Economic evaluations of radioembolization with Itrium-90 microspheres in hepatocellular carcinoma: a systematic review

J. C. Alonso1, I. Casans2, F. M. González3, D. Fuster4, A. Rodríguez5, N. Sánchez4, I. Oyagüez6, R. Burgos7, A. O. Williams8, and N. Espinoza6*

Abstract

**Background:** Transarterial radioembolization (TARE) with yttrium-90 microspheres is a clinically effective therapy for hepatocellular carcinoma (HCC) treatment. This study aimed to perform a systematic review of the available economic evaluations of TARE for the treatment of HCC.

**Methods:** The Preferred Reported Items for Systematic reviews and Meta-Analyses guidelines was followed by applying a search strategy across six databases. All studies identified as economic evaluations with TARE for HCC treatment in English or Spanish language were considered. Costs were adjusted using the 2020 US dollars based on purchasing-power-parity ($US PPP).

**Results:** Among 423 records screened, 20 studies (6 cost-analyses, 3 budget-impact-analyses, 2 cost-effectiveness-analyses, 8 cost-utility-analyses, and 1 cost-minimization analysis) met the pre-defined criteria for inclusion. Thirteen studies were published from the European perspective, six from the United States, and one from the Canadian perspectives. The assessed populations included early- (n = 4), and intermediate-advanced-stages patients (n = 15). Included studies were evaluated from a payer perspective (n = 20) and included both payer and social perspective (n = 2). TARE was compared with transarterial chemoembolization (TACE) in nine studies or sorafenib (n = 11). The life-years gained (LYG) differed by comparator: TARE versus TACE (range: 1.3 to 3.1), and TARE versus sorafenib (range: 1.1 to 2.53). Of the 20 studies, TARE was associated with lower treatment costs in ten studies. The cost of TARE treatment varied widely according to Barcelona Clinic Liver Cancer (BCLC) staging system and ranged from 1311 $US PPP/month (BCLC-A) to 71,890 $US PPP/5-years time horizon (BCLC-C). The incremental cost-utility ratio for TARE versus TACE resulted in a 17,397 $US PPP/Quality-adjusted-Life-Years (QALY), and for TARE versus sorafenib ranged from dominant (more effectiveness and lower cost) to 3363 $US PPP/QALY.

**Conclusions:** Economic evaluations of TARE for HCC treatment are heterogeneous. Overall, TARE is a cost-effective short- and long-term therapy for the treatment of intermediate-advanced HCC.

**Keywords:** Carcinoma, Hepatocellular, Liver neoplasms, Radiotherapy, Yttrium-90, Cost, Systematic review

**Background**

Hepatocellular carcinoma (HCC) is the most common type of primary neoplasm of the liver, the sixth most common cancer, and the third leading cause of cancer death globally [1–3]. Liver cancer mortality accounts for 8.4% of all cancer deaths as of 2020 [3]. Patients with...
HCC have a significant humanistic and economic burden [4]. The annual direct costs for HCC patients, regardless of stage or treatment, ranged from $29,354.47 to $58,529.45 per patient in the United States. Also, indirect costs, such as reduced labour productivity, account for 10.8% ($49.1 million) of the overall annual cost (direct and indirect) of HCC [4].

The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used and most frequently recommended by scientific societies. This is the only system that relates the prognostic evaluation (based on 5 stages) to the different treatment options [1, 2]. The recently updated BCLC guideline recommends first-line treatments such as ablation, resection, transplantation, and transarterial radioembolization (TARE) as an option for patients in the early stages of the disease (BCLC-0, BCLC-A) or patients with a tumour size ≤ 8 cm who are not eligible for ablative techniques or resection. For the intermediate stage (BCLC-B), treatment options include transplantation for patients with well-defined nodules, transarterial chemoembolization (TACE) for patients with the preserved portal flow, and a defined tumour burden, or systemic therapy. For advanced-stage (BCLC-C), systemic therapy based on immunotherapy (a combination of atezolizumab and bevacizumab) is the main treatment option, and the second line option is tyrosine kinase inhibitors (TKIs). The treatment option in the terminal stage (BCLC-D) is palliative care [2].

The characteristics of the predominant arterial flow in patients with HCC have justified treatment with intraarterial therapies, such as TARE with yttrium 90 microspheres (90Y-TARE) as a therapeutic option for HCC. 90Y-TARE has demonstrated clinical efficacy as an alternative treatment for HCC in radiological response and shown adequate safety profile in patients in different stages of the disease [2]. In the early to intermediate stage of HCC, treatment with TARE prolongs the time to progression, which reduces the withdrawal from transplant or surgical resection waiting lists [5, 6]. In the advanced stage of HCC, available evidence (the SARAH [7] and SIRveNIB [8] studies) has determined 90Y-TARE presents an efficacy profile and survival benefit compared to sorafenib. Also, when the combination of 90Y-TARE with sorafenib was evaluated (the SORAMIC study [9]), the toxicity was no greater than sorafenib monotherapy [9].

A recent update of the European Society of Medical Oncology (ESMO) clinical practice guidelines recommends using 90Y-TARE as an alternative treatment in the early and intermediate stages of HCC. The guideline recommends using TARE in exceptional circumstances, patients with diseases limited to the liver or with a good liver function but for whom TACE or systemic therapy is not possible [10]. Two types of microspheres are known to include the beta 90Y emitter: glass (TheraSphere®) [11] and resin (SIR-Spheres®) microspheres [12]. Additionally, there is a third type based on holmium-166 (166Ho, QuiremSpheres®) [13] that was not included in the review due to limited clinical evidence, as indicated by the National Institute for Clinical Excellence (NICE) [14].

In addition to the clinical evidence, economic studies justify the use of new innovative therapies to optimize clinical outcomes in the context of the National Health System (NHS). Given the clinical benefits, limited economic resources, and greater emphasis placed on strengthening healthcare systems, there is an inherent need to generate economic evidence that enhances efficiency and prioritizes the available health resources [15]. Subsequently, a review of the economic benefits of 90Y-TARE in the HCC population needs to be established. Thus, this systematic review aimed to review and summarize the economic evaluations of the use of 90Y-TARE for the treatment of primary hepatic neoplasms, specifically HCC.

Methods

Search strategy and identification of studies

A systematic review of all economic evaluations on TARE for the treatment of HCC and published in Spanish and English was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology [16, 17].

The search strategy was designed using the Population, Intervention, Comparison, Outcomes (PICO) methodological. Also, Boolean operators without limitations and by these criteria: type of study, language, or year of publication (except the limitation of the search of communications to congresses to a 5-year period) were applied. A manual search of the citations of the initially selected articles was performed to identify potentially relevant additional publications. Key search terms included “Hepatocarcinoma”, “Hepatic neoplasms”, “Primary liver tumour”, “Primary liver tumours”, “Liver metastases”, “Secondary liver cancer”, “Hepatocellular carcinoma”, “HCC”, “Intrahepatic cholangiocarcinoma”, “Colorectal metastasis”, “Colorectal metastases”, “Colorectal carcinoma”, “Colorectal neoplasms”, “Colon”, “Neuroendocrine tumours”, “Yttrium-90”, “90Y”, “90-Y”, “Y-90”, “Y90”, “radioembolization”, “transarterial radioembolization”, “transcatheter arterial radioembolization”, “TARE”, “Selective internal radiation therapy”, “SIRT”, “sirtuins”, “TheraSphere”, “SIR-Spheres”, “SIR-Spheres”, “Cost”, “Cost utility”, “Cost benefit”, “Cost efficiency”, “Cost analysis”, “Budget impact” and “economic evaluation” (Additional file 1).

Databases were searched for all economic evaluations using 90Y-TARE for hepatic neoplasms published until May 2021. The following electronic databases
were explored: Medline through PubMed, Embase, The Cochrane Library, and MEDES; health technology assessment agencies, including the European Network for Health Technology Assessment (EUnetHTA), Network of Health Technology Assessment Agencies (REDETS), and the National Institute for Health and Care Excellence (NICE); and communications from international conferences, including the Cardiovascular and Interventional Radiological Society of Europe (CIRSE), European Conference on Interventional Oncology (ECIO), European Association of Nuclear Medicine (EANM), Society of Interventional Oncology (SIO), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), European Congress of Radiology (ECR) and Society of Nuclear Medicine and Molecular Imaging (SNMMI).

Inclusion and exclusion criteria
Studies that performed an economic evaluation of 90Y-TARE as a single treatment, as a combination treatment, or as part of a treatment sequence, regardless of the line of treatment, disease, or comparator, were considered. Studies that did not comply with the inclusion criteria were excluded. Economic evaluations that did not refer to 90Y-TARE as part of their development or evaluation were excluded. The inclusion and exclusion criteria were first applied to the titles and abstracts of the publications, and the full texts of the selected studies were reviewed.

Data extraction
Two independent authors (NE and IO) executed the search strategy and independently screened all studies. Possible discrepancies after the review were resolved through discussion and consensus among the authors. Data was extracted using a standardized template (reviewed by NE and IO) and the parameters collected include author/s, year and country of publication, type of economic evaluation defined as full (cost-effectiveness analysis [CEA], cost-utility analysis [CUA], and cost-minimization analysis [CMA]) and partial (cost-analysis [CA] and budget-impact-analysis [BIA]) economic evaluations, perspective, time horizon, type of model, evaluated comparative alternatives, patient characteristics, cost estimation, health outcomes, and cost-effectiveness results. Cost estimates were extracted as reported in the publication, converted to euros (€), and inflated to 2020 (€, 2020) using the reference exchange published by the European Central Bank. Inflation rates were derived from the Organisation for economic co-operation and development (OECD). To eliminate differences in the purchasing power across the different currencies and countries, a purchasing power parity factor (PPP) was performed to convert the costs to international dollars (US$ PPP) [18].

