

Protocol

Clinical Application of Radioembolization in Hepatic Malignancies: Protocol for a Prospective Multicenter Observational Study

Thomas Helmberger^{1*}; Dirk Arnold^{2*}; José I Bilbao^{3*}; Niels de Jong^{4*}; Geert Maleux^{5*}; Anders Nordlund^{6*}; Bora Peynircioglu^{7*}; Bruno Sangro^{8,9,10*}; Ricky A Sharma^{11*}; Agnes Walk^{4*}

¹Department of Radiology, Neuroradiology and Minimal-Invasive Therapy, Klinikum Bogenhausen, München, Germany

²Oncology and Hematology, Asklepios Tumorzentrum Hamburg, Asklepios Klinik Altona, Hamburg, Germany

³Interventional Radiology, Clinica Universidad de Navarra, Pamplona, Spain

⁴Cardiovascular and Interventional Radiological Society of Europe, Vienna, Austria

⁵Radiologie, Universitair Ziekenhuis Leuven, Leuven, Belgium

⁶Trial Form Support Aktiebolag, Lund, Sweden

⁷Department of Radiology, School of Medicine, Hacettepe University, Ankara, Turkey

⁸Liver Unit, Clínica Universidad de Navarra, Pamplona, Spain

⁹Instituto de Investigación Sanitaria de Navarra, Pamplona, Spain

¹⁰Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas, Pamplona, Spain

¹¹National Institute for Health Research University College London Hospitals Biomedical Research Centre, University College London Cancer Institute, University College London, London, United Kingdom

* all authors contributed equally

Corresponding Author:

Niels de Jong

Cardiovascular and Interventional Radiological Society of Europe

Neutorgasse 9

Vienna, 1010

Austria

Phone: 43 1904200347

Email: dejong@cirse.org

Abstract

Background: Radioembolization, also known as transarterial radioembolization or selective internal radiation therapy with yttrium-90 (90Y) resin microspheres, is an established treatment modality for patients with primary and secondary liver tumors. However, large-scale prospective observational data on the application of this treatment in a real-life clinical setting is lacking.

Objective: The main objective is to collect data on the clinical application of radioembolization with 90Y resin microspheres to improve the understanding of the impact of this treatment modality in its routine practice setting.

Methods: Eligible patients are 18 years or older and receiving radioembolization for primary and secondary liver tumors as part of routine practice, as well as have signed informed consent. Data is collected at baseline, directly after treatment, and at every 3-month follow-up until 24 months or study exit. The primary objective of the Cardiovascular and Interventional Radiological Society of Europe Registry for SIR-Spheres Therapy (CIRT) is to observe the clinical application of radioembolization. Secondary objectives include safety, effectiveness in terms of overall survival, progression-free survival (PFS), liver-specific PFS, imaging response, and change in quality of life.

Results: Between January 2015 and December 2017, 1047 patients were included in the study. The 24-month follow-up period ended in December 2019. The first results are expected in the third quarter of 2020.

Conclusions: The CIRT is the largest observational study on radioembolization to date and will provide valuable insights to the clinical application of this treatment modality and its real-life outcomes.

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KEYWORDS

hepatocellular carcinoma; metastasis; observational study; registries; therapeutic embolization; liver; yttrium-90; radioisotope brachytherapy

Introduction

Primary hepatic malignancies are among the most common cancers of solid organs worldwide and are the fourth to fifth leading cause of death. From the primary liver diseases cirrhosis and hepatocellular carcinoma (HCC), about 180,000 and 75,000 patients, respectively, will die per year in Europe [1,2]. Significant rises in incidence rates for hepatic inflammation, fibrosis, and cirrhosis—predisposing factors for HCC—are expected for the next decade with causes such as autoimmune disease, drug-related effects, or nonalcoholic fatty liver disease [2]. About 4 million people per year are affected by cancer in Europe; 30% to 80% of these patients might develop hepatic metastases [3].

