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Impact of primary tumor side on survival outcomes in untreated patients with metastatic colorectal cancer when selective internal radiation therapy is added to chemotherapy: combined analysis of two randomized controlled studies

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CONFLICTS OF INTEREST

PG reports honoraria from Sirtex for participation in advisory boards and for giving presentations. VH has received honoraria from Amgen, Roche, Sanofi and Sirtex for consulting roles, participation in advisory boards, and his institution has received study grants from Amgen, Merck, Roche, Sanofi and Sirtex. JT has received honoraria from Genentech, Merck Serono, Amgen, Celgene, Sanofi, Eli Lilly/ImClone Systems. JR reports personal fees from Sirtex during the conduct of the study and grants from Sirtex outside the submitted work (FOXFIRE). MP reports research funding and personal fees from Sirtex Medical. NS has received honoraria from Sirtex Medical outside the submitted work (FOXFIRE) Speakers Bureau (SIRFLOX). MF has received grants from Sirtex during the conduct of the study (FOXFIRE). VG has received compensation for participation in Advisory Committees from Sirtex. MVB and HZ have received compensation from Sirtex for statistical analysis and interpretation. GVH has received compensation for participation in Advisory Committees from Sirtex. All remaining authors have declared no conflicts of interest.

MICROABSTRACT

Primary tumor side is emerging as a prognostic factor for patients with liver metastatic colorectal cancer (mCRC). In a combined analysis of data from two randomized studies the addition of selective internal radiation therapy (SIRT) to first-line chemotherapy in patients with mCRC was associated with statistically and clinically significant overall survival gains in patients with a right-sided primary tumor.

ABSTRACT

Background: Primary tumor side is emerging as a major prognostic factor for patients with metastatic colorectal cancer (mCRC). To determine whether outcomes differ between patients with mCRC with right-sided primary (RSP) tumors and those with left-sided primary (LSP) tumors, in patients who received selective internal radiation therapy (SIRT) plus mFOLFOX6 chemotherapy, compared with those who received chemotherapy alone, survival outcome data were examined from two randomized studies.

Patients and methods: Separate and combined analyses were performed on data from the SIRFLOX and FOXFIRE Global trials, which compared chemotherapy plus SIRT with chemotherapy in patients with mCRC liver metastases. Primary tumor side was prospectively collected. The principal outcome measure was overall survival (OS) by treatment and primary tumor side.

Results: In the combined analysis of all 739 patients enrolled, SIRT had no impact on OS (median 24.3 v 24.6 months; hazard ratio [HR], 1.021; $P = .810$). For the 179 patients (24.2%) with a RSP tumor, OS was improved with the addition of SIRT (median 22.0 v 17.1 months HR, 0.641; $P = .008$). The addition of SIRT was not associated with a significant difference in OS among the 540 patients with a LSP tumor (median 24.6 v 26.6 months; HR, 1.120, $P = .264$). A test of treatment interaction by primary tumor side was statistically significant for RSP and SIRT ($P = .002$).

Conclusions: The addition of SIRT for patients with RSP tumors, but not LSP, was associated with a statistically and clinically significant OS gain.

KEY WORDS

mCRC; SIRT; overall survival; right-sided primary; left-sided primary

ABBREVIATIONS

CI – confidence interval

CT – computed tomography

EGFRi – epidermal growth factor receptor inhibitor

FFG – FOXFIRE Global

HR – hazard ratio

LSP – left sided primary

mCRC – metastatic colorectal carcinoma

OS – overall survival

PFS - progression free survival

SF – SIRFLOX

SIRT - selective internal radiation therapy

ACCEPTED MANUSCRIPT

Introduction

For patients with metastatic colorectal cancer (mCRC) a right-sided primary (RSP) tumor is a poor prognostic factor.^{1,2} RSP patients with *RAS* wild-type tumors also derive limited or no benefit from epidermal growth factor receptor inhibitors (EGFRi).² Additional first-line therapeutic strategies for RSP patients are therefore eagerly sought.

Early studies demonstrated the benefit of adding selective internal radiation therapy (SIRT) to a fluoropyrimidine in patients with mCRC liver metastases.^{3,4} More recently, the SIRCLOX (SF), FOXFIRE Global (FFG) and FOXFIRE (FF) studies randomized patients to receive oxaliplatin-based chemotherapy alone, or with SIRT.⁵⁻⁷ A pre-planned meta-analysis of all three studies found no significant impact of SIRT on overall survival (OS) or PFS.⁸

Here, in a *post-hoc* analysis of data from the SF-FFG studies, where data on the primary tumor location were collected prospectively, we explore the impact of primary tumor side on therapy received in first and later lines of therapy, adverse events and survival outcomes.

Methods

The SF-FFG studies were conducted in accordance with the Declaration of Helsinki and approval was obtained from institutional review boards for each participating center.

Study design and participants

Study protocols for the SF-FFG studies have been published.^{5,6} Inclusion criteria were identical.

Patients were randomized 1:1 to receive either modified FOLFOX6 (mFOLFOX6; Control group) or mFOLFOX6 plus SIRT (SIR-Spheres; Sirtex Medical, North Sydney, Australia; SIRT group). Intent to use bevacizumab was declared before randomization. For patients treated with SIRT, the oxaliplatin dose was reduced for the first three cycles and bevacizumab was to be added from cycle 4 of chemotherapy. Patients were stratified based on bevacizumab treatment intent, on liver-only versus extrahepatic metastases, extent of tumor involvement of the liver ($\leq 25\%$ or $> 25\%$) and investigational center. SIRT was administered on day 3 or 4 of chemotherapy cycle 1 or 2.

