Review Article

Selective internal radiation therapy across Barcelona Clinic Liver Cancer (BCLC) stages of hepatocellular carcinoma: literature review

Paul Vigneron[1,2,3#], Maria Stella Franzè[2,3,4#^], Julia Chalaye[5^], Vania Tacher[2,3,6^], Anna Sessa[1,2,3^], Alain Luciani[2,3,6^], Hicham Kobeiter[2,3,6], Hélène Regnault[1,3^], Ancuta Bejan[1], Julien Calderaro[2,3,7], Rami Rhaiem[3,8,9^], Daniele Sommacale[2,3,10], Giovanni Raimondo[4^], Vincent Leroy[1,2,3], Raffaele Brustia[2,3,10^], Giuliana Amaddeo[1,2,3^]

[1]Department of Hepatology, Assistance Publique-Hôpitaux de Paris, Henri Mondor-Albert Chenevier University Hospital, Créteil, France; [2]Université Paris-Est Créteil, UPEC, Créteil, France; [3]INSERM, Unit U955, Team 18, Créteil, France; [4]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [5]Department of Nuclear Medicine, Assistance Publique-Hôpitaux de Paris, Henri Mondor-Albert Chenevier University Hospital, Créteil, France; [6]Department of Medical Imaging, Assistance Publique-Hôpitaux de Paris, Henri Mondor-Albert Chenevier University Hospital, Créteil, France; [7]Department of Pathology, Assistance Publique-Hôpitaux de Paris, Henri Mondor-Albert Chenevier University Hospital, Créteil, France; [8]Department of Hepatobiliary, Pancreatic and Digestive Surgery, Robert Debré University Hospital, Reims, France; [9]University of Reims Champagne-Ardenne, Reims, France; [10]Department of Digestive and Hepatobiliary Surgery, Assistance Publique-Hôpitaux de Paris, Henri Mondor-Albert Chenevier University Hospital, Créteil, France

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study material or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Giuliana Amaddeo, MD, PhD. Department of Hepatology, Assistance Publique-Hôpitaux de Paris, Henri Mondor-Albert Chenevier University Hospital, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France; Université Paris-Est Créteil, UPEC, Créteil, France; INSERM, Unit U955, Team 18, Créteil, France. Email: giuliana.amaddeo@aphp.fr.

Background and Objective: Selective internal radiation therapy (SIRT) represents an endovascular treatment option for patients with hepatocellular carcinoma (HCC). Its use is widely recognized in the intermediate and advanced HCC, but it has become more prevalent in recent years in different Barcelona Clinic Liver Cancer (BCLC) stages. The aim of this review is to summarize the role of SIRT and its clinical implications through different stages of HCC.

Methods: A literature review of papers on this topic was performed using PubMed MEDLINE, focusing exclusively on the role of yttrium-90 SIRT across all BCLC stages and comparing it with other treatments. Only English-language papers currently available until September 2023 were considered.

Key Content and Findings: Many studies have shown that SIRT is a promising tool with multiple uses, such as tumour control in the context of bridge-to-liver transplantation or resection, tumour downstaging, and curative therapy in selected patients. Therefore, according to the recent update of BCLC staging system criteria, SIRT now emerges as a potential curative treatment for early-stage HCC patients, serving as an alternative when ablation or resection is not feasible. It is also a promising treatment compared to transarterial chemoembolization (TACE) as well as in combination with immunotherapies.

Conclusions: SIRT is a safe and effective treatment for selected patients at all BCLC stages of HCC. Therefore, due to its numerous advantages, SIRT may prove useful in many complex HCC treatment

^ ORCID: Maria Stella Franzè, 0000-0002-9815-5275; Julia Chalaye, 0000-0001-7987-6969; Vania Tacher, 0000-0002-7162-5425; Anna Sessa, 0000-0001-5168-6135; Alain Luciani, 0000-0003-0331-9474; Hélène Regnault, 0000-0001-6810-9406; Rami Rhaiem, 0000-0002-8569-6523; Giovanni Raimondo, 0000-0003-3112-8587; Raffaele Brustia, 0000-0001-6426-9533; Giuliana Amaddeo, 0000-0003-2554-1877.

situations in the near future.

Keywords: Hepatocellular carcinoma (HCC); radioembolization; yttrium-90 (^{90}Y); selective internal radiation therapy (SIRT); transarterial radioembolization (TARE)

Submitted Oct 03, 2023. Accepted for publication Mar 20, 2024. Published online Jun 06, 2024.
doi: 10.21037/hbsn-23-504
View this article at: https://dx.doi.org/10.21037/hbsn-23-504

Introduction

Hepatocellular carcinoma (HCC), which is the most prevalent primary liver cancer, represents the third largest contributor to global cancer mortality, impacting over one-third of patients who are diagnosed with advanced liver disease at the time of HCC diagnosis (1).

Surgical resection is the most useful treatment for HCC, and liver transplantation (LT) represents the greatest potential cure for survival. However, most patients with HCC are diagnosed at intermediate or advanced stages, when approximately 70% of cases lose the window for curative treatments (ablation or resection). In this way, locoregional therapies (LRT) have various potential roles for patients with unresectable tumours or those beyond the selection criteria. In particular, selective internal radiation therapy (SIRT), also called transarterial radioembolization (TARE), is a locoregional treatment for liver tumours that consists of the arterial infusion of resin microspheres or a glass matrix labelled integrated to a radiotherapeutic agent such as yttrium-90 (^{90}Y) by applying the concentration of high radiation energy in the tumour tissue without damaging the surrounding liver parenchyma. The significance of SIRT is widely acknowledged in the management of intermediate and advanced HCC, especially in individuals affected by portal vein thrombosis (2). Contraindications to SIRT include significant liver dysfunction/decompensation, Child-Pugh (CP) score > B7, presence of clinical ascites, pregnancy, irregularities in hepatic venous anatomy that preclude radioembolization, pathological shunt fraction causing a lung dose of ≥30 Gy in a single application or digestive shunt that could not be embolized, and abnormal laboratory values. Additionally, although not absolute recommendations, a white blood cell count <2,500 cells/mm^3, neutrophil count <1,500 cells/mm^3, platelet count <60,000 cells/mm^3, alanine transaminase or aspartate transaminase more than five times the normal value, bilirubin >2 mg/dL, albumin <3 mg/dL, and creatinine >2.5 mg/dL have been proposed as limits to therapy (3). A high liver tumor burden (>50%) or significant extra-hepatic disease are not direct contraindications to SIRT, but they have been associated with worse treatment outcomes (4-6).

Nevertheless, according to the recent update of Barcelona Clinic Liver Cancer (BCLC) staging system criteria, SIRT now emerges as a potential curative treatment for early-stage HCC patients, serving as an alternative when ablation or resection is not feasible. Regardless, SIRT has a role as a bridge treatment, a tumour downstaging and a control tumour progression before liver resection (LR) or LT (7,8).

In this context, thanks also to the recently published DOSIPHERE-01 randomized multicentre open-label phase II trial, there has been growing interest in dosimetry-guided personalization of SIRT with the goal of improving tumoricidal effect, response rate and overall survival (OS) (9). Additionally, in the LEGACY study, the emerging change in the technique of SIRT follows a complete treatment response of early HCC (BCLC A) (10). Therefore, personalized dosimetry is now recommended by several international expert groups, partly based on the concept that SIRT can provide significantly better time to progression (TTP) than transarterial chemoembolization (TACE) with favourable survival in BCLC stages A–C (9,11,12).

Although some studies have shown conflicting results, new positive clinical outcomes with SIRT in the treatment of HCC at all BCLC stages are emerging (7). In this review, we present an update on treatment with SIRT in patients with early, intermediate and locally advanced HCC. We present this article in accordance with the Narrative Review reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-504/rc).

