Economic Evaluations of Radioembolization With Itrium-90 Microspheres in Hepatocellular Carcinoma: a Systematic Review

JC Alonso
Nuclear Medicine Department, Hospital Gregorio Marañón, Madrid
I Casans
Nuclear Medicine Department, Hospital Clínico Universitario, Valencia
FM González
Nuclear Medicine Department, Hospital Universitario Central, Asturias
D Fuster
Nuclear Medicine Department, Hospital Clinic, Barcelona
A Rodríguez
Nuclear Medicine Department, Hospital Virgen de las Nieves, Granada
N Sánchez
Nuclear Medicine Department, Hospital Clinic, Barcelona
I Oyagüez
Pharmacoeconomics & Outcomes Research Iberia (PORIB), Madrid
R Burgos
Boston Scientific Iberia, Madrid
AO Williams
Boston Scientific Marlborough, Massachusetts
N Espinoza (nespinoza@porib.com)
Pharmacoeconomics & Outcomes Research Iberia (PORIB), Madrid

Research Article

Keywords: Hepatocellular carcinoma, radioembolization, yttrium-90, TARE, cost, systematic review

Posted Date: April 25th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1500796/v1

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. Conversions were performed using 2020 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) were finally included (13 European, 6 USA and 1 Canadian). 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) (n=9) or sorafenib (n=11). Life-years gained for TARE ranged from 1.3 to 3.1 vs. TACE and from 1.1 to 2.53 for TARE vs. sorafenib. TARE was associated with lower treatment cost in ten studies. TARE cost varied widely according to Barcelona Clinic Liver Cancer (BCLC) staging system and ranged from 1,311 PPP/month (BCLC-A) to 71,890 PPP/horizon time 5 years (BCLC-C). The incremental cost-utility ratio for TARE vs TACE resulted in a $PPP 17,397/Quality-adjusted-Life-Years (QALY) (n=1) and for TARE vs. sorafenib ranged from dominant (more effectiveness and lower cost) to 3,363 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.

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 $29,35447 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, or transplantation, and transarterial radioembolization (TARE) as an option for patients in 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 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). In the terminal stage (BCLC-D), the treatment option is palliative care[2].

The characteristics of the predominant arterial flow in patients with HCC have justified treatment with intra-arterial therapies, such as TARE with yttrium 90 microspheres (^{90}Y-TARE) as a therapeutic option for the treatment of HCC. ^{90}Y-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 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 ^{90}Y-TARE presents an efficacy profile and survival benefit comparable to that of treatment with sorafenib. When the combination of ^{90}Y-TARE with sorafenib was evaluated (the SORAMIC study[9]), toxicity was no greater than sorafenib monotherapy[9]. A recent update of the European Society of Medical Oncology (ESMO) clinical practice guidelines includes recommendation for the use of ^{90}Y-TARE as an alternative treatment in the early and intermediate stage of HCC. The guideline recommends the use of TARE in exceptional circumstances in patients with disease limited to the liver and good liver function 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 (^{166}Ho, 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 evidence that enhances resource efficiency and the prioritization of the available health resources[15]. Subsequently, a review on the economic benefits of ^{90}Y-TARE in the HCC population needs to be established. This systematic review aimed to review the economic evaluations of the use of ^{90}Y-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] was followed.

The search strategy was designed using the Population, Intervention, Comparison, Outcomes (PICO) methodology. Also, Boolean operators without limitation by 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”, “SIRSpheres”, “Cost”, “Cost utility”, “Cost benefit”, “Cost efficiency”, “Cost analysis”, “Budget impact” and “economic evaluation” (Appendix 1).

Databases were searched for all economic evaluations using ^{90}Y-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 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 ^{90}Y-TARE as a single treatment, or as a combination treatment, or 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 ^{90}Y-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 following 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 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 and includes low (< 50%), medium (50% and 80%), and high (> 80%) of the items were fulfilled. 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 were excluded as were focused on 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

An overview of the included studies is provided in Table 1. Eleven of the 20 studies (55%) were complete economic evaluations[20–30] and nine (45%) studies were partial evaluations[31–39]. Using the CHEERS checklist, the thirteen articles were of high quality (mean score of 94%), and seven abstracts and poster were of lower quality assessment (mean score of 56%) because these had less breadth of data.

Full economic evaluations

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 US [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 studies reported on the use of three types of microspheres, including QuiremSpheres®[28]. The main comparators were TACE[20–23] and sorafenib[24–30, 30], in addition to transarterial embolization (TAE)[22], TACE with doxorubicin-releasing particles (DEB-TACE)[22] and lenvatinib[28].

Regarding the pharmacoeconomic parameters, out of the 11 studies, two were CEA[20, 21], eight were CUA[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 of them utilized decision trees modelling [28], while cost minimisation did not specify the type of model[25]. The time horizon ranging from 5 years[20, 21, 30] to lifetime of the patient[23, 26, 27, 29]. The payer's perspective predominated in ten out of eleven studies, although one study focused on the social perspective[28]. 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]); two studies [20, 21] compared TARE with TACE, while a third study[22] included TACE and two other comparators, TAE and DEB-TACE, and a fourth 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; the reports included patients with 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[24–27, 29, 30] reported only sorafenib as a comparator, and one publication[28] included lenvatinib in the assessment. Additionally, these seven studies evaluated patients with 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 with TARE therapy than with TACE[20–22], and this finding was independent of the patient's BCLC-A, B or C in three studies [20–22]. The fourth publication presented a higher cost in TS sequence's therapy than TTS sequence (47% of patients with sorafenib) in patients with intermediate disease[23].

