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## Original Article

## Analysis of a National Programme for Selective Internal Radiation Therapy for Colorectal Cancer Liver Metastases

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## Abstract

**Aims:** Patients with chemotherapy-refractory colorectal cancer liver metastases have limited therapeutic options. Selective internal radiation therapy (SIRT) delivers yttrium 90 microspheres as a minimally invasive procedure. This prospective, single-arm, observational, service-evaluation study was part of National Health Service England Commissioning through Evaluation.

**Methods:** Patients eligible for treatment had histologically confirmed carcinoma with liver-only/liver-dominant metastases with clinical progression during or following oxaliplatin-based and irinotecan-based chemotherapy. All patients received SIRT plus standard of care. The primary outcome was overall survival; secondary outcomes included safety, progression-free survival (PFS) and liver-specific PFS (LPFS).

**Results:** Between December 2013 and March 2017, 399 patients were treated in 10 centres with a median follow-up of 14.3 months (95% confidence interval 9.2–19.4). The median overall survival was 7.6 months (95% confidence interval 6.9–8.3). The median PFS and LPFS were 3.0 months (95% confidence interval 2.8–3.1) and 3.7 months (95% confidence interval 3.2–4.3), respectively. During the follow-up period, 143 patients experienced an adverse event and 8% of the events were grade 3.

**Conclusion:** Survival estimates from this pragmatic study show clinical outcomes attainable in the National Health Service comparable with previously published data. This study shows the value of a registry-based commissioning model to aid national commissioning decisions for highly specialist cancer treatments.

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**Keywords:** Brachytherapy; colorectal cancer; commissioning models; liver metastases; molecular radiotherapy; transarterial radio-embolisation

## Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the UK. Liver metastases are common among patients with CRC; resection of the primary and metastatic tumours is favoured where possible, but most (70–80%) patients are unsuitable for liver surgery [1]. Systemic chemotherapy is

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the standard treatment for unresectable metastatic disease, which may be combined with biological agents such as epidermal growth factor receptor inhibitors (cetuximab or panitumumab) or vascular endothelial growth factor inhibitors (bevacizumab). For patients with advanced metastatic CRC (mCRC) who have progressed after standard first- and second-line therapies, the aim of third-line treatments is to prolong life, improve symptoms and maintain an acceptable quality of life. Currently there are limited options available for patients with unresectable, chemotherapy-refractory mCRC (termed the ‘salvage setting’).

Selective internal radiation therapy (SIRT), also called transarterial radio-embolisation or radio-embolisation, is a form of arterially delivered brachytherapy. It involves delivering microspheres containing a beta-emitting radionuclide, yttrium 90 (Y-90), directly into the tumour via the hepatic artery using a percutaneous transarterial approach [2,3]. The efficacy of SIRT is supported by an evidence base comprised largely of single-arm studies and three comparative studies (Supplementary Table S1).

Commissioning through Evaluation (CtE) is a national programme led by National Health Service (NHS) England that enables highly specialist treatments to be commissioned in selected provider centres with a planned evaluation phase [4]. The evaluation is commissioned by the National Institute for Health and Care Excellence (NICE) and carried out by an independent research group, which assesses the clinical and cost-effectiveness of the intervention in a specific population. The aim of the programme was to evaluate the impact of SIRT on overall survival, progression-free survival (PFS) and liver-specific PFS (LPFS), and to assess safety.

## Materials and Methods

### Study Design

This prospective, single-arm, observational, service-evaluation study was carried out between December 2013 and February 2017 in 10 NHS hospitals in England (Cambridge University Hospitals NHS Foundation Trust, Kings College Hospital NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust, Newcastle-upon-Tyne Hospitals NHS Trust, Nottingham University Hospitals NHS Trust, Oxford University Hospitals NHS Foundation Trust, The Christie NHS Foundation Trust, The Royal Free London NHS Foundation Trust, University Hospital Southampton NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust). SIRT was provided as routine care at these centres and therefore this study was designated as a service-evaluation project within the NHS; patient consent for all procedures therefore used the sites’ routine NHS clinical governance processes. The SIRT registry is an online registry hosted by the British Society of Interventional Radiology incorporating national data on radio-embolisation of primary and secondary liver tumours. It holds de-identified data, and only those data relevant to this CtE study were extracted for analysis and transferred to an

independent research group, Cedar (Cardiff and Vale University Health Board), for analysis.

### Population

Adults with unresectable, chemotherapy-refractory, CRC liver metastases were eligible for treatment. Inclusion criteria included: histologically confirmed carcinoma with liver-specific or liver-dominant metastases not amenable to curative liver surgical resection; unequivocal and measurable computed tomography evidence of liver metastases not treatable by surgical resection or local ablation with curative intent; World Health Organization performance status 0–2; life expectancy >3 months; evidence of clinical progression during or after both oxaliplatin-based and irinotecan-based chemotherapy, unless the patient had a specific contraindication to chemotherapy or did not tolerate either regimen; adequate haematological and hepatic function as follows: serum bilirubin =  $1.5 \times$  upper limit of normal; absolute neutrophil count  $>1.5 \times 10^9/l$ , platelets  $>100 \times 10^9/l$ ; albumin = 30 g/l; no central nervous system metastases or bone metastases, but patients were permitted to have limited extrahepatic disease (e.g. lung metastases, multiple lymph nodes or low-volume peritoneal disease, but the multidisciplinary team must have agreed that the extrahepatic disease was probably not life-threatening or a cause for significant morbidity if the liver metastases can be controlled with locally directed therapy); no evidence of ascites or cirrhosis.