A RSP was any primary proximal to the splenic flexure; a LSP included a primary at or distant to the splenic flexure. OS and PFS data were examined by tumor side in patients who did and did not receive SIRT in addition to chemotherapy.

Treatment and assessments

For the SF-FFG studies, patients randomized to receive SIRT underwent a standard workup and treatment as previously described.⁵ Patients were treated until disease progression. Assessment was performed by CT scan of the chest and abdomen every 8 weeks until progression and, following extra-hepatic progression, every 12 weeks until hepatic progression. Tumor response rate and progression free survival were PFS were determined from these serial CT scans using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 criteria. Subsequent therapy was recorded and patients were followed until death. Adverse events were recorded and rated according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Outcomes and statistical analysis

All efficacy measures were assessed in the intent-to-treat (ITT) population. A statistical analysis of the combined patient-level data from the two trials was implemented. Balance of sidedness (RSP, LSP) compared to demographic and baseline variables used a two-sample t-test and Chi-square test. Median time-to-event estimates and 95% confidence intervals (CI) used Kaplan-Meier estimates, and treatment arms were compared using the stratified log-rank test, stratified by protocol. Response rates were compared between treatment arms using a Chi-square test of proportions stratified by protocol. The statistical significance of sidedness (RSP, LSP) was tested in a multivariable protocol-stratified Cox proportional hazards model with terms representing treatment (SIRT, Control), side (RSP, LSP), and the interaction of treatment by side. Univariate and multivariable Cox proportional hazards models in patients with LSP were stratified by protocol and included variables: treatment (SIRT, Control), bevacizumab received (yes, no), extra-hepatic metastases (EHM) at randomization (yes, no), tumor burden (>25%, ≤25%), primary tumor *in-situ* (yes, no), synchronous disease (metastatic spread <120 days post-diagnosis, metachronous), age

(≥ 65 years, < 65 years) and gender (male, female). Model selection for multivariable models for RSP was by backwards elimination with a threshold of $P < .15$ for inclusion in the model. All hypothesis tests were two-sided. Post-progression treatment and adverse event were compared between treatment arms by side using a Chi-square test. $P < .05$ was used to define statistical significance. The statistical analysis was performed with SAS (version 9.4, SAS Institute, Cary, NC) software.

Results

Patients and treatment

Between October 2006 and April 2013 for SF ($n = 530$), and May 2013 and April 2015 for FFG ($n = 209$), 739 patients were enrolled and randomly assigned to either mFOLFOX6 ($\pm$ bevacizumab at investigators' discretion; $n = 367$) or mFOLFOX6 ($\pm$ bevacizumab) plus SIRT ($n = 372$; Figure 1). As of 23 December 2016, median follow-up was 22.2 months, with median follow-up 21.8 months (range 0.03–90.7) for SF and 24.1 months (range 0.03–40.0) for FFG.

In the combined SF-FFG population, 179 (24.2%) patients had RSP, 540 (73.1%) had LSP, 16 (2.2%) patients had primary tumors in both sides, and the primary site was not recorded for four patients (0.5%). Patients with RSP were older than those with LSP (64.4 versus 61.6 years; $P = .002$) and a higher proportion were female (42.5% 32.0%; $P = .011$). Baseline characteristics of all patients shown in Appendix A, Table A1.

In the combined SF-FFG population, 6 patients (6.1%) with RSP and 27 (10.2%) with LSP assigned to SIRT did not receive SIRT. Another 10 (10.2%) patients with RSP and 21 (8.0%) with LSP did not receive SIRT to both hepatic lobes. Patients randomized to SIRT were less likely to receive bevacizumab than Control patients (54.1% versus 65.4%; $P = .125$, and 51.1% versus 61.6%; $P = .014$ for RSP and LSP patients, respectively).

Overall survival and progression-free survival

Over the follow-up period 548 deaths (74.2%) occurred in the ITT population ($n = 739$): 424 (80.0%) in SF and 124 (59.3%) in FFG. The median OS of RSP patients randomized into the Control arm was 17.1 months, compared with 26.6 months for LSP patients in the Control arm ($P < .001$). In the SIRT arm, the median OS of RSP and LSP patients was 22.0 and 24.6 months, respectively ($P = .165$).

For all patients, the median OS in the SIRT arm was 24.3 months, compared with 24.6 months (hazard ratio [HR] 1.021; 95% CI, 0.863–1.207; $P = .810$) in the Control group (Table 1; Appendix A, Figure A1). Median OS was significantly increased for RSP patients in the SIRT arm, compared with the Control group; 22.0 versus 17.1 months (HR 0.641; 95% CI, 0.461–0.890; $P = .008$; Table 1; Figure 2A; Figure 3). For LSP patients there was no difference in OS between the SIRT and Control groups: median, 24.6 versus 26.6 months (HR 1.120; 95% CI, 0.918–1.368; $P = .264$; Table 1; Figure 2B; Figure 3). Results for both the SF and FFG studies were consistent: in RSP patients, median OS for SIRT versus Control patients was 21.7 versus 17.1 months ($P = .05$) in SF and 24.5 versus 16.6 months ($P = .048$) in FFG: a test of treatment-by-side interaction for OS was statistically significant ($P = .002$). In multivariable treatment models of OS in RSP treatment with SIRT remained statistically significant when adjusted for prognostic and stratification variables (HR, 0.621; 95% CI, 0.445–0.867; $P = .005$; Table 2).