Quality assessment
The methodological quality of the included studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [19]. CHEERS includes a 24-item checklist and assigns a score of 1 if the explicit parameters contemplated in the studies were met (“YES”) and a score of 0 if they were not (“NO”). The full (CEA, CUA, and CMA) economic evaluations were evaluated against a 24-item checklist, and the partial (CA and BIA) were evaluated against a 20-item-checklist. This difference was due to the 4 items (items 9, 10, 12, and 21) not being applicable to the study type. An internal classification criterion was developed to assess and categorize the quality of included studies as low (<50%), medium (50% and 80%), and high (>80%). The final included studies were independently reviewed by co-authors (NE and IO).

Results
Study selection
The database search identified 423 studies records, of which 394 were excluded as duplicates or did not meet the inclusion criteria. A total of 29 full-text studies were screened, of which nine studies were excluded due to: metastasis of colorectal cancer (n = 7), metastasis of neuroendocrine tumours of hepatic origin (n = 1), and intrahepatic cholangiocarcinoma (n = 1). Twenty studies met the eligibility criteria. A flow diagram of records founds, screened, selected, and full-text studies evaluated is shown in Fig. 1.

Overview of the included studies
Eleven of the 20 studies (55%) were full economic evaluations [20–30] and nine studies (45%) were partial evaluations [31–39] (Table 1). Using the CHEERS checklist, the thirteen articles were of high quality (mean score of 94%), and seven abstracts/poster were of lower quality assessment (mean score of 56%), mainly because of the limited breadth of data.

Full economic evaluations (n = 11)
Characteristics of the included studies
Eleven publications were categorized as full economic evaluations (7 articles [20, 22, 23, 26, 28–30] and 4 congress communications [21, 24, 25, 27]). Seven were published from a European perspective [22–26, 28, 29] and four from the USA [20, 21, 27, 30]. The HCC population studied were mainly patients with HCC in the intermediate and advanced stages (8 of 11 publications: one BCLC-B [23], four BCLC-C [24, 25, 27, 30], and three grouped stages BCLC-B and BCLC-C [26, 28, 29]); one
publication grouped early and intermediate stages [22], and two publications grouped all three stages (BCLC-A, B and C) [20, 21].

Regarding the type of microsphere evaluated, three publications did not specify the type of microsphere [21, 26, 27]; two studies referred to TheraSphere® [22, 24], two studies referred to SIR-Spheres® [25, 29], three studies referred to both types (TheraSphere® and SIR-Spheres®) [20, 23, 30], and one study reported the use of three types of microspheres, including QuiremSpheres® [28]. The main comparators were TACE [20–23] and sorafenib [24–30], in addition to transarterial embolization (TAE) [22], TACE with doxorubicin-releasing particles (DEB-TACE) [22] and lenvatinib [28].

Regarding the pharmacoeconomic parameters, two of the eleven studies were CEA [20, 21], eight were ACU [22–24, 26–30], and one was a CMA [25]. Six of the eleven studies used a Markov modelling [22–24, 26, 27, 30], two studies utilized Monte-Carlo modelling [20, 21], two were survival-based models [28, 29], and one utilized decision trees modelling [28]. The cost minimisation study did not specify the type of model [25] used. The time horizon ranged from 5 years [20, 21, 30] to lifetime [23, 26, 27, 29]. The payer’s perspective predominated (10 of 11 publications), although one study focused on the social perspective [28]. The outcome measures included overall survival (OS), life month gained (LMG), life years gained (LYG), quality-adjusted life years (QALY), incremental cost-effectiveness ratios (ICERs), incremental cost-utility ratios (ICURs), willingness-to-pay (WTP), and incremental net monetary benefit (NMBs). The characteristics of the full economic evaluations are summarized in Table 2.

**TARE versus TACE**  TACE therapy was one of the comparators considered in four of the eleven studies [20–23];
| Section/item | Full economic evaluations | Partial economic evaluations |
|--------------|---------------------------|-------------------------------|
|              | USA | Italy | United Kingdom | USA | Italy | United Kingdom |
| Rostambeigi 2014 [20] | Rostambeigi 2014 [21] | Marqueen 2015 [24] | Palermo 2015 [25] | Rognoni 2017 [26] | Walton 2020 [28] | Manas 2021 [22] | Muszbek 2020 [29] | Hubert 2016 [32] | Ray 2019 [33] | Ljuboja 2015 [31] | Colombo 2018 [36] | Rognoni 2018 [37] | Muszbek 2019 [33] | Muszbek 2021 [34] | Pollock 2020 [39] |
| 1 Title | a | b | b | a | a | b | a | a | a | a | a | a | b | a | a | a | a | a | a |
| 2 Abstract | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3 Background and objectives | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 |
| 4 Study population, objectives, and subgroups | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 5 Setting and location | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 6 Perspective | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 7 Comparators | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 8 Time horizon | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 |
| 9 Discount rate | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 10 Selections of health outcomes | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 11 Measurement of effectiveness | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 12 Measurement and valuation of preference-based outcomes | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 13 Estimating resources and costs | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 14 Currency, price date, and conversion | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 15 Choice of model | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 16 Assumptions | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| 17 Analytic methods | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 18 Study parameters | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
Table 1 (continued)

| Section/item                  | Full economic evaluations | Partial economic evaluations |
|-------------------------------|---------------------------|-----------------------------|
|                               | USA                       | Italy                       | United Kingdom               | Canada | USA | Italy | United Kingdom |
| Rostambeigi 2014 [20]         | b                         | a                           | b                            | b      | a   | a     | b             |
| Rostambeigi 2014 [21]         | b                         | a                           | b                            | b      | a   | a     | b             |
| Parikh 2018 [27]              | b                         | a                           | b                            | b      | a   | a     | b             |
| Marqueen 2018 [30]            | b                         | a                           | b                            | b      | a   | a     | b             |
| Rognoni 2017 [26]             | b                         | a                           | b                            | b      | a   | a     | b             |
| Rognoni 2018 [23]             | b                         | a                           | b                            | b      | a   | a     | b             |
| Chaplin 2015 [24]             | b                         | a                           | b                            | b      | a   | a     | b             |
| Palmer 2017 [25]              | b                         | a                           | b                            | b      | a   | a     | b             |
| Walton 2020 [28]              | b                         | a                           | b                            | b      | a   | a     | b             |
| Manas 2021 [22]               | b                         | a                           | b                            | b      | a   | a     | b             |
| Muszbek 2020 [29]             | b                         | a                           | b                            | b      | a   | a     | b             |
| Hubert 2016 [32]              | b                         | a                           | b                            | b      | a   | a     | b             |
| Ray 2012 [34]                 | b                         | a                           | b                            | b      | a   | a     | b             |
| Ljubojca 2021 [35]            | b                         | a                           | b                            | b      | a   | a     | b             |
| Colombo 2015 [31]             | b                         | a                           | b                            | b      | a   | a     | b             |
| Lucà 2018 [36]                | b                         | a                           | b                            | b      | a   | a     | b             |
| Rognoni 2018 [37]             | b                         | a                           | b                            | b      | a   | a     | b             |
| Muszbek 2019 [33]             | b                         | a                           | b                            | b      | a   | a     | b             |
| Muszbek 2021 [38]             | b                         | a                           | b                            | b      | a   | a     | b             |
| Pollock 2020 [39]             | b                         | a                           | b                            | b      | a   | a     | b             |

19 Incremental costs and outcomes 1 0 1 1 1 1 0 1 1 1 1 0 1 1 1 1 1 1 1 0
20 Characterizing uncertainty 1 0 1 1 1 1 1 1 1 1 1 1 0 1 1 1 0 1 0 0
21 Characterizing heterogeneity 0 0 0 1 1 1 0 0 1 1 1 NA NA NA NA NA NA NA NA
22 Discussion 1 1 0 1 1 1 0 0 1 1 1 0 1 1 1 1 1 1 1 0
23 Source of funding 0 0 0 1 1 1 1 1 1 1 1 0 0 1 1 1 1 1 1 0
24 Conflicts of interest 1 0 1 1 1 0 0 1 1 1 1 0 0 1 1 1 1 0 0 0

Total 17 11 14 24 24 23 11 14 24 24 24 12 18 19 18 17 20 13 12 20

% (n) 71% 46% 58% 100% 100% 96% 46% 58% 100% 100% 100% 60% 90% 95% 90% 85% 100% 65% 60% 100%

a Article
b Oral communications and abstracts
two studies [20, 21] compared TARE with TACE, a third study [22] included TACE and two other comparators (TAE and DEB-TACE), and lastly publication reported TACE as part of a sequence of therapies (TARE, TACE and possibly sorafenib [TTS sequence] versus TARE plus sorafenib [TS sequence]) [23]. The stages of the evaluated patients were heterogeneous; early [20–22], intermediate [20–23], and advanced [20, 21] disease.

**TARE versus TKI** Seven studies [24–30] used systemic therapy as a comparator; 6 studies [24–27, 29, 30] reported only sorafenib as a comparator, and one study [28] included lenvatinib. Additionally, these seven studies evaluated patients with the intermediate-advanced disease.

**Results of the full economic evaluations**

The costs and health outcomes reported in the eleven studies were heterogeneous (Table 3).

**TARE versus TACE** Four studies reported higher costs (TARE versus TACE) [20–22], and this finding was independent of the patient’s BCLC-A, B, or C in three studies. The fourth publication presented a higher cost in TS sequence therapy than TTS sequence (47% of patients with sorafenib) in patients with the intermediate disease [23].

In one study, the health outcomes reported for patients in the intermediate stage showed a benefit of TARE over TACE in terms of LYG and QALY [22]. The study evaluated sequences of therapies, TTS (with optional sorafenib), and showed a greater incremental benefit than TS for LYG and QALYs [23]. Two studies [20, 21] reported the benefits for TARE in the advanced stage (BCLC-C), with lower benefits compared to TACE in the early and intermediate stages.

