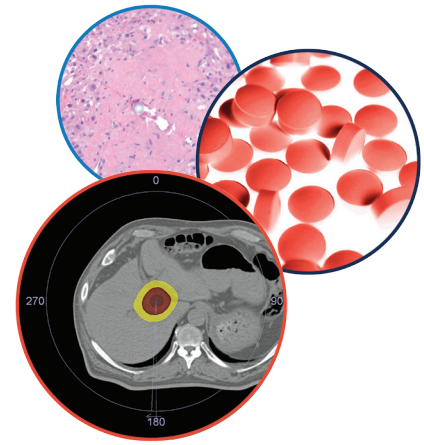
REVIEW

Current role of transarterial chemoembolization and radioembolization in the treatment of metastatic colorectal cancer



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Practice Points

- Liver-directed therapies have gained increasing clinical use in interventional oncology for palliative treatment of tumors that are confined to the liver and are not amenable to resection or ablation.
- The management of unresectable chemorefractory liver metastases from colorectal cancer is a clinical challenge.
- In the absence of effective chemotherapeutic agents in the salvage setting, liver-directed therapies, such as transcatheter arterial chemoembolization (TACE), including TACE with drug-eluting beads, and radioembolization, should be considered.
- With the advent of Yttrium-90 and TACE with drug-eluting beads irinotecan, clinicians have a chance to use radioembolization and one of the newer chemotherapy agents in the treatment of metastatic colorectal cancer. Both treatments as salvage therapy (either with or without chemotherapy) appear to demonstrate consistent survival benefits and the delay of disease progression.
- The combination of drug-eluting beads irinotecan with systemic chemotherapy before chemoresistance develops may be the treatment combination to consider in the future.

SUMMARY In this article, we review two liver-directed therapies that are currently used for the palliative treatment of primary and secondary hepatic malignancies, transcatheter arterial chemoembolization (TACE), including a new type of TACE with drug-eluting beads, and radioembolization. Important developments and administration techniques for all therapies are discussed, as well as their integration into the current routine clinical care for management of metastatic colorectal cancer. According to published data from clinical trials, as presented in this review, both radioembolization and TACE/TACE with drug-eluting beads have been proven to be safe and effective in selected patients with chemorefractory liver metastases from colorectal cancer. For patients with unresectable liver-only or liver-dominant disease who have failed standard chemotherapy options or for whom chemotherapy is contraindicated, new modalities, such as those discussed, are particularly valid and promising if clinical guidelines for patient selection and treatment administration are followed.

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Future Medicine part of fsg

The last decade has seen important developments in the treatment of metastatic colorectal cancer (CRC), particularly in the use of newer multidrug regimens and their combination with targeted local-regional therapies. A shift toward multiagent treatment strategies, including a variety of chemotherapy agents and monoclonal antibodies, has improved response rates and prolonged survival among patients with advanced CRC [1–4]. Fluorouracil (5FU) and leucovorin (LV) still constitute the foundation of most chemotherapy regimens for patients with advanced CRC, and response rates have increased from 12% with 5FU/LV alone to 50% or more with the addition of either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX), with or without bevacizumab, cetuximab or panitumumab [1,2,5,6].

However, even though these advances in biologic and chemotherapeutic agents have improved survival times from approximately 12 to 16 months with 5FU-containing chemotherapy regimens [6] to 20 months or more in some studies [2–4], CRC remains a leading cause of death, accounting for nearly 10% of all cancer deaths in the USA [7]. Surgery can cure approximately 90% of CRCs when they are diagnosed early [7]. A significant proportion of patients (25–60%) who are diagnosed with CRC, however, will develop liver metastases throughout the course of their disease. Surgical extirpation is the only potentially curative treatment option for CRC liver metastases [8,9]. Unfortunately, potentially curative liver resection is currently only possible in 10 to 15% of patients with metastatic CRC (mCRC) [10]. Patients who undergo a complete surgical resection have an increased 5-year survival rate of 30–40% [9,11]. Nevertheless, approximately 60–90% of patients who were treated with neoadjuvant chemotherapy and liver resection will experience a recurrence of their liver tumors [12]. The ongoing challenge is, therefore, how to successfully achieve local control or increase the proportion of patients able to undergo liver resection [10], decrease the risk of recurrence and prolong survival of patients who remain unsuitable for resection [13,14].

Over the past two decades, several liver-directed therapies have been developed to help improve local control of primary and secondary tumors. In this article, we focus on two liver-directed therapies that are currently used for the palliative treatment of primary and secondary hepatic malignancies, transcatheter arterial chemoembolization (TACE), including a new type of TACE with drug-eluting beads (DEB-TACE), and radioembolization. Clinical trials have demonstrated that radioembolization combined with various chemotherapy regimens is associated with a more prolonged and durable response compared with chemotherapy alone [15–18], whereas radioembolization alone can have clinically relevant benefits for chemotherapy-refractory patients with liver-predominant disease [19–21].

The aim of this article is to discuss the integration of radioembolization and chemoembolization (with and without drug-eluting beads) into the current routine clinical care for the management of liver-only or liver-dominant mCRC. Important developments and administration techniques are reviewed, with an emphasis on the most relevant published data from clinical trials.

