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Radioembolization for hepatocellular carcinoma: current role and future directions – the medical oncologist's perspective

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Hepatic Oncology

Practice points

- Radical therapies such as resection, radiofrequency ablation or transplantation are considered the gold standard for early-stage hepatocellular carcinoma.
- Where patients with hepatocellular carcinoma are not suitable for radical therapies, radioembolization with yttrium-90 is a promising new liver-directed therapy.
- Multiple large series have reported encouraging efficacy data with yttrium-90, including downstaging to resection or transplantation in some patients.
- Careful, multidisciplinary patient selection is required to achieve the best outcomes.
- To minimize the risk of uncommon but potentially major adverse events, radioembolization should be administered by an experienced interventional radiologist.
- The results of multiple randomized studies of radioembolization alone or in combination with other treatments, are compared with current standard of care.

SUMMARY The incidence and impact of hepatocellular carcinoma (HCC) continues to increase worldwide. While radical therapies such as resection, radiofrequency ablation or transplantation are potentially curative for patients with early-stage HCC, the majority of patients in routine practice present with more advanced tumors, where treatment goals are palliation and extending survival. With multiple new and promising treatment options emerging for these patients, the challenge for the medical oncologist is how best to integrate these therapies into routine clinical practice. Here we review the most recent data on the efficacy and safety of yttrium-90 radioembolization in HCC, the considerations involved in patient selection, and the optimal assessment and management of patients receiving treatment. We also examine the potential impact of several ongoing clinical trials.

KEYWORDS:

- hepatocellular carcinoma
- radioembolization • SIRT
- ⁹⁰Y

Background

In hepatocellular carcinoma (HCC), tumor growth frequently occurs in the context of underlying cirrhosis, and tumor progression as well as the cirrhosis can have an impact on survival. Radical therapies such as resection, radiofrequency ablation (RFA) or transplantation are considered the gold standard for early-stage HCC [1]. However, in practice, the majority of patients present with unresectable tumors falling beyond the Milan criteria for transplantation. Factors that frequently preclude the use of curative therapies include patients presenting with intermediate- or advanced-stage disease characterized by multinodular disease (>5 tumor nodules), extensive cirrhosis and consequent poor functional liver reserve, or tumor proximity to critical structures, for example, bile ducts, or tumor invasion of the

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portal vein (portal vein thrombosis [PVT]) [1]. Therefore, unresectable HCC remains a significant problem requiring alternative treatment options with palliative intent or with the potential to downstage or downsize tumors to radical treatment (resection/ablation/transplantation). Here we review the role of radioembolization. Note: a review of other local therapies is beyond the scope of this paper.

Treatment of unresectable HCC

Standard therapies for unresectable HCC that is not amenable to ablation or transplantation, vary by disease stage and include transcatheter arterial chemoembolization (TACE) for early- and intermediate-stage disease, and the systemic oral multikinase inhibitor sorafenib in advanced disease [1]. (A newer type of TACE with drug-eluting beads [DEB-TACE] is now increasingly being used for intermediate-stage HCC).

Transarterial liver-targeted therapies are particularly relevant in HCC based on the tendency of these tumors to remain predominantly liver confined [2]. TACE and DEB-TACE are two such therapies that combine the antitumor effect of targeted chemotherapy with tumor ischemia/hypoxia induced by a strong embolic effect [3].

For a radiosensitive tumor such as HCC that is confined to the liver, radioembolization (RE) with yttrium-90 (⁹⁰Y) microspheres represents a promising therapeutic option based on the ability to deliver intrahepatic localized radiation preferentially to the tumor, combined with minimal embolic effect (RE microspheres are substantially smaller in size to those used for DEB-TACE or TACE) [3].

There are two commercially available preparations of radioactive microspheres, SIR-Spheres® (resin microspheres, Sirtex Medical, Ltd, Sydney, Australia) and TheraSphere® (glass microspheres, BTG plc, London, UK), which have been studied extensively in HCC. Despite some differences in the physical properties of the microspheres, results from large, multicenter case series indicate resin and glass microspheres are associated with equivalent clinical outcomes in HCC (response to treatment, survival, safety/tolerability) [4,5].

From a practical or clinical standpoint, HCC cases are often considered solely the realm of hepatologists and hepatobiliary surgeons. However, differing clinical settings worldwide mean that in many countries, patients with HCC often present first to medical oncologists

who are now increasingly involved in diagnosing and managing HCC cases – including making treatment decisions and coordinating patient care and follow-up, ideally as part of a multidisciplinary team.

Therefore, the present review has been written for the medical oncologist, for whom the role of emerging therapies such as RE for unresectable HCC may seem confounding, especially in the context of disease stage and current standard regimens. We highlight the evidence of the efficacy and safety profile of RE in unresectable HCC with a focus on recent large, multicenter case series (bearing in mind the limitations of the evidence). The aim is to assist medical oncologists to understand the potential role for RE at specific stages of disease. We use evidence-based predictors of treatment response to emphasize and guide careful patient selection – a crucial step for optimizing clinical outcomes. The review also lists upcoming trials and explores the many remaining challenges yet to be addressed in this complex field.

Efficacy of RE in unresectable HCC

Over the past decade and especially in recent years, numerous large series (predominantly retrospective series and some noncontrolled prospective studies) have reported the efficacy of RE with ⁹⁰Y resin or glass microspheres in patients with unresectable HCC, including those with advanced disease (Table 1) [4–13]. Tumor response rates (complete response + partial response) of 12–54% have been reported using WHO or RECIST criteria, and up to 77% using EASL criteria (which also measures lesion necrosis) – Figures 1 & 2. Disease control rates achieved were high, ranging from 76 to 97% of patients treated in these studies (Table 1).