The ICERs of TARE versus TACE presented monthly (LMG) [20] and annual costs (LYG) [22]. Additionally, two studies [22, 23] presented ICUR results (£/QALY), and one study did not present any ratios [21]. For the early and intermediate stages of the disease, one study (Manas et al. [22]) presented an ICER of £ 12,833/LYG (£, 2020) (12,291 SUS PPP/LYG) and established the ICUR of TARE versus TACE at £ 17,279/QALY (£, 2020) (17,397 SUS PPP/QALY), with a 76.5% probability of being profitable considering a cost-effectiveness threshold of £ 20,000/QALY (€, 2020). In the intermediate stage, one study evaluated two treatment sequences and reported that TTS (with sorafenib in 47% of patients), including TARE, was the dominant strategy (i.e., it offered greater effectiveness with lower associated cost). When compared to TS, an 83% probability of being efficient based on a threshold of £ 50,000/QALY was estimated [23]. In the advanced stage, TARE was superior to TACE (ICER 8 $US PPP/LMG) when the intervention was evaluated in one lobe and obtained an ICER of $ 356/LMG ($) (2013) (399 $US PPP/LMG) when the two-lobe intervention was evaluated [20]. TARE was inferior (with lower effectiveness and higher associated cost) when used in the early and intermediate stages [20]. The second publication by Rostambeigi et al. [21] did not detail the calculation of ICERs.

**TARE versus TKI** Six [24–26, 28–30] of the seven studies compared TARE with sorafenib in patients with intermediate-advanced stage and reported lower costs for TARE (differences between 1454 to 46,982 $US PPP). However, Parikh et al. [27] evaluated a similar group of patients and reported conflicting cost results, a difference attributable to the source of the clinical trial efficacy parameters.

The benefits for health outcomes were greater for TARE [24–26, 29] than sorafenib in four of the seven studies (maximum QALY gained was 0.540 in BCLC-B, 0.27 in BCLC-C, and 0.601 in both stages); two studies [27, 28] showed greater health benefits for sorafenib (maximum QALY gained was 0.09), and one study [30] reported differing results depending on the source of clinical efficacy.

For patients with advanced-stage, TARE therapy was considered superior to sorafenib in five [24–26, 29, 30] of the seven studies when the SARAH RCT clinical parameters were used [7] as the source of clinical efficacy. The remaining two studies [27, 28] reported sorafenib was superior to TARE in patients with intermediate-advanced stage.

**Study quality reporting assessment**

Included studies categorized as full economic evaluations were appraised for their quality: six of the eleven studies (55%) [22, 23, 26, 28–30] had a high score when evaluated with the 24-item checklist (mean compliance: = 99%). Approximately, 27% (3 of 11) and 18% (2 of 11) of the studies had a moderate score (mean compliance: 66%) [20, 25, 27] and a low score (mean compliance of 46%) [21, 24], respectively.

**Partial economic evaluations (n = 9)**

**Characteristics of the included studies**

Nine publications were partial evaluations (6 articles [31, 34–37, 39] and 3 congress communications [32, 33, 38]). Six publications were from the European perspective [31, 33, 36–39]), two from the United States [34, 35], and one from the Canadian perspective [32]. The HCC population included patients with intermediate and advanced stages in seven of the nine studies [31–33, 36–39]; five
Table 2: Descriptive analysis of full economic evaluations for hepatocellular carcinoma

| Author, year, publication | Patient's characteristics | Treatments | Analysis type/ model | Perspective/ time horizon | Cost | Outcomes |
|---------------------------|--------------------------|------------|----------------------|--------------------------|------|----------|
| TARE versus TACE          |                          |            |                      |                          |      |          |
| Rostambeigi, 2014 [20]    | USA                      | BCLC-A, BCLC-B, BCLC-C | TARE versus TACE, TheraSphere<sup>™</sup> SIR-Spheres<sup>®</sup> | CEA/Monte Carlo | Payer/5 years | Direct cost (medical) | OS and incremental cost |
| Rostambeigi, 2014 [21]    | USA                      | BCLC-A, BCLC-B, BCLC-C | TARE versus TACE, TARE versus sorafenib | CEA/Monte Carlo | Payer/5 years | ND | OS, procedure-and complications costs, and incremental cost |
| Manas, 2021 [22]          | United Kingdom           | BCLC-A, BCLC-B | TARE versus TACE, TARE versus SIR-Spheres<sup>®</sup> | CEA/Monte Carlo | Payer/20 years | Direct cost (medical) | Downstaging<sup>a</sup>, LYG, QALY, ICUR (£/QALY) |
| Rognoni, 2018 [23]        | Italy                    | BCLC-B | TARE versus TACE, TARE versus sorafenib | CUA/Markov | Payer/lifetime | Direct cost (medical) | Cost, QALY, ICUR (£/QALY), WTP a £50,000/QALY |
| TARE versus TKIs          |                          |            |                      |                          |      |          |
| Chaplin, 2015 [24]        | United Kingdom           | BCLC-C<sup>b</sup> | TARE versus sorafenib | TheraSphere<sup>™</sup> SIR-Spheres<sup>®</sup> | CUA/Markov | Payer/10 years | ND | Cost, TTP, SG y ICUR (£/QALY), |
| Palmer, 2017 [25]         | United Kingdom           | BCLC-C | TARE versus sorafenib | SIR-Spheres<sup>®</sup> | Cost-minimization analysis | Payer/ND | Direct cost (medical) | Cost (£), principals factors cost, QALY |
| Rognoni, 2017 [26]        | Italy                    | BCLC-B, BCLC-C | TARE versus sorafenib | CUA/Markov | Paye lifetime | Direct cost (medical) | Cost, QALY, ICUR (£/QALY), WTP a €38,500 (–€30,000)/QALY ICUR (£/QALY) |
| Parikh, 2018 [27]         | United Kingdom           | BCLC-C<sup>c</sup> | TARE versus sorafenib | CUA/Markov | Paye lifetime | Direct cost (medical) | Cost, QALY, ICUR (£/QALY), |
| Walton, 2020 [28]         | United Kingdom           | BCLC-B, BCLC-C (Child–Pugh A and ineligible a CTT) | TARE versus TKIs, TheraSphere<sup>™</sup> SIR-Spheres<sup>®</sup> QuiremSpheres<sup>®</sup> | CUA/Partitioned survival model and decision tree | Paye and social/10 years | Direct and indirect cost | ICUR (£/QALY), incremental net monetary (NMB) |
| Muszbek, 2020–21 [29]     | United Kingdom           | BCLC-B<sup>d</sup>, BCLC-C<sup>d</sup> | TARE versus sorafenib | SIR-Spheres<sup>®</sup> | CUA/Partitioned survival model | Payer/lifetime | Direct cost (medical) | Cost, LYG, QALY, ICUR (£/QALY), WTP a £20,000, INB |
| Marqueen, 2021 [30]       | United Kingdom           | BCLC-C | TARE versus sorafenib | TheraSphere<sup>™</sup> SIR-Spheres<sup>®</sup> | CUA/Markov | Payer/5 years | Direct cost (medical) | Cost, QALY, ICUR (£/QALY), WTP a $100,000/QALY o $200,000/QALY |

BCLC Barcelona Clinic Liver Cancer classification, CEA cost-effectiveness analysis, CTT conventional transarterial therapy, CUA cost-utility analysis, DEB-TACE doxorubicin eluting bead transarterial chemoembolization, HCC hepatocellular carcinoma, ICER cost-effectiveness incremental ratio, ICUR incremental cost-utility ratio, LYG life-years gained, ND no data, OS overall survival, QALY quality-adjusted life years, TACE transarterial chemoembolization, TAE transarterial embo  

<sup>a</sup> Downstaging: decrease in tumour burden that allows patients to be rescued for treatments such as liver transplantation  
<sup>b</sup> Assumed clinical characteristics of two separate RCTs: TheraSphere (Salem et al. 2011) and sorafenib (Phase III SHARP RCT-Llovet et al. 2018)  
<sup>c</sup> Patients with unresectable HCC and Child–Pugh class A cirrhosis  
<sup>d</sup> BCLC-B o BCLC-C (not appropriate to TACE); HCC with low tumour burden (< 25%) and good liver function (albumin–bilirubin [ALBI] grade 1)
studies [31, 32, 36, 37, 39] reported the inclusion of patients as BCLC-B or BCLC-C, and two studies defined the intermediate or advanced stage as unresectable HCC (Muszbek et al.) [33, 38]. Of the two remaining studies, one (Ray et al.) [34] described HCC in a way that can be assumed to correspond to an early BCLC-A stage (male patient 65 years old with unresectable solitary HCC of 3 cm isolated in 1 lobe, not suitable for transplantation), and the second study (Ljuboja et al.) [35] did not define the population.

Three of the nine studies evaluated SIR-Spheres® [31, 35, 39], one included TheraSphere® [32], three considered both TheraSphere® and SIR-Spheres® [36–38], and two did not specify the type of microsphere evaluated. The comparators were TACE [31, 32, 34, 35, 38], ablative therapy [34, 35] and systemic therapies (sorafenib [31, 33, 36, 37, 39] and lenvatinib [39]).

Regarding the time horizon, six studies were CA [31, 33–36, 38] and reported time horizons ranging from 1 month to 2 years. The remaining three studies were BIA [32, 37, 39] and reported time horizons ranging from 3 years to a lifetime horizon. The payer’s perspective was most frequently used (100%); with the exception of one study that considered the social perspective [38]. The HCC stages of the study population, the comparators, and the outcome measures considered in the partial economic evaluations are highlighted in Table 4.