The health outcomes reported for patients in the intermediate stage showed a benefit of TARE over TACE in terms of LYG and QALY in one study[22]. The study evaluated sequences of therapies, TTS (with optional sorafenib) showed a greater incremental benefit than TS in terms of 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 entailed grouping difficulties because these outcomes were presented both monthly (LMG)[20] and annually (LYG)[22]. Additionally, two studies[22, 23] presented ICUR results (€/QALY), and one study did not present any ratios[21]. For early and intermediate stages of disease, one study (Manas et al.[22]) presented an ICER of £ 12,833/LYG (£, 2020) (12,291 $US PPP/LYG) and established the ICUR of TARE versus TACE at £ 17,279/QALY (£, 2020) (17,397 $US 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 TTS (with sorafenib in 47% of patients), which includes 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 in the intermediate-advanced stage and reported lower costs for TARE (differences between 1,454 to 46,982 $US PPP). However, Parikh et al.[27] also evaluated costs in 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 for 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 publication[30] presented 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.

Assessment of quality of full economic evaluations

Included studies categorized as full economic evaluations were appraised for their quality and reported as: six of the eleven studies (55%)[22, 23, 26, 28–30] had a high score, with a mean compliance of 99% of the 24 evaluated items. Three of the eleven studies (27%) had a moderate score (mean compliance of 66%)[20, 25, 27] while the remaining two studies (18%) had a mean compliance of 46%[21, 24].

Partial economic evaluations

Characteristics of the included studies

Nine publications were categorized as 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 comprised of patients with intermediate and advanced stage in seven of nine studies[31–33, 36–39]; five studies [31, 32, 36, 37, 39] reported the inclusion of patients classified 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 one lobe, not suitable for transplantation), and the second study (Ljuboja et al.)[35] did not define the population.

The evaluated microspheres, of the nine studies, three referred to 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 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 the entire life of the patient. The payer's perspective was most frequently used; 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 partial economic evaluations. 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 only 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 different stages of 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 stage were reported in three studies (BCLC-A[34], BCLC-B[33] and BCLC-C[38]), and one publication (Ljuboja, 2021)[35] did not report stages (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:9,577 – 35,855 $US PPP) treatments[31, 33–35], ablative therapy (range: 3,790 – 11,135 $US PPP) [34, 35] or sorafenib (12,460 $US PPP) [31]. However, one study (Muszbek et al.)[33] reported similar costs of TARE and TACE regardless of whether the costs were obtained from the official source of costs for the NHS or by using the microcosting methodology[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 year 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 in the management of patients with advanced HCC, showing a 54–79% 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 a period of 5 years. The second BIA (Pollock et al.)[39]

evaluated the scenario with TARE versus the scenario 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 period of 3 years.

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 results ion the survival rates[36], number of events (deaths or hospitalizations) avoided[37], incremental LYG[39] and proportion 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[39] reported an incremental LYG of 0.009 with TARE (1.176 LYG) compared to sorafenib (1.168 LYG) indicated that 71 additional patients would benefit from treatment with curative intent over a 3-year period.

Assessment of quality of partial economic evaluations

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

Discussion

This systematic review included 20 studies that reported economic evaluations of ^{90}Y-TARE therapy. To our knowledge, this is the first systematic review on the economic evidence of ^{90}Y-TARE therapy in hepatic neoplasms that included HCC. Though a recent systematic review of HCC was published by Walton et al.[28] with the objective of performing a cost-utility analysis; therefore, that publication was included in this review. On the other hand, a recently published systematic review of TARE utilized a cost-utility analysis with the objective of evaluating the incremental QALYs in different HCC sub-populations[41].

In this review, the cost of ^{90}Y-TARE was associated with lower treatment costs than comparators (sorafenib) and presented a higher cost item than other comparators (TACE or ablative therapy). However, the BIA conducted in Canada reflected cost savings associated with ^{90}Y-TARE, even when the incremental cost of the device acquisition was considered[32]. Though, studies that compared ^{90}Y-TARE with TACE did not account for AEs such as postembolization syndrome[20, 22], this is crucial as lower repetition rate is associated with TARE than with TACE[22, 31]. Also, the evidence showed that glass microspheres, a type of ^{90}Y-microspheres, has lower procedure requirements (1.1–1.2) than resin microspheres (1.2–1.6)[33]. Considering that the glass and resin microspheres contain up to 20 GBq and 10 GBq fixed, respectively; and that the specific activity of each microsphere at the calibration time is much higher for glass microspheres (i.e., approximately 4500 Bq/microsphere at calibration, in contrast to approximately 50 Bq/microsphere for resin microspheres), if similar activity is prescribed, the glass microsphere would have the lowest embolic effect [42].

Health outcomes vary with greater health benefits associated with TARE 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 suggest that TARE may be more beneficial as it offers a greater possibility for curative intent in patients with intermediate disease[22]. Similarly, these results suggest that a greater number of patients with advanced disease can obtain greater clinical benefit from TARE, although at a greater cost[25]. Compared with sorafenib, if the same clinical efficacy is assumed for both alternatives[24–27, 29, 30], greater benefit can be obtained using TARE, since the lower overall cost of TARE means that a greater number of patients can be treated with the same budget line[32, 37, 39].

There are several strengths to our study. This review included a strict inclusion criterion to include only economic evaluations on TARE in liver neoplasms. An extensive search strategy was conducted by performing a search of 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.

Several 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 with different currencies or did not report the reference year for cost items collected. Regardless, costs were transformed to 2020 ($US PPP costs). Also, studies with missing reference year were assumed to be same as cost reference sources or the study's publication year. Fourth, the internal evaluation of the study quality varied. The evaluation of the methodological quality of the included studies showed considerable differences. Since some studies (n = 7) were available in conference communication format (oral communications or abstracts), with no full-text version available as at the time of this review, this limited the analysis and evaluation of these results. Even though some included studies were abstracts, it is important to note that the results showed some similarities with other studies with full manuscripts.