### Procedures

Each site followed their local process for undertaking SIRT procedures. All patients received a hepatic arteriogram and a liver-to-lung breakthrough nuclear medicine scan to ensure suitability and to plan the delivery of the Y-90 microspheres. Selective coil embolisation of arteries to the stomach, duodenum or other visceral structures was carried out as required to prevent non-target Y-90 delivery. SIRT was carried out using an established method. One of two brands of Conformité Européenne-marked active implantable medical devices was used to carry out the SIRT procedure: (i) SIR-Spheres (Sirtex Medical Ltd, Australia) resin microspheres; (ii) TheraSphere (Biocompatibles UK Ltd, UK) glass microspheres. Dosing of SIR-Spheres and TheraSpheres was carried out as per manufacturer instructions. It should be noted that the dosing method is different for the two products, so the activity administered in GBq cannot be directly compared [5]. Administration of concomitant chemotherapy and post-SIRT chemotherapy was at the discretion of the treating clinician. Sites were expected to follow up patients every 2–3 months after their SIRT procedure until liver progression was confirmed on scan. Adverse events were assessed and recorded throughout the follow-up period.

### Data Collection and Outcomes

Data were collected by clinical teams and entered into an anonymised online registry. The final dataset was extracted

in March 2017 and sent to Cedar for analysis. The full evaluation report from the SIRT CtE project has recently been published online by NHS England [6]. Patients with a missing diagnosis or missing SIRT administration date were excluded from the analysis. Data were only collected on patients who received SIRT.

Overall survival was defined as the duration from the first SIRT procedure until death from any cause. Patients with no date of death recorded were right censored at the date at which they were lost to follow-up. Survival proportions at 3, 6, 12, 24 and 36 months were reported for patients for whom these data were available. Hepatic and extrahepatic tumour response assessments were carried out locally by a radiologist and recorded in the SIRT registry. Typically, the Response Evaluation Criteria for Solid Tumours (RECIST) were used [7]. PFS was defined as the duration from the first SIRT administration to the earliest date of detection of progressive disease (either hepatic or extrahepatic) by computed tomography, magnetic resonance imaging or positron emission tomography scan, or to the date of death from any cause if progression was not recorded. Patients with no progressive disease recorded were censored at the most recent date of non-progression (complete response, partial response or stable disease). LPFS was defined as the duration from the first SIRT administration to the date of progression in the liver or death from any cause. Patients with no progressive disease in the liver were censored at the most recent date of non-progression in the liver. Adverse events were recorded using Common Terminology Criteria for Adverse Events version 4.0. Causality was determined by the treating physician on site.

### Statistical Analysis

The sample size of the study was estimated by NHS England based on the number of patients who could be treated at 10 specialist centres over a 3-year period [6]. All statistical analyses were conducted in IBM SPSS Statistics version 21.0.0.0 (IBM Corp. Armonk, NY, USA) or R (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>).

Descriptive statistics for continuous variables were reported as appropriate. For each statistical comparison, *P*-values and confidence intervals were reported. *P* < 0.05 was considered statistically significant and all tests were two-sided. Median overall survival, PFS and LPFS were estimated using the Kaplan–Meier analysis [8]. Survival curves were presented with 95% confidence intervals and numbers at risk displayed. Potentially important baseline covariates were agreed in advance and tested to identify statistically significant prognostic factors associated with survival in the CRC cohort using the pairwise Log-rank test. Hazard ratios for baseline covariates were estimated for overall survival by univariate Cox proportional hazards models. The following covariates were selected: number of previous lines of chemotherapy (categories: 0, 1, 2, 3, 4), Eastern Cooperative Oncology Group (ECOG) performance status (categories: 0, 1, 2), age (either as continuous or categories:

<65 years, 65 years), sex, primary tumour *in situ* or not, prior biological therapy (including bevacizumab, cetuximab, aflibercept, panitumumab), presence of extrahepatic metastases (categories: yes, no), extent of liver involvement (continuous or categories: <25%, 25–50%, >50%), prior liver surgery (categories: yes, no), number of liver tumours (categories: 1–5, 6–10, >10). The reverse Kaplan–Meier method was used to calculate the median follow-up time.

## Results

### Patient Characteristics

Data from 474 patients were included in the database; of these 460 were valid data entries. Cases on the register with no diagnosis or no SIRT procedure date were excluded, leaving 399 valid CRC patients for the analysis; patients were followed up for a median of 14.3 months (95% confidence interval 9.2–19.4). Fifteen cases were excluded for the following reasons: (i) missing diagnosis; (ii) no treatment data; (iii) no SIRT procedure date. Sixty-seven per cent of patients were men and had a median age of 66 years. Most patients had an ECOG performance score of 0 or 1 (93%) and most did not have extrahepatic metastatic disease (60%) (Table 1). Almost all patients (98%) had received prior systemic chemotherapy or biologics and 78% had received two or three lines of prior chemotherapy, consisting predominantly of fluoropyrimidine-, oxaliplatin- or irinotecan-based regimens. The median duration from primary and metastatic diagnoses to the first SIRT procedure was 2.1 years and 1.8 years, respectively (Table 1).

