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Lower Gastrointestinal Cancers (AB Benson, Section Editor)

Radioembolization as a Treatment Strategy for Metastatic Colorectal Cancer to the Liver: What Can We Learn from the SIRFLOX Trial?

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Opinion statement

In the setting of liver metastases from colorectal cancer (CRC), radioembolization with yttrium-90 has been used to treat chemotherapy refractory disease with a growing interest to establish its efficacy in prospective trials combined with first- and second-line chemotherapy. SIRFLOX is an ongoing, multi-center, phase 3 randomized trial comparing first-line chemotherapy alone or in combination with yttrium-90 radioembolization in patients with CRC who have isolated liver metastases or liver-dominant metastases. Preliminary results from SIRFLOX demonstrate that radioembolization combined with first-line chemotherapy is safe and feasible. There was no significant difference in median overall

progression-free survival (PFS) between the combined radioembolization-chemotherapy and chemotherapy-only arms (10.7 versus 10.2 months). Although the trial did not meet its primary endpoint of improved median PFS, there was a significant increase in the median hepatic PFS (20.5 versus 12.6 months; $p = 0.02$) favoring the combination arm. Thus, combining radioembolization with chemotherapy in the first-line setting may be most effective for liver-limited metastatic CRC. Since radioembolization targets liver disease, it is plausible that the trial failed to achieve an improvement in PFS given that 40 % of the SIRFLOX population had extra-hepatic disease. It is also possible that the overall median PFS may be a poor surrogate endpoint, and other endpoints like overall survival still needs to be delineated in this setting. In addition, it is crucial to document improvement or delay in time to deterioration in quality of life symptom endpoints in this population. SIRFLOX is the first of three prospective studies that assess the efficacy of adding radioembolization to first-line chemotherapy, and the combined data from these trials will provide the necessary power for an overall survival analysis. The final results of SIRFLOX will be eagerly awaited to determine if the increased hepatic PFS in preliminary data will translate to increased overall survival benefit.

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and women, but the second most common cause of cancer-related death [1]. Between 19 and 24 % of patients present with distant colorectal metastases, and up to 60 % are expected to develop metastases at some point in their disease course [2, 3]. Five-year survival in patients with distant disease at diagnosis is estimated at 13.1 % [2]. The liver is the most common site of distant metastases, and the majority of deaths from metastatic colorectal cancer are thought to be due to hepatic involvement [4]. Extra-hepatic metastases, more than three tumors, and a disease-free interval of less than 12 months are factors that suggest a poorer prognosis [5–9].

While a subset of patients with disease isolated to the liver or lung is potentially curable by surgery, most patients with colorectal hepatic metastases (CHMs) are not cured. A meta-analysis performed by Kanas in 2012 on survival for surgical management of CHM found that the median 5-year survival was 38 % (range 16–74 %) and the median 10-year survival was 26 % (range 9–69 %) [10]. However, it is estimated that only 20 % of patients with CHM are eligible for resection [11]. Thus, the majority of patients with CHM are not eligible for surgery, and, even with surgical treatment, a large proportion of patients will have recurrence of disease that will eventually progress to death [12, 13].

For most patients with CHM, systemic chemotherapy is the main treatment option. In patients with liver-only or liver-dominant metastatic disease who do not meet surgical criteria, liver-directed therapies, including intra-arterial embolization, can be considered.

Chemotherapy

For patients who receive only best supportive care, the median survival for metastatic colorectal cancer is approximately 5–6 months [14, 15]. With modern chemotherapies, the median overall survival has increased to >2 years [16]. While the efficacy of modern chemotherapy regimens has contributed to this increased survival, other factors such as better supportive care at the end of life and lead time bias with patients being diagnosed at an earlier point in their disease course, thus entering clinical trials earlier, have also contributed to longer reported survival times [17].