Conclusion

Despite these limitations, this review suggests that ^{90}Y-TARE contributes to the reduction of the hospital resources utilization 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, ^{90}Y-TARE is a cost-effective therapy for the treatment of patients with liver neoplasms or HCC in the intermediate and advanced-stages. Since these results could potentially be impacted by clinical practice

guidelines or new therapies, such as personalized dosimetry with ^{90}Y-TARE, which shows significant clinical improvement in the objective response rate and OS in patients with locally advanced HCC[43], we recommend future economic evaluations on ^{90}Y-TARE. Therefore, it is necessary economic evaluations which explore the cost-effectiveness of personalised dosimetry, using resource consumption in routine clinical practice and categorised disease stag is performed.

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

ECIO: European Conference on Interventional Oncology

ECR: European Congress of Radiology

ESMO: European Society of Medical Oncology

EUNetHTA: European Network for Health Technology Assessment

HCC: Hepatocellular carcinoma

HTA: health technology assessment

ICER: Incremental cost-effectiveness ratio

ICUR: 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 sequence: TARE, TACE and possibly sorafenib

TKIs: Tyrosine kinase inhibitors

WTP: Willingness-to-pay

^{90}Y-TARE: TARE with yttrium 90 microspheres

Declarations

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

The version contains supplementary information.

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.

Conflict of Interest:

ARF has received consultancy and proctor fees from Boston Scientific. ICT has received lecture fee from Sirtex Medical. FMG, DF, JCA, NS, have no relevant financial or non-financial interests to disclose. AW, RB is employee at Boston Scientific Corp. NE, IO has received research support from Boston Scientific.

Funding:

Not applicable

Authors' contributions

All authors provided input into the writing, reviewing and revision of the manuscript.

Acknowledgements:

Not applicable

Author details (ORCID)

Alonso JC[1] (0000-0002-1615-9724), Casans I[2] (0000-0002-3249-9446), González FM[3], Fuster D[4] (0000-0003-0906-0627), Rodríguez A[5] (0000-0002-6068-3160), Sánchez N[4] (0000-0002-8565-1552), Oyagüez I[6] (0000-0002-3047-6152), Burgos R[7] (0000-0003-4295-8033), Williams AO[8], Espinoza N[6] (0000-0002-8116-6963)

[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]Pharmacoeconomics & Outcomes Research Iberia (PORIB), Madrid, Spain

