# Transarterial Treatment of Colorectal Cancer Liver Metastases with Irinotecan-Loaded Drug-Eluting Beads: Technical Recommendations

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## ABSTRACT

Transcatheter hepatic arterial administration of irinotecan-loaded drug-eluting beads (DEBIRI) is used to treat liver-only or liver-dominant metastatic disease from colorectal cancer (CRC). Eligibility for DEBIRI should be established in each individual patient by a multidisciplinary team based on comprehensive clinical, imaging, and laboratory assessment. Standardization of DEBIRI technique and protocols would be expected to lead to improved efficacy and safety. The present article provides a set of technical recommendations for the use of DEBIRI in the treatment of hepatic CRC metastases.

## ABBREVIATIONS

CRC = colorectal cancer, DEBIRI = irinotecan-loaded drug-eluting bead

Colorectal cancer (CRC) is the third most common malignancy in men and the second in women, affecting more than 1.2 million people per year worldwide (1). The development of metastases is the main cause of death in patients with CRC. Surgical resection is the first-line treatment for hepatic CRC metastases (2,3). Unfortunately, despite the progress of modern surgical techniques, radical resection is possible only in 10%–25% of patients with CRC metastases confined to the liver (4). Several interventional locoregional treatments, including—among others—transcatheter hepatic arterial administration of drug-eluting beads or yttrium-90 ($^{90}$Y) radioactive microspheres, have been used in patients with unresectable liver-only or liver-dominant metastatic disease (5,6).

In particular, studies have suggested that transarterial injection of irinotecan-loaded drug-eluting beads (DEBIRI) may offer a novel approach to locoregional hepatic chemotherapy. Pharmacokinetic analyses have shown the bioavailability from DC Bead (Biocompatibles UK, Farnham, United Kingdom)–based delivery of irinotecan is double that of intravenous infusion, attributable to reduced drug clearance for the former (7). Experimental animal studies (8) have confirmed that DEBIRI induces lower early serum levels of irinotecan, a high and prolonged intratumoral level of irinotecan, and a greater rate of tumor necrosis compared with intraarterial or intravenous injection of irinotecan. Pilot clinical trials have suggested that DEBIRI treatment—administered in combination with systemic 5-fluorouracil

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and oxaliplatin in chemotherapy-naive patients or as a stand-alone regimen in patients with disease refractory to multiple lines of intravenous chemotherapy—may result in high rates of tumor response (9–11). In a randomized controlled study (12), DEBIRI showed a significant overall survival benefit with respect to a systemic regimen including irinotecan, 5-fluorouracil, and leucovorin in a series of 74 patients who had received at least two or three lines of chemotherapy. Further randomized controlled studies are required to understand the applicability of these findings to patients at different stages of disease treatment and underlying tumor biology and to confirm the correlation between high rates of tumor response and overall survival benefit.

Standardization of DEBIRI technique and protocols would be expected to lead to improved efficacy and safety. Most adverse events associated with DEBIRI can be predicted based on careful analysis of pretreatment- and treatment-related factors (13). With this in mind, a panel of physicians met to develop a set of technical recommendations for the use of DEBIRI in the treatment of hepatic CRC metastases. The document refers to the use of the embolic microsphere DC Bead (Biocompatibles UK), which has been the most extensively described for irinotecan delivery (14). The recommendations may not be relevant to other drugs or devices, as it has been shown that bead type and drug nature have a significant influence on loading and elution characteristics (15).

## THE PANEL

The group of physicians, all of whom had considerable experience in the field, included one surgical oncologist and eight interventional radiologists, practicing in different geographical regions (three in North America, one in South America, four in Europe, and one in Australia). The recommendations were collaboratively generated during a meeting held in April 2012.

## TECHNICAL RECOMMENDATIONS

### Patient Selection

The proposed algorithm for the clinical management of patients with liver metastases from CRC is shown in the Figure. Patients who are not candidates for potentially curative treatment may be considered for locoregional therapy with DEBIRI or $^{90}$Y radioembolization if they have liver-only or liver-dominant metastatic disease and the level of hepatic parenchymal involvement does not exceed 60%. Liver-dominant metastatic disease is defined as 80% or more of the overall total body metastatic tumor burden located in the liver. Locoregional therapy can also be used to downstage disease in patients with initially unresectable liver metastases or in combination with systemic regimens (14,16,17).

Candidates for DEBIRI treatment must have no contraindications for transcatheter procedures or irinotecan administration as assessed via a careful evaluation of their general condition, organ function, and laboratory values. Patients should generally have a life expectancy of more than 3 months and an Eastern Cooperative Oncology Group performance status score lower than 2. There is no formal agreement on what is considered sufficient organ function, particular adequate liver function. In a multiinstitutional registry, a bilirubin level higher than 2 mg/dL with more than 50% liver involvement was an independent predictor of ad-