**TARE versus TACE** Treatment with TACE was considered as a comparator in five [31–35] of the nine studies. Four of five studies reported the stages of HCC (early [34], intermediate, and/or advanced stages [31–33]). In studies of intermediate-stage HCC, one study compared only TACE versus TARE [33], two studies [31, 32] included sorafenib in addition to TACE, and two studies [34, 35] reported including radiofrequency ablation (RFA).

**TARE versus TKI** Four studies [36–39] used systemic therapy as a comparator: three [36–38] reported sorafenib as a comparator, while one [39] publication also included lenvatinib in the assessment. All four studies considered patients in the intermediate-advanced stage.

**Results of the partial economic evaluations** The costs and health outcomes were heterogeneous, mainly due to the type of economic evaluation performed and the grouping of patients with the different stages of the disease. Aggregated data for intermediate and advanced stages (BCLC-B combined with BCLC-C) were reported in five studies [31, 32, 36, 37, 39]. Data differentiated by HCC stages was reported in three studies (BCLC-A [34], BCLC-B [33], and BCLC-C [38]), and one publication [35] did not report the stage of disease (Table 5).

**TARE versus TACE** Four CAs [31, 33–35] and one BIA [32] compared TARE versus TACE. The CA studies mostly indicated higher treatment costs (range: 11,572–42,368 $US-PPP) with TARE than with TACE (range: 9577–35,855 $US PPP) treatments [31, 33–35], ablative therapy (range: 3790–11,135 $US PPP) [34, 35] or sorafenib (12,460 $US PPP) [31]. However, one study (Muszbek et al.) [33] reported similar costs for TARE and TACE regardless of whether the costs were obtained from the official source (the NHS) or via a micro-costing approach [40]. Furthermore, Colombo et al. [31] highlighted the omission of the costs of unplanned hospitalization and adverse events (AEs) from their assessment. However, Ray et al. [34] established that in the early stage (based on a hypothetical cohort of patients older than 65 years) TARE had lower costs than TACE in more than one-third of the simulations of the evaluated scenarios. The BIA [32] study found cost savings with TARE during 3 consecutive years (savings of 40,699; 64,454, and 82,437 $US PPP at years 1, 2, and 3, respectively) of evaluation in a simulated population of 200 patients in a Canadian hospital.

No health outcomes were reported in the five studies that compared TARE with TACE. However, Colombo et al. [31] evaluated the treatment patterns in four centres in Italy and found TACE as the treatment of choice for intermediate HCC and sorafenib as the most commonly used first-line treatment for advanced HCC.

**TARE versus TKI** The cost comparisons of TARE versus TKI (2 CA [36, 38] and 2 BIA [37, 39]) reported dissimilar results for TARE in patients with intermediate and/or advanced-stage disease. The CA by Lucà et al. [36] reported significantly lower cost for TARE (18,096 $US PPP) than sorafenib subgroup (28,520 $US PPP). Besides, the CA by Muszbek et al. [38] identified significant changes in the clinical practices for the management of advanced HCC patients, showing a 54 to 79% decrease in monthly costs compared to previous surveys. The BIA published by Rognoni et al. [37] from the Italian Health perspective was estimated to save € 7 million with the progressive increase in the use of TARE (from 20 to 50%) instead of sorafenib over 5 years. The second BIA (Pollock et al.) [39] evaluated TARE versus without TARE in four European countries (Spain, France, Italy, and the United Kingdom) and reported the use of TARE in Spain would generate a cost savings of 26.5% over a 3-year period.

Within the type of resources used, the pharmacological cost, the work-up, the number of procedures and the management of AEs were identified as cost drivers for TARE and TKIs. Only three [36, 37, 39] of the four studies provided health outcomes in the survival rates [36], the number of events (deaths or hospitalizations) avoided [37], incremental LYG [39], and the proportion
### Table 3
Results of full economic evaluations for hepatocellular carcinoma

| Author, year publication (year cost) | Stage | Comparators | Costs | Outcome’s health | Ratio cost/outcome’s health |
|-------------------------------------|-------|-------------|-------|------------------|-----------------------------|
|                                     |       |             | Original cost | Adjusted to $US PPP [18] | LYG | QALY | ICER $/LYG | ICUR $/QALY | ICER $US PPP/LYG | ICUR $US PPP/QALY |
| Rostambeigi, 2014 [20] (2013)a     | BCLC-A | TACE        | $2094  | 2347             | 39.5 | ND   | TACE versus ND | $33/LMG | ND | TACE versus ND |
|                                     |       | TARE (I)    | $1770  | 1311             | 29.7 | ND   | TACE versus ND | $37/LMG | ND | TACE versus ND |
|                                     |       | TARE (II)   | $2688  | 3013             | 29.7 | ND   | TACE versus ND | $61/LMG | ND | TACE versus ND |
|                                     |       |             | Δ = $ 324 | Δ − 363         | Δ 9.8 | ND   | TACE versus ND | [− $ 732 LYG]* | [− $ 820/LYG]* | TACE versus ND |
|                                     | BCLC-B | TACE        | $2326  | 2607             | 22.9 | ND   | TACE versus TACE | $67/LMG | ND | TACE versus TACE |
|                                     |       | TARE (I)    | $2789  | 3126             | 16.0 | ND   | TACE versus TACE | [− $ 804 LYG]* | [− $ 901/LYG]* | TACE versus TACE |
|                                     |       | TARE (II)   | $4240  | 4753             | 16.0 | ND   | TACE versus TACE | $277/LMG | ND | TACE versus TACE |
|                                     |       |             | Δ = $ 463 | Δ 1914         | Δ 6.9 | ND   | TACE versus TACE | [− $ 3324 LYG]* | [− $ 3726/LYG]* | TACE versus TACE |
|                                     | BCLC-C | TACE        | $2679  | 3003             | 13.3 | ND   | TACE versus TACE | $7/LMG | ND | TACE versus TACE |
|                                     |       | TARE (I)    | $2652  | 2973             | 17.1 | ND   | TACE versus TACE | [Dominant]* | [Dominant]* | TACE versus TACE |
|                                     |       | TARE (II)   | $4031  | 4518             | 17.1 | ND   | TACE versus TACE | $356/LMG | ND | TACE versus TACE |
|                                     |       |             | Δ = $ 51914 | Δ 51352       | Δ 3.8 | ND   | TACE versus TACE | [− $ 4272 LYG]* | [− $ 4788/LYG]* | TACE versus TACE |
| Rostambeigi, 2014 [21] (2013)a     | BCLC-A, BCLC-B, and BCLC-C | TACE | $17,000 | 19,055 | ND | ND | ND | ND | TACE versus TACE | TACE versus TACE |
|                                     |       | TARE        | $49,000 | 54,924 | ND | ND | ND | ND | TACE versus TACE | TACE versus TACE |
| Manas, 2021 [22] (2020)            | BCLC-C | TARE-TACE   | Δ $500  | Δ 560  | 3.05 | 2.24 | TARE versus TARE | £ 12,808 | £ 17,279 | TARE versus TARE |
|                                     | BCLC-A, BCLC-B | TARE (1st) | £ 49,583 | £ 49,921 | 2.14 | 1.57 | TARE versus TARE | £ 17,059 | £ 23,020 | TARE versus TARE |
|                                     |       | TACE        | £ 37,038 | £ 37,291 | 2.14 | 1.57 | TARE versus TARE | £ 13,833 | £ 17,300 | TARE versus TARE |
|                                     |       | DEB-TACE    | £ 33,206 | £ 33,432 | 2.14 | 1.57 | TARE versus TARE | £ 17,291 | £ 23,177 | TARE versus TARE |
|                                     |       | TAE         | £ 37,015 | £ 37,267 | 2.14 | 1.57 | TARE versus TARE | £ 17,291 | £ 23,177 | TARE versus TARE |

WTP (£20,000/QALY): 15.9% (TARE vs. DEB-TACE) to 76.8% (TARE vs. TACE)/WTP (£30,000/QALY): 88.6% (TARE vs. DEB-TACE) to 98.7% (TARE vs. TAE)
| Author, year publication (year cost) | Stage | Comparators | Costs | Outcome's health | Ratio cost/outcome's health |
|------------------------------------|-------|-------------|-------|------------------|----------------------------|
|                                    |       |             | Original cost | Adjusted to $US PPP [18] | LYG | QALY | ICER €/LYG | ICUR €/QALY | ICER $US PPP/LYG | ICUR $US PPP/QALY |
| Rognoni, 2018 [23] (2016)          | BCLC-B | TTS (47% sorafenib) | € 36,509 | 37,137 | 3.494 | 1.385 | – | TTS Dominant |
|                                    |       | TS | € 42,812 | 43,591 | 2.361 | 0.937 | – | – |
|                                    |       | Δ – € 6303 | Δ – 6418 | Δ – 1.133 | Δ 0448 | – | – |
|                                    |       | TTS WTP ($50,000/QALY): 83% | – | – |
| Chaplin, 2015 [24] (2015)a          | BCLC-C | TARE (T™) | £ 21,441 | 22,763 | ND | 1.12 | ND | TARE Dominant |
|                                    |       | Sorafenib | £ 34,050 | 36,150 | ND | 0.85 | ND | ND |
|                                    |       | Δ – £ 12,609 | Δ – 13,387 | Δ | – 0.27 | – | – |
|                                    |       | TARE versus sorafenib | – | – |
|                                    |       | TTP (months): 6.2 versus 4.9 | – | – |
|                                    |       | OS (months): 13.8 versus 9.7 | – | – |
| Palmer, 2017 [25] (2017)            | BCLC-C | TARE (S®) | £ 8909 in favour of TARE | 9374 favour of TARE | ND | Δ 000.79 in favour of TARE | ND | TARE cost-effective |
|                                    |       | Sorafenib | – | – |