[7]Boston Scientific Iberia, Madrid, Spain

[8]Boston Scientific Marlborough, Massachusetts, USA

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, Ávila MA, Ayuso C, Mínguez B, Varela M, et al.Diagnosis and treatment of hepatocellular carcinoma. Update of the consensus document of the AEEH, AEC, SEOM, SERAM, SERVEI, 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 March 2, 2022).
4. Kohn CG, Singh P, Korytowsky B, Caranfa 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, Guiu 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, Khasbazar A, Ong J, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients with Hepatocellular Carcinoma. J Clin Oncol 2018;36:1913–21. https://doi.org/10.1200/JCO.2017.76.0892.
9. Ricke J, Klümpen 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/eupdate-hepatocellular-carcinoma-treatment-recommendations (accessed November 5, 2021).
11. Boston Scientific. TheraSphereTM Y-90 glass microspheres 2021. https://www.bostonscientific.com/en-US/products/cancer-therapies/therasphere-y90-glass-microspheres.html (accessed December 2, 2021).
12. Sirtex. SIR-Spheres® Y-90 resin microsphere 2021. https://www.sirtex.com/eu/clinicians/ (accessed December 2, 2021).
13. Terumo. QuiremSpheres® Microspheres 2021. https://www.terumo-europe.com/en-emea/products/quiremspheres%E2%84%A2-microspheres (accessed December 16, 2021).
14. National Institute for Clinical Excellence (NICE). Selective internal radiation therapies for treating hepatocellular carcinoma. Guidance. 2021. https://www.nice.org.uk/guidance/ta688 (accessed December 16, 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–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:n160. https://doi.org/10.1136/bmj.n160.
18. Organisation for Economic Cooperation and Development (OECD). Conversion rates - Purchasing power parities (PPP) 2020. https://doi.org/10.1787/1290ee5a-en.
19. Husereau 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 2013;14:367–72. https://doi.org/10.1007/s10198-013-0471-6.
20. Rostambeigi N, Dekarske AS, Austin EE, Golzarian J, Cressman EN. Cost Effectiveness of Radioembolization Compared with Conventional Transarterial Chemoembolization for Treatment of Hepatocellular Carcinoma. J Vasc Interv Radiol 2014;25:1075–84. https://doi.org/10.1016/j.jvir.2014.04.014.
21. Rostambeigi N, Dekarske A, Austin E, Golzarian J, Cressman E. Simulation study on cost-effectiveness of radioembolization compared with trans-arterial chemoembolization for hepatocellular carcinoma [abstract]. J Vasc Interv Radiol 2014;25:S104–5. https://doi.org/10.1016/j.jvir.2013.12.292.
22. Manas D, Bell JK, Mealing S, Davies H, Baker H, Holmes H, et al. The cost-effectiveness of TheraSphere in patients with hepatocellular carcinoma who are eligible for transarterial embolization. Eur J Surg Oncol 2021;47:401–8. https://doi.org/10.1016/j.ejso.2020.08.027.
23. Rognoni C, Ciani O, Sommariva S, Tarricone R. Cost–effectiveness analysis of treatments involving radioembolization in intermediate-stage hepatocellular carcinoma. J Comp Eff Res 2018;7:209–21. https://doi.org/10.2217/cer-2017-0050.
24. Chaplin S, Taylor M, Lapon J, White J. Economic evaluation of glass yttrium-90 microspheres versus sorafenib for the treatment of advanced hepatocellular carcinoma: cost effectiveness analysis in the United Kingdom. Cardiovasc Intervent Radiol 2015;38:S279–80.
25. Palmer D, Ross P, Shah T, Yu D, Shergill S, Patterson K, et al. Cost effectiveness of selective internal radiation therapy (SIRT) with Y-90 resin microspheres versus sorafenib in Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma patients in the UK. Ann Oncol 2017;28:v239–40. https://doi.org/10.1093/annonc/mdx369.087.
26. Rognoni C, Ciani O, Sommariva S, Tarricone R. Real-World Data for the Evaluation of Transarterial Radioembolization versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. Value Health 2017;20:336–44. https://doi.org/10.1016/j.jval.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. Hepatology 2018;68(Suppl. 1):532A–3A.
28. Walton M, Wade R, Claxton L, Sharif-Hurst S, Harden M, Patel J, et al. Selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma: systematic review, network meta-analysis and economic evaluation. Health Technol Assess 2020;24:1–264. https://doi.org/10.3310/hta24480.
29. Muszbek N, Remak E, Evans R, Brennan VK, Colaone F, Shergill S, et al. Cost-utility analysis of selective internal radiation therapy with Y-90 resin microspheres in hepatocellular carcinoma. Future Oncol Lond Engl 2021;17:1055–68. https://doi.org/10.2217/fon-2020-1004.
30. Marqueen KE, Kim E, Ang C, Mazumdar M, Buckstein M, Ferket BS. Cost-Effectiveness Analysis of Selective Internal Radiotherapy with Yttrium-90 Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma.JCO Oncol Pract 2021;17:e266–77. https://doi.org/10.1200/OP.20.00443.
31. Colombo G, Cammà C, Attili A, Ganga R, Gaeta G, Franzini JM, et al.Patterns of treatment and costs of intermediate and advanced hepatocellular carcinoma management in four Italian centers. Ther Clin Risk Manag 2015:1603. https://doi.org/10.2147/TCRM.S88208.
32. Hubert MM, Karellis 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:A308. https://doi.org/10.1016/j.jval.2016.03.671.
33. Muszbek N, Evans R, Remak E, Brennan V, Colaone F, Shergill S. PCN98 Cost-Comparison Analysis of Selective Internal Radiation Therapy (SIRT) and Transarterial Chemoembolisation (TACE) in unresectable Hepatocellular Carcinoma (HCC). Value Health 2019;22:S455. https://doi.org/10.1016/j.jval.2019.09.295.
34. 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.
35. Ljuboja D, Ahmed M, Ali A, Perez E, Subrize MW, Kaplan RS, et al.Time-Driven Activity-Based Costing in Interventional Oncology: Cost Measurement and Cost Variability for Hepatocellular Carcinoma Therapies. J Am Coll Radiol 2021:S1546144021002945. https://doi.org/10.1016/j.jacr.2021.03.027.
36. Lucà MG, Nani R, Schranz M, De Giorgio M, Iegri C, Agazzi R, et al.Treatment of hepatocellular carcinoma: a cost analysis of yttrium-90 transarterial radioembolization versus sorafenib. Future Oncol 2018;14:727–35. https://doi.org/10.2217/fon-2017-0566.
37. Rognoni C, Ciani O, Sommariva S, Bargellini I, Bhoori S, Cioni R, et al. Trans-arterial radioembolization for intermediate-advanced hepatocellular carcinoma: a budget impact analysis. BMC Cancer 2018;18:715. https://doi.org/10.1186/s12885-018-4636-7.
38. Muszbek N, Evans R, Remak E, Brennan VK, Colaone F, Shergill S. Changes in Health State Costs in Hepatocellular Carcinoma (HCC). ISPOR Int Soc Pharmacoeconomics Outcomes Res 2019 https://www.ispor.org/heor-resources/presentations-database/presentation/euro2019-3119/97618 (accessed April 7, 2021).
39. Pollock RF, Colaone F, Guardiola L, Shergill S, Brennan VK. A cost analysis of SIR-Spheres yttrium-90 resin microspheres versus tyrosine kinase inhibitors in the treatment of unresectable hepatocellular carcinoma in France, Italy, Spain and the UK. J Med Econ 2020;23:593–602. https://doi.org/10.1080/13696998.2020.1731213.
40. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for The Economic Evaluation of Health Care Programmes. vol. 54. 2002.
41. Pollock RF, Colaone F, Shergill S, Brennan VK, Agirrezabal I. Effects of Trial Population Selection on Quality of Life and Healthcare Decision-Making: A Systematic Review and Example in the Treatment of Hepatocellular Carcinoma with Radioembolization. Clin Outcomes Res CEOR 2021;13:835–41. https://doi.org/10.2147/CEOR.S319857.

42. Weber M, Lam M, Chiesa C, Konijnenberg M, Cremonesi M, Flamen P, et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging 2022. https://doi.org/10.1007/s00259-021-05600-z.
43. 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.

Tables

Table 1 is available in the Supplementary Files section

Table 2

Descriptive analysis of complete economic evaluations for hepatocellular carcinoma (HCC).

