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Selective Internal Radiation Therapy in the Multidisciplinary Management of Liver Metastases From Colorectal Carcinoma

Leila Tchelebi, MD, and Navesh K. Sharma, DO, PhD, FACRO

Colorectal cancer (CRC) is the fourth most common cancer in the United States. Most patients diagnosed with CRC will eventually develop metastases. The liver is the most common site of metastases from CRC and liver metastases are the most common cause of death for patients with CRC. Selective internal radiotherapy (SIRT) using yttrium 90 microspheres has emerged as a safe and effective treatment modality for controlling hepatic tumor burden in inoperable patients with liver-only or liver-predominant metastatic CRC. This article serves to review the available data on SIRT in the treatment of liver metastases from CRC in the salvage and first-line setting. Recently published phase III randomized data showing a significant improvement in liver progression-free survival from the addition of SIRT to standard chemotherapy in the first-line setting, while demonstrating no significant improvement in overall survival, will be reviewed. In addition, the present article examines the role of SIRT in the management of CRC liver metastases from right-sided colon cancers in which SIRT has been shown to improve overall survival when combined with chemotherapy in the first-line setting and explores appropriate patient selection for future studies.

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and the fourth most common cancer in the United States. Approximately 700,000 people die each year from the disease.[1] While only about 20% of those initially diagnosed with metastatic CRC (mCRC) present with metastatic disease, approximately half will eventually do so during the course of their disease process. Given that the median survival for mCRC has been reported as high as 31 months[2] with improvements in systemic therapy, an increasingly high number of patients are living to demonstrate more complex tumor growth and metastasis patterns. The liver is the most common site of metastasis and liver metastases are the most common cause of death for patients with CRC.[3-5]

Department of Radiation Oncology, Penn State University Hershey College of Medicine, Hershey, PA.

Address reprint requests to Navesh K. Sharma, DO, PhD, FACRO, Department of Radiation Oncology, Penn State University Hershey College of Medicine, 500 University Drive, CH63, Hershey, PA 17033. E-mail: Nsharma2@pennstatehealth.psu.edu

Historically, surgical resection has been the preferred method of treating liver-predominant hepatic metastases in colorectal carcinoma and has been shown to result in 5-year overall survival (OS) rates of up to 58%.[6-9] However, 85% of patients with liver metastases are not able to undergo surgical resection of their liver lesions.[10] Selective internal radiotherapy (SIRT) has emerged as a therapeutic alternative to surgery for patients with liver metastases from CRC.

SIRT relies on the injection of radioactive microspheres into branches of the hepatic artery. The therapy's success relies on the unique blood supply of the liver whereby metastatic liver tumors are primarily fed by branches of the hepatic arteries, in contrast to the normal hepatocytes that derive a majority of their blood supply from the portal venous system.[11] In addition, metastatic tumor neovasculature can be approximately 20-400 times as dense as that of normal hepatic tissue. This allows intra-arterial radionuclide therapy to potentially deliver ablative doses of radiation selectively to tumor cells while sparing healthy hepatocytes.[12-15] Unlike surgery, SIRT is not limited by the number or sites of liver metastases and chemotherapy does not need to be withheld for prolonged periods prior to treatment delivery.

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Yttrium-90 (Y-90) is the most commonly used radionuclide used to label microspheres. It undergoes primarily beta-decay, emitting a high energy photon in the process, with minimal soft-tissue penetration.[12] The mean penetration of the B-radiation is estimated at 2.5 mm with a maximum penetration of approximately 1 cm. Consequently, SIRT utilizing Y-90 is able to deliver more than 100-120 Gy of ionizing radiation to the tumor, while remaining within tissue tolerance of the normal liver due to limited penetration of beta radiation beyond its concentration around tumor vasculature.[14,16]

There are two commercially available Y-90 labeled microspheres, resin microspheres, SIR-Spheres (SIRTEX Medical Inc, Woburn, MA), and glass microspheres, Therasphere (BTG International, West Conshohocken, PA). While SIR-Spheres and Therasphere have slightly different physical properties, they can sometimes be used interchangeably in primary hepatic malignancies.[12] Theraspheres, however, are not FDA approved in the United States and the majority of data in mCRC, including phase III randomized trials, has been obtained using SIR-Spheres.