Curative treatment of a hepatic malignancy by liver transplantation, resection, and local ablation can be applied in only about 10% to 25% of cases. Unfortunately, the vast majority of patients do not qualify for these therapies. Various kinds of systemic treatments including chemotherapy, biological therapy, and cancer immunotherapy are offered to this group of patients [4-7]. There is a substantial subset of patients with liver-limited disease that are not suitable for surgical or percutaneous ablative therapies, who experienced early recurrences or no response, significant side effects, or intolerance when treated with systemic therapies. In this setting, transarterial therapies such as chemoembolization, chemoperfusion, or radioembolization (eg, selective internal radiation therapy or transarterial radioembolization) may offer substantial therapeutic improvement [4,7]. Furthermore, these therapies may allow a reduction of systemic side effects, extend periods of freedom from chemotherapy, and prime the liver for other potential local treatment options such as surgery or local ablation [8-11].

Several current, large-scale randomized controlled trials (RCTs) could define the role of radioembolization in first-line and second-line therapy regimens in more advanced primary and secondary liver malignancies [12-15]. Based on this data, current guidelines suggest radioembolization should be considered as a component of the “tool-box” [5,6] in the treatment of HCC, cholangiocarcinoma, and metastatic colorectal cancer (mCRC) following progression after standard therapies or intolerance to other therapies [4,16].

Nevertheless, there is still limited information and understanding of the application of radioembolization in a real-life clinical setting [13,17]. Recent observational studies conducted in the United Kingdom describe the outcome of the real-life application of radioembolization in patients with colorectal liver metastases and intrahepatic cholangiocarcinoma [18,19]. However, similar real-world data from other countries and from patients with other liver malignancies such as HCC are needed by physicians, patients, and paying bodies. More observational data on the use of radioembolization in various clinical settings would elucidate the position of radioembolization in clinical practice and additionally provide data for less established uses of radioembolization, as in metastatic liver disease from other primaries (eg, breast cancer, malignant melanoma, or pancreatic cancer) [20,21].

To further improve the understanding of the real-life clinical application of radioembolization and its impact on clinical practice, the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) initiated the *CIRSE Registry for SIR-Spheres Therapy (CIRT)* for patients treated with radioembolization with yttrium-90 (90Y) resin microspheres (SIR-Spheres, Sirtex Medical Pty Limited; St. Leonards, NSW, Australia). CIRT will collect data on how radioembolization is embedded in real-life clinical practice as well as effectiveness, safety, technical considerations, and patient-reported quality of life (QOL).

Methods

Study Design and Objectives

CIRT is a prospective, multicenter, single-device, noninterventional study of patients with liver tumors treated with radioembolization in daily routine practice as a standard of care. The primary objective is to observe the real-life clinical application of radioembolization and the impact of the treatment in clinical practice. This objective is described by: type of liver cancer, intention of treatment, prior hepatic procedures, associated systemic therapy, and postradioembolization hepatic procedures.

Secondary objectives are effectiveness, safety, technical considerations, and patient-reported outcome measures (see [Textbox 1](#)).

Textbox 1. Secondary end points.**Effectiveness end points**

- Overall survival
- Progression-free survival
- Hepatic progression-free survival (ie, liver-specific progression-free survival)
- Imaging response

Safety end points

- Day-of-treatment complications
- Adverse events
- Laboratory values

Technical considerations end points

- Patient-related characteristics
- Treatment-related characteristics
- Treatment administration
- Procedure-related outcomes

Patient-reported outcome end points

- Quality of life questionnaire C30
- Additional hepatocellular carcinoma module for patients with hepatocellular carcinoma

Site Selection and Patient Enrollment

Sites that incorporated radioembolization in their standard of care armamentarium and had a minimum amount of experience with the procedures were considered for invitations to participate in the study (ie, 10 or more treatments in the last 12 months and a career history of at least 40 cases). The selected sites were limited to centers in the European Union, Switzerland, Turkey, and Israel. A multidisciplinary steering committee containing experts from the field of medical oncology, diagnostic and interventional radiology, hepatology, surgery, and nuclear medicine developed a list of sites that met the selection criteria and continued to update this list throughout the course of the study. All sites that met the selection criteria were invited directly by the steering committee.