RE can reduce tumor burden in HCC, resulting in tumor downstaging to resection or transplantation in some patients [14–17]. In patients downstaged to transplantation after RE, analysis of explant livers showed that RE induced complete pathological necrosis in 89% of lesions with pretreatment size less than 3 cm [18].

Median tumor progression intervals varied with disease stage. Median TTP (time to progression) after RE ranged from 25.1 months (BCLC-A) to 13 months (BCLC-B) and 6–7 months for BCLC-C disease [5,13].

Median overall survival post RE in HCC patients ranged from 9.4 to 20.5 months for entire cohorts in large series (Table 1). Survival

Table 1. Response rates and median overall survival after ⁹⁰Y radioembolization for unresectable hepatocellular carcinoma.

Study reference and study population by BCLC disease stage (if reported)	WHO or RECIST response (change in tumor volume)			EASL response (volume + necrosis) (CR + PR [%])	Median overall survival (95% CI:)	Ref.
	CR (%)	PR (%)	Disease control (CR + PR + SD [%])			
Lau (n = 71)		27			9.4 months (1.8–46.4)	[6]
Kulik (n = 108)		42	77	70	No PVT: 15.4 months Branch PVT: 10 months Main PVT: 4.4 months	[7]
Salem (n = 245) [†] BCLC-A: 17% BCLC-B: 28% BCLC-C: 52% BCLC-D: 3%	0	44	NR	59	BCLC-A: 26.9 months BCLC-B: 17.2 months BCLC-C: 7.3 months BCLC-D: 2.5 months	[5]
Strigari [§] (n = 73)	1	53	97	77	NR	[8]
Hilgard (n = 76) [‡] Advanced HCC	0	15		40	16.4 months	[9]
Iñarrairaegui (n = 72) BCLC-A: 19% BCLC-B: 46% BCLC-C: 35%	0	12	78	NR	13 months (9.6–16.3)	[10]
Carr (n = 99)	3	38	76		11.5 months	[11]
Salem (n = 123) BCLC-A: 35% BCLC-B: 53% BCLC-C: 10% BCLC-D: 2%		49	NR	72	All patients: 20.5 months (15.7–29.1) BCLC-A: 27.3 months BCLC-B: 17.2 months BCLC-C: 22.1 months BCLC-D: 2.4 months	[12]
Mazzaferro (n = 53) BCLC-B: 33% BCLC-C: 67%	NR	40 [§]	79	40	All patients: 15 months (12.0–18.0) BCLC-B: 18 months BCLC-C: 13 months	[13]
Sangro (n = 325) BCLC-A: 16% BCLC-B: 26.8% BCLC-C: 56.3% BCLC-D: 0.9%	NR	NR	NR	NR	All patients: 12.8 months (10.9–15.7) BCLC-A: 24.4 months BCLC-B: 16.9 months BCLC-C: 10 months BCLC-D: 5.2 months	[4]

[†]Total study population = 291 patients (survival results reported for 245 without extrahepatic metastases at baseline, of these 234 had imaging follow-up for response rate evaluation).

[‡]Total study population = 108 patients (radiologic response evaluation possible in 76 patients).

[§]RECIST criteria used.

[¶]CR + PR.

BCLC: Barcelona clinic liver cancer staging; CR: Complete response; EASL: European association for the study of liver; HCC: Hepatocellular carcinoma; NR: Not reported; PR: Partial response; PVT: Portal vein thrombosis; SD: Stable disease.

duration varied by disease stage – with the longest median survival times (20.5–27.9 months) seen in patients with early-stage (BCLC-A) HCC, decreasing to 16.9–18 months in BCLC-B (intermediate-stage disease) and patients with BCLC-C (advanced) disease experiencing shorter survival of 7.3–10 months (Table 1).

The 2011 ENRY study reported by Sangro *et al.* was the first large, multicenter

evaluation of RE and included the largest series of HCC patients (n = 325), of whom a third were followed prospectively [4]. For the entire cohort, survival varied significantly by baseline characteristics including BCLC stage (Table 1), ECOG performance status, hepatic function (Child-Pugh class, ascites and baseline bilirubin), tumor burden (number of nodules, α -fetoprotein) and presence of extrahepatic disease (Table 2). Longer

Figure 1. Response to radioembolization in a patient (male; 66 years) with hepatocellular carcinoma. Computerized tomography image prior to radioembolization – lesion diameter 65.2 mm.

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median survival was noted in patients with ECOG 0 compared with ECOG 1–2; or with one to five tumor nodules versus those with more than five nodules; in patients without extrahepatic disease compared with those with extrahepatic disease; with INR less than 1.2 versus those with INR more than 2; and in those with baseline bilirubin ≤ 1.5 mg/dl versus bilirubin > 1.5 mg/dl (Table 2). Median survival was longer in patients with a patent portal vein versus those with PVT (branch or main).

Studies of locoregional therapies in HCC are limited by the lack of randomized controlled trials. Comparing data across studies is challenging given the variation in patient selection and follow-up, and in the absence of randomized studies, formal meta-analysis of the studies cannot be performed. Nevertheless, a substantial body of data including recent reports of three large series of patients undergoing RE ($n = 724$ in total) at separate institutions worldwide has demonstrated similar outcomes, supporting the potential therapeutic benefit of RE in patients with unresectable HCC [4,5,9].

Collectively, the authors of the two largest series conclude their results provide sound indication that RE with ^{90}Y microspheres may produce a clinically relevant survival benefit across different tumor stages, including for patients

with advanced disease who typically have few treatment options [4,5].

Multivariate predictors of survival after RE in HCC

Data from the two largest series indicate that prognosis after RE largely depends on hepatic function and tumor burden [4,5].