Author, year, publication type and country	Patient's characteristics	Treatments		Analysis type/ Model	Perspective / Time horizon	Cost	Outcomes
		Comparators	Microspheres				
TARE vs TACE							
Rostambeigi, 2014[20] *Original article* USA	BCLC-A BCLC-B BCLC-C	TARE vs TACE	TheraSphere™ SIR-Spheres®	CEA / Monte Carlo	Payer/ 5 years	Direct cost (medical)	OS and incremental cost
Rostambeigi, 2014[21] *Communication at congress* USA	BCLC-A BCLC-B BCLC-C	TARE vs TACE	ND	CEA / Monte Carlo	Payer / 5 years	ND	OS, procedure- and complications costs, and incremental cost
Manas, 2021[22] *Original article* United Kingdom	BCLC-A BCLC-B	TARE vs TACE, TAE o DEB-TACE	TheraSphere™	CUA / Markov	Payer / 20 years	Direct cost (medical)	Downstaging[a], LYG, QALY, ICER(£/LYG) y ICUR(£/QALY)
Rognoni, 2018[23] *Original article* Italy	BCLC-B	TTS: TARE+TACE+ sorafenib (on 47% of patients) TS: TARE+sorafenib	TheraSphere™ SIR-Spheres®	CUA / Markov	Payer / lifetime	Direct cost (medical)	Cost, QALY, ICUR (€/QALY), WTP a €50,000/QALY
TARE vs TKIs							
Chaplin, 2015[24] *Communication at congress* United Kingdom	BCLC-C[b]	TARE vs sorafenib	TheraSphere™	CUA / Markov	Payer / 10 years	ND	Cost, TTP, SG y ICUR (£/QALY),
Palmer, 2017[25] Communication at congress United Kingdom	BCLC-C	TARE vs sorafenib	SIR-Spheres®	Cost-minimization analysis	Payer / ND	Direct cost (medical)	Cost (£), principals factors cost, QALY.
Rognoni, 2017[26] *Original article* Italy	BCLC-B BCLC-C	TARE vs sorafenib	ND	CUA / Markov	Payer / lifetime	Direct cost (medical)	Cost, QALY, ICUR (€/QALY), WTP a €38,500(~£30,000) /QALY
Parikh, 2018[27] *Communication at congress* USA	BCLC-C[c]	TARE vs sorafenib	ND	CUA / Markov	Payer / lifetime	Direct cost (medical)	ICUR ($/QALY)
Walton, 2020[28] Systematic review an economic evaluation United Kingdom	BCLC-B BCLC-C (*Child–Pugh A e ineligible a CTT)*	TARE vs TKIs	TheraSphere™ SIR-Spheres® QuiremSpheres®	CUA / Partitioned survival model and decision tree	Payer and social/ 10 years	Direct and indirect cost	ICUR (£/QALY), incremental net monetary (NMB)
Muszbek, 2020-21[29] Original article United Kingdom	BCLC-B[d] BCLC-C[d]	TARE vs sorafenib	SIR-Spheres®	CUA / Partitioned survival model	Payer / lifetime	Direct cost (medical)	Cost, LYG, QALY, ICUR (£/QALY), WTP a £20.000, INB
Marqueen, 2021[30] Original article USA	BCLC-C	TARE vs sorafenib	TheraSphere™ SIR-Spheres®	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: LYG: life-years gained, ND: no data, OS: overall survival, QALY: quality-adjusted life years, TACE: transarterial chemoembolization, TAE: transarterial embolization, TARE: transarterial radioembolization, TKI: tyrosine kinase inhibitors, TTP: time to progression, TTS sequency: TARE, TACE and optional sorafenib (sorafenib was administered on 47% of patients), WTP: willingness-to-pay.

a. Downstaging: decrease in tumour burden that allows patients to be rescued for treatments such as liver transplantation. **b.** Assumed clinical characteristics of two separate RCTs: TheraSphere (Salem et al. 2011) and sorafenib (Phase III SHARP RCT-Llovet et al. 2018). **c.** Patients with unresectable HCC and Child–Pugh class A cirrhosis. **d.** BCLC-B o BCLC-C (not appropriate to TACE): HCC with low tumour burden (≤25%) and good liver function (albumin–bilirubin [ALBI] grade 1).

Table 3

Results of publications of complete evaluations for hepatocellular carcinoma (HCC).

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
TARE vs TACE										
Rostambeigi, 2014[20] (2013)[a]			*Monthly* [b]		*OS months*					
	BCLC-A	TACE	$ 2,094	2,347	39.5	ND	TACE vs.	ND	TACE vs.	ND
		TARE (I)	$ 1,770	1,311	29.7	ND	$33/LMG	ND	37/ LMG	ND
			Δ -$ 324	Δ -363	Δ 9.8		[$ 396 LYG]*		[444 /LYG]*	
		TARE (II)	$ 2,688	3,013	29.7	ND	$61/LMG	ND	68/LMG	ND
			Δ $ 594	Δ 666	Δ 9.8		[-$ 732 LYG]*		[-820/LYG]*	
	BCLC-B	TACE	$ 2,326	2,607	22.9	ND	TACE vs.		TACE vs.	
		TARE (I)	$ 2,789	3,126	16.0	ND	$67/LMG	ND	75/LMG	ND
			Δ $ 463	519	Δ 6.9		[-$ 804 LYG]*		[-901/LYG]*	
		TARE (II)	$ 4,240	4,753	16.0	ND	$277/LMG	ND	310/LMG	ND
			Δ $1,914	2,145	Δ 6.9		[-$3.324 LYG]*		[-3,726/LYG]*	
	BCLC-C	TACE	$ 2,679	3,003	13.3	ND	TACE vs.		TACE vs.	
		TARE (I)	$2,652	2,973	17.1	ND	$7/LMG	ND	8/LMG	ND
			Δ -$27	Δ -30	Δ 3.8		[dominant]*		[dominant]*	
		TARE (II)	$4,031	4,518	17.1	ND	$356/LMG	ND	399/LMG	ND
			Δ $1,352	Δ 1,515	Δ 3.8		[$ 4.272 LYG]*		[-4,788 /LYG]*	
Rostambeigi, 2014[21] (2013)[a]					*OS months*					
	BCLC-A, BCLC-B, and BCLC-C	TACE	$ 17,000	19,055	BCLC-A: 37 BCLC-B: 22 BCLC-C: 12	ND	ND	ND	ND	ND
		TARE	$ 49,000	54,924	BCLC-A: 32 BCLC-B: 18 BCLC-C: 19	ND	ND	ND	ND	ND
	BCLC-C	TARE-TACE	Δ $ 500	Δ 560		ND	ND	ND	ND	ND
Manas, 2021[22][c] (2020)	BCLC-A, BCLC-B	TARE (T^{TM})	£ 49,583	49,921	3.05	2.24	TARE vs.	TARE vs.	TARE vs.	TARE vs.
		TACE	£ 37,038	37,291	2.14	1.57	£ 12,808	£ 17,279	12,291	17,397
		DEB-TACE	£ 33,206	33,432	2.14	1.57	£ 17,059	£ 23,020	17,175	23,177
		TAE	£ 37,015	37,267	2.14	1.57	£ 12,833	£ 17,300	12,921	17,418
					Δ 0.91	Δ 0.67	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)			
Rognoni, 2018[23] (2016)	BCLC-B	TTS (47% sorafenib)	€ 36,509	37,137	3.494	1.385	-	TTS Dominant		

