Quality of life in the FOXFIRE, SIRFLOX, and FOXFIRE-Global randomised trials of selective internal radiotherapy for metastatic colorectal cancer

J. Wolstenholme[1] *, F. Fusco[1,2] *, A.M. Gray[1], J. Moschandreas[3,4], P. S. Virdee[3], S. Love[3], G. Van Hazel[5], P. Gibbs[6], H.S. Wasan[7], R. A. Sharma[8].

[1]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, GB

[2]Centre for Health Economics, University of York, Heslington, Alcuin 'A' Block, York YO10 5DD, UK

[3]Centre for Statistics in Medicine, University of Oxford, Oxford, GB

[4]Centre for the Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, GB

[5]University of Western Australia, University of Western Australia, Perth, WA, AU

[6]Western Hospital, Western Hospital, Footscray, VIC, AU

[7]Oncology, Imperial College Healthcare NHS Trust & Imperial College, London, GB

[8]NIHR University College London Hospitals Biomedical Research Centre, UCL Cancer Institute, University College London, London, GB

* Equal contribution

Corresponding Authors:

Professor Ricky A. Sharma

University College London Hospitals Biomedical Research Centre

UCL Cancer Institute, University College London

London, GB

Tel: +442031082212

E-mail: ricky.sharma@ucl.ac.uk

Professor Alastair M. Gray

Health Economics Research Centre

Nuffield Department of Population Health

University of Oxford, Oxford, GB

Tel: +441865 289279

Email: alastair.gray@dph.ox.ac.uk

Keywords:

Quality of Life; colorectal adenocarcinoma; liver; metastasis; radiotherapy()()

List of abbreviations

Selective internal radiotherapy (SIRT)

health related quality of life (HRQOL)

colorectal cancer (CRC)

metastatic CRC (mCRC)

FOXFIRE (FFr)

SIRFLOX (SF)

FOXFIRE-Global (FFrG)

European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30)

EORTC Colorectal Liver Metastases cancer module (EORTC QLQ-LMC21)

overall survival (OS)

liver metastases from colorectal cancer (LMCRC)

yttrium-90 (Y-90)

randomised clinical trials (RCTs)

first-line leucovorin-oxaliplatin-fluorouracil chemotherapy (FOLFOX)

SIRT plus FOLFOX (SIRT+FOLFOX)

progression-free survival (PFS)

World Health Organisation **(**WHO**)**

intention-to-treat (ITT)

adverse events (AEs)

ordinary least squares (OLS)

missing at random (MAR)

missing not at random (MNAR)

Article category: Short Reports

Novelty and Impact

With a total of 1,103 patients, this is the largest analysis of patient-reported outcomes for Selective internal radiotherapy (SIRT), and it is also the largest prospective quality of life (QOL) study performed in the field of Interventional Oncology.

Following an initial non-clinically important deterioration up to 3 months post-SIRT, our results indicate that SIRT can be added to first-line leucovorin-oxaliplatin-fluorouracil chemotherapy without a detrimental impact on QOL.

Abstract

Selective internal radiotherapy (SIRT) is a liver-directed treatment involving injection of yttrium-90 microspheres in to the blood supply of liver tumours. There are very few studies assessing health related quality of life (HRQOL) in patients treated with SIRT. Patients with liver metastases from colorectal cancer (CRC) were randomised in the FOXFIRE (FFr) (ISRCTN83867919), SIRFLOX (SF) (NCT00724503) and FOXFIRE-Global (FFrG) (NCT01721954) trials of first-line oxaliplatin-fluorouracil (FOLFOX) chemotherapy combined with SIRT versus FOLFOX alone. HRQOL was assessed using the 3-level EQ-5D, European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) and EORTC Colorectal Liver Metastases cancer module (EORTC QLQ-LMC21) at baseline, ≤3 months, 6-months, 12-months, and annually thereafter from randomisation, and at disease progression. Analyses were conducted on an intention-to-treat basis. In total, 554 patients were randomised to SIRT+FOLFOX and 549 patients to FOLFOX alone. HRQOL was statistically significant lower in SIRT+FOLFOX patients ≤3 months after SIRT administration in all 3 instruments, particularly global health, physical and role functioning, and symptoms of fatigue, nausea/vomiting and appetite loss. By accepted thresholds, these differences were deemed not clinically important. Differences between SIRT+FOLFOX and FOLFOX alone over the 2-year follow up and at disease progression were also not clinically important. Although there is some decrease in HRQOL for up to 3 months following SIRT, the addition of SIRT to FOLFOX chemotherapy does not change HRQOL to a clinically important degree in metastatic CRC patients.

