Colorectal Hepatic Metastasis

The past, present, and future role of liver-directed therapy.

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Patients with colorectal liver metastases (CRLM) represent an underserved population who may benefit from liver-directed therapy. Although the classic paradigm of liver-directed therapies is to apply treatments with curative intent, the body of evidence has matured, suggesting that noncurative intent may be beneficial. Liver-directed therapies in the palliative setting may also improve patient quality of life as well as survival. This article provides insight and perspective on the role of ablation and embolization strategies in the context of contemporary management of CRLM.

CRLM PRESENTATION

Systemic chemotherapeutic options have undergone a paradigm shift that has resulted in survivability of noncurative patient populations in the range of 30 months with the most aggressive first-line therapies.[1] The majority of consensus guidelines structure an algorithmic approach to treatment, with first-line doublet plus biologic therapy, second-line crossover therapy, and third-line regorafenib (Stivarga, Bayer HealthCare Pharmaceuticals, Inc.), based on patient tolerance.[2] Despite these benefits, liver metastasis represents the site of progression in the majority of patients, thus leading to the rationale behind liver-directed therapies in CRLM.

SURGICAL RESECTION: SETTING THE BAR

Surgical resection remains the cornerstone of objective therapies directed at colorectal hepatic metastases. Nonrandomized, large, retrospective, population-based studies have demonstrated a very clear survival advantage for patients undergoing surgical resection compared to those deemed unresectable or not undergoing surgical resection, with 5-year survival for surgical resection approaching 30% to 50% as compared to almost 0% without surgical resection.[3-5]

Unfortunately, despite the intent to cure, the majority of patients will present with disease recurrence in the liver only or with synchronous disease both within and outside of the liver. Furthermore, in the majority of patients, uncontrolled tumor progression is identified at death.[6] In a retrospective analysis of more than 1,600 patients undergoing curative-intent surgical resection for CRLM (in the prebiologic era), de Jong and colleagues reported an overall intrahepatic recurrence rate of 56% with more than two-thirds of patients presenting with recurrence in the liver (n = 946).[7]

As a result of the well-recognized high incidence of intrahepatic recurrence even in the setting of resection for curative intent, we must begin to look at a strategy for the treatment of metastatic colorectal carcinoma that encompasses a spectrum of therapies corresponding to the continuum and evolution of the natural biology of metastatic colorectal disease. In this way, surgical resection represents the standard, as curative intent may allow a small percentage of patients to enjoy true disease-free cure. The remainder of patients will present with recurrence of disease, and of these, a large percentage will present with liver-only recurrence. In these patients, it is clear that surgery represents a cytoreductive therapy that may improve survival based on the following postulates that also apply to other liver-directed therapies, such as embolization and ablation:

- Alteration of tumor biology from cytoreduction of tumor burden leading to fewer mutations
- Decreasing tumor burden, resulting in protection of the liver
- Maintaining downstream options for future liver-directed therapy

EVIDENCE FOR USE OF ABLATION

Percutaneous, laparoscopic, and open ablative therapies are used in three scenarios: (1) small-burden oligometastatic disease that may be surgically resectable or ablatable with curative intent; (2) unresectable metastatic disease

AT A GLANCE

Acronyms of Chemotherapy Regimens

BEV	Bevacizumab
CET	Erbitux
DEBIRI	Drug-eluting bead with irinotecan
FOLFIRINOX	Folinic acid (leucovorin), 5-fluorouracil, irinotecan, oxaliplatin
FOLFOX	Folinic acid (leucovorin), 5-fluorouracil, oxaliplatin
mFOLFOX-6	Modified FOLFOX
FOLFOXIRI	Folinic acid (leucovorin), 5-fluorouracil, oxaliplatin, irinotecan
FOLFIRI	Folinic acid (leucovorin), 5-fluorouracil, irinotecan
OxMdG	Oxaliplatin, 5-fluorouracil, folinic acid
REG	Regorafenib
SIRFLOX	SIRT, mFOLFOX
XELOX	Capecitabine, oxaliplatin
ZAL	Aflibercept

with lesions that are well defined, fit size criteria, and are few in number; and (3) local recurrence of disease after the completion of surgical resection (not discussed). These approaches incorporate a philosophy of treating all visible disease with a locally curative intent at different junctures in the continuum of disease presentation.