Methods

An accurate systematic literature search was conducted using PubMed MEDLINE and the following keywords: “SIRT”, “Selective internal radiation therapy”, “TARE”, “trans-arterial radioembolization”, “hepatocellular

Table 1 The search strategy summary

Items	Specification
Date of search	3 Apr 2023 to 30 Sep 2023
Databases searched	PubMed MEDLINE
Search terms used	SIRT and HCC, selective internal radiation therapy and HCC, TARE and HCC, transarterial radioembolization and HCC, radioembolization and HCC, yttrium-90 and HCC
Timeframe	January 2009 to September 2023
Inclusion and exclusion criteria	Only original papers and clinical trials in English language were included. Expert reviews, meta-analysis, comments and editorials were excluded
Selection process	M.S.F., P.V., G.A. conducted the research of studies independently and after the results were matched for the selection of those finally included in this review

carcinoma", "yttrium-90", "radioembolization". A literature review of papers on this topic was performed using PubMed MEDLINE, focusing exclusively on the role of yttrium-90 SIRT across all BCLC stages and comparing it with other treatments. Only English-language papers currently available until September 2023 were considered. Original papers and clinical trials were included in this review, while reviews, meta-analyses, comments, and editorials were excluded (*Table 1*).

Radioembolization across BCLC stages of HCC

The feasibility and safety of SIRT in unresectable HCC patients have been demonstrated in many retrospective multicentre studies (5,6,13-16) and subsequently validated in prospective nonrandomized studies (2). Thus, although SIRT was initially reserved for advanced stages, recent data suggest that it could favourably be compared with TACE in intermediate stages, especially since its tolerance is better (17,18).

Over time, SIRT has been evaluated across all stages of BCLC in pioneer centres. The first studies began when there was the necessity to test other therapies where validated treatments were not being performed for several reasons. Thus, in 2010, Salem *et al.* reported the outcomes of 291 HCC patients (48, 83, 107 and 7 at BCLC stages A, B, C and D, respectively) treated by SIRT. It was shown that survival differed between patients with CP A and B disease (P=0.002), but in particular, TTP and OS decreased with increasing BCLC stage (5). Similarly, in a multicentre analysis conducted at eight European centres, the median OS after SIRT in HCC patients was 12.8 months (24.4, 16.9 and 10.0 months for BCLC A, B and C, respectively) (15).

Thus, gradually over 2010, SIRT has been established as a safe and efficient treatment option in all stages of HCC, also thanks to the growing experience (especially in expert centres) with curative (bridge or downstaging or tumoricidal radiation) or palliative aims (*Figure 1*). In particular, SIRT appeared well tolerated and effective in a cohort of Asian patients with BCLC stage A–C HCC (66% of whom had hepatitis B virus infection), but at the same time, there was a significant association between tumour response and BCLC stage (P=0.003) (19).

It may also be important to consider the impact of previous treatment on tolerability and survival after SIRT. In fact, in an analysis conducted at eight European centres, radioembolization was used as first-line treatment in 57.5% of patients and as second-line in 34.2% of cases. These two groups showed no significant differences in OS among all BCLC stages (P=0.98) (20). Furthermore, Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and modified RECIST (mRECIST) seem to be the best compromise between reproducibility and the ability to predict OS in patients with HCC treated with radioembolization (21). In this context, a personalized method is useful to calculate the prescribed activity for a better response (22). Thus, the use of SIRT in real-life clinical practice was also observed in a large, European-wide multicentre prospective observational study, and it was found that partition model dosimetry resulted in improved OS compared to body surface area calculations (P=0.01) (23).

Radioembolization in BCLC 0/A stage HCC patients

According to the recent update of the BCLC staging system criteria, the first treatment options considered for

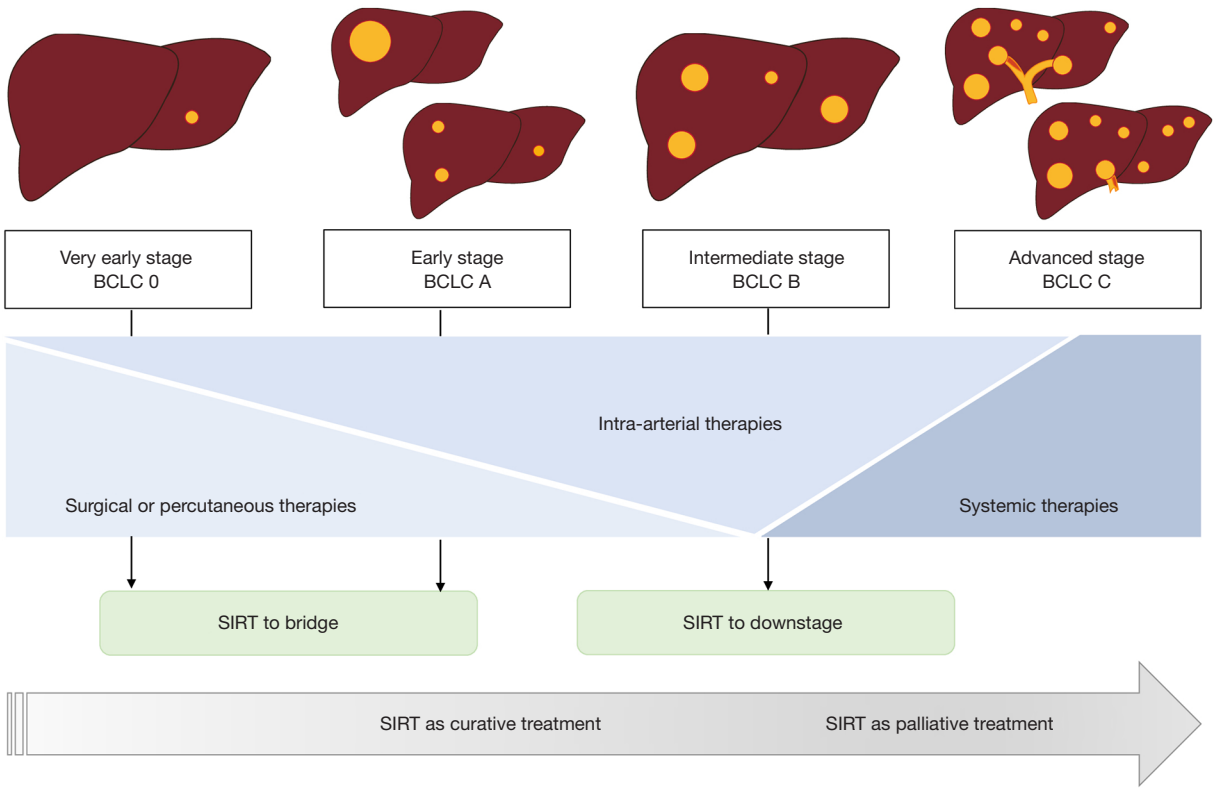

Figure 1 Role of SIRT across BCLC stages of HCC. BCLC, Barcelona Clinic Liver Cancer; SIRT, selective internal radiation therapy; HCC, hepatocellular carcinoma.

very early (0) or early (A) stage HCC patients are ablation, LR and LT. However, these new recommendations take into consideration SIRT as an alternative to surgery or radiological local therapy with a curative intent, especially for downstaging and bridging to LT or LR (*Table 2*). In elderly patients, SIRT could also be a good curative therapy option if there is no possibility to perform ablation or resection for any reason (location of nodules and difficult to treat, availability of technique in the centre, contraindication to surgery, etc.) (7,8).

Radiation segmentectomy (RS)

In recent years, RS, also defined as "superselective" SIRT, has proven its safety and effectiveness in BCLC stage 0 and A HCC patients with small lesions confined to ≤2 liver segments through the infusion of a calculated dose into a segmental vessel (25,26). Indeed, this technique enables the escalation of the ^{90}Y dose directly to the tumour while minimizing radiation exposure to the surrounding healthy hepatic tissue. It has demonstrated initial outstanding tumour response rates and has shown improved OS compared to other lobar treatments (24,43). Afterwards, these data were confirmed by two multicentre studies on treatment-naïve solitary HCC ≤5 cm. The first study reported complete response (CR), partial response (PR), and stable disease (SD) in 47%, 39% and 12% of 102 HCC patients, respectively (by using mRECIST criteria), with a median TTP of 33.1 months (26), whereas the second study reported a tumour response in 86% of cases at 6 months [by using European Association for the Study of Liver (EASL) Criteria], a median TTP of 2.4 years and an OS of 6.7 years (28). Even in a retrospective analysis, overall response rates (ORR) and median progression-free survival (PFS) were higher for RS *vs.* TACE (84% *vs.* 58% and 564 *vs.* 271 days, respectively), while the OS rates were not different between the two groups (27).

