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Evidence-Based Integration of Yttrium-90 Radioembolization in the Contemporary Management of Hepatic Metastases from Colorectal Cancer

David S. Wang, MD, John D. Louie, MD, and Daniel Y. Sze, MD, PhD

Hepatic metastases are common in patients with metastatic colorectal cancer and are frequently the most life-threatening source of morbidity and mortality. The contemporary management of patients with liver-dominant or liver-only metastatic colorectal cancer is characterized by resection of metastases when feasible and successive lines of systemic treatment regimens consisting of chemotherapy drugs and/or targeted biological agents. Yttrium-90 radioembolization has emerged as a promising liver-directed therapy for patients with unresectable colorectal cancer liver metastases (CLM). The integration of radioembolization into the current treatment algorithm for unresectable CLM is dependent on the line of therapy it is being considered and whether it is to be used alone or in combination with systemic treatment options. This article provides background information on the current management of CLM and uses this framework to discuss the existing data that define when and how radioembolization can benefit patients with CLM.

KEYWORDS colorectal liver metastasis, yttrium-90, radioembolization, selective internal radiation therapy, liver-directed therapy, colorectal cancer

Introduction

Worldwide, colorectal cancer (CRC) is the third most commonly diagnosed cancer and a leading cause of cancer-related mortality.[1] Related to portal venous drainage of the colon and rectum, the liver is the most common and often predominant site of metastasis, occurring in up to 60% of CRC patients during the course of their disease.[2,3] In 20%-35% of patients with metastatic CRC (mCRC), the liver is the only site of distant spread. The presence of CRC liver metastases (CLM) portends a poor prognosis since liver failure from hepatic disease progression is a common cause of death.[4]

As blood supply to hepatic metastases is almost exclusively arterial, whereas normal liver parenchyma is supplied mostly by the portal venous system,[5] several liver-directed transarterial therapies have been used in clinical practice for locoregional control of CLM. These include transarterial radioembolization (TARE) with yttrium-90 (^{90}Y) microspheres, chemoembolization with irinotecan-eluting beads, chemoembolization with chemotherapy-ethiodized oil emulsion, and hepatic arterial infusion of chemotherapy.[6] Among these, the accumulated clinical evidence to date is most robust for TARE with ^{90}Y microspheres.

TARE, also known as selective internal radiation therapy, is a form of intra-arterial brachytherapy where microspheres loaded with the beta particle emitter ^{90}Y are delivered via catheters placed into tumor-supplying hepatic arteries. There are currently 2 commercially available TARE devices: the resin-based microsphere SIR-Spheres (Sirtex Medical Ltd, North Sydney, NSW, Australia), and the glass microsphere TheraSphere (BTG International, Ottawa, Canada). In the United States, only the resin microsphere is approved by the FDA for use in CLM patients, specifically in conjunction with hepatic

Division of Interventional Radiology, Stanford University School of Medicine, Stanford, CA.
Address reprint requests to David S. Wang, MD, Division of Interventional Radiology, Stanford University School of Medicine, 300 Pasteur Drive, H3630, Stanford, CA 94305-5642. E-mail: davidwang@stanford.edu

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arterial infusion of floxuridine.[7] The bulk of the published literature on TARE for CLM is with resin microspheres, either used alone or in combination with chemotherapy.

The contemporary management of CLM is characterized by algorithmic evidence-based treatment recommendations covering various stages in the course of disease.[8,9] Although TARE has emerged as a safe and effective liver-directed treatment for select patients with unresectable liver-dominant or liver-only mCRC, the specific timings and clinical indications where TARE provides meaningful clinical benefit are continuously being refined as data accumulate. The aims of this article are to summarize and discuss the existing evidence supporting the integration of TARE into the current treatment paradigm for management of CLM.