Radioembolization

Developments & administration

Radioembolization is a procedure in which glass or resin microspheres incorporating the radioactive isotope Yttrium-90 (^{90}Y) are directly injected into the hepatic arteries perfusing the tumor [22]. To date, more than 20,000 patients have been treated worldwide with both resin and glass ^{90}Y microspheres for primary and secondary liver tumors. Based on this extensive clinical experience, the safety profile of radioembolization is well established. Initial studies of resin ^{90}Y in humans were reported in the late 1970s [23].

Two radioembolic products are commercially available. TheraSphere (glass microspheres) gained a Humanitarian Device Exception from the US FDA in 1999 for the treatment of unresectable hepatocellular carcinoma (HCC) in the USA (TheraSphere Yttrium-90 microspheres [package insert]; MDS Nordion, ON, Canada, 2004). SIR-Spheres® (resin microspheres) gained full premarket approval from the FDA in 2002 for the treatment of unresectable colorectal liver metastases in conjunction with intrahepatic fluorodeoxyuridine (floxuridine [FUDR]; SIR-Spheres Yttrium-90 microspheres [package insert]; Sirtex Australia, New South Wales, Australia, 2004).

The rationale behind radioembolization is the uniquely organized hepatic circulation with dual supply to the liver. While the portal venous system supplies 80% or more of the blood to normal liver, the hepatic artery provides up to 20% of the blood to normal liver. In the presence of tumor

growth in the liver, the hepatic artery is the main supply of blood to liver tumors, as opposed to the normal liver parenchyma. Since ^{90}Y microspheres are delivered to the arterial supply of the tumor(s), they concentrate selectively in the tumor compartment within the liver. The tissue penetration distance of ^{90}Y, combined with preferential uptake into hypervascular liver tumors, allows radioembolization to achieve doses as high as 150 Gy without the clinical complications seen with external beam radiation [24–27]. The parasitic effect of the tumor protects the normal liver and radioactive microspheres ultimately lodge within the targeted vascular beds of tumor tissue where they reduce the blood flow and deliver ^{90}Y brachytherapy [28].

Patients considered for radioembolization must have hepatic tumors that cannot be surgically resected or ablated with curative intent, liver-dominant tumor burden and sufficient functional liver reserve with minimal extrahepatic disease [29]. Arterial shunting from the liver to the lungs and major arterial reflux from the hepatic vasculature to arteries supplying the GI tract are contraindications [29].

Although radioembolization was initially used as salvage therapy for patients following sequential chemotherapy [30,31], there are currently several prospective randomized studies being undertaken to evaluate its use when administered concurrently with first- or second-line chemotherapy.

The treatment guidelines of the National Comprehensive Cancer Network (NCCN) version 3.2013 [32] consider radioembolization a 'category 3' recommendation. A category 2B recommendation is made according to NICE UK. Based upon the current evidence, including a large number of nonrandomized studies in the chemotherapy-refractory setting, plus randomized studies combining radioembolization with chemotherapy, and the author's extensive clinical experience with radioembolization, as well as the clinical experience of other expert physicians, we consider the intervention appropriate; it is effective in unresectable mCRC in combination with first to nth line chemotherapy, as well as in the salvage situation.

Current clinical evidence

■ Radioembolization combined with first-line chemotherapy

Gray *et al.* reported findings of a Phase III randomized trial of 74 patients comparing ^{90}Y microspheres plus first-line intrahepatic FUDR versus FUDR alone in patients with unresectable CRC. Only patients with nonresectable metastases limited to the liver and lymph nodes in the porta hepatis, who had a WHO performance status of 0–2, were included in the study. All patients had bilobar liver metastases that were unable to be treated by any form of local ablation. While 29% of patients in the ^{90}Y plus FUDR group had a tumor burden >25%, 33% of patients in the FUDR-alone group had a tumor burden >25%. A single dose of ^{90}Y added to intrahepatic chemotherapy was associated with significant increases in response rate (complete response [CR] plus partial response [PR]; 44 vs 18%) and time to progression (TTP; 15.9 vs 9.7 months). One- and two-year survival for patients receiving ^{90}Y was 72 and 39%, compared with 68 and 29% for intrahepatic chemotherapy alone. One patient (3%) underwent a successful complete liver resection following radioembolization and intrahepatic FUDR [15].

Van Hazel *et al.* conducted a randomized controlled trial comparing ^{90}Y microspheres plus first-line systemic 5FU/LV chemotherapy versus 5FU/LV alone in 21 patients with unresectable liver metastases from CRC. Only patients with liver metastases that could not be treated by resection or any locally ablative technique, who had a WHO performance status <3 and no CNS metastases were included in the study. All patients had multiple bilobar liver metastases, with a tumor burden of >25% in 30% of patients in the ^{90}Y plus 5FU/LV group and 27% of patients in the 5FU/LV-alone group. A single dose of ^{90}Y added to chemotherapy was associated with significant increases in response rate (CR plus PR; 91 vs 0%), TTP (18.6 vs 3.6 months) and median overall survival (OS; 29.4 vs 12.8 months) compared with systemic chemotherapy alone [16].

Sharma *et al.* completed a Phase I study in 20 patients with inoperable liver metastases from CRC using ^{90}Y microspheres with concomitant systemic oxaliplatin and 5FU/LV (modified FOLFOX4) chemotherapy. Only patients with liver metastases that were not treatable by surgical resection or local ablation, who had a WHO performance status of 0–2 and no CNS metastases were included in the study. Median tumor involvement of the liver was 32.5% (range: 5–60) in all patients, with 35% of patients having liver-only disease. The reported objective response rate (ORR) was 90% with a disease

control rate of 100%. Progression-free survival (PFS) was 9.3 months and time to liver progression 12.3 months. Three out of 20 patients (15%) were downstaged, and two patients (10%) underwent a complete liver resection [17].

