Transarterial Chemoembolization with Irinotecan Beads in the Treatment of Colorectal Liver Metastases: Systematic Review

Arthur J. Richardson, MBBS, FRACS, Jerome M. Laurence, MBChB, MRCS, PhD, FRACS, and Vincent W.T. Lam, MBBS, MS, FRACS

ABSTRACT

Purpose: For patients with unresectable colorectal liver metastasis (CRLM), transarterial embolization with the use of drug-eluting beads with irinotecan (DEBIRI) represents a novel alternative to systemic chemotherapy or local treatments alone. The present systematic review evaluates available data on the efficacy and safety of DEBIRI embolization.

Materials and Methods: A comprehensive search of medical literature identified studies describing the use of DEBIRI in the treatment of CRLM. Data describing adverse events, pharmacokinetics, tumor response, and overall survival were collected.

Results: Five observational studies and one randomized controlled trial (RCT) were reviewed. A total of 235 patients were included in the descriptive analysis of observational studies. Postembolization syndrome was the most common adverse event. Peak plasma levels of irinotecan were observed at 1–2 hours after administration. Wide variations in tumor response were observed. The median survival time ranged from 15.2 months to 25 months. In the RCT, treatment with DEBIRI was superior to systemic chemotherapy with 5-fluorouracil/leucovorin/irinotecan in terms of quality of life and progression-free survival.

Conclusions: For patients with unresectable CRLM, particularly after failure to respond to first-line regimens, DEBIRI represents a novel alternative to systemic chemotherapy alone, transarterial embolization with other agents, or other local treatments (eg, microwave or radiofrequency ablation). In these reports, DEBIRI was safe and effective in the treatment of unresectable CRLM. Further RCTs comparing DEBIRI with alternative management strategies are required to define the optimal role for this treatment.

ABBREVIATIONS

CR = complete response, CRLM = colorectal liver metastasis, DEB = drug-eluting bead, DEBIRI = drug-eluting beads with irinotecan, 5-FU = 5-fluorouracil, FOLFIRI = 5-fluorouracil/leucovorin/irinotecan, FOLFOX = 5-fluorouracil/leucovorin/oxaliplatin, OS = overall survival, PFS = progression-free survival, PR = partial response, QoL = quality of life, RCT = randomized controlled trial, SD = standard deviation

Colorectal cancer is the third most common cancer worldwide (1). Synchronous colorectal liver metastases (CRLMs) will be present at the time of diagnosis in 15%–20% of patients, and another 50% of patients will develop metachronous CRLM (2). Nevertheless, although the liver is the sole site of metastatic disease in as many as 40% of patients, CRLM is resectable in fewer than 20% of cases (3). Until the past decade, 5-fluorouracil (5-FU) and leucovorin were the standard chemotherapy for unresectable CRLMs, and this doubled median survival to approximately 12 months (4). The use of irinotecan and oxaliplatin have improved median survival times to approximately 20 months (5), with a small additional benefit from the addition of biologic agents such as bevacizumab and cetuximab (6,7). Nevertheless, many patients are unable to undergo surgery and have to be treated with other techniques.

Transarterial chemoembolization, combines injection of drug and embolic material and has mostly been used in hypervascular tumors such as hepatocellular carcinoma and neuroendocrine liver metastases (8,9). The use
of drug-eluting beads (DEBs), which can be loaded with irinotecan, allows drug release after the DEBs are trapped in the tumoral circulation, and was first reported for the treatment of CRLM in 2006 (10). Although DEB with irinotecan (DEBIRI) therapy is not currently approved by the United States Food and Drug Administration, there is an increasing body of data from clinical trials. In the present systematic review, we aim to evaluate the available data on the efficacy and safety of DEBIRI in the treatment of CRLM.