Introduction

Approximately 1.3 million patients are diagnosed with colorectal cancer (CRC) worldwide each year, with more than 40% developing metastases.(1) Liver metastases are the most common cause of death in metastatic CRC (mCRC) patients, with 13% 5-year overall survival (OS) in the USA.(1) Survival may increase to up to 40% after complete liver metastases resection,(2) but only 20% of patients with liver metastases from colorectal cancer (LMCRC) are eligible for resection.(3) For inoperable patients, one way of improving liver control and reducing tumour size is Selective Internal Radiation Therapy (SIRT). SIRT delivers millions of microspheres containing the β-emitter, yttrium-90 (Y-90), into the arterial supply of the liver, selectively targeting radiotherapy to liver tumours and preserving the healthy liver. We recently reported combined results from the FOXFIRE (FFr), SIRFLOX (SF) and FOXFIRE-Global (FFrG) randomised clinical trials (RCTs), which compared first-line leucovorin-oxaliplatin-fluorouracil chemotherapy (FOLFOX) alone to SIRT plus FOLFOX (SIRT+FOLFOX) in LMCRC patients not eligible for resection/ablation. This combined analysis confirmed better liver-specific disease control and improved radiological responses in patients receiving SIRT+FOLFOX, but with no improvement in overall or progression-free survival (PFS).(4)

Since the principal indication for SIRT worldwide is patients with LMCRC who are refractory to standard chemotherapies and for whom the prognosis is less than 12 months,(5) health-related quality of life (HRQOL) is an extremely important clinical outcome when discussing the potential value of SIRT with patients who have few other treatment options. Existing evidence on this is currently limited,(6) and this study provides a unique opportunity to report comprehensive data on HRQOL in

patients treated with this highly specialised form of radiotherapy. The aim of this study was to compare HRQOL between LMCRC patients receiving SIRT plus FOLFOX and FOLFOX alone as first-line treatment

Material and methods

Between October 11, 2006, and December 23, 2014, patients aged ≥ 18 years providing written informed consent were randomised to either FOLFOX (systemic leucovarin-oxaliplatin-fluorouracil) or SIRT+FOLFOX within 3 international, multi-centre, phase III RCTs (FFr, SF and FFrG). FFr was approved by the National Research Ethics Service Committee South Central- Berkshire (REC reference: 09/H0505/1). The protocols were approved by ethics committees at each of the 182 centres from the 14 countries involved in the study. The inclusion criteria included eligibility for systemic chemotherapy as first-line treatment for mCRC with liver-only or liver dominant metastases with or without the primary tumour in situ, and World Health Organisation (WHO) performance status ≤1. Trial designs and eligibility criteria were pre-specified to be similar, as an a priori plan to combine the studies to produce a HRQOL analysis with increased power to detect differences. Further details on inclusion criteria, randomisation and study protocols have been published previously.(4, 7-9).

Treatment

FOLFOX treatment was planned to continue until evidence of treatment failure (FFrG, SF) or for a maximum of 12 cycles (FFr) (each cycle lasted 14 days). To

deliver SIRT, SIR-Spheres® Y-90 resin microspheres (Sirtex Medical Limited, Sydney, Australia) were delivered into the arterial supply of the liver under fluoroscopic guidance, resulting in selective targeting by high-dose radiotherapy. Full details, including treatment doses, have been published previously.(4)

Instruments

HRQOL was assessed using the EQ-5D-3L and the EORTC QLQ-C30 with the EORTC colorectal liver cancer module (EORTC QLQ-LMC21). (10-12)

The EQ-5D-3L is a generic HRQOL instrument with five questions covering mobility, usual activities, self-care, pain/discomfort, and anxiety/depression, and three responses for each question: no, some or extreme problems.(10) Overall EQ-5D-3L utility-scores can be derived for each health state, with 1 corresponding to full health and 0 to death. The minimum clinically significant difference in EQ-5D scores in cancer has been reported as 0.06.(13) In this analysis, utility was calculated using US scores.(14)

The EORTC QLQ-C30 is a generic cancer HRQOL questionnaire employing 30 items to assess 5 functional scales, 9 symptom scales/items and a global health status scale. Functional and symptom scales/items have 4 response levels (ranging from not at all to very much), while the global health status scale relies on two items, with 7 response levels ranging from very poor to excellent. A standardised score ranging from 0 to 100 is calculated from the items.(12) A high score in the functional scale or global health status represents better quality of life. Conversely, a high symptom scale should be interpreted as poorer health status. The EORTC QLQ-C30

has been tested in different cancer populations and has been shown to have good validity, reliability and responsiveness. (15)