For all patients, median PFS in the chemotherapy plus SIRT group was 11.1 months compared with 10.6 months in the Control group (HR 0.902; 95% CI, 0.773–1.053; $P = .193$; Table 1; Appendix A Figure A1B). For patients with RSP tumor, median PFS in the SIRT group was 10.8 months, compared with 8.7 months in the Control group (HR, 0.734; 95% CI, 0.534–1.010; $P = .057$; Table 1; Figure 2C). Results for both studies were consistent: in RSP patients, median PFS for SIRT-treated versus Control patients was 9.9 versus 8.4 months (HR 0.714; 95% CI, 0.486–1.048; $P = .085$) in SF and 11.5 versus 9.1 months (HR 0.781; 95% CI, 0.442–1.380; $P = .395$) in FFG. A multivariable model was statistically significant for SIRT treatment (HR 0.708, 95% CI, 0.511–0.981; $P = .038$), bevacizumab use, extrahepatic metastases and synchronous

disease (Appendix A, Table A2) in improved PFS in patients with RSP. Median PFS in the liver for patients with RSP tumor was 13.2 months in the SIRT group versus 9.6 months in the Control group (HR 0.580; 95% CI, 0.417–0.808; $P = .001$), and in patients with LSP tumor was 15.3 versus 12.5 months, respectively (HR, 0.792; 95% CI, 0.656–0.956; $P = .015$).

Response and resection rates

Objective response data (complete [CR] or partial [PR]) over the study duration is summarized in Appendix A, Table A3. For RSP tumors, an objective response over the study duration was achieved in 73 patients (74.5%) in the SIRT arm versus 51 patients (63.0%) in the Control arm ($P = .323$). For LSP tumors, an objective response over the study duration was achieved in 195 patients (73.9%) in the SIRT arm versus 191 patients (69.2%) in the Control arm ($P = .263$).

Over the follow-up period, 111 patients (15%) had at least one partial hepatic resection, including 21 (11.7%) of 179 RSP and 86 (15.9%) of 540 LSP patients. Of the 21 RSP patients that underwent resection, 12 (12.2%) of 98 were in the SIRT group and 9 (11.1%) of 81 in the Control group.

A multivariate Cox proportional hazards analysis stratified by protocol demonstrated that resection made a statistically significant positive contribution to OS in patients with an RSP (HR 0.659, 95% CI 0.353–0.189; $P = .001$).

Later lines of therapy

For RSP patients, 67 (68.4%) who received SIRT and 55 (67.9%) of Control group ($P = .95$) went on to receive further systemic therapy, compared with 180 (68.2%) and 213 (77.2%), respectively, in LSP patients ($P = .019$) (Appendix A, Table A4). The interaction between treatment and further systemic therapy with anti-VEGF agents including bevacizumab was not statistically significant ($P = .560$).

The safety population of 720 patients included 176 patients with RSP and 526 patients with LSP (18 patients had both or an unknown side). Treatment-emergent grade ≥ 3 adverse events (AEs) were reported in 77.2% of SIRT patients and 77.4% of Control patients with RSP ($P = 1.000$) and 84.4% and 71.3% ($P < .001$), respectively, of patients with LSP (Appendix, Table A5). There was no significant difference in the proportion of RSP and LSP patient with grade ≥ 3 AEs. There were nine deaths due to AEs in the SIRT arm (eight LSP patients and one RSP patient; Appendix, Table A5); these deaths were due to hepatic failure in three patients, which was associated with a general deterioration in physical health in one of these patients, radiation hepatitis in one patient, intestinal perforation in one patient, peritonitis in one patient, hepatic cirrhosis and ascites in one patient, respiratory failure with dyspnea in one patient, and febrile neutropenia in one patient.

Discussion

Primary tumor side is emerging as an important prognostic and predictive marker for patients with mCRC.² Here the data were analyzed from the SF-FFG studies performed in the first-line setting that enrolled patients with liver dominant or liver only disease. The known poor outcome for patients with RSP treated with standard therapy is confirmed. We report a substantial gain of 4.9 months in median OS (HR 0.641; $P = .008$) for RSP patients when SIRT was added to standard first-line combination chemotherapy.

The consistent gains in OS achieved with the addition of SIRT in patients with RSP in both the SF and FFG studies (4.8 and 7.9 months gain of median OS, respectively) suggest this finding is not the consequence of a chance imbalance of prognostic factors. Further, the difference was maintained in a multivariable analysis and a test of treatment interaction by side for OS also proved statistically significant ($P = .002$). The gains in PFS seen in multivariable analysis are consistent with the OS differences in the RSP patients being driven by the addition of SIRT to first-line chemotherapy.

As previously reported for all patients in the SIRFLOX study an increase in liver response rate did not translate into an increase in hepatic resection rates⁷ and this is not driving the improved survival outcomes observed here. The lack of impact on the number of patients undergoing liver resection possibly reflects ongoing uncertainty during the study regarding the safety of resection after SIRT. Notably, a recent assessment of SIRFLOX images by hepatobiliary surgeons blinded to study arm, time point and clinical characteristics, concluded that the addition of SIRT led to more patients having resectable disease.⁹ Also a recently-reported study concluded that surgery post-SIRT is safe.¹⁰ So potentially with a more aggressive approach to hepatic resection a greater impact on survival could be achieved with the addition of SIRT in RSP patients. The low rates of resection in SIRFLOX may also reflect the high proportion of patients (40%) that had extra-hepatic metastases, and the requirement for all patients to be reviewed by a multi-disciplinary panel for resectability.