Cost drivers: workup and administrations for TARE and duration of treatment for sorafenib

| Rognoni, 2017 [26] (2015)          | BCLC-B | TARE | € 31,071 | 31,644 | 2.531 | 1.178 | TARE versus TARE versus TARE versus TARE versus |
|                                    |       | Sorafenib | € 29,289 | 29,829 | 1.575 | 0.638 | 1865 | 3302 | 1899 | 3363 |
|                                    |       | Δ – € 1782 | Δ 1815 | Δ 0.956 | Δ 0540 | TARE versus TARE versus TARE versus TARE versus |
|                                    |       | WTP ($38500/QALY): 99.2% | – | – |
|                                    | BCLC-C | TARE | € 21,961 | 22,366 | 1.445 | 0.639 | ND | TARE Dominant |
|                                    |       | Sorafenib | € 30,750 | 31,317 | 1.306 | 0.568 | – | ND |
|                                    |       | Δ – € 8788 | Δ – 8950 | Δ 0.139 | Δ 0071 | – | – |
|                                    |       | WTP ($38,500/QALY): 98.2% | – | – |
| Author, year publication (year cost) | Stage | Comparators | Costs | Outcome's health | Ratio cost/outcome's health |
|-------------------------------------|-------|-------------|-------|-----------------|---------------------------|
|                                     |       |             | Original cost | Adjusted to $US PPP [18] | LYG | QALY | ICER $/LYG | ICUR $/QALY | ICER $US PPP/LYG | ICUR $US PPP/QALY |
| Parikh, 2018 [27] (2018)³ | BCLC-C | Pooled data | $61,897 | $65,295 | ND | 0.81 | $19,534 | ND | 20,606 |
|                                    |       | TARE        | $63,313 | $66,789 | ND | 0.88 |          |          |          |
|                                    |       | Sorafenib   | $63,131 | $66,789 | ND | 0.88 |          |          |          |
|                                    |       | Δ − $1416   | $1416  | $1494  | ND | Δ − 0.07 |          |          |          |
| CT SARAH                           |       | TARE        | $64,805 | $68,363 | ND | 0.78 |          |          |          |
|                                    |       | Sorafenib   | $63,216 | $66,687 | ND | 0.87 | Sorafenib Dominant | Sorafenib Dominant |
|                                    |       | Δ $1589     | $1589  | $1676  | ND | Δ − 0.09 |          |          |          |
| CT SiReNIB                         |       | TARE        | $57,473 | $60,628 | ND | 0.84 | $107,927 | ND | 113,852 |
|                                    |       | Sorafenib   | $63,447 | $66,930 | ND | 0.90 |          |          |          |
|                                    |       | Δ − $5974   | $5974  | $6302  | ND | Δ − 0.06 |          |          |          |
| Walton, 2020 [28] (2017/2018)     | BCLC-B and BCLC-C | Deterministic | TARE (T™) | £29,888 | £30,922 | 1.110 | 0.764 | NMB ($) | TARE (T™) versus NMB ($) | TARE (T™) versus NMB ($) |
|                                    |       | TARE (S§)   | £30,107 | £31,148 | 1.110 | 0.764 | −218 | +Costly | 226 | +Costly |
|                                    |       | TARE (Q®)   | £36,503 | £37,766 | 1.110 | 0.764 | −664 | +Costly | −6843 | +Costly |
|                                    |       | Lenvatinib  | £30,005 | £31,043 | 1.243 | 0.841 | 97 | 28,728 | 100 | 29,722 |
|                                    |       | Sorafenib   | £32,082 | £33,192 | 1.183 | 0.805 | 1090 | 2911 | 3012 |
|                                    |       | Δ − £5974   | £5974  | £6302  | ND | Δ − 0.06 |          |          |          |
|                                    |       | Probabilistic | TARE (T™) | £30,014 | £31,052 | 1.111 | 0.765 | NMB ($) | TARE (T™) versus NMB ($) | TARE (T™) versus NMB ($) |
|                                    |       | TARE (S§)   | £30,196 | £31,240 | 1.111 | 0.765 | −2154 | Dominated | −2229 | Dominated |
|                                    |       | TARE (Q®)   | £36,613 | £37,879 | 1.111 | 0.765 | −2323 | Dominated | −2403 | Dominated |
|                                    |       | Lenvatinib  | £29,658 | £30,684 | 1.244 | 0.841 | −2306 | 174,320 | −2366 | 180,349 |
|                                    |       | Sorafenib   | £32,444 | £33,566 | 1.202 | 0.825 | −8741 | Dominated | −9043 | Dominated |
| Author, year publication (year cost) | Stage | Comparators |
|-------------------------------------|-------|--------------|
| Muszbek, 2020–21 [29] (2018/2019) BCLC-B and BCLC-C | TARE (S®) | £ 29,530 30,085 2.637 1.982 TARE Dominant TARE Dominant |
| Sorafenib | £ 30,957 31,539 1.890 1.381 ND | TARE (S®) \(\Delta - £ 1427\) \(\Delta - 1454\) \(\Delta 0.748\) \(\Delta 0.0601\) TARE Dominant \(\Delta - £ 2374\) ND \(\Delta - 2719\) |
| Marqueen, 2021 [30] (2016/2017) BCLC-C | Pooled data | Sorafenib | £ 78,859 84,868 0.88 Sorafenib versus Sorafenib versus |
| TARE | £ 58,397 62,847 0.87 | ND | $ 1,280,224 ND 1,377,777 |
| \(\Delta £ 20,462\) \(\Delta £ 22,061\) \(\Delta 0.02\) | Sorafenib WTP ($200,000/QALY): 1% |
| CT SARAH | Sorafenib | £ 72,899 78,454 0.83 Sorafenib versus Sorafenib versus |
| TARE | £ 66,000 71,890 0.84 | ND | TARE dominant ND TARE dominant |
| \(\Delta £ 6099\) \(\Delta £ 6564\) \(\Delta 0.01\) | Sorafenib versus Sorafenib versus |
| CT SiRveNIB | Sorafenib | £ 89,806 96,649 0.91 Sorafenib versus Sorafenib versus |
| TARE | £ 46,151 49,668 0.86 | ND | $ 753,412 ND 810,822 |
| \(\Delta £ 43,655\) \(\Delta £ 46,982\) \(\Delta 0.06\) | Sorafenib versus Sorafenib versus |

BC base case, BCLC Barcelona Clinic Liver Cancer classification, CT clinical trial, DEB-TACE doxorubicin eluting bead transarterial chemoembolization, HCC hepatocellular carcinoma, O confidence interval, ICER cost-effectiveness incremental ratio, ICUR incremental cost-utility ratio, INB incremental net benefit, LYG life years gained, LMG life months gained, ND no data, NMB net monetary benefit, OS overall survival, QALY quality-adjusted life years, TACE transarterial chemoembolization, TAE transarterial embolization, TARE transarterial radioembolization, TAE (II) unilobar, TARE (IIb) bilobar, TARE (S®) transarterial radioembolization with SIR-Spheres®, TARE (T™) transarterial radioembolization with TheraSphere™, TARE(Q®) transarterial radioembolization with QuiremSpheres®, TKI tyrosine kinase inhibitors, TTP time to progression, TTS sequencyTARE, TACE and optional sorafenib (sorafenib was administered on 47% of patients), WTP willingness-to-pay

* Determined by calculations assuming a year has 12 months
* Year of unspecified cost, estimated from the proposed cost reference sources
* The procedure is repeated every 10 months until 5 years
* Number of patients downstaged (out of 1000 patients): 842 TheraSphere™ and 452 TACE, DEB-TACE and TAE
* TARE allows downstaging for subsequent treatment with curative intent: 13.5% TARE versus 2.1% sorafenib (base case considering SARAH study data), and 5.1 TARE versus 1.4% sorafenib in the ITT population
| Author, year, publication type and country | Patient's characteristics | Treatments | Microspheres | Analyses type/characteristics, source, and costs | Perspective/ time horizon | Outcomes |
|------------------------------------------|---------------------------|------------|--------------|-------------------------------------------------|--------------------------|----------|
| Ray, 2012 [34] Original article USA     | BCLC-A<sup>a</sup>        | TARE versus TACE versus RFA | ND           | CA/ Multiple scenarios for Medicare using a decision tree and Monte Carlo model  
Direct healthcare costs: Medicare reimbursement for hospital and repeat procedures comes from the literature | Payer/ 2 years | Estimated cost of each procedure  
Repetition rate to consider a strategy as optimal |
| Ljuboja, 2021 [35] Original article USA | ND                        | TARE versus TACE versus ablative therapy | SIR-Spheres® | CA/TDABC (retrospective and prospective) carried out in a tertiary care hospital  
Direct health costs: In-hospital costs (from admission to discharge) of the treatments evaluated | Payer/1 year | Estimated cost of each procedure  
(estimate of 4 patients per alternative evaluated)  
Cost drivers |
| Colombo, 2015 [31] Original article Italy | BCLC-B and BCLC-C         | TARE versus TACE versus Sorafenib | SIR-Spheres® | CA/Retrospective in 4 centres.  
Data from 137 patients [BCLC-B (n = 80) and BCLC-C (n = 57)] out of a total of 285  
Direct healthcare costs: Cost of treatments (TARE, TACE and sorafenib) and associated drugs, diagnostic and laboratory tests, administration (consumables and professionals) and monitoring (visits) | Payer/ 1 year | Estimated cost of each procedure  
Average number of treatments per year |
| Muszbek, 2019 [33] Communication at congress United Kingdom | BCLC-B<sup>b</sup>      | TARE versus TACE | TheraSphere<sup>™</sup> SIR-Spheres® | CA/Multiple scenarios of resource consumption (retrospective and expert) and costs (reference costs or microcosting)  
Direct health costs: Cost of treatments, administration, management of AE and hospitalisation costs | Payer/ ND | Estimated cost range for each alternative  
Cost drivers |
| Hubert, 2016 [32] Communication at congress Canada | BCLC-B BCLC-C<sup>c</sup> | TARE versus TACE<sup>e</sup>  
TARE versus sorafenib | TheraSphere<sup>™</sup> | BIA/Epidemiological of a hospital  
Direct healthcare costs: Cost of treatments (pharmacological and devices), administration (key cost drivers) and management of AE | Payer/ 3 years | Annual (reimbursement) cost per alternative for a hospital treating 200 HCC patients annually |
### Table 4 (continued)