Eligible patients consist of any adult patients treated with radioembolization with 90Y resin microspheres for primary or secondary liver tumors that have signed the informed consent form. No formal sample size calculation was made. The steering committee reasoned that about 1000 patients could be recruited during a period of 3 years, and this would be sufficient to observe the real-life clinical application of radioembolization.

Site enrollment was from August 2014 until April 2017. Patients were included from January 2015 until December 2017. Follow-up data collection ended in December 2019.

This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. This study was approved by the local ethics committees of participating centers.

Data Collection

Patients enter the study by accepting participation and signing the informed consent form. Baseline data is collected upon allocation. Data on how the treatment was performed and its day-of-treatment outcomes are collected on the day of treatment. The patient is then followed for a maximum of 24 months or until study exit (see [Figure 1](#)). Guidelines for radioembolization advise that posttreatment assessments should be performed every 3 months [22]. However, the final decisions on treatment and follow-up schedules are determined by the site-specific medical teams.

Baseline assessments included patient demographics, medical history related to the underlying disease and cancer treatment, as well as cancer type and stage for patients with HCC ([Table 1](#)). The technical aspects that may determine how radioembolization is performed or impacts procedure-related outcomes were documented at the time of treatment. Time to event end points and safety end points were collected at every follow-up. In addition to demographic and clinical data, patient-reported outcomes are measured using the European Organisation for the Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 (QLQ-C30) [23,24]. The questionnaire was provided before the treatment, shortly after the treatment, and at every follow-up. When this was not feasible on site, patients were approached via letters or phone calls organized by the study center responsible for the patient. For patients with HCC, in addition to the QLQ-C30, the HCC module was provided to assess factors related to chronic liver disease, as well as issues related to the primary tumor and its treatment [25]. The QLQ-C30 and HCC module were made

available to each patient in their local language, using questionnaires translated and validated by EORTC [26-28].

Demographic and clinical data obtained from medical examinations, medical records, and QOL forms were transferred into an electronic case report form (e-CRF). Patient data was pseudonymized by each site without a centralized pseudonymization policy, and data collection was done according to the General Data Protection Regulation and stored in an encrypted form on a state-of-the-art server in Vienna, Austria. The e-CRF was accessible through a custom-built online

database developed by ConexSys Inc (Lincoln, RI) and installed on the CIRSE server in Vienna, Austria. Access to the system is password protected. Statistical analysis will be performed by an independent statistician.

Data quality was ensured through regular remote monitoring of data entered into the database. Remote monitoring includes regular information on data quality (query reports), inclusion of patients, and follow-ups. No on-site monitoring or source data verification was performed due to limited resources.

Figure 1. Flowchart of patient inclusion and measurement time points. CIRT: Cardiovascular and Interventional Radiological Society of Europe Registry for SIR-Spheres Therapy.