MATERIALS AND METHODS

Literature Search Strategy

A systematic review was conducted by two authors (A.J.R. and V.L.). The following electronic databases were searched: Medline (1950–2012), Embase (1974–2012), the Cochrane controlled trials register, and the science citation index. Combinations of Medical Subject Headings as well as key words including the following were searched: “liver metastases,” “colorectal cancer,” “chemoembolization,” “drug-eluting beads,” “DEBIRI,” and “irinotecan.” The literature search was not restricted by language but was restricted to human trials. The last search was done September 25, 2012, and a manual search of all relevant articles was performed.

Study Selection

The study evaluation was performed by two reviewers (A.J.R. and V.L.). Reviews, case reports, conference abstracts, and nonhuman studies were excluded. Abstracts of the remaining studies were retrieved and then reviewed for relevance. The full texts of previously selected articles were thoroughly reviewed. Studies from which a decision could not be made based on the abstract were also reviewed. When multiple publications were identified from the same or overlapping patient series, only the most complete or recent publication was included.

Data Extraction and Critical Appraisal

Two reviewers (A.J.R. and V.L.) independently appraised each article to extract a predefined dataset that included the dates during which the treatment was conducted, the details of the metastatic colorectal cancer (including size, location in the liver, and extrahepatic disease), other treatment (including chemotherapy and surgery), nature of DEBIRI (DEBs used, preparation, dose and number of sessions), adverse events, treatment response, survival, and pharmacokinetics. The extracted data were then cross-checked between the two authors to rule out discrepancy. In the event of disagreement, a third reviewer (J.L.) extracted the data. Because of the lack of a control group in the majority of the included reports and the heterogeneity present among the selected studies, a metaanalysis could not be carried out. Qualitative systematic review was performed without comparator group by full tabulation of the results.

RESULTS

The search strategy is depicted in the Figure. The publication by Morise et al (11) had only four patients with incomplete follow-up data and was therefore excluded from analysis. After exclusion of dual publications (10,12–17), there were six studies included in the review (Table 1) (14,15,17–20). The inclusion and exclusion