In total, 114 patients (29%) had between one and five tumours; 44% had more than 10 tumours. The median overall tumour to liver volume ratio was 15% (interquartile range 7–27%) reported in 270 patients. The median bilirubin and albumin values before SIRT were 9.0 µmol/l (interquartile range 6.0–12.0) and 37.0 g/l (interquartile range 33.0–41.0), respectively.

### Treatment and Follow-up

Relevant visceral arteries were embolised during the work-up procedure in 52% of patients (Table 2). As is the practice in the UK, most patients received SIRT as a single procedure targeting the whole liver (52% split microsphere administration; 17% single microsphere administration). A very small proportion (3%) of patients had sequential lobes treated in two (or more) sessions. Based on the prior experience of the treating centres, most SIRT treatments (86%) were conducted using resin Y-90 microspheres, with a mean prescribed activity of 1.74 GBq (standard deviation 2.13); 14% of treatments used glass Y-90 microspheres, with a mean prescribed activity of 4.18 GBq (standard deviation 1.71). Most patients (88%) had a hospital stay of 1 or 2 nights for the treatment. Chemotherapy was delivered concomitantly in 35% of cases (predominantly 5-fluorouracil and oxaliplatin) and a minority of cases (22%) went on to receive further post-SIRT chemotherapy during their follow-up phase (Table 2).

**Table 1**  
Patient characteristics

| Parameter                                                              | Data for 399 patients<br>(number (%) unless<br>otherwise stated) |
|------------------------------------------------------------------------|------------------------------------------------------------------|
| Total number of patients                                               | 399                                                              |
| Age at time of procedure (years)                                       | Median 66 (IQR 57–72)                                            |
| Male/female (%)                                                        | 266 (67%)/133 (33%)                                              |
| Baseline ECOG score                                                    |                                                                  |
| 0: fully active                                                        | 201 (50%)                                                        |
| 1: restricted                                                          | 170 (43%)                                                        |
| 2: ambulatory                                                          | 13 (3%)                                                          |
| 3: capable                                                             | 1 (0.3%)                                                         |
| Missing                                                                | 14 (4%)                                                          |
| Limited extrahepatic disease                                           |                                                                  |
| Yes                                                                    | 159 (40%)                                                        |
| No                                                                     | 236 (60%)                                                        |
| Location of metastatic disease                                         |                                                                  |
| Lung                                                                   | 106                                                              |
| Lymph nodes                                                            | 40                                                               |
| Other                                                                  | 34                                                               |
| Primary tumour resected                                                |                                                                  |
| Yes                                                                    | 226 (57%)                                                        |
| No                                                                     | 123 (31%)                                                        |
| Missing                                                                | 50 (13%)                                                         |
| Years from primary diagnosis to<br>SIRT procedure ( <i>n</i> = 321)    | Median 2.1 (IQR 1.5–3.2)                                         |
| Years from metastatic diagnosis<br>to SIRT procedure ( <i>n</i> = 313) | Median 1.8 (IQR 1.2–2.6)                                         |
| Number of previous<br>chemotherapy lines                               |                                                                  |
| 1                                                                      | 34 (9%)                                                          |
| 2                                                                      | 222 (56%)                                                        |
| 3                                                                      | 87 (22%)                                                         |
| ≥4                                                                     | 34 (9%)                                                          |
| Missing                                                                | 22 (6%)                                                          |
| Prior chemotherapy received<br>(including biologics)                   |                                                                  |
| Fluoropyrimidine-based                                                 | 282 (71%)                                                        |
| Oxaliplatin                                                            | 303 (76%)                                                        |
| Irinotecan                                                             | 302 (76%)                                                        |
| Capacitabine                                                           | 155 (39%)                                                        |
| Bevacizumab                                                            | 119 (30%)                                                        |
| Cetuximab                                                              | 109 (27%)                                                        |
| Aflibercept                                                            | 25 (6%)                                                          |
| No chemotherapy recorded                                               | 53 (13%)                                                         |
| Prior adjuvant therapy                                                 |                                                                  |
| Yes                                                                    | 85 (21%)                                                         |
| No                                                                     | 303 (76%)                                                        |
| Missing                                                                | 11 (3%)                                                          |
| Prior hepatic procedures*                                              |                                                                  |
| Yes                                                                    | 110 (28%)                                                        |
| No                                                                     | 289 (72%)                                                        |

ECOG, Eastern Cooperative Oncology Group; SIRT, selective internal radiation therapy; IQR, interquartile range.

\* Hepatic surgical, ablative, vascular or radiotherapy procedures.

### Survival

Death was recorded in 240 (60%) patients; 139 (35%) patients were censored at their last recorded follow-up date; the survival status of 20 patients (5%) was unknown.