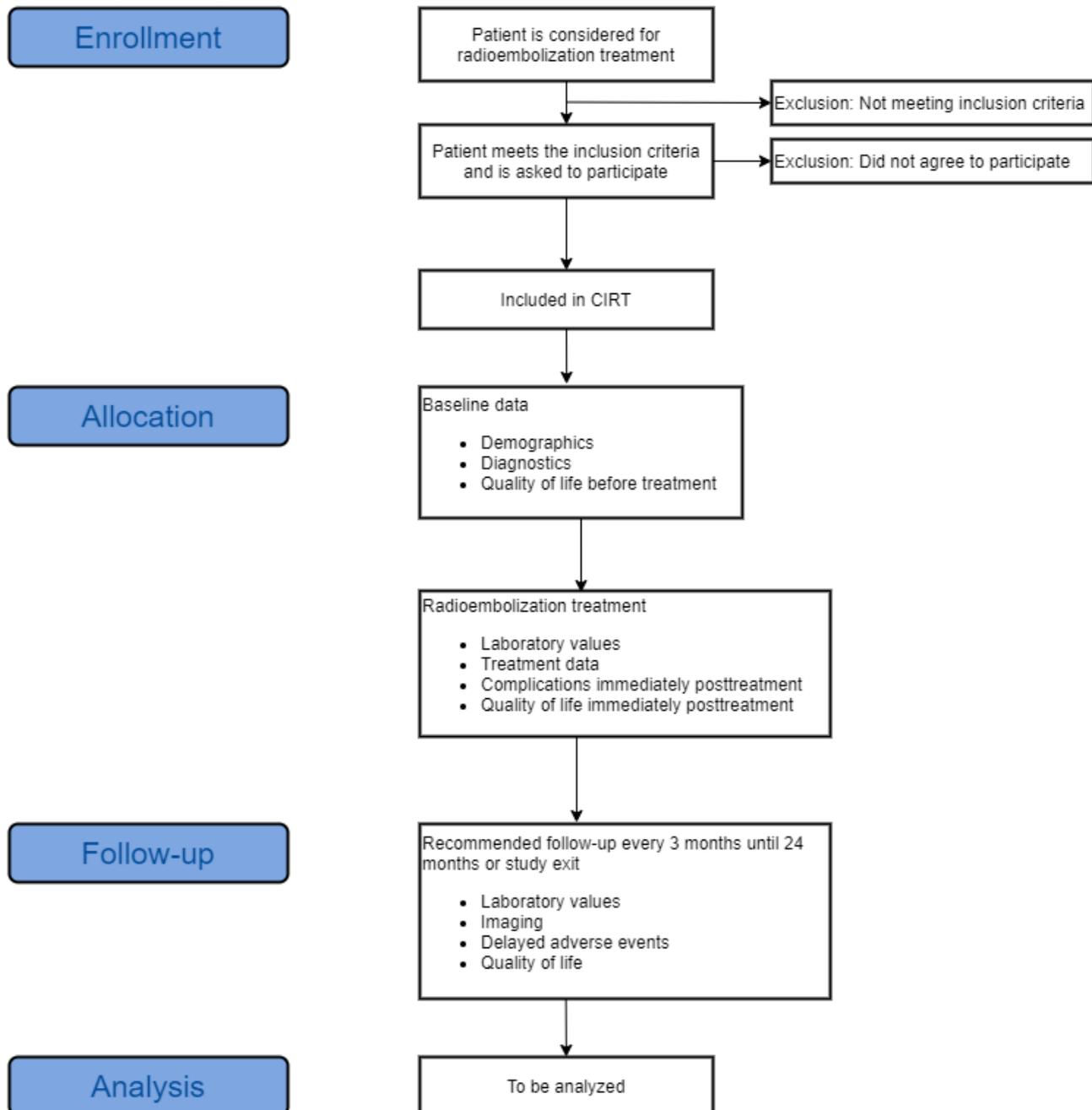


Table 1. Time of measurement for each end point and associated measurements.

End point	Baseline measurement	Day of treatment measurement	Follow-up measurement
Real-life application of radioembolization	<ul style="list-style-type: none"> Type of liver cancer Prior hepatic procedures Associated systemic therapy (prior systemic therapy) 	<ul style="list-style-type: none"> Intention of treatment 	<ul style="list-style-type: none"> Postradioembolization hepatic procedures Postradioembolization systemic chemotherapy
Effectiveness end points	N/A ^a	<ul style="list-style-type: none"> Treatment date 	<ul style="list-style-type: none"> Date of effectiveness event (OS^b, PFS^c, hepatic PFS, IR^d)
Safety end points	N/A	<ul style="list-style-type: none"> Severe day of treatment complications (Grade 3-4)^e 	<ul style="list-style-type: none"> Adverse events (Grade 1-5)^e Abnormal laboratory values
Technical considerations end points	<ul style="list-style-type: none"> Patient-related characteristics Prior hepatic procedures Physical characteristics (body surface area, lung shunt study [%], Eastern Cooperative Oncology Group performance status) 	<ul style="list-style-type: none"> Treatment planning Treatment administration Procedure-related outcomes 	N/A
Patient-reported outcome end points	<ul style="list-style-type: none"> EORTC^f QLQ-C30^g Additional module for HCC^h 	N/A	<ul style="list-style-type: none"> EORTC QLQ-C30 Additional module for HCC

^aN/A: not applicable.