This chemoradiation regime forms the basis for two ongoing Phase III studies (SIRFLOX and FOXFIRE). The goal of these studies is to investigate whether radioembolization used in combination with chemotherapy can offer patient outcome advantages that are superior to chemotherapy alone [33,34].

Radioembolization combined with second- or third-line chemotherapy

Van Hazel *et al.* conducted a Phase I study to evaluate the maximum-tolerated dose of concomitant irinotecan and radioembolization in 25 5FU-refractory patients with CRC liver metastases. Patients with WHO performance status of 0–2 and liver metastases that were not treatable by surgical resection or local ablation were included in the study. Patients with CNS metastases were excluded. Median tumor involvement of the liver was 20% (range: 5–60) in all patients with 52% of patients having liver-only disease. A maximum-tolerated dose was not reached and the results were promising, as demonstrated by an overall response rate of 48%, a disease control rate (CR, PR and stable disease [SD]) of 87%, a median PFS of 6 months, time to liver progression of 9.2 months and a median OS of 12.2 months [18].

A prospective multicenter evaluation of radioembolization (with concurrent 5FU at investigator discretion) was conducted by Lim *et al.* in 30 patients with inoperable liver metastases from CRC who had failed 5FU-based chemotherapy. All patients were required to have measurable disease in the liver, with extrahepatic disease (apart from brain metastases) allowed (20% of patients) if the liver was the dominant site of disease. Patients with a poor performance status (Eastern Cooperative Oncology Group [ECOG] >2) were excluded. One patient (3%) achieved a CR and 33% of patients had a PR, with the median duration of response being 8.3 months and median TTP 5.3 months. The investigators reported a complete liver resection in one patient (3%) following radioembolization and 5FU. Overall treatment-related toxicity was acceptable [20].

One randomized controlled study is currently underway (EPOCH), investigating radioembolization (glass microspheres) plus second-line chemotherapy versus second-line chemotherapy alone following failed first-line chemotherapy. PFS will be the primary objective of the trial, with the goal to enroll 360 patients [35].

Radioembolization as salvage therapy in chemorefractory mCRC

There are a number of prospective and retrospective clinical studies which have addressed the use of ^{90}Y microspheres (either alone or combined with chemotherapy) as a salvage treatment in patients with mCRC that is refractory to standard-of-care chemotherapy options.

A multicenter randomized Phase III study was conducted by Hendlisz *et al.* to assess the addition of ^{90}Y microspheres to continuous 5FU infusion versus continuous 5FU infusion alone. All 44 patients had failed oxaliplatin- and irinotecan-based regimens. Patients with liver-only disease not amenable to curative surgery or local ablation and resistant or intolerant to standard chemotherapy were included in the study. Patients with ECOG >2 or extrahepatic disease were excluded. In total, 38% of patients in the ^{90}Y plus 5FU group had ≥5 baseline liver metastases and 44% of patients in the 5FU-alone group had ≥5 lesions. The median time to liver progression (primary end point of the trial) was significantly longer in patients receiving radioembolization plus 5FU (5.5 months) compared with 5FU alone (2.1 months). The median TTP anywhere in the body was also significantly longer (4.6 vs 2.1 months), median survival was 10 months in the radioembolization plus 5FU treatment arm versus 7.3 months in the 5FU-only arm. By design, patients in the control arm who received 5FU alone were able to receive resin-spheres as salvage therapy on disease progression, therefore OS was increased in both arms. One patient (5%) was reported to have undergone a complete liver resection following radioembolization and 5FU [36].

A prospective Phase II trial of 29 patients conducted by Seidensticker *et al.* demonstrated that radioembolization significantly extended both OS and PFS in patients with chemorefractory mCRC treated with ^{90}Y resin microspheres, compared with a matched pair of 29 patients receiving supportive care. Patients in this study had failed all chemotherapy options and were ineligible for all other forms of tumor-directed therapy. Patients also had liver-dominant mCRC with extensive liver involvement (median of 30% tumor burden in the ^{90}Y group and 25% in the supportive care group) and none or only nonprogressive extrahepatic deposits. Radioembolization

provided substantial clinical benefit as evidenced by a significant stabilization in liver disease and prolonged survival in patients with refractory mCRC. After radioembolization, a PR was observed in 12 patients (41.4%) and SD in five patients (17.2%). Median PFS was 5.5 months and median survival 8.3 months in the radioembolization group, compared with 2.1 (PFS) and 5.5 months (OS) in the control group receiving supportive care. On multivariate analysis, radioembolization was the most significant predictor of survival [37].

Cosimelli *et al.* conducted a prospective Phase II multicenter trial in 50 patients with highly chemorefractory mCRC. In total, 76% of these patients had received four or more lines of chemotherapy. Most presented with synchronous disease (72%), more than four liver metastases (58%), 25–50% replacement of total liver volume (60%) and bilateral spread (70%). All patients had unresectable liver metastases and limited extrahepatic disease. The ORR (primary end point of the trial) was 24%, which reached the predetermined criteria for significance, with SD in another 24% of patients. The treatment response after radioembolization was highly predictive of prolonged survival, with a median OS of 13 months and a significant difference between responders and nonresponders (16 vs 8 months, respectively). Furthermore, two patients (4%) were sufficiently downstaged to enable potentially curative liver resection of three or more segments [21].

