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Authors

Marsala, Andrew
Lee, Edward W
Padia, Siddharth A

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Yttrium-90 Radioembolization for Metastatic Colorectal Cancer: Outcomes by Number of Lines of Therapy

Andrew Marsala, MD[1] Edward W. Lee, MD, PhD[1] Siddharth A. Padia, MD[1]

[1] Division of Interventional Radiology, Department of Radiology, David Geffen School of Medicine at University of California, Los Angeles, California

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Address for correspondence Siddharth A. Padia, MD, Division of Interventional Radiology, Department of Radiology, David Geffen School of Medicine at University of California, Los Angeles, 757 Westwood Plaza, Room 2125, Los Angeles, CA 90095 (e-mail: spadia@mednet.ucla.edu).

Abstract

Metastatic colorectal cancer represents the most common liver malignancy, and imparts a very poor prognosis for those who develop this disease. Unlike primary liver tumors such as hepatocellular carcinoma, which largely develops in patients with underlying cirrhosis, most metastatic liver tumor patients have normal underlying liver function. Owing to this, most will succumb to tumoral replacement of the liver rather than from underlying liver dysfunction. Radioembolization represents a treatment modality that can be used in multiple fashions to treat one or both lobes of the liver. Techniques depend on whether the procedure is used as first-line, second/third-line, or as salvage therapy. Outcomes and complications of radioembolization are presented in this article, as well as background information on colorectal cancer and systemic therapies.

Keywords
- colorectal cancer
- interventional radiology
- radioembolization
- chemotherapy
- transarterial therapy

Objectives: Upon completion of this article, the reader will be able to discuss the role of radioembolization in patients with colorectal cancer metastatic to the liver, including the indications for treatment, outcomes, and complications associated with the treatment.

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Radioembolization is an effective locoregional therapy used to treat liver metastases from colorectal cancer. Data of varied robustness support its use potentially across all lines of chemotherapy. How to best integrate radioembolization into the treatment paradigm remains the subject of ongoing research. The benefits of radioembolization are well established in the salvage therapy population and guidelines published in 2016 by the European Society for Medical Oncology (ESMO) recommend consideration of radioembolization in this setting.[1] This review will discuss current standard-of-care treatment options for patients with metastatic colorectal cancer (mCRC) and the studies supporting the integration of radioembolization into various lines of chemotherapy.

Background: Colorectal Cancer and Systemic Therapy

Colorectal cancer is the fourth leading cause of cancer-related death in the United States. Approximately 134,490 new cases are diagnosed each year and up to 60% will develop liver metastases.[2,3] Among patients with liver metastases, only 10 to 20% are resectable for a cure.[4] The majority of remaining candidates undergo treatment with systemic chemotherapy, with the goal of tumor control to prolong

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survival. While advances in chemotherapy and the addition of biologic agents have extended survival and may even increase the number of patients eligible for resection, chemorefractory liver metastases remain a life-limiting factor for most patients.[5–8]

Combination cytotoxic chemotherapy represents the current standard of care in the treatment of unresectable mCRC. A full discussion of all the chemotherapeutic regimens is beyond the scope of this document, but can be found in both the National Comprehensive Cancer Network (NCCN) and ESMO treatment guidelines for colorectal cancer.[1,9] The most commonly used first-line systemic regimen is the combination of a fluoropyrimidine (intravenous 5-fluorouracil with leucovorin) and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Both regimens have been shown to have comparable survival times.[10] Bevacizumab, a vascular endothelial growth factor A–targeting monoclonal antibody, is often added to these regimens.[11]

Patients inevitably fail their initial chemotherapy regimen due to either tumor progression or intolerance to the medications. For second-line therapy, patients frequently switch to the other combined regimen (e.g., FOLFOX to FOLFIRI).[10] Bevacizumab has also been studied in the second-line setting and shown to have benefit, although the results are less dramatic when compared with its use in the first-line setting.[12] Since individual agents are often added or subtracted to these regimens due to the desire to achieve higher efficacy or reduce toxicity, the definition of "lines of chemotherapy" is often blurred.[13] For example, after an initial "induction" chemotherapy regimen of FOLFOX with bevacizumab, one may choose to change to a long-term maintenance regimen of an oral fluoropyrimidine (e.g., capecitabine) with bevacizumab (CAPOX).[14,15] Furthermore, many patients may go on chemotherapy "holidays" due to long-standing toxicity, and may eventually resume their prior regimen.