![Figure. Flowchart showing the search strategy used to identify studies. (Available in color online at www.jvir.org.)]
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>No. of Pts.</th>
<th>Age (y)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Previous Systemic Chemotherapy</th>
<th>Median OS</th>
<th>Tumor Response at 6 mo</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eichler et al (20), 2012</td>
<td>11</td>
<td>64 (45–85)*</td>
<td>1–8 unresectable metastases confined to liver; ECOG PS ≤ 1, life expectancy &gt; 6 mo, adequate liver/renal/hematologic function</td>
<td>Extrahepatic metastases; tumor involving &gt; 30% of liver volume; contraindications to irinotecan; active bacterial, viral, or fungal infection; concurrent malignancy; malignancy in past 5 y</td>
<td>In 5 pts.</td>
<td>NS</td>
<td>Intrahepatic progression at 6 mo (n = 7), SD (n = 2), PR (n = 2)</td>
<td>Total n = 41; pain (63%), nausea (22%), vomiting (19.5%); 61% mild, 31% moderate</td>
</tr>
<tr>
<td>Martin et al (18), 2012</td>
<td>10</td>
<td>63 (48–84)*</td>
<td>≥ 1 measurable liver metastasis &gt; 1 cm; liver-dominant disease (≥ 80% tumor body burden confined to liver), &lt; 60% liver replacement by tumor, patent main PV, ECOG PS ≤ 2, life expectancy &gt; 3 mo</td>
<td>Eligible for curative treatment (resection or RF ablation)</td>
<td>None for metastatic disease</td>
<td>15.2 mo (range, 6.5–45.5 mo); 4 pts. underwent liver resection</td>
<td>CR (n = 1); DOD (n = 1), not assessed (n = 1)</td>
<td>Total n = 99; 98 grade 1/2; hypertension (80%), abdominal pain (40%), nausea (40 %); grade 3 (n = 1 admission with hypertension)</td>
</tr>
<tr>
<td>Vogl et al (19), 2012</td>
<td>77 (irinotecan and mitomycin)</td>
<td>61 (36–78)*</td>
<td>Unresectable liver metastasis, surgical contraindications/refusal; adverse reaction/lack of response to systemic chemotherapy</td>
<td>Extrahepatic metastases, tumor load &gt; 70% of liver, poor general condition (Karnofsky PS &gt; 70%), poor liver/renal function, ascites, partial/complete PV thrombosis, respiratory/cardiovascular failure</td>
<td>All patients (oxaliplatin)</td>
<td>22.5 mo (range, 7–70 mo), some pts. with residual lesions treated with laser thermotherapy</td>
<td>NS</td>
<td>All grade 1/2</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>No. of Pts.</th>
<th>Age (y)</th>
<th>Inclusion Criteria</th>
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<th>Previous Systemic Chemotherapy</th>
<th>Median OS</th>
<th>Tumor Response at 6 mo</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al (17), 2011</td>
<td>55</td>
<td>60 (34–82)</td>
<td>Confirmed diagnosis of liver-dominant metastatic CRC, defined previous chemotherapy and reasons for abandoning it</td>
<td>NS</td>
<td>FOLFOX and bevacizumab alone (n = 17); FOLFOX and bevacizumab, FOLFIRI, cetuximab (n = 14); ≥ 3 regimens (n = 14)</td>
<td>19 mo</td>
<td>CR (n = 7); PR (n = 19); PD (n = 8); DOD (n = 5)</td>
<td>Total n = 28; 21 grade 1/2; grade ≥ 3 (n = 7; liver dysfunction, n = 3; cholecystitis, anorexia, myocardial infarction causing death, n = 1 each)</td>
</tr>
<tr>
<td>Aliberti et al (14), 2011</td>
<td>82</td>
<td>61.8 (46–82)</td>
<td>Histologically proven liver metastasis; primary resected or unresectable liver disease; liver-dominant tumor (25%–50% of liver replaced)</td>
<td>ECOG PS &lt; 2, nutritional impairment, poor liver/renal function, ascites, PV thrombosis</td>
<td>≥ 2 lines of systemic chemotherapy with PD/no response</td>
<td>25 mo (range, 6–34 mo); 2 pts. treated with liver resection free of disease at 14 and 18 mo</td>
<td>NS</td>
<td>Grade 3 pain (n = 20); grade 1/2 events NS</td>
</tr>
<tr>
<td>Fiorentini et al (15), 2012</td>
<td>36</td>
<td>64 (44–77)</td>
<td>Histologically proven unresectable liver metastasis occupying &lt; 50% of liver parenchyma, no extrahepatic disease</td>
<td>Previous liver RT, embolization, ascites, poor liver/renal function</td>
<td>≥ 2/3 lines of systemic chemotherapy</td>
<td>NS</td>
<td>NS</td>
<td>Total n = 77 grade 2/3: pain (30%), vomiting (25%), asthenia (20%)</td>
</tr>
</tbody>
</table>

CR = complete response, CRC = colorectal cancer, DOD = death of disease, ECOG = Eastern Cooperative Oncology Group, FOLFIRI = 5-fluorouracil/leucovorin/irinotecan, FOLFOX = 5-fluorouracil/leucovorin/oxaliplatin, NS = not specified, OS = overall survival, PD = progressive disease, PR = partial response, PS = performance status, PV = portal vein, RF = radiofrequency, RT = radiation therapy, SD = stable disease.

