization [65]. Another multicenter trial by Hickey *et al*, published in 2016, presented the results of radioembolization with glass microspheres in 531 patients with unresectable colorectal metastases from 8 institutions. Patients had a median OS of 9.6 months from the time of radioembolization. If we consider that the response rate drops to 10% with third-line systemic chemotherapy and the median survival to 5-8 months, adding radioembolization to the treatment strategy at this time seems to have a clear benefit [68].

The efficacy of TARE as first-line therapy has been studied thoroughly in 3 large trials with similar design, beginning in 2006 with the Sirflox study [69], followed by the Foxfire and the Foxfire global, investigating the effect of radioembolization when added to first-line chemotherapy for the treatment of metastatic colorectal cancer. The combined data from these studies were rather disappointing. Despite an improved response within the liver and liver PFS there was no difference in OS, perhaps because of the progression of extrahepatic disease. Further subanalysis, however, showed that for right-sided primary tumors, which had a poorer prognosis, there was a 4.9-month improvement in OS for those treated with systemic chemotherapy plus TARE compared with those treated with systemic therapy alone, whereas for left-side primaries there was no difference [70]. Based on these data, TARE is currently not recommended as first-line therapy for patients with non-resectable CRLM; a better means of selecting the subgroup of patients who would benefit needs to be defined.

All these local ablative and locoregional therapies have been incorporated in the toolbox of the updated ESMO guidelines for the treatment of metastatic colorectal cancer as potential treatment options for patients with metastatic colorectal cancer. In patients with oligometastatic disease, thermal ablation alone or in combination with surgical resection may be applied, either initially, or possibly after induction treatment with systemic therapy. The aim for these patients is to achieve long-term disease control and potential cure without continued systemic therapies. In patients with more advanced liver-limited disease, chemoembolization and radioembolization are recommended, once other chemotherapeutic options fail, aiming at local tumor control with the ultimate goal being OS prolongation [71].

Concluding remarks

Colorectal cancer remains one of the most common cancers worldwide, while hepatic metastases account for the greatest proportion of morbidity and mortality from the disease after resection of the primary cancer. Over the past several decades, interventional oncological treatments have greatly evolved and have expanded to play an important role in the management of these patients. As we continue to advance clinically and technologically in the field of interventional oncology, our goal is continue the refinement of regional and systemic therapies aimed at the prolongation of survival of patients with CRLM.

Intra-arterial therapies with ^{90}Y and TACE have been studied thoroughly for converting patients with unresectable HCC to surgical candidates and are worthy of investigation in CRLM. Local ablations have shown an immunoregulatory effect in preclinical and clinical studies. Percutaneous ablation could be used beneficially to optimize the immunotherapy treatments currently being developed for colorectal cancer, in order to reduce both local and remote tumor recurrence. Finally, a combination of percutaneous ablation and intra-arterial therapies might confer benefit in patients with CRLM and requires further study.

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