Y-90 Radioembolization for Colorectal Liver Metastases

Intra-arterial treatment options based on current data.

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The National Cancer Institute estimated that 102,480 new cases of colon cancer and 40,340 new cases of rectal cancer would be diagnosed in 2013. The combined estimated deaths from colorectal cancer (CRC) were 50,830.[1] Liver metastases develop secondary to hematogenous spread through the portal venous system. The only treatment that is considered curative is surgical resection.[2] Due to factors including tumor size, location, multifocality, or inadequate hepatic reserve, < 20% of patients are candidates for resection. Chemotherapy with or without resection has been considered the first-line therapy.[3]

ALTERNATE TREATMENT OPTIONS

For patients who have recurrent metastatic disease to the liver while on systemic chemotherapy or those who cannot tolerate chemotherapy, alternate treatments may be considered. These treatments include percutaneous ablation, transarterial chemoembolization (TACE), and transarterial radioembolization.[4] Radioembolization uses the radioactive isotope yttrium-90 (Y-90), which is incorporated into glass or resin microspheres that are directly infused into the hepatic arteries supplying the tumor. This can deliver radiation doses as high as 150 Gy without developing the complications seen with external beam therapy. In cases of multiple lesions, transarterial therapy is preferred over percutaneous ablation.

Combination transarterial therapy and ablation may also be considered in appropriate cases to provide local treatment to liver metastases with minimized damage to adjacent normal liver parenchyma.[5] Until recently, systemic chemotherapy with or without resection was employed as first-line therapy to treat liver-dominant metastatic disease, with liver-directed therapies considered after liver metastases continued to progress while the patient was on systemic chemotherapy. Metastatic disease to the liver is the major cause for mortality in patients with advanced CRC; therefore, treating liver metastases is imperative to prolonging overall survival rates.

TACE IN THE LITERATURE

In 2009, the Society of Interventional Radiology position statement on TACE for hepatic malignancies was published in the *Journal of Vascular and Interventional Radiology*.[6] The statement noted that TACE is a safe, proven, and effective technique for the treatment of malignancies, including hepatocellular carcinoma, neuroendocrine tumors, ocular melanoma, cholangiocarcinoma, and sarcoma. The statement also included TACE as having a possible palliative role in CRC patients with hepatic dominant metastatic disease, and consideration of TACE should be made on a case-by-case basis.

Various studies have addressed the efficacy and safety profile of Y-90 compared to TACE. Hong et al compared TACE and radioembolization as salvage therapy in patients with CRC and liver-dominant metastases.[7] The study included 36 patients, 21 who underwent TACE and 15 who were treated with radioembolization. There was no significant difference in survival benefit comparing TACE (median survival, 7.7 months; 1-year survival, 43%; 2-year survival, 10%; 5-year survival, 0%) with radioembolization (median survival, 6.9 months; 1-year survival, 34%; 2-year survival, 18%; 5-year survival, 0%). Mortality rates were similar, but there was a difference in the number of repeat Y-90 procedures required: 43% of TACE patients required multiple treatments, whereas only 20% of radioembolization patients needed more than one treatment. The need for repeat procedures raises the question of possible cost savings with Y-90 compared to

TACE. The 30-day mortality rate was the same for both TACE (5.4%) and radioembolization (5.2%).

THERAPY SELECTION AND STUDY DATA

With both therapies showing no difference in overall survival, selection of therapy can be influenced by factors such as patient tolerance and side effects. Radioembolization, as opposed to TACE, does not require inpatient hospitalization. Goin et al[8] and Gilbertson et al[9] noted this factor translates to better quality-of-life assessment by patients. In addition, several side effects were noted to be more frequently reported in patients who received TACE versus Y-90 ($P < .05$), including diarrhea, fever, chills, and anorexia.

As data on the efficacy of radioembolization with Y-90 has accrued from various studies, there has been a shift toward considering radioembolization as the preferred transarterial therapy. Jakobs et al performed a retrospective review of 41 patients who had failed systemic chemotherapy and developed worsening CRC liver metastases and were treated with radioembolization using resin microspheres.[10] Treatment was administered in a single session to the entire liver. Disease response was determined according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1 criteria on CT or magnetic resonance imaging performed at 1.3 to 3.7 months (mean, 2.6 mo) after therapy.