*Mean (range).
†Events coded per Medical Dictionary for Regulatory Activities terminology for reporting adverse events.
‡Median (range).
§Adverse events graded per Common Terminology Criteria for Adverse Events, version 3.
criteria for treatment, along with the use of previous systemic chemotherapy, are noted in Table 1. With the exception of one study (18), all patients had received one or more lines of systemic chemotherapy before being treated with DEBIRI. DEBIRI was administered as monotherapy in all but two studies, both by Martin et al (17,18). There were five observational studies and one randomized trial (15). The latter was analyzed separately, leaving a total of 235 patients included in the descriptive analysis of observational studies. Technical aspects of DEBIRI (dosage of irinotecan, DEB preparation, and treatment schedule) are summarized in Table 2 (14,15,17–20). The technical aspects of embolization (initial angiography, selection of embolization target, and embolization endpoint) are summarized in Table 3 (14,15,17–20).

Adverse Events

Adverse events were reported in all studies (14,15,17–20). Common Terminology Criteria for Adverse Events, version 3, were used in all but one study (14,15,17–19). Eichler et al (20) used the Medical Dictionary for Regulatory Activities terminology for reporting of adverse events. The adverse events are summarized in Table 1. There was one death related to the procedure, which resulted from a myocardial infarction. Post-embolization syndrome, which involved abdominal pain, nausea, and vomiting, was the most common adverse event reported. This was reported as mild in the studies of Eichler et al (20) and Martin et al (17,18) and made up 40%–63% of adverse events. In the study of Aliberti et al (14), abdominal pain was reported as present within 6 hours of the procedure in 40% of patients and was reported as severe in 25% of patients. In the study by Vogl et al (19), it was stated that mild abdominal pain was the most common adverse event reported, but the percentage was not defined.

Hypertension was the second most common adverse event reported. It seems most likely that hypertension was related to pain (the most common complication), as it was transitory with a temporal coincidence during the post-procedural course. Its incidence was not reported in the paper by Vogl et al (19). In the paper by Aliberti et al (14), it was reported as not occurring in the first 24 hours after the procedure. Eichler et al (20) reported hypertension as making up less than 10% of adverse events, and Martin et al (17,18) reported hypertension as making up 4% of adverse events. Martin et al (17,18) reported that hypertension made up 80% of adverse events. One patient in this series required an overnight hospital stay for severe hypertension. There was one device-related infection reported, but no episodes of significant bleeding.

Pharmacokinetics

The pharmacokinetics of DEBIRI were evaluated in the two of the smaller studies (18,20). Eichler et al (20)
showed that the plasma half-life of irinotecan was 1.6–7.2 hours (mean, 4.6 h), with a half-life of 7.6–8.5 hours (mean, 12.4 h) for its metabolite SN-38. Martin et al (18) reported that the plasma levels of irinotecan and SN-38 had mostly cleared by 4 hours, with essentially undetectable levels at 24 hours. Both studies (18,20) reported that the peak plasma levels were seen at 1–2 hours after administration. Significantly, neither study reported any toxicity directly relatable to irinotecan administration.

**Tumor Response**

In four studies (14,17,19,20), the Response Evaluation Criteria In Solid Tumors (21) were used to evaluate the efficacy of treatment. Response rates at 6 months are summarized in Table 1. Eichler et al (20) reported that, 6 months following initial treatment, seven of the initial 11 patients (63%) had intrahepatic progression of disease. They described a partial response (PR) to treatment in two patients (18%), and stable disease was reported in two patients (18%). Vogl et al (19) reported that the mean diameter of the liver metastases before treatment was 3.49 cm (range, 1.3–7.3 cm; standard deviation [SD], 1.41), which decreased to 2.92 cm (range, 1–5 cm; SD, 1.41) after the final treatment. This represented a decrease of 16.3%, which was statistically significant (P < .001). Martin et al (17), in their group of 55 patients who had been heavily pretreated with systemic chemotherapy, reported a 3-month complete response (CR) in seven patients (12%) and a PR in 29 patients (53%). A 6-month CR was reported in seven patients (12%) and a PR in 21 patients (38%). At 12 months, a CR was seen in eight patients (15%) and a PR in 14 patients (25%). The authors made the point that, if a response was achieved at 6 months, it appeared to be durable to 12 months (17). Aliberti et al (14) reported that all 82 patients treated showed a significant (75%–100%) reduction of metastatic contrast enhancement at 1 month. A therapeutic response was noted in 78% of patients at 3 months. Additionally, they reported that 75 of 82 patients (90%) declared a general improvement in quality of life (QoL), which lasted 32 weeks (range, 3–39 wk) (14). In the latest study by Martin et al (18), four of 10 patients underwent liver resection, at which time pathologic response rates were reported as being greater than 95%. It is important to remember that this group of patients was also receiving 5-FU/leucovorin/oxaliplatin (FOLFOX). The authors reported overall response rates of 100% at 3 months, 80% at 6 months, 60% at 9 months, and 50% at 12 months (18).