The OS gains observed with the addition of SIRT in RSP patients were achieved despite SIRT-treated patients receiving less systemic therapy in the first line setting, notably less bevacizumab. Some patients (6.1%) randomized to receive SIRT did not receive SIRT and some (10.2%) did not receive per protocol bilobar treatment. Also, some patients randomized to the Control arm received SIRT (7.4%) after protocol therapy. Notably, for the RSP patients the rates of severe AEs in SIRT-treated and control patients were similar and the addition of SIRT to first-line chemotherapy did not compromise the delivery of later lines of therapy.

There are a number of potential explanations for the observed OS benefit being seen only in RSP patients. Using more active therapies in the first line setting could have a greater impact in patients with a RSP due to the poorer prognosis in these patients. In a subgroup analysis of the TRIBE study¹¹, initial triplet chemotherapy plus bevacizumab versus initial doublet chemotherapy plus bevacizumab significantly improved PFS in patients with a RSP, whereas the impact in LSP was not significant. While not reaching statistical significance the favourable hazard ratio for PFS in patients with a *BRAF* mutated tumor, another poor prognosis subset, has also been widely commented on. Unlike patients with a LSP and a *RAS* wildtype tumor there is no further active

biologic therapy for any patients with a RSP. The well described biologic differences between primary tumor sides may potentially create a differential response to radiation therapy, however to our knowledge this has not previously been suggested or studied.

A limitation of this analysis is that patients were not stratified according to primary tumor side. We also currently lack a full biological explanation for these side-dependent differences. The embryological origins of the right versus left colon and rectum are distinct² and many differences in molecular characteristics are described for RSP and LSP², but the impact of these, if any, on SIRT benefit is unknown. While any available molecular data was collected prospectively routine testing was not yet universal over the time period these studies were conducted and RAS and RAF data is available on less than half of the patients. Efforts to collect further molecular and biomarker data, both standard and exploratory, are planned. We note there is no significant detriment to OS from adding SIRT in the larger LSP group, where the median survival for patients randomized to SIRT was 24.6 versus 26.6 months in the Control arm ($P = .264$). Overall, we believe the results of this study do not have implications for SIRT use in later lines of mCRC therapy, where the available data indicate a benefit from treating all patients.¹²⁻¹⁵

Conclusion

In conclusion, the observed poor prognosis for mCRC patients with RSP and a greater benefit for SIRT in RSP patients, add to the already substantial literature on primary tumor side-based differences in mCRC outcomes. These data further support a side-based approach to initial treatment selection in the pursuit of a personalized approach to mCRC management. This potentially includes the use of SIRT as part of the first-line treatment for some RSP patients with liver-only or liver-dominant disease, given the lack of survival benefit from initial treatment with EGFR inhibitors in RSP patients and that many will not be fit for triplet chemotherapy, which is the only other alternative beyond doublet chemotherapy plus bevacizumab. Further studies of the impact of primary tumor side in mCRC patients treated with SIRT and the potential drivers of side-based differences are warranted.

- Primary tumor side is emerging as an important prognostic and predictive marker for patients with mCRC. Patients with RSP tumors have been reported to have a poor prognosis with standard therapy and further treatment options are being sought.
- In this combined analysis of data from two randomized trials, SIRLOX and FOXFIRE Global, the addition of SIRT with ⁹⁰yttrium resin microspheres to first-line chemotherapy in patients with mCRC was associated with statistically and clinically significant OS gains in patients with a RSP tumor.
- These findings add to the already substantial information on primary tumor side-based differences in mCRC outcomes.
- These data support a side-based approach to treatment selection in mCRC management, including use of SIRT as part of the first-line treatment of RSP patients with liver-only or liver-dominant metastases.

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REFERENCES

1. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: A systematic review and meta-analysis. *JAMA Oncol.* 2017;3(2):211-219.
2. Stintzing S, Tejpar S, Gibbs P, Thiebach L, Lenz HJ. Understanding the role of primary tumour localisation in colorectal cancer treatment and outcomes. *Eur J Cancer.* 2017;84:69-80.
3. Gray B, Van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. *Ann Oncol.* 2001;12(12):1711-1720.
4. Van Hazel G, Blackwell A, Anderson J, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. *J Surg Oncol.* 2004;88(2):78-85.
5. Gibbs P, GebSKI V, Van Buskirk M, et al. Selective Internal Radiation Therapy (SIRT) with yttrium-90 resin microspheres plus standard systemic chemotherapy regimen of FOLFOX versus FOLFOX alone as first-line treatment of non-resectable liver metastases from colorectal cancer: the SIRQLOX study. *BMC Cancer.* 2014;14:897.
6. Virdee PS, Moschandreas J, GebSKI V, et al. Protocol for combined analysis of FOXFIRE, SIRQLOX, and FOXFIRE-Global randomized phase III trials of chemotherapy +/- Selective Internal Radiation Therapy as first-line treatment for patients with metastatic colorectal cancer. *JMIR Res Protoc.* 2017;6(3):e43.
7. van Hazel GA, Heinemann V, Sharma NK, et al. SIRQLOX: Randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus Selective Internal Radiation Therapy in patients with metastatic colorectal cancer. *J Clin Oncol.* 2016;34:1723-1731.
8. Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRQLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol.* 2017;18(9):1159-1171.