Overall survival was 7.6 months (95% confidence interval 6.9–8.3) (Figure 1). Survival rates were 92% at 3 months post-SIRT, 83% at 6 months, 30% at 12 months and 7% at 24 months. No patients survived to 36 months.

Subgroup analysis identified four covariates that resulted in a statistically significant difference in median overall survival (Table 3). Overall survival was significantly longer in patients who did not have extrahepatic metastasis (Log-rank test,  $P = 0.021$ ); the hazard ratio was 0.74 (95% confidence interval 0.57–0.96; univariate Cox proportional hazards  $P = 0.022$ ). Overall survival also differed significantly between the categories of number of liver tumours (Log-rank test,  $P = 0.008$ ); the hazard ratio was 1.67 (95% confidence interval 1.06–2.62;  $P = 0.027$ ) when the group of six to 10 tumours was compared with the reference group of one to five tumours; the hazard ratio was 1.61 (95% confidence interval 1.17–2.21) when the group of >10 tumours was compared with the reference group. Overall survival was longer in males compared with females (Log-rank test,  $P = 0.012$ ); the hazard ratio was 1.389 (95% confidence interval 1.073–1.800;  $P = 0.013$ ). Overall survival was also related to the percentage tumour to liver volume measurements at baseline (Log-rank test,  $P < 0.001$ ); the hazard ratio was 1.955 (95% confidence interval 1.424–2.685) comparing the category of tumour to liver volume >25% to 50% with the reference category of =25%; the hazard ratio was 2.994 (95% confidence interval 1.791–5.005) when the category of >50% was compared with the reference category. No significant difference in survival was observed using the covariates of prior chemotherapy lines, ECOG performance status, age and prior liver procedures (Table 3).

Progression or death was observed in a total of 331 (269 patients' disease progressed [67%]; 62 patients died before progression [16%]) and 24 (6%) patients were censored at the last imaging date when no progression was recorded. The progression status of 24 patients (6%) was unknown. The median PFS was 3.0 months (95% confidence interval 2.8–3.1) (Figure 2). Liver-specific progression or death was observed in 299 (75%) patients, 53 (13%) patients were censored and 43 (11%) were excluded. The median LPFS was 3.7 months (95% confidence interval 3.2–4.3) (Figure 2). Hepatic progression and extrahepatic progression were recorded on the same date in 81% of patients where both dates were recorded. Extrahepatic progression occurred before hepatic progression in 16% of patients.

### Safety

In total, 11 patients (3%) experienced severe day-of-treatment complications (Table 4). Severe adverse events within the first week after SIRT were rare; three patients experienced grade 3 fatigue in the 7 days after SIRT and one patient experienced grade 3 abdominal pain in the first week after SIRT. One hundred and forty-three patients experienced an adverse event. In total, 253 adverse events were recorded, of which 19 (8%) were grade 3 or above (Table 4). The most common events were mild fatigue and abdominal pain (grade 1–2). Relatedness of complications