**Overall Survival**

Median survival (Table 1) was estimated in four studies (14,17–19) and ranged from 15.2 months to 25 months (range, 6–70 mo). Eichler et al (20) calculated the probability of disease progression by using the Kaplan–Meier method. They reported a median time to progression from

**Table 1. Tumor Response**

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Selection of Embolization Technique</th>
<th>Initial Angiography Technique</th>
<th>Technical Aspects of Embolization Techniques in Published Studies (14,15,17–20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eichler et al (20), 2012</td>
<td>Lobar embryolization technique</td>
<td>Diagnostic angiogram obtained to evaluate HA supply and verify portal patency</td>
<td>Infusion of beads stopped if embolization endpoint (complete stasis of blood) was achieved before full dose delivery; no additional embolic agent to achieve endpoint</td>
</tr>
<tr>
<td>Martin et al (18), 2012</td>
<td>Lobar embryolization technique</td>
<td>Initial angiogram obtained through femoral/axillary artery puncture to identify origin of right/left HA</td>
<td>Segmental/subsegmental embolization technique; no patient underwent global chemoembolization</td>
</tr>
<tr>
<td>Vogl et al (19), 2012</td>
<td>Segmental subsegmental embolization technique</td>
<td>Introduction of selective catheter through femoral artery; vascular anatomy of HA determined</td>
<td>NS</td>
</tr>
<tr>
<td>Martin et al (17), 2011</td>
<td>Segmental subsegmental embolization technique</td>
<td>4.5-F pigtail catheter through celiac trunk; advanced beyond GDA</td>
<td>Infusion of beads stopped if embolization endpoint (complete stasis of blood) was achieved before full dose delivery; no additional embolic agent to achieve endpoint</td>
</tr>
<tr>
<td>Martin et al (18), 2012</td>
<td>Lobar/segmental embryolization lesion feeding arteries</td>
<td>4.5-F Cobra catheter placed in celiac trunk, advanced beyond GDA</td>
<td>Infusion of beads stopped if embolization endpoint (complete stasis of blood) was achieved before full dose delivery; no additional embolic agent to achieve endpoint</td>
</tr>
<tr>
<td>Fiorentini et al (15), 2012</td>
<td>Lobar/segmental embryolization lesion feeding arteries</td>
<td>4.5-F pigtail catheter through mesenteric arteries to check accessory right HA; 4.5-F Cobra catheter placed in celiac trunk, advanced beyond GDA</td>
<td>Infusion of beads stopped if embolization endpoint (complete stasis of blood) was achieved before full dose delivery; no additional embolic agent to achieve endpoint</td>
</tr>
</tbody>
</table>

HA = hepatic artery, GDA = gastroduodenal artery, NS = not specified.
the time of the first treatment of 154 days (95% confidence interval, 17–291 d). Additionally, Martin et al (17), in a group of 55 patients, reported a median progression-free survival (PFS) of 11 months, with 55% of patients being alive at 1 year. For those patients with liver-only disease, the PFS was 15 months, which equated to a 1-year overall survival (OS) rate of 75%. This was the same as the OS for the entire patient cohort, including patients with liver-only disease and those with extrahepatic disease.