Kennedy *et al.* reported a retrospective multicenter review of 208 patients with unresectable, chemorefractory mCRC predominantly involving the liver. Patients had already received and failed standard first-, second- and third-line therapies for their primary tumor and were not candidates for radiofrequency ablation, TACE, resection, intensity-modulated radiation therapy, or stereotactic radiotherapy. Patients with an ECOG >2 were excluded. The response rate by computed tomography was 35.5%, with disease stabilization in another 55% of patients, and the response rate by PET was 85%. Treatment response after radioembolization was highly predictive of prolonged survival, with a median OS of 10.5 months for responders versus 4.5 months for nonresponders or historical controls [38].

The largest, most comprehensive study to date evaluating the use of radioembolization in 506 patients with chemorefractory liver metastases from CRC was reported by Kennedy *et al.* Active extrahepatic disease was present at first radioembolization in 35% of patients, the majority (90%) had received prior chemotherapy. The median OS for these heavily pretreated patients (all patients had failed first-line, 93% had failed second-line and 87% had failed third-line chemotherapy) was 9.6 months for the first radioembolization treatment [39].

Table 1 summarizes key studies reported to date using radioembolization in the treatment of unresectable colorectal liver metastases.

Table 1. Key prospective and retrospective studies for radioembolization in metastatic colorectal cancer.

Study (year)	Analysis	Regimen	Line†	Patients (n)	Ref.
Radioembolization combined with first-line chemotherapy					
Gray *et al.* (2001)	Prospective	^{90}Y resin m + FUDR HAC vs FUDR HAC	1–2	36 vs 34	[15]
Van Hazel *et al.* (2004)	Prospective	^{90}Y resin m + 5FU/LV vs 5FU/LV	1	11 vs 10	[16]
Sharma *et al.* (2007)	Prospective	^{90}Y resin m + FOLFOX	1	25	[17]
Radioembolization combined with second- or third-line chemotherapy					
Van Hazel *et al.* (2009)	Prospective	^{90}Y resin m + irinotecan	2–4	25	[18]
Lim *et al.* (2005)	Prospective	^{90}Y resin m ± 5FU	2	30	[20]
Radioembolization as salvage therapy in chemorefractory mCRC					
Hendlisz *et al.* (2010)	Prospective	^{90}Y resin m + 5FU vs 5FU	Salv	21 vs 23	[36]
Seidensticker *et al.* (2012)	Prospective	^{90}Y resin m vs matched control	Salv	29 vs 29	[37]
Cosimelli *et al.* (2010)	Prospective	^{90}Y resin m	Salv	50	[21]
Kennedy *et al.* (2006)	Retrospective	^{90}Y resin m	Salv	208	[38]
Kennedy (2012)	Retrospective	^{90}Y resin m	Salv	506	[39]

†1: first-line treatment; 2: second-line; 4: fourth-line.
5FU: 5-fluorouracil; FOLFOX: 5-fluorouracil, oxaliplatin and leucovorin; FUDR: Floxuridine; HAC: Hepatic arterial chemotherapy; LV: Leucovorin; m: Microspheres; mCRC: Metastatic colorectal cancer; Salv: Salvage therapy of chemotherapy refractory disease.

Transarterial chemoembolization

Developments & administration

TACE is a form of intra-arterial catheter-based chemotherapy that selectively delivers high doses of chemotherapy to the tumor bed, while sparing the surrounding liver tissue [40].

TACE with use of anticancer drugs has been in clinical practice since the 1980s and was first introduced by Yamada *et al.* in the late 1970s [41,42]. The method was designed to improve chemoinfusion with the intention to expose tumors to higher concentrations of chemotherapy with minimal systemic bioavailability. The concept of chemoembolization is to administer one or more chemotherapeutic agents into the hepatic arteries supplying the tumor. This is followed by embolization of the target vessels with agents such as gelfoam, polyvinyl alcohol or acrylic copolymer gelatin particles [43]. The high first-pass effect of chemotherapeutic agents, augmented by prolonged intracellular drug levels from embolic effects on the tumor vasculature, produces a high rate of local response [44]. Despite TACE being established as a technique, to date there are no randomized controlled trials comparing TACE with no treatment in order to support its use for the treatment of colorectal liver metastases. Hunt *et al.* published the only randomized controlled trial comparing hepatic artery embolization (HAE) or hepatic arterial infusion chemotherapy (HAI) with no treatment. In total, 61 patients with unresectable colorectal liver metastases were randomized, 20 to receive no treatment, 22 to receive HAE, and 19 to receive HAI with 5FU and degradable starch microspheres. Median survival from diagnosis of metastases was 9.6 months for controls, 8.7 months for the HAE group and 13 months in the HAI group. The greatest benefit was achieved in the subgroup with <50% tumor burden at baseline (median survival from diagnosis was 10 months for controls, 10.2 months for the HAE group and 23.6 months in the HAI group) [45].

The treatment guidelines of the NCCN version 1.2013 [46] consider chemoembolization a category 3 recommendation based on insufficient data and variations in techniques among institutions. We agree with the above NCCN recommendation, especially since randomized studies are lacking in mCRC; however, Phase II studies support the use of TACE for colorectal liver metastases [47,48].