Fluoropyrimidines are used as a part of most chemotherapy regimens to treat metastatic colorectal cancer. 5-fluorouracil (5-FU), which is usually given with leucovorin (folinic acid, LV), and capecitabine, an oral agent, enzymatically converted to 5-FU within tumor cells, being the two most commonly used. First-line chemotherapy options for metastatic colorectal cancer include 5-FU plus LV treatment combined with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), as well as capecitabine combined with oxaliplatin (CAPOX or XELOX). The most commonly used first-line therapy in the USA is FOLFOX, with approximately 55 % of patients also receiving bevacizumab, an antibody targeting vascular endothelial growth factor (VEGF) [18]. Regimens using irinotecan are often used as second-line therapy. Antiepidermal growth factor receptor (EGFR) monoclonal antibodies such as cetuximab or panitumumab are used in patients with RAS wild-type tumors [18]. Additional treatment options for refractory disease include the VEGF inhibitors aflibercept and ramucirumab, the tyrosine kinase inhibitor regorafenib, and the oral antimetabolite cytotoxic agent trifluridine-tipiracil (TAS-102), recently FDA approved.

Patients appear to benefit the most from being exposed to all potential chemotherapeutic agents rather than from a particular single treatment or a specific sequence of treatments. Grothey et al. showed that the proportion of patients who received all potentially active chemotherapy agents for CRC strongly correlated with overall survival, although this is likely influenced by immortal time bias [19, 20].

The initial trials employing first-line FOLFOX demonstrated objective response rates (ORRs) of approximately 50 % based on World Health Organization criteria (at least 50 % decrease in the sum of the products of the perpendicular diameters of measurable lesions for at least 4 weeks) [21–24]. Recent trials assessing the addition of bevacizumab or cetuximab to first-line therapy have shown ORR of approximately 60 % based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [24–26]. Recent trials have shown second-line FOLFIRI to have a response rate based on RECIST of approximately 11–12 % and median overall survival of approximately 12 months [27, 28]. The use of aflibercept in addition to FOLFIRI in second-line therapy further has demonstrated increased survival to 13.5 months [29]. In a meta-analysis assessing gains in overall survival from chemotherapeutic treatment of metastatic colorectal cancer from 1993 to 2015, Jawed et al. found the median ORR (WHO and RECIST criteria) for first-line chemotherapy to be 39.5 % and for second-line and beyond chemotherapy to be 8.6 % [17].

Once patients with CRC metastases have progressed on current chemotherapeutic regimens, median overall survival decreases to 4–5 months when treated with best supportive care [30–32]. As a salvage agent, regorafenib has shown an increase in overall survival of 6.4 versus 5 months in one study [32] and of 8.8 versus 6.3 months in a second study [31], but ORR have been small, ranging from 1 to 4 %.

Chemoembolization

Intra-arterial embolotherapy has been considered for those with chemorefractory CHM with disease confined to the liver. Transcatheter arterial bland embolization (TAE) and chemoembolization (TACE)

utilize the predominant arterial supply of liver tumors to directly deliver embolic material without (TAE) and with (TACE) chemotherapy, respectively, to destroy tumor cells. Two delivery methods have been used to deliver chemotherapeutics in TACE: Lipiodol-based (Lipiodol, Guerbet, Paris, France) and drug-eluting bead particles (DEBs). Lipiodol delivery involves the creation of an emulsion of the radiopaque oil and chemotherapeutics such as doxorubicin, cisplatin, and/or mitomycin C. Delivery of DEBs utilizes ionic interactions between the positively charged chemotherapeutic, most commonly irinotecan, and negatively charged eluting particles to load drug onto particles, which then release the dose within the target tissue [33, 34].

Early experience with TAE for CHM demonstrated no benefit [35]. Chemoembolization has shown more promise, with the use of TACE in the salvage setting achieving median overall survival of 9–14 months from the time of chemoembolization; however, most studies investigating conventional Lipiodol-based chemoembolization for CHM have been criticized for not including control groups [36–40]. Moreover, a 2013 Cochrane review did not support the use of (chemo)embolization outside of randomized clinical trials [41]. More recent promise has been shown with the use of irinotecan eluting particles (DEBIRI) in the salvage setting [33, 42–47]. A single, small randomized trial using DEBIRI has shown improved medial survival (22 versus 15 months; $p = 0.031$) [42]. However, the statistical rigor and patient population of this study have been questioned [48]. Further randomized studies are required to validate the early results with DEBIRI.