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
		TS	€ 42,812	43,591	2.361	0.937				
			Δ - € 6,303	Δ - 6,418	Δ - 1.133	Δ 0.448	TTS WTP (€50,000/QALY): 83%			
TARE vs TKI										
Chaplin, 2015[24] (2015)[a]	BCLC-C	TARE (T^{TM})	£ 21,441	22,763	ND	1.12	ND	TARE Dominant	ND	TARE Dominar
		Sorafenib	£ 34,050	36,150	ND	0.85	ND			
			Δ - £ 12,609	Δ - 13,387	ND	Δ 0.27	ND			
					TARE vs sorafenib TTP (months): 6.2 vs 4.9 OS (months): 13.8 vs 9.7					
Palmer, 2017[25] (2017)	BCLC-C	TARE (S®)	£ 8,909 in favour of TARE	9,374	ND	Δ 0.0079 in favour of TARE	ND	TARE cost-effective	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 vs.	TARE vs.	TARE vs.	TARE vs.
		Sorafenib	€ 29,289	29,829	1.575	0.638	1.865	3,302	1,899	3,363
			Δ € 1,782	Δ 1,815	Δ 0.956	Δ 0.540	WTP (€38.500/QALY): 99,2%			
	BCLC-C	TARE	€ 21,961	22,366	1.445	0.639	ND	TARE Dominant	ND	TARE Dominar
		Sorafenib	€ 30,750	31,317	1.306	0.568				
			Δ - € 8,788	Δ - 8,950	Δ 0.139	Δ 0.071	WTP (€38.500/QALY): 98,2%			
Parikh, 2018[27] (2018)[a]	BCLC-C	**Pooled data**						Sorafenib vs.		Sorafenil vs.
		TARE	$ 61,897	65,295	ND	0.81	ND	$ 19,534	ND	20,606
		Sorafenib	$ 63,313	66,789	ND	0.88				
			Δ - $ 1,416	Δ - 1,494	ND	Δ - 0.07				
		EECC SARAH						Sorafenib vs.		Sorafenil vs.
		TARE	$ 64,805	68,363	ND	0.78		TARE vs.		TARE vs.
		Sorafenib	$ 63,216	66,687	ND	0.87	ND	Sorafenib Dominant	ND	Sorafenil Dominar

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
			Δ $ 1,589	Δ 1,676	ND	Δ - 0.09				
		EECC SIRveNIB						Sorafenib vs.		Sorafenil vs.
		TARE	$ 57,473	60,628	ND	0.84	ND	$ 107,927	ND	113,852
		Sorafenib	$ 63,447	66,930	ND	0.90				
			Δ - $ 5,974	Δ - 6,302	ND	Δ - 0.06				
Walton, 2020[28] (2017/2018)	BCLC-B BCLC-C	**Deterministic**								
		TARE (T^{TM})	£ 29,888	30,922	1.110	0.764	*NMB (£)*	TARE (T^{TM}) vs.	*NMB (£)*	TARE (T^{TM}) vs.
		TARE (S®)	£ 30,107	31,148	1.110	0.764	*-218*	+ costly	*226*	+ costly
		TARE (Q®)	£ 36,503	37,766	1.110	0.764	*-6,614*	+ costly	*-6,843*	+ 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	*1,090*	2,911	*1,128*	3,012
		Probabilistic								
		TARE (T^{TM})	£ 30,014	31,052	1.111	0.765	*NMB (£)*	TARE (T^{TM}) vs.	*NMB (£)*	TARE (T^{TM}) vs.
		TARE (S®)	£ 30,196	31,240	1.111	0.765	*-2,154*	Dominated	-2,229	Dominat
		TARE (Q®)	£ 36,613	37,879	1.111	0.765	*-2,323*	Dominated	-2,403	Dominat
		Lenvatinib	£ 29,658	30,684	1.244	0.841	*-2,306*	174,320	-2,386	180,349
		Sorafenib	£ 32,444	33,566	1.202	0.825	*-8,741*	Dominated	-9,043	Dominat
Muszbek, 2020-21[29][d] (2018/2019)	BCLC-B BCLC-C	TARE (S®)	£ 29,530	30,085	2.637	1.982		TARE Dominant		TARE Dominar
		Sorafenib	£ 30,957	31,539	1.890	1.381	ND	- £ 2,374	ND	- 2,719
			Δ- £ 1,427	Δ - 1,454	Δ 0.748	Δ 0.601	TARE (S®) WTP (£ 20,000): 95%. INB (£) at threshold of £20,000: £ 13,443.			
Marqueen, 2021[30] (2016/2017)	BCLC-C	**Pooled data**								
		Sorafenib	$ 78,859	84,868		0.88		Sorafenib vs.		Sorafenil vs.
		TARE	$ 58,397	62,847		0.87	ND	$ 1,280,224	ND	1,377,77
			Δ $20,462	Δ 22,061		Δ 0.02	Sorafenib WTP ($200,000/QALY): 1%			
		EECC SARAH								
		Sorafenib	$ 72,899	78,454		0.83		Sorafenib vs		Sorafenil vs
		TARE	$ 66,800	71,890		0.84	ND	TARE dominant	ND	TARE dominan

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
			Δ $ 6,099	Δ 6,564		Δ -0.01				
		EECC SIRveNIB								
		Sorafenib	$ 89,806	96,649		0.91		Sorafenib vs		Sorafenil vs
		TARE	$ 46,151	49,668		0.86	ND	$ 753,412	ND	810,822
			Δ $43,655	Δ 46,982		Δ 0.06				