| Author, year, publication type and country | Patient’s characteristics | Treatments | Microspheres | Analyses type/characteristics, source, and costs | Perspective/time horizon | Outcomes |
|-------------------------------------------|--------------------------|------------|--------------|-------------------------------------------------|--------------------------|----------|
| Lucà, 2017 [36] Original article Italy    | BCLC-B                   | TARE versus sorafenib | TheraSphere™, SIR-Spheres® | CA/Retrospective observational study (one centre), comparing a subgroup of sorafenib (SOR3)\(^d\) with the TARE group  Direct healthcare costs: Cost of treatments (drug and devices), administration, monitoring and hospitalisation costs  | Payer/272 days          | Estimated cost of each procedure OS rates |
| Muszbek, 2019 [38] Communication at congress United Kingdom | BCLC-C\(^b\) | TARE versus sorafenib | ND | CA/Costs by health status obtained from literature, registers, and surveys (5 experts)  Direct health costs (historical and current): administration, monitoring, hospitalisation costs  | Payer y social/1 month | Comparative cost of resources by state of health between 2007 and 2015 |
| Rognoni, 2018 [37] Original article Italy | BCLC-B (Post-TACE) BCLC-C\(^c\) | TARE versus sorafenib | TheraSphere™, SIR-Spheres® | BIA/Markov  Source: Three Italians oncology centres  Direct healthcare costs: Cost of treatments (pharmacological and devices), administration, monitoring, hospitalisation costs and AE management and second-line treatments  | Payer/5 years and lifetime | Estimated cost of each procedure Economic impact  No. of deaths avoided No. of hospitalisations |
| Pollock, 2020 [39] Original article United Kingdom | BCLC-B (not eligible to TACE) BCLC-C (eligible) | TARE versus TKIs [95% sorafenib/ lenvatinib 5%] | SIR-Spheres® | BIA/Markov  Source: CT SARAH  Direct healthcare costs: Cost of treatments (pharmacological and devices), administration, monitoring, hospitalisation costs and AE management and second-line treatments  | Payer/3 years | Economic impact in Spain, France, Italy and United Kingdom |

\(^a\) AE adverse events, BIA budget impact analysis, CA cost analysis, CT clinical trial, ND no data, RFA radiofrequency ablation, SOR subgroup of patients with sorafenib, TACE transarterial chemoembolization, TAE transarterial embolization, TARE transarterial radioembolization, TKI tyrosine kinase inhibitors, TDABC time-drive activity-based costing
\(^b\) BCLC classification not specified, stage interpreted according to patient type characteristics (3 cm isolated HCC in one lobe)
\(^c\) Unspecified BCLC classification, stage interpreted according to pathology and comparator characteristics (TACE-eligible unresectable HCC). BCLC-C stage with and without portal vein thrombosis
\(^d\) Patient flow: total patients treated with sorafenib (SOR) were divided into two groups according to treatment duration (SOR1 ≤ 2 months, SOR2 > 2 months). SOR2 patients who met criteria for TARE treatment (unilobar HCC, no metastases) were reassigned to SOR3 (24 patients: 54% BCLC-B, 46% BCLC-C)
\(^e\) Consider conventional TACE or DEB-TACE
Table 5  Results of partial economic evaluations for hepatocellular carcinoma

| Author, year publication (year cost) | Stage | Comparators | Costs | Resource consumption and health outcomes |
|-------------------------------------|-------|-------------|-------|------------------------------------------|
|                                     |       |             | Original cost | Adjusted to SUS PPP [18] |                                    |
|                                     |       |             | Decision tree | Monte Carlo | Decision tree | Monte Carlo |
|                                     |       |             | $ 35,618 ($35,629 ± 9930) | $ 30,143 ($30,107 ± 19,109) | $ 9361 ($9362 ± 2535) | $ 35,618 ($35,629 ± 9930) | $ 30,143 ($30,107 ± 19,109) | $ 9361 ($9362 ± 2535) |
| TARE                                | BCLC-A |             | $ 1656 (8%) | $ 371 (2%) | $ 18,791 (90%) | $ 1676 | 376 | 19,022 |
| TACE                                | ND    | Total cost/patient | $ 20,818 (100%) | $ 1656 (8%) | $ 371 (2%) | $ 18,791 (90%) | $ 1676 | 376 | 19,022 |
| RFA                                 |       | Equipment    | $ 1947 (38%) | $ 212 (4%) | $ 2930 (58%) | 1971 | 215 | 2966 |
|                                     |       | Consumables  | $ 1114 (30%) | $ 205 (5%) | $ 2425 (65%) | 3837 | 208 | 2455 |
| TARE                                | BCLC-B | Annual cost/patient | £ 12,026–£ 21,425 | £ 12,442–22,166 | £ 11,185–£ 15,636 | £ 9257–£ 14,167 | £ 12,442–22,166 | £ 11,185–£ 15,636 |
| TACE                                | BCLC-C | Monthly cost/patient | £ 2009 (€ 17,753) | £ 5410 (€ 17,753) | £ 2009 (€ 17,753) | £ 5410 (€ 17,753) | £ 2009 (€ 17,753) | £ 5410 (€ 17,753) |
| Sorafenib                            |       | Annual cost/patient | £ 26,629 | £ 13,687 | £ 24,60 | £ 24,60 |
|                                     |       | Monthly cost/patient | £ 5,195 | £ 2,648 | £ 7,172 | £ 7,172 |
|                                     |       | Average number of treatments per year: | TARE 1.50 | TACE 2.53 | Sorafenib 6.08 |

The total number of repetitions to considered TARE an optimal strategy:
- TARE repetition rate: 1–10%
- TACE repetition rate: 82–77%
TARE would be an optimal strategy versus TACE in 33.4 to 36.4% of cases.

Consumables reported for the highest cost in all three procedures, with a single consumable accounting for more than 30% of the total cost of each procedure.
Table 5 (continued)

| Author, year publication (year cost) | Stage | Comparators | Costs | Adjusted to $US PPP [18] | Resource consumption and health outcomes |
|-------------------------------------|-------|-------------|-------|--------------------------|----------------------------------------|
| Hubert, 2016 [32] (2016)b          | BCLC-B BCLC-C | TARE, TACE and sorafenib | BIA HCC patients (n = 200 annual)<!-- TARE saved: --> | Year 1: $37,000 Year 2: $55,000 Year 3: $75,000 TARE was associated with cost savings and reduced use of hospital resources | Costs at 3rd year (n = 200 patients) were device acquisition ($207,000 [227,526 $US PPP]), administration cost savings of $281,000 (308,864 $US PPP) and AE management savings of $1000 (1099 $US PPP) |
| Lucà, 2017 [36] (2017)b            | BCLC-B BCLC-C | Total cost per patient | TARE €17,761 Sorafenib (SOR3) €27,992 | 18,096 28,520 | At 2 years, the survival rate of TARE versus sorafenib SOR3 was significantly higher (p = 0.012). There was no significant difference in OS in the Kaplan–Meier analysis of SOR3 and TARE (p = 0.446) |

TARE cost was significantly lower than sorafenib (p = 0.028). Limitations: small number of patients (n = 24) and the lack of randomisation in treatment type assignment.
| Author, year publication (year cost) | Stage | Comparators | Costs | Adjusted to SUS PPP [18] |
|-------------------------------------|-------|-------------|-------|-------------------------|
|                                    |       |             | Original cost |                                    |
|                                    |       |             | Health status cost per month |                                    |
|                                    |       |             | Pre | Progression | Post | Health status cost per month | Pre | Progression | Post |
|                                    |       |             | € 246 | € 208 | € 499 | 251 | 212 | 508 |
|                                    |       | TARE        | £ 246 | £ 208 | £ 499 |
|                                    |       | TKI         | £ 287 | £ 208 | £ 287 |
|                                    |       |             | Cost drivers in pre- and post-progression |                                    |
|                                    |       |             | 2018/2019: diagnostic procedures (53%) and medical consultations (45%) |                                    |
|                                    |       |             | 2007/2015: hospitalisations (41%) and social care (42%) |                                    |
|                                    |       |             |                                    |                                    |
| Muszbek, 2019 [38] (2018/2019)    | BCLC-CΔ | BCLC-CΔ     | € 33,040 | € 28,003 |                                    |
|                                    |       | TARE        | € 33,040 | € 28,003 |
|                                    |       | Sorafenib   | € 29,935 | € 29,716 |
|                                    |       | BCLC-C      | € 22,526 | € 21,456 |
|                                    |       | Sorafenib   | € 31,526 | € 31,430 |
|                                    |       |             |                                    |                                    |
| Rognoni, 2018 [37] (2018)         | BCLC-B | BCLC-B      | € 30,139,457 | € 28,461,565 |                                    |
|                                    |       | TARE        | € 30,139,457 |                                    |
|                                    |       | Sorafenib   | € 29,633,336 |                                    |
|                                    |       | BCLC-C      | € 29,239,463 |                                    |
|                                    |       | Sorafenib   | € 28,685,595 |                                    |
|                                    |       | BIA considering increased use of TARE (stage BCLC-B and C): |                                    |
|                                    |       | Year 0 (TARE 20%, SOR 80%): | € 30,139,457 | € 28,461,565 |
|                                    |       | Year 1 (TARE 30%, SOR 70%): | € 29,633,336 | € 29,950,035 |
|                                    |       | Year 2 (TARE 30%, SOR 70%): | € 29,239,463 | € 29,551,953 |
|                                    |       | Year 3 (TARE 40%, SOR 60%): | € 28,685,595 | € 28,992,165 |
|                                    |       | Year 4 (TARE 40%, SOR 60%): | € 28,311,921 | € 28,614,498 |
|                                    |       | Year 5 (TARE 50%, SOR 50%): | € 27,793,820 | € 28,090,860 |

Cost drivers in pre- and post-progression:
2018/2019: diagnostic procedures (53%) and medical consultations (45%)
2007/2015: hospitalisations (41%) and social care (42%)

Costs 2007/2015 versus costs 2018/2019:
Monthly cost is lower in the pre-progression and post-progression states (by 55% and 80%, respectively), due to reduced hospitalizations and social care.