In the 2011 ENRY study, in multivariate analyses, performance status, disease burden (number of nodules), presence of extrahepatic disease and liver function (as measured by total bilirubin > 1.5 mg/dl) were the most significant independent predictors of survival after treatment (Table 3) [4]. Within the background of BCLC staging, multivariate analysis indicated increased tumor burden (represented by multinodularity and bilobar involvement) or aggressiveness (reflected by high AFP, PVT or poor performance status) and worsened liver function (reflected by increased bilirubin or INR) provide additional prognostic information [4]. Specific multivariate predictors of survival for each BCLC stage also were defined (Table 3).

Salem *et al.*'s analysis of long-term outcomes in a large prospective study of 291 patients treated with ^{90}Y glass microspheres corroborated the above findings [5]. The authors reported age; sex; performance status; portal hypertension; tumor distribution; baseline bilirubin, albumin and AFP levels; and radiological response to treatment (WHO response or EASL response), were multivariate prognostic indicators of survival.

Taken together the data provide important information to the clinician regarding patient selection when considering RE for unresectable HCC, underscoring the importance of choosing patients with preserved hepatic function, good performance status and liver-confined disease in order to optimize results of this therapy.

RE for HCC: safety & toxicity

The presence of underlying cirrhosis with variably compromised liver function is a confounding factor in the majority of HCC cases. In practice, studies to date have included large numbers of patients with cirrhosis (often the majority of patients), and in doing so have repeatedly demonstrated the safety of RE in the presence of underlying cirrhosis, provided patients have good hepatic function before treatment [4,5,7,19]. However, a recent study found that cirrhosis is an independent risk factor for radioembolization-induced liver disease (REILD), a rare but

clinically relevant complication of RE [20]. In this series, among patients with cirrhosis, the presence of small liver volume (<1.5 l), abnormal bilirubin at baseline (>1.2 mg/dl) or treatment in a selective fashion were independently associated with the development of REILD. The study's authors have developed a modified protocol for RE delivery that significantly reduces the risk of REILD [20].

In large series of HCC patients treated with RE, common procedure-related adverse events were usually mild (grade 1/2) and included nausea/vomiting and abdominal pain, with very few grade III events. The most common symptom was development of transient fatigue in approximately 50% of patients, which typically occurred in the first few weeks after RE and lasted 1–2 weeks [4,5]. Fatigue was most commonly reported in patients with advanced disease [4]. Typically, adverse events were easily controlled with medication if necessary and usually subsided in less than 48 h [4]. Grade 3–4 elevations in bilirubin varied from 5.8 to 19%, consistent with previous findings as well as the natural biology of HCC [4,5].

Acute (and at times late developing) and potentially severe GI adverse effects, for example, radiation gastroduodenitis, gastroduodenal ulcers and rarely, pancreatitis may occur as a consequence of microsphere deposition into nontarget organs. Unidentified or inadequately occluded collateral vessels may cause off-target microsphere delivery and irradiation of the gastric or duodenal mucosa [21]. Therefore, meticulous pretreatment workup and microsphere administration technique in the hands of an experienced interventional radiologist are crucial to minimize the risk of GI complications. The incidence of gastric ulceration is reportedly less than 5% if proper percutaneous techniques are used [22]. Accordingly, in experienced centers, adverse effects relating to delivery of microspheres into nontarget tissues were infrequent – with low rates of gastric ulceration reported in the two largest studies of RE for HCC (0–3.7%) [4,5].

On the issue of tolerability and patient age, two comparative retrospective analyses of outcomes in elderly (≥ 70 years) versus younger patients who underwent RE for various hepatic tumors [23] or specifically for HCC in the ENRY study [24], showed the procedure is well tolerated by elderly patients – with no significant difference in efficacy (overall survival) or tolerability between the younger versus

Figure 2. Computerized tomography image at 6 months post radioembolization demonstrating partial response by RECIST criteria with significant tumor shrinkage (nearly 50% reduction in tumor size from baseline).

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elderly cohort. In elderly and younger patients with HCC common, procedure-related adverse events were predominantly grade 1–2 and of short duration [24].

It is important to proactively minimize the risk of RE-related adverse effects and manage those that do occur. In a recent sister publication on RE for colorectal cancer hepatic metastases, we have described in detail, the potential RE-related adverse effects and included a practical guide for the clinician on prophylaxis and/or management of these effects [25].

RE in patients with HCC & PVT

Unresectable HCC may be complicated by tumor invasion of the portal vein, which is a significant risk factor for intrahepatic and extrahepatic metastases [26]. For untreated HCC with PVT, the prognosis is extremely poor with a reported median survival of only 2.7 months [27].

In PVT, the hepatic artery may be the sole source of blood supply to the liver parenchyma. In such cases, embolic therapies such as TAE, TACE and DEB-TACE are considered contraindicated due to the increased risk of hepatic decompensation as blood flow via an obstructed

Table 2. ENRY study: median survival after radioembolization (all patients) based on baseline characteristics.			
Variable	Category	Median overall survival (months) (95% CI:)	p
ECOG performance status	0	16.9 (13.6–19.6)	<0.001
	1–2	9.9 (7.4–10.9)	
	3–4	5.2 (2.2–NR)	
Total bilirubin	≤1.5 mg/dl	15.1 (12.4–17.9)	0.002
	>1.5 mg/dl	8.8 (5.5–11.7)	
INR	≤1.2	15.5 (12.6–18.4)	<0.001
	>1.2	8.6 (7.0–10.9)	
Number of nodules	1–5	16.8 (13.6–22.1)	<0.001
	>5	10.0 (7.7–11.4)	
Bilobar disease	No	16.8 (11.9–22.5)	0.005
	Yes	11.4 (9.9–13.8)	
Portal vein occlusion	No	15.3 (12.4–18.4)	0.003
	Yes (branch/main)	10.0 (6.5–11.8)	
Extrahepatic disease	No	14.1 (11.7–16.8)	0.001
	Yes	7.4 (4.8–13.1)	
AFP	≤400 ng/ml	18.4 (15.1–20.8)	<0.001
	>400 ng/ml	9.7 (7.4–11.7)	
ECOG: Eastern Cooperative Oncology Group; INR: International normalized ratio; NR: Normalized ratio. Data taken from [4].			

portal vein cannot compensate for diminished hepatic perfusion from an embolized hepatic artery. A minimally embolic therapy such as ⁹⁰Y microspheres that causes minimal occlusion of the hepatic artery may be a therapeutic alternative for these patients with compromised portal flow.