Potentially Surgically Resectable Oligometastatic Small-Burden Disease

Large retrospective studies demonstrate an ability to provide lasting local control of disease, in addition to progression-free survival, in patients presenting with liver-only oligometastatic disease with lesions < 3 cm. As demonstrated by Kim et al (n = 480) patients presenting with solitary lesions < 3 cm have the same survival benefit as compared to patients undergoing surgical resection.[8] Berber and Siperstein reported similar 5-year actuarial survival results with laparoscopic radiofrequency ablation (n = 68) as compared to surgical resection (n = 90) in the subset of curative-intent patients.[9] Only one study to date comparing radiofrequency ablation to surgical resection in a randomized prospective fashion demonstrated a significantly increased local recurrence rate with radiofrequency ablation and no significant change in overall survival.[10]

Nonresectable Multicentric Disease

The majority of the published literature compares the historical surgical resection survival data with radiofrequency ablation. It is important to note that selection bias was inherent in these studies because patients underwent ablation only when deemed nonsurgically resectable (in a nonrandomized fashion). Therefore, survival data remain controversial when comparing surgery with ablation given the current paradigms of therapy. Most recently, Ruers et al reported the 8-year follow-up data for CLOCC, a prospective, randomized trial of nonsurgically resectable patients (n = 119) undergoing either control arm conventional chemotherapy or radiofrequency ablation when possible (lesions < 4 cm and < 10 lesions on presentation). Survival benefit was clearly demonstrated, with a durable effect in 8-year progression-free survival (2% vs 22%), median survival (9.92 vs 16.82 months), and overall survival (8.9% vs 35.9%).[11] This study represents the strongest body of evidence for ablation in surgically unresectable patients and will likely not be replicated due to the accepted incorporation of ablation in the treatment algorithm.

New Ablation Technologies and Application

New technologies have emerged that involve different methods of generating ablative energy as compared to conventional radiofrequency ablation. Cryoablation utilizes the Joule–Thomson effect to generate areas of extreme cold (−140°C), resulting in cellular disruption through ice formation, as well as secondary apoptosis. Microwave ablation generates heat by friction arising from proton procession as opposed to electron flux, resulting in a significantly larger potential energy transfer and larger ablation zone. Irreversible electroporation, which is a predominantly nonthermal ablation technique, applies rapid

applications of high voltage of electricity to disrupt cellular membranes. Other minimally invasive techniques that fall into this category include stereotactic ablative radiotherapy and intrahepatic brachytherapy.[12]

Although these new and exciting technologies allow for greater versatility in terms of anatomic location (within and outside the liver) and size, the majority of the advantages are technical (ie, ablation can be targeted adjacent to vascular structures or bile ducts, it is faster, or potentially larger ablation volumes). No head-to-head study has demonstrated a true advantage of any of these new technologies, and thus the therapeutic decision should not be dictated on the specific technology but rather the potential for technical success based on appropriate tumor biology. Most recently, Huo et al concluded in their meta-analysis that both microwave ablation and radiofrequency ablation are effective, but there is no clear indication of superiority of one technology over another.[13]

EMBOLIZATION

Drug-eluting beads with irinotecan (Camptosar, Pfizer Inc.) therapy (DEBIRI), and selective internal radiation therapy (SIRT) with yttrium-90 (Y-90) microspheres represent the majority of published literature in the setting of colorectal carcinoma. Although there was a historical interest in lipiodol-based chemoembolization, no significant published literature has established a role in the setting of metastatic colorectal carcinoma. Several commercial products are available in DEBIRI and SIRT categories, with varying degrees of evidence and support (Table 1).