Radioembolization

Radioembolization is a well-tolerated transcatheter intra-arterial brachytherapeutic option that delivers radioactive particles to hepatic tumors via their nutrient arteries. For patients with CHM having liver-only or liver-limited disease, radioembolization has been used for disease refractory to chemotherapy and in combination as a part of first-line therapy.

The agent used for hepatic radioembolization is the high-radiation beta-emitter, yttrium-90 (^{90}Y). As the mean tissue penetration of ^{90}Y is 2.5 mm with a maximum of 1.1 cm, adjacent normal liver parenchyma is spared. Currently, two delivery mechanisms are utilized: ^{90}Y-labeled resin microspheres (SIR-Spheres®, Sirtex Medical Limited, North Sydney, Australia) and ^{90}Y-labeled glass microspheres (Therasphere®, BTG International, UK). SIR-Spheres® are resin-based microspheres that are coated with ^{90}Y leading to a lower density and lower specific activity than glass-based microspheres. Resin-based spheres range in size from 20 to 60 μm. SIR-Spheres® have FDA approval as an internal brachytherapy device for the treatment of unresectable CHM with adjuvant hepatic artery infusion of floxuridine. TheraSpheres® are glass microspheres in which ^{90}Y is a component of the glass. These glass spheres have a higher specific activity than resin spheres and range in size from 15 to 35 μm. TheraSpheres® have a humanitarian device exemption in the USA for use in patients with unresectable hepatocellular carcinoma with/out portal vein thrombosis.

Radioembolization for chemotherapy refractory disease

Radioembolization has been increasingly employed for patients with CHM with liver-only or liver-dominant disease refractory to chemotherapy. A number of studies suggest that patients may benefit from radioembolization with either ^{90}Y-labelled glass or resin microspheres. The outcomes from these studies are remarkably similar and consistent.

A recent study by Saxena et al. of 302 patients who underwent ^{90}Y-labeled resin microsphere radioembolization for unresectable, chemorefractory CHM demonstrated a median OS of 10.5 months from time of radioembolization, with an ORR (according to RECIST) of 39 % [49••]. A previous study by Kennedy et al. of 208 patients showed a similar median OS of 10.5 months for responding patients to ^{90}Y-labeled resin microsphere radioembolization, while non-responders had a far worse (4.5 months) median survival [50]. The largest series using resin microspheres, the Metastatic colorectal cancer liver metastases Outcomes after RadioEmbolization (MORE) study, included 606 patients and demonstrated an overall survival of 9.6 months, slightly less than the studies mentioned above [51••]. However, the MORE study included patients prior to 2004, which is the year biologic agents were introduced as a part of the chemotherapy regimen and has been shown to be an independent predictor of improved survival [52••]. In addition, the MORE study showed that patients with extra-hepatic disease benefit less from radioembolization: 35 % of patients in the MORE study had extra-hepatic disease, and the survival for patients without extra-hepatic disease was significantly longer than those with extra-hepatic disease (12.1 versus 7.4 months; $p < 0.001$).

The data for glass microsphere radioembolization for unresectable, chemorefractory disease is very similar to that for resin microspheres with reported median OS of 10.6 months from the time of radioembolization [52••, 53••]. A single-center study of 214 patients demonstrated that survival was longest in patients who had received ≤2 cytotoxic agents, who had not received biologic agents, and who were treated in an earlier stage of disease, thus supporting the use of radioembolization earlier in the course of disease [52••]. In a multi-institutional study of 531 patients in which 38 % of patients had limited extra-hepatic disease, Hickey et al. showed that performance status, tumor burden <25 %, having received ≤2 chemotherapeutic agents, and a lack of extra-hepatic metastases all predicted better survival outcomes [53••]. Similar to previous studies, this study demonstrated that survival in patients without extra-hepatic disease was considerably longer (14.4 versus 6.6 months; $p < 0.001$). The multitude of studies examining radioembolization for unresectable, chemotherapy refractory disease is summarized in Table 1 and shows a similar median OS from the time of first radioembolization with an average of 10.9 months [49••, 51••, 52••, 54–63].