Furthermore, RS was effective in achieving comparable tumour response and OS while maintaining a similar safety profile compared to microwave ablation (MWA) in the treatment of HCC lesions ≤4 cm in size (29). Even

Table 2 Studies evaluating SIRT as potentially curative treatment in patients with unresectable hepatocellular carcinoma

Author (year)	SIRT procedure	Country	SIRT modality	Sample size of HCC treated with SIRT (n)
Riaz *et al.*, 2011 (24)	Radiation segmentectomy	USA	Glass microspheres	84
Padia *et al.*, 2014 (25)	Radiation segmentectomy	USA	Glass microspheres	20
Vouche *et al.*, 2014 (26)	Radiation segmentectomy	USA	Glass microspheres	102
Padia *et al.*, 2017 (27)	Radiation segmentectomy	USA	Glass microspheres	101
Lewandowski *et al.*, 2018 (28)	Radiation segmentectomy	USA	Glass microspheres	70
Arndt *et al.*, 2021 (29)	Radiation segmentectomy	USA	Glass microspheres	34
Kim *et al.*, 2022 (30)	Radiation segmentectomy	USA	Glass microspheres	29
De la Garza-Ramos *et al.*, 2022 (31)	Radiation segmentectomy	USA	Glass microspheres	57
Gaba *et al.*, 2009 (32)	Radiation lobectomy	USA	Glass microspheres	20
Vouche *et al.*, 2013 (33)	Radiation lobectomy	USA	Glass microspheres	67
Bekki *et al.*, 2021 (34)	Radiation lobectomy	France/Japan/USA	Glass and Resin microspheres	22
Mohamed *et al.*, 2016 (35)	Bridge-to-LT	USA	NS	9
Salem *et al.*, 2016 (36)	Bridge-to-LT	USA	Glass microspheres	24
Zori *et al.*, 2020 (37)	Bridge-to-LT	USA	Glass and resin microspheres	28
Lewandowski *et al.*, 2009 (38)	Bridge-to-LT/downstaging	USA	Glass microspheres	43
Gabr *et al.*, 2017 (39)	Bridge-to-LT/downstaging	USA	Glass microspheres	93
Gabr *et al.*, 2021 (40)	Bridge-to-LT/downstaging	USA	Glass microspheres	207
Villalobos *et al.*, 2021 (41)	Bridge-to-LT/downstaging	USA	Glass microspheres	135
Assalino *et al.*, 2020 (42)	Downstaging	France/Italy/Poland/ Switzerland/USA	NS	9

LT, liver transplantation; SIRT, selective internal radiation therapy; NS, not specified; HCC, hepatocellular carcinoma.

in patients with unresectable very early- to early-stage HCC considered unsuitable for ablation for location, RS demonstrated effectiveness, with a minimal occurrence of severe adverse events (30).

The recent LEGACY multicentre study of 162 patients with unresectable HCC ≤8 cm treated with SIRT with a curative or a bridge-to-transplantation intent reported an ORR of 72.2%, of whom 76.1% exhibited a duration of response (DoR) ≥6 months, as well as a 3-year OS of 86.6% (10). In this way, 45 patients (27.8%) were bridged to LT or resection, 67% of whom had complete pathological necrosis (CPN) (40). Of note, the majority of the tumours included in the LEGACY study had a size smaller than 3 cm, with a median tumour size of 2.6 cm (range, 0.9–8.1 cm). This is important because it is the first clinical trial that reported radioembolization as a curative-intent treatment. However, while safety and efficacy data for local therapies are well established, SIRT may be considered for patients with a single nodule measuring less than 8 cm, CP score A and Eastern Cooperative Oncology Group (ECOG) Performance status (PS) 0/1 (10). Thus, a recent study investigated the treatment outcomes of 123 patients with these specific characteristics, analysing the results of RS and surgical resection as their respective treatment modalities. Although the median TTP significantly differed between the two treatments (21.9 *vs.* 29.4 months, P=0.03), the OS was not reached in either cohort. However, RS had a lower incidence of major adverse events compared to surgical resection (P<0.001) (31).

Radioembolization from BCLC A to C stages HCC in patients with potentially curative treatment

HCC patients with BCLC A to C could be treated with SIRT if other treatment is not available with good effectiveness and well tolerance in specialized centres according to multidisciplinary decisions. Data about the versatile application of SIRT for all stages of BCLC were extensively confirmed in a 15-year 1,000-patient (26% BCLC A, 15% B, 54% C, 4% D) experience analysis that led to an institutional decision to prioritize SIRT as the primary transarterial locoregional treatment for HCC, as it can allow a reduced number of sessions, better quality of life (QoL) and longer TTP when compared with TACE (16). Regardless, it is always important to consider liver function, as confirmed in a study that evaluated SIRT in 74 BCLC B/CP-A HCC patients, since baseline albumin has proven to be a significant prognosticator of OS and in association with bilirubin of time to persistent CP-B or CP-C HCC (44). Furthermore, it has been shown that when treating less than 14.5% of the liver with glass microspheres, patients with albumin-bilirubin grade 2 and CP-B liver function are less likely to experience an increase in the respective grade or class (45).

Radiation lobectomy (RL)

RL is a modified version of the traditional radioembolization procedure designed to capitalize on the liver's volumetric changes resulting from the infusion of ^{90}Y into a specific lobe. These changes include atrophy of the ipsilateral lobe and hypertrophy of the contralateral lobe, which the technique aims to exploit (32,46). In particular, since some HCC patients are unresectable because of a small future liver remnant (FLR), RL has become a safe and effective option compared to portal vein embolization (PVE) (16). However, although FLR hypertrophy takes a longer time (2–6 months), RL could provide an advantage in controlling tumour growth during the time of contralateral hypertrophy (47,48).

Currently, there is a limited amount of comparative data available in the literature that directly compares the outcomes of PVE and RL in HCC patients (33,34). In a cohort of 67 HCC patients with right unilobar tumours and without previous LRT, volumetric changes with FLR hypertrophy after RL reached 1% and 45% at 1 and 9 months later, respectively (P<0.001) (33). A few years later, the CPN rates and the degree of FLR hypertrophy were evaluated in liver tissue preparation of unresectable HCC and were found to be higher after radioembolization than after PVE (50% *vs.* 0%, 63% *vs.* 36%, P<0.01) 1 and 5 months after preparation, respectively (34).

Despite the lack of further data, RL represents a promising variant of SIRT, and it could be useful to evaluate whether FLR hypertrophy also corresponds to an increase in functional gain.

Bridge-to-transplantation

SIRT has proven to be a valid and safe bridging therapy for candidates for LT with more than 6 months of waiting time. In a retrospective study, 11 patients (26%) treated with TACE and 9 patients (21%) treated with SIRT were transplanted after treatment, and one patient in each group was downstaged to resection. In fact, 2/11 patients in the TACE group and 2/9 in the SIRT group experienced recurrence after LT, resulting in a respectively 1-year recurrence-free survival (RFS) rate of 73% and 89%, but with a significantly longer TTP after SIRT than TACE (P=0.005) (38). Mohamed *et al.* demonstrated in a study with a cohort of 60 liver transplanted patients (47 inside the Milan criteria) a higher rate of radiological CR after SIRT (33%) than after TACE, radiofrequency ablation (RFA) or stereotactic body radiotherapy (SBRT) (25%, 22%, and 8.6%, respectively). In addition, complete pathologic responses in liver explants were greater after SIRT (75%) than after RFA (60%), TACE (41%) or SBRT (28.5%) as a bridge to LT (35). Although there was no difference in terms of median survival time to LT in 45 HCC patients randomized to SIRT or TACE in a randomized controlled trial (RCT), fewer dropouts on the LT waiting list (2/15 in the SIRT group *vs.* 3/10 in the TACE group) were observed (36). Even in a study with 172 HCC patients (66% BCLC A, 22% BCLC B), a significantly longer time on the waiting list and fewer intra-arterial therapy sessions were observed in HCC patients treated with SIRT than TACE (P=0.02, P=0.02, respectively). In contrast, post-LT outcomes were similar between patients treated with SIRT or TACE: median time to recurrence (P=0.48), RFS (P=0.84) and OS (not reached in the SIRT group, as 57% of patients were still alive at 100 months *vs.* median OS of 84.2 months after TACE, P=0.57) (39). Similarly, Zori *et al.* demonstrated that SIRT could be linked to enhanced tumour control and a lower incidence of recurrence after LT, with significantly less microvascular invasion on liver explants of patients treated before LT with SIRT than TACE (3.6% *vs.* 27%, P=0.01) (37). Instead, in a recent single-center study, SIRT was shown to be an effective

treatment for HCC in the context of bridging to LT. Notably, patients achieved complete/extensive tumor necrosis and better RFS compared to those with partial tumour necrosis (P<0.0001) (40). This may be important to provide future support for the implementation of neoadjuvant treatment prior to LT.