This article serves to review the available data on SIRT in the treatment of liver metastases from CRC with an emphasis on recently published phase III randomized data.

SIRT as Salvage for Chemotherapy-Refractory Patients

Initially, interest in SIRT emerged in the salvage setting for patients who had liver-only or liver-dominant disease refractory to first-line chemotherapy (Table 1). Van Hazel et al conducted a phase I trial assessing the safety of SIRT with increasing doses of irinotecan in patients who previously failed fluorouracil-based therapy.[17] The authors established 100 mg/m^2 as the maximum tolerated dose of irinotecan with SIRT with self-limited grade 3 toxicities and no grade 4 or 5 toxicities observed. The authors found that at 3 months after treatment, the median CEA level had decreased by 82%. Of patients, 48% experienced a partial response to treatment, 39% had stable disease, and 13% progressed. The median progression-free survival (PFS) was 6 months, but median PFS in the liver was 9.2 months. Median OS was 12.2 months.

Hendlisz et al later published a prospective, multicenter, randomized phase III study comparing chemotherapy alone vs chemotherapy plus SIRT in patients with mCRC refractory to standard chemothertapy.[18] The authors enrolled 46 patients with unresectable, chemotherapy-refractory liver-limited mCRC and randomized them to receive either protracted intravenous infusion of fluorouracil (IV-FU) or IV-FU plus SIRT. Overall response rates (ORRs) did not differ between the two arms (0% for chemotherapy alone vs 9.5% for chemotherapy plus SIRT, P = 0.22) but disease control rates including partial responders and those with stable disease was higher in the study arm (35% vs 86% in favor of SIRT, P = 0.001). Median time to liver progression was longer in the SIRT arm vs the IV-FU alone arm (5.5 months vs 2.1 months, P = 0.003). Median time to tumor progression was also longer in the combined modality arm (4.5 vs 2.1 months, P = 0.03). There was no difference in median OS between the treatment arms (7.3 months for the control arm vs 10 months for the study arm, P = 0.80). There were no statistically significant differences in adverse events between the two groups. The authors concluded that SIRT in combination with IV-FU was a valid option for patients with mCRC confined to the liver who had failed first-line chemotherapy. While SIRT did not affect survival outcomes, the treatment resulted in improvements in both local control and overall disease progression, without adding to toxicity.

The role of SIRT has also been investigated in heavily pretreated patients who have progressed through multiple lines of systemic chemotherapy with liver-predominant disease. Cosimelli et al published their phase II data analyzing the safety and efficacy of SIRT in patients with CRC liver metastases in the salvage setting.[19] The authors enrolled 50 patients who had progressed after receiving four or more lines of systemic therapy including at least one oxaliplatin- and one irinotecan-containing regimen. The ORR was 24%. Two percent had a complete response, 22% had a partial response, 24% had stable disease, and 44% progressed. Treatment response was independent of performance status, number of metastases, and size of the metastases. The median time to progression was 3.7 months and the median OS was 12.6 months. There was a statistically significant difference observed between the patients who responded to SIRT vs nonresponders (16 months vs 8 months, respectively, P = 0.0006). The treatment was very well tolerated with only grades 1 and 2 adverse events reported.

Table 1 Studies of SIRT in the Salvage Setting

Author	N	Treatment	ORR (%)	Median PFS (mo)	Median Liver-PFS (mo)	Median OS (mo)
Van Hazel et al[17]	25	Irinotecan + SIRT	48	6	9.2	12.2
Hendlisz et al[18]	46	IV-FU vs IV-FU + SIRT	0 vs 9.5 (P = 0.22)	2.1 vs 4.5 (P = 0.03)	2.1 vs 4.5 (P = 0.003)	7.3 vs 10 (P = 0.80)
Cosimelli et al[19]	50	SIRT alone	24	3.7	–	12.6
Seidensticker et al[20]	58	BSC vs BSC + SIRT	58.6 (SIRT group)	2.1 vs 5.5 (P < 0.01)	–	3.5 vs 8.3 (P < 0.001)
Kennedy et al[21,22]	606	SIRT alone	–	–	–	10

BSC, best supportive care; IV-FU, intravenous infusion of fluorouracil; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SIRT, selective internal radiation therapy.

