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The evolving role of selective internal radiation therapy in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) remains a major global oncological burden, accounting for over 900,000 new diagnoses and more than 800,000 deaths each year. Most patients present with intermediate or advanced disease on a background of cirrhosis, restricting curative strategies such as surgical resection or liver transplantation to only 20-30% of cases. Selective internal radiation therapy (SIRT), also known as yttrium-90 transarterial radioembolization, exploits the preferential arterial blood supply of HCC to deliver high-dose beta radiation selectively to tumor tissue while sparing non-tumorous liver parenchyma, thereby inducing targeted DNA damage and apoptosis with minimal ischemic injury.

Evidence updated to November 2025 from randomized controlled trials, large registries, and recent meta-analyses demonstrates that SIRT provides overall survival comparable to transarterial chemoembolization (TACE), while consistently improving progression-free survival, time-to-progression, objective response rates, and patient-reported quality of life. These benefits are particularly evident in patients with large tumors, bilobar involvement, or TACE-refractory disease. Importantly, SIRT enables effective downstaging to liver transplantation eligibility according to Milan or University of California San Francisco criteria in approximately 40-66% of cases, with pathological complete response rates approaching 90% when applied as radiation segmentectomy.

SIRT shows a favorable safety profile, with grade ≥3 adverse events in only 11-18% of patients, minimal post-embolization syndrome, and radioembolization-induced liver disease in fewer than 5%, preserving liver function and quality of life. Current European Association for the Study of the Liver (EASL 2024) and American Association for the Study of Liver Diseases (AASLD 2023) guidelines recognize SIRT as an alternative locoregional therapy in selected intermediate-stage and carefully chosen advanced-stage HCC patients. Emerging innovations continue to refine outcomes.

Introduction

Hepatocellular carcinoma (HCC) remains one of the most pressing global oncological challenges, ranking as the sixth most common malignancy and the third leading cause of cancer-related mortality, with over 900,000 new cases diagnosed annually and mortality exceeding 800,000 deaths.[1]

This neoplasm, which often progresses insidiously on a background of chronic liver cirrhosis primarily driven by hepatitis B or C virus infection, alcohol abuse, or non-alcoholic steatohepatitis, is typically diagnosed at intermediate or advanced stages, restricting curative options such as hepatic resection or liver transplantation to only 20-30% of patients.[2]

In this setting, locoregional therapies play a pivotal role, aimed not only at controlling tumor growth and delaying systemic progression but also at preserving residual liver function and, in selected cases, facilitating downstaging to radical treatments.[3]

Among these, selective internal radiation therapy (SIRT), also known as transarterial radioembolization (TARE), has emerged as an innovative and highly selective approach that exploits the preferential arterial vascularization of HCC to deliver yttrium-90 (90Y)-loaded microspheres, inducing targeted tumor necrosis while minimally affecting healthy parenchyma.[4] Food and Drug Administration-approved in 2002 for unresectable HCC, SIRT has gained substantial ground supported by robust evidence from randomized controlled trials (RCTs) and recent meta-analyses demonstrating superior overall survival (OS) and progression-free survival (PFS), together with a more favorable safety profile compared with conventional transarterial chemoembolization (TACE).[5]

This review, updated to November 2025 and based on a rigorous selection of studies published on PubMed from 2009 onward, aims to comprehensively and integratively outline the mechanisms of action, clinical indications, oncological efficacy, safety profile, and future perspectives of SIRT in HCC, emphasizing its role within a multimodal therapeutic paradigm that incorporates immunotherapy and systemic therapies.

Methods

This narrative review was conceived to provide a comprehensive and clinically oriented synthesis of the available evidence on the use of locoregional radioembolization in the management of HCC. A structured literature search was performed using the PubMed/Medline database, covering publications from January 2009 to November 2025. This time frame was selected to encompass the period of modern clinical application of radioembolization techniques, including advances in dosimetry, procedural standardization, and integration with contemporary systemic therapies.

The search strategy was designed to ensure broad coverage while preserving clinical relevance and was based on combinations of free-text keywords and commonly used indexing terms. Search terms included “hepatocellular carcinoma”, “selective internal radiation therapy”, “transarterial radioembolization”, “yttrium-90”, “radioembolization”, “personalized dosimetry”, “radiation segmentectomy”, “portal vein tumor thrombosis”, “BCLC”, “TACE-refractory”, “downstaging”, and “liver transplantation”. Boolean operators were applied to combine disease-related and treatment-related terms. In addition, reference lists of key articles and recent reviews were manually screened to identify further relevant studies not retrieved through the primary search.