9. Garlipp B, Gibbs P, van Hazel G, et al. e. REsect: Blinded assessment of resectability of previously unresectable colorectal cancer liver metastases following chemotherapy $\pm$ Y90-radioembolization. Presented at the Paper presented at: 12th Biennial European-African Hepato-Pancreato-Biliary Association (E-AHPBA) Congress; May 23-26, 2017; Mainz, Germany.
10. Pardo F, Sangro B, Lee RC, et al. The Post-SIR-Spheres Surgery Study (P4S): retrospective analysis of safety following hepatic resection or transplantation in patients previously treated with selective internal radiation therapy with yttrium-90 resin microspheres. *Ann Surg Oncol*. 2017;24:2465–2473.
11. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med*. 2014;371(17):1609-18
12. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol*. 2010;28(23):3687-3694.
13. Bester L, Meteling B, Pocock N, et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. *J Vasc Interv Radiol*. 2012;23(1):96-105.
14. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol*. 2012;35(5):1066-1073.
15. Kennedy AS, Ball D, Cohen SJ, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for (90)Y resin microspheres. *J Gastrointest Oncol*. 2015;6(2):134-142.

Table 1. Overall survival and progression-free survival, for all patients and by primary tumor side (ITT population)

Table 1. Overall survival and progression-free survival, for all patients and by primary tumor side (N = 1 population)								
Primary tumor side	Study cohort	Control Arm ^a			SIRT Arm ^b			P Value
		n	Median, months	(95% CI)	n	Median, months	(95% CI)	
Overall survival								
All patients	SIRFLOX	263	24.5	(21.8–26.3)	267	22.6	(21.0–25.6)	.676
	FOXFIRE Global	104	25.0	(22.1–28.5)	105	25.9	(23.1–28.9)	.789
	SIRFLOX + FOXFIRE Global	367	24.6	(22.2–26.3)	372	24.3	(21.9–25.9)	.810
Right-Side CRC	SIRFLOX	55	17.1	(13.9–19.8)	72	21.7	(16.9–25.6)	.054
	FOXFIRE Global	26	16.6	(9.6–22.1)	26	24.5	(19.2–28.9)	.048
	SIRFLOX + FOXFIRE Global	81	17.1	(13.9–19.9)	98	22.0	(18.9–25.6)	.008
Left-Side CRC	SIRFLOX	201	26.4	(24.6–30.0)	188	24.4	(21.7–26.3)	.321
	FOXFIRE Global	75	27.4	(24.1–33.2)	76	25.9	(22.1–31.3)	.608
	SIRFLOX + FOXFIRE Global	276	26.6	(24.8–29.9)	264	24.6	(22.3–26.7)	.264
Progression-free survival								
All patients	SIRFLOX	263	10.5	(9.4–11.4)	267	10.9	(9.8–11.5)	.563
	FOXFIRE Global	104	11.2	(9.4–12.6)	105	11.9	(10.3–14.4)	.127
	SIRFLOX + FOXFIRE Global	367	10.6	(9.6–11.6)	372	11.1	(10.2–11.9)	.193
Right-Side CRC	SIRFLOX	55	8.4	(7.8–11.1)	72	9.9	(8.6–11.5)	.084
	FOXFIRE Global	26	9.1	(5.2–12.8)	26	11.5	(6.1–14.5)	.394
	SIRFLOX + FOXFIRE Global	81	8.7	(7.8–10.9)	98	10.8	(9.3–12.4)	.056
Left-Side CRC	SIRFLOX	201	10.7	(9.6–12.4)	188	11.2	(9.9–12.6)	.849
	FOXFIRE Global	75	11.7	(9.4–12.6)	76	11.9	(9.6–15.6)	.143
	SIRFLOX + FOXFIRE Global	276	10.8	(9.9–12.3)	264	11.4	(10.1–12.6)	.351

Median estimation from Kaplan-Meier estimation, and p-value by log-rank test.

^a mFOLFOX6 ± bevacizumab

^b mFOLFOX6 + SIRT ± bevacizumab

Abbreviations: ITT, intent-to-treat; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; bev, bevacizumab; SIRT, selective internal radiation therapy; N, number; 95% CI, 95% confidence interval; CRC, colorectal cancer.

Table 2. Univariate and multivariable Cox proportional hazards model for overall survival in patients with right-sided primary tumors in the SIRFLOX and FOXFIRE Global studies (ITT population)

Model	Parameter(s) (Effect vs Reference)	HR	(95% CI)	P
Univariate Models	Treatment (SIRT + CT vs CT)	0.641	(0.461–0.890)	.008
	Bevacizumab used (Yes vs No)	0.987	(0.704–1.383)	.940
	EHM at randomization (Yes vs No)	1.351	(0.957–1.907)	.088
	Tumor burden (>25% vs ≤25%)	1.773	(1.254–2.508)	.001
	Primary tumor in situ (Yes vs No)	1.865	(1.318–2.638)	<.001
	Synchronous disease (Yes vs No)	1.426	(0.747–2.721)	.282
	Age (≥65 vs <65)	1.140	(0.823–1.579)	.430
	Gender (male vs female)	0.990	(0.709–1.382)	.951
Multivariate Backwards Elimination Model ^a	Treatment (SIRT + CT vs CT)	0.621	(0.445–0.867)	.005
	EHM at randomization (Yes vs No)	1.308	(0.928–1.843)	.125
	Tumor burden (>25% vs ≤25%)	1.620	(1.100–2.384)	.014
	Primary tumor in situ (Yes vs No)	1.494	(1.020–2.188)	.039

Abbreviations: ITT, intent-to-treat; HR, Hazard Ratio; 95% CI, 95% confidence interval; CT: chemotherapy; SIRT, selective internal radiation therapy; EHM, extra-hepatic metastases.

^aModel selection for multivariable models for RSP was by backwards elimination with a threshold of $P < .15$ for inclusion in the model

Figure 1. CONSORT diagram

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Figure 2. Overall survival (A: in right-sided primary CRC; B: in left-sided primary CRC) and progression-free survival (C: in right-sided primary CRC; D: in left-sided primary CRC) by primary tumor side (ITT population)

ITT, intent-to-treat; n, number; OS, overall survival; PFS, progression-free survival; 95% CI, 95% confidence interval; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; bev, bevacizumab; SIRT, selective internal radiation therapy; CT: chemotherapy (mFOLFOX6 [$\pm$ bev]).