Considering TARE/sorafenib utilisation rates of 30%/70% (year 1), 40%/60% (year 3) and 50%/50% (year 5–10), it was estimated:
– Nº. deaths avoided: 2 in 5 years and 14 in 10 years
– Nº of hospitalizations avoided due to hepatic decompensation: 32 in 5 years.
Table 5 (continued)

| Author, year publication (year cost) | Stage | Comparators | Costs | Adjusted to SUS PPP [18] | Resource consumption and health outcomes |
|-------------------------------------|-------|-------------|-------|--------------------------|------------------------------------------|
|                                     |       |             | Original cost |                        |                                          |
|                                     |       |             |                   | Adjusted to $US PPP [18] |                                          |
|                                     |       |             | BIA at 3 years |                   |                                          |
|                                     |       |             | France (n=699) |                   |                                          |
|                                     |       |             | Italy (n=629) |                   |                                          |
|                                     |       |             | Spain (n=497) |                   |                                          |
|                                     |       |             | UK (n=465) |                   |                                          |
| Pollock, 2020 [39] (2018)           | BCLC-B, BCLC-C | With TARE | € 23,234,726 | € 21,323,136 | € 18,905,157 | € 15,746,274 | £ 15,746,274 | 23,816,048 | 21,551,022 | 21,597,385 | 16,290,893 | The highest resource consumption was: |
|                                     |       |             |                   |                   |                                          |
|                                     |       |             | With TARE |                   |                                          |
|                                     |       |             | Italy (n=629) |                   |                                          |
|                                     |       |             | Spain (n=497) |                   |                                          |
|                                     |       |             | UK (n=465) |                   |                                          |
|                                     |       |             | Cost savings |                   |                                          |
|                                     |       |             | (with vs. without TARE) |                   |                                          |
|                                     |       |             | 11.7% |                   | 54% | 265% | 7.7% |                                          |
|                                     |       |             |                   |                   |                                          |

AE adverse events, BCLC Barcelona Clinic Liver Cancer classification, BIA budget impact analysis, HCC hepatocellular carcinoma, IHS Italian health system, ND no data, OS overall survival, RFA radiofrequency ablation, SOR sorafenib, SOR3 subgroup of patients with sorafenib, TACE transarterial chemoembolization, TARE transarterial radioembolization, TKI tyrosine kinase inhibitors

a BCLC classification not specified, stage interpreted according to patient type characteristics (3 cm isolated HCC in one lobe)

b Cost year not specified, estimated from the proposed cost reference sources

c The BIA considering 200 annual HCC patients (66% were treatment-eligible patients, of which 8, 13 and 17 patients were treated with TARE in years 1, 2 and 3, respectively)

d Unspecified BCLC classification, stage interpreted according to pathology and comparator characteristics (TACE-eligible unresectable HCC)
of patients receiving treatment with curative intent [39]. The CA by Lucà et al. [36] estimated that TARE had significantly higher medium-term survival rates than sorafenib (TARE 64.1% vs. sorafenib 24.3%; \( p = 0.012 \)) after 2 years of follow-up of patients with intermediate-advanced HCC. The BIA by Rognoni et al. [37] reported a greater number of deaths avoided (2 and 14 deaths in 5 and 10 years, respectively) and fewer hospital admissions due to hepatic decompensation (32 hospitalizations avoided in 5 years) in the intermediate-advanced stage. The BIA by Pollock et al. [39] reported an incremental LYG of 0.009 with TARE (1.176 LYG) compared to sorafenib (1.168 LYG) and reported that 71 additional patients would benefit from treatment with curative intent over a 3-year period.

**Study quality reporting assessment**

Approximately six [31, 34–37, 39] of the nine studies (67%) had a high score when evaluated with a 20-items checklist (mean compliance: 93%). The remaining three studies (33%) were rated as having a moderate quality (mean compliance: 62%) [32, 33, 38].

**Discussion**

This review demonstrates that there is evidence that \(^{90}\text{Y}\)-TARE is a potentially cost-effective therapy for the treatment of HCC in the intermediate and advanced stages. \(^{90}\text{Y}\)-TARE was associated with lower treatment costs than sorafenib but higher treatment costs when compared to TACE or ablative therapy. However, the BIA conducted in Canada reflects cost savings associated with \(^{90}\text{Y}\)-TARE, even when the incremental cost of the device acquisition was considered [32]. Though, studies that compared \(^{90}\text{Y}\)-TARE with TACE did not account for AEs (postembolization syndrome) [20, 22], a key cost component and lower repetition rate associated with TARE than with TACE [22, 31].

Health outcomes vary with maximum health benefits associated with TARE when compared with TACE for intermediate- [22] and advanced-stage patients [20, 21] and when compared with sorafenib for intermediate- [26] and advanced-stage patients [24–26, 29, 36, 37, 39]. However, the comparison of the effectiveness of TARE versus TACE suggests that TARE may be more beneficial to intermediate HCC as it offers a greater possibility for curative intent in these patients [22]. Similarly, these results suggest that a greater number of patients with advanced HCC can obtain greater clinical benefits from TARE, though at a higher cost [25]. Compared with sorafenib and assuming the same clinical efficacy [24–27, 29, 30], maximum health benefits could be obtained using TARE, given the lower overall cost of TARE reported in studies [24, 25, 27, 29, 30]. Thus, assuming the same health resources for TARE and sorafenib, a greater number of patients could potentially be treated with TARE than with sorafenib, given the cost savings of TARE [32, 37, 39].

Several strengths to our study exist. To our knowledge, this is the first systematic review of the economic evidence of \(^{90}\text{Y}\)-TARE therapy in hepatic neoplasms that included HCC. This review included a strict inclusion criterion focusing on economic evaluations on TARE in liver neoplasms. An extensive search strategy was conducted by performing a search of both English and Spanish studies from the international bibliographic databases with the largest number of indexed publications (Medline and EMBASE) and of a database of publications in Spanish (MEDES). Also, with the goal of identifying the greatest possible number of studies, communications presented at various international conferences were consulted.

Some limitations to our study exist. First, given English and Spanish studies were included in our review, this may lead to excluding other potential economic evaluations published in other languages. As such, there is a potential for publication bias. Second, the diversity of methodologies used and the different parameters such as a variety of sources of clinical efficacy, comparators, and time horizons may limit the external validity of the results. Third, costs were reported for different dates and currencies, or did not report the reference year for cost items collected. Regardless, costs were adjusted to 2020 ($US PPP costs). Also, studies with missing reference years were assumed to be the same as cost reference sources or the study’s publication year. Fourth, the internal evaluation of the study quality varied as the appraisal of the quality of studies showed considerable differences across studies. Given we included conference abstracts (\( n = 7 \)) with no full-text version available at the time of this review, this limited the analysis and appraisal of the results. Even though some included studies were abstracts, it is important to note that the results showed similarities with other studies with full manuscripts.

Economic outcomes are dependent on pathology management and affect resource consumption during patient HCC management. The development of new systemic therapies in recent years [41], along with the availability of new diagnostic algorithms for HCC [42], could modify clinical practice guidelines due to earlier detection of the pathology. Another relevant issue is the influence of the radiologist’s experience with liver images on determining treatment response [43]. Furthermore, personalised dosimetry with \(^{90}\text{Y}\)-TARE has shown significant clinical improvement in objective response rate and OS in patients with locally advanced HCC [44]. These parameters are related to resource consumption in clinical practice and may affect the results reported here.
Conclusion
This review suggests that 90Y-TARE contributes to the reduction of hospital resource and therefore reduces costs, improves patient outcomes, and improves the value and efficiency in hospitals. Overall, TARE is a cost-effective short- and long-term treatment for HCC, driven by increased LYG compared to other HCC therapies. Given the evidence highlighted in this review, 90Y-TARE is a cost-effective therapy for treating patients with liver neoplasms or HCC in the intermediate and advanced stages. Since clinical practice guidelines or new therapies could potentially impact these results, we recommend future economic evaluations focusing on 90Y-TARE from different cost perspectives.

Abbreviations
AE: Adverse events; BC: Base case; BCLC: Barcelona Clinic Liver Cancer; BIA: Budget-impact-analysis; CA: Cost-analysis; CEA: Cost-effectiveness-analysis; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; CI: Confidence interval; CIRSE: Cardiovascular and Interventional Radiological Society of Europe; CMA: Cost-minimization-analysis; CT: Clinical trial; CTT: Conventional transarterial therapy; CUA: Cost-utility-analysis; DEB-TACE: Doxorubicin eluting bead transarterial chemoembolization; EANM: European Association of Nuclear Medicine; ECOI: European Conference on Interventional Oncology; ECR: European Congress of Radiology; ESMO: European Society of Medical Oncology; EUWEHTA: European Network for Health Technology Assessment; HCC: Hepatocellular carcinoma; HTA: Health technology assessment; ICER: Incremental cost-effectiveness ratio; ICR: Incremental cost-utility ratio; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; LMG: Life month gained; LYG: Life years gained; NHS: National Health System; NICE: National Institute for Health and Clinical Excellence; NMB: Net monetary benefit; OECD: Organization for Economic Co-operation and Development; OS: Overall survival; PPP: Purchasing power parity; PRISMA: Preferred Reporting items for Systematic Reviews and Meta-Analyses; QALY: Quality-adjusted life year; REDETS: Network of Health Technology Assessment Agencies; RFA: Radiofrequency ablation; SIO: Society of Interventional Oncology; SNMMI: Society of Nuclear Medicine and Molecular Imaging; SOR: Subgroup or patients with sorafenib; TACE: Transarterial chemoembolization; TAE: Transarterial embolization; TARE: Transarterial radioembolization; TDABC: Time-drive activity-based costing; TS: TARE plus sorafenib; TTP: Time to progression; TTS: TACE and possibly sorafenib; TNs: Tyrosine kinase inhibitors; WTP: Willingness-to-pay; 90Y-TARE: TARE with yttrium 90 microspheres.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12876-022-02396-6.