Indeed, emerging evidence indicates that while outcomes are typically more favorable for patients without PVT, RE (with resin or glass ⁹⁰Y microspheres) confers meaningful efficacy (median survival of 10 months) with acceptable tolerability in patients with HCC and PVT (Table 4) – patients with occlusion of the segmental or lobar branch of the portal vein having been most extensively studied [4,7,28].

In a single-center study of 25 patients with unresectable HCC presenting with branch or

main PVT that were treated with ⁹⁰Y resin microspheres over a 6-year period, disease control was achieved in 66.7% of patients at 2 months and 50% at 6 months, with a median survival time of 10 months [28]. The authors reported no evidence of compromised vascular supply such as post-embolization syndrome, altered liver function or acute ischemic hepatitis. After RE, there was no significant difference in liver function from baseline (although a statistically significant but clinically irrelevant increase in bilirubin levels from baseline was noted).

Kulik *et al.* conducted a Phase II study of 108 patients with HCC (34% of whom had PVT) who underwent RE with glass microspheres at two centers [7]. In the entire cohort, significantly longer median survival post RE (15.6 months) was observed in patients without

Table 3. Multivariate predictors of survival after radioembolization (ENRY study).			
Category	Prognostic variable	Hazard ratio (95% CI:)	p
All patients	Number of nodules >5	1.76 (1.32–2.35)	<0.001
	ECOG performance status	1.39 (1.14–1.70)	0.001
	Extrahepatic disease	1.91 (1.17–3.13)	0.010
	INR >1.2	1.47 (1.04–2.09)	0.028
BCLC-A	INR >1.2	5.26 (1.72–16.09)	0.004
BCLC-B	AFP >400 ng/ml	2.98 (1.62–5.48)	<0.001
	Total bilirubin >1.5 mg/dl	2.91 (1.20–7.06)	0.019
BCLC-C	Number of nodules >5	1.59 (1.10–2.29)	0.014
	INR >1.2	1.52 (1.05–2.21)	0.028
BCLC: Barcelona clinic liver cancer staging; ECOG: Eastern Cooperative Oncology Group; INR: International normalized ratio. Reproduced with permission from [4] © American Association for the Study of Liver Diseases (2011).			

Table 4. Survival after radioembolization with ⁹⁰Y microspheres in patients with hepatocellular carcinoma and portal vein thrombosis.

Author/study	PVT status at baseline	Median overall survival (months)	p	Ref.
Iñarrairaegui	Branch/main PVT present	10		[28]
Kulik	All patients			[7]
	No PVT	15.3		
	Branch PVT	10.0	0.0052	
	Main PVT	4.4		0.1028
	Patients with cirrhosis			
	No PVT	12.7		
	Branch PVT	8.6		
	Main PVT	4.9		
	Patients without cirrhosis			
	No PVT	26.7		
Sangro	All patients			[4]
	No PVT	15.3	0.003	
	Branch/main PVT	10.0		
	BCLC-C disease			0.826
	No PVT	9.3		
	Branch/main PVT	10.2		

BCLC: Barcelona Clinic Liver Cancer Staging; PVT: Portal vein thrombosis.

PVT. However, patients with branch/lobar PVT fared relatively well with a median survival of 10.1 months (Table 4). This difference was limited to patients without cirrhosis.

RE was not associated with significant liver-related adverse events. Among patients who experienced elevated bilirubin after RE, much of this was considered attributable to tumor progression rather than treatment toxicity. Of note, branch PVT and non-PVT patients experienced a similar frequency of elevated bilirubin, indicating that RE in the presence of branch/lobar PVT does not increase the risk of hepatic decompensation. In this study, the presence of cirrhosis was a risk factor for worsening ascites (again considered to be attributable to the vascular invasion rather than increased radiation toxicity) [7].

The recent large European multicenter series of 325 patients with HCC treated with ⁹⁰Y resin microspheres corroborates the above results [4]. Investigators noted longer median survival in patients without PVT at baseline (Table 4), although importantly, they reported no significant difference in median survival after RE among patients with a patent portal vein versus those with a branch occlusion ($p = 0.124$). Additionally, in patients with BCLC-C disease, median overall survival after treatment was approximately 10 months, regardless of whether PVT was evident at baseline (Table 4).

While the optimal treatment regimen for patients with HCC and PVT remains unknown, the replicable median overall survival of around 10 months associated with RE is substantially greater than the reported 2.7 months for untreated HCC with PVT [27]. Additionally, given the acceptable toxicity profile of RE in patients with branch PVT, RE appears to be a meaningful therapeutic option in this challenging group of patients. However, prospective studies are needed to more clearly define the efficacy and safety of RE in patients with HCC and PVT.

RE versus TACE for unresectable HCC: clinical outcomes

With promising evidence for RE as a treatment strategy for unresectable HCC, the comparative efficacy and safety of RE versus TACE is of particular interest. However, a randomized head-to-head trial of RE versus TACE in HCC with a primary endpoint of overall survival appears unfeasible due to the requirement of more than 1000 subjects to establish survival equivalence [12]. Additionally, the heterogeneous regimen, technique and timing of TACE (treat on a schedule vs treat on progression) poses a further practical barrier to standardization across centers, especially in a very large study.