The EORTC QLQ-LMC21 consists of four symptom scales and 9 symptom items. The items of the EORTC QLQ-LMC21 are combined to obtain standardised scores ranging from 0 to 100,(11) where high scores represent high levels of symptoms. Clinically important differences for both EORTC instruments have been categorised as follows: a 5-10 point difference in the mean score is considered small, 10-20 points moderate and over 20 points considered a large difference.(16)

Paper versions of the HRQOL questionnaires were completed by patients before any treatment started, during chemotherapy, at 6-months, 12-months, annually thereafter until death or 5 years post-randomisation, and at disease progression. During the first 6-months, the time-points varied slightly between the the trials: further details are given in the supplementary material.

Outcomes

HRQOL from the combined FFr-SF-FFrG trials was an important secondary objective in the clinical trials (9) and the pre-specified outcomes were: EORTC QLQ-C30 global health status at 12-months, and EORTC QLQ-LMC21 fatigue scale at ≤3-months. It was hypothesised that patients receiving SIRT+FOLFOX would report better HRQOL at 12-months after randomisation than FOLFOX patients – primarily in EORTC QLQ-C30 global health status.

Statistical analysis

All analyses were conducted on an intention-to-treat (ITT) basis, except the safety analysis, which was conducted on an as-treated basis. Responses by groups were summarised using mean scores and standard errors at each time-point. Differences at baseline in the scores of EORTC and EQ-5D-3L were compared between arms using the Wilcoxon rank sum test and t-test, respectively. ANCOVA was used to analyse differences between arms for EQ-5D-3L, EORTC QLQ-C30 and EORTC QLQ-LMC21 scores for all time-points.

HRQOL at progression is reported by time intervals based on the acute, subacute and chronic side effects which may result from SIRT [6] and compared with HRQOL at the previous reported time-point. Data on adverse events (AEs) were available for all three trials (4) and were collected until 28 days after trial treatment or 7 months from randomisation, whichever was earlier. The impact of having AEs with a severity grade ≥3 on HRQOL was tested using ordinary least squares (OLS) regression with a treatment-AE interaction term. The pre-specified outcomes were also tested using OLS regression and introducing an interaction term for pre-specified subgroups (presence of extra-hepatic metastases, primary tumour in situ, liver tumour burden >25%, age ≥65 years, ITT with biological agents) and post-hoc subgroups (Bevacizumab given, gender, synchronous disease, primary tumour location right or left and WHO performance status). The safety and subgroup analyses are reported in supplementary material.

To allow for repeated measures from participants, we used a longitudinal linear mixed-effect model, with treatment group as fixed-effect and time and patient-specific random-effect.

All differences between arms in scale scores were adjusted for the respective baseline score and any baseline score registering a statistically significant difference.

The robustness of our estimates was tested by sensitivity analyses, in which we 1) recalculated the EQ-5D-3L utility-scores using the UK tariff(10), and 2) repeated all analyses having imputed missing data under missing at random (MAR) and missing not at random (MNAR) assumptions for the pre-specified outcomes and for EQ-5D-3L utility-scores at ≤3-months.(17) Details of imputation methods are reported in supplementary material.

All hypothesis tests were two-sided with a 5% significance level. All analyses were performed using STATA version 14 (StataCorp, College Station, TX).

Data Availability

Data will be made available upon reasonable request, following approval of requests by Trial Sponsors.

Results

We compared HRQOL between LMCRC patients receiving SIRT plus FOLFOX and FOLFOX alone as first-line treatment using two cancer-specific HRQOL questionnaires at multiple time-points: the EORTC QLQ-C30 instrument with QLQ-LMC21 module, and the generic EQ-5D-3L instrument. The ITT population included 1,103 patients (Appendix figure 1). Baseline characteristics were balanced across the study arms.(4) 65.6% were men and median age was 63 years at baseline. In

73.7% of patients the primary cancer site was the colon and 35.5% of patients had extra-hepatic metastases.

Since available numbers after 24 months were too low to support robust analyses, here we report the results for baseline (1,017 patients responding out of 1,103 alive (92.2%)), 3-months (902 / 1079 (83.6%)), 12-months (156 / 273 (57.1%)) and 24-months (159 / 555 (28.7%)). (4) Results at 6-months and at disease progression for the EORTC QLQ-LMC21 are also omitted here because of low response rates. These results are available in appendices 8–10 of supplementary material, while appendix 18 reports response numbers at each time-point for each questionnaire.

