Title: Analysis of a national programme for selective internal radiation therapy for colorectal cancer liver metastases

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up period, 143 patients experienced an adverse event and 8% of the events were grade =3. Survival estimates from this pragmatic study demonstrate clinical outcomes attainable in the NHS comparable to previously published data. This study demonstrates the value of a registry-based commissioning model to aid national commissioning decisions for highly specialist cancer treatments.

Analysis of a national programme for selective internal radiation therapy for colorectal cancer liver metastases

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ABSTRACT (189 words)

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 NHS England Commissioning through Evaluation. 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. Primary outcome was overall survival; secondary outcomes included safety, progression-free survival (PFS) and liver-specific PFS (LPFS). Between December 2013 and March 2017, 399 patients were treated in 10 centres with median follow-up 14.3 months (95% CIs 9.2-19.4).

Median overall survival was 7.6 months (95% CIs 6.9 – 8.3). Median PFS and LSPFS were 3.0 months (95% CIs 2.8-3.1) and 3.7 months (95% CIs 3.2-4.3), respectively. During the follow-up period, 143 patients experienced an adverse event and 8% of the events were grade =3. Survival estimates from this pragmatic study demonstrate clinical outcomes attainable in the NHS comparable to previously published data. This study demonstrates the value of a registry-based commissioning model to aid national commissioning decisions for highly specialist cancer treatments.

KEY WORDS: colorectal cancer; liver metastases; trans-arterial radio-embolization; molecular

radiotherapy; brachytherapy; commissioning models

ABBREVIATIONS: Adverse Events (AEs), Best Supportive Care (BSC),British Society of Interventional Radiology (BSIR), Conformité Européene (CE), Confidence Intervals (CIs), Complete Response (CR), Colorectal Cancer (CRC), Common Terminology Criteria for Adverse Events (CTCAE), Commissioning through Evaluation (CtE), Eastern Cooperative Oncology Group (ECOG), Epidermal Growth Factor Receptor (EGFR), Concomitant Oxaliplatin-Fluorouracil (FOLFOX), Hazard Ratios (HRs), Liver-Specific

Progression-Free Survival (LPFS), Metastatic CRC (mCRC), National Health Service (NHS), National Institute for Health and Care Excellence (NICE), Overall Survival (OS), Progression-Free Survival (PFS), Partial Response (PR), Randomised Controlled Trial (RCT), Progressive Disease (PD), Radio-Embolisation/Radio-Embolization (RE), Response Evaluation Criteria for Solid Tumours (RECIST), Radiation-Induced Liver Disease (RILD), Stable Disease (SD), Selective Internal Radiation Therapy (SIRT), Transarterial Radioembolisation (TARE), Vascular Endothelial Growth Factor (VEGF)

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FULL TEXT

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 the majority (70-80%) of patients are unsuitable for liver surgery [1]. Systemic chemotherapy is the standard treatment for unresectable metastatic disease, which may be combined with biological agents such as EGFR (epidermal growth factor receptor) inhibitors (cetuximab or panitumumab) or VEGF (vascular endothelial growth factor) inhibitors (bevacizumab). For patients with advanced metastatic CRC (mCRC) who have progressed following 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 radioembolisation (TARE) or radio-embolisation/radio-embolization (RE), 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 the National Health Service (NHS) England which 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 (OS), 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 sites' routine NHS clinical governance processes. The SIRT registry is an online registry hosted by the British Society of Interventional Radiology (BSIR) incorporating national data on radio-embolisation of primary and secondary liver tumours. It holds deidentified data, and only those data relevant to this CtE study was 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 CT evidence of liver metastases not treatable by surgical resection or local ablation with curative intent; WHO performance status of 0–2; life expectancy > 3 months; evidence of clinical progression during or following 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 x ULN; absolute neutrophil count > 1.5 x 10^9/L, platelets > 100 x 10^9/L; albumin = 30 g/L; no central nervous system metastases or bone metastases, but patients were permitted to have limited extra-hepatic disease (e.g. lung metastases, multiple lymph nodes or low-volume peritoneal disease, but the Multi-Disciplinary Team must have agreed that the extra-hepatic disease was not likely to be 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 as required to prevent non-target Y-90 delivery. SIRT was carried out using an established method. One of two brands of Conformité Européene (CE)-marked active implantable medical devices were 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 2 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 to 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.

OS 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 (PD; either hepatic or extrahepatic) by CT, MRI, or PET scan, or to the date of death from any cause if progression was not recorded. Patients with no PD recorded were censored at the most recent date of non-progression (complete response (CR) or partial response (PR) or stable disease (SD)). LSPFS 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 PD in the liver were censored at the most recent date of non-progression in the liver. Adverse events (AEs) were recorded using Common Terminology Criteria for Adverse Events (CTCAE) 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) 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-value and confidence intervals (CIs) were reported. P-values at <0.05 were considered statistically significant and all tests were two-sided. Median OS, PFS, and LPFS were estimated using the Kaplan-Meier analysis [8]. Survival curves were presented with 95% CIs 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 (HRs) 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 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% CIs 9.2-19.4).