Doxorubicin is the most commonly used drug for TACE, whereas the combination of doxorubicin, mitomycin C and cisplatin is preferred in the USA. The chemotherapeutic agent is usually mixed with lipiodol, an oily contrast agent that acts as a delivery vehicle for the drug and lodges near the tumor. Several embolic agents may be injected to enhance the effects of intra-arterial drug delivery. Gelatin sponge powder and pledgets and polyvinyl alcohol are the most commonly used agents [40].

TACE is currently considered the worldwide standard of care for patients with unresectable HCC who have preserved performance status and liver function without vascular invasion or extrahepatic disease. The procedure has a proven survival benefit when compared with best supportive care in select patient populations with unresectable HCC [49,50].

Current clinical evidence

TACE as salvage therapy in chemorefractory mCRC

In 1998, Tellez *et al.* reported a Phase II trial of TACE in 30 patients with mCRC who had failed standard of care systemic chemotherapy. Patients had adequate performance status (ECOG 0–2) and multiple liver lesions not amenable to full resection. Radiologic responses occurred in 63% of patients and 95% had a decrease of at least 25% of the baseline carcinoembryonic antigen level. Median OS for all patients was 8.6 months. The authors concluded that TACE is a feasible treatment that results in high response rates with mild-to-moderate toxicity for patients with mCRC who have experienced failure with other systemic treatments [47].

The Puget Sound Oncology Group performed a retrospective study in the USA on 32 patients with unresectable colorectal metastases of whom 44% had previously failed one or more systemic chemotherapy options. Patients had a good performance status (Southwest Oncology Group 0–2), and the majority had bilobar liver metastases; small volume (non-dominant) extrahepatic metastases were permitted provided the most immediately life-threatening disease was in the liver. A regimen of alternating regional TACE was delivered between cycles of protracted continuous infusion of 5FU as systemic chemotherapy. Response rates of up to 70% were observed (no patients had a complete response, 40% of patients had a partial response, 20% had a minor response and 10% had stable disease), with a median OS

of 14.3 months. OS at 1 and 2 years was 57 and 19%, respectively. The authors concluded that alternating systemic 5FU and regional TACE is an active and feasible regimen with manageable toxicities in this patient group [48].

In 2006, Geschwind *et al.* reported on patients with CRC of whom the majority had previously been treated with systemic chemotherapy, and demonstrated that TACE can prolong survival. Median survival time was 7.7 months, with 1-, 2-, and 5-year survival rates of 43, 10 and 0%, respectively [51].

More recent experience with TACE by Albert *et al.* was reported in 121 patients who received chemoembolization with cisplatin, doxorubicin and mitomycin C at monthly intervals for one to four sessions. Indication for treatment was most commonly failure of systemic chemotherapy to control unresectable liver-dominant disease. In 49% of patients the diagnosis of synchronous liver metastases was made at the time of primary diagnosis and 46% had extrahepatic metastasis at the time of their first chemoembolization treatment. A response rate (PR plus SD) of 43% was observed (there were no complete responders), with a median OS of 27 months from development of liver metastases, and 9 months from chemoembolization [52].

A Phase I/II study in 24 patients with unresectable colorectal liver metastases reported on the use of TACE with cisplatin powder after FOLFOX failure. In total, 75% of patients had synchronous hepatic metastases and 75% had no extrahepatic disease. Liver metastases were bilobar in 92% of patients and represented a tumor burden of >25% in 50% of patients. In the Phase II portion, a tumor response rate of 61.1% was achieved with a median hepatic PFS and OS of 8.8 and 21.1 months, respectively. The procedure was well tolerated [53].

The largest prospective study to date evaluating local tumor control and survival after repeated TACE in 463 patients with unresectable liver metastases from CRC was reported by Vogl *et al.* All patients had previously not responded to systemic chemotherapy and 67% of patients had multiple (≥5) metastases at the time of initial chemoembolization. The tumor load of the liver was restricted to less than 70% of the total liver volume. The presence of extrahepatic metastases and a poor performance status (Karnofsky status ≤70%) were both exclusion criteria for the trial. Evaluation of local tumor control resulted in a PR of 14.7% and SD of 48.2%. The 1-year survival rate after chemoembolization was 62%, and the 2-year survival rate was 28%. Median survival from the start of TACE was 14 months [54].

Neoadjuvant TACE in mCRC

An important application of TACE in patients with mCRC is to downstage initially unresectable liver metastases by neoadjuvant chemoembolization therapy. This can be complemented with surgery or different ablative techniques.

Vogl *et al.* evaluated a treatment protocol with repeated TACE before laser-induced thermotherapy (LITT) in patients with unresectable liver metastases that are too large for LITT alone. A total of 162 patients who had unresectable liver metastases, with the largest lesion being 80 mm in diameter, and no more than four lesions were treated with TACE. In total, 50.6% of cases responded to TACE, with a mean reduction in tumor size of 35%, and were treated with LITT. Median survival of patients who responded to this combined treatment was 26.2 months; in patients treated with only TACE, median survival was 12.8 months. The authors showed that repeated TACE can reduce the size of liver metastases with a diameter larger than 50 mm so that safe ablation of the lesions is possible They concluded that combined with an ablation procedure such as LITT, TACE allows an increase in local tumor control and survival [55].