Instead, a number of studies have compared the results of cohorts of patients with

unresectable HCC receiving TACE against a concurrent or sequential cohort undergoing RE. The analyses indicate equivalent duration of survival in patients undergoing RE and those treated with TACE – with RE exhibiting an improved toxicity profile [12,29–31].

Salem *et al.* analyzed results for 245 treatment-naïve patients with unresectable HCC (122 treated with TACE and 123 who underwent RE) and found RE was associated with longer median time to tumor progression (13.3 vs 8.4 months for TACE; $p = 0.046$) [12]. There was no significant difference in overall survival between the two groups. Both groups experienced fatigue, nausea and anorexia. However, authors noted significant differences in certain toxicities. Patients receiving TACE were more likely to experience abdominal pain ($p < 0.001$) and exhibited significantly higher hepatic transaminase elevation ($p = 0.004$). At baseline, both groups had comparable rates of portal hypertension, ascites, cirrhosis, tumor distribution, bilirubin and cancer stage (UNOS, BCLC and Child-Pugh). However, patients undergoing RE were significantly older than TACE-treated patients. Despite this, RE was a well-tolerated outpatient treatment with no hospitalizations (underscoring a lower need for inpatient resource utilization) [12].

Similarly, Lance and colleagues assessed 73 patients with unresectable HCC who received TACE or RE at a single institution [29]. Both groups were similar in terms of baseline patient and tumor characteristics. In this study, RE conferred no survival advantage over TACE. However, there was a significant difference in the mean total hospitalization time (defined as duration of the initial hospitalization plus any rehospitalization within 30 days) – 3.5 days for TACE versus 0.5 days for RE; $p < 0.001$. While the rate of postembolization syndrome was similar in the two groups, the severity of the syndrome was increased in TACE-treated patients, with significantly more patients requiring additional hospitalization and treatment ($p < 0.02$). There were no significant differences between groups in major or minor complication rates associated with adverse effects other than postembolization syndrome.

Kooby *et al.* evaluated concurrent cohorts of 27 patients with HCC undergoing RE and 44 patients receiving TACE. They found equivalent response to therapy and overall survival in both groups but significantly greater overall

toxicity and length of hospitalization in the TACE group [30].

A retrospective case-control analysis of safety and efficacy outcomes in patients with intermediate-stage HCC (and without PVT) who underwent TACE ($n = 55$) or RE ($n = 61$) also reported no significant difference in efficacy (overall survival and tumor response rates) between the two therapies [31]. RE led to a higher incidence of fatigue ($p = 0.003$) but lower incidence of fever ($p = 0.02$) than did TACE. Patients undergoing RE received fewer treatments ($p < 0.001$) and required less hospitalizations than TACE-treated patients (98% of TACE patients were hospitalized for ≥ 1 day while 97% of patients undergoing RE were treated as outpatients; $p < 0.001$).

Finally, a survival study, which compared 99 patients with unresectable HCC who received RE first line, with a preceding cohort of 691 patients who underwent TACE, also demonstrated equivalent survival outcomes [11]. Combined with data from a previous study, these investigators concluded that compared with TACE, RE confers equivalent survival but has a qualitatively better toxicity profile.

A recent small prospective study by Salem *et al.* investigated the impact of RE ($n = 29$) or TACE ($n = 27$) on health-related quality of life (QoL) in patients with HCC at 2 and 4 weeks post-treatment [32]. In this study, despite the inclusion of patients with more advanced disease, the RE cohort exhibited significantly better QoL based on social well-being, functional well-being and embolotherapy-specific scores with a trend toward better overall QoL (there was no significant difference in overall FACT-Hep health-related QoL scores due to the small sample size). The data suggest the improved toxicity profile of RE may confer a significant improvement in some QoL parameters.

Note: to date there are no analyses of RE versus DEB-TACE – the latter being a strongly embolic therapy with equivalent to greater efficacy than TACE that produces similar adverse events at a lower frequency [3]. A head-to-head trial of RE versus DEB-TACE is currently underway (Table 5).

RE compared with standard of care for advanced HCC

Sorafenib is the current standard treatment for advanced HCC [1]. The efficacy of RE versus that of sorafenib in advanced disease is currently being addressed via three randomized

Table 5. Upcoming clinical trials of radioembolization in hepatocellular carcinoma.

Trial name and NCT ID	Location	Study arms	Primary endpoint	Ref.
SARAH NCT01482442	France	Sorafenib versus SIR-Spheres® (resin microspheres) in advanced HCC	Overall survival	[55]
SORAMIC NCT01126645	Europe	Sorafenib and micro-therapy guided by primovist-enhanced MRI in patients with inoperable liver cancer: (a) Local ablation group (early-stage HCC): RFA + sorafenib versus RFA (b) Palliative treatment group (unresectable HCC): RE (SIR-Spheres®) + sorafenib versus sorafenib	Time to recurrence Overall survival Additional endpoint: Is Primovist®-enhanced MRI noninferior or superior to contrast-enhanced multislice CT for patient stratification to a palliative vs local ablation strategy	[56]
SIRveNIB NCT01135056	Asia-Pacific	Sorafenib versus SIR-Spheres (resin microspheres) in locally advanced HCC	Overall survival	[57]
TRACE NCT01381211	Belgium, The Netherlands	TACE-DEB versus TheraSphere® (glass microspheres) for HCC	TTP	[58]
PREMIERE NCT00956930	USA	TACE (mitomycin + doxorubicin + cisplatin) versus TheraSphere® (glass microspheres) for liver cancer that cannot be treated with RFA or surgery	TTP	[59]
Yes-P NCT01887717	USA	Sorafenib versus TheraSphere® (glass microspheres) for advanced HCC with PVT	Overall survival	[60]
STOP-HCC NCT01556490	USA, Canada, France	Sorafenib versus sorafenib + TheraSphere® (glass microspheres) for advanced HCC	Overall survival	[61]

CT: Computerized tomography; HCC: Hepatocellular carcinoma; PVT: Portal vein thrombosis; RE: Radioembolization; RFA: Radiofrequency ablation; TTP: Time to progression.

head-to-head trials in France, Asia and USA (Table 5).

