

# Arterial Oncologic Interventions for Liver-Dominant Metastases

The current state of evidence for arterial interventions for liver metastases.

**BY W. BRAD BUTLER, BS, AND DANIEL B. BROWN, MD**

Interventional oncology (IO) is a subspecialty of interventional radiology (IR) that has added a number of therapeutic options for cancer patients, with a positive impact on survival demonstrated in certain conditions. The treatment of hepatocellular carcinoma (HCC), either as destination therapy or as a bridge to liver transplantation, is the most widely accepted intra-arterial IO intervention. However, the relative role of IO in metastatic disease is less defined. This article reviews the state of evidence for IO in the management of metastatic liver disease, primarily focusing on arterial therapy.

## DIFFERENCES IN TREATING PRIMARY AND METASTATIC DISEASE

HCC is increasing in incidence and remains chemo-resistant. More than 50% of patients with HCC will undergo transarterial chemoembolization (TACE) during the course of their treatment. Significant improvement in overall survival (OS) has been demonstrated in separate randomized controlled trials in 2002,<sup>1,2</sup> as well as in a later meta-analysis. Further technical refinements such as use of C-arm CT, development of better microcatheters, and referrals of advanced patients for sorafenib or hospice have continued to improve survival. As a result, OS to 4 years for patients treated with destination therapy is being increasingly reported, with some studies showing even longer OS rates. TACE is well represented in guidelines from a variety of organizations, including the National Comprehensive Cancer Network (NCCN) and the American Association for the Study of Liver Diseases.

In contrast, virtually all unresectable hepatic metastatic disease is principally treated with combinations of chemotherapy, biologic therapy, and immunother-

apy. These therapeutic decisions are a result of large-scale, prospective, randomized trials that developed well-defined algorithms for a number of tumor types. An example of this approach is the addition of oxaliplatin or irinotecan to the previous standard therapy for colorectal cancer, 5-fluorouracil and leucovorin. OS nearly tripled following development and evaluation of these agents. Similarly powered prospective randomized trials had not been performed using arterial-directed therapy for metastatic disease until recently. As a result, most interventional radiologists treat metastatic disease from colon cancer, breast cancer, or most other metastatic tumors after systemic therapy options are exhausted or limited. The lone exception has been neuroendocrine tumors (NETs), in which embolotherapy of lower-grade tumors has been the standard of care.

## COLORECTAL CANCER

In contrast to the previously described medical oncology trials, IO research has been largely retrospective, single-center reviews of 100 patients or fewer. Two of the largest prospective randomized clinical trials in IO were published in 2016 and 2017, respectively.<sup>3,4</sup> Both studies centered on the addition of yttrium-90 (Y-90) to standard first-line chemotherapy for metastatic colorectal cancer. The SIRFLOX study compared the addition of Y-90 resin microspheres to standard first-line oxaliplatin-based chemotherapy (FOLFOX) plus or minus bevacizumab versus chemotherapy alone, with a primary endpoint of progression-free survival (PFS).<sup>3</sup> In total, 530 patients were randomized. Although hepatic PFS was superior in the study group (20.5 months vs 12.5 months for controls;  $P = .002$ ), overall PFS was not improved with the addition of Y-90 (10.2 months vs 10.7 months for

controls;  $P = .43$ ). Toxicities were evaluated using the National Cancer Institute Common Toxicity Criteria, version 3.0. Complications directly attributable to Y-90 (gastric/duodenal ulcer and ascites) were significantly more common in the study group ( $P < .05$  for both). Treatment-associated mortality was similar between groups.

OS results from SIRFLOX were combined with two other similarly structured prospective randomized phase 3 trials (FOXFIRE and FOXFIRE Global).<sup>4</sup> All trials completed 2 years of patient follow-up with 1,103 total patients. In the combined cohort, 549 patients received FOLFOX and 554 received FOLFOX plus Y-90. There was no increase in median OS with the addition of Y-90 to first-line chemotherapy (22.6 months vs 23.3 months in the control group;  $P = .61$ ). The absence of an increase in OS was despite complete or partial responses in 72% of Y-90 recipients versus 63% in the chemotherapy only arm ( $P = .012$ ). Mirroring the SIRFLOX PFS outcomes, patients receiving Y-90 plus chemotherapy had a lower incidence of initial intrahepatic progression (31% vs 49% in the chemotherapy alone arm). Despite the hepatoprotective effect of adding Y-90, initial progressive disease outside the liver was more common in the Y-90 plus chemotherapy group (54% vs 36% of the control group). Grade 3 or greater toxicities in the Y-90 arm were significantly higher than the chemotherapy alone arm (74% vs 67%;  $P = .0089$ ).

Based on the outcomes of these trials, it is clear that Y-90 should not be used as part of first-line therapy for colorectal cancer. However, these outcomes do not mean that Y-90 is not beneficial for patients with liver-dominant colorectal cancer. Possible utilizations include:

- **Consolidation therapy.** After 12 doses/6 months of first-line therapy, there is a plateau of benefit from further administration of oxaliplatin or irinotecan. With oxaliplatin, there is also a cumulative risk of neuropathy. At this time point, many medical oncologists switch to maintenance with 5-fluorouracil/leucovorin. Patients with liver-dominant metastatic disease at this point of first-line therapy are an intriguing group because extrahepatic disease has remained under control with treatment. This subset of patients could potentially perform better than the FOXFIRE group.
- **Second-line therapy.** One reason the first-line trials failed may have been that first-line therapy is extremely effective. The response rate and PFS for second-line therapy is much lower than first-line therapy. A second-line trial combining chemotherapy and Y-90 in patients with liver-dominant

metastases may select patients with more appropriate biology. The EPOCH trial (NCT01483027) is a prospective randomized trial evaluating standard second-line chemotherapy (either irinotecan or oxaliplatin) alone or combined with Y-90. Trial participants will receive the agent that was not used during first-line therapy. The primary endpoint of this trial is PFS.

- **Salvage.** OS after second-line therapy is poor and is usually  $< 1$  year. In multiple salvage trials, Y-90 has achieved OS ranging from 10 to 12 months. Most chemotherapy drugs used in salvage perform similarly. There is a potential opportunity to combine Y-90 with salvage agents (biologic or immunotherapy) to confer a longer survival benefit.

## NEUROENDOCRINE TUMORS

Embolization has been a mainstay treatment for patients with liver-dominant neuroendocrine metastases with symptoms related to hormone production or bulk secondary to large-volume disease distending the liver capsule. A variety of embolic techniques have been successfully used, including Y-90, chemoembolization with Lipiodol (Guerbet LLC) or drug-eluting beads, and bland embolization using particles alone. Direct prospective comparison of these techniques has not been performed. A multicenter retrospective study included patients receiving Y-90, Lipiodol chemoembolization, and bland embolization.<sup>5</sup> Among the three groups, there was no significant difference in hepatic PFS or OS. Bland embolization resulted in significantly more grade 3 toxicity from pain, whereas Y-90 resulted in more hepatic dysfunction.

Potential issues with liver dysfunction in long-term survivors with NETs treated with Y-90 have been retrospectively evaluated in two articles. Su et al reported on 54 patients with  $> 2$  years of follow-up, with 39 patients undergoing bilobar treatment.<sup>6</sup> In the bilobar therapy group, 22 patients had imaging findings suggestive of cirrhosis and eight patients developed clinical signs of hepatic decompensation. Although the Y-90 treatment may have contributed, six of the eight patients had progressive liver disease with more than 50% volume replacement and/or had received hepatotoxic chemotherapy. Another study by Tomozawa et al evaluated 93 patients with NETs who underwent Y-90 radioembolization.<sup>7</sup> In this group, 45 patients had bilobar treatment. A total of 52 patients underwent imaging and completed more than 1 year of follow-up, including 29 patients from the bilobar Y-90 cohort. Of these patients, five (17%) had ascites, six (21%) had hepatic surface nodularity suggesting cirrhosis, six (21%) had splenomegaly, and two (7%) had varices.

Patients with low-grade mid-gut NETs can live more than 10 years from the time of initial locoregional therapy. This patient group is distinctly different compared to the majority of patients referred for Y-90. In salvage treatment of many other types of metastatic disease, 1 year of survival is considered a benchmark of clinical success. Postprocedural recovery from Y-90 is easier than from chemoembolization and embolization. However, the cirrhotic-like changes identified years after Y-90 therapy raise questions about the appropriateness of this therapy in patients with expected multiyear survival.

Another issue with the use of Y-90 in patients with NETs is when peptide receptor radionuclide therapy with lutetium-177 (Lu-177) dotatate is being considered. This agent is FDA approved in the United States for mid-gut NETs and is administered intravenously four times at 1-month intervals.<sup>8</sup> The long-term effects and toxicities of Lu-177 remain to be defined in patients with survival exceeding 10 years. Some practitioners may use Lu-177 after failure of conservative measures to avoid hepatic toxicity. In our practice, patients with mid-gut NETs who may be eventual candidates for Lu-177 referred for arterial bridging therapy are currently being treated with Lipiodol chemoembolization to avoid potential toxicity from Y-90 and the postembolization pain of bland embolization. Additionally, this leaves the liver radiation naive to facilitate Lu-177 at a later time. In patients with a significant disease burden who are older or otherwise frail, we still consider using Y-90.

### ACQUIRING BETTER DATA

The published literature for other metastases is not impactful enough to merit inclusion in the NCCN guidelines. Regarding arterial therapy, IR is fairly represented for HCC and NET. The only representation of interventional therapy in any NCCN guideline is for treatment of metastatic colorectal carcinoma, but it is mentioned as a footnote after 10 pages of systemic chemotherapy options. Currently, IR treatment is not mentioned in the guidelines for breast, melanoma, sarcoma, pancreatic, or lung cancer. Most interventional radiologists have treated these types of cases, albeit in small numbers, and anecdotal successes are frequently discussed. These experiences do not translate to impactful publications. Additionally, on a case-by-case level, getting insurance preapproval is frequently challenging, leading to issues in treating patients in a timely manner.

Prospective trials are expensive, difficult to design and recruit patients to, and have no guarantee of success. To improve trial success, a more cost-effective

strategy gaining traction is the collection of registry data as a preliminary determination of efficacy and target population. In such a setting, individual sites can enroll, treat, and follow patients using local guidelines. Imaging response and toxicity are pooled among the centers. Another reason is that the cost-effective research data enable more centers to participate in some aspects of research, as many lack the resources for a prospective trial.

### RESIN Liver Tumor Registry

Launched in 2015, the RESIN liver tumor registry includes 40 sites and continues to grow. Driven by real-world evidence, community and academic centers are nearly equally represented. This approach is unique in IR research given that approximately 80% of operators self-identify as community or private practice physicians, whereas most research is driven by the smaller number of practitioners in academic centers. RESIN also includes 10 of 27 NCCN and 16 of 49 National Cancer Institute comprehensive cancer centers. As of August 2018, over 1,100 patients have been enrolled. To date, enrollment is split nearly equally by community and nonuniversity hospital centers. Given the broad cross-section of included practitioners, RESIN will provide insight into areas of IR practice that have not previously been studied.

Of the 1,100 enrolled patients, nearly two-thirds have metastatic disease. Within this subpopulation, approximately two-thirds remained on systemic therapy while undergoing Y-90 treatment. These data will be an area of great interest moving forward—a key to acceptance of IO therapies by other cancer specialists will include incorporation of locoregional therapies into existing paradigms. When Y-90 or chemoembolization is used as monotherapy for salvage at the end stage of disease, patients frequently have declining performance status, a predictor of short survival. A principal use of Y-90 for metastatic colorectal cancer is after failure of first- and second-line therapy. A number of patients have been treated with Y-90 while on biologic therapies. Identifying combinations of Y-90 and biologic or immunotherapies with clinical benefit and low toxicity will provide valuable background data to identify prospective future trials. Indeed, several trials are currently exploring combination therapies involving immunotherapy and transarterial embolization.

### CONCLUSION

Intra-arterial therapy continues to be used for patients with liver-dominant metastatic disease that is refractory to systemic therapy. The EPOCH trial may potentially identify an earlier role for Y-90 in colorectal cancer patients. With the approval of Lu-177 for NETs,

treatment options for these patients before receiving radionuclide therapy are evolving. Our current practice is shifting back toward Lipiodol chemoembolization to maximize long-term therapeutic options. Other tumors have less robust data. Hopefully, the RESIN registry will provide useful data identifying optimal treatment scenarios for these malignancies. ■

1. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. 2002;35:1164-1171.
2. Llovet JM, Real MI, Montana X, et al. Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Lancet*. 2002;359:1734-1739.
3. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2016;34:1723-1731.
4. Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomized, phase 3 trials. *Lancet Oncol*. 2017;18:1159-1171.
5. Chen JX, Rose S, White SB, et al. Embolotherapy for neuroendocrine tumor liver metastases: prognostic factors for hepatic progression-free survival and overall survival. *Cardiovasc Intervent Radiol*. 2017;40:69-80.
6. Su YK, Mackey RV, Riaz A, et al. Long-term hepatotoxicity of yttrium-90 radioembolization as treatment of metastatic neuroendocrine tumor to the liver. *J Vasc Interv Radiol*. 2017;28:1520-1526.
7. Tomozawa Y, Jahangiri Y, Pathak P, et al. Long-term toxicity after transarterial radioembolization with yttrium-90 using resin microspheres for neuroendocrine tumor liver metastases. *J Vasc Interv Radiol*. 2018;29:858-865.
8. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125-135.

---

**W. Brad Butler, BS**

Second-Year Student  
AU/UGA Partnership  
Medical College of Georgia  
Augusta, Georgia  
Wilbutler@augusta.edu

*Disclosures: None.*

**Daniel B. Brown, MD**

Professor of Radiology and Biomedical Engineering  
Director, Interventional Oncology  
Vanderbilt University Medical Center  
Nashville, Tennessee  
daniel.b.brown@vumc.org

*Disclosures: Consultant to BTG International and Bard/BD Interventional; research support from Sirtex Medical, Inc.*

---