Table 2 outlines key studies using TACE in the treatment of unresectable colorectal liver metastases.

Chemoembolization with drug-eluting beads

■ Developments & administration

A new variation of TACE is DEB-TACE, a relatively new mechanism of enhancing the delivery of anticancer agents to the site of the tumor. It involves the loading of the chemotherapeutic agent in drug-eluting beads, which allows for a slow and controlled release of the chemotherapy. The unique properties of drug-eluting beads, once injected near the tumor, are a slow and controlled release of the drug, which results in anti-tumoral effects. Significant reductions in peak plasma concentrations have been observed when compared with conventional chemoembolization [56], which may enable patients to better tolerate the cytotoxic

Table 2. Key prospective and retrospective studies for transcatheter arterial chemoembolization in metastatic colorectal cancer.

Study (year)	Analysis	Regimen	Patients (n)	Ref.
TACE as salvage therapy in chemorefractory mCRC				
Tellez *et al.* (1998)	Prospective	TACE (cisplatin, doxorubicin + mitomycin C)	30	[47]
Bavisotto *et al.* (1999)	Prospective	Alternating TACE (cisplatin) and PCI-5FU	27	[48]
Geschwind *et al.* (2006)	Prospective	TACE (cisplatin, doxorubicin + mitomycin C)	21	[51]
Albert *et al.* (2011)	Retrospective	TACE (cisplatin, doxorubicin + mitomycin C)	121	[52]
Nishiofuku *et al.* (2013)	Prospective	TACE (cisplatin)	24	[53]
Vogl *et al.* (2009)	Prospective	TACE (mitomycin C alone vs mitomycin C + gemcitabine vs mitomycin C + irinotecan)	243 vs 153 vs 67	[54]
Neoadjuvant TACE in mCRC				
Vogl *et al.* (2003)	Prospective	TACE (mitomycin C)	162	[55]

5FU: 5-fluorouracil; mCRC: Metastatic colorectal cancer; PCI: Protracted continuous infusion; TACE: Transarterial chemoembolization.

agents used. Due to sustained release, greater amounts of the chemotherapeutic agent are sequestrated by the tumor resulting in a more pronounced tumor response.

There are two types of beads currently available for drug loading: DC Beads (Biocompatibles, Surrey, UK) and QuadraSphere (Biosphere Medical Inc., MA, USA) [40]. DC Beads have CE mark approval for TACE of mCRC and can be loaded with doxorubicin or irinotecan for drug delivery during TACE. QuadraSphere can be loaded with doxorubicin or cisplatin. These beads have CE mark approval for TACE of HCC in conjunction with doxorubicin [40].

Similar to conventional TACE, DEB-TACE is considered as a palliative option for patients with unresectable HCC who have preserved performance status and liver function. DEB-TACE may also be used for the palliation of unresectable neuroendocrine liver metastases and unresectable metastases from CRC. The procedure has been used successfully as an adjunctive therapy to liver resection or as a bridge to liver transplantation, and before or after radiofrequency ablation [57–59]. The treatment guidelines of the NCCN version 3.2013 advise that drug-eluting beads irinotecan (DEBIRI) should be considered selectively and only at institutions with experience [32]. No category recommendations have been made.

We basically agree with the above, however, the findings of recent studies and data from Phase II/III trials support the use of DEBIRI in mCRC; it is feasible and safe with an acceptable tumor response. DEBIRI may be the treatment to consider in the future in combination with systemic chemotherapy at an early line of therapy.

Current clinical evidence

■ DEB-TACE combined with first-line chemotherapy

Martin *et al.* conducted a Phase I trial with irinotecan drug-eluting beads plus concomitant systemic 5FU and oxaliplatin (modified FOLFOX) in ten chemonaive patients with unresectable liver metastases from CRC. In total, 50% of the patients had extrahepatic disease and the extent of overall tumor burden in the liver was 100% in 50% of patients, 95% in 20% of patients and 80% in 30% of patients. The initial 9- and 12-month response rates have been 100% (two CR and eight PR), and 40% of patients were successfully downstaged to resection and/or ablation with a median OS of 15.2 months. Adverse events were minimal with no dose-limiting toxicities [60].

■ DEB-TACE as salvage therapy in chemorefractory mCRC

Martin *et al.* reported findings of a single-arm study of 55 mCRC patients receiving TACE with DEBIRI. All patients had failed oxaliplatin- and irinotecan-based systemic chemotherapy, and biological agents. In total, 31% of patients had synchronous hepatic metastases with 60% of patients having three or more liver tumors. Liver involvement was >25% in 64% of patients. The study met its primary end points 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 PFS of 11 months. The authors concluded that the ability to deliver a large dose of hepatic-specific cytotoxic agents to the liver can potentially lead to improvements in response rates and PFS [61].

Aliberti *et al.* recently reported on a Phase II study of TACE with DEBIRI in 82 patients with unresectable mCRC liver metastases who had failed previous chemotherapy. The median liver substitution was 33% (range: 25–50) and all patients were in good physical condition with an ECOG of 0 in 49% of patients, 1 in 37% and 2 in 15%. All patients had previously undergone at least two lines of systemic chemotherapy and had either developed progressive disease or had not responded to chemotherapy. Responses were 78% at 3 months with a median duration of response of 6 months. The median OS was 25 months with PFS at 8 months. The authors concluded that TACE with DEBIRI could be proposed as palliative therapy for unresectable and chemotherapy-resistant liver metastases from CRC [62].