**Table 2**

Treatment planning and procedure details

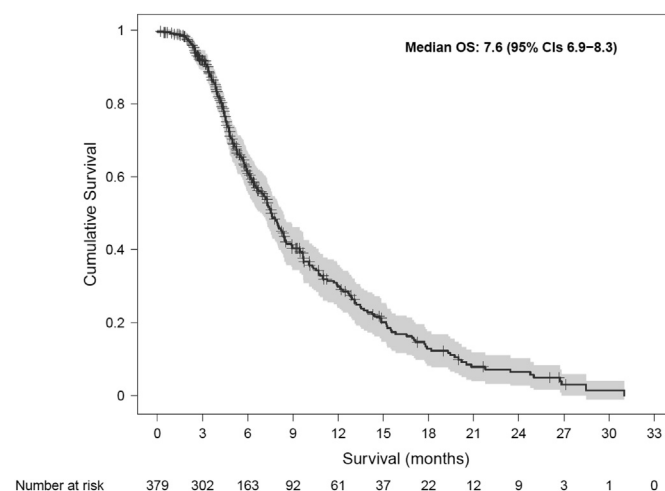
| Parameter                                            | Data for 399 patients (number (%) unless otherwise stated) |
|------------------------------------------------------|------------------------------------------------------------|
| Location of liver tumour(s)                          |                                                            |
| Bilobar                                              | 304 (76%)                                                  |
| Left                                                 | 28 (7%)                                                    |
| Right                                                | 59 (15%)                                                   |
| Missing                                              | 8 (2%)                                                     |
| Number of liver tumours                              |                                                            |
| 1–5                                                  | 114 (29%)                                                  |
| 6–10                                                 | 52 (13%)                                                   |
| >10                                                  | 174 (44%)                                                  |
| Uncountable                                          | 33 (8%)                                                    |
| Missing                                              | 26 (7%)                                                    |
| Bilirubin (μmol/l) prior to SIRT                     | Median 9.0                                                 |
| (n = 384)                                            | (IQR 6.0–12.0)                                             |
| Albumin (g/l) prior to SIRT                          | Median 37.0                                                |
| (n = 359)                                            | (IQR 33.0–41.0)                                            |
| Arteries embolised before SIRT therapy               |                                                            |
| Yes                                                  | 208 (52%)                                                  |
| No                                                   | 108 (27%)                                                  |
| Missing                                              | 83 (21%)                                                   |
| SIRT procedure target/type                           |                                                            |
| Whole liver (split administration in single session) | 206 (52%)                                                  |
| Whole liver (single catheter)                        | 68 (17%)                                                   |
| Whole liver (sequential lobar/ two sessions)         | 13 (3%)                                                    |
| Right lobe                                           | 61 (15%)                                                   |
| Left lobe                                            | 20 (5%)                                                    |
| Segmental                                            | 20 (5%)                                                    |
| Missing                                              | 11 (3%)                                                    |
| Number of administrations                            |                                                            |
| 1                                                    | 172 (43%)                                                  |
| 2                                                    | 101 (25%)                                                  |
| 3                                                    | 9 (2%)                                                     |
| Missing                                              | 117 (29%)                                                  |
| SIRT microsphere brand                               |                                                            |
| SIR-Spheres™ (resin)                                 | 343 (86%)                                                  |
| TheraSphere™ (glass)                                 | 53 (13%)                                                   |
| Missing                                              | 3 (0.8%)                                                   |
| Percentage tumour to liver volume                    | Median 15.0                                                |
| (n = 341)                                            | (IQR 7.0–30.0)                                             |
| Prescribed activity (GBq) for SIR-spheres (n = 271)  | Median 1.64                                                |
|                                                      | (IQR 1.28–1.93)                                            |
| Prescribed activity (GBq) for TheraSphere (n = 34)   | Median 3.91                                                |
|                                                      | (3.45–5.31)                                                |
| Length of stay in hospital following SIRT procedure  |                                                            |
| 1 night                                              | 265 (66%)                                                  |
| 2 nights                                             | 87 (22%)                                                   |
| 3 nights                                             | 12 (3%)                                                    |
| 4 nights                                             | 8 (2%)                                                     |
| >4 nights                                            | 10 (3%)                                                    |
| Concomitant chemotherapy administered with SIRT      |                                                            |
| Yes                                                  | 141 (35%)                                                  |
| No                                                   | 242 (61%)                                                  |
| Missing                                              | 16 (4%)                                                    |

**Table 2** (continued)

| Parameter                                        | Data for 399 patients (number (%) unless otherwise stated) |
|--------------------------------------------------|------------------------------------------------------------|
| Concomitant chemotherapy received                |                                                            |
| 5-fluorouracil                                   | 99 (25%)                                                   |
| Oxaliplatin                                      | 31 (8%)                                                    |
| Irinotecan                                       | 24 (6%)                                                    |
| Capecitabine                                     | 9 (2%)                                                     |
| Cetuximab                                        | 7 (2%)                                                     |
| Post-SIRT chemotherapy received during follow-up |                                                            |
| Yes                                              | 89 (22%)                                                   |
| No                                               | 214 (54%)                                                  |
| Missing                                          | 96 (24%)                                                   |

SIRT, selective internal radiation therapy; IQR, interquartile range.

and adverse events to the SIRT procedure were not routinely recorded. Events categorised as ‘other’ with a free-text description accounted for 53 (21%) of the total. Seven events of grade 3 or above were recorded in the ‘other’ category, which were as follows: acute kidney injury (grade 3; occurred 28 days after SIRT), bowel obstruction (grade 3; 21 days after SIRT); liver abscess (grade 3; 138 days after SIRT), skin rash (grade 3; 90 days after SIRT), delirium/dementia (grade 4; 79 days after SIRT), pulmonary emboli (grade 4; 47 days after SIRT); sepsis (grade 4; 18 days after SIRT). In total, 353 events were recorded as abnormal laboratory values (Table 4). The most common biochemical event categories were raised aspartate aminotransferase (22%), raised alanine aminotransferase (21%) and hypoalbuminaemia (19%). Eighteen of the 353 events (5%) were grade 3. No severe cases of radiation-induced liver disease (RILD), gastrointestinal ulceration, radiation pneumonitis, radiation cholecystitis or radiation pancreatitis were recorded.



**Fig 1.** Kaplan–Meier curve of overall survival following selective internal radiation therapy in patients with metastatic colorectal cancer liver metastases. Ninety-five per cent confidence intervals are shaded; the numbers at risk at 3-month intervals are displayed.