Tables 1 and 2 report scores for the scales and global health measure of the EORTC QLQ-C30. SIRT+FOLFOX patients reported statistically significantly worse outcomes than FOLFOX patients at ≤3-months in several scales, but none of these differences were clinically significant. Thereafter, the EORTC QLQ-C30 registered no differences between study arms, apart from more pain symptoms at 12-months and fewer dyspnoea symptoms at 24-months in SIRT+FOLFOX patients.

Appendix 19 reports scores for the EORTC QLQ-LMC21 symptom scales for which there were statistically significant differences between groups. SIRT+FOLFOX patients reported significantly more fatigue at 3-months but fewer symptoms of sore mouth/tongue. The only change to reach a threshold for clinical significance was an improvement in peripheral neuropathy in SIRT+FOLFOX patients, related to less exposure to oxaliplatin chemotherapy in that group. Greater fatigue in SIRT+FOLFOX patients persisted at 12-months, and patients in this arm also experienced more dry mouth at 12-months and more pain at 24-months. The remaining scales are shown in the appendix 11 of supplementary material.

Table 3 reports average EQ-5D-3L utility-scores at each time-point. There was no difference between groups at baseline. Patients in the SIRT+FOLFOX arm showed slightly lower utility levels at ≤3 months, and this small difference persisted at 12-months, but not at 24-months.

Appendices 12 and 13 of the supplementary material show HRQOL among patients experiencing disease progression. Both the EORTC QLQ-C30 and EQ-5D showed larger reductions in the FOLFOX arm in HRQOL at disease progression compared to the previous time-point, some of which were almost clinically significant. However, HRQOL generally appeared to be higher in the FOLFOX group prior to progression, and as a result there was no clear overall difference by arm in levels of HRQOL at disease progression.

Adjusted differences from baseline in each pre-specified outcome and EQ-5D utility-scores using a longitudinal linear mixed-effect model are displayed in the supplementary material (appendix figure 4). Results were similar to the primary analysis, showing a statistically significant decrement in HRQOL in SIRT+FOLFOX patients at ≤3-months.

The number of adverse events was associated with a statistically significant decrement in global health status and EQ-5D-3L utility-scores in both arms, but there was no evidence that this adverse effect was smaller amongst SIRT+FOLFOX patients once the treatment effect and an interaction term between treatment and number of AEs was included in the model (appendix 14 and appendix figure 2). The subgroup analysis did not provide evidence on relevant differences between study arms in any of the subgroups assessed (appendix 15-17 and appendix figure 3).

Calculating EQ-5D-3L utility-scores using UK rather than US scores did not alter the results (appendix 1). Similarly, using multiple imputation assuming MNAR did not change the results unless extreme values were employed in the analysis (appendix 2-7).

Discussion

We found a statistically significant deterioration in HRQOL in SIRT+FOLFOX patients for up to 3 months after SIRT administration across all three instruments employed in this study, but these changes did not reach thresholds for clinical importance. Although patients in the combination treatment arm experienced more fatigue, a common side effect of SIRT, than those in the chemotherapy-alone group, they experienced significantly lower levels of sore mouth/tongue and peripheral neuropathy than the chemotherapy-alone group, likely due to the dose reduction of oxaliplatin mandated for 3 cycles for patients in the SIRT+FOLFOX arm of the study. Thereafter, we found no clinically meaningful differences in HRQOL between the SIRT+FOLFOX and FOLFOX alone study arms or at disease progression. These results were confirmed in the longitudinal linear model.

The small impairment in HRQOL observed in the SIRT-FOLFOX patients did not appear to be related to the higher number of AEs observed in these patients, suggesting that poorer HRQOL in SIRT+FOLFOX might be a direct result of SIRT administration. Whereas post-hoc subgroup analysis suggested better OS in patients treated with FOLFOX plus SIRT when the primary tumour location was right-sided (18), our HRQOL analysis showed no such difference between patients with right-

sided versus left-sided primary tumours. The results were robust to different methods used to impute the missing data.