The same group conducted a Phase III prospective randomized controlled trial, reported by Fiorentini *et al.*, comparing DEBIRI (36 patients) with systemic FOLFIRI (38 patients) in mCRC. All patients had CRC with unresectable liver metastases occupying less than 50% of the liver and no evidence of extrahepatic disease. All patients had received at least two or three lines of chemotherapy and the percentage of liver involvement was ≤25% in 52 cases and ≤50% in 22 cases. The study met its primary and secondary end points by demonstrating that the median OS (primary end point) is significantly longer for DEBIRI (22 months) versus 15 months for FOLFIRI. PFS was also significantly longer for DEBIRI (7 months) versus 4 months for FOLFIRI. Extrahepatic progression had occurred in all patients by the end of the study (at a median time of 13 months for DEBIRI vs 9 months for FOLFIRI), and the quality of life was better in the DEBIRI group, with an acceptable toxicity profile. The authors concluded that this study was the first to provide evidence that an infusion of embolic beads preloaded with irinotecan provides superior survival with better physical functionality when compared with the same chemotherapy administered systemically [63].

Table 3 outlines key studies using DEB-TACE in the treatment of unresectable colorectal liver metastases.

Comparison of transcatheter therapies

There are currently no randomized studies comparing the safety and efficacy of radioembolization to TACE. The first randomized trial to prospectively compare the efficacy of radioembolization to TACE with doxorubicin drug-eluting beads in unresectable HCC is currently underway [64].

The only existing trial to compare salvage therapy for liver metastases from CRC between radioembolization versus TACE was reported by Hong *et al.* in 2009. Median survival times were 6.9 months for patients treated with radioembolization versus 7.7 months for patients receiving TACE (p = 0.27).

The 1-, 2- and 5-year survival rates were 34, 18 and 0%, respectively, for radioembolization, compared with 43, 10 and 0%, respectively, for TACE. One major complication (2.7%) occurred in the TACE group, and no major complications were observed in the radioembolization group [65].

All other trials, comparing either TACE with DEB-TACE, or radioembolization with TACE have been performed in patients with HCC. The PRECISION V trial (a prospective, randomized controlled study in 212 patients with HCC) compared TACE versus TACE with doxorubicin drug-eluting beads. Although no significant survival benefit was detected, TACE with doxorubicin-loaded beads demonstrated a higher CR rate, ORR and disease control compared with conventional TACE (27 vs 22%, 52 vs 44% and 63 vs 52%, respectively). Also, in a subset analysis, DEB-TACE was better tolerated by more advanced patients compared with TACE [66].

A retrospective analysis of DEB-TACE versus TACE in patients with unresectable HCC found a survival advantage and better safety profile of TACE with doxorubicin drug-eluting beads compared with conventional TACE [67].

Salem *et al.* performed a comparative effectiveness analysis of radioembolization versus

Table 3. Key prospective studies for transarterial chemoembolization with drug-eluting beads in metastatic colorectal cancer.

Study (year)	Analysis	Regimen	Patients (n)	Ref.
DEB-TACE combined with first-line chemotherapy				
Martin *et al.* (2012)	Prospective	DEB-TACE (irinotecan) plus modified FOLFOX	10	[60]
DEB-TACE as salvage therapy in chemorefractory mCRC				
Martin *et al.* (2010)	Prospective	DEB-TACE (irinotecan)	55	[61]
Aliberti *et al.* (2011)	Prospective	DEB-TACE (irinotecan)	82	[62]
Fiorentini *et al.* (2012)	Prospective	DEB-TACE (irinotecan) vs FOLFIRI	36 vs 38	[63]

DEB-TACE: Transarterial chemoembolization with drug-eluting beads; FOLFIRI: Irinotecan, 5-fluorouracil and leucovorin; FOLFOX: 5-fluorouracil, oxaliplatin and leucovorin; mCRC: Metastatic colorectal cancer.

TACE in 245 patients with HCC. There was a trend that patients treated with radioembolization had a higher response rate than with TACE (49 vs 36%, respectively). Adverse events, clinical toxicities and TTP (13.3 vs 8.4 months, respectively) were improved with radioembolization compared with TACE. Median OS was not statistically different (20.5 vs 17.4 months, respectively) [68].

Lance *et al.* performed a comparative analysis of the safety and efficacy of TACE and radioembolization in 73 patients with unresectable HCC. There was no significant difference in survival between the radioembolization and TACE cohorts (8 vs 10.3 months). However, patients treated by TACE had significantly higher rates of hospitalization as a result of postembolization syndrome [69].

Discussion

All liver-directed therapies discussed in this review have been proven to be safe and effective in the salvage treatment of chemorefractory liver metastases from CRC. Commonly, both radioembolization and TACE/DEB-TACE are almost exclusively used in this group of patients.

The data reported in prospective and retrospective studies of radioembolization as salvage therapy (either with or without chemotherapy) appear to demonstrate consistent survival benefits and delay of disease progression [21,36–39]. Some studies have also reported the sufficient downsizing of tumors in patients with previously unresectable, chemorefractory disease to enable potentially curative liver resection [21,36].