In the interim, Sangro *et al.* have addressed the issue by analyzing pertinent data on RE and sorafenib to date. They compared results from subgroup analysis of 299 patients treated with sorafenib in the SHARP trial to that of 199 patients treated with ⁹⁰Y microspheres (ENRY study) who fulfilled the same inclusion criteria, in other words, Child-Pugh class A and either BCLC-C, or BCLC-B with prior TACE or bulky disease (bilobar or >5 nodules). The authors noted equivalent median overall survival in comparable groups of patients treated with RE or sorafenib [33].

With regard to advanced disease as a whole, Sangro *et al.* compared subgroup data from studies of patients who underwent RE, against studies of sorafenib-treated patients and once again reported similar survival outcomes. In patients with advanced disease, median overall survival ranged from 6 to 10 months with RE and 6.5 to 10.7 months in the Phase III clinical trials of sorafenib in the same group of patients [33].

A recent single-center retrospective study by Gramenzi *et al.* compared the outcomes achieved with sorafenib (n = 74) or RE (n = 63) at their institution in patients with intermediate, locally advanced HCC that were potentially amenable to either therapy [34]. Median overall survival was comparable for sorafenib (14.4 months; 95% CI: 4.3–24.5) and RE (13.1 months; 95% CI: 6.1–20.2) as were 1-, 2- and 3-year survival outcomes (sorafenib: 52.1, 29.3, 14.7%; RE: 51.8, 27.8, 21.6%). The efficacy outcomes remained equivalent even after propensity matching of the two groups to minimize the impact of any confounding factors. In addition, two patients in the RE group achieved successful tumor downstaging and later underwent transplantation. Downstaging was not observed in any sorafenib-treated patients.

In the context of less advanced disease, Sangro *et al.* also performed analyses of studies with RE or TACE in early and intermediate-stage disease noting equivalent median overall survival for RE- and TACE-treated patients,

corroborating the survival data discussed in the previous section [33]. Therefore, collectively, the evidence to date broadly suggests survival equivalence between RE and standard of care across all disease stages in HCC.

RE & sorafenib: sequential or combination therapy

Recent reports have provided preliminary data on the safety implications of RE and sorafenib used sequentially or in combination in different settings [35,36]. A small, pilot randomized controlled trial investigated the safety of combination of sorafenib and RE compared with RE alone in 20 HCC patients awaiting transplantation [35]. Preliminary survival outcomes were similar between the two groups. Median time-to-transplant was similar between the two groups ($p = 0.35$). Survival rates were 70% (RE) and 72% (sorafenib + RE) at 3 years ($p = 0.57$). However, combination therapy was associated with a trend toward higher rates of acute cellular rejection and of biliary complications post-transplant. In the sorafenib group, there were 4/8 peritransplant (<30 days) biliary complications ($p = 0.029$) and 3/8 acute rejections ($p = 0.082$); and none in the RE-only group [35]. All patients in the combination arm required sorafenib dose reductions. These data do raise a safety concern regarding combination therapy, at least in the transplant setting, which requires further investigation.

A recent open-label, prospective, single-arm Phase II multicenter study in the Asia-Pacific region is the first to report on the safety and efficacy of RE followed by sorafenib in 29 patients with BCLC-B or BCLC-C HCC [36]. The overall response rate (CR + PR) was 25% while 54% exhibited stable disease, and two patients achieved sufficient response to enable radical therapy (RFA). The investigators reported that adverse events were manageable, however 15 cases (52%) were grade 3 or higher. Toxicities in five patients (17%) occurred post RE and prior to sorafenib administration; all were grade 1–2 except one grade 3 ascites. After sorafenib administration, patients experienced toxicities consistent with the known safety profile of sorafenib.

RE for downstaging HCC to resection or transplantation

In addition to its palliative effect, RE may facilitate downstaging of unresectable HCC – either decreasing the tumor burden to the extent that the patient subsequently meets the criteria for

transplantation (i.e., UNOS T3 to T2) or shrinking inoperable tumors to the degree that they become resectable or ablatable. Downstaging may be planned or may occur as an unintended consequence of palliative treatment. This suggests a potential role for SIRT in downsizing/downstaging inoperable tumors to potentially curative therapies, in other words, resection, ablation or transplantation.

In a proportion of patients with unresectable HCC undergoing RE, tumor downstaging has been achieved in a number of studies, and in turn many of these patients underwent radical therapies [6,16,17,37,38]. Promising downstaging rates of 42–66% have been reported in cohorts of T3 patients, although the varying criteria employed to define downstaging limits comparison between the studies [16,17,37].

In one study ($n = 35$), 66% of patients with UNOS T3 HCC were downstaged after RE to either T2 status, lesion <3.0 cm (RFA candidate), or resection – 19/34 (56%) were downstaged from T3 to T2 following treatment and 11/34 (32%) were downstaged to target lesions measuring ≤ 3.0 cm [16]. Of those downstaged, eight patients underwent transplantation and one was resected. For the entire cohort (including those patients whose tumors were not downstaged), the authors reported overall survival of 84, 54 and 27% at 1, 2 and 3 years, respectively and median survival of 800 days.

Lewandowski *et al.* have reported significantly higher downstaging rates with RE than with TACE in a study of 86 patients with UNOS T3 HCC who received TACE ($n = 43$) or RE ($n = 43$) where both groups had similar baseline patient and tumor characteristics [17]. Both groups experienced statistically significant reductions in tumor size from baseline. However, downstaging rates were 58% (RE) versus 31% (TACE); $p = 0.023$ – with the trend favoring RE being maintained for all lesion sizes.