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Figure 3. Forest plot and univariate Cox proportional hazards model of overall survival by primary tumor side (ITT population)

Abbreviations: ITT, intent-to-treat; HR: Hazard Ratio; 95% CI: 95% confidence interval; CRC, colorectal cancer; SIRT, selective internal radiation therapy.

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[†] Test for interaction between treatment and primary tumor side of overall survival was statistically significant: $P = .002$.

SIRFLOX

FOXFIRE Global

A

B

C

D

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	Page
Principal Investigators	3
Table A1. Patient characteristics and treatment received by primary tumor side (ITT population)	4
Table A2. Univariate and multivariable Cox proportional hazards model for progression-free survival in patients with right-sided primary tumors in the SIRFLOX and FOXFIRE Global studies	6
Table A3. Imaging response by primary tumor side (ITT population)	7
Table A4. Post-progression treatment received	8
Table A5. Summary of adverse events of grade ≥ 3	... 9
Figure A1. Overall survival (A) and progression-free survival (B) in all patients (ITT population).	10

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Table A1. Patient characteristics and treatment received by primary tumor side (ITT population)

Variable	All Patients				Right-Sided Primary CRC		Left-Sided Primary CRC	
	Control Arm ^a	SIRT Arm ^b	Right-Sided Primary CRC	Left-Sided Primary CRC	Control Arm	SIRT Arm	Control Arm	SIRT Arm
	N = 367	N = 372	N = 179	N = 540	N = 81	N = 98	N = 276	N = 264
Age, years, mean ±SD	62.4 ±10.89	62.2 ±10.64	64.4 ±10.43	61.6 ±10.75	65.1 ±10.10	63.7 ±10.70	61.5 ±11.07	61.6 ±10.43
Gender:								
Female	132 (36.0)	126 (33.9)	76 (42.5)	173 (32.0)	39 (48.1)	37 (37.8)	90 (32.6)	83 (31.4)
Male	234 (63.8)	246 (66.1)	103 (57.5)	367 (68.0)	42 (51.9)	61 (62.2)	186 (67.4)	181 (68.6)
Unknown	1 (0.3)	0	0	0	0	0	0	0
WHO PS:								
0	228 (62.1)	237 (63.7)	111 (62.0)	346 (64.1)	47 (58.0)	64 (65.3)	178 (64.5)	168 (63.6)
1	137 (37.3)	134 (36.0)	68 (38.0)	192 (35.6)	34 (42.0)	34 (34.7)	97 (35.1)	95 (36.0)
Unknown	1 (0.3)	1 (0.3)	0	2 (0.4)	0	0	1 (0.4)	1 (0.4)
Liver tumor burden	12.3 (22.7) ^c	12.0 (24.4) ^c	14.0 (28.0) ^c	12.0 (22.8) ^c	14.0 (24.0) ^c	14.1 (29.0) ^c	11.6 (23.0) ^c	12.0 (22.8) ^c
>25%	100 (27.2)	112 (30.1)	59 (33.0)	149 (27.6)	24 (29.6)	35 (35.7)	74 (26.8)	75 (28.4)
Extrahepatic metastases	131 (35.7)	138 (37.1)	69 (38.5)	193 (35.7)	28 (34.6)	41 (41.8)	99 (35.9)	94 (35.6)
Primary tumor <i>in situ</i>	180 (49.0)	169 (45.4)	77 (43.0)	265 (49.1)	37 (45.7)	40 (40.8)	140 (50.7)	125 (47.3)
Synchronous disease	333 (90.7)	330 (88.7)	166 (92.7)	480 (88.9)	78 (96.3)	88 (89.8)	247 (89.5)	233 (88.3)
Primary tumor side								
Right sided	81 (22.1)	98 (26.3)	179 (100)	0	81 (100)	98 (100)	0	0
Left sided	276 (75.2)	264 (71.0)	0	540 (100)	0	0	276 (100)	264 (100)
Both	8 (2.2)	8 (2.2)	0	0	0	0	0	0
Unknown	2 (0.5)	2 (0.5)	0	0	0	0	0	0
KRAS status								
Wild-type	69 (18.8)	65 (17.5)	21 (11.7)	111 (20.6)	13 (16.0)	8 (8.2)	55 (19.9)	56 (21.2)
Mutant	49 (13.4)	41 (11.0)	33 (18.4)	53 (9.8)	18 (22.2)	15 (15.3)	28 (10.1)	25 (9.5)
Unknown	249 (67.8)	266 (71.5)	125 (69.8)	376 (69.6)	50 (61.7)	75 (76.5)	193 (69.9)	183 (69.3)
Bevacizumab ITT	234 (63.8)	233 (62.6)	115 (64.2)	338 (62.6)	55 (67.9)	60 (61.2)	172 (62.3)	166 (62.9)
Bevacizumab administered	229 (62.4)	195 (52.4)	106 (59.2)	305 (56.5)	53 (65.4)	53 (54.1)	170 (61.6)	135 (51.1)
Oxaliplatin cycles	10.0 (5.0) ^c	10.0 (5.0) ^c	9.4 (5.6) ^c	10.0 (5.0) ^c	10.0 (5.0) ^c	9.0 (6.0) ^c	10.0 (5.0) ^c	10.0 (5.0) ^c
SIRT administered	na	339 (91.1)	92 (93.9) ^d	237 (89.8) ^d	na	92 (93.9)	na	237 (89.8)
SIRT administered to both lobes (per protocol)	na	306 (82.3)	82 (83.7) ^d	216 (81.8) ^d	na	82 (83.7)	na	216 (81.8)
Activity administered, GBq,	na	1.37 (0.8) ^c	1.4 (0.7) ^c	1.37 (0.8) ^c	na	1.4 (0.7) ^c	na	1.37 (0.8) ^c

NOTE. Data are presented as No. (%) unless indicated otherwise. There is no statistically significant difference between the treatment groups overall, right and left sided tumors for any of the variables presented.