No case of complete response was observed. There were seven cases (17%) of partial response, 25 patients (61%) with stable disease, and four patients (9.8%) with progressive disease. Median overall survival was 10.5 months, with improved survival seen in patients with declining carcinoembryonic antigen (19.1 mo in responders vs 5.4 mo in nonresponders) and imaging response (29.3 mo in responders vs 4.3 mo in nonresponders, $P = .0001$). Longer survival was seen in patients with tumor burden replacing < 25% of liver volume and patients with no extrahepatic metastases.

Bester et al conducted a retrospective cohort study that compared radioembolization alone with systemic chemotherapy and supportive care in patients with liver-dominant metastatic cancer in the salvage setting.[11] Salvage patients were defined as those with unresectable liver metastases who no longer qualified for resection, percutaneous ablation, or TACE and who also had tumors that were refractory to systemic chemotherapy. The study assessed the difference in overall survival rates, as well as safety and adverse events. It included 339 patients with liver-dominant metastatic disease from various malignancies who were treated with radioembolization. Two hundred twenty-four of the 339 patients had metastatic CRC. Fifty-one patients who did not meet the inclusion criteria for radioembolization due to variant arterial anatomy risking GI deposition of Y-90, large hepatopulmonary shunt, or refusal of the procedure were treated with standard care. Of the patients with metastatic CRC, 85% had an ECOG (Eastern Cooperative Oncology Group) score of 0, and most had 0% to 25% of the liver replaced by tumor. For the 224 CRC patients, median overall survival was 11.9 months compared to 6.6 months in the standard care cohort. In the non-CRC group, median overall survival was 12.7 months compared to 3.6 months in the standard care cohort.

Kennedy et al performed a retrospective review from seven institutions of 208 patients treated with radioembolization using resin microspheres.[12] All patients had been treated previously with systemic chemotherapy and had progressive disease. The median survival was 10.5 months for responders, but only 4.5 months for nonresponders. Imaging and biomarker response was also assessed. CT partial response of 35%, positron emission tomography response of 91%, and reduction in carcinoembryonic antigen of 70% were noted.

The study also raised the question of whether there would be a survival difference if brachytherapy were used in patients who had not been exposed to the maximum systemic chemotherapy regimen. Kennedy et al later published a consensus panel report suggesting guidelines for treatment and dose reporting for brachytherapy set forth by the Radioembolization Brachytherapy Consortium.[15] The objective of the guidelines was to aid clinicians in reproducing uniform patient workup, treatment, and reporting, which can further define the safety and role of Y-90 microspheres in the context of currently available therapies. Salem and Thurston also published a series of articles that outline a standardized approach to the workup and treatment of primary and secondary liver malignancies.[16-18]

Benson et al reported results of a nonrandomized, prospective phase II trial evaluating radioembolization of liver metastases using glass microbeads.[13] The prospective, multicenter study included 151 patients with hepatic metastases from various cancers, all of whom failed systemic chemotherapy. This group included 61 patients with metastatic CRC, all of whom had advanced disease when they enrolled. Median progression-free survival was 2.9 months, and median survival from day 1 of treatment was 8.8 months for the CRC group. The rate of disease control (complete response, partial response, and stable disease) was 34%.

The data among centers were reproducible, as was the technique and dose administered; this reproducibility was lacking in previous studies and may contribute to the variability in patient survival rates reported by other

TABLE 1. OUTCOMES OF RADIOEMBOLIZATION FOR TREATING COLORECTAL LIVER METASTASES AS SALVAGE THERAPY

Study	Number of Patients	Median Overall Survival (mo)	Objective Response Rate (%)*	Stable Disease (%)
Jakobs et al[10]	42	10.5	17	61
Bester et al[11]	224	11.9	Not reported	Not reported
Kennedy et al[12]	208	10.5 responders, 4.5 nonresponders	35	55
Benson et al[13]	61	8.8	3	31
Cosimelli et al[14]	50	12.6	24	24

**Objective response rate indicates complete response plus partial response.*

Y-90 studies. The findings of this study helped launch three prospective, randomized phase III trials using Y-90 glass microspheres to treat liver malignancies.