Seidensticker et al performed a matched-pair analysis comparing patients receiving SIRT plus best supportive care (BSC) vs BSC alone for extensive liver metastases refractory to all recommended chemotherapy.[20] The authors matched 58 patients (29 SIRT plus BSC and 29 BSC alone) treated as salvage with extensive liver involvement. Of SIRT patients, 41.4% achieved a partial response to treatment, 17.2% had stable disease, and 37.9% progressed. The median PFS in patients who underwent radioembolization was 5.5 months vs 2.1 months in those receiving BSC alone. The median OS was significantly improved for patients receiving SIRT in addition to BSC compared to those receiving BSC alone (median survival of 8.3 vs 3.5 months, $P < 0.001$). On multivariate analysis, treatment with radioembolization was the only significant predictor for improved survival (hazard ratio 0.3, confidence interval 0.16-0.55, $P < 0.001$).

In the MORE (Metastatic Colorectal Cancer Liver Metastases after RadioEmbolization) study, Kennedy et al conducted the largest retrospective analysis of heavily pretreated patients with liver-dominant metastases from CRC receiving SIRT.[21] They collected data, through an independent data collection agency, on 606 consecutive patients at 11 experienced centers across the United States who received radioembolization after failing a median of 2 lines of prior chemotherapy with fluoropyrimidine-based treatment combined with oxaliplatin or irinotecan with or without bevacizumab. The median OS for all 606 patients was 9.6 months. The authors found that median OS rates of patients differed significantly between patients receiving SIRT as a second, third, and greater than or equal to fourth line of treatment after chemotherapy (13 months vs 9 months, vs 8 months, respectively, $P < 0.001$). There were no differences in adverse events across treatment lines. OS was significantly prolonged in patients with an Eastern Cooperative Oncology Group (ECOG) score of 0 as compared to those with ECOG ≥ 1 ($p = 0.009$). The authors concluded that SIRT results in favorable outcomes for patients who have limited therapeutic options remaining, without an unfavorable toxicity profile.

In 2017, the authors published an updated analysis of long-term survivors from the MORE study.[22] The updated median OS was 10 months at a median follow-up of 9.5 months. Factors affecting survival were the same as those reported in the original study, namely, ECOG performance status, extent of liver involvement, poor baseline liver function, pretreatment anemia, lung shunt fraction, and the number of prior lines of chemotherapy. Interestingly, age did not affect efficacy or toxicity, as OS and the toxicity profile was similar between patients 75 years or older and those younger than 75 years of age. Long-term results of the study indicate that SIRT is a well-tolerated and effective treatment option for patients with advanced mCRC, regardless of age, who have failed all prior treatments.

SIRT in First-Line Treatment of Liver-Only or Liver-Predominant mCRC

The efficacy of treatment with SIRT in the first-line setting for patients with unresectable mCRC was demonstrated in early studies from the 1990s (Table 2). In 1992, Gray et al reported on 29 patients with nonresectable liver metastases from CRC treated with SIRT.[23] The authors found that 88% of patients experienced a 50% decrease in CEA levels before and after treatment. They also found a 50% decrease in tumor volume in 48% of patients with administration of SIRT leading them to conclude that SIRT results in high rates of tumor regression for patients with liver metastases from CRC. Stubbs et al reached a similar conclusion 9 years later when they published their experience on SIRT in patients with liver metastases from primary colon cancer.[24] The authors found a fall in CEA and regression in tumor volumes in over 90% of patients they studied. OS at 12 months was 46% and was primarily determined by the development of extrahepatic metastases.