The literature selection included RCTs, prospective and retrospective observational cohort studies, propensity score-matched analyses, large multicenter or registry-based studies, and systematic reviews and meta-analyses published in the English language. Studies were included based on methodological quality and relevance to clinical practice, particularly with regard to patient selection, technical aspects, oncological efficacy, safety outcomes, and quality-of-life measures.

Case reports, small case series, conference abstracts, editorials, and non-peer-reviewed sources were excluded.

Priority was given to studies reporting clinically meaningful endpoints, including OS, PFS, time-to-progression (TTP), objective response rate (ORR), downstaging to liver transplantation criteria, treatment-related toxicity, and health-related quality of life. When available, evidence derived from randomized trials was clearly distinguished from results obtained from observational studies, subgroup analyses, or propensity score-matched comparisons, and interpreted accordingly.

To contextualize the role of radioembolization within established treatment algorithms, current international clinical practice guidelines and consensus documents from the EASL, the American Association for the Study of Liver Diseases, and the Barcelona Clinic Liver Cancer (BCLC) group were also reviewed. These sources were used to frame indications, patient selection criteria, and the evolving positioning of this treatment relative to other locoregional and systemic therapeutic options.

Given the heterogeneity of study designs, patient populations, technical approaches, and outcome reporting across the available literature, data synthesis was performed using a qualitative narrative approach rather than a formal systematic review or meta-analysis. Findings were interpreted with consideration of methodological limitations and level of evidence, with the aim of providing a balanced and clinically meaningful overview rather than quantitative pooled estimates.

Results

Mechanisms of action and technical procedure

The pathophysiological rationale of SIRT is rooted in the distinctive angiogenesis of HCC, a tumor that derives 70-90% of its blood supply from the hepatic artery, in stark contrast to healthy liver parenchyma, which is predominantly nourished by the portal venous system.[6] This vascular dichotomy enables highly selective targeting: 90Y microspheres, available in resin (SIR-Spheres®) or glass (TheraSphere®) matrices with diameters of 20-60 μm, are infused *via* arterial catheter and become trapped within tumor sinusoidal capillaries, emitting high-energy β radiation (mean 0.937 MeV) with a half-life of 64 hours and tissue penetration limited to 2.5-11 mm.[7] Tumoral absorbed doses commonly exceed 100-200 Gy, while dosimetry aims to maintain non-tumoral liver exposure within safe thresholds, particularly in cirrhotic patients, to reduce the risk of radioembolization-induced liver disease (REILD).[4] Therapeutic infusion, typically 1.5-3 GBq in unilobar or bilobar sessions, is followed by magnetic resonance (MR) imaging or positron emission tomography/computed tomography at 4-6 weeks, using mRECIST criteria to assess response.[8] Emerging innovations, such as holmium-166 (166Ho) microspheres for MR-compatible imaging and real-time dosimetry or pressure-enabled delivery systems for deeper penetration in poorly vascularized tumors, promise further refinement, reducing intraoperative variability and expanding applicability in infiltrative HCC or portal vein tumor thrombosis (PVTT).[9]

Clinical indications and patient selection

Updated 2024 EASL and 2023 AASLD guidelines position SIRT as an alternative/selective option to TACE within BCLC B, especially in TACE-unsuitable or specific scenarios (large/bilobar disease), within a personalized strategy.[10] In BCLC A, for single nodules >3 cm not amenable to percutaneous ablation, SIRT functions as radiation segmentectomy—delivering ablative doses >190 Gy to limited segments—with pathological complete response rates approaching 90%, comparable to surgical resection and ideal as a bridge-to-transplant strategy.[11] In advanced BCLC C limited to segmental PVTT without symptomatic extrahepatic metastases, SIRT is recommended in patients with Eastern Cooperative Oncology Group performance status 0-1 and preserved liver function

(Child-Pugh A or B7, bilirubin 3 g/dL, and pre-treatment evaluation to exclude biliary obstruction or hypersensitivity).[12] Absolute contraindications include obstructive biliary invasion, decompensated cirrhosis (Child-Pugh C), or diffuse extrahepatic infiltration, whereas relative contraindications (*e.g.*, main-branch PVTT) require personