Yttrium-90 Radioembolization is a Viable Treatment Option for Unresectable, Chemorefractory Colorectal Cancer Liver Metastases: Further Evidence in Support of a New Treatment Paradigm

Ryan Hickey, MD, Robert Lewandowski, MD, and Riad Salem, MD, MBA

Department of Radiology, Division of Vascular and Interventional Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL

Saxena et al. provide further evidence of the safety and efficacy of yttrium 90 radioembolization for the treatment of chemorefractory colorectal liver metastases with the publication of outcomes in more than 300 patients treated during a 7-year period. The reported survival rates and low grade of toxicities complement a growing body of evidence in favor of transarterial radioembolization for the treatment of a disease with an otherwise dismal prognosis. Saxena et al. joins a series of recent publications that are helping to define a new and promising treatment paradigm for colorectal liver metastases, which remains one of the most common causes of cancer-related mortality.

The authors add to a worldwide experience of reproducible outcomes with radioembolization for colorectal liver metastases. They remind us that patients with chemorefractory colorectal liver metastases have a median survival of only 4–6 months with best supportive care.¹ In the setting of such chemorefractory disease, Saxena et al. report a median overall survival of 10.5 months from first Y90 radioembolization, which is nearly identical to the 10.6-month median survival most recently reported by Lewandowski et al. in a study of 214 patients treated with glass Y90 microspheres over 12 years,² and a median survival of 10.5 months reported by Kennedy et al. among responders in a multi-institutional review of 208 patients treated with resin Y90 microspheres.³

The study confirms that Y90 radioembolization is safe in patients who have received multiple lines of chemotherapy,

with the vast majority of clinical toxicities being low-grade and self-limited. Indeed, recent phase 1 studies indicate that Y90 radioembolization can be safely combined with the radiosensitizing oral chemotherapeutic capecitabine, establishing a new front against colorectal liver metastases utilizing the synergistic effects of chemoradiation. Our group performed a dose-escalation study of Y90 radioembolization with capecitabine in which Y90 doses were escalated in the setting of full-dose capecitabine. We reported that the maximum-tolerated dose of glass Y90 microspheres in conjunction with capecitabine exceeds 170 Gy for the treatment of hepatic metastases, the majority of which were colorectal metastases.⁴ Cohen et al. reported the safety of Y90 radioembolization administered during escalating doses of capecitabine and found that resin Y90 microspheres could be safely administered with the maximum standard dose of capecitabine (1,000 mg/m² b.i.d.) for patients with hepatic metastases, more than 70 % of whom had colorectal metastases.⁵ Given the limitations of external beam radiation in the treatment of hepatic metastases,⁶ Y90 radioembolization provides the critical radiation component of chemoradiation. Whereas the incidence of radiation-induced liver disease is unacceptably high following external beam radiation at tumoricidal doses, Y90 radioembolization offers high-dose treatment of multiple lesions in a single setting.

The initial foundation has been established for incorporating Y90 into the standard treatment regimen of chemorefractory liver metastases of colorectal cancer. Nonetheless, several questions remain to be answered. In order to determine the most effective time at which radioembolization should be performed, the imprecise term “line of chemotherapy” needs to be clarified. Investigators must try to separate patients who have discontinued a chemotherapeutic regimen and started another due to

clinical toxicities from those who have begun a new regimen as a result of disease progression.

In addition, there is frequent discussion of the effects of chemotherapy—not to mention molecularly targeted agents, such as bevacizumab—on the integrity of and flow through hepatic vasculature. Changes in hepatic arterial flow dynamics as a result of an extensive chemotherapy history could influence the optimal timing of radioembolization as it may limit microsphere infusion and dose delivery.

Finally, the “gold standard” of clinical evidence is still lacking for radioembolization and colorectal liver metastases, namely, prospective, randomized control trials. Ongoing clinical trials to address this need include SIR-FLOX, which is an international phase 3 trial evaluating the addition of Y90 radioembolization with SIR-Spheres to standard-of-care, first-line chemotherapy for patients with colorectal liver metastases. FOXFIRE is a similarly designed trial taking place throughout the United Kingdom. The EPOCH trial is a multi-institutional phase 3 clinical trial in the United States evaluating TheraSphere in patients with metastatic colorectal cancer of the liver who have failed first-line chemotherapy. Patients are randomized to receive standard-of-care second-line chemotherapy with or without radioembolization with TheraSphere.

With this largest series to date, the global experience of Y90 radioembolization for colorectal liver metastases has taken yet another step forward. While several important clinical questions remain to be addressed, the promise of a safe and efficacious treatment option for one of the most common malignancies appears to be on the horizon.

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