This early data, demonstrating high response rates to SIRT, led to the development of prospective studies comparing SIRT to standard cytotoxic chemotherapy for patients with CRC liver metastases. In a phase II trial by Van Hazel

Table 2 Studies of SIRT in the First-Line Setting

Author	N	Treatment	ORR (%)	Median PFS (mo)	Median Liver-PFS (mo)	Liver Progression (%)	Median OS (mo)
Van Hazel et al[25]	21	5FU/LV vs 5FU/LV + SIRT	0 vs 73 ($P < 0.001$)	4 vs 19 ($P < 0.001$)	–	–	13 vs 29 ($P = 0.02$)
Gray et al[26]	74	FU vs FU + SIRT	18 vs 44	10 vs 16 ($P = 0.001$)	–	–	16 vs 18 ($P = 0.018$)
Sharma et al[29]	20	FOLFOX + SIRT	–	9	12	–	–
van Hazel et al[30]	530	mFOLFOX vs mFOLFOX + SIRT	68.1 vs 76.4 ($P = 0.113$)	10.2 vs 10.7 ($P = 0.43$)	12.6 vs 20.5 ($P = 0.002$)	–	–
Wasan et al[33]	1103	FOLFOX vs FOLFOX + SIRT	63 vs 72 ($P = 0.0012$)	10.3 vs 11 ($P = 0.11$)	–	39 vs 22 ($P < 0.001$)	23.3 vs 22.6 ($P = 0.061$)

FOLFOX, fluorouracil + leucovorin + oxaliplatin; IV-FU, intravenous infusion of fluorouracil; mFOLFOX, fluorouracil + leucovorin + oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SIRT, selective internal radiation therapy; 5FU/LV, 5-fluorouracil/leucovorin.

et al, the authors enrolled 21 patients with liver metastases from CRC and randomized them to receive 5FU/LV with or without SIRT.[25] The authors found that the response rate using Response Evaluation Criteria in Solid Tumors criteria was greater among patients receiving both SIRT plus chemotherapy, vs chemotherapy alone. The time to disease progression was also improved for patients receiving combination therapy with SIRT (19 vs 4 months, $P < 0.0005$). Median OS was longer for those receiving SIRT (29 vs 13 months, $P = 0.02$).In addition, patients receiving SIRT received at least twice as many cycles of chemotherapy than patients receiving chemotherapy alone. Grades 3 and 4 toxicity was worse in the SIRT group; however, there was no difference in quality of life between the two groups.

In 2001, Gray et al published the first randomized phase III trial of chemotherapy plus SIRT vs chemotherapy alone, leading to FDA approval of SIRT in the United States.[26] The investigators enrolled 74 patients with unresectable liver metastases from colorectal adenocarcinoma and randomized them to receive either floxuridine chemotherapy for 18 cycles or until disease progression with or without SIRT. The authors found that partial and complete response rates were significantly greater for patient receiving SIRT when measured by tumor areas (44 vs 18%, $P = 0.010$), tumor volumes (50 vs 24%, $P = 0.03$), and CEA (72 vs 47%, $P = 0.004$). The median time to disease progression within the liver was significantly longer for patients receiving SIRT when measured by tumor areas (10 vs 16 months, $P = 0.00$) or tumor volumes (8 vs 12 months, $P = 0.04$). There was a trend toward improved median survival for patients receiving SIRT plus chemotherapy, but this was not statistically significant (18 vs 16 months, $P = 0.018$). There was no difference in grades 3 and 4 treatment related toxicity or in quality of life between the two groups. The authors concluded that SIRT substantially increased tumor repose rates and PFS in patients with mCRC over systemic chemotherapy alone. Importantly, while most patients did eventually succumb to their disease, liver metastases were not the primary cause of death for most patients.

As multiagent systemic chemotherapy with 5FU, LV, and oxaliplatin was shown to improve survival among patients with mCRC over single-agent chemo,[27,28] studies emerged assessing the safety and efficacy of FOLFOX in combination with SIRT. A phase I study by Sharma et al was conducted to test the tolerability of SIRT with FOLFOX chemotherapy.[29] Twenty patients with unresectable liver metastases from CRC who were chemotherapy naïve were enrolled on the study. All patients received FOLFOX chemotherapy with escalating doses of oxaliplatin for a maximum of 12 cycles. SIR-Spheres were administered on the third of fourth day of the first cycle. The primary endpoint was toxicity. The authors found that neutropenia was the dose-limiting toxicity and was recorded in 12 patients. The maximum tolerated dose of oxaliplatin in combination with FU, LV, and SIRT was 60 mg/m^2 for the first three cycles. Median PFS was 9 months and median time to progression in the liver was 12 months.