Randomized Trial
In the randomized controlled trial (RCT) trial by Fiorentini et al (15), 74 patients were randomized to receive two cycles of DEBIRI treatment (n = 36) or eight cycles of 5-FU/leucovorin/irinotecan (FOLFIRI) systemic chemotherapy (n = 28). The patient groups were comparable in terms of demographics, disease extent, and previous treatment. All patients had histologically confirmed unresectable colorectal metastasis, confined to the liver and occupying less than 50% of its volume. They had all received at least two or three lines of systemic chemotherapy before DEBIRI treatment. The OS rates at 24 months and 30 months, respectively, were 56% and 34% for the DEBIRI group versus 32% and 9% for the FOLFIRI group (P = .031). Median survival and PFS were 22 and 7 months, respectively, in the DEBIRI group, versus 15 and 4 months in the FOLFIRI group (15).

Toxicity varied significantly between the two groups. Neutropenia was seen in 4% of patients in the DEBIRI group versus 44% in the FOLFIRI group (P < .0001), diarrhea occurred in 6% of the DEBIRI group versus 18% of the FOLFIRI group (P = .073), and mucositis occurred in 1% of the DEBIRI group versus 20% of the FOLFIRI group (P = .00002). The only toxicity more common in the DEBIRI group was pain (30% vs 0% in FOLFIRI group). The authors concluded that, in terms of OS, PFS, and QoL, treatment with DEBIRI was statistically superior to FOLFIRI (15).

DISCUSSION
Surgical resection of CRLM remains the most efficacious treatment, with 5-year survival rates ranging from 29% to 70% (22,23). However, surgical resection is possible in only approximately 25% of patients. Even in patients who have undergone resection, the recurrence rate can be as high as 75% (24). Therefore, there remains a need for palliative treatments and therapies that can downstage disease to the extent of resectability.

The results of the present systematic review suggest that DEBIRI treatment may be associated with a median survival time of 15–25 months. This is broadly equivalent to the outcomes achieved for unresectable CRLM with the use of best-practice systemic chemotherapy (5). Significantly, conventional first-line chemotherapy had failed in the majority of patients included in this review. However, there appeared to be an improvement in disease-free survival associated with DEBIRI. Based on Response Evaluation Criteria In Solid Tumors, the PR and CR rates varied from 36% to 78%. Moreover, it appeared that, in those patients who had a response at 6 months, this was a durable response to 12 months.

Chemoembolization with the use of modern angiographic techniques make it possible to selectively deliver the material to the tumor so there is minimal release of chemotherapy agents into surrounding tissues (25). Moreover, the procedure can be repeated and is associated with minimal morbidity. Two of the studies reviewed (18,20) showed that plasma levels of irinotecan and its active agent SN-38 were almost undetectable 24 hours after administration, despite these investigators having been able to deliver doses of irinotecan many times the systemic toxic dose.

Adverse events are uncommon with DEBIRI. The most common appears to be postembolization syndrome. Hypertension appears to be the second most common adverse event, but is self-limiting. In the present review, adverse events in the more serious category were rare, with only one death reported as a result of a myocardial infarction. In a review of 2,300 transarterial chemoembolization procedures for a variety of indications, Sakamoto et al (26) reported 102 complications (4.4%), of which 39 were related to catheter dissections or perforations.

There was only one comparative study included in the present review (15). Although patients were randomly allocated to treatment groups, there was no information regarding the methods of sequence generation, blinding (of participants or those conducting outcomes assessments), or allocation concealment. There was little information regarding methods used to ensure the quality of outcome data reporting or freedom from selective reporting of outcomes. Despite the fact that the study (15) included only a small number of participants, DEBIRI was found to be significantly superior to FOLFIRI in terms of OS, PFS, QoL, toxicity, and financial cost. However, because of deficiencies in the methodologic quality of the study, the conclusions must be interpreted with caution. Confirmation of these data in high-quality RCTs is required before widespread change of practice is undertaken.