DEBIRI

Polyvinyl alcohol-based microspheres with statically charged sulfonyl groups (DC Bead, BTG Interventional Medicine) have been studied. Acryl-amine–derived superabsorbent microspheres (QuadraSphere, Merit Medical Systems, Inc.) and proprietary polylactic acid polymer microspheres (Tandem, CeloNova BioSciences, Inc.) also have the ability to load and elute ionically charged chemotherapies, with elution characteristics that vary based on size and the substrate of the microsphere. Optimal techniques and standardization of particle size/drug modulation have yet to be defined. It is important to note that all of these commercially available products are considered off-label for use in metastatic colorectal carcinoma.

A brief description regarding the metabolism and elution properties of drug-eluting beads is warranted to provide a better understanding and context to the current body of evidence. The goal of DEBIRI (using irinotecan) is to concentrate irinotecan (the prometabolite) into its active form (SN-38) near or in the tumor to elicit the biological effect. However, the majority of the conversion occurs primarily in the normal liver parenchyma as opposed to the tumor. DEBIRI results in maximum intrahepatic accumulation of irinotecan, while decreasing systemic exposure and induction of ischemia secondary to mechanical arterial occlusion. The typical dose of irinotecan is 100 mg loaded on a single vial of drug-eluting beads, which is administered by a lobar approach. Per one protocol, unilobar hepatic disease is treated with

TABLE 1. LEVEL OF EVIDENCE FOR ABLATION AND EMBOLIZATION IN METASTATIC COLORECTAL CANCER		
Platform	**Technology**	**AHRQ Level of Evidence**
Ablation	Radiofrequency	I
	Microwave	III
	Cryoablation	IV
	Irreversible electroporation	IV
Embolization	Lipiodol-based TACE	IV
	Acryl-amine DEBIRI	IV
	PVA DEBIRI	I
	Glass SIRT	II/III
	Resin-coated SIRT	I
Abbreviations: AHRQ, Agency for Healthcare Research & Quality; PVA, polyvinyl alcohol; TACE, transarterial embolization.		
I = High-quality, multicentered or single-centered, randomized controlled trial with adequate power; or systematic review of these studies.		
II = Lesser-quality randomized controlled trial, prospective cohort or comparative study, or systematic review of these studies.		
III = Retrospective cohort or comparative study, case-control study, or systematic review of these studies.		
IV = Case series with pre/posttest or only posttest.		
V = Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research, or "first principles."		

two DEBIRI infusions separated by 4 weeks, whereas bilobar disease is treated with four lobar infusions every 2 weeks, alternating between the right and left hepatic lobes.[14]

A multicenter prospective study evaluated patients with metastatic colorectal cancer of the liver who failed systemic chemotherapy and who were treated with DEBIRI via a consecutive lobar hepatic approach (median dose, 100 mg irinotecan administered per treatment).[15] Progression-free survival was 11 months, and overall survival was 19 months. In another prospective single-arm study in which patients were treated with DEBIRI after at least two lines of chemotherapy, progression-free survival was 8 months, and median survival was 25 months.[16]

Martin et al recently reported results of a multicenter clinical trial that randomized patients to one of two first-line treatment regimens for unresectable colorectal liver metastases: (1) modified FOLFOX-6 (mFOLFOX-6) and bevacizumab; and (2) mFOLFOX-6, bevacizumab, and DEBIRI (FOLFOX-DEBIRI).[17] The treatment protocol consisted of administration of systemic chemotherapy on days 0 and 14 and DEBIRI chemoembolization on days 7 and 21. The overall response rate, which was the primary endpoint, was significantly greater in the FOLFOX-DEBIRI group compared to the mFOLFOX-6/bevacizumab group at 2, 4, and 6 months. At 6 months, there was a 76% overall response rate in FOLFOX-DEBIRI group versus 60% in the mFOLFOX-6/bevacizumab group (P = .05). The FOLFOX-DEBIRI group had improved median progression-free survival compared to the mFOLFOX-6/bevacizumab arm (15.3 months vs 7.6 months) as well as significantly increased downsizing to resection (35% vs 16%; P = .05). Of note, there were significantly more grade 3 and 4 toxicities in the FOLFOX-DEBIRI arm related to postembolization syndrome after DEBIRI administration. However, chemotherapy-associated adverse events were similar in both arms, and DEBIRI did not result in treatment delay or augment the toxicity of systemic chemotherapy.