A 2014 review of radioembolization for chemorefractory disease showed that studies on radioembolization include patients with advanced disease who have failed a median of three different chemotherapy regimens and who tend to have bilobar disease [64•]. Further, 33 % of studies included patients with extra-hepatic disease. This review found that the median OS after radioembolization treatment was 12 months, median time to disease

Table 1. Survival in patients with chemotherapy refractory disease treated with radioembolization

Authors	Year published	No. of patients	Median overall survival[a] (months)
Kennedy et al.	2006	208	10.5
Jacobs et al.	2008	36	10.5
Mulcahy et al.	2009	72	14.5
Cianni et al.	2009	41	11.6
Cosimelli et al.	2010	50	12.6
Evans et al.	2010	140	7.9
Hendlisz et al.	2010	46	10.0
Bester et al.	2012	224	11.9
Lewandowski et al.	2014	214	10.6
Saxena et al.	2015	302	10.5
Golfieri et al.	2015	52	11.0
Kennedy et al.	2015	606	9.6
Hickey et al.	2015	531	10.6

[a]Median overall survival from time of first radioembolization

progression was 4.9 months, and median time to intra-hepatic disease progression was 9 months [64•]. Despite this immense data, radioembolization remains a category 3 recommendation in the National Comprehensive Cancer Network (NCCN) guidelines [65]. However in 2014, the European Society of Medical Oncology (ESMO) included radioembolization as a potential treatment option for patients with liver-limited CRC metastases who have failed available chemotherapeutic options [66]. While there is a potential bias of selecting healthier patients to undergo radioembolization, nevertheless, the median OS for these refractory patients treated with radioembolization is generally better than for salvage chemotherapies [31, 32].

First-line radioembolization

There has been considerable interest in combining systemic chemotherapy with loco-regional therapies to treat CHM. SIR-Spheres® received FDA approval in the USA for the treatment of unresectable CHM based on a randomized controlled trial [67]. In this study, 74 patients with CHM and no extra-hepatic disease were randomized to receive hepatic arterial infusion chemotherapy with floxuridine alone or combined with a single administration of intra-hepatic arterial ^{90}Y-labeled resin microspheres. The radioembolization arm had a higher complete response rate of 44 versus 18 % in the control arm ($p = 0.01$), as well as a longer median time to liver progression of 16 versus 10 months in the control arm ($p = 0.04$) [67]. Toxicity between the two arms was similar. These findings were supported by a phase II randomized control trial of 21 patients that compared 5-FU/leucovorin alone or preceded by a single injection of ^{90}Y-labeled resin microspheres [68]. In addition to an improved time to disease progression (18.6 versus 3.6 months; $p < 0.0005$) and response rate (50

versus 0 %), this trial also showed a longer median survival in patients receiving radioembolization (29.4 versus 12.8 months; $p = 0.02$). However, there was greater toxicity in the combination arm, with three cases of neutropenia and one death due to neutropenic sepsis [68]. Additional support for radioembolization came from Hendlisz et al. in their phase 3 trial of 46 patients with unresectable CHM and no extra-hepatic disease in which patients received 5-FU alone or preceded by a single injection of ^{90}Y-labeled microspheres [61]. Patients in the radioembolization arm had better time to liver progression (5.5 versus 2.1 months; $p = 0.03$) and overall disease control rate (86 versus 35 %; $p = 0.001$). No significant difference was found in the median overall survival (7.3 months for the chemotherapy arm and 10.0 months for the chemotherapy and radioembolization arm; $p = 0.80$). However, the studies just mentioned did not use contemporary chemotherapeutic regimens.

Combining ^{90}Y radioembolization with modern chemotherapeutic regimens has been assessed in phase 1 studies and found to be safe [69, 70]. Sharma et al. demonstrated that combining ^{90}Y radioembolization with FOLFOX and van Hazel et al. showed that combining ^{90}Y radioembolization with irinotecan had acceptable safety profiles [69, 70]. When used with capecitabine, a phase 1 study demonstrated that a dose of radioembolic exceeding 170 Gy could be safely administered [71]. In a recent retrospective analysis, Kosmider et al. demonstrated that combining radioembolization with modern chemotherapeutics was safe [72]. Further, this study again demonstrated that the presence of extra-hepatic disease portended a much worse prognosis: Patients with extra-hepatic disease had a median survival of 13.4 months compared to 37.8 months in patients without extra-hepatic disease ($p = 0.03$) [72].