The role of DEBIRI as a strategy for downstaging unresectable CRLM with a view toward resection is unclear. There is increasing evidence that patients whose disease is rendered resectable after chemotherapy may have a survival equivalent to those patients whose disease was initially resectable (27,28). A recent systematic review of conversion chemotherapy for CRLMs (29) concluded that an objective response was achieved in 64% of cases, and that 22.5% of patients underwent macroscopically curative resection. Bower et al (16) looked specifically at the effect of DEBIRI on surgical
downstaging and found that 11 of 55 patients (20%) were able to be treated with liver resection or ablation. With a median follow-up of 12 months, nine patients had recurrence. In this cohort (16), the median disease-free interval was 9 months (range, 6–18 mo), with 80% of recurrences being extrahepatic. The overall pathologic response rate was 90% (range, 30%–90%). In a separate series of 10 patients reported by Martin et al (4), disease subsequently became resectable. A greater than 95% pathologic response was seen in this group (18), with the added benefit that none of these patients developed significant steatohepatitis. On this basis, a reasonable approach for treatment with a view to downstaging of disease would be systemic chemotherapy with FOLFOX (with or without the addition of bevacizumab) combined with DEBIRI. Although the main concern with this approach would be hepatic toxicity, it is likely that this would be no greater than that of FOLFOX and bevacizumab alone.

QoL is an important issue for all patients with cancer, but particularly in those whose disease is not curable and who are undergoing palliative treatment. It does appear that DEBIRI is well tolerated and has few side effects. Fiorentini et al (15) found a significantly improved QoL for patients undergoing DEBIRI treatment versus those undergoing treatment with FOLFIRI. The difference in duration of improvement significantly favored DEBIRI. This group also addressed the issue of cost. They compared the cost of two treatments with DEBIRI (including interventional radiology) to that of commonly used systemic alternatives. Six months of treatment with FOLFOX and bevacizumab, 6 months of treatment with FOLFIRI, and 6 months of treatment with FOLFIRI and cetuximab cost 11.3, 4.5, and 10.9 times as much as DEBIRI, respectively.

Among the studies analyzed here, there was considerable variability in the efficacy and toxicity outcomes reported. This heterogeneity is likely a consequence not only of differences in the dose of irinotecan per treatment and the number of treatment sessions per patient, but also outcome assessments and quality of reporting. All but one study in this review was observational with no direct comparator group, and the RCT included (15) was of poor methodologic quality. Systematic investigation of the optimal treatment protocol in comparison with other available options will be an essential element of further studies of DEBIRI treatment.

Another emerging therapy for the treatment of unresectable liver metastases is the use of yttrium-90 (90Y)–loaded microspheres. These microspheres, made of resin or glass, are embolized via the hepatic artery and deliver localized high-dose radiation (30). This type of therapy does involve more planning—particularly with regard to radiation dose—and intervention than DEBIRI, and delivers brachytherapy rather than chemotherapy (31,32). There are a number of nonrandomized observational studies of 90Y with or without chemotherapy (33,34), which have reported a median OS of 10–29 months, not significantly different that the survival times reported with the use of systemic chemotherapy alone. We are aware of only one prospective trial of 90Y as salvage therapy for disease refractory to modern chemotherapy with oxaliplatin and irinotecan (35). In this small study, there was no significant difference in OS between the two groups, although there was some improvement in time to progression in the 90Y group (35). As there are no data comparing 90Y versus DEBIRI for unresectable CRLM, this question requires further research.

The present systematic review suggests that DEBIRI can provide a median survival equivalent to that associated with standard systemic chemotherapy, and may also be useful in downstaging unresectable CRLM to resectable status with minimal toxicity and acceptable cost. DEBIRI treatment merits further study in larger multicenter trials to define its optimal indications.

REFERENCES