Cosimelli et al conducted a multicenter phase II clinical trial, which was the first prospective evaluation of radioembolization in patients with colorectal liver metastases who failed previous oxaliplatin- and irinotecan-based systemic chemotherapy regimens.[14] Of the 50 patients included, the confirmed overall response rate (partial or complete response) was 24% (95% confidence interval [CI], 12.2–35.8) by RECIST, which met the criteria for significance (P = .05). One patient (2%) had a complete response, 11 (22%) had partial response, 12 (24%) had stable disease, and 22 (44%) had progressive disease. Median time to progression and progression-free survival was 3.7 months (95% CI, 2.6–4.9), and median overall survival was 12.6 months (95% CI, 7–18.3). A summary of the mentioned studies for use of brachytherapy in the salvage setting for liver-dominant metastatic CRC is listed in Table 1.

SALVAGE THERAPY

The current oncologic practice is to refer patients for radioembolization to be implemented as salvage therapy after they have developed worsening hepatic metastases while on systemic therapy. Radioembolization should be initiated as soon as possible if systemic treatment failure has occurred. Introducing radioembolization earlier in the treatment process, as first- or second-line therapy, has been suggested.

Multiple studies have evaluated concurrent systemic therapy and radioembolization of liver metastases and the impact on clinical response and survival. An early phase II trial by Van Hazel et al randomized 21 patients with untreated, advanced colorectal liver metastases to systemic fluorouracil and leucovorin alone or systemic fluorouracil and leucovorin plus a single treatment with Y-90 resin microspheres administered on the third or fourth day of the second cycle of chemotherapy.[19] Baseline patient and tumor characteristics were similar for both groups. Response rates were determined using RECIST version 1 criteria on follow-up CT scans. The response for the chemotherapy plus radioembolization group (best confirmed response: 8 partial response, 3 stable disease, 0 progressive disease) was significantly better than the chemotherapy-alone group (best confirmed response: 0 partial response, 6 stable disease, 4 progressive disease). The time to disease progression was longer for the chemotherapy plus radioembolization group and was significantly better than the chemotherapy-alone group (18.6 vs 3.6 mo, P < .0005). Median survival was also better for the combination therapy group (29.4 vs 12.8 mo, P = .02). Patients reported similar quality-of-life scores in both groups. This small phase II trial demonstrated the potential benefit of introducing radioembolization earlier to patients than it had been in the past and prompted further trials to define the role of treatment with radioembolization as part of first-line therapy.

Hendlisz et al published a multicenter, prospective, randomized, phase III trial that compared intravenous fluorouracil infusion alone with intravenous fluorouracil plus radioembolization with resin microspheres in patients with unresectable CRC liver metastases.[20] The study included 44 patients, 21 of whom were randomized to fluorouracil protracted intravenous infusion 300 mg/m^2 on days 1 through 14 every 3 weeks. Twenty-three patients were randomized to radioembolization plus intravenous fluorouracil 225 mg/m^2 on days 1 through 14, then 300 mg/m^2 on days 1 through 14 every 3 weeks. Imaging response on follow-up fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) was assessed using the RECIST version 1 criteria. Median time to liver progression was 2.1 months in the fluorouracil-only group and 5.5 months in the