Contemporay Management of Colorectal Cancer Liver Metastases

While a comprehensive review of the latest treatment guidelines for mCRC is beyond the scope of this paper, a basic understanding of the current standard of care treatment strategies is necessary to provide a framework to contextualize the data on TARE for CLM.[8,9]

Surgical Resection

The first critical step in the treatment algorithm for CLM is to determine whether a patient has resectable liver metastases. For patients deemed resectable, surgical resection is potentially curative with reported 5- and 10-year survival rates of up to 58% and 36%, respectively.[10-12] Unfortunately, only 20%-30% of CLM patients are candidates for surgical resection at the time of presentation.[13] Local tumor ablation is an alternative treatment option for select patients who may not tolerate surgery.[14]

Systemic Chemotherapy

For patients with unresectable CLMs, combination systemic chemotherapy with or without molecularly targeted biological agents is standard of care treatment with the palliative goal of prolonging survival and maintaining quality of life. In some highly select cases, systemic therapy may sufficiently downstage patients to allow conversion from initially unresectable to resectable status.[8,9]

Significant advancements were made in the last 2 decades with the development of irinotecan and oxaliplatin-based chemotherapy regimens and the advent of targeted biological agents. Modern frontline systemic therapy regimens have increased median overall survivals (OS) to near 30 months compared to 12 months with previous generation treatments.[15,16] There are currently 9 different classes of drugs for mCRC: fluoropyrimidines (fluorouracil [5-FU], given intravenously with leucovorin [LV]; capecitabine, given orally), irinotecan, oxaliplatin, epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab, vascular endothelial growth factor (VEGF) inhibitors bevacizumab and ziv-aflibercept, VEGF receptor 2 inhibitor ramucirumab, multikinase inhibitor regorafenib, trifluridine-tipiracil (TAS-102), and the immunotherapy drugs nivolumab and pembrolizumab.

The most commonly used initial or first-line systemic regimen is 5-FU/LV combined with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), often with the addition of bevacizumab.[17,18] Patients inevitably fail first and subsequent lines of systemic therapy due to progression of disease, lack of treatment response, development of resistance, or intolerance of toxicities. Second-line therapies usually consist of changing to the other doublet chemotherapy regimen not initially used, such as FOLFOX to FOLFIRI. Irinotecan-based regimens are common as second-line therapy. Third-line treatment options include TAS-102, regorafenib, and cetuximab or panitumumab for *RAS* wild-type tumors if EGFR-inhibitor naïve.[19] Therapeutic efficacy progressively declines with each successive line of therapy.

^{90}Y Radioembolization for Unresectable Colorectal Cancer Liver Metastases

Although there has been a recent paradigm shift in the systemic treatment of mCRC to a "continuum of care" model where many CRC drugs are adaptively incorporated into individualized treatment plans,[20] the "lines of therapy" model is used here to compartmentalize the data on ^{90}Y TARE for unresectable CLM.

Radioembolization as Salvage (≥Third-Line) Therapy

The first patients with unresectable liver-only or liver-dominant mCRC treated with TARE were those with chemotherapy refractory disease, defined here as having had failed first and second-line standard systemic therapies, which typically means prior exposure to 5-FU, oxaliplatin, and irinotecan. A great majority of the prospective (Table 1) and retrospective (Table 2) published studies on TARE for unresectable CLM are in the salvage setting.

In a phase II multicenter prospective clinical trial of TARE in 50 CLM patients who failed prior oxaliplatin- and irinotecan-based chemotherapy regimens, Cosimelli et al reported median time to progression (TTP) and progression free survival (PFS) of 3.7 months and median OS of 12.6 months from time of therapy initiation.[21] In a matched-pair study of 58 chemorefractory CLM patients, 29 patients were prospectively treated with TARE with best supportive care (BSC) and retrospectively compared with matched controls who received BSC alone.[22] Median OS was significantly prolonged with TARE plus BSC versus BSC alone (8.3 vs 3.5 months, $P < 0.001$). In a unique multicenter phase III prospective randomized controlled trial (RCT) by Hendlisz et al, 44 chemorefractory liver-only mCRC patients were randomized to either combination TARE with 5-FU infusion or 5-FU alone.[23] The combined TARE plus 5-FU cohort demonstrated longer median TTP in the liver (5.5 vs 2.1 months, $P = 0.03$) and a trend toward improved median OS (10.0 vs