Downstaging of HCC for curative treatment

Currently, there is a lack of standardized criteria for downstaging in HCC, leading to the adoption of diverse criteria in various studies. This heterogeneity makes it challenging to compare results across different research endeavors. The field of downstaging conversion therapy remains relatively unknown, presenting several challenges, such as the need for clearer criteria to identify "potentially resectable" HCC patients, define successful criteria for downstaging, and determine the optimal treatment approach to maximize the effectiveness of downstaging therapy (37,39,49).

Lewandowski *et al.*, in the same study mentioned above, reported a higher response rate for patients treated with SIRT by using glass microspheres than for patients treated with TACE (PR rates 61% *vs.* 37%) in a cohort of 86 HCC patients without PVI or extrahepatic metastases (82% BCLC B, 18% BCLC C). More patients were downstaged from United Network for Organ Sharing (UNOS) T3 to UNOS T2 (58% *vs.* 18%, P=0.02) after SIRT than after TACE (38). Interestingly, in a multicentre retrospective study, the 5-year OS reported in 30 BCLC C HCC patients who underwent LT after achieving complete radiological regression of vascular invasion with locoregional (9 patients treated with SIRT) or surgical therapies was 60% (42). During a 15-year follow-up, the OS from LT was evaluated very long (12.5 years) in a cohort of 207 HCC patients who underwent LT after SIRT (169 patients bridged/38 patients downstaged) (40).

Nevertheless, it is important to take into account that certain baseline patient characteristics, such as a lower albumin-bilirubin grade, lower CP score, lower BCLC stage, HCC diagnosis through dynamic contrast-enhanced imaging on CT scan or magnetic resonance imaging (MRI), normal or higher albumin levels, reduced tumour burden severity, left lobe HCC disease, absence of hepatitis B virus-related cirrhosis, and the presence of baseline abdominal pain or fatigue, may be linked to an increased probability of bridging or downstaging, ultimately making the patient eligible for LT (41).

Radioembolization vs. TACE

TACE is approved as one of the standard treatments for intermediate stage HCC according to international guidelines (1). Nevertheless, the heterogeneity of the BCLC B stage is due to different tumour burdens and levels of liver function impairment. Radioembolization may be a better treatment than TACE, mainly in BCLC-B2 substage HCC (50). Furthermore, with extensive intrahepatic spread and macrovascular tumour invasion, HCC becomes untreatable with TACE. Thus, in the last 15 years, many expert centres have led many studies to compare both treatment modalities and have proposed SIRT as a valid alternative treatment for this subset of patients (*Table 3*). In fact, SIRT has demonstrated a profile of effectiveness comparable to TACE in terms of disease control rate (DCR), disease response rate (DRR), TTP, downstaging, bridge to transplantation and OS, with fewer adverse events postembolization (7). As proof of this, it was demonstrated how SIRT outperformed conventional TACE (cTACE) for downstaging HCC (58% *vs.* 31%) and OS without censoring to radical therapies such as LT or LR (P=0.008) but not in censored cases (P=0.18) (38). Similarly, Carr *et al.* defined that patients treated with SIRT had a significantly longer OS than those treated with cTACE (P<0.05) (51), but this was not confirmed in the study conducted by Kooby *et al.* (P=0.74) (52). Even in a study with a long follow-up of 9 years, although TTP was longer following radioembolization than TACE (P=0.046), there was a trend but not a statistical significance for DRR (P=0.10) and median survival times (P=0.23) (6). Likewise, in two other retrospective studies and one prospective study, although CR was more common but not statistically superior after SIRT than after TACE, there were no differences in median OS (17,54,55). Thereafter, in the previously mentioned randomized phase II PREMIERE trial a significantly longer TTP was reported after SIRT than TACE (P=0.001), without a difference in OS (P=0.54) (36).

Radioembolization might be more advantageous than TACE in terms of safety and QoL due to the minor risk of postembolization syndrome, the probability of a greater response and fewer sessions needed. The SIRTACE trial was the first multicentre open-label prospective RCT of single-session SIRT with ^{90}Y-resin microspheres *vs.* multiple-session TACE in patients with unresectable primary HCC, and despite the evidence of similar results in terms of DCR and OS, it suggested SIRT as an alternative option for patients with HCC who are potential candidates

Table 3 Studies comparing TACE versus SIRT in patients with unresectable hepatocellular carcinoma

Author (year)	Enrolment period	Country	Study design	TACE modality	SIRT modality	Sample size (n)	
						TACE	SIRT
Lewandowski *et al.*, 2009 (38)	January 2000 to December 2008	USA	Retrospective	cTACE	Glass microspheres	150	126
Carr *et al.*, 2010 (51)	1992 to 2000/2000 to 2005	USA	Retrospective	cTACE	Glass microspheres	691	99
Kooby *et al.*, 2010 (52)	January 1996 to December 2006	USA	Retrospective	cTACE	Resin microspheres	44	27
Lance *et al.*, 2011 (53)	August 2007 to April 2010	USA	Retrospective	cTACE and DEB-TACE	Glass and resin microspheres	35	38
Salem *et al.*, 2011 (6)	9-year period	USA	Retrospective	cTACE	NS	122	123
Moreno-Luna *et al.*, 2013 (54)	April 2005 to February 2008	USA	Retrospective	cTACE	Glass microspheres	55	61
She *et al.*, 2014 (55)	August 2009 to April 2013	China	Retrospective	cTACE	Resin microspheres	16	16
Pitton *et al.*, 2015 (56)	April 2010 to July 2012	Germany	RCT	DEB-TACE	Resin microspheres	12	12
El Fouly *et al.*, 2015 (17)	November 2009 to October 2011	Germany/ Egypt	Prospective non-RCT	cTACE	Glass microspheres	42	44
Kolligs *et al.*, 2015 (18)	July 2007 to June 2011	Germany/ Spain	RCT	cTACE	Resin microspheres	15	13
Akinwande *et al.*, 2015 (57)	September 2007 to October 2013	USA	Prospective non-RCT	DEB-TACE	Glass microspheres	291	28
Salem *et al.*, 2016 (36)	October 2009 to October 2015	USA	RCT	cTACE	NS	21	24
Soydal *et al.*, 2016 (58)	June 2008 to November 2014	Turkey	Retrospective	cTACE	Resin microspheres	40	40
Akinwande *et al.*, 2016 (59)	2007 to 2013	USA	Prospective non-RCT	DEB-TACE	Glass microspheres	28	20
McDevitt *et al.*, 2017 (60)	March 2007 to August 2012	USA	Retrospective	DEB-TACE	Glass microspheres	24	26
Padia *et al.*, 2017 (27)	2010 to 2015	USA	Retrospective	cTACE and DEB-TACE	Glass microspheres	77	101
Biederman *et al.*, 2018 (8)	January 2012 to January 2016	USA	Retrospective	DEB-TACE	Glass microspheres	877	534
Kirchner *et al.*, 2019 (61)	November 2014 to March 2016	Germany	Prospective non-RCT	cTACE and DEB-TACE	Glass microspheres	46	21
Delicque *et al.*, 2019 (62)	May 2013 to May 2018	France	Retrospective	DEB-TACE or cTACE	Glass and resin microspheres	63	23
Hirsch *et al.*, 2021 (63)	October 2006 to February 2018	Australia	Retrospective	DEB-TACE	Resin microspheres	90	80
Kim *et al.*, 2021 (64)	March 2012 to December 2017	South Corea	Propensity matched study	cTACE	Glass and resin microspheres	83	54
Dhondt *et al.*, 2022 (65)	September 2011 to March 2018	Belgium	RCT	DEB-TACE	Glass microspheres	34	38
Chung *et al.*, 2023 (66)	September 2009 to March 2021	Korea	Retrospective	cTACE and DEB-TACE	Glass and resin microspheres	144	31

cTACE, conventional transarterial chemoembolization; DEB-TACE, drug eluting bead transarterial chemoembolization; SIRT, selective internal radiation therapy; NS, not specified; RCT, randomized controlled trial.

for TACE (18). Nevertheless, this was refuted by a single-centre retrospective study with 80 unresectable HCC patients (BCLC B or C stages), where those treated with SIRT had significantly longer OS than patients treated with TACE (39.2±4.62 *vs.* 30.6±3.68 months; P=0.01) (59). Moreover, SIRT was confirmed as an independent prognostic factor compared with TACE for OS (P=0.02) (64). Finally, only one study evaluated the liver function deterioration by using the model for end-stage liver disease (MELD) score variations after cTACE or SIRT in patients with unresectable unilobar HCC. The mean Delta MELD (defined as post treatment minus pre-treatment MELD score) was greater in the TACE group than in the SIRT group (P=0.02), and SIRT was independently associated with a lower Delta MELD score than TACE (P=0.02) (62).