To date, there are no randomized controlled trials comparing TACE with no treatment to support its use for the treatment of colorectal liver metastases. However, several studies performed in the USA suggest that TACE is associated with improved survival in patients with chemorefractory mCRC without significant toxicity [47–48]. The largest prospective nonrandomized study by Vogl *et al.* showed that median survival time for patients with mCRC was 38 months from the primary diagnosis of liver metastases and 14 months from the beginning of chemoembolization therapy [54]. These results are in comparison to 7–8 months survival for untreated patients [55].

Combined with systemic chemotherapy or targeted systemic treatments, transcatheter therapies are likely to improve survival and prolong disease control in patients with metastatic colorectal disease [15–17,36,51]. For the first-line treatment of patients with or without extrahepatic metastases, radioembolization has shown to augment the treatment response of systemic chemotherapy in mCRC [15–17]. PFS, OS and response rates compare favorably with Phase II/III data on modern chemotherapy regimens (with or without biologics) [2,70–72]. As radioembolization is increasingly used earlier in the treatment paradigm, data of larger randomized controlled trials will be important to investigate whether its use in combination with chemotherapy can offer patient outcome advantages that are superior to chemotherapy alone. A number of large randomized controlled trials (including SIRFLOX, FOXFIRE and EPOCH) are still ongoing, investigating the role of radioembolization in combination with chemotherapy for the treatment of mCRC in the first- and second-line setting [33–35]. The increased response rate with radioembolization plus first- or second-line chemotherapy support the early use of this treatment to augment the regional response of chemotherapy in the liver and increase the number of patients who can be surgically resected [15–17].

Studies that have investigated radioembolization in combination with second- or third-line chemotherapy have reported ORRs in 30–48% of patients [18,20]. This compares favorably with modern chemotherapy in similar settings.

Despite the lack of randomized controlled trials comparing radioembolization with TACE, a comparative effectiveness study demonstrated that radioembolization was associated with reduced toxicity and longer TTP when compared with conventional TACE [68]. A prospective randomized study did not demonstrate a survival benefit of TACE with doxorubicin drug-eluting beads compared with conventional TACE, however, DEB-TACE was better tolerated by more advanced HCC patients [66]. Another retrospective analysis of DEB-TACE versus TACE in patients with unresectable HCC found a survival advantage and better safety profile of TACE with doxorubicin drug-eluting beads compared with conventional TACE [67].

Phase II/III data on TACE with DEBIRI in patients with chemorefractoy liver metastases from CRC achieved response rates of 78%, with median survival times of 22–25 months and PFS of 7–8 months [62]. These results are encouraging and indicate that DEBIRI could be proposed as a palliative therapy for unresectable and chemotherapy-resistant liver metastases from

CRC [62,63]. The Phase III trial also provided evidence that the infusion of beads with irinotecan provides superior survival with better physical functionality when compared with the same chemotherapy administered systemically [63].

Our recommendation for patient selection criteria for radioembolization are inoperable colorectal liver metastases in conjunction with or without chemotherapy in the salvage setting. For patients with unresectable liver-only or liver-dominant disease who have failed standard chemotherapy or where chemotherapy is contraindicated, radioembolization has a particular application. Also, quality of life issues play an important role in the consideration of suitability for radioembolization, with older or frail patients and patients with intolerable side effects to chemotherapy still being able to undergo this therapy. Radioembolization can also be performed in patients who have previously received local-regional therapies, such as radiofrequency ablation, TACE, DEB-TACE or previous surgery. Since there is minimal alteration in vascularity and minimal-to-moderate embolic phenomena with radioembolization, this treatment should also be well tolerated in patients with portal vein thrombosis.

Our suggested exclusion criteria for radioembolization are limited hepatic reserve with clinical and pathological evidence of liver failure, a pretreatment 99m technetium-labeled macroaggregated albumin lung shunt study demonstrating the potential for >30 Gy exposure to the lungs, and a pretreatment hepatic angiogram demonstrating the potential for deposition of microspheres in the GI tract or other organs that cannot be corrected by angiographic embolization.

Conclusion & future perspective

At present and while we are awaiting the completion of larger randomized trials such as SIRFLOX, FOXFIRE and EPOCH, we have level 2–3 evidence to prove that radioembolization is effective in combination with first to nth line chemotherapy, as well as in the salvage situation.

For TACE, the presence of portal vein thrombosis without cavernous transformation and hepatopetal flow is a well-accepted relative contraindication. In 1998, Tellez reported his results concluding that chemoembolization is a feasible treatment for patients with mCRC of the liver who have experienced failure of systemic therapies [47]. However, randomized studies are lacking and the impact on survival is currently unknown.

In the use of DEB-TACE, the unique properties of the beads allow for fixed dosing and the ability to release the chemotherapeutic agent in a sustained and controlled manner. Taylor *et al.* reported that significant reductions in peak plasma concentrations have been observed when compared with conventional chemoembolization [56]. Due to sustained release, greater amounts of the chemotherapeutic agent are sequestrated by the tumor resulting in a more pronounced tumor response. Based on the results of Phase II/III studies and a multi-institutional prospective trial [61–63], it can be concluded that the ability to deliver large doses of hepatic-specific cytotoxic agents to the liver can potentially lead to improvements in response rates and PFS. If response rates can be achieved early – that is, within the first 3–6 months following treatment – through appropriate patient selection it could lead to more durable response rates. The combination of DEBIRI with systemic chemotherapy before chemoresistance develops may be the treatment combination to consider in the future.

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