Beyond second-line therapy, defined regimens become harder to define and therapy often centers on receptor types identified at biopsy. In patients who have a KRAS wild-type genetic profile, cetuximab and panitumumab, chimeric anti-EGFR antibodies have demonstrated improved response rates and progression-free survival when used in the second-line setting.[16,17] It has also been shown to give an overall survival benefit over best supportive care in the chemorefractory patient population.[18]

BRAF mutations occur in 5% of patients with mCRC, and its presence confers an aggressive subtype of tumor biology. This mutation is typically associated with early chemotherapy resistance and inferior overall survival.[19] As a result, many medical oncologists will consider a highly aggressive first-line regimen, such as combining oxaliplatin, irinotecan, and bevacizumab (FOLFOXIRI plus bevacizumab).[20] Similar to patients with KRAS mutant profiles, the benefit of anti-EGFR therapy (e.g., cetuximab, panitumumab) is limited.

In chemorefractory disease, several third-line agents can be considered, including cetuximab or panitumumab alone or in combination with irinotecan. Also approved for use in this setting is regorafenib, a multikinase small-molecule inhibitor. In chemorefractory disease, both of these agents demonstrated minimal improvement in survival, albeit with significant rates of toxicity.[21,22] The choice of regimen depends on several factors, such as efficacy and toxicity, previous treatment received, and tumor genetics.

Other biologic agents include ramucirumab, a human monoclonal antibody to the extracellular domain of VEGFR-2, and ziv-aflibercept, a recombinant fusion protein that inhibits VEGF. When used as a part of second-line therapy, ziv-aflibercept demonstrated modest improvements in survival.[23] However, significant toxicities associated with ziv-aflibercept have limited its use.

Radioembolization in the First-Line Setting

Several studies have been conducted and several are underway to determine where radioembolization best fits in the treatment algorithm of liver-dominant mCRC. Longer survival times from the first radioembolization treatment are expectedly observed when it is used early in the course of a patient's disease.[24,25] However, when survival is calculated from the diagnosis of the primary tumor or from the diagnosis of hepatic metastases, a statistically significant difference has not been demonstrated when radioembolization is used early (two or less prior cytotoxic chemotherapy agents) versus later (three or more prior cytotoxic chemotherapy agents) in the course of disease.[24] A randomized phase II trial comparing first-line 5-fluorouracil/leucovorin plus radioembolization to 5-fluorouracil/leucovorin alone in 21 patients yielded positive results. Patients were stratified by the presence or absence of extrahepatic metastatic disease and the degree of liver involvement (<25% or >25%). Compared with chemotherapy alone, the 5-fluorouracil/leucovorin plus radioembolization group demonstrated significantly improved response rate (73% best objective response vs. 0%, $p < 0.001$), increased time to progression (18.6 vs. 2.6 months, $p < 0.0005$), increased overall survival (29.4 vs. 12.8 months, $p = 0.02$), and improved health-related quality of life compared with baseline.[26] However, since the publication of these pivotal trials, the addition of oxaliplatin or irinotecan to standard first-line systemic chemotherapy has significantly improved outcomes for chemotherapy-naïve patients. A subsequent single-arm phase I trial demonstrated an objective response rate of 90% and confirmed the safety of radioembolization administered as a part of an oxaliplatin-based chemotherapy regimen.[27]

SIRFLOX, the first large-scale randomized phase III trial integrating radioembolization with first-line chemotherapy, compared the more modern FOLFOX-based regimen (plus or minus bevacizumab) to FOLFOX plus radioembolization.[28] A total of 530 patients were enrolled at 87 institutions with progression-free survival as the primary endpoint. Treatment with FOLFOX plus radioembolization significantly delayed disease progression in the liver (20.5 vs. 12.6 months, $p = 0.002$) but failed to improve overall progression-free survival compared with treatment with FOLFOX alone (10.7 vs. 10.2 months, $p = 0.43$). Given that radioembolization is a targeted locoregional therapy, Sangha et al postulated that failure to reach the primary endpoint may be related to extrahepatic metastatic disease that was present in 40% of patients enrolled.[29] Overall survival, a secondary endpoint

of the SIRFLOX trial, will be analyzed in combination with the FOXFIRE and FOXFIRE global trials currently underway. It should also be noted that toxicities were increased in the radioembolization group (grade $\geq$3: 85 vs. 73%). In the radioembolization group, higher rates of neutropenia, thrombocytopenia, fatigue, and abdominal pain were noted. Gastric or duodenal ulcers occurred in 3.7% and hepatic failure or radiation hepatitis occurred in 2% of patients. Significant toxicities from radioembolization may preclude patients from receiving adequate systemic agents in the future, which may ultimately limit their overall survival.