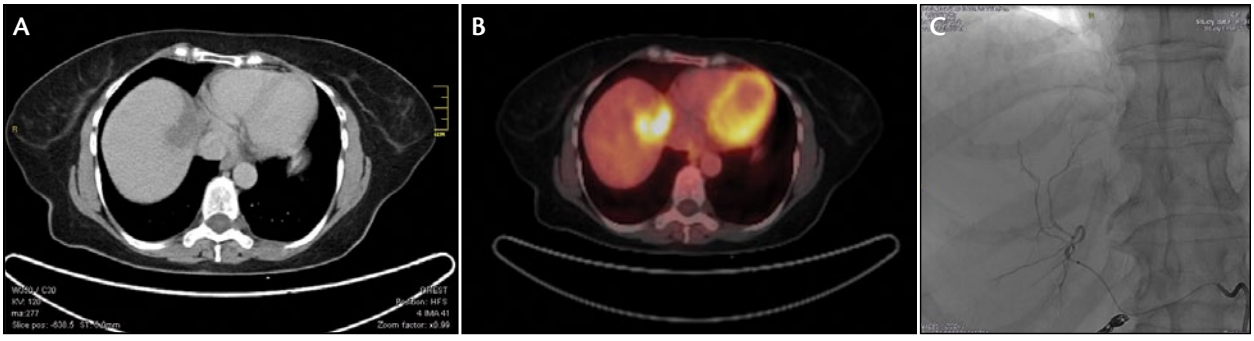

Figure 1. Metastatic CRC treated with Y-90 resin microspheres as salvage therapy shows partial response after radioembolization. Axial noncontrast CT (A) and axial-fused FDG PET/CT (B) of a patient with liver metastases from colorectal carcinoma before treatment shows large hypermetabolic liver lesion. Arteriogram obtained during radioembolization to the target area (C).

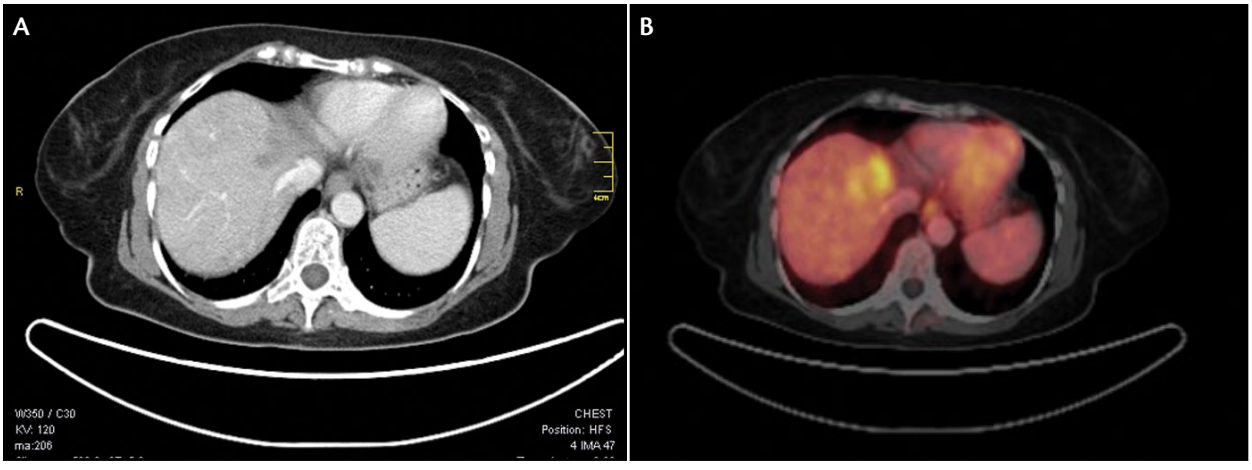

Figure 2. Axial contrast-enhanced CT (A) and axial-fused FDG PET/CT (B) after radioembolization show partial response, with reduction in size and reduction in hypermetabolism associated with the treated lesion.

fluorouracil-plus-radioembolization group. Median time to tumor progression was 2.1 months in the fluorouracil-only group and 4.5 months in the fluorouracil-plus-radioembolization group. Median overall survival was 7.3 months in the fluorouracil-only group and 10 months in the fluorouracil-plus-radioembolization arm.

Additional studies have been published assessing the use of systemic chemotherapy plus radioembolization as a first-line therapy for treating colorectal liver metastases. These include a study by Kosmider et al,[21] which retrospectively reviewed 19 patients with unresectable colorectal liver metastases who were treated with FOLFOX or 5-fluorouracil/leucovorin plus radioembolization. Posttreatment imaging analysis was performed with CT using RECIST criteria. The overall response rate was 84% (2 complete response, 14 partial response, 1 stable disease, 2 progressive disease). Median progression-free survival was 10.4 months, and median overall survival was 29.4 months. Survival analysis was further subdivided into patients without and with extrahepatic disease. Progression-free survival (10.7 mo vs 3.6 mo, $P = .09$) and median overall survival (37.8 mo versus 13.4 mo, $P = .03$) were better in the subset of patients without extrahepatic disease at diagnosis. This was yet another study demonstrating the need to accrue more data regarding incorporating Y-90 into earlier therapy—perhaps first line.