Following the promising results of their phase I/II data that established the maximum tolerated dose of oxaliplatin-fluorouracil chemotherapy in combination with SIRT, the FOXFIRE group of studies was conducted to compare FOLFOX with SIRT vs FOLFOX alone as first-line treatment for mCRC with liver-only or liver-predominant metastases.[30-32] These three prospective randomized controlled, phase III clinical trials were conducted in 14 countries and enrolled over 1100 patients. The designs of the 3 trials and their inclusion criteria were intentionally similar so that their results could be prospectively combined for analysis of OS and secondary endpoints. FOXFIRE and SIRFLOX were originally planned as two complimentary trials, however, because FOXFIRE took longer than expected to achieve accrual goals, a third independent trial, FOXFIRE-Global, was added. Both FOXFIRE and SIRFLOX stratified patients according to the presence of extrahepatic metastases, extent of tumor involvement of the liver, investigational center, and intention to treat with a biologic agent (bevacizumab in the case of SIRFLOX).

SIRFLOX was the first of these three randomized controlled trials presented investigating the safety and efficacy of SIRT with chemotherapy for patients with nonresectable liver-only or liver-dominant mCRC.[30] This multicenter trial included patients who were 18 years or older, with an ECOG performance status of 0-1, histologically proven adenocarcinoma of the colon or rectum, with proven liver metastases, and a life expectancy of at least 3 months. Only patients who had not yet received systemic chemotherapy for their mCRC were included. The hepatic metastases in patients enrolled on these studies were required to have been deemed unresectable.

The trial compared systemic chemotherapy using modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX) with or without Y-90 resin microspheres (SIR-Spheres). Bevacizumab was allowed at the discretion of the investigator but only at cycle four of chemotherapy and beyond in patients receiving SIRT. In addition, Oxaliplatin was delivered at 60 mg/m^2 for the first three cycles in patients receiving SIRT due to the data from Sharma et al. The control arm received mFOLFOX with or without Bevacizumab until disease progression or dose-limiting toxicity, while the intervention arm received the same with SIRT (whole liver with dosimetry based on empiric published tables and not body surface area methodology) administered on either day 3 or 4 of cycle 1 or 2 of chemotherapy. The primary endpoint of the trial was PFS at any site. Secondary endpoints included PFS in the liver, tumor response rate in the liver, tumor response rate at any site, liver resection rate, hepatic and extra hepatic recurrence rate, health-related quality of life, toxicity and safety, and OS.

The results of the study were mixed. The authors found that median PFS at any site was similar in the two groups (10.2 vs 10.7 months, $P = 0.43$), however, the addition of SIRT showed a significant improvement in median PFS within the liver (12.6 vs 20.5 months, $P = 0.002$). In patients with liver-only metastases, the improvement in median liver PFS was even more notable (12.4 vs 21.1 months, $P = 0.03$) A higher proportion of control patients had liver-only progression (77% vs 52.4% for the control and SIRT arms, respectively, $P < 0.001$), whereas a higher proportion of

SIRT patients had first progression outside the liver, particularly in the lung. The objective response rate (ORR) at any site according to Response Evaluation Criteria in Solid Tumors criteria was not statistically significantly different between the two arms (68.1% vs 76.4%, $P = 0.113$). The ORR (68.8% vs 78.7%, $P = 0.042$) and the complete response rate within the liver (1.9% vs 6%, $P = 0.02$) were significantly improved with SIRT. There was no difference in the rate of liver resection between the two arms (13.7% in the control arm, vs 14.2% in the SIRT arm, $P = 0.857$). In terms of safety, there was no difference in grade 3 or higher adverse events in the SIRT vs control patients (73% vs 85%, $P = 0.516$).