A recent systematic literature review of evidence on SIRT in the management of advanced colorectal cancer among RCTs identified 2 studies that assessed HRQOL in SIRT patients. (6) Neither used the EQ-5D or EORTC instruments, and the sample sizes were significantly smaller than our study (21 and 70 patients respectively). The lack of explicit values for differences between study arms and small sample sizes make direct comparisons problematic. Nevertheless, our results are in contrast to the improvement in HRQOL over the first 18 months observed in the early study by Gray et al.(19)

The study presented here has limitations. Firstly, our main analyses suffered from low response rates, especially from 6-months to 24-months. We excluded HRQOL questionnaires at time-points after 24-months from the main analysis due to low response rates and consequently may have underestimated long-term HRQOL benefits or harms of SIRT. Additionally, slightly higher response rates were also observed in the FOLFOX+SIRT group compared to the FOLFOX group at several time-points. Although the reasons for the low response rates and the difference in completion rates between groups were not clear, they may have had some influence on the results. However, we mitigated the influence of low response rates on our results using multiple imputation methods. Moreover, our multiple imputation equation included mortality and morbidity measures to capture any differences due to disease severity resulting in lower response rate, and we also considered the consequences of violating the MAR assumption by using MNAR imputation. Our conclusions remained unaltered unless assuming implausibly large departures from

MAR scores (e.g. 17.5 points in EORTC scores), which are very unlikely to be observed in clinical practice.

Secondly, significant changes in the management of LMCRC occurred during the 8-year recruitment period of the three trials, which may have influenced our results.(20) In the FFr-SF-FFrG studies, participants were significantly more likely to receive bevacizumab if they were in the FOLFOX group than if they were in the FOLFOX+SIRT group.(4) Furthermore, after 6 months of protocol chemotherapy, participants in the FOLFOX+SIRT group were significantly less likely to receive other cytotoxic chemotherapies or monoclonal antibodies than patients in the FOLFOX group.(4) On account of this discrepancy, it was not possible to adjust for subsequent lines of therapy, but it is notable that there were no significant differences in HRQOL observed between the two groups. A cost-effectiveness analysis is currently underway to assess the impact of patients receiving less subsequent cytotoxic chemotherapies or monoclonal antibodies following SIRT, and achieving similar overall survival and HRQOL.

Despite these limitations, the current study is the largest prospective, randomised clinical trial of SIRT to report patient-reported outcomes. Such data are now widely accepted as an important part of the evaluation of new Interventional Oncology treatments in patients with mCRC. Although the routine use of SIRT in combination with oxaliplatin-based, first-line chemotherapy in unselected LMCRC patients is not supported by the clinical results of the combined FFr, SF and FFrG analysis, we could not find evidence that any impairment in HRQOL in SIRT patients after 3 months reaches levels that would conventionally be considered clinically significant.

Acknowledgements:

The FFr trial was developed by the National Cancer Research Institute Colorectal Clinical Study Group and the NIHR Clinical Research Network and equivalents in devolved nations, and was sponsored by the University of Oxford. The SIRFLOX and FOXFIRE-Global studies were sponsored by Sirtex Technology Pty Ltd. The Centre for Statistics in Medicine, Oxford provided statistical input (supported by Cancer Research UK (grant C5529/A16895)) We thank Georgie Perry and Rhona Atkin for secretarial support. This work was supported by the Bobby Moore Fund of Cancer Research UK (A8971 CRUK/07/030) and Sirtex Technology Pty Ltd (FFr, FFrG and SF). A Gray is partly supported by the NIHR Biomedical Research Centre, Oxford. The FFrG and SR trials are registered at ClinicalTrials.gov, numbers: NCT01721954 and NCT00724503. The FFr trial is registered at Isrctn.com, number: ISRCTN83867919.

Conflict of Interests Statement:

AG reports grants from Cancer Research UK during the conduct of the study. JMo reports grants from Cancer Research UK and Sirtex Medical, during the conduct of the study; and non-financial support from Sirtex Medical, outside the submitted work.

PSV reports grants from Sirtex Medical and Cancer Research UK, during the conduct of the study.

SL reports grants from Sirtex Medical and Cancer Research UK, during the conduct of the study.

HSW reports grants, personal fees, non-financial support, and other uncompensated work from Sirtex Medical and Merck Serono; personal fees and non-financial support from Celgene; grants and non-financial support from Pfizer; personal fees and non-financial support from Roche and Lily outside the submitted work.

GvH reports personal fees and non-financial support from Sirtex Medical, during the conduct of the study; and personal fees and non-financial support from Sirtex Medical, outside the submitted work.

PG reports personal fees from SIRTEX; grants and personal fees from Roche, Amgen, Pfizer, Merck, Bayer, and Servier, during the conduct of the study.