^bOS: overall survival.

^cPFS: progression-free survival.

^dIR: imaging response.

^eGrading according to Common Terminology Criteria for Adverse Events version 4.03.

^fEORTC: European Organisation for the Research and Treatment of Cancer.

^gQLQ-C30: Quality of Life Questionnaire C30.

^hHCC: hepatocellular carcinoma.

Statistical Analysis

All patients who were found eligible, enrolled in the registry, underwent radioembolization treatment, and have the minimum amount of data required will be included in analysis. Patients for which the amount of data collected is too scarce to warrant meaningful analysis will be excluded. The number of excluded patients and reason for exclusion will be reported.

Data regarding the primary end point, safety, and technical considerations will be presented by summaries (eg, counts, means, standard deviations) and descriptive statistics. The

number of missing observations will be given in all summary tables. Time to event end points will be described graphically through the Kaplan-Meier analysis (including 95% CIs for median survival). The Cox regression will be used to assess the impact of the covariates for time to event end points (Table 2).

Hazard ratios and their 95% CIs will be presented together with *P* values. Sensitivity analyses of time to event data will be performed where censored patients with less than 6 weeks of follow-up will be included as worst case (ie, death or progression).

Table 2. Covariates for time to event end points.

Covariate	Variables
Age (years)	≤69 and ≥70
Sex	Male, female
Number of lines of previous chemotherapy	0, 1, 2-5, ≥6
Primary tumor in situ	Yes, no
Eastern Cooperative Oncology Group performance status	0, 1, and ≥2
Presence of extrahepatic metastases	Yes, no
Prior liver procedures	Yes, no
Number of liver tumors	1, 2-5, and ≥6
Percentage tumor to liver volume	Continuous

QOL is measured with the EORTC QLQ-C30, a questionnaire developed to assess the QOL in patients with cancer. The QLQ-C30 includes five functional scales, three symptom scales, a global health status scale, and six single items. The functional and symptom status of the QLQ-C30 will be assessed according to the scoring manual developed and validated by EORTC [29]. Patients who die during follow-up will be included in the QOL analyses until their date of death. The focus of these analyses will be on patients who are alive at the time point of analysis.

To document the safety and effectiveness of radioembolization and subsequent surgical or interventional procedures, the data will be broken down into subgroups as defined for the covariate analyses above.

Missing data can be expected in the event of a study site failing to enter certain data into the e-CRF, or a patient's withdrawal of consent or being lost to follow-up. Given the descriptive and exploratory nature of CIRT, all available data will be used, and no imputations of missing data will be made. The amount of missing data will be summarized and the subset of patients with missing data will be compared with patients included in the analysis.

In the effectiveness analyses, patients withdrawing consent or being lost to follow-up will be censored at the last time they were observed as being alive (overall survival) or at the time of their last magnetic resonance imaging scan from which disease progression could have been determined (progression-free survival [PFS]). Patients who die during the course of their follow-up in the registry will be regarded as having disease progression in the analyses of PFS and liver-specific PFS.

Missing data for QOL will be handled in line with the suggestions in the EORTC scoring manual for QLQ-C30; the amount of and reasons for completely missing forms will be analyzed and multiple imputations will be used for a part of the completely missing forms (ie, forms considered to be missing at random or due to administrative failure) [29].

Results

Between August 2014, and April 2017, 63 hospitals that met the selection criteria were invited, 36 (57%) of which were activated (ie, were trained, had access to database, were eligible to include patients), of which 29 (81%) enrolled patients.

A total of 1047 patients were collected during the trial period between January 1, 2015, and December 31, 2017. Follow-up data collection ended on December 31, 2019. Final results are expected to be published in 2020 or 2021.

Discussion

Summary

CIRT is the first European-wide prospective observational study of patients with liver tumors treated with radioembolization as the standard of care and will provide an important addition to the body of knowledge on radioembolization treatment.