**Table 3**

Kaplan–Meier analysis and univariate Cox proportional hazards model of survival by baseline characteristics. Statistically significant *P*-values are shown in bold

| Subgroup                                                                                                | <i>n</i> (patients) | <i>n</i> (events) | Median overall survival (months) | Overall survival 95% confidence interval | Hazard ratio (95% confidence interval) | <i>P</i> -value  |
|---------------------------------------------------------------------------------------------------------|---------------------|-------------------|----------------------------------|------------------------------------------|----------------------------------------|------------------|
| Number of lines of previous chemotherapy (including biologics); Log-rank test <i>P</i> = 0.098          |                     |                   |                                  |                                          |                                        |                  |
| 1 line*                                                                                                 | 32                  | 19                | 11.3                             | 4.9–17.6                                 | Reference                              | Reference        |
| 2 lines                                                                                                 | 210                 | 127               | 7.0                              | 6.2–7.8                                  | 1.506 (0.926–2.448)                    | 0.099            |
| 3 lines                                                                                                 | 85                  | 58                | 8.9                              | 6.7–11.2                                 | 1.143 (0.680–1.921)                    | 0.614            |
| ≥4 lines                                                                                                | 33                  | 27                | 7.3                              | 5.1–9.4                                  | 1.732 (0.959–3.127)                    | 0.069            |
| Primary tumour <i>in situ</i> ; Log-rank test <i>P</i> = 0.079                                          |                     |                   |                                  |                                          |                                        |                  |
| Yes                                                                                                     | 117                 | 82                | 7.4                              | 6.0–8.7                                  | 1.282 (0.973–1.689)                    | 0.077            |
| No                                                                                                      | 217                 | 136               | 8.9                              | 7.4–10.3                                 | Reference                              | Reference        |
| Prior biological therapy (includes bevacizumab, cetuximab, aflibercept); Log-rank test <i>P</i> = 0.783 |                     |                   |                                  |                                          |                                        |                  |
| No                                                                                                      | 189                 | 112               | 7.6                              | 6.6–8.6                                  | Reference                              | Reference        |
| Yes                                                                                                     | 190                 | 128               | 7.4                              | 6.5–8.4                                  | 1.036 (0.803–1.338)                    | 0.783            |
| ECOG performance status; Log-rank test <i>P</i> = 0.180                                                 |                     |                   |                                  |                                          |                                        |                  |
| 0*                                                                                                      | 192                 | 124               | 8.4                              | 6.9–9.8                                  | Reference                              | Reference        |
| 1                                                                                                       | 162                 | 96                | 6.6                              | 5.5–7.7                                  | 1.252 (0.956–1.640)                    | 0.103            |
| 2                                                                                                       | 13                  | 12                | 6.3                              | 2.0–10.6                                 | 0.854 (0.465–1.567)                    | 0.610            |
| Presence of extrahepatic metastases; Log-rank test <i>P</i> = <b>0.021</b>                              |                     |                   |                                  |                                          |                                        |                  |
| Yes*                                                                                                    | 151                 | 100               | 7.1                              | 5.7–8.4                                  | Reference                              | Reference        |
| No                                                                                                      | 225                 | 137               | 8.1                              | 6.9–9.2                                  | 0.738 (0.568–0.957)                    | <b>0.022</b>     |
| Age (continuous)                                                                                        |                     |                   |                                  |                                          |                                        |                  |
| Age (categories); Log-rank test <i>P</i> = 0.316                                                        |                     |                   |                                  |                                          |                                        |                  |
| <65 years*                                                                                              | 172                 | 113               | 8.2                              | 6.9–9.5                                  | Reference                              | Reference        |
| ≥65 years                                                                                               | 206                 | 126               | 7.4                              | 6.4–8.3                                  | 1.140 (0.882–1.473)                    | 0.317            |
| Prior liver procedures; Log-rank test <i>P</i> = 0.114                                                  |                     |                   |                                  |                                          |                                        |                  |
| Yes*                                                                                                    | 104                 | 63                | 7.1                              | 6.2–7.9                                  | 1.262 (0.944–1.685)                    | 0.116            |
| No                                                                                                      | 275                 | 177               | 9.7                              | 8.9–10.4                                 | Reference                              | Reference        |
| Number of liver tumours; Log-rank test <i>P</i> = <b>0.008</b>                                          |                     |                   |                                  |                                          |                                        |                  |
| 1–5*                                                                                                    | 107                 | 58                | 11.3                             | 8.7–13.8                                 | Reference                              | Reference        |
| 6–10                                                                                                    | 50                  | 28                | 6.7                              | 3.8–9.5                                  | 1.666 (1.059–2.621)                    | <b>0.027</b>     |
| >10                                                                                                     | 167                 | 117               | 7.3                              | 6.2–8.3                                  | 1.608 (1.171–2.208)                    | <b>0.003</b>     |
| Sex; Log-rank test <i>P</i> = <b>0.012</b>                                                              |                     |                   |                                  |                                          |                                        |                  |
| Female                                                                                                  | 129                 | 96                | 6.4                              | 5.2–7.7                                  | 1.389 (1.073–1.800)                    | <b>0.013</b>     |
| Male                                                                                                    | 250                 | 144               | 8.2                              | 7.2–9.2                                  | Reference                              | Reference        |
| Percentage tumour to liver volume (continuous)                                                          |                     |                   |                                  |                                          |                                        |                  |
| Percentage tumour to liver volume; Log-rank test <i>P</i> < <b>0.001</b>                                |                     |                   |                                  |                                          |                                        |                  |
| ≤25%                                                                                                    | 226                 | 135               | 9.4                              | 8.0–10.9                                 | Reference                              | Reference        |
| >25%–50%                                                                                                | 80                  | 57                | 5.3                              | 4.4–6.2                                  | 1.955 (1.424–2.685)                    | <b>&lt;0.001</b> |
| >50%                                                                                                    | 22                  | 17                | 5.3                              | 6.8–8.2                                  | 2.994 (1.791–5.005)                    | <b>&lt;0.001</b> |

ECOG, Eastern Cooperative Oncology Group.