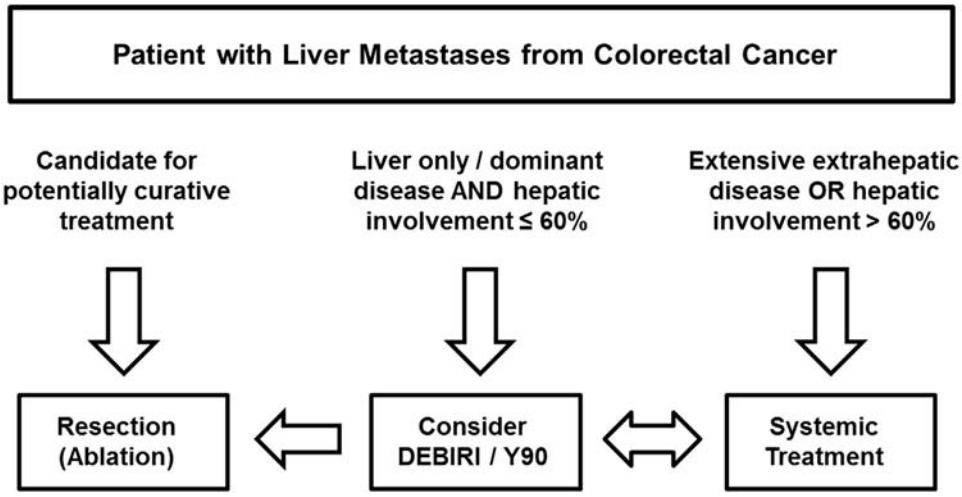


**Figure.** Proposed algorithm for the clinical management of patients with hepatic CRC metastases. Patients who are candidates for potentially curative treatment undergo surgical resection; ablation can be used in combination with resection or in patients who are rejected for surgery. Patients who are not candidates for potentially curative treatment may be considered for locoregional therapy with DEBIRI or $^{90}$Y radioembolization if they have liver-only or liver-dominant metastatic disease and the level of hepatic parenchymal involvement does not exceed 60%. Liver-dominant metastatic disease is defined as 80% or more of the overall total body metastatic tumor burden located in the liver. Locoregional therapy can be used to downstage disease in patients with initially unresectable liver metastases or in combination with systemic regimens.

verse events and significantly greater hospital length of stay (13). Eligibility for DEBIRI treatment should ultimately be established in each individual patient by a multidisciplinary team based on comprehensive clinical, imaging, and laboratory assessment.

## Periprocedural Medication

Periprocedural medication is extremely important to reduce incidence and severity of adverse events associated with DEBIRI injection. Abdominal pain is the most frequent side effect. Several protocols have been used to achieve pain control, including intravenous administration of analgesic agents and intraarterial injection of lidocaine (see Injection). The use of bilateral paravertebral block has also been proposed as an effective mean for pain control (18). Periprocedural medication should be administered at the physician's discretion according to standard hospital protocols.

## Choice of DC Bead Size and Loading Dose

Use of DC Bead (100–300 μm) or DC Bead M1 (70–150 μm) is recommended for a standard procedure. Each vial of DC Bead contains 2 mL of beads and should be loaded with 100 mg irinotecan hydrochloride trihydrate (loading dose, 50 mg/mL of beads). DC Bead is suitable for loading irinotecan hydrochloride trihydrate (available as a concentrate that contains 20 mL/mL) only. In the case of significant arterioportal or hepatic venous shunting, embolization of the shunt with large-size embolic material is recommended before DEBIRI administration. Angiographic confirmation that the shunt is no longer present must be obtained before DEBIRI injection can be performed, and a larger bead size may be preferred.

## Planned Dose of Irinotecan

Defining the amount of liver disease is integral to determining the treatment plan (13). The following protocols are recommended as standard approaches:

***Unilobar Disease.*** In the case of unilobar disease, two lobar treatments should be planned, each with 100 mg irinotecan loaded in one DC Bead vial, separated by 3–4 weeks. Obtaining confirmation that the liver enzymes have returned to baseline levels before performing the second treatment is recommended.

***Bilobar Disease.*** For bilobar disease, four lobar treatments should be planned, each with 100 mg irinotecan loaded in one DC Bead vial, every 2 weeks (ie, first 100 mg to the right lobe, followed by 100 mg to the left 2 weeks later, followed by a further 100 mg to the right after another 2 weeks, then 100 mg to the left after another 2 weeks). Obtaining confirmation that the liver enzymes have returned to baseline levels before performing each subsequent treatment is recommended. The use of a whole-liver treatment in a single session, with separate right and left lobar injections and administration of an overall dose as high as 200 mg irinotecan loaded in two DC Bead vials, has been reported in the setting of a clinical trial in carefully selected patients (12). In a multiinstitutional registry (13), administration of more than 100 mg irinotecan in a single session was shown to be an independent predictor of adverse events and significantly greater hospital length of stay.

## DC Bead Dilution

For dilution, it is recommended to remove excess—ie, supernatant—irinotecan solution from the vial of irinotecan-loaded DC Bead before mixing with the contrast medium/water mixture. At least 5–10 mL of nonionic contrast medium/water mixture should be used per 1 mL of beads (ie, 10–20 mL of contrast medium/water mixture are required to dilute one vial of DC Bead). Loaded DC Bead should be mixed only with nonionic contrast media. Contrast agents containing salts may cause some of the irinotecan to be pulled from DC Bead before it is delivered to the liver. If using isoosmolar contrast media containing salts, the total volume per vial should be reduced to less than 5 mL. The product should be used soon after mixing, and a good suspension of beads in the contrast medium/water mixture should be ensured before delivery.