^a mFOLFOX6 ± bevacizumab

^b mFOLFOX6 + SIRT ± bevacizumab

^c median (interquartile range)

^d (%) of SIRT arm

Abbreviations: ITT, intent-to-treat; CRC, colorectal cancer; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; bev, bevacizumab; SIRT, selective internal radiation therapy; *N*, number; SD, standard deviation; WHO PS, WHO performance status; na, not applicable; GBq, gigabecquerel.

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Table A2. Univariate and multivariable Cox proportional hazards model for progression-free survival in patients with right-sided primary tumors in the SIRFLOX and FOXFIRE Global studies

Model	Parameter(s) (Effect versus Reference)	HR	(95% CI)	P value
Univariate Models	Treatment (SIRT + CT versus CT)	0.734	(0.534–1.010)	.057
	Bevacizumab used (Yes versus No)	0.695	(0.503–0.961)	.028
	EHM at randomization (Yes versus No)	1.359	(0.977–1.890)	.069
	Tumor burden (>25% versus ≤25%)	1.342	(0.961–1.874)	.084
	Primary tumor <i>in situ</i> (Yes versus No)	1.378	(0.994–1.910)	.055
	Synchronous disease (Yes versus No)	1.759	(0.947–3.270)	.074
	Age (≥65 versus <65)	1.134	(0.830–1.550)	.429
	Gender (male versus female)	0.945	(0.690–1.294)	.724
Multivariable	Treatment (SIRT + CT versus CT)	0.708	(0.511–0.981)	.038
Backwards	Bevacizumab used (Yes versus No)	0.537	(0.379–0.761)	< .001
Elimination	EHM at randomization (Yes versus No)	1.721	(1.214–2.441)	.002
Model ^a	Synchronous disease (Yes versus No)	2.595	(1.317–5.113)	.006

Abbreviations: HR, Hazard Ratio; 95% CI, 95% confidence interval; CT: chemotherapy EHM, extra-hepatic metastases.

^aModel selection for multivariable models for RSP was by backwards elimination with a threshold of $P < .15$ for inclusion in the model

Table A3. Imaging response by primary tumor side (ITT population)

Response	All Patients			Right-Sided Primary CRC			Left-Sided Primary CRC		
	Control Arm ^a N = 367	SIRT Arm ^b N = 372	P value ^c	Control Arm ^a N = 81	SIRT Arm ^b N = 98	P value ^c	Control Arm ^a N = 276	SIRT Arm ^b N = 264	P value ^c
Any site			.004			.193			.021
Complete response (CR)	6 (1.6)	19 (5.1)		0 (0)	4 (4.1)		6 (2.2)	15 (5.7)	
Partial response (PR)	242 (65.9)	258 (69.4)		51 (63.0)	69 (70.4)		185 (67.0)	180 (68.2)	
Stable disease	73 (19.9)	49 (13.2)		16 (19.8)	13 (13.3)		55 (19.9)	35 (13.3)	
Progressive disease	22 (6.0)	32 (8.6)		7 (8.6)	10 (10.2)		15 (5.4)	22 (8.3)	
Not available	24 (6.5)	14 (3.8)		7 (8.6)	2 (2.0)		15 (5.4)	12 (4.5)	
Objective Response Rate (CR + PR)	248 (67.6)	277 (74.5)	.124	51 (63.0)	73 (74.5)	.323	191 (69.2)	195 (73.9)	.263
Hepatic			< .001			.187			.003
Complete response (CR)	8 (2.2)	29 (7.8)		0 (0)	5 (5.1)		8 (2.9)	24 (9.1)	
Partial response (PR)	244 (66.5)	261 (70.2)		52 (64.2)	68 (69.4)		186 (67.4)	184 (69.7)	
Stable disease	71 (19.3)	48 (12.9)		15 (18.5)	16 (16.3)		54 (19.6)	31 (11.7)	
Progressive disease	20 (5.4)	20 (5.4)		7 (8.6)	7 (7.1)		13 (4.7)	13 (4.9)	
Not available	24 (6.5)	14 (3.8)		7 (8.6)	2 (2.0)		15 (5.4)	12 (4.5)	
Hepatic Best Response (CR + PR)	252 (68.7)	290 (78.0)	0.018	52 (64.2)	73 (74.5)	.415	194 (70.3)	208 (78.8)	.024

NOTE. Data are presented as No. (%) unless indicated otherwise.

^a mFOLFOX6 ± bevacizumab

^b mFOLFOX6 + SIRT ± bevacizumab

^c P-values for response comparison (CR, PR, SD, PD) for SIRT + mFOLFOX6 versus mFOLFOX6 in combined studies, stratified by protocol.

Abbreviations: ITT, intent-to-treat; CRC, colorectal cancer; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; bev, bevacizumab; SIRT, selective internal radiation therapy; n, number.