FOXFIRE was a parallel trial also investigating the safety and efficacy of SIRT in patients with mCRC, conducted in the United Kingdom.[32] It was a multicenter, open label, parallel two-arm randomized controlled trial that included patients with histologically proven CRC with liver-only or liver-dominant metastases not amenable to surgical resection. Similar to the SIRFLOX study, eligible patients were at least 18 years of age with a WHO performance status of 0 or 1, a life expectancy of at least 3 months, and who were eligible for multiagent first-line systemic chemotherapy.[31]

The trial randomized patients in a 1:1 fashion to receive radiosensitizing chemotherapy with OxMdG (oxaliplatin, 5-fluorouracil, and folic acid) with or without SIRT using Y-90 resin microspheres (SIR-Spheres). Patients in the control arm received 12 cycles of OxMdG while those in the treatment arm received the same chemotherapy regimen with SIRT administered on the third or fourth day of the second chemotherapy cycle. Patients could receive anti-VEGF or anti-EGFR treatment at the discretion of the treating physician. The primary endpoint of FOXFIRE was OS. Secondary endpoints included safety, PFS, liver-specific PFS, response and resection rate, time until next therapy, patient-reported outcomes, and cost effectiveness.

FOXFIRE-Global mirrored the trial design of FOXFIRE but was conducted at 69 treatment centers globally to increase number of analyzable patients for the combined analysis. Patients with unresectable liver-only or liver-dominant mCRC were randomized in a 1:1 fashion to receive mFOLFOX6 until disease progression or dose-limiting toxicity, with or without Y-90 resin microspheres on day 3 or 4 of cycle 1 of chemotherapy. Bevacizumab could be given at the discretion of the treating physician. The primary endpoint was OS analyzed in a pooled analysis with patients from all three trials.

A combined analysis of these three trials was reported by Wasan et al.[33] There was no difference in OS between patients receiving SIRT plus FOLFOX vs FOLFOX alone ($P = 0.61$). The median OS was 22.6 months in the combination arm vs 23.3 months in the FOLFOX alone arm. There was also no observed difference in the median PFS between the two groups, 11 months for the SIRT group compared to 10.3 months in the FOLFOX alone group (P 0.11). The cumulative incidence of progression within the liver within the first 12 months of follow-up was significantly lower in the SIRT plus FOLFOX group compared to the FOLFOX alone group (22% vs 39%, $P < 0.0001$). The cumulative incidence of progression outside the liver or death before radiological progression within the liver was higher in the FOLFOX plus SIRT group (19% vs 33%, $P < 0.0001$), reflecting improved liver specific disease control with the addition of SIRT. The odds of developing a grade 3 or higher adverse event was higher in the combined treatment group (OR 1.42, $P = 0.009$). Serious adverse events of any grade occurred in 43% of patients receiving FOLFOX alone vs 54% receiving a combination of SIRT plus FOLFOX.

The authors concluded that SIRT in combination with FOLFOX chemotherapy did not show a benefit to the addition of SIRT on OS in patients with liver-only or liver-dominant metastases from CRC in the first-line setting. Per the authors of the analysis, this finding can in part be attributed to the high proportion of patients who developed progression outside the liver in the SIRT plus chemotherapy group. Regardless of the higher failure rate outside the liver in the SIRT arm, the significant improvement in liver disease control observed with the addition of SIRT did not improve OS, leading the authors to conclude that the early use of SIRT in the first-line treatment of mCRC cannot be universally recommended at this time.[33]

SIRT and Right-Sided Colon Cancer

Recently, data has emerged demonstrating that tumor location is of prognostic significance in CRC.[34-37] Loupakis et al evaluated the association between tumor location and survival in patients from three prospective trials, a pharmacogenetics translational study and two randomized phase III studies, and found that patients with right-sided tumors had inferior OS compared to patients with left sided tumors.[34] Similarly, Tejpar et al conducted a retrospective analysis of the randomized phase III CRYSTAL and FIRE-3 trials, studying the benefit of cetuximab added to multiagent systemic chemotherapy in mCRC, and found that, among RAS wild-type patients, those with left-sided tumors had markedly improved OS, PFS and ORR compared to those with right-sided tumors.[38] Furthermore, they found that cetuximab added to FOLFIRI significantly improved OS in patients with left-sided tumors, whereas it has no effect on those with cancers of the right colon. In their systematic review and meta-analysis, Petrelli et al found that left-sided primary tumor location was associated with a statistically significantly reduced risk of death (hazard ratio 0.82, confidence interval 0.79-0.84, $P < 0.001$) compared to right-sided tumors independent of stage and adjuvant treatment.[37] Given the inferior outcomes observed in patients with right-sided colon cancers, investigating therapeutic strategies to improve outcomes is of interest.