## Catheter Positioning

A lobar approach should be used whenever possible. The oncologic rationale for lobar administration is linked with the reported 60% recurrence rate within 2 years after liver surgery with curative intent as a result of undetected micrometastatic disease and the histologic proof that undetected micrometastatic lesions within a lobar embolization zone can be treated with DEBIRI as effectively as lesions that are identified preoperatively and more selectively embolized (19,20). For the lobar approach, the catheter should be placed into the right or left hepatic artery, with the clinician paying attention to identifying the origin of the cystic artery as well as other arteries supplying flow to extrahepatic organs. If identified, these vessels must be embolized or avoided by placing the catheter tip well beyond the origin of these vessels. In addition, forward flow into the desired vessel must be maintained because inadvertent administration or reflux of beads into these extrahepatic vessels would be undesirable. The use of a microcatheter is recommended to prevent vasospasm during catheterization and help avoid reflux during injection because of better flow than after probing with a 5-F catheter. In patients with reduced liver function or reduced liver reserve as a result of earlier surgical resection (but without absolute contraindications to DEBIRI), a more conservative approach with more selective catheter placement and a segmental or regional treatment may be recommended.

### Injection

The injection must be very slow. An injection rate of approximately 1 mL of the bead/contrast medium suspension per minute is recommended. Injection of intra-arterial 1% lidocaine (4–10 mL split before and near the end of DEBIRI administration) has been shown to reduce adverse events and hospital length of stay (13). Care should be taken to avoid sedimentation of the beads in the syringe by rotating the syringes or using a three-way stopcock to gently suspend the beads in the solution.

### Embolization Endpoint

The goal of transcatheter treatment with DEBIRI is to deliver the planned dose of anticancer agent, not to occlude the vessel. In a multiinstitutional registry (13), achievement of complete stasis was an independent predictor of adverse events and significantly greater hospital length of stay.

It is important to maintain forward flow into the vessel throughout the procedure. If "near-stasis" is observed during the injection (ie, the contrast medium column does not clear within two to five heartbeats) before the full planned dose has been administered, the injection should be stopped at that time, regardless of the amount of beads that have been actually delivered to avoid reflux of embolic material. On the contrary, if the full planned dose can be administered without observing near-stasis during the injection, no additional embolic material of any kind should be injected following the delivery of DEBIRI.

### Posttreatment Imaging and Follow-up

Imaging assessment should be performed at least 4 weeks after the completion of the treatment plan described earlier to evaluate tumor response. Tumor swelling and internal necrosis may be responsible for an increase in overall tumor diameter at early follow-up scans, potentially leading to incorrect diagnoses of tumor progression. Unmasking of small tumor foci as a result of internal necrosis may also simulate the emergence of new tumor lesions and lead to incorrect classification of the case as progression. Assessment of tumor vascularity with the use of triple-phase contrast-enhanced computed tomography or dynamic contrast-enhanced magnetic resonance imaging is recommended. It is acknowledged that existing criteria reporting radiologic response may not accurately predict pathologic tumor response (21). More data are needed concerning the use of positron emission tomography after DEBIRI treatment. Changes in serum levels of carcinoembryonic antigen should be monitored.

Decisions on patient management should be reached in a multidisciplinary setting, taking into account whether any concomitant systemic therapy is being administered and the patient's ability to tolerate further DEBIRI treatments.

In case a complete response is achieved on imaging with regard to the hepatic metastatic tumor burden, no further DEBIRI treatment is indicated, and the patient should be closely monitored for recurrence according to hospital protocols for follow-up. In case of hepatic tumor recurrence, the patient can be considered for repeat DEBIRI treatment, provided that the eligibility criteria are still met.

In case viable metastatic disease is observed within the liver, the patient can be considered for repeat DEBIRI treatment, provided that the liver remains the sole or the dominant site of disease. Obtaining confirmation that the liver enzymes have returned to baseline before scheduling repeat DEBIRI treatment is recommended. If only a relatively small amount of viable metastatic disease remains in the liver ($< 20\%$ of initial hepatic metastatic tumor burden) and systemic therapy is being given, deferring further DEBIRI treatment and monitoring the patient with repeat imaging may be a valuable option.

## FINAL REMARKS

The technical recommendations reported here are aimed at ensuring a consistent use of DEBIRI in the treatment of hepatic CRC metastases. However, given the many patient- and tumor-related variables that play a role in the decision-making process, this document is intended as no more than a general guideline. We fully acknowledge that, given the complexity of the disease, individual patient and tumor characteristics may require a different approach with respect to the one recommended here. For no reason should a clinician adhere to the present technical recommendations if, in his/her opinion, a different approach is required in the individual patient to be treated. Finally, it is imperative that physicians are fully aware of the spectrum of potential adverse events associated with DEBIRI to prevent complications or manage them properly.

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