BC: base case, BCLC: Barcelona Clinic Liver Cancer classification, CT: clinical trial, DEB-TACE: doxorubicin eluting bead transarterial chemoembolization, HCC: hepatocellular carcinoma, CI confidence interval, ICER: cost-effectiveness incremental ratio, ICUR: incremental cost-utility ratio, INB: Incremental net benefit, LYG: life years gained, LMG: life moth 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, TARE (I): unilobar, TARE (II): bilobar, TARE (S®): transarterial radioembolization with SIR-Spheres®, TARE (T^{TM}): transarterial radioembolization with TheraSphere^{TM}, TARE (Q®): transarterial radioembolization with QuiremSpheres®, TKI: tyrosine kinase inhibitors, TTP: time to progression, TTS sequency: TARE, TACE and optional sorafenib (sorafenib was administered on 47% of patients), WTP: willingness-to-pay.

a. Year of unspecified cost, estimated from the proposed cost reference sources. **b.** The procedure is repeated every 10 months until 5 years. **c.** Number of patients downstaged (out of 1000 patients): 842 TheraSphere^{TM} and 452 TACE, DEB-TACE and TAE. **d.** TARE allows downstaging for subsequent treatment with curative intent: 13.5% TARE vs 2.1% sorafenib (base case considering SARAH study data), and 5.1 TARE vs 1.4% sorafenib in the ITT population.

* Determined by calculations assuming a year has 12 months.

Table 4

Descriptive analysis of partial economic evaluations for hepatocellular carcinoma (HCC).

Author, year, publication type and country	Patient's characteristics	Treatments	Microspheres	Analyses type / Characteristics, source, and costs	Perspective/ Time horizon	Outcomes
TARE vs TACE and ablative therapy						
Ray, 2012[34] *Original article* USA	BCLC-A[a]	TARE vs TACE vs RFA	ND	CA/ Multiple scenarios for Medicare using a decision tree and Monte Carlo model. Direct healthcare cost: 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 vs TACE vs 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.
TARE vs TACE and TARE vs TKI						
Colombo, 2015[31] *Original article* Italy	BCLC-B and BCLC-C	TARE vs TACE vs 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[b]	TARE vs TACE	TheraSphere™ 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[c]	TARE vs TACE[e] TARE vs sorafenib	TheraSphere™	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.
TARE vs TKI						
Lucà, 2017[36] *Original article* Italy	BCLC-B BCLC-C	TARE vs 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 días	Estimated cost of each procedure. OS rates
Muszbek, 2019[38] *Communication at congress* United Kingdom	BCLC-C[b]	TARE vs sorafenib	ND	CA / Costs by health status obtained from literature, registers, and surveys (5 experts). Direct health costs (historical and current): administration, monitoring and hospitalisation costs. Social care	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 vs 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

Author, year, publication type and country	Patient's characteristics	Treatments	Microspheres	Analyses type / Characteristics, source, and costs	Perspective/ Time horizon	Outcomes
Pollock, 2020[39] *Original article* United Kingdom	BCLC-B *(not eligible to TACE)* BCLC-C *(eligible)*	TARE vs TKIs [95% sorafenib/ lenvatinib 5%]	SIR-Spheres®	BIA / Markov Source: CT SARAH	Payer/ 3 years	Economic impact in Spain, France, Italy and United Kingdom.

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

a. BCLC classification not specified, stage interpreted according to patient type characteristics (3cm isolated HCC in one lobe). **b.** Unspecified BCLC classification, stage interpreted according to pathology and comparator characteristics (TACE-eligible unresectable HCC). **c**. BCLC-C stage with and without portal vein thrombosis. **c.** Advanced with tumour macrovascular invasion without extrahepatic spread and good liver function **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 publications of partial evaluations for hepatocellular carcinoma (HCC).

Author, year publication (year cost)	Stage	Comparators	Costs						
			Original cost				Adjusted to $US PPP [18]		
TARE vs TACE vs Ablative therapy									
Ray, 2012[34] (2010)	BCLC-A[a]		**Decision tree**		**Monte Carlo**		**Decision tree**		**Monte Carlo**
		TARE	$ 35,618		$ 35,629 ± 9,930		42,368		42,381± 11,812
		TACE	$ 30,143		$ 30,107 ± 19,109		35,855		35,812 ± 22,730
		RFA	$ 9,361		$ 9,362 ± 2,555		11,135		11,136 ± 3,309
Ljuboja, 2021[35] (2020)b	ND		**Total cost /patient**	**Personal**	**Equipment**	**Consumables**	**Total cost /patient**	**Personal**	**Equipment**
		TARE	$20,818 (100%)	$ 1,656 (8%)	$ 371 (2%)	$ 18,791 (90%)	21,074	1,676	376
		TACE	$ 5,089 (100%)	$ 1,947 (38%)	$ 212 (4%)	$ 2,930 (58%)	5,152	1,971	215
		Ablation	$ 3,744 (100%)	$ 1,114 (30%)	$ 205 (5%)	$ 2,425 (65%)	3,790	3,837	208
TARE vs TACE and/or TKI									
Colombo, 2015[31] (2014)	BCLC-B BCLC-C		**Annual cost/patient**		**Monthly cost/patient**		**Annual cost/patient**		**Monthly cost/patie**
		TARE	26,106 €		17,404 €		26,629		17,753
		TACE	13,418 €		5,304 €		13,687		5,410
		Sorafenib	12,215 €		2,009 €		12,460		12,710
Muszbek, 2019[33] (2018/2019)	BCLC-B[b]		**Annual cost/patient**				**Annual cost/patient**		
		TARE (T™)	£ 12,026 - £ 21,425				12,442 - 22,166		
		TARE (S®)	£ 11,185 - £ 15,636				11,572 - 16,177		
		TACE	£ 9,257 - £ 14,167				9,577- 14,657		
Hubert, 2016[32] (2016)[b]	BCLC-B BCLC-C	TARE, TACE and sorafenib	BIA HCC patients (n=200 annual)[c]. TARE saved:				BIA HCC patients (n=200 annual). TARE saved		
			Year 1: $ 37,000				Year 1: 40,699		
			Year 2: $ 55,000				Year 2: 64,454		
			Year 3: $ 75,000				Year 3: 82,437		
			TARE was associated with cost savings and reduced use of hospital resources.						
TARE vs TKI									
Lucà, 2017[36] (2017)[b]	BCLC-B BCLC-C		**Total cost per patient**				**Total cost per patient**		
		TARE	€ 17,761				18,096		
		Sorafenib (SOR3)	€ 27,992				28,520		
			TARE cost was significantly lower than sorafenib (p=0.028). Limitations: small number of patients (n=24) and the l treatment type assignment.						
Muszbek, 2019[38]	BCLC-C[d]		**Health status cost per month**				**Health status cost per month**		