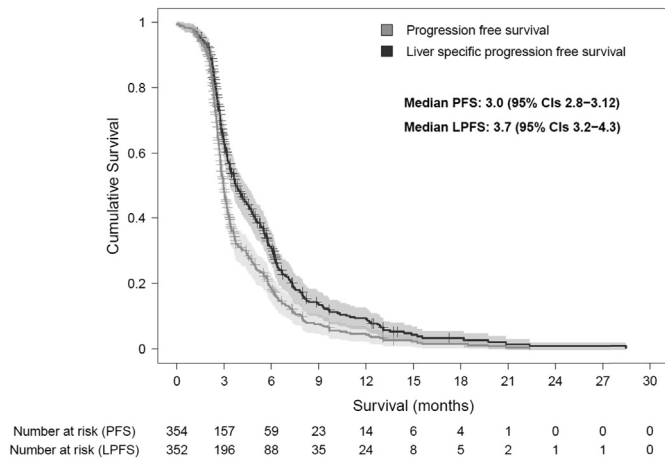
\* Reference category for univariate Cox regression analysis.

## Discussion

SIRT is reimbursed for the treatment of liver metastases from CRC in most developed countries at a national or regional level (Supplementary Table S2), but its effect on overall survival and cost-effectiveness in patients with CRC liver metastases has not been shown in prospective, randomised phase III studies. As prospective, randomised controlled clinical trials can take a decade or longer to address specific research questions [9], some health systems have opted to study the treatment in a registry-based commissioning model to address specific deficiencies in the published literature and to accelerate advancement to full commissioning. This study was specifically commissioned to provide ‘real-world’ evidence on the survival of patients

treated with SIRT in a salvage setting to inform future commissioning policy decisions.

Patients with unresectable CRC liver metastases whose disease has progressed following chemotherapy have very few treatment options. New locoregional liver-directed therapies, such as SIRT or transarterial chemo-embolisation with drug-eluting beads, are emerging but have not yet become the standard of care. Patients in the control arm of clinical trials treated with best supportive care (BSC) in a salvage setting have a median overall survival ranging from 2.4 months [10] to 6.6 months [11]. In this same population, NICE has recommended trifluridine-tipiracil on the basis of two randomised controlled trials (RCTs) that showed an improvement in overall survival by 2.0–2.4 months above BSC [11,12]. We carried out a systematic evidence review of



**Fig 2.** Kaplan–Meier curve of progression-free survival and liver-specific progression-free survival after selective internal radiation therapy in patients with metastatic colorectal cancer. Ninety-five per cent confidence intervals are shaded; numbers at risk at 3-month intervals are displayed.

studies of unresectable, chemotherapy-refractory patients with CRC liver metastases treated with SIRT, which identified 23 studies (one RCT, two retrospective comparative studies and several single-arm observational studies) reporting

overall survival ([Supplementary Table S1](#)). For 2517 patients in these studies, the pooled weighted overall survival estimate was 9.6 months (95% confidence interval 8.9–10.4; range 6.0–12.7 months). The patients included in our study had similar performance status and a similar rate of extra-hepatic disease (around 40% of patients). Ongoing clinical studies are listed in [Supplementary Table S3](#).

Published evidence on the efficacy of SIRT in the salvage setting is of limited quality and at risk of bias. Statistically significant improvements in overall survival in patients treated with SIRT were observed in two retrospective studies: patients receiving BSC survived for a median of 6.6 months compared with 11.9 months in patients who received SIRT [13] or 8.3 months versus 3.5 months [14]. In a small ( $n = 44$  total) RCT comparing fluorouracil chemotherapy alone to SIRT plus chemotherapy, PFS and LPFS were improved in the SIRT arm (PFS 2.1 versus 4.5 months; hazard ratio 0.51;  $P = 0.03$ ; LPFS 2.1 versus 5.5 months; hazard ratio 0.38;  $P = 0.003$ ), showing prolonged control of liver tumour growth [15]. In this trial, patients were permitted to cross-over after progression. The overall survival estimate reported in our dataset of 7.6 months aligns with the SIRT arm of the retrospective comparative study by Seidensticker *et al.* [14]. It also consistent with the lower end of the range of