After DEBIRI administration, typical postembolization syndrome symptoms, including abdominal pain, nausea, vomiting, and fever, are common. In one study, abdominal pain was seen in as many as 40% of patients after treatment and was severe in 25% of patients.[16] Mild fever, nausea, and transient transaminitis were observed in 80%, 27%, and 70% of patients, respectively. Hypertension is the second most common adverse event and may be secondary to pain. Periprocedural medications include preprocedural and intraprocedural opioids, intra-arterial lidocaine (1%, 2–4 mL) prior to DEBIRI administration, postprocedural patient-controlled analgesia, antiemetics, and antibiotics.

SIRT/Radioembolization/Y-90/Transarterial Radioembolization (TARE)

Y-90 radioactive microspheres are available as a poly(methyl methacrylate) microsphere coated with a resin loaded with radioactive Y-90 (SIR-Spheres, Sirtex Medical Limited) and a glass microsphere with Y-90 incorporated within the glass matrix (TheraSphere, BTG Interventional Medicine). The resin-based microsphere is the only Y-90 microsphere approved for use in CRLM, indicated in first-line treatment as an adjunct to floxuridine (FUDR) infusion.

Currently, there is level I evidence relating to an improvement in either progression-free survival, time to progression, or overall survival for the use of resin Y-90 in the following scenarios: first-line therapy as an adjunct to FUDR infusion (which is the on-label use) and chemorefractory liver-dominant disease. Level II evidence for resin microspheres exists for contemporary first-line chemotherapy and second-line chemotherapy. Safety has been demonstrated across all lines of therapy, as evidenced by a recent retrospective review by Kennedy et al of 606 patients, which revealed no significant variation in toxicities.[18] The largest prospective study to date relating to locoregional therapy in the setting of CRLM is the SIRFLOX trial.

The SIRFLOX Trial

SIRFLOX is an international, phase 3, randomized, controlled trial examining the use of Y-90–loaded, resin-coated microspheres in the first-line setting of metastatic colorectal carcinoma in 530 patients. The trial was designed as an open-label study, with randomization to two arms. The control arm consisted of standard first-line chemotherapy (oxaliplatin, leucovorin, 5-fluorouracil, and an institutional choice as to whether to use bevacizumab in the first-line setting) (Figure 1).

Two major abstracts have been presented with respect to the study, one at the American Society of Clinical Oncology 2015 meeting[19] and the second at the 2015 World Congress of Gastrointestinal Cancer 2015.[20] Interestingly, SIRFLOX permitted the enrollment of (and recruited) up to 40% of the patients with extrahepatic disease. The reported results are as follows:

- SIRFLOX failed its primary endpoint of all-site progression-free survival, with progression-free survival at any site at 10.2 months in the control arm versus 10.7 months in the treatment arm (hazard ratio [HR], 0.93 [95% confidence interval {CI}, 0.77–1.12]; P = .43).
- The secondary endpoint of progression-free survival within the liver was dramatically different at 12.6 months in the control arm versus 20.5 months in the treatment arm (HR, 0.69 [95% CI, 0.55–0.90]; P = .002).
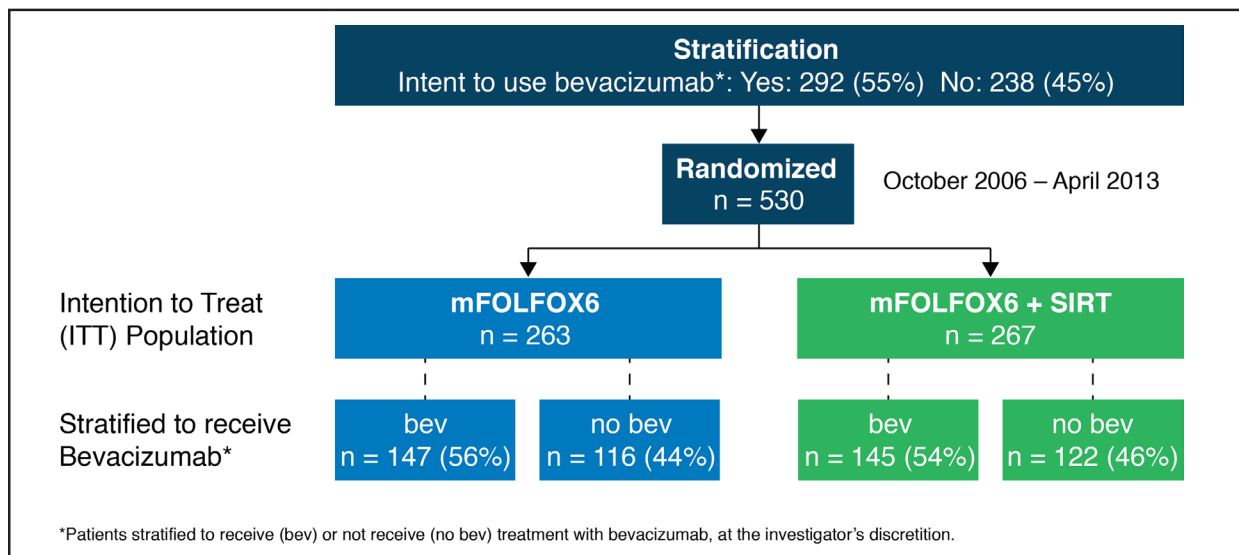
Figure 1. Flowchart of the SIRFLOX study. (Adapted from Gibbs P, Heinemann V, Sharma N, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab [bev] versus mFOLFOX6 + selective internal radiation therapy [SIRT] ± bev in patients [pts] with metastatic colorectal cancer [mCRC]. J Clin Oncol. 2015;33[suppl]:Abstract 3502.)

- Subset analysis of patients with liver-only disease revealed a further benefit in this patient population, with progression-free survival at 12.4 months in the control arm versus 21.1 months in the treatment arm (HR, 0.64 [95% CI, 0.48–0.86]; $P = .0003$).
- Other than a reported 3.7% ulceration rate in the SIRT arm, toxicities in both cohorts were considered acceptable and expected.
- A significantly higher number of patients were able to undergo a downstaged surgical resection in the intervention arm versus the control arm.
- The introduction of bevacizumab, based on intent-to-treat analysis, did not affect toxicity or the efficacy of response within the liver.

Upon initial analysis, the reporting of a negative primary outcome would seem disappointing and potentially a setback for the technology platform. However, unique to this clinical study is the fact that both the control and intervention arms had the same degree/intensity of chemotherapy for the treatment of extrahepatic disease. To put it another way, both the control and intervention arms treated extrahepatic disease in the same way—with systemic chemotherapy. Therefore, the strongest and most encouraging point is actually with respect to the liver specifically, which has been demonstrated in systemic therapies to be a surrogate of survival.[21] Furthermore, SIRFLOX study was specifically designed to work in conjunction with two other major phase 3 clinical trials: FOXFIRE, an NHS-sponsored trial executed in the United Kingdom, and FOXFIRE Global, essentially an extension of FOXFIRE.[22] All three studies are similar in design, with the aggregated data of both overall survival and progression-free survival anticipated sometime in 2017. These studies represent 1,103 patients and the largest randomized controlled trials ever conducted in interventional oncology and the fourth-largest ever in medical oncology.

The safety of glass microspheres has been demonstrated in a number of recent publications relating to colorectal carcinoma, an off-label indication within the United States. In a retrospective review of 68 patients, Abbott et al reported that toxicities were well accepted across all lines of chemotherapy.[23] The study further substantiated a previous study demonstrating minimal toxicity and safety in patients with CRLM, with a median time to hepatic progression of 15.4 months in 72 patients across multiple lines of chemotherapy. Prior to Y-90, the number of chemotherapy drugs patients were exposed to was three drugs for 28 patients (38%), two drugs for 30 patients (42%), and one drug for 10 patients (14%).[24] This population was expanded, and similar conclusions were drawn in a larger cohort of 214 patients across multiple lines of chemotherapy.[25]