Only a few studies have also compared SIRT and drug-eluting bead TACE (DEB-TACE) during the last decade, but the data now available are more heterogeneous and sometimes contradictory. Some studies reported similar results in terms of TTP, PFS and OS in patients with unresectable HCC treated with both endovascular treatments (8,56,60). In particular, TTP (P=0.03) and OS (P<0.001) were reported to be greater with DEB-TACE than with SIRT (63). These data were also confirmed in a single-centre prospective RCT (TRACE) that compared SIRT with DEB-TACE in patients with BCLC A/B not eligible for LR or thermoablation. The median TTP and OS were significantly higher in the SIRT arm than in the DEB-TACE arm (P=0.002 and P=0.006, respectively) (65).

Contrasting data are reported in the studies comparing SIRT *vs.* cTACE or DEB-TACE. Lance *et al.* showed no significant difference in OS between the SIRT and cTACE or DEB-TACE cohorts (P=0.33) (53). Contrary, in another study the ORRs were 84% for SIRT and 58% for TACE (P<0.001), and there was a higher PFS and OS in the SIRT group than in the TACE group (P=0.002, P=0.35, respectively) (27).

Even when QoL was compared in patients who underwent TACE (cTACE or DEB-TACE) or SIRT, the first treatment showed a slightly but not significantly higher decrease in QoL than the second (61). Although SIRT serves as a viable treatment alternative for a significant proportion of HCC cases, a subset of patients is not eligible for radioembolization. Thus, in a recent study, patients treated with cTACE or DEB-TACE (because not eligible for SIRT) were more favourable for early HCC progression. By comparing 144 patients who underwent SIRT and 31 patients who underwent TACE, the SIRT-ineligible group showed shorter TTP (P=0.02) and OS (P=0.12) than the SIRT-eligible group (66).

Several conflicting studies have been reported on this topic, and a trend towards better clinical outcomes with SIRT compared to TACE has been observed. In addition, BCLC B patients treated with SIRT have similar outcomes to those treated with other LRT, but SIRT might also have some advantages over TACE, such as the reduced number of treatment sessions for achieving similar results, which may be useful in certain situations. However, further clinical trials comparing SIRT with cTACE or DEB-TACE are still needed. Akinwande *et al.* showed in both prospective open noncontrolled studies comparing DEBs loaded with doxorubicin (DEB-DOX) and SIRT in unresectable HCC how OS and DCR were greater with DEB-DOX TACE than with SIRT and how the former was safer with lower toxicity than the latter for patients with PVI (57,59).

Sequential or combined treatment: *TACE plus SIRT*

HCC unresponsive to more cycles of TACE can be switched to another alternative and safe transarterial radiological treatment, SIRT. This concept was extensively demonstrated in a study with 30 patients refractory to TACE and after treatment with SIRT. The median OS after the first TACE and after SIRT was 32.3 months [95% confidence interval (CI): 17.2–42.1] and 14.8 months (95% CI: 8.33–26.5), respectively (67). Furthermore, SIRT was defined as a safe treatment, because no grade 4 or 5 adverse events occurred within 3 months after the procedure, and the most common clinical and biochemical grade 3 adverse events (fatigue in the 20% of cases and bilirubin increase in the 10%, respectively) were observed more often after treatment of the whole liver than the lobar or segmental treatment (67). Another analysis of 29 HCC patients who received DEB-TACE prior to SIRT was conducted to determine the response on MRI with mRECIST and the apparent diffusion coefficient (ADC) change relative to pre-SIRT imaging (ADCratio). In particular, there was no significant difference in survival between responders and non-responders determined by mRECIST (P=0.06), but responders determined by ADCratio had significantly better survival than non-responders (P=0.01) (68). In addition, in a recent study conducted by Vardar *et al.*, the efficacy of TACE and SIRT combination in HCC patients was investigated, by treating with TACE the areas previous targeted by SIRT but without CR or with progression. Patients who received TACE after SIRT to the same area

Table 4 Studies comparing SIRT versus systemic therapy (sorafenib) in patients with unresectable hepatocellular carcinoma and without potentially curative treatment

Author (year)	Enrolment period	Country	Study design	SIRT modality	Sample size (n)
Vilgrain *et al.*, 2017 (71)	December 2011 to March 2015	France	RCT	Resin microspheres	147 SIRT; 206 sorafenib
Chow *et al.*, 2018 (72)	July 2010 to May 2016	Asia-Pacific countries	RCT	Resin microspheres	182 SIRT; 178 sorafenib
Ricke *et al.*, 2019 (73)	January 2011 to April 2016	Europe/Turkey	RCT	Resin microspheres	216 SIRT + sorafenib; 208 sorafenib alone

SIRT, selective internal radiation therapy; RCT, randomized controlled trial.

targeted by SIRT had a significantly longer median OS and median TTP than patients who did not receive any additional transarterial therapy in the areas targeted by SIRT (P=0.003, P=0.02, respectively) (69).

The addition of TACE to radioembolization as treatment in unresectable HCC patients has not yet been extensively studied because there are few studies, but it could be a better option to consider in unresponsive cases to one transarterial treatment type.

In conclusion, SIRT is a safe and useful treatment in the setting of bridging to LT or downstaging therapy with promising results compared to TACE. However, the heterogeneity of the technique used within SIRT itself and of populations as well as the lack of standardized criteria in the downstaging setting make it impossible at this time to draw a general conclusion on the superiority of SIRT over other LRT.

Radioembolization of BCLC C stage HCC in patients without potentially curative treatment

Radioembolization vs. systemic therapy

Radioembolization has emerged as a well-established and effective treatment option for advanced-stage HCC, addressing gaps that exist in other therapies and leveraging the growing expertise within specialized centres (*Figure 1*). In fact, in a recent Radiation-Emitting SIR-Spheres in Non-Resectable (RESiN) liver tumour registry, the outcomes and toxicities of SIRT in patients with BCLC C HCC stratified into three groups based on tumour location, ECOG and CP were evaluated in the real world. Although there was no statistically significant difference in OS among the three groups (P=0.60), the Cox proportional hazard analysis predicted short OS for CP class B/C patients (P=0.01), without an association of macrovascular invasion (P=0.50) and ECOG score ≥1 (P=0.30) (70).

Furthermore, despite the growing diffusion of immunotherapies and the consideration of atezolizumab/bevacizumab as first-line therapy in BCLC C stage HCC patients, SIRT has been evaluated as an effective therapy for patients with locally advanced HCC with PVI (*Table 4*). In particular, because of the need to better identify good candidates for SIRT, a prognostic score in patients with nonmain PVI was proposed by considering bilirubin level, extension of portal vein tumour thrombosis and tumour burden (74).

Evidence regarding safety and effectiveness of SIRT in advanced HCCs conducted to perform more RCTs. In the SARAH (multicentre, open-label, phase III) RCT, patients with locally advanced HCC or new HCC not eligible for surgical resection, LT, thermal ablation, or HCC with two unsuccessful rounds of TACE were randomized to receive radioembolization with ^{90}Y-loaded resin microspheres (n=237) or oral sorafenib (n=222). It was noted that median OS did not significantly differ between the two groups (P=0.18) (71), but health-related quality of life (HRQoL) was preserved longer with SIRT than with sorafenib (75).