Radioembolization in Second/Third-Line Therapy

Phase I trial data also support the use of radioembolization with second- and third-line chemotherapy regimens. Irinotecan plus radioembolization yielded an overall response rate of 48% and a disease control rate of 87% in patients who had failed prior 5-FU chemotherapy. One-third of patients had failed at least two lines of chemotherapy and almost two-thirds had failed oxaliplatin-based regimens. Median progression-free survival was 9.2 months in the liver and 12.2 months overall.[30] A randomized, prospective trial of radioembolization in patients who have failed first-line systemic chemotherapy is currently underway.

Radioembolization for Salvage Therapy

The vast majority of studies assessing the benefit of radioembolization for mCRC are in the salvage setting. Of course, the strict definition of "salvage" is not mutually agreed upon. But most studies consider "salvage" patients as those who have failed multiple lines of chemotherapy, are ineligible for other therapies, and continue to have progressive disease by imaging.[5] Favorable prognostic factors in this population include an acceptable performance status (i.e., Eastern Cooperative Oncology Group (ECOG) 0, lower tumor burden, and the absence of extrahepatic disease.[25,31]

A prospective, multicenter, randomized trial compared fluorouracil alone to fluorouracil plus radioembolization in the salvage setting.[32] A total of 44 patients were included in the analysis, and radioembolization demonstrated superior progression-free survival (4.5 vs. 2.1 months, $p = 0.03$) and a trend toward improved overall survival (10.0 vs. 7.3 months, $p = 0.80$). Despite performing radioembolization in the salvage setting where patients had already been exposed to numerous lines of chemotherapy, radioembolization was well tolerated, and significant toxicities were lower than that in the control group.

In a comparative retrospective study of 339 patients with chemorefractory malignancies metastatic to the liver treated with radioembolization, a cohort of 224 patients with mCRC was subselected.[6] The patients were primarily ECOG 0 (85%) and without extrahepatic disease (62%). Eighty-seven percent of patients had bilobar disease, though less than 25% of the liver was involved in most patients. After a single round of radioembolization, these patients were compared with a smaller cohort who also had been referred for radioembolization but considered unsuitable due to variant arterial anatomy not correctable by prophylactic coil embolization, degree of hepatopulmonary shunting, refusal to consent, or having chosen another treatment option (e.g., a biologic agent). Median overall survival in the radioembolization cohort was 11.9 months, compared with 6.6 months in the supportive care cohort ($p = 0.001$). The ulceration rate in the treated population in this study was 3.2%, which may in part be due to some cases with poor arterial flow from multiple lines of systemic chemotherapy.

Similar results were described in a retrospective matched-pair comparison of radioembolization plus best supportive versus best supportive care alone.[5] Following initial matching for prior treatment history and tumor burden, 29 matching pairs were identified based on percentage of liver involved, synchronous versus metachronous metastases, stable versus increasing alkaline phosphatase, and a carcinoembryonic antigen (CEA) greater than or less than 200 ng/mL. Sixteen (55.2%) matched all four criteria, 11 (37.9%) matched three criteria, and 2 pairs (6.9%) matched two criteria. Approximately 50% of all patients had extrahepatic disease, which, to undergo radioembolization, needed to be stable. Overall survival was significantly longer for the treatment group (8.3 vs. 3.5 months, $p < 0.001$). This was apparent at just 3 months at which time 97% of the treatment group was alive versus just 59% of the best supportive care (BSC)-only group. At 12 months, 24% of the treatment group was alive versus 0% of the BSC-only group. Univariate analysis determined that radioembolization and performance status significantly reduced the risk of death. Multivariate analysis determined that radioembolization predicted significantly prolonged survival and extent of liver involvement was associated with a significantly increased risk of death. Of note, almost one-third of patients who underwent radioembolization were later able to receive chemotherapy.

Radioembolization-induced liver disease (REILD) is an uncommon outcome after radioembolization, characterized by clinical onset of hepatic dysfunction, fatigue, and ascites, in the absence of tumor progression. While in some cases REILD can be reversible, in others this can progress to liver failure and death. Studies have shown that multiple lines of chemotherapy increase the risk of REILD.[33] Therefore, in the salvage setting after patients have been exposed to numerous chemotherapy agents, the risk of REILD is perhaps greater compared with a scenario where radioembolization is done earlier in the course of disease (►**Fig. 1**).