Fifteen cases were excluded for the following reasons: i) missing diagnosis; ii) no treatment data; iii) no SIRT procedure date. Patients were 67% male and had a median age of 66 years. Most patients had an ECOG performance score of 0 or 1 (93%) and the majority did not have extrahepatic metastatic disease (60%) (Table 1). Almost all patients (98%) had received prior systemic chemotherapy or biologics, and 78% had received 2 or 3 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).

A total of 114 patients (29%) of patients had between 1 and 5 tumours, and 44% had more than 10 tumours. The median overall tumour to liver volume ratio was 15% (IQR 7-27%) reported in 270 patients. Median bilirubin and albumin values prior to SIRT were 9.0 μmol/L (IQR 6.0-12.0) and 37.0 g/L (IQR 33.0-41.0), respectively.

Treatment and follow-up

Relevant visceral arteries were embolised during the work-up procedure in 52% 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, the majority of SIRT treatments (86%) were conducted using resin Y-90 microspheres, with a mean prescribed activity of 1.74 GBq (SD 2.13); 14% of treatments used glass Y-90 microspheres, with a mean prescribed activity of 4.18 GBq (SD1.71). 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-FU and oxaliplatin) and a minority of cases (22%) went on to receive further post-SIRT chemotherapy during their follow-up phase (Table 2).

Survival

Death was recorded in 240 (60%) patients; 139 (35%) patients were censored at their last recorded follow-up date, and the survival status of 20 patients (5%) was unknown. OS was 7.6 months (95% CIs 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). OS was significantly longer in patients who did not have extrahepatic metastasis (log-rank test, p-value=0.021); the HR was 0.74 (95% CIs 0.57-0.96; univariate Cox proportional hazards p-value=0.022). OS also differed significantly between the categories of number of liver tumours (log-rank test, p-value=0.008); the HR was 1.67 (95% CIs 1.062.62; p=0.027) when the group of 6-10 tumours was compared to the reference group of 1-5 tumours; the HR was 1.61 (95% 1.17-2.21) when the group of >10 tumours was compared to the reference group. OS was longer in males compared to females (log-rank test, p-value=0.012); the HR was 1.389 (95% CIs 1.073-1.800; p=0.013). OS was also related to the percentage tumour to liver volume measurements at baseline (log rank test, p<0.001); the HR was 1.955 (95% CIs 1.424-2.685) comparing the category of tumour to liver volume >25% to 50% with the reference category of =25%; the HR was 2.994 (1.791-5.005) when the category of >50% was compared to 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' diseased 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. Median PFS was 3.0 months (95% CIs 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. Median LPFS was 3.7 months (95% CIs 3.2-4.3) (Figure 2). Hepatic progression and extrahepatic

progression was 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

A total of 11 patients (3%) experienced severe day-of-treatment complications (Table 4). Severe AEs within the first week after SIRT were rare; 3 patients experienced grade =3 fatigue in the 7 days after SIRT, and 1 patient experienced grade =3 abdominal pain in the first week after SIRT. A total of 143 patients experienced an AE. A total of 253 AEs 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 and AEs 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 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). A total of 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 hypoalbuminemia (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.

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 colorectal liver metastases has not been shown in prospective, randomised phase III studies. Since 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 loco-regional liver-directed therapies, such as SIRT or trans-arterial 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 OS ranging in studies from 2.4 months [10] to 6.6 months [11]. In this same population, NICE has recommended trifluridine-tipiracil on the basis of two RCTs which showed an improvement in OS by 2.0-2.4 months above BSC [11, 12]. We performed a systematic evidence review of studies of unresectable, chemotherapy-refractory patients with colorectal cancer liver metastases treated with SIRT, which identified 23 studies (1 RCT, 2 retrospective comparative studies, and several single-arm observational studies) reporting OS (Supplementary Table S1). For 2,517 patients in these studies, the pooled weighted OS estimate was 9.6 months (95% CIs 8.9-10.4; range 6.0 to 12.7 months). The patients included in our study had similar performance status and a similar rate of extrahepatic 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 OS in patients treated with SIRT were observed in 2 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) randomised controlled trial (RCT) comparing fluorouracil chemotherapy alone to SIRT plus chemotherapy, progression-free survival (PFS) and liver-specific PFS (LPFS) were improved in

the SIRT arm (PFS 2.1 vs 4.5 months; HR 0.51; p=0.03; LPFS 2.1 vs 5.5 months; HR 0.38; p=0.003) demonstrating prolonged control of liver tumour growth [15]. In this trial, patients were permitted to cross-over following progression. The OS 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 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 metastatic CRC 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 National Health Service.