Table 1 Radioembolization as Salvage Therapy: Prospective and Matched-Pair Studies

Reference (y)	Study Type	Treatment	N	ORR (%)	SD (%)	Median TTP or PFS (mo)	Median OS (mo)
Cosimelli et al[21] (2010)	Prospective, phase II	^{90}Y TARE	50	24.0	24.0	TTP 3.7; PFS 3.7	12.6
Seidensticker et al[22] (2012)	Matched-pair	^{90}Y TARE + BSC	29	41.4	17.2	PFS 5.5	8.3
		BSC	29	NR	NR	PFS 2.1	3.5
Hendlisz et al[23] (2010)	Prospective, phase III RCT	^{90}Y TARE + 5-FU	21	9.5	76.2	TTP liver 5.5; TTP 4.5	10.0*
		5-FU	23	0	34.7	TTP liver 2.1; TTP 2.1	7.3
Golfieri et al[24] (2015)	Prospective	^{90}Y TARE	52	64.7	17.6	NR	11.0

BSC, best supportive care; N, number of patients; NR, not reported; ORR, objective response rate (complete response + partial response); OS, overall survival from time of first radioembolization treatment; PFS, progression free survival; RCT, randomized controlled trial; SD, stable disease; TTP, time to progression; ^{90}Y TARE, transarterial radioembolization with resin microspheres; 5-FU, fluorouracil.
*Did not reach statistical significance.

Table 2 Radioembolization as Salvage Therapy: Retrospective Studies

Reference (y)	N	Median Overall Survival* (mo)
Kennedy et al[25] (2006)	208	10.5 (responders)
Jakobs et al[26] (2008)	41	10.5
Cianni et al[27] (2009)	41	11.6
Evans et al[28] (2010)	140	7.9
Nace et al[29] (2011)†	34†	8.2
Bester et al[30] (2012)	224	11.9
Martin et al[31] (2012)	24	8.9
Sofocleous et al[32] (2015)	53	12.7
Saxena et al[33] (2015)	91 failed 2 lines of chemotherapy	10.5
	52 failed ≥ 3 lines of chemotherapy	5.6
Hickey et al[34] (2016)	295‡	9.2
Jakobs et al[35] (2017)	104	10.2
Kennedy et al[36] (2017)	184 failed 2 lines of chemotherapy	9.1
	158 failed ≥ 3 lines of chemotherapy	8.1
Turk et al[37] (2018)	43§	12.8

*Overall survival is from time of first radioembolization treatment.
†Of the 41 patients in this study, only the 34 patients who did not receive concomitant hepatic arterial infusion of floxuridine were included.
‡All patients were treated with glass microspheres and failed prior chemotherapy regimens, which included 5-fluorouracil, oxaliplatin, and irinotecan.
§Twenty-seven patients were treated with resin microspheres, 16 were treated with glass microspheres.
All other studies in this table used resin microspheres only.

7.3 months, $P = 0.80$). Notably, combination therapy did not result in increased toxicities.

With 606 patients from 11 centers, the MORE study is the largest retrospective study on the treatment of unresectable CLM with TARE using resin microspheres across different lines of therapy.[36] Fifty-six percent of these patients previously failed 2 or more lines of systemic chemotherapy. Median OS after TARE was used as third-line (N = 184) or fourth-line or later (N = 158) therapy were 9.1 and 8.1 months, respectively. Results were similar in a multicenter study of 531 patients with unresectable CLM who were treated with TARE using glass microspheres.[34] In this study, 295 patients failed prior systemic therapies which included all 3 of 5-FU, oxaliplatin, and irinotecan. Median OS after TARE in this subgroup was 9.2 months. In both studies, negative prognostic factors included increased lines of prior chemotherapy, presence of extrahepatic disease (EHD), high intrahepatic tumor burden, and poor performance status.[34,36]

As shown in Tables 1 and 2, when TARE was used as salvage, third-line or later monotherapy in unresectable CLM patients who failed at least 2 prior lines of systemic therapy, OS ranged from 8 to 13 months with a median of 10 months. These survival times compare favorably to modern systemic agents used in the third-line setting. In the large RCTs of regorafenib and TAS-102 in mCRC patients, median survivals were 6.4 and 7.1 months, respectively.[38,39] In mCRC patients who have exhausted all treatment options and receive BSC alone, expected survival is 4-6 months.[22,38,39] TARE confers a meaningful survival benefit in the salvage setting.