SIRFLOX

SIRFLOX, a phase 3 multi-center, multi-national, randomized trial comparing first-line chemotherapy with FOLFIRI (with the addition of bevacizumab at discretion of the investigator) alone or in combination with ^{90}Y-labeled resin microspheres in 530 patients with isolated liver or liver-dominant CHM, is being conducted [73]. The primary endpoint of the study is PFS. Secondary endpoints include progression-free survival in the liver, tumor response rate in the liver, tumor response rate at any site, hepatic resection rate, and toxicity. Patients with liver-dominant but extra-hepatic disease were included and made up 40 % of the study population. These patients could have up to five lung metastases (<1 cm in size) and abdominal lymph node involvement (<2 cm). Approximately 45 % of patients in the study did not have the primary tumor removed.

Preliminary results of SIRFLOX were presented at the 2015 Annual American Society of Clinical Oncology meeting [73]. At a median follow-up of 36.1 months, there was no significant difference in median overall PFS between combined radioembolization-chemotherapy and chemotherapy alone (10.7 versus 10.2 months). However, median hepatic PFS was significantly longer in the radioembolization versus the control arm (20.5 versus 12.6 months; $p = 0.02$). Given the significantly longer hepatic PFS, the lack of difference in overall PFS could be attributed to progression of extra-hepatic disease. The presence of extra-hepatic disease has been demonstrated to have worse survival [63, 72, 74, 75]. Thus, the lack of significant improvement in overall progression-free survival

in these early results is not surprising, as 40 % of patients in SIRFLOX had evidence of extra-hepatic disease. As radioembolization would only act on the disease in the liver, activity against extra-hepatic disease would be primarily provided by systemic chemotherapy, which was the same regimen in both arms. Interestingly, the addition of bevacizumab improved hepatic PFS equally by 2.1 months in both the control and radioembolization arms.

The effect of radioembolization on hepatic PFS was further stratified based on the presence or absence of extra-hepatic metastases. In patients with CHM who had liver-only disease, the hepatic PFS in the radioembolization arm was 21.1 versus 12.4 months ($p = 0.003$) in patients receiving only systemic chemotherapy. However, for patients with CHM who had extra-hepatic disease, the hepatic PFS for those receiving radioembolization was 16.7 versus 12.6 months ($p = 0.147$) in patients receiving only systemic chemotherapy [73]. Thus, hepatic PFS is increased for CHM patients with liver-only and extra-hepatic disease, but only significantly so in patients with liver-only disease suggesting that those patients derive the most benefit from ^{90}Y-labeled microsphere radioembolization.

The reported ORR (using RECIST version 1.0) in the liver was higher with radioembolization (78.7 versus 68.8 %; $p = 0.04$), and the rate of complete response was significantly higher with radioembolization (6.0 versus 1.9 %; $p = 0.02$).

The SIRFLOX preliminary data showed higher rates of neutropenia (41 versus 29 %), febrile neutropenia (6 versus 1.9 %), and thrombocytopenia (9.7 versus 2.6 %) in the radioembolization arm of SIRFLOX [73]. There was no increase in the rate of diarrhea or nausea.

With respect to radioembolization-related complications, there was a 0.8 % risk of radiation hepatitis/radiation-induced liver disease (RILD), a 1.2 % risk of hepatic failure, and a 3.7 % risk of GI ulceration [73]. These rates of radioembolization-related complications were higher than recent studies. The largest study examining the use of ^{90}Y-labeled resin microspheres for CHM, the MORE study, reported a rate of RILD of 0.5 %, while the largest study using ^{90}Y-labeled glass microspheres, Hickey et al. in 2015, did not report any incidence of RILD [51••, 53••]. While the incidence of RILD using ^{90}Y-labeled resin microspheres has been reported to be as high as 4 % in an older study, this data was from a multi-center study where one center accounted for 75 % of cases of RILD [76]. Further, the MORE study had a rate of hepatic failure of 0.8 %, while another large series using ^{90}Y-labeled resin microspheres, Saxena et al. in 2015, had a hepatic failure rate of 0.3 % [49••, 51••]. Hickey et al. reported no incidence of hepatic failure in their recent series employing ^{90}Y-labeled glass microspheres [53••]. The incidence of GI ulceration ≥grade 3 in the MORE and Saxena et al. studies ranged from 1 to 1.7 %, while the Hickey et al. series did not report any cases of GI ulceration [49••, 51••, 53••]. However, earlier studies using ^{90}Y-labeled resin microspheres had reported similar rates of GI ulceration to SIRFLOX [77].