Additional file 1. Terminology of searching strategy in PubMed.

Acknowledgements
Not applicable.

Author contributions
All authors provided input into the writing, reviewing and revision of the manuscript. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request. The version contains additional information. The additional information of search strategy is in the Additional file 1.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
NEC and IO, are employees of Pharmacoeconomics & Outcomes Research Iberia (PORIB), a consultancy specialising in economic evaluation of health interventions, which has received private financial support from Boston Scientific in relation to the development of this work, including research, interpretation and writing of the manuscript. AF has received consultancy and proctor fees from Boston Scientific. ICT has received lecture fee from Sirtex Medical. FMG, DF, ICA, NS, have no relevant financial or non-financial interests to disclose. AW, RB are employees at Boston Scientific Corp. NE, IO has received research support from Boston Scientific.

Author details
1 Nuclear Medicine Department, Hospital Gregorio Marañón, Madrid, Spain. 2 Nuclear Medicine Department, Hospital Clínico Universitario, Valencia, Spain. 3 Nuclear Medicine Department, Hospital Universitario Central, Asturias, Spain. 4 Nuclear Medicine Department, Hospital Clinic, Barcelona, Spain. 5 Nuclear Medicine Department, Hospital Virgen de las Nieves, Granada, Spain. 6 Pharmaeconomics & Outcomes Research Iberia (PORIB), P. Joaquín Rodrigo 4 - letra I, 28224 Pozuelo de Alarcón, Madrid, Spain. 7 Boston Scientific Iberia, Madrid, Spain. 8 Boston Scientific, Marlborough, MA, USA.

Received: 29 March 2022 Accepted: 20 June 2022
Published: 2 July 2022

References
1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet Lond Engl. 2018;391:1301–14. https://doi.org/10.1016/S0140-6736(18)30010-2.
2. Reig M, Forner A, Avila MA, Ayuso C, Minguez B, Varela M, et al. Diagnosis and treatment of hepatocellular carcinoma. Update of the consensus document of the AEEH, AEC, SEOM, SERAM, SERVI, and SETH. Med Clin (Barc). 2021;156:463.e1–463.e30. https://doi.org/10.1016/j.medcli.2020.09.022.
3. World Health Organization. Global Cancer Observatory (GCO). Cancer Today 2020. http://gco.iarc.fr/today/home. Accessed 2 Mar 2022.
4. Kohn CG, Singh P, Korytowsky B, Caranta JT, Miller JD, Sill BE, et al. Humanistic and economic burden of hepatocellular carcinoma: systematic literature review. Am J Manag Care. 2019;25:SP61–73.
5. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2016;151:1155–1163.e2. https://doi.org/10.1053/j.gastro.2016.08.029.
6. Garlipp B, de Baere T, Damm R, Irmscher R, van Buskirk M, Stübs P, et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. Hepatol Baltim Md. 2014;59:1864–73. https://doi.org/10.1002/hep.26947.
7. Vilgrain V, Pereira H, Assenat E, Guigu B, Ilonca AD, Pageaux G-P, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised
controlled phase 3 trial. Lancet Oncol. 2017;18:1624–36. https://doi.org/10.1016/S1470-2045(17)30683-6.
8. Chow PKH, Gandhi M, Tan S-B, Khin MW, Khasabazar A, Ong J, et al. SIR-veNiB: selective internal radiation therapy versus sorafenib in Asia-pacific patients with hepatocellular carcinoma. J Clin Oncol. 2018;36:1915–21. https://doi.org/10.1002/jco.20170.760892.
9. Ricke J, Klumpe HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol. 2019;71:1164–74. https://doi.org/10.1016/j.jhep.2019.08.006.
10. European Society for Medical Oncology (ESMO). Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. 2021. https://www.esmo.org/guidelines/gastrointestinal-cancers/hepatocellular-carcinoma/eudapt-hepatocellular-carcinoma-treatment-recommendations. Accessed 5 Nov 2021.
11. Boston Scientific. TheraSphere™ Y-90 glass microspheres 2021. https://www.bostonscientific.com/en-US/products/cancer-therapies/thera sphere-y90-glass-microsphere.html. Accessed 2 Dec 2021.
12. Sirtex. SIR-Spheres® Y-90 resin microsphere 2021. https://www.sirtex.com/eu/clinicians/. Accessed 2 Dec 2021.
13. Terumo. QuiremSpheres® Microspheres 2021. https://www.terumo-europe.com/en-eome/products/quiremspheres%e2%84%A2-microspheres. Accessed 16 Dec 2021.
14. National Institute for Clinical Excellence (NICE). Selective internal radiation therapy for treating hepatocellular carcinoma. Guidance. 2021. https://www.nice.org.uk/guidance/ta688. Accessed 16 Dec 2021.
15. López Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, et al. A proposed guideline for economic evaluation of health technologies. Gac Sanit. 2010;24:154–70. https://doi.org/10.1016/j.gaceta.2009.07.011.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. https://doi.org/10.1136/bmj.b2535.
17. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n1660. https://doi.org/10.1136/bmj.n1660.
18. Organisation for Economic Co-operation and Development (OECD). Conversion rates—purchasing power parities (PPP). 2020. https://go.worldbank.org/2ZB79QF9DD.
19. Husseaua D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Eur J Health Econ. HEPAC Health Econ Prev Care. 2015;16:S279–80. https://doi.org/10.1007/s10198-014-0671-z.
20. Retambeigi N, Dekarske AS, Austin EE, Golzarian J, Cressman EN. Cost-effectiveness of radioembolization compared with conventional transarterial chemoembolization for hepatocellular carcinoma: a cost analysis from a hospital perspective. Value Health. 2016;19:4308. https://doi.org/10.1016/j.val.2016.03.671.
21. Muszbek N, Evans R, Remak E, Brennan V, Colaone F, Shergill S. PCN98 cost-comparison analysis of selective internal radiation therapy (SIRT) and transarterial chemoembolization (TACE) in unresectable hepatocellular carcinoma (HCC). Value Health. 2019;22:5485. https://doi.org/10.1016/j.jval.2019.09.295.
22. Ray CE, Battaglia C, Libby AM, Prochazka A, Xu S, Funaki B. Interventional radiologic treatment of hepatocellular carcinoma—a cost analysis from the payer perspective. J Vasc Interv Radiol. 2012;23:306–14. https://doi.org/10.1016/j.jvir.2011.11.016.
23. Hubert MM, Karelis A, Sherman M, Gill S, Beecroft R, Sampalis JS. Beyond budget silos-budget impact analysis of transarterial radioembolization with yttrium-90 glass microspheres for hepatocellular carcinoma from a hospital perspective. Value Health. 2016;19:4308. https://doi.org/10.1016/j.jval.2016.03.671.
24. Muszbek N, Evans R, Remak E, Brennan V, Colaone F, Shergill S. Changes ion Health State Costs in Hepatocellular Carcinoma (HCC). ISPOR Int Soc Pharmaeconomics Outcomes Res n.d. https://www.ispor.org/health-economics-outcomes-research-database/presentation/euro2019-3119?n=7618. Accessed 7 Apr 2021.
25. Parikh N, Singal A, Kulik L, Hutton D. Cost-effectiveness of sorafenib versus selective internal radiation therapy for patients with advanced hepatocellular carcinoma. Health Technol Assess. 2016;20:1–99. https://doi.org/10.3310/hta20084.
26. Parikh N, Singal A, Kulik L, Hutton D. Cost-effectiveness of sorafenib versus selective internal radiation therapy for patients with advanced hepatocellular carcinoma. Value Health. 2017;20:336–44. https://doi.org/10.1016/j.val.2016.09.2397.
27. Parikh N, Singal A, Kulik L, Hutton D. Cost-effectiveness of sorafenib versus selective internal radiation therapy for patients with advanced hepatocellular carcinoma. JCO Oncol Pract. 2021;17:e266–77. https://doi.org/10.1200/OP.20.00443.
28. Parikh N, Singal A, Kulik L, Hutton D. Cost-effectiveness of sorafenib versus selective internal radiation therapy for patients with advanced hepatocellular carcinoma. J CO. 2021;17:e266–77. https://doi.org/10.1200/OP.20.00443.
29. Parikh N, Singal A, Kulik L, Hutton D. Cost-effectiveness of sorafenib versus selective internal radiation therapy for patients with advanced hepatocellular carcinoma. JCO Oncol Pract. 2021;17:e266–77. https://doi.org/10.1200/OP.20.00443.
43. Tovoli F, Renzulli M, Negrini G, Brocchi S, Ferrarini A, Andreone A, et al. Inter-operator variability and source of errors in tumour response assessment for hepatocellular carcinoma treated with sorafenib. Eur Radiol. 2018;28:3611–20. https://doi.org/10.1007/s00330-018-5393-3.
44. Garin E, Palard X, Rolland Y. Personalised dosimetry in radioembolisation for HCC: impact on clinical outcome and on trial design. Cancers. 2020;12:1557. https://doi.org/10.3390/cancers12061557.

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