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 was 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 patients' 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 to 9.2 months (9 studies; 437 patients) for PFS, and 2.0 to 9.0 months (8 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 likely inflate the survival estimate. We report a 0.7-month higher liver-specific PFS compared to 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 radiation-induced liver disease (RILD), were very rare or not reported at all in our cohort. Two patients experienced mild (grade 1) RILD 84 days and 194 days following 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 appears to be related to the combination of SIRT with concomitant chemotherapy since, 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 which can inform treatment discussions with patients. Patients with no extrahepatic metastases, fewer than 6 tumours, and a tumour-to-liver volume percentage of less than 25% appeared 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 demonstrated 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 OS, PFS and LPFS which are consistent with previously published smaller studies. This study demonstrates the value of a registry-based commissioning model with a systematic research evaluation to aid national commissioning decisions for a highly specialist cancer treatment.

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REFERENCES

[1] Zampino, M.G., E. Magni, P.S. Ravenda, C.A. Cella, G. Bonomo, P. Della Vigna, *et al.* Treatments for colorectal liver metastases: A new focus on a familiar concept. Crit Rev Oncol Hematol, 2016. 108: p. 154163.

[2] Giammarile, F., L. Bodei, C. Chiesa, G. Flux, F. Forrer, F. Kraeber-Bodere, *et al.* EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging, 2011. 38(7): p. 1393-406.

[3] Nicolay, N.H., D.P. Berry, and R.A. Sharma, Liver metastases from colorectal cancer: radioembolization with systemic therapy. Nat Rev Clin Oncol, 2009. 6(12): p. 687-97.

[4] Sharma, R.A., C. Cummins, and A. Crellin, Selective internal radiotherapy of the liver: at the crossroads of interventional oncology research and national health service commissioning. Clin Oncol (R Coll Radiol), 2014. 26(12): p. 733-5.

[5] Kennedy, A., S. Nag, R. Salem, R. Murthy, A.J. McEwan, C. Nutting, *et al.* Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys, 2007. 68(1): p. 13-23.

[6] NHS England. Independent evaluation of the Selective Internal Radiation Therapy Commissioning through Evaluation scheme: Evaluation Report. 2017 April 2018]; Available from: https://www.england.nhs.uk/publication/independent-evaluation-of-the-selectiveinternal-radiation-therapy-commissioning-through-evaluation-scheme/

[7] Eisenhauer, E.A., P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45(2): p. 228-47.

[8] Kaplan, E.L. and P. Meier, Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association, 1958. 53(282): p. 457-481.

[9] Franklin, J.M., V. Gebski, G.J. Poston, and R.A. Sharma, Clinical trials of interventional oncology-moving from efficacy to outcomes. Nat Rev Clin Oncol, 2015. 12(2): p. 93-104.

[10] Hickish, T., T. Andre, L. Wyrwicz, M. Saunders, T. Sarosiek, J. Kocsis, *et al.* MABp1 as a novel antibody treatment for advanced colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol, 2017. 18(2): p. 192-201.

[11] Yoshino, T., N. Mizunuma, K. Yamazaki, T. Nishina, Y. Komatsu, H. Baba, *et al.* TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol, 2012. 13(10): p. 993-1001.

[12] Mayer, R.J., E. Van Cutsem, A. Falcone, T. Yoshino, R. Garcia-Carbonero, N. Mizunuma, K. *et al.* Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med, 2015. 372(20): p. 1909-19.

[13] Bester, L., B. Meteling, N. Pocock, N. Pavlakis, T.C. Chua, A. Saxena, *et al.* Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J Vasc Interv Radiol, 2012. 23(1): p. 96-105.

[14] Seidensticker, R., T. Denecke, P. Kraus, M. Seidensticker, K. Mohnike, J. Fahlke, *et al.* Matched-pair comparison of 12 radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol, 2012. 35(5): p. 1066-73.

[15] Hendlisz, A., M. Van den Eynde, M. Peeters, G. Maleux, B. Lambert, J. Vannoote, *et al.* Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin

microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol, 2010. 28(23): p. 3687-94.

[16] Sridhara, R., S.J. Mandrekar, and L.E. Dodd, Missing data and measurement variability in assessing progression-free survival endpoint in randomized clinical trials. Clin Cancer Res, 2013. 19(10): p. 2613-20.

[17] Zacharias, A.J., T.T. Jayakrishnan, R. Rajeev, W.S. Rilling, J.P. Thomas, B. George, *et al.* Comparative Effectiveness of Hepatic Artery Based Therapies for Unresectable Colorectal Liver Metastases: A Meta-Analysis. PLoS One, 2015. 10(10): p. e0139940.

[18] Saxena, A., L. Bester, L. Shan, M. Perera, P. Gibbs, B. Meteling, *et al.* A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol, 2014. 140(4): p. 537-47.

[19] Wasan, H.S., P. Gibbs, N.K. Sharma, J. Taieb, V. Heinemann, J. Ricke, *et al.* 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): p. 11591171.

Analysis of a national programme for selective internal radiation therapy for colorectal cancer liver metastases

HIGHLIGHTS:

- Selective internal radiotherapy is an interventional treatment for liver metastases
- This was a large, prospective, single arm, observational, service evaluation study
- Acceptable safety profile demonstrated in a real-world service setting
- Overall survival confirmed findings of published retrospective series
- Registry-based studies aid national commissioning decisions

CONFLICTS OF INTEREST STATEMENT

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