Even in another phase III trial, SIRveNIB (SIRT *vs.* sorafenib), there was no significant difference in terms of OS between patients treated with ^{90}Y resin microspheres SIRT and those treated with sorafenib (P=0.36) (72). Only in the SORAMIC trial, where sorafenib was compared to the combination of SIRT (^{90}Y-resin) and sorafenib, did the addition of radioembolization to sorafenib not lead to a significant improvement in OS (P=0.95) (73). All these three studies did not meet their primary endpoints, and probably even the absence of personalized dosimetry contributed to their negativity. However, in the SARAH trial, a post hoc analysis of dosimetry revealed that OS was longer in patients who received at least 100 Gy than in others

(P<0.001) (76).

In addition, due to their immunomodulatory effects, the combination of SIRT with immune checkpoint inhibitors (ICIs) has been shown to enhance the systemic inflammatory response as well as to increase the antitumour response. Since 2020, atezolizumab [antibody against programmed cell death-ligand 1 (PD-L1)] combined with bevacizumab [antibody against vascular endothelial growth factor (VEGF)] has become the standard of care in patients with advanced HCC (77). Unfortunately, there are few studies comparing the outcomes between SIRT and the combination of atezolizumab/bevacizumab. Therefore, no conclusion can be drawn at this time on the superiority of one over the other for these patients. However, a recent anchored matching-adjusted indirect comparison of time to deterioration in QoL in patients with unresectable HCC from the SARAH and IMbrave150 trials reported a trend but not a statistically significant difference (8.64 *vs.* 11.23 months, respectively; P=0.73) (77). Furthermore, although SIRT may achieve a similar time to deterioration in QoL compared with atezolizumab-bevacizumab, both seem to be more efficacious than sorafenib in maintaining HRQoL (78).

However, several clinical trials are evaluating the safety and efficacy of ICIs and SIRT. An ongoing phase I study (NCT03812526) is currently investigating the efficacy of combining nivolumab [an antibody targeting programmed cell death-1 (PD-1)] with SIRT following surgical resection, with a primary endpoint of recurrence rate. Additionally, an early phase I study (NCT03099564) is exploring the combination of pembrolizumab (antibody against PD-1) with SIRT in patients with HCC who are not eligible for surgical resection or LT, with a primary endpoint of 6-month PFS. Another phase I study (NCT05701488) is assessing the safety and tolerability of tremelimumab [antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)] and durvalumab (antibody against PD-L1) with or without SIRT in participants with resectable HCC after surgical resection. Conversely, a phase Ib trial (NCT04605731) is underway to assess the safety of durvalumab in combination with tremelimumab or durvalumab alone following SIRT in patients diagnosed with unresectable locally advanced BCLC B/C HCC who have CP A and a tumour burden of less than 50%. The primary outcome of this trial is to determine the ORR based on RECIST, mRECIST, and immune mRECIST criteria.

A multicentre randomized phase II trial (NCT05063565) is currently underway to assess the effectiveness of combining SIRT with durvalumab and tremelimumab compared to SIRT alone, focusing on ORR and response duration in treatment-naïve HCC patients who are not eligible for curative treatments or have chosen not to undergo them. Similarly, another phase II randomized trial (NCT04522544) aims to investigate the safety and efficacy of durvalumab plus tremelimumab after TACE or SIRT in patients with multifocal HCC or with a single nodule who are not eligible for curative treatments or those with hepatic veins or PVI. The phase II study NCT04522544 is assessing immunotherapy with durvalumab and tremelimumab in combination with either SIRT or TACE for intermediate stage HCC with a pick-the-winner design.

Furthermore, a multicentre randomized phase II trial (NCT04541173) is currently underway to assess the treatment of patients with CP A and BCLC B HCC who are not suitable candidates for surgical treatments. The trial compares two treatment arms: one receiving SIRT alone and the other receiving SIRT followed by atezolizumab plus bevacizumab, with the primary endpoint to evaluate the 1-year PFS rate. The multinational, phase II, parallel-arm, double-blind, placebo-controlled, two-arm study (NCT05377034) was designed to assess the efficacy and safety of SIRT followed by atezolizumab plus bevacizumab (study arm) *vs.* SIRT followed by placebo (control arm) in patients with locally advanced HCC.

The ongoing multicentre open-label single-arm study, registered as NCT03380130, is currently assessing the effectiveness of nivolumab as a treatment for HCC patients who qualify for LRT following SIRT. Additionally, an open-label phase II trial conducted in a single centre, registered as NCT03033446, is investigating the combination of SIRT and nivolumab in Asian patients with advanced HCC.

While the 2022 BCLC update suggests considering SIRT as a treatment option for early-stage HCC, it is worth noting that there is extensive utilization of SIRT as a first-line therapy in clinical practice for patients with advanced HCC.

Nevertheless, SIRT in combination with immunotherapies could be of useful relevance in the near future in advanced HCC treatment.

Cost effectiveness of SIRT

Despite the high cost of transarterial and systemic therapies, SIRT is a cost-effective short- and long-term therapy for the treatment of intermediate-advanced HCC (79).

Treatment strategies and related costs for BCLC B or C stage HCC were investigated in four Italian centres, and the

total costs of treatment per patient amounted to 12,214.54€ with sorafenib, 13,418.49€ with TACE, and 26,106.08€ with SIRT (80). Some studies have shown that SIRT has the potential to be a cost-effective alternative to sorafenib in patients with unresectable HCC (81-83). In the same way, Rognoni *et al.* demonstrated how the progressive increase in utilization rates of SIRT over sorafenib in the next 5 years is projected to result in a global cost savings of approximately 7 million Euros (84). Recently, Marqueen *et al.* conducted a study to compare the cost-effectiveness of SIRT and sorafenib from the perspective of the United States health care sector. They estimate higher costs and quality-adjusted life years (QALYs) over a 5-year timeframe for sorafenib than SIRT by employing a probabilistic sensitivity analysis. They further highlighted that sorafenib would only be deemed economically attractive when its current price decreased by more than 50% in comparison to SIRT (85). Another cost-effectiveness analysis was performed to compare SIRT, TACE and percutaneous ablation as bridging therapy. Among these options, ablation emerged as the dominant strategy, displaying the lowest expected cost and highest effectiveness. Furthermore, the probabilistic sensitivity analysis indicated that ablation was the most cost-effective strategy prior to LT in 93.9% of simulations (86).

Based on these data, economic evaluations of SIRT for HCC treatment are heterogeneous, especially in the health care sectors of several countries worldwide. Different parameters may influence these contrasting outcomes in terms of the economic benefits of SIRT. In particular, these causes may depend on the different management of HCC that has changed in recent years due to the development of new systemic therapies and the availability of new diagnostic algorithms capable of influencing a different consumption of resources. However, technical parameters such as the radiologist's experience in determining treatment response, the use of personalized dosimetry, the worldwide geographic distribution of HCC aetiologies, or varied treatment decisions across different countries also represent relevant issues for defining heterogeneous consumption resources in the clinical practice of HCC management with numerous economic implications as well as different cost-effectiveness ratios of SIRT.

Conclusions

Radioembolization is a safe and effective treatment for selected patients at all BCLC stages of HCC, and it has many benefits with curative and palliative intents by improving QoL. However, this technique is not commonly available worldwide, and studies are often reported by expert centres. Because of its advantages in many situations, SIRT is a promising treatment for HCC patients, possibly in combination with other treatments, such as immunotherapy.

SIRT has shown encouraging outcomes, exhibiting similar OS, TTP, and radiological response rates when compared to other established treatment approaches across all stages of BCLC. Additionally, SIRT can be employed as a treatment method for downstaging HCC patients who initially exceed the criteria for LT, serving as a bridge to LT, and it can also be combined with other modalities, such as RL or segmentectomy.