The EPOCH trial, a second-line phase 3, randomized, controlled trial of patients with liver-only metastatic disease is actively recruiting and will hopefully further the body of evidence with respect to SIRT and the use of glass microspheres in the treatment of metastatic colorectal cancer.[26]
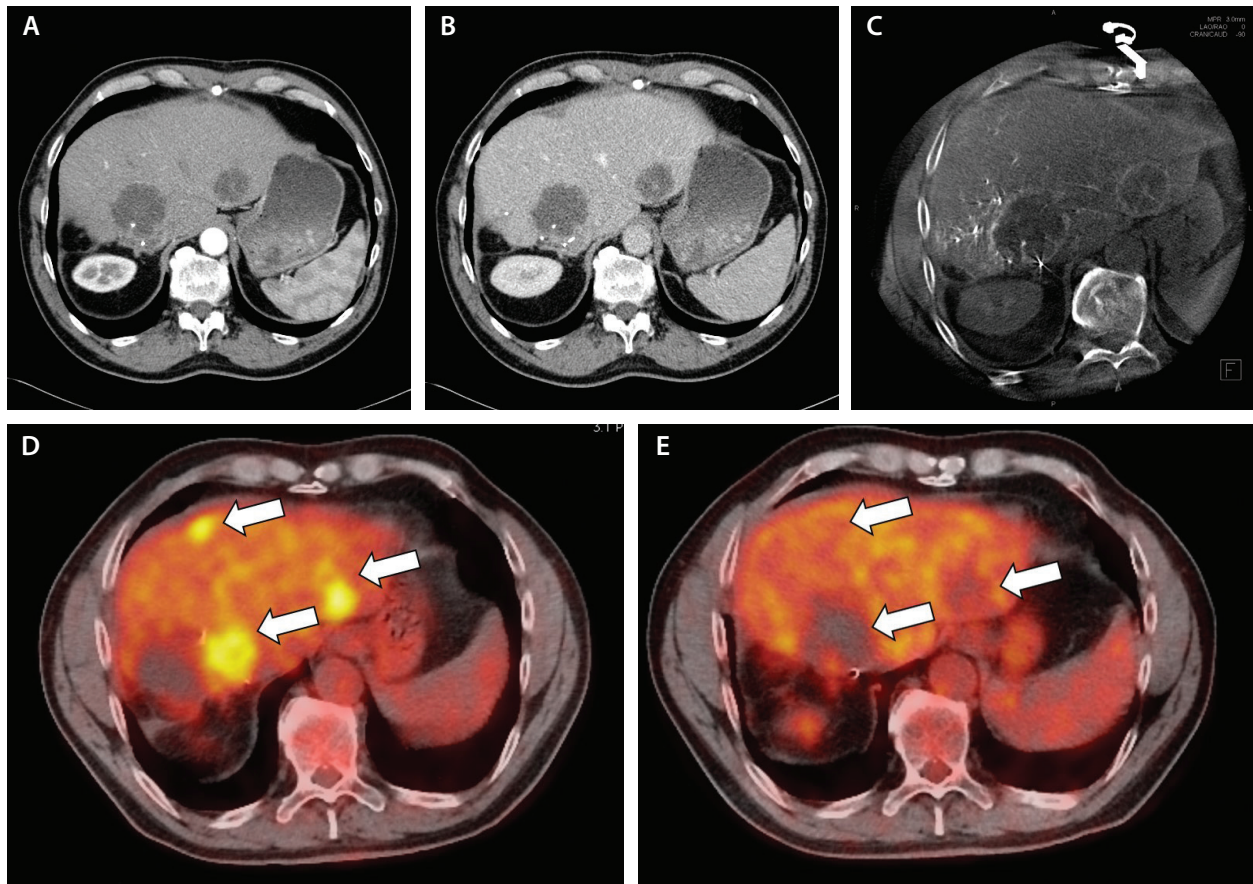
Figure 2. A 46-year-old man with stage IV CRLM, postsurgical resection, who was chemorefractory. Arterial and portal venous phase CT revealed hypoattenuating metastatic disease (A, B). DynaCT (Siemens Healthcare) demonstrated clear hypervascularity of the peripheral rim, not clearly demonstrated on CT (C). Pre-SIRT fluorodeoxyglucose-positron emission tomographic CT revealed metabolically active lesions (arrows) (D). At 1-month post-SIRT, there was no metabolic activity and a dramatic response in tumor markers (E).