Conclusion

The overall body of data for radioembolization and the presented data for SIRFLOX demonstrate that radioembolization for CHM is safe and well tolerated. Moreover, SIRFLOX demonstrates that while combining

radioembolization and first-line chemotherapy does appear to slightly increase the side effects usually associated with chemotherapy, the concurrent use of radioembolization and full-dose chemotherapy is safe and feasible, building on previous dose escalation studies [69, 70]. The preliminary SIRFLOX data also suggests that there is a learning curve to the use of radioembolization. While the rates of radioembolization-related complications such as GI ulceration were larger than recent series, they were similar to those in early studies of radioembolization for CHM [51••, 53••, 77]. This may be accounted for by the fact that there were some centers in SIRFLOX performing radioembolization for the first time.

The majority of patients who have received radioembolization for CHM have done so in the setting of chemotherapy refractory disease, a population that has a shorter life expectancy than the SIRFLOX study population. Thus, as the longer term effects of radioembolization on liver toxicity and portal hypertension has not been well studied, the use radioembolization as a first-line treatment in a larger patient set may uncover longer term liver toxicities than are currently appreciated. These potential toxicities might limit the use of radioembolization early in the disease course. Consequently, it will be interesting to compare the results of the first-line SIRFLOX data with the EPOCH trial data, a randomized phase 3 trial investigating radioembolization as a part of second-line therapy for CHM. The best time to combine radioembolization and chemotherapy may have to do with these potential toxicities.

The preliminary data for SIRFLOX suggests that combining radioembolization and chemotherapy will be best for disease limited to the liver, as there was an increased hepatic PFS with no significant increase in overall PFS. However, given that 40 % of the SIRFLOX study population is comprised of patients with extra-hepatic disease, overall PFS may be a poor choice as a surrogate endpoint. It should not be surprising that overall PFS would not be affected by radioembolization, a therapy that only targets liver disease. Given that the majority of deaths from metastatic colorectal cancer are thought to be due to hepatic involvement, first-line radioembolization that controls liver disease could still result in an overall survival benefit while having no effect on overall PFS. Although it is biased and difficult to do cross-trial comparisons, the subset of patients with liver-only disease will need to be closely evaluated as it mimics the similar populations studied in existing surgical and hepatic arterial infusion trials.

SIRFLOX is the first of three studies that assess the efficacy of adding ^{90}Y-labeled resin microsphere radioembolization to first-line chemotherapy in the treatment of metastatic colorectal cancer with liver-only and liver-dominant disease. The other two are FOXFIRE, a UK-based randomized phase 3 trial, and FOXFIRE Global, an international randomized phase 3 trial [78]. All three studies have completed patient accrual with a combined sample size of 1103 patients [73]. The combined data from these prospective randomized trials will provide the necessary power for an overall survival analysis on the use of radioembolization as a part of first-line treatment for CHM.

While the SIRFLOX preliminary results are not yet definitively practice changing, they do indicate that combining radioembolization and systemic chemotherapy as a part of first-line therapy is safe and results in increased liver PFS. The final results of the trial will be eagerly awaited to see if the increased liver PFS in the preliminary data will translate to increased overall survival for CHM patients.

Compliance with Ethical Standards

Conflict of Interest

Bippan Singh Sangha declares that he has no conflict of interest.
Halla Nimeiri declares that she has no conflict of interest.
Ryan Hickey declares that he has no conflict of interest.
Riad Salem has received compensation from BTG for service as a consultant.
Robert J. Lewandowski has received compensation from BTG for service as a consultant.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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