Interactions with Systemic Agents

Care must be taken when combining radioembolization with systemic agents to minimize toxicity and potentially maximize efficacy. For mCRC, recent exposure to biologic agents, especially bevacizumab, can result in significant vascular compromise. This manifests as small caliber hepatic arteries, poor hepatic arterial flow, or frequent spam and dissection after catheterization (►**Fig. 2**).[34] In general, it is advisable to

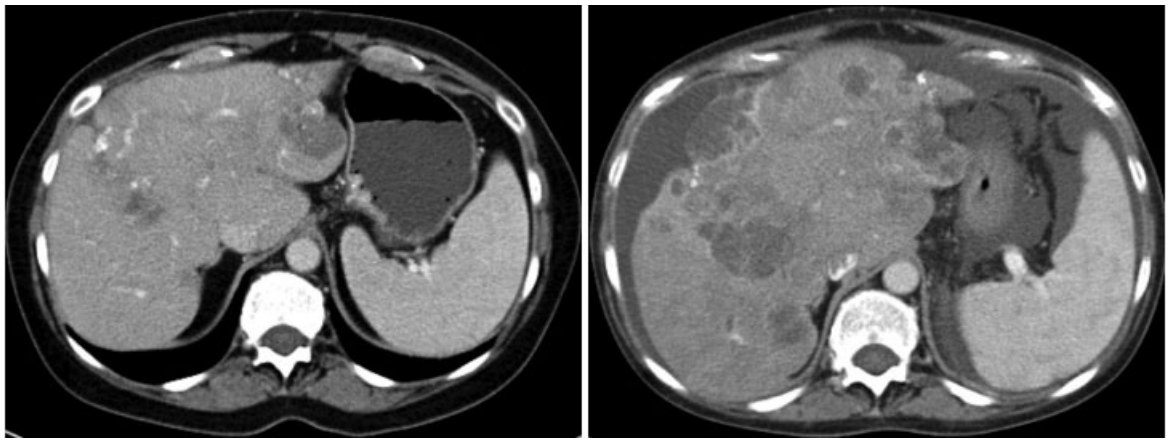

Fig. 1 Radioembolization-induced liver disease. A 55-year-old woman with metastatic colorectal cancer had progressed after numerous lines of chemotherapy (**a**). Two months after radioembolization, she developed ascites, fatigue, and liver dysfunction (**b**).

hold bevacizumab for at least 4 to 6 weeks before mapping angiography.[35]

Oxaliplatin, often used in first- and second-line systemic regimens, is a radiosensitizer which can potentiate the effects of radioembolization. In a phase I dose-escalation study of oxaliplatin when combined with radioembolization, grade 3 and 4 toxicities were observed at significant levels at the highest doses of oxaliplatin.[27] Based on this study, the authors advised a maximum oxaliplatin dose of 60 mg/m^2 when patients are treated with radioembolization.

Irinotecan, which is often used in first- and second-line regimens, has a known synergistic effect with external beam radiation in patients with lung cancer.[36] Van Hazel et al tested maximum tolerated dose of irinotecan when combined with radioembolization in a dose-escalation phase I study.[30] In this study of 25 patients, the maximum tolerated dose of irinotecan was not reached using resin microspheres with body surface area dosimetry, and therefore the dose of irinotecan of 100 mg/m^2 was recommended.

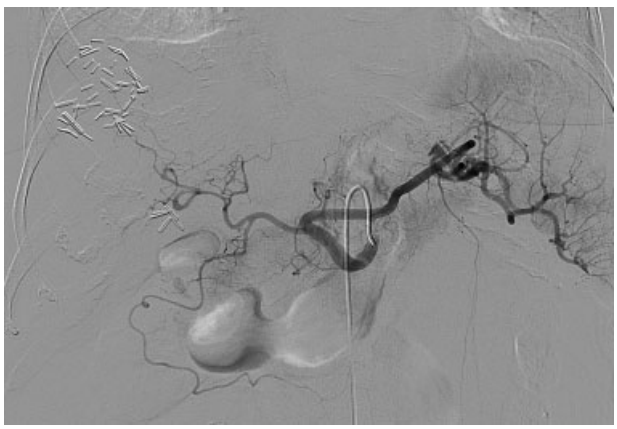

Fig. 2 Effect of biologic agents on arterial vasculature. A 61-year-old woman with metastatic colorectal cancer underwent mapping angiogram for planned radioembolization, 3 weeks after her most recent dose of bevacizumab. The hepatic arterial branches are markedly diminutive in caliber with poor antegrade flow. A repeat angiogram (not shown) 3 weeks later showed normal caliber vessels, which were conducive to safe ^{90}Y microsphere delivery.

Conclusion

Numerous studies have demonstrated the utility of radioembolization for patients with mCRC at various stages. Despite these results, there is currently no conclusive evidence for the use of radioembolization in combination with modern-day first-line chemotherapy in prolonging overall survival. The vast majority of evidence continues to support the use of radioembolization in the salvage setting, and promising results have been shown when used earlier in the course of patients' disease. Knowledge of patients' recent systemic agent exposure will help the interventionalist to minimize toxicity and potentially improve outcomes.

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