Indeed a recent systematic review concluded that successful tumor downstaging after RE, to within Milan criteria for transplantation is feasible in HCC [39]. The authors analyzed eight studies with a total of 720 patients who presented with disease outside the Milan criteria and who underwent transplantation following downstaging post RE. The rate of successful downstaging varied from 24 to 69% with reported 1-, 3- and 5-year survival rates of 82–100%, 79–100% and 54.6–94%, respectively – in other words, comparable survival to

that seen in patients presenting with tumors that fall within the Milan criteria at diagnosis [39].

Finally, the above results were corroborated in a 2012 study that compared long-term outcomes in 6/21 UNOS T3 patients who were downstaged after RE and acceded to radical treatment versus the remaining 15 who were treated and did not undergo radical therapy [37]. Patients in this study had a high tumor burden (median tumor diameter 11.2 cm). Regardless, downstaging was achieved even in large tumors, with reported long-term overall survival of 75% at 3 years in patients who were treated radically (a rate comparable to patients with early-stage disease treated radically at diagnosis). Overall survival varied significantly between those treated radically (OS not reached after a median follow-up of 41.5 months) and those who received palliative treatment only (22.0 months; 95% CI: 15.0–30.9).

International consensus recommendations for liver transplantation in HCC state “*no recommendation can be made for preferring a specific locoregional therapy for downstaging over others*” [40], indicating that among the locoregional therapies, RE may be a viable therapeutic option for downstaging to transplantation.

Aside from tumor downstaging/downsizing, several retrospective studies have reported the observation that lobar administration of RE can induce significant hypertrophy of the contralateral lobe [41–45]. However, despite consistent reporting of this phenomenon in a number of studies, the observations need to be interpreted with caution – as the extent of hypertrophy was variable and the factors predicting this response are unclear.

RE for HCC: practical considerations

The effectiveness and tolerability of RE should be balanced against the cost of ^{90}Y microspheres and procedural considerations. The process for patient selection and administering RE necessitates the formation of a multidisciplinary board of specialists from interventional radiology, nuclear medicine, medical oncology, hepatology, radiation oncology and surgical oncology and requires ready access to an experienced interventional radiologist to ensure the pretreatment angiography is expertly interpreted and that RE is administered as safely as possible.

However, the above should in turn be weighed against the costs of multiple inpatient admissions for repeat TACE treatments and hospitalizations due to the increased severity of postembolization

syndrome with TACE, and against the high costs of drug-eluting beads and biological agents such as sorafenib.

Clearly the cost–effectiveness of any therapy remains an important consideration, particularly in the current era of increasing financial constraints potentially limiting the delivery of effective therapies. Due to substantial variations in the cost of administering a dose of ^{90}Y across settings and countries, it is not possible to provide a standardized cost for a single dose at this time. Cost-benefit analyses across different treatment settings will be an important part of further research.

Role of RE in the treatment of unresectable HCC: which patients?

The level of evidence (predominantly retrospective analyses and some noncontrolled prospective series) is a limitation for RE studies in HCC – an ongoing controversy acknowledged by experts [33,46]. Nevertheless, recent reports of large series of patients treated at independent institutions worldwide have consistently described promising efficacy and an acceptable safety profile for RE in unresectable HCC, even in advanced disease [4,5,9]. Consequently, experts agree that a body of evidence supports RE in carefully selected patients with unresectable HCC (**Box 1**) [33,46]. Supporting this is the NICE guidance document (July 2013), which recommends RE for appropriately selected patients with primary HCC [47].

It is important to bear in mind that post-treatment prognosis is dependent on baseline hepatic function and intrahepatic and extrahepatic tumor burden [4,5]. Therefore, even within the potential indications for RE, careful patient selection remains key to optimal use of this therapy. Adequate functional liver reserve, good performance status (ECOG 0), preserved hepatic function (bilirubin <1.5 mg/dl; Child-Pugh class A or up to B in limited circumstances) and absence of significant extrahepatic disease are prerequisites when considering treatment with ^{90}Y microspheres in HCC.

Radiologic response to RE in HCC: clinical implications

Notwithstanding the technical challenges involved in assessing radiological response to RE, studies have shown strong correlation in HCC between radiological response to treatment and clinical outcomes [5,50].

Box 1. Potential indications for radioembolization with ^{90}Y microspheres in unresectable hepatocellular carcinoma[†].

- Patients with intermediate-stage (Barcelona clinic liver cancer staging B [BCLC-B]) hepatocellular carcinoma (HCC) [4];
- Who are poor candidates for TACE (e.g., bilobar disease or multiple, i.e., >5 tumor nodules) or;
- Who have failed prior transcatheter arterial chemoembolization (TACE) or progressed after TACE or arterial embolization.
- Patients with advanced-stage HCC (BCLC-C), particularly those with portal vein thrombosis (solitary tumors invading a segmental or lobar branch of the portal vein) [4,5];
- Those with advanced disease who have progressed after sorafenib or when sorafenib is contraindicated [33].
- Patients whose disease falls outside the criteria for surgery, ablation or transplantation, where downstaging may enable the use of radical therapies. This includes patients with early-stage (BCLC-A) disease where ablation is precluded by tumor positioning – for example, in the dome, on the surface of the liver or in proximity to large bile ducts or blood vessels [33];
- [†]Note: Absolute contraindications include: technical contraindication to intra-arterial treatment; pregnancy; any clinical or laboratory evidence of hepatic failure; poor ECOG PS; extensive extrahepatic disease; decompensated cirrhosis (CPT ≥ 8 , jaundice, encephalopathy, refractory ascites, hepatorenal syndrome); massive tumor with both lobes involved (tumor burden >75% of liver parenchyma); and lung or GI shunts that cannot be corrected. Relative contraindications include renal impairment or untreated varices at high risk of bleeding [46,48,49].