Gibbs et al conducted an analysis of data from the SIRFLOX and FOXFIRE Global trials assessing the effect of primary tumor side on survival outcomes in patients with mCRC receiving SIRT with chemotherapy.[39] The authors

analyzed OS and PFS data for patients enrolled on SIRFLOX and FOXFIRE stratified by tumor location. They found that the median OS for patients with right-sided primaries was significantly higher for patients in the SIRT arm compared to the control group (22 vs 17 months, $P = 0.008$). For patients with left-sided tumors, on the other hand, there was no benefit in terms of OS to the addition of SIRT (24.6 vs 26.6 months, $P = 0.264$). The OS benefit for right-sided primaries persisted even when each study was analyzed separately (21.7 vs 17.1, $P = 0.05$, in SIRFLOX and 24.5 vs 16.6 months, $P = 0.048$, in FOXFIRE). PFS for patients receiving SIRT was not different based on tumor location. Thus, while there was no survival benefit to the addition of SIRT to chemotherapy for patients overall in FOXFIRE group of studies, there was an improvement in survival for patients with right-sided primaries.

Ongoing Trials

There are a number of ongoing clinical trials assessing the safety and efficacy of SIRT in combination with other systemic agents for both mCRC and also for liver metastases from other primary sites. One such study is a phase I trial (NCT02602327) of Tas-102, an oral nucleoside antitumor agent, and SIRT for chemorefractory mCRC. The study is currently open to accrual. The primary endpoint is safety. Radiographic response rates, PFS, hepatic PFS, extrahepatic PFS, OS, and biomarker (ie, CEA) response rates are all secondary outcomes. A phase II was recently completed conducted to determine the safety of regorafenib in combination with SIRT for mCRC (NCT02195011). Finally, a randomized phase III trial is currently recruiting to evaluate an intensified maintenance treatment of SIRT in combination with simplified maintenance chemotherapy compared to simplified chemotherapy maintenance alone, in patients with stable disease after 3-6 months induction therapy. The primary endpoints are time to first progression with secondary endpoints of OS and PFS (NCT01895257).

Conclusions

Over the last several decades, SIRT using Y-90 resin microspheres has emerged as a safe and effective treatment option for patients with liver-only or liver-predominant metastases from CRC. While the FOXFIRE series of randomized phase III trials failed to show an improvement in OS with the addition of SIRT to multiagent fluorouracil-based chemotherapy in the primary setting, there was a significant improvement in liver PFS in every cohort, regardless of tumor location, with half as many patients progressing within the liver in the SIRT plus chemotherapy group compared to those receiving chemotherapy alone. These results indicate that the treatment may be particularly effective for patients with liver-only or truly liver-predominant disease and should not be overlooked as an effective liver-directed option. In a randomized controlled clinical trial setting, there was a clear and substantial liver PFS benefit when using combined modality therapy compared with full dose chemotherapy alone in the primary setting highlighting its efficacy over systemic therapy alone in controlling liver metastases. It may also be an option in patients with liver-only disease to offer a "chemo holiday." Furthermore, SIRT did confer a 5 month OS benefit among patients with right-sided colon cancer, indicating that it may be of particular benefit among these patients known to have inferior outcomes. While randomized phase III data is limited in the salvage setting, there is robust data available indicating a survival benefit among these patients, in particular among those who have failed multiple lines of chemotherapy and have limited treatment options remaining.

As newer and more targeted chemotherapeutic regimens are emerging in the treatment of mCRC to treat extrahepatic disease, the addition of SIRT to these regimens may ultimately result in improvements in OS. More studies are needed to evaluate the role of SIRT with these newer regimens incorporating biologic agents such as cetuximab and panitumumab, which have shown promising results in the salvage setting.[40,41] However, unlike in the previous randomized clinical trials, careful patient selection, possibly after initial treatment with systemic therapy, may be essential to identify those patients who truly will present with liver-predominant metastases and who may benefit most from liver-directed therapy with SIRT.

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