Despite a patient population heavily pretreated with chemotherapy, TARE in chemorefractory CLM patients has proven to be safe with an acceptable toxicity profile that has been well characterized and easily managed.[40] The notable exception is radioembolization-induced liver disease, a rare complication of TARE characterized by hyperbilirubinemia, ascites, and general hepatic dysfunction in the absence of tumor progression or bile duct obstruction.[41] Prior exposure to multiple systemic chemotherapy drugs increases the risk for radioembolization-induced liver disease; thus, earlier use of TARE may limit this risk.

Table 3 Radioembolization as Second-Line Therapy

Reference (y)	N	Median Overall Survival* (mo)
van Hazel et al[42] (2009)	25†	12.2
Saxena et al[33] (2015)	159	12.0
Hickey et al[34] (2016)	231‡	14.7
Kennedy et al[36] (2017)	206	13.2

*Overall survival is from time of first radioembolization treatment.
†Patients were treated with radioembolization with concomitant irinotecan systemic therapy. Of the 25 patients, 17 (68%) failed 1 prior line of systemic chemotherapy, 6 failed 2 lines, and 2 failed 3 lines.
‡All patients were treated with glass microspheres. Of the 231 patients, 216 (93.5%) failed prior treatment with 1 or 2 of 5-fluorouracil, oxaliplatin, and irinotecan. Fifteen received none of these 3 agents.
All other studies in this table used resin microspheres only.

Radioembolization as Second-Line Therapy

In the 3 largest retrospective studies on TARE for unresectable CLM, the reported median OS specific for patients who underwent TARE as second-line monotherapy ranged from 12 to 14.7 months (Table 3).[33,34,36] These survival outcomes are comparable to that of contemporary second-line chemotherapy RCTs. In mCRC patients previously treated with an oxaliplatin-based, first-line chemotherapy regimen, median OS for second-line FOLFIRI without and with aflibercept were 12.1 and 13.5 months, respectively.[43]

The role of TARE when used in combination with chemotherapy in the second-line setting will be better defined after completion of the EPOCH trial, an ongoing multicenter phase III RCT, where unresectable CLM patients who failed first-line chemotherapy are randomized to receive standard of care second-line chemotherapy alone or combined with TARE with glass microspheres.[44]

Radioembolization as First-Line Therapy

Since several previous studies demonstrated apparently improved outcomes when TARE was used earlier in the course of patients' disease,[33,34,36] more recent research focused on integrating TARE into first-line therapy for unresectable CLM, not as monotherapy but in combination with systemic chemotherapy regimens (Table 4).

The rationale for combined modality therapy is 2-fold: (1) CLM is by definition a systemic disease and thus systemic treatment is needed for control of extrahepatic metastases; (2) oxaliplatin, irinotecan, and in particular 5-FU have radiosensitizing effects that can potentiate locoregional TARE of CLM.[49]

In the first RCT to combine TARE with systemic chemotherapy, van Hazel et al randomized 21 CLM patients to receive systemic 5-FU/LV alone or with concurrent TARE as first-line therapy (Table 4).[46] The addition of TARE resulted in markedly improved median OS of 29.4 months and objective response rate (ORR) of 91% compared to 12.8 months ($P = 0.02$) and 0% ($P < 0.001$), respectively, for the chemotherapy only group. The trial was closed early because of the dramatic benefit and the ethical concerns with continued randomization. A retrospective study of TARE combined with FOLFOX or 5-FU/LV systemic chemotherapy as initial therapy for CLM reported similar median OS of 29.4 months and ORR of 84% (Table 4).[48] Median OS was significantly better in patients with liver-only metastases compared to those with EHD (37.8 vs 13.4 months, $P = 0.03$).