Table A4. Post-progression treatment received

Post-progression treatment	Right-Sided Primary CRC			Left-Sided Primary CRC		
	Control Arm ^a n = 81	SIRT Arm ^b n = 98	P value	Control Arm ^a n = 276	SIRT Arm ^b n = 264	P value
Any chemotherapy	55 (67.9)	67 (68.4)	.947	213 (77.2)	180 (68.2)	.019
Irinotecan	51 (63.0)	57 (58.2)	.515	194 (70.3)	155 (58.7)	.005
Anti-VEGF	24 (29.6)	33 (33.7)	.564	107 (38.8)	79 (29.9)	.031
Anti-VEGF RCT [†]	2 (3.6)	1 (1.4)	.410	4 (1.4)	3 (1.1)	.748
Oxaliplatin	16 (19.8)	28 (28.6)	.174	85 (30.8)	67 (25.4)	.162
Anti-EGFR	14 (17.3)	14 (14.3)	.584	93 (33.7)	63 (23.9)	.012
Regorafenib	2 (2.5)	7 (7.1)	.156	17 (6.2)	19 (7.2)	.629
TAS-102	1 (1.2)	3 (3.1)	.412	4 (1.4)	3 (1.1)	.748
TAS-102 RCT ^c	0 (0)	0 (0)	(no test)	0 (0)	1 (0.4)	.328
Mitomycin	2 (2.5)	4 (4.1)	.552	17 (6.2)	10 (3.8)	.207
SIRT	6 (7.4)	6 (6.1)	.733	45 (16.3)	9 (3.4)	< .001
Chemoembolization	1 (1.2)	1 (1.0)	.892	5 (1.8)	8 (3.0)	.356

NOTE. Data are presented as No. (%).

^a mFOLFOX6 ± bevacizumab^b mFOLFOX6 + SIRT ± bevacizumab[†] Patients recruited in subsequent independent RCT and randomized to placebo versus active agent (Anti-VEGF or TAS-102), for whom unblinded data is not available.

Abbreviations: CRC, colorectal cancer; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; bev, bevacizumab; SIRT, selective internal radiation therapy; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; RCT, randomized controlled trial.

Table A5. Summary of adverse events of grade ≥ 3 *

Adverse Events	Right-Sided Primary CRC			Left-Sided Primary CRC		
	Control Arm ^a	SIRT Arm ^b	<i>P</i> value	Control Arm ^a	SIRT Arm ^b	<i>P</i> value
Safety population	84 (100)	92 (100)		289 (100)	237 (100)	
Any grade ≥ 3 AE ^c	65 (77.4)	71 (77.2)	1.00	206 (71.3)	200 (84.4)	< .001
Neutropenia	23 (27.4)	40 (43.5)	.029	76 (26.3)	90 (38.0)	.005
Febrile neutropenia	1 (1.2)	6 (6.5)	.120	7 (2.4)	19 (8.0)	.004
Thrombocytopenia	0 (0.0)	11 (12.0)	< .001	8 (2.8)	17 (7.2)	.02
Leukopenia	1 (1.2)	6 (6.5)	.120	7 (2.4)	10 (4.2)	.32
Diarrhea	8 (9.5)	3 (3.3)	.120	26 (9.0)	23 (9.7)	.88
Peripheral neuropathy	10 (11.9)	5 (5.4)	.177	21 (7.3)	13 (5.5)	.48
Pulmonary embolism	1 (1.2)	0 (0.0)	.477	16 (5.5)	12 (5.1)	.85
Fatigue	5 (6.0)	12 (13.0)	.131	14 (4.8)	23 (9.7)	.04
Nausea/vomiting	4 (4.8)	6 (6.5)	.749	11 (3.8)	16 (6.8)	.16
Abdominal pain	3 (3.6)	8 (8.7)	.217	5 (1.7)	21 (8.9)	< .001
Hyperglycemia	5 (6.0)	1 (1.1)	.105	9 (3.1)	4 (1.7)	.40
Hypertension	7 (8.3)	2 (2.2)	.088	11 (3.8)	10 (4.2)	.83
SIRT-associated AEs^d						
Gastric/ duodenal ulcer	0 (0.0)	2 (2.2)	.498	1 (0.3)	7 (3.0)	.03
Ascites	1 (1.2)	1 (1.1)	1.00	0 (0.0)	8 (3.4)	.002
Hepatic failure	0 (0.0)	1 (1.1)	1.00	0 (0.0)	4 (1.7)	.04
Radiation hepatitis	0 (0.0)	0 (0.0)	1.00	0 (0.0)	2 (0.8)	.20
Any grade 5 AE ^e	3 (3.6)	1 (1.1)	.349	3 (1.0)	8 (3.4)	.07
Treatment-related grade 5 AEs ^f	2 (2.4)	1 (1.1)	.606	2 (0.7)	6 (2.5)	.15

NOTE. Data are presented as No. (%).

*According to Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Abbreviations: CRC, colorectal cancer; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; bev, bevacizumab; SIRT, selective internal radiation therapy; AE, adverse event.

^a mFOLFOX6 $\pm$ bevacizumab^b mFOLFOX6 + SIRT $\pm$ bevacizumab^cAll grade ≥ 3 AEs occurring with an incidence of $\geq 5\%$ in either study arm, irrespective of attribution to treatment.^dAEs typically associated with SIRT.^eOccurring with an incidence of $\geq 0\%$ in either study arm, irrespective of attribution to treatment.^fAttributed to either or both treatments.

Figure A1. Overall survival (A) and progression-free survival (B) in all patients (ITT population).

A

B

Abbreviations: ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; 95% CI, 95% confidence interval; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; bev, bevacizumab; SIRT, selective internal radiation therapy; CT: chemotherapy (mFOLFOX6 [± bev]).