Although initially perceived as a palliative measure for patients with HCC, radioembolization has now evolved into a significant component of the comprehensive care provided to individuals with HCC across a wide range of clinical indications.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-504/rc

Peer Review File: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-504/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-504/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
2. Mazzaferro V, Sposito C, Bhoori S, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology 2013;57:1826-37.
3. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys 2007;68:13-23.
4. Sangro B, Bilbao JI, Iñarrairaegui M, et al. Treatment of hepatocellular carcinoma by radioembolization using 90Y microspheres. Dig Dis 2009;27:164-9.
5. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010;138:52-64.
6. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011;140:497-507.e2.
7. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76:681-93.
8. Biederman DM, Titano JJ, Korff RA, et al. Radiation Segmentectomy versus Selective Chemoembolization in the Treatment of Early-Stage Hepatocellular Carcinoma. J Vasc Interv Radiol 2018;29:30-37.e2.
9. Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol 2021;6:17-29.
10. Salem R, Johnson GE, Kim E, et al. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. Hepatology 2021;74:2342-52.
11. Gregory J, Tselikas L, Allimant C, et al. Defining textbook outcome for selective internal radiation therapy of hepatocellular carcinoma: an international expert study. Eur J Nucl Med Mol Imaging 2023;50:921-8.
12. Garin E, Tselikas L, Guiu B, et al. Long-Term Overall Survival After Selective Internal Radiation Therapy for Locally Advanced Hepatocellular Carcinomas: Updated Analysis of DOSISPHERE-01 Trial. J Nucl Med 2024;65:264-9.
13. Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology 2008;47:71-81.
14. Hilgard P, Hamami M, Fouly AE, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology 2010;52:1741-9.
15. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology 2011;54:868-78.
16. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging 2019;46:1695-704.
17. El Fouly A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? Liver Int 2015;35:627-35.
18. Kolligs FT, Bilbao JI, Jakobs T, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int 2015;35:1715-21.
19. Woo HY, Kim DY, Heo J, et al. Effect of yttrium-90 radioembolization on outcomes in Asian patients with early to advanced stage hepatocellular carcinoma. Hepatol Res 2017;47:387-97.
20. Sangro B, Maini CL, Ettorre GM, et al. Radioembolisation in patients with hepatocellular carcinoma that have previously received liver-directed therapies. Eur J Nucl Med Mol Imaging 2018;45:1721-30.
21. Ghosn M, Derbel H, Kharrat R, et al. Prediction of overall survival in patients with hepatocellular carcinoma treated with Y-90 radioembolization by imaging response criteria. Diagn Interv Imaging 2021;102:35-44.
22. Reizine E, Chalaye J, Mule S, et al. Utility of Early Posttreatment PET/CT Evaluation Using FDG or (18) F-FCH to Predict Response to (90)Y Radioembolization

in Patients With Hepatocellular Carcinoma. AJR Am J Roentgenol 2022;218:359-69.
23. Kolligs F, Arnold D, Golfieri R, et al. Factors impacting survival after transarterial radioembolization in patients with hepatocellular carcinoma: Results from the prospective CIRT study. JHEP Rep 2023;5:100633.
24. Riaz A, Gates VL, Atassi B, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. Int J Radiat Oncol Biol Phys 2011;79:163-71.
25. Padia SA, Kwan SW, Roudsari B, et al. Superselective yttrium-90 radioembolization for hepatocellular carcinoma yields high response rates with minimal toxicity. J Vasc Interv Radiol 2014;25:1067-73.
26. Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology 2014;60:192-201.
27. Padia SA, Johnson GE, Horton KJ, et al. Segmental Yttrium-90 Radioembolization versus Segmental Chemoembolization for Localized Hepatocellular Carcinoma: Results of a Single-Center, Retrospective, Propensity Score-Matched Study. J Vasc Interv Radiol 2017;28:777-785.e1.
28. Lewandowski RJ, Gabr A, Abouchaleh N, et al. Radiation Segmentectomy: Potential Curative Therapy for Early Hepatocellular Carcinoma. Radiology 2018;287:1050-8.
29. Arndt L, Villalobos A, Wagstaff W, et al. Evaluation of Medium-Term Efficacy of Y90 Radiation Segmentectomy vs Percutaneous Microwave Ablation in Patients with Solitary Surgically Unresectable < 4 cm Hepatocellular Carcinoma: A Propensity Score Matched Study. Cardiovasc Intervent Radiol 2021;44:401-13.
30. Kim E, Sher A, Abboud G, et al. Radiation segmentectomy for curative intent of unresectable very early to early stage hepatocellular carcinoma (RASER): a single-centre, single-arm study. Lancet Gastroenterol Hepatol 2022;7:843-50.
31. De la Garza-Ramos C, Montazeri SA, Croome KP, et al. Radiation Segmentectomy for the Treatment of Solitary Hepatocellular Carcinoma: Outcomes Compared with Those of Surgical Resection. J Vasc Interv Radiol 2022;33:775-785.e2.
32. Gaba RC, Lewandowski RJ, Kulik LM, et al. Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Ann Surg Oncol 2009;16:1587-96.
33. Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol 2013;59:1029-36.
34. Bekki Y, Marti J, Toshima T, et al. A comparative study of portal vein embolization versus radiation lobectomy with Yttrium-90 micropheres in preparation for liver resection for initially unresectable hepatocellular carcinoma. Surgery 2021;169:1044-51.
35. Mohamed M, Katz AW, Tejani MA, et al. Comparison of outcomes between SBRT, yttrium-90 radioembolization, transarterial chemoembolization, and radiofrequency ablation as bridge to transplant for hepatocellular carcinoma. Adv Radiat Oncol 2016;1:35-42.
36. Salem R, Gordon AC, Mouli S, et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology 2016;151:1155-1163.e2.
37. Zori AG, Ismael MN, Limaye AR, et al. Locoregional Therapy Protocols With and Without Radioembolization for Hepatocellular Carcinoma as Bridge to Liver Transplantation. Am J Clin Oncol 2020;43:325-33.
38. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009;9:1920-8.
39. Gabr A, Abouchaleh N, Ali R, et al. Comparative study of post-transplant outcomes in hepatocellular carcinoma patients treated with chemoembolization or radioembolization. Eur J Radiol 2017;93:100-6.
40. Gabr A, Kulik L, Mouli S, et al. Liver Transplantation Following Yttrium-90 Radioembolization: 15-Year Experience in 207-Patient Cohort. Hepatology 2021;73:998-1010.
41. Villalobos A, Wagstaff W, Guo M, et al. Predictors of Successful Yttrium-90 Radioembolization Bridging or Downstaging in Patients with Hepatocellular Carcinoma. Can J Gastroenterol Hepatol 2021;2021:9926704.
42. Assalino M, Terraz S, Grat M, et al. Liver transplantation for hepatocellular carcinoma after successful treatment of macrovascular invasion - a multi-center retrospective cohort study. Transpl Int 2020;33:567-75.
43. Gordon AC, Gabr A, Riaz A, et al. Radioembolization Super Survivors: Extended Survival in Non-operative Hepatocellular Carcinoma. Cardiovasc Intervent Radiol 2018;41:1557-65.
44. Ranganathan S, Gabr A, Entezari P, et al. Radioembolization for Intermediate-Stage Hepatocellular