Data from several large RCTs on mCRC and HCC were published while CIRT was already ongoing and more can be expected in the future [12,30,31]. However, these studies provide insufficient data with respect to “real life” clinical practice since there may be patient cohorts that benefit more from radioembolization than the patient cohorts included in these trials [32-34]. CIRT was designed to also explore patient cohorts for which less data is available. The writing group hopes that the outcomes of CIRT would provide valuable insights in these less explored patient populations to gain further insight into real world clinical practice of radioembolization. The extent to which this data relates to the overall body of data available on radioembolization will be discussed in the results publication.

Limitations

The single-arm observational study nature of the study design implies that several limitations need to be considered. The absence of a contemporaneous comparator group may limit our interpretation of the clinical data reported. Despite this, important positive features of the study are the long-term data collection for patients included and the valuable information collected on health-related QOL. The size of the study should enhance patient selection by providing new information on the patient subgroups that benefit most from this treatment in day-to-day clinical practice.

Furthermore, selection bias could occur at several stages of the study. An element of site selection was introduced when the Steering Committee created a list of sites that met the selection criteria of minimal expertise with radioembolization treatment. The potential of patient selection bias is addressed by a contractual agreed upon prospective design, whereby sites agreed to present the possibility to participate in the CIRT to all eligible patients consecutively.

Another source for bias relates to drop-out during follow-up. The sites included in the study have been advised to continue patient follow-up at least 24 months after the first treatment. However, patients may be lost to follow-up or withdraw their consent at any time. Loss to follow-up may relate to the course of disease or site procedures; for example, when a patient is treated at a participating site but followed-up by their referring physician, sometimes in another country. It will therefore not always be possible for study sites to collect additional follow-up data and the patient will be reported as lost to follow-up. Baseline characteristics will be compared between those lost to follow-up and those who have follow-up data to assess differences with the potential to bias results. Notable differences on a background characteristic will prompt additional analyses where the sensitivity of the results to that background characteristic will be further assessed.

Conclusion

To date, the CIRT is the largest observational study on the use of radioembolization with 90Y resin microspheres. The objective of the study was to observe the real-life clinical application of radioembolization and its impact in clinical practice. Currently, radioembolization has a position in the guidelines for the treatment of HCC, cholangiocarcinoma, and mCRC, and more data is warranted on the possibilities that this treatment has for

these diseases. Furthermore, additional data is needed for the effects of other lines of therapy and treatment of liver metastatic disease from other primary sites. Observing a large study population may reveal treatment aspects that would justify a wider application of this innovative treatment.

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Conflicts of Interest

Author TH received speaker honoraria from SIRTEX Medical Europe. Author DA received consulting fees and speaker honoraria from TERUMO, Boston Scientific, SIRTEX Medical Europe, and Biocompatibles. Author JB received speaker honoraria and consultation fees from SIRTEX Medical Europe. Author BS received scientific grants from Bristol-Myers-Squibb and SIRTEX Medical Europe; consultation fees and speaker honoraria from Astra Zeneca, Bayer, Bristol-Myers-Squibb, Ipsen, SIRTEX Medical Europe, and Terumo; consultation fees from Adaptimmune, BTG, Eli Lilly, and Onxeo; and fees for data review activities from Roche and BTG. Author RS received scientific grants from SIRTEX Technology and consultation fees from SIRTEX Medical Ltd. Author GM received speaker fees from SIRTEX Medical Europe. Authors NdJ, AN, BP, and AW reported no conflicts of interest.

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Abbreviations

CIRSE: Cardiovascular and Interventional Radiological Society of Europe

CIRT: Cardiovascular and Interventional Radiological Society of Europe Registry for SIR-Spheres Therapy.

e-CRF: electronic case report form

EORTC: European Organization for the Research and Treatment of Cancer

HCC: hepatocellular carcinoma

mCRC: metastatic colorectal cancer

PFS: progression-free survival

QLQ-C30: quality of life questionnaire C30

QOL: quality of life

RCT: randomized controlled trials

SIR: selective internal radiation

90Y: yttrium-90.

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