Although 5-FU/LV alone is no longer standard frontline therapy for mCRC, the van Hazel et al study raised concerns for increased myelosuppression with combination therapy.[46] Sharma et al performed a phase I study in chemotherapy-naïve CLM patients where escalating oxaliplatin doses (30-85 mg/m^2) were given as part of a FOLFOX systemic chemotherapy regimen in combination with TARE.[47] With a dose-limiting toxicity of increased neutropenia observed with the

Table 4 Radioembolization with Chemotherapy as First-Line Therapy: Early Studies

Reference (y)	Study Type	Treatment	N	ORR (%)	SD (%)	Median TTP or PFS (mo)	Median OS (mo)
Gray et al[45] (2001)	Prospective, phase III RCT	^{90}Y TARE + HAI FUDR	36	44.4	36.1	TTP liver 15.9	2 y: 39%*
		HAI FUDR	34	17.6	38.22	TTP liver 9.7	2 y: 29%
van Hazel et al[46] (2004)	Prospective, phase II RCT	^{90}Y TARE + 5-FU/LV	11	90.9	9.1	TTP 18.6	29.4
		5-FU/LV	10	0	60.0	TTP 3.6	12.8
Sharma et al[47] (2007)	Prospective, phase I	^{90}Y TARE + FOLFOX4 with oxaliplatin dose escalation	20	90.0	00.0	TTP liver 12.3; PFS 9.3	NR
Kosimder et al[48] (2011)	Retrospective	^{90}Y TARE + 5-FU/LV (N = 7) or FOLFOX (N = 12)	19	84.2	5.3	TTP liver 15.8; PFS 10.4	29.4

FOLFOX, leucovorin, fluorouracil, oxaliplatin; FUDR, floxuridine; 5-FU/LV, fluorouracil / leucovorin; HAI, hepatic arterial infusion; N, number of patients; NR, not reported; ORR, objective response rate (complete response + partial response); OS, overall survival from time of randomization or first treatment; PFS, progression free survival; RCT, randomized controlled trial; SD, stable disease; TTP, time to progression; ^{90}Y TARE, transarterial radioembolization with resin microspheres.
*Did not reach statistical significance.

highest dose, the recommended maximum-tolerated dose (MTD) of oxaliplatin was 60 mg/m^2 for safe combination therapy of FOLFOX plus TARE. A similar dose escalation study of systemic irinotecan combined with TARE used as second-line or later treatment found combination therapy to be safe at all doses tested as a MTD was not reached.[42] Efficacy outcomes of these studies are detailed in Tables 4 and 3, respectively.

These small studies laid the foundation for the large-scale SIRFLOX (N = 530) phase III multicenter RCT and its companion trials FOXFIRE (N = 364) and FOXFIRE-Global (N = 209), which were designed to evaluate the efficacy and safety of combination FOLFOX systemic chemotherapy and TARE with resin microspheres as first-line therapy for CLM (Table 5).[50,51] In all 3 trials, chemotherapy-naïve CRC patients with liver metastases not suitable for resection or ablation without or with limited EHD were randomized to receive either FOLFOX chemotherapy plus TARE or FOLFOX alone. The addition of bevacizumab (or cetuximab for FOXFIRE) was allowed for both arms at the discretion of the treating investigator. The systemic regimens for both groups were similar except in the TARE treatment arm the oxaliplatin dose was reduced for cycles 1-3 per the Sharma et al phase I study,[47] and targeted biological agents were not started until after TARE was administered during cycle 1 or 2 of chemotherapy. The primary endpoint for the SIRFLOX study was PFS.[50] OS was the primary endpoint for preplanned combined analysis of the 3 RCTs.[51]