Carcinoma Maintains Liver Function and Permits Systemic Therapy at Progression. J Vasc Interv Radiol 2023;34:968-75.
45. De la Garza-Ramos C, Overfield CJ, Montazeri SA, et al. Biochemical Safety of Ablative Yttrium-90 Radioembolization for Hepatocellular Carcinoma as a Function of Percent Liver Treated. J Hepatocell Carcinoma 2021;8:861-70.
46. Saini A, Wallace A, Alzubaidi S, et al. History and Evolution of Yttrium-90 Radioembolization for Hepatocellular Carcinoma. J Clin Med 2019;8:55.
47. Liebl M, Pedersoli F, Zimmermann M, et al. Induction of Contralateral Hepatic Hypertrophy by Unilobar Yttrium-90 Transarterial Radioembolization versus Portal Vein Embolization: An Animal Study. J Vasc Interv Radiol 2021;32:836-842.e2.
48. Garlipp B, de Baere T, Damm R, et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. Hepatology 2014;59:1864-73.
49. Sun HC, Zhu XD. Downstaging Conversion Therapy in Patients With Initially Unresectable Advanced Hepatocellular Carcinoma: An Overview. Front Oncol 2021;11:772195.
50. Cappelli A, Sangro P, Mosconi C, et al. Transarterial radioembolization in patients with hepatocellular carcinoma of intermediate B2 substage. Eur J Nucl Med Mol Imaging 2019;46:661-8.
51. Carr BI, Kondragunta V, Buch SC, et al. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. 2010; 116:1305-14.
52. Kooby DA, Egnatashvili V, Srinivasan S, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol 2010;21:224-30.
53. Lance C, McLennan G, Obuchowski N, et al. Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. J Vasc Interv Radiol 2011;22:1697-705.
54. Moreno-Luna LE, Yang JD, Sanchez W, et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. Cardiovasc Intervent Radiol 2013;36:714-23.
55. She WH, Cheung TT, Yau TC, et al. Survival analysis of transarterial radioembolization with yttrium-90 for hepatocellular carcinoma patients with HBV infection. Hepatobiliary Surg Nutr 2014;3:185-93.
56. Pitton MB, Kloeckner R, Ruckes C, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 2015;38:352-60.
57. Akinwande O, Philips P, Scoggins C, et al. Radioembolization Versus Chemoembolization (DEBDOX) for the Treatment of Unresectable Hepatocellular Carcinoma: A Propensity Matched Study. Anticancer Res 2016;36:239-46.
58. Soydal C, Arslan MF, Kucuk ON, et al. Comparison of survival, safety, and efficacy after transarterial chemoembolization and radioembolization of Barcelona Clinic Liver Cancer stage B-C hepatocellular cancer patients. Nucl Med Commun 2016;37:646-9.
59. Akinwande O, Kim D, Edwards J, et al. Is radioembolization ((90)Y) better than doxorubicin drug eluting beads (DEBDOX) for hepatocellular carcinoma with portal vein thrombosis? A retrospective analysis. Surg Oncol 2015;24:270-5.
60. McDevitt JL, Alian A, Kapoor B, et al. Single-Center Comparison of Overall Survival and Toxicities in Patients with Infiltrative Hepatocellular Carcinoma Treated with Yttrium-90 Radioembolization or Drug-Eluting Embolic Transarterial Chemoembolization. J Vasc Interv Radiol 2017;28:1371-7.
61. Kirchner T, Marquardt S, Werncke T, et al. Comparison of health-related quality of life after transarterial chemoembolization and transarterial radioembolization in patients with unresectable hepatocellular carcinoma. Abdom Radiol (NY) 2019;44:1554-61.
62. Delicque J, Hermida M, Piron L, et al. Intra arterial treatment of hepatocellular carcinoma: Comparison of MELD score variations between radio-embolization and chemo-embolization. Diagn Interv Imaging 2019;100:689-97.
63. Hirsch RD, Mills C, Sawhney R, et al. SIRT Compared with DEB-TACE for Hepatocellular Carcinoma: a Real-world Study (the SITAR Study). J Gastrointest Cancer 2021;52:907-14.
64. Kim MA, Jang H, Choi NR, et al. Yttrium-90 Radioembolization Is Associated with Better Clinical Outcomes in Patients with Hepatocellular Carcinoma Compared with Conventional Chemoembolization: A Propensity Score-Matched Study. J Hepatocell Carcinoma

2021;8:1565-77.
65. Dhondt E, Lambert B, Hermie L, et al. (90) Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial. Radiology 2022;303:699-710.
66. Chung SW, Cho H, Shin H, et al. Transarterial chemoembolization as an alternative to radioembolization is associated with earlier tumor recurrence than in radioembolization-eligible patients. Front Oncol 2023;13:1081479.
67. Klompenhouwer EG, Dresen RC, Verslype C, et al. Safety and Efficacy of Transarterial Radioembolisation in Patients with Intermediate or Advanced Stage Hepatocellular Carcinoma Refractory to Chemoembolisation. Cardiovasc Intervent Radiol 2017;40:1882-90.
68. Klompenhouwer EG, Dresen RC, Verslype C, et al. Transarterial Radioembolization Following Chemoembolization for Unresectable Hepatocellular Carcinoma: Response Based on Apparent Diffusion Coefficient Change is an Independent Predictor for Survival. Cardiovasc Intervent Radiol 2018;41:1716-26.
69. Vardar BU, Meram E, Karaoglu K, et al. Radioembolization Followed by Transarterial Chemoembolization in Hepatocellular Carcinoma. Cureus 2022;14:e23783.
70. Goswami P, Adeniran OR, K Frantz S, et al. Overall survival and toxicity of Y90 radioembolization for hepatocellular carcinoma patients in Barcelona Clinic Liver Cancer stage C (BCLC-C). BMC Gastroenterol 2022;22:467.
71. Vilgrain V, Pereira H, Assenat E, 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.
72. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol 2018;36:1913-21.
73. Ricke J, Klümpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol 2019;71:1164-74.
74. Spreafico C, Sposito C, Vaiani M, et al. Development of a prognostic score to predict response to Yttrium-90 radioembolization for hepatocellular carcinoma with portal vein invasion. J Hepatol 2018;68:724-32.
75. Pereira H, Bouattour M, Dioguardi Burgio M, et al. Health-related quality of life in locally advanced hepatocellular carcinoma treated by either radioembolisation or sorafenib (SARAH trial). Eur J Cancer 2021;154:46-56.
76. Hermann AL, Dieudonné A, Ronot M, et al. Relationship of Tumor Radiation-absorbed Dose to Survival and Response in Hepatocellular Carcinoma Treated with Transarterial Radioembolization with (90)Y in the SARAH Study. Radiology 2020;296:673-84.
77. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
78. Agirrezabal I, Brennan VK, Colaone F, et al. Transarterial Radioembolization Versus Atezolizumab-Bevacizumab in Unresectable Hepatocellular Carcinoma: A Matching-Adjusted Indirect Comparison of Time to Deterioration in Quality of Life. Adv Ther 2022;39:2035-51.
79. Alonso JC, Casans I, González FM, et al. Economic evaluations of radioembolization with Itrium-90 microspheres in hepatocellular carcinoma: a systematic review. BMC Gastroenterol 2022;22:326.
80. Colombo GL, Cammà C, Attili AF, et al. Patterns of treatment and costs of intermediate and advanced hepatocellular carcinoma management in four Italian centers. Ther Clin Risk Manag 2015;11:1603-12.
81. Lucà MG, Nani R, Schranz M, et al. Treatment of hepatocellular carcinoma: a cost analysis of yttrium-90 transarterial radioembolization versus sorafenib. Future Oncol 2018;14:727-35.
82. Muszbek N, Remak E, Evans R, et al. Cost-utility analysis of selective internal radiation therapy with Y-90 resin microspheres in hepatocellular carcinoma. Future Oncol 2021;17:1055-68.
83. Claxton L, Walton M, Sharif-Hurst S, et al. The Cost-Effectiveness of Selective Internal Radiation Therapies Compared With Sorafenib for Treating Advanced Unresectable Hepatocellular Carcinoma in the United Kingdom. Value Health 2022;25:787-95.
84. Rognoni C, Ciani O, Sommariva S, et al. Trans-arterial radioembolization for intermediate-advanced hepatocellular carcinoma: a budget impact analysis. BMC Cancer 2018;18:715.
85. Marqueen KE, Kim E, Ang C, et al. Cost-Effectiveness Analysis of Selective Internal Radiotherapy With Yttrium-90 Versus Sorafenib in Locally Advanced

Hepatocellular Carcinoma. JCO Oncol Pract 2021;17:e266-77.
86. Wu X, Heller M, Kwong A, et al. Cost-Effectiveness Analysis of Interventional Liver-Directed Therapies for a Single, Small Hepatocellular Carcinoma in Liver Transplant Candidates. J Vasc Interv Radiol 2023;34:1237-1246.e3.

Cite this article as: Vigneron P, Franzè MS, Chalaye J, Tacher V, Sessa A, Luciani A, Kobeiter H, Regnault H, Bejan A, Calderaro J, Rhaiem R, Sommacale D, Raimondo G, Leroy V, Brustia R, Amaddeo G. Selective internal radiation therapy across Barcelona Clinic Liver Cancer (BCLC) stages of hepatocellular carcinoma: literature review. HepatoBiliary Surg Nutr 2024;13(6):974-990. doi: 10.21037/hbsn-23-504