Author, year publication (year cost)	Stage	Comparators	Costs						
			Original cost				Adjusted to $US PPP [18]		
			Pre	Progression	Post		Pre	Progression	
		TARE	£ 246	£208	£499		251	212	
		TKI	£ 287	£208	£287		292	212	
			Cost drivers in pre- and post-progression 2018/2019: diagnostic procedures (53%) and medical consultations (45%). 2007/2015: hospitalisations (41%) and social care (42%).						
Rognoni, 2018[37] (2018/2019)			5 years	Lifetime			5 years	Lifetime	
	BCLC-B	TARE	€ 33,040	€ 28,003			33,393	28,302	
		Sorafenib	€ 29,935	€ 29,716			30,255	30,034	
	BCLC-C	TARE	€ 22,526	€ 21,456			22,767	21,685	
		Sorafenib	€ 31,526	€ 31,430			31,863	31,766	
	BCLC-B, BCLC-C	BIA considering increased use of TARE (stage BCLC-B and C):					BIA considering increased use of TARE:		
		Year 0 (TARE 20%, SOR 80%):		€ 30,139,457			Year 0	30,461,565	
		Year 1 (TARE 30%, SOR 70%):		€ 29,633,336			Year 1	29,950,035	
		Year 2 (TARE 30%, SOR 70%):		€ 29,239,463			Year 2	29,551,953	
		Year 3 (TARE 40%, SOR 60%):		€ 28,685,595			Year 3	28,992,165	
		Year 4 (TARE 40%, SOR 60%):		€ 28.311.921			Year 4	28,614,498	
		Year 5 (TARE 50%, SOR 50%):		€ 27.793.820			Year 5	28,090,860	
Pollock, 2020[39] (2018)	BCLC-B, BCLC-C	BIA at 3 years	France (n=699)	Italy (n=629)	Spain (n=497)	UK (n=465)	France (n=699)	Italy (n=629)	Spain (n=497)
		With TARE	€ 23,234,726	€ 21,323,136	€ 18,905,157	£ 15,746,274	23,816,048	21,551,022	21,597,385
		Without TARE	€ 26,314,378	€ 22,531,440	€ 25,172,537	£ 17,054,914	26,972,751	22,772,239	25,496,295
		Cost savings (With vs without TARE)	11.7%	5.4%	26.5%	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 (3cm 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).

Figures

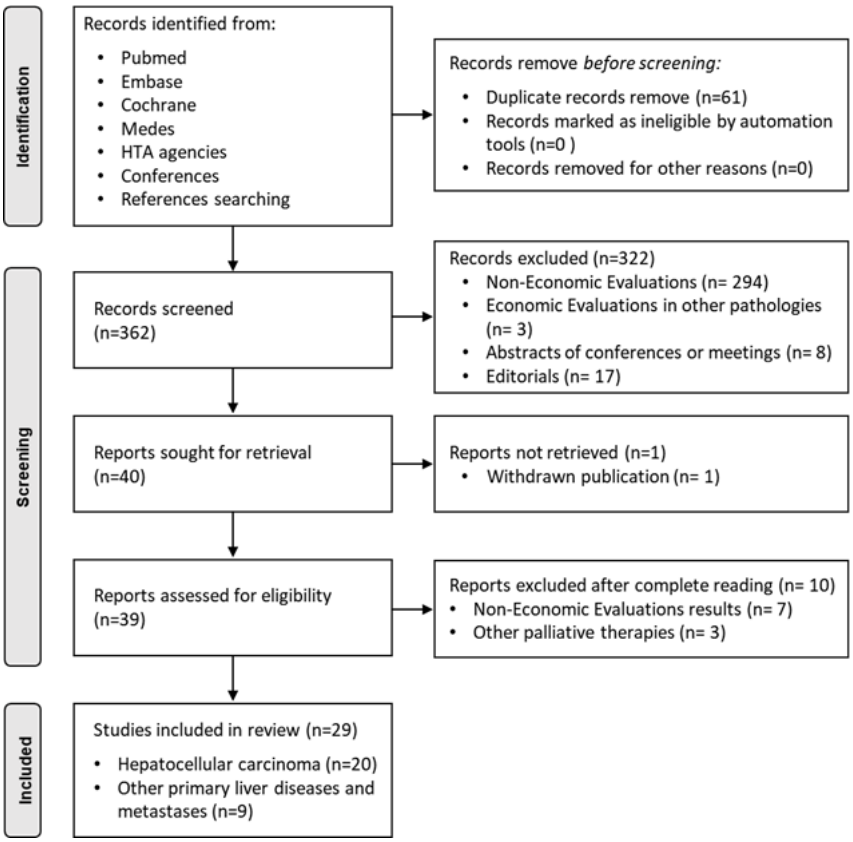

Figure 1

Bibliographic selection based on the PRISMA criteria.

HTA: health technology assessment agencies

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PaperRSY90HCCsupplementary.docx
- Table1.docx