In the SIRFLOX study, first-line treatment with FOLFOX plus TARE significantly improved ORR (78.7% vs 68.8%, P = 0.042) and delayed disease progression in the liver (20.5 vs 12.6 months, P = 0.002), but did not prolong overall PFS (10.7 vs 10.2 months, P = 0.43) compared to FOLFOX alone (Table 5).[50] In the pooled analysis of 1103 patients from the 3 RCTs, the addition of TARE to first-line FOLFOX chemotherapy also did not improve overall PFS (11.0 vs 10.3 months; P = 0.11) as well as OS (22.6 vs 23.3 months, P = 0.61) compared to FOLFOX alone (Table 5).[51] There was also no difference in post-treatment resection rates between the 2 groups. In subgroup analyses, only those patients with right-sided primary tumors, which is associated with worse prognosis and response to standard systemic therapies,[52] demonstrated significantly improved survival with the addition of TARE (22.0 vs 17.1 months, P = 0.007).[53] In the subgroup of 713 patients with liver-only disease, there was no significant OS difference between the treatment arms. Moreover, grade 3 or higher toxicities, including neutropenia and TARE-specific toxicities, were higher in the combined FOLFOX plus TARE group.

Summary and Recommendations

The integration of ^{90}Y TARE into the current treatment paradigm for unresectable CLM is dependent on the line of therapy it is being considered and whether it is used alone or in combination with modern systemic chemotherapy regimens.

A large body of evidence exists supporting the use of TARE as salvage monotherapy for patients with unresectable liver-only or liver-dominant mCRC who have failed 2 or more prior lines of systemic chemotherapy (Tables 1 and 2). Relative to current systemic third-line or later treatment options and BSC, TARE confers a meaningful survival benefit with low toxicities in this setting. Guidelines published by the National Comprehensive Cancer Network (category 2A recommendation)[8] and the European Society for Medical Oncology (grade B recommendation)[9] endorse TARE as a treatment option for patients with chemorefractory liver-dominant mCRC.

The data supporting the application of TARE alone as second-line therapy for unresectable CLM are limited but show survival outcomes comparable to that of contemporary second-line systemic chemotherapy regimens (Table 3). However, additional evidence is needed before TARE can be recommended for unresectable CLM patients who are refractory to first-line systemic therapy. Results from the EPOCH trial are awaited to define the role of TARE when combined with standard of care chemotherapy as second-line treatment.

The SIRFLOX, FOXFIRE, and FOXFIRE-Global RCTs evaluated the efficacy and safety of combination FOLFOX systemic chemotherapy and TARE as first-line therapy for patients with unresectable CLM. Despite improved liver-specific disease control and radiological response, the addition of TARE to first-line FOLFOX did not translate to increased

Table 5 Radioembolization with Chemotherapy as First-Line Therapy: Recent Randomized Controlled Trials

Trial (y)	Treatment	N	ORR (%)	Median PFS Liver (mo)	Median PFS Any Site (mo)	Median OS (mo)
SIRFLOX[50] (2016)	^{90}Y TARE + FOLFOX ± bev	267	78.7	20.5	10.7	NR
	FOLFOX ± bev	263	68.8	12.6	10.2	NR
SIRFLOX/FOXFIRE/FOXFIRE-Global[51] (2017)	^{90}Y TARE + FOLFOX ± bev/cet	554	75.8	NR	11.0	22.6
	FOLFOX ± bev/cet	549	63.8	NR	10.3	23.3

bev, bevacizumab; bev/cet, bevacizumab or cetuximab; FOLFOX, leucovorin, fluorouracil, oxaliplatin (modified FOLFOX6 for SIRFLOX and FOXFIRE-Global, oxaliplatin modified de Gramont chemotherapy [OxMdG] for FOXFIRE); N, number of patients; NR, not reported; ORR, objective response rate in the liver (complete response + partial response); OS, overall survival from time of randomization; PFS, progression free survival from time of randomization; ^{90}Y TARE, transarterial radioembolization with resin microspheres.

overall PFS or OS compared to chemotherapy alone (Table 5).[50,51] The routine early integration of TARE in combination with oxaliplatin-based, first-line chemotherapy cannot be recommended at this time as initial therapy for all patients with unresectable CLM. In subgroup analyses, however, a significant survival benefit was observed in patients with right-sided primary tumors who received combination therapy compared to FOLFOX alone. As several systemic chemotherapy studies have demonstrated worse response to treatment and prognosis in patients with right-sided primary tumors versus those with left-sided tumors,[52] further studies designed to define the potential benefit of TARE in this specific patient population are warranted.

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