**Table 4**

Total number of patients with severe day-of-treatment complications and total number of all-cause adverse events and abnormal laboratory value events

| Severe day-of-treatment complications     | Number of patients       |                                         |
|-------------------------------------------|--------------------------|-----------------------------------------|
| Yes                                       | 11 (3%)                  |                                         |
| No                                        | 375 (94%)                |                                         |
| Missing                                   | 13 (3%)                  |                                         |
| Adverse event category                    | Number of adverse events | Number of grade $\geq 3$ adverse events |
| Fatigue                                   | 89                       | 8                                       |
| Abdominal pain                            | 58                       | 3                                       |
| Nausea                                    | 22                       | 0                                       |
| Vomiting                                  | 14                       | 0                                       |
| Fever                                     | 10                       | 1                                       |
| Gastritis                                 | 5                        | 0                                       |
| Gastrointestinal ulcer                    | 1                        | 0                                       |
| REILD                                     | 1                        | 0                                       |
| Radiation pneumonitis                     | 0                        | 0                                       |
| Radiation cholecystitis                   | 0                        | 0                                       |
| Radiation pancreatitis                    | 0                        | 0                                       |
| Other                                     | 53                       | 7                                       |
| Total adverse events                      | 253                      | 19                                      |
| Abnormal laboratory result event category | Number of events         | Number of grade $\geq 3$ events         |
| AST increased                             | 79                       | 0                                       |
| ALT increased                             | 73                       | 1                                       |
| Hypoalbuminaemia                          | 67                       | 4                                       |
| Hyperbilirubinaemia                       | 44                       | 8                                       |
| INR increased                             | 1                        | 0                                       |
| Neutrophil count decreased                | 10                       | 3                                       |
| Platelet count decreased                  | 28                       | 0                                       |
| Other                                     | 51                       | 2                                       |
| Total abnormal laboratory result events   | 353                      | 18                                      |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; REILD, radio-embolisation-induced liver disease; INR, International Normalised Ratio.

previously published data. It is possible that this may be due to the patient selection that occurs during a clinical trial, leading to inclusion of patients who may be in worse health in this registry-based study.

The study reported here is the largest, prospective, registry-based study to examine the survival of patients with unresectable, chemotherapy-refractory mCRC treated with SIRT. Unfortunately, the ‘real-world’ setting of the treatment and data collection in NHS centres resulted in missing data and in variability in the assessment criteria, which does add some uncertainty to the conclusions. However, the real-life setting may have led to the inclusion of a patient population more representative of the patients to be treated within the NHS.

The absence of a contemporaneous comparator group limits our interpretation of the clinical data reported. As a registry study, no minimum follow-up was specified. However, long-term data were available for most of the patients included. Data collection for health-related quality of life questionnaires varied significantly between centres. High levels of missing data meant that reliable conclusions about the impact of SIRT on patient quality of life could not be drawn from this study. Despite these reservations, the clinical data presented here will aid treatment decisions reached between clinicians and patients in day-to-day practice.

PFS and LPFS in this cohort were 3.0 months and 3.7 months, respectively. Both values are at the lower end of the range from published studies of 2.8–9.2 months (nine studies; 437 patients) for PFS and 2.0–9.0 months (eight studies, 376 patients) for LPFS ([Supplementary Table S1](#)). PFS estimates should be interpreted with caution given the inherent risk of bias in this measure [16]; PFS relies on interval-censored data, which will probably inflate the survival estimate. We report a 0.7 month higher LPFS compared with PFS, which mirrors results from other studies [15].

In this study, severe complications on the day of treatment were rare. Adverse events in the follow-up period occurred in 36% of patients. Abdominal pain and fatigue were the most common severe (grade 3) adverse events. Clinically important events, such as RILD, were very rare or not reported at all in our cohort. Two patients experienced mild (grade 1) RILD 84 days and 194 days after SIRT. These rates are lower than those in the published literature [17,18].

We recently reported that the combination of SIRT with concomitant oxaliplatin–fluorouracil (FOLFOX) chemotherapy in the first-line treatment of liver metastases from CRC [19] resulted in neutropenia, febrile neutropenia, thrombocytopenia, fatigue and abdominal pain occurring at a significantly greater frequency in the arm receiving SIRT, albeit at a frequency and severity that was expected and medically manageable. This adverse event profile seems to be related to the combination of SIRT with concomitant chemotherapy, as in the study reported here, in which 65% patients did not receive chemotherapy with SIRT in the salvage setting, severe complications were far less common.

A critical factor in deciding how SIRT should be used in the salvage setting is patient selection. Important subgroups have been identified in this study that can inform treatment discussions with patients. Patients with no

extrahepatic metastases, fewer than six tumours and a tumour-to-liver volume percentage of less than 25% seemed to do better with SIRT, although definite conclusions cannot be drawn without a comparator group. In the recently reported first-line studies [19], an exploratory subgroup analysis showed that patients with liver metastases from right-sided primary CRC may benefit from the combination of SIRT plus concomitant FOLFOX chemotherapy more than patients with liver metastases from left-sided primaries. At the time of designing the registry for the study reported here, this information was not known, so the location of the primary tumour was not one of the fields included in the registry.

Despite the limitations of the registry-based approach, this study shows that this approach to data collection in the health service can accrue rapidly and provide clinically meaningful data. The study has confirmed that SIRT is safe and well tolerated in patients who have previously received multiple lines of chemotherapy and it has shown that SIRT in this population results in overall survival, PFS and LPFS that are consistent with previously published smaller studies. This study shows the value of a registry-based commissioning model with a systematic research evaluation to aid national commissioning decisions for a highly specialist cancer treatment.

## Conflicts of Interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clon.2018.09.002>.

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