RAS is a consultant for and reports grants and personal fees from Sirtex Medical and BTG, during the conduct of the study; and reports personal fees from Affidea, AstraZeneca, Boston Scientific, Cancer Research Technology, Eisai, Terumo, and Varian, outside the submitted work.

References

1. National Cancer Institute. SEER Stat Fact Sheets: Colon and Rectum Cancer, 2003-2009. https://seer.cancer.gov/statfacts/html/colorect.html 2019 [cited 2017 19 December].

2. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, Alexander DD, Choti MA, Poston G. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol. 2012;4:283-301.

3. Jones RP, Poston GJ. Resection of Liver Metastases in Colorectal Cancer in the Era of Expanding Systemic Therapy. Annu Rev Med. 2017;68:183-96.

4. Wasan HS, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, Peeters M, Findlay M, Weaver A, Mills J, Wilson C, Adams R, Francis A, Moschandreas J, Virdee PS, Dutton P, Love S, Gebski V, Gray A, van Hazel G, Sharma RA. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017;18(9):1159-71.

5. NHS England: Independent evaluation of the Selective Internal Radiation Therapy Commissioning through Evaluation scheme. https://www.england.nhs.uk/publication/independent-evaluation-of-the-selective-internal-radiation-therapy-commissioning-through-evaluation-scheme/ 2019 [

6. Townsend AR, Chong LC, Karapetis C, Price TJ. Selective internal radiation therapy for liver metastases from colorectal cancer. Cancer Treat Rev. 2016;50:148-54.

7. Dutton SJ, Kenealy N, Love SB, Wasan HS, Sharma RA. FOXFIRE protocol: an open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional Selective Internal Radiation Therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. BMC Cancer. 2014;14:497.

8. Gibbs P, Gebski V, Van Buskirk M, Thurston K, Cade DN, Van Hazel GA. 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 SIRFLOX study. BMC Cancer. 2014;14:897.

9. Virdee PS, Moschandreas J, Gebski V, Love SB, Francis EA, Wasan HS, van Hazel G, Gibbs P, Sharma RA. Protocol for Combined Analysis of FOXFIRE, SIRFLOX, 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.

10. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.

11. European organisation for research and treatment of cancer: EORTC quality of life questionnaire Colorectal liver cancer module (EORTC QLQ-LMC21) scoring manual. http://www.eortc.be/qol/files/ScoringInstructions/LMC21_summary.pdf 2019 [

12. European organisation for research and treatment of cancer: EORTC quality of life questionnaire (EORTC QLQ-C30) scoring manual. http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf 2019 [

13. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.

14. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care. 2005;43(3):203-20.

15. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. J Clin Oncol. 1995;13(5):1249-54.

16. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139-44.

17. Leacy FP, Floyd S, Yates TA, White IR. Analyses of Sensitivity to the Missing-at-Random Assumption Using Multiple Imputation With Delta Adjustment: Application to a Tuberculosis/HIV Prevalence Survey With Incomplete HIV-Status Data. Am J Epidemiol. 2017;185(4):304-15.

18. Gibbs P, Heinemann V, Sharma NK, Taieb J, Ricke J, Peeters M, Findlay M, Robinson B, Jackson C, Strickland A, Gebski V, Van Buskirk M, Zhao H, van Hazel G. Effect 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. Clinical colorectal cancer. 2018;17(4):e617-e29.

19. Gray B, Van Hazel G, Hope M, Burton M, Moroz P, Anderson J, Gebski V. 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):1711-20.

20. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii1-9.

Table 1. Mean scores (standard error) [number of patients] for the EORTC QLQ-C30 functional scales and global health, differences (p-value; 95% confidence interval) adjusted for respective baseline scores and cognitive functioning score at baseline.