Gulec et al conducted a prospective, phase II clinical trial with an in vivo double-arm control assessing systemic chemotherapy plus radioembolization with Y-90 resin microspheres compared to chemotherapy alone.[22] Eighteen patients with bilobar liver metastases were treated with systemic chemotherapy (FOLFOX6 [fluorouracil plus leucovorin and oxaliplatin] for first-line treatment, n = 16; or FOLFIRI [folinic acid plus fluorouracil and irinotecan hydrochloride] for second-line treatment, n = 2) and radioembolization of only one lobe of the liver. The difference in response between

TABLE 2. COMPARISON OF SYSTEMIC CHEMOTHERAPY PLUS SIRT AND CHEMOTHERAPY ALONE*

Period	Mean Decrease in TLG Values (%)			Mean Decrease in Functional Tumor Volume (%)			Mean Decrease in Tumor Volume (%)		
	Chemotherapy + SIRT	Chemotherapy Only	*P* Value	Chemotherapy + SIRT	Chemotherapy Only	*P* Value	Chemotherapy + SIRT	Chemotherapy Only	*P* Value
1 mo	86.26 ± 18.57	31.74 ± 80.99	< .01	80.47 ± 25.67	41.32 ± 58.46	.01	39.67 ± 31.06	18.5 ± 64.64	.09
2–4 mo	93.13 ± 11.81	40.8 ± 73.32	.01	90.67 ± 17.01	46.67 ± 60.59	< .01	66.53 ± 25.53	31.13 ± 73.15	.04
6–8 mo	90.55 ± 19.75	54.91 ± 38.55	< .01	82.22 ± 38.85	56 ± 28.93	.08	72.75 ± 24.94	52.5 ± 50.03	.2

Abbreviations: SIRT, selective internal radiation therapy.
**Data from Gulec et al.*[22]

the lobes treated with systemic chemotherapy alone and systemic chemotherapy plus radioembolization was assessed using serial FDG PET/CT performed at 1 month, 2 to 4 months, and 6 to 8 months after Y-90 treatment. For each diagnostic PET/CT, standard uptake value, functional tumor volume, and total lesion glycolysis (TLG) calculations were measured. A summary of the findings for mean decrease in TLG values, functional tumor volume, and tumor volume in patients with tumors receiving chemotherapy plus selective internal radiation therapy (SIRT) and chemotherapy-only treatment are presented in Table 2. The superiority of FDG PET/CT for follow-up imaging was noted in this study and has been proposed by various authors because of its metabolism-based imaging (Figures 1 and 2).[23-25]

ONGOING CLINICAL TRIALS

The potential survival benefit of radioembolization plus systemic chemotherapy as first- or second-line treatment in liver-dominant metastatic CRC needs to be established with studies that include larger populations. There are various ongoing clinical trials evaluating the role of Y-90 in the treatment of patients with metastatic CRC and other solid tumors with liver metastases as first- and second-line therapy. For example, EPOCH is a randomized phase III trial that has enrolled approximately 360 patients. Its primary outcome is progression-free survival comparing second-line chemotherapy plus radioembolization to chemotherapy alone in patients with unresectable metastatic liver CRC who have progressed on oxiplatin- or irinotecan-based first-line chemotherapy. The estimated primary completion date is September 2016.

Several trials are also being conducted using Y-90 resin microspheres as first- and second-line therapies. The SIRFLOX and SIR-step studies are comparing systemic chemotherapy to systemic chemotherapy plus SIRT as first-line therapy in patients with metastatic CRC to the liver. The SIR-KRAS study is comparing systemic chemotherapy to chemotherapy plus SIRT as second-line therapy in patients with metastatic CRC to the liver. The FOXFIRE study is comparing FOLFOX plus biologic agent to FOLFOX plus biologic agent and SIRT. The InSIRT study is looking at SIRT as a second-line treatment for CRC liver metastases.

Data from the ongoing clinical trials may assist in answering valuable questions regarding survival benefits provided by radioembolization when used as first- and second-line therapy. Currently, data support that radioembolization does provide a survival benefit compared to supportive care in patients who have developed progressive liver metastases while on systemic chemotherapy. In addition, as various studies have noted, outcomes are poorer when a larger volume of liver is occupied by tumor. This highlights the need to refer patients for radioembolization as soon as it is known that hepatic metastases have progressed on systemic therapy. ■

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