In their report of long-term outcomes in a heterogeneous group of 291 patients with HCC who underwent RE, Salem *et al.* observed significantly reduced risk of death in those who exhibited radiological response by WHO criteria versus nonresponders, for all stages of disease – BCLC-A (HR 0.15); BCLC-B (HR 0.36); BCLC-C (HR 0.26) [5].

Similarly, in patients with unresectable HCC with Child-Pugh score ≤ 7 and no extrahepatic metastases or PVT at baseline who were treated with locoregional therapies (e.g., RE or TACE), a recent study showed good correlation between radiological response (complete response + partial response) at 6 months and survival [50]. Therefore, the authors suggest the goal of locoregional therapies in HCC should be to achieve a radiologic response (complete or partial response) rather than stabilizing disease. Additionally, given the challenges in conducting studies with a primary endpoint of survival, the authors propose considering the potential utility of radiographic response as a prognostic

indicator of survival in HCC clinical trials.

In a different study, Riaz *et al.* observed good correlation between radiologic response to RE and pathologic necrosis in HCC [18]. In this series of 35 patients with HCC treated with RE who later underwent transplantation, investigators correlated radiographic findings with explant pathology. The study showed radiographic changes (by WHO or EASL criteria) in size of a tumor and in the amount of enhancing tissue, predicted histologic necrosis.

In a series of 245 patients with HCC treated with locoregional therapies Riaz *et al.* found good agreement between RECIST and WHO guidelines but low correlation between each of these and EASL [51]. They also noted the dominant lesion (primary index lesion) can be used to measure response to therapy.

Another study compared combinations of WHO, EASL and RECIST guidelines in assessing the response to locoregional therapies in HCC [52]. The authors determined the EASL $\times$ WHO scoring system provides a simple,

clinically applicable method of assessing response and radiological-pathological correlation.

Tumor biomarkers of response to RE

In patients with advanced HCC, serum AFP concentration greater than 200 ng/ml is an independent risk factor for survival [53]. A study by Riaz and coworkers indicates that in addition to radiographic findings, serum AFP reduction appears to be a clinically meaningful tumor biomarker in HCC after transarterial locoregional therapies such as RE and that alongside imaging, AFP response may serve as an ancillary indicator of response, tumor progression and survival [54].

The study involved subgroup analysis of 125 patients with baseline AFP >200 ng/ml (from a series of 463 patients with HCC who underwent TACE or RE). The authors found AFP response (defined as >50% reduction from baseline AFP levels) to be a reliable predictor of tumor response, TTP, PFS and OS [54]. Given the shorter median time to AFP response (3.3 months) compared with WHO response (5.6 months), the data also suggest that AFP reduction is an important early indicator of tumor response. Lack of AFP response may also provide clinicians an earlier opportunity to seek alternative treatments [54].

In addition to AFP, the tumor biomarkers Ang2 and VEGF have been identified as strong independent predictors of survival in advanced HCC [53]. The role of these and other biomarkers in evaluating the response to RE is yet to be determined.

Conclusion

Treatment decisions for HCC involve a number of factors, including tumor size/burden, morphology and location, presence or absence of extrahepatic metastases, comorbidity (e.g., cirrhosis; portal hypertension) and the patient's performance status.

For medical oncologists and hepatologists managing patients with unresectable HCC and preserved hepatic function, good performance status and liver-confined disease, RE offers a promising additional therapeutic alternative beyond TACE and sorafenib. Patient selection remains key – in carefully selected patients RE may have a role in intermediate (BCLC-B) and in advanced (BCLC-C) disease (particularly when PVT is present) and potentially, in a limited capacity in early-stage disease.

Clearly a number of questions and challenges remain, some of which are being addressed through upcoming trials. These will more clearly define the role of RE at various stages of HCC – with studies relating to RE in advanced disease in the context of the current standard therapy (sorafenib) being of particular interest.

Future perspective

The encouraging evidence supporting the potential role of RE in the management of unresectable HCC also highlights the many unanswered questions and challenges, underscoring the need for further prospective studies. Questions such as: are there additional tumor biomarkers or patient characteristics that (prior to RE) could help predict a greater likelihood of achieving complete or partial response to RE or tumor downstaging to radical therapies? What proportion of successfully downstaged HCC patients undergo resection/transplantation? Do factors other than patient preference hinder radical therapies after downstaging? While transplant-approved patients awaiting a donor organ may elect to receive RE in the interim, is there a clearly-defined role for RE as a bridge to transplantation to arrest tumor progression?

Additional questions include – what are the indications for repeat RE in HCC (does repeat RE performed after partial response confer a definitive clinical benefit?). Note: considering repeat RE in some circumstances may be appropriate – experienced centers have reported performing repeat RE to improve a partial response or to treat tumors arising in a contralateral lobe [4]. These approaches warrant further study.

What is the optimal management strategy for patients who exhibit stable disease after RE? Is there a role for RE sequentially or in combination with sorafenib for advanced HCC, including patients with PVT? Would the use of radiosensitizing chemotherapeutic agents such as fluorouracil and oxaliplatin confer benefit? Is there a role for VEGF inhibition in the event that RE might upregulate VEGF? When PVT is evident, does RE alter metastatic dissemination of the tumor? For patients with advanced disease, should systemic therapies be considered in close proximity to RE or at tumor progression? How does hepatic function deterioration at tumor progression impact patient management? Finally, where does RE stand in the context of newer agents being studied in HCC (e.g., bevacizumab)? Upcoming clinical trials will address some of these questions,

particularly regarding RE and current regimens such as sorafenib and TACE (Table 5).

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