SIRT and Surgical Resection

One critical question addressed by the P4A group at the International Hepato-Pancreato-Biliary Association 2015 meeting is whether the implementation of SIRT may result in long-term complications following surgical resection of a previously irradiated liver in the setting of systemic chemotherapy. Pardo et al have retrospectively evaluated the potential risk associated with SIRT in 100 patients who had undergone successful downstaging or intent to treat with surgical resection. Major complications and/or death were only observed in more aggressive surgical resection, including trisegmentectomy, and ALPSS (associated liver partition and portal vein ligation for staged hepatectomy) procedure, both of which also independently increase the risk associated with surgical resection. If patients underwent any of the aforementioned procedures, there was a 21% chance of 90-day mortality, with median time between treatment to surgical resection of 25 months.

However, there were no issues relating to previous chemotherapy, and otherwise, surgical resection was conducted safely without major complication.[27]

Reports of increasing future liver remnant in unresectable liver cancers as bridge to resection have been provided by a number of publications, utilizing both glass and resin-based microspheres. In the Northwestern experience, 83 patients undergoing right radiation lobectomy with glass microspheres were examined. Eight patients were diagnosed with metastatic colorectal carcinoma. From these data, one patient underwent successful right lobectomy, with volumetric changes of contralateral hypertrophy that facilitated the surgical resection.[28] Similar findings have been reported utilizing resin-coated microspheres.[29]

CONCLUSION

All liver-directed therapies represent cytoreductive strategies that are designed to treat disease that is restricted
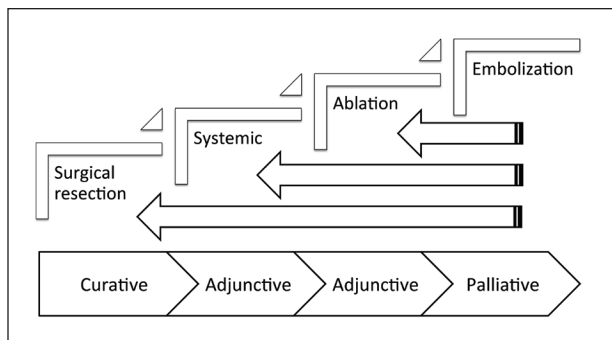
Figure 3. Ablation and embolization are often adjunctive and palliative treatments (steps), only considered after treatment for curative intent is no longer an option (bottom arrowheads). Recent data have suggested that ablation and embolization strategies should be considered as adjunctive procedures so that patients can be reevaluated for curative-intent options (middle arrows).

to the liver, and in the majority of cases, disease that is radiographically visible. At presentation, CRLM is by definition a systemic disease, requiring systemic therapy as a backbone to treatment. However, the evidence favors improved survival through targeted treatment of visible disease despite the high incidence of in-organ recurrence. Taking this into consideration, the treatment of liver metastases in the setting of colorectal carcinoma generally follows a progression that begins with surgical resection (or in rare cases curative-intent ablation), leading into unresectable (curative-intent) ablation, and then to embolization (Figure 2).

The ability to downstage patients to either surgical resection (due to situations involving discordant progression in response) requires the continued review and adjudication of multidisciplinary teams in order to facilitate and reevaluate patients on an individual basis, utilizing experience and published literature as guidance (Figure 3). As such, a wide range of evidence with respect to the technologies and indications for the treatment of liver-dominant colorectal carcinoma exists.

Ongoing clinical trials designed to focus on survival are forthcoming and will shed light not only on the specific therapy platforms, but also on the impact of liver-directed therapies on survival in the palliative setting. In short, the principles and science suggest a role for liver-directed therapy at multiple points of intervention within an individual patient's cancer journey. ■

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