	Baseline	≤3 months[#]	12 months	24 months
Physical functioning				
FOLFOX	83.7 (0.8) [499]	81.6 (0.9) [446]	80.0 (1.3) [239]	71.7 (4.1) [32]
SIRT+FOLFOX	83.9 (0.8) [511]	79.3 (0.9) [453]	79.3 (1.3) [262]	77.2 (4.4) [29]
Difference	0.3 (0.81; -2.0 to 2.6)	-2.9 (0.0070; -5.1 to -0.8)**	-2.7 (0.12; -6.1 to 0.7)	4.6 (0.43; -7.03 to 16.25)
Role functioning				
FOLFOX	75.5 (1.3) [497]	72.7 (1.3) [444]	74.2 (1.8) [238]	65.6 (6.4) [31]
SIRT+FOLFOX	74.4 (1.3) [509]	69.0 (1.3) [452]	72.1 (1.8) [262]	76.4 (5.6) [29]
Difference	-1.1 (0.54; -4.7 to 2.5)	-4.1 (0.015; -7.4 to -0.8)*	-3.4 (0.18; -8.3 to 1.5)	15.4 (0.10; -3.1 to 34.0)
Emotional functioning				
FOLFOX	77.6 (0.9) [499]	81.5 (0.9) [430]	80.4 (1.4) [238]	82.0 (2.6) [31]
SIRT+FOLFOX	79.9 (0.9) [503]	83.2 (0.9) [447]	83.9 (1.2) [253]	78.8 (3.8) [28]
Difference	2.3 (0.07; -0.2 to 4.8)	0.5 (0.67; -1.7 to 2.7)	2.1 (0.24; -1.4 to 5.7)	-1.8 (0.69; -11.2 to 7.5)
Cognitive functioning				
FOLFOX	87.0 (0.8) [499]	86.5 (0.9) [431]	84.3 (1.4) [238]	78.0 (3.7) [31]
SIRT+FOLFOX	89.5 (0.7) [503]	86.5 (0.9) [447]	84.7 (1.1) [253]	85.1 (3.4) [28]
Difference	2.5 (0.022; 0.4 to 4.7)*	-1.7 (0.13; -4.0 to 0.5)	-2.1 (0.21; -5.4 to 1.2)	7.6 (0.16; -3.1 to 18.3)
Social functioning				

FOLFOX	77.8 (1.1) [498]	74.9 (1.3) [431]	77.7 (1.7) [238]	74.2 (6.2) [31]
SIRT+FOLFOX	76.6 (1.2) [503]	74.4 (1.3) [446]	76.1 (1.7) [252]	75.0 (5.0) [28]
Difference	-1.2 (0.45; -4.5 to 2.0)	-0.6 (0.70; -3.9 to 2.62)	-2.3 (0.31; -6.9 to 2.2)	2.9 (0.75; -14.9 to 20.6)
Global health status				
FOLFOX	68.3 (1.0) [499]	69.3 (1.0) [431]	70.2 (1.3) [236]	67.2 (3.5) [32]
SIRT+FOLFOX	67.8 (0.9) [502]	65.7 (1.0) [446]	69.3 (1.4) [253]	70.8 (3.9) [28]
Difference	-0.6 (0.67; -3.2 to 2.1)	-3.9 (0.002; -6.4 to -1.5)**	-2.1 (0.25; -5.6 to 1.5)	4.6 (0.41; -6.6 to 15.8)

[#] ≤3 months time-point includes 1 month and cycle 4. * p<0.05 ** p<0.01

Table 2. Mean scores (standard error) [number of patients] for the EORTC QLQ-C30 symptom scales, differences (p-value; 95% confidence interval) adjusted for respective baseline scores and cognitive functioning score at baseline.

	Baseline	≤3 months[#]	12 months	24 months
Fatigue				
FOLFOX	29.2 (1.1) [499]	34.2 (1.2) [446]	31.5 (1.6) [239]	32.8 (5.1) [32]
SIRT+FOLFOX	30.8 (1.1) [511]	38.7 (1.1) [453]	33.4 (1.5) [261]	36.2 (4.9) [29]
Difference	1.6 (0.28; -1.3 to 4.6)	4.7 (0.001; 1.9 to 7.6)**	3.4 (0.11; -0.8 to 7.5)	4.5 (0.55; -10.4 to 19.5)
Nausea and vomiting				
FOLFOX	6.5 (0.6) [499]	8.8 (0.7) [445]	7.8 (1.0) [236]	8.9 (2.9) [32]
SIRT+FOLFOX	7.8 (0.7) [511]	10.9 (0.8) [453]	7.5 (0.9) [261]	14.4(3.8) [29]
Difference	1.4 (0.15; -0.5 to 3.3)	2.6 (0.017; 0.5 to 4.7)*	0.2 (0.90; -2.3 to 2.8)	3.6 (0.45; -5.8 to 12.9)
Pain				
FOLFOX	20.5 (1.1) [502]	17.2 (1.1) [446]	18.4 (1.6) [240]	16.7 (3.8) [33]
SIRT+FOLFOX	21.0 (1.1) [513]	17.8 (1.1) [456]	23.4 (1.6) [261]	21.8 (4.9) [29]
Difference	0.5 (0.75; -2.5 to 3.4)	0.9 (0.53; -2.0 to 3.8)	6.5 (0.0030; 2.2 to 10.8)**	2.6 (0.69; -10.4 to 15.5)
Dyspnoea				
FOLFOX	11.9 (0.9) [499]	13.3 (1.1) [444]	15.1 (1.4) [239]	30.1 (6.3) [31]
SIRT+FOLFOX	12.6 (1.0) [511]	14.8 (1.0) [452]	13.3 (1.5) [261]	13.8 (4.5) [29]
Difference	0.8 (0.57; -1.8 to 3.4)	2.3 (0.08; -0.3 to 5.0)	-1.5 (0.43; -5.3 to 2.3)	-16.7 (0.040; -32.6 to -0.8)*
Insomnia				

FOLFOX	26.8 (1.3) [496]	27.8 (1.5) [445]	21.4 (1.7) [237]	28.1 (5.4) [32]
SIRT+FOLFOX	27.5 (1.3) [511]	29.6 (1.4) [452]	25.3 (1.9) [260]	23.0 (4.7) [29]
Difference	0.7 (0.69; -2.9 to 4.3)	2.0 (0.28; -1.7 to 5.7)	4.3 (0.10; -0.8 to 9.3)	-4.0 (0.61; -19.7 to 11.7)
Appetite loss				
FOLFOX	19.8 (1.2) [497]	17.0 (1.2) [444]	17.8 (1.8) [238]	20.4 (5.3) [31]
SIRT+FOLFOX	21.3 (1.3) [511]	21.4 (1.3) [453]	18.9 (1.7) [261]	23.0 (4.7) [29]
Difference	1.5 (0.41; -2.1 to 5.0)	5.3 (0.002; 2.0 to 8.7)**	2.6 (0.31; -2.4 to 7.5)	-2.5 (0.75; -18.3 to 13.2)
Constipation				
FOLFOX	14.7 (1.1) [498]	16.9 (1.2) [429]	14.4 (1.6) [236]	15.1 (4.0) [31]
SIRT+FOLFOX	15.6 (1.2) [499]	19.7 (1.3) [446]	14.0 (1.5) [254]	14.3 (3.6) [28]
Difference	1.0 (0.54; -2.2 to 4.1)	2.0 (0.24; -1.4 to 5.4)	0.9 (0.69; -3.5 to 5.3)	-1.5 (0.78; -11.8 to 8.9)
Diarrhoea				
FOLFOX	14.6 (1.1) [497]	16.3 (1.2) [431]	14.5 (1.6) [237]	10.8 (4.2) [31]
SIRT+FOLFOX	12.6 (1.0) [501]	10.9 (1.0) [448]	12.3 (1.4) [252]	15.4 (4.6) [26]
Difference	-2.0 (0.18; -4.9 to 0.9)	-4.1 (0.009; -7.2 to -1.1)**	-1.9 (0.38; -6.1 to 2.3)	8.4 (0.18; -4.0 to 20.8)
Financial difficulties				
FOLFOX	18.1 (1.3) [494]	17.4 (1.4) [430]	15.4 (1.7) [238]	12.9 (4.0) [31]
SIRT+FOLFOX	17.9 (1.3) [500]	18.1 (1.3) [443]	18.4 (1.8) [252]	9.5 (3.4) [28]
Difference	-0.2 (0.94; -3.8 to 3.5)	0.5 (0.76; -2.6 to 3.5)	2.8 (0.22; -1.6 to 7.3)	-3.5 (0.49; -13.5 to 6.5)

[#]≤3 months time-point includes 1 month and cycle 4. * p<0.05 ** p<0.01

Table 3. Mean scores (standard error) [number of patients] for the EQ-5D-3L utility-scores (US) , differences (p-value; 95% confidence interval) adjusted for respective baseline scores and cognitive functioning score at baseline.

	Baseline	**≤3 months[#]**	**12 months**	**24 months**
FOLFOX	0.840 (0.006) [507]	0.846 (0.007) [417]	0.841 (0.010) [215]	0.814 (0.021) [74]
SIRT+FOLFOX	0.837 (0.006) [510]	0.828 (0.008) [431]	0.831 (0.010) [253]	0.810 (0.019) [85]
Difference	-0.002 (0.806; -0.020 to 0.015)	-0.023 (0.024; -0.043 to -0.003)*	-0.028 (0.040; -0.055 to -0.001)*	-0.018 (0.53; -0.077 to 0.040)

≤ 3 months time-point includes cycle 4 and 3 months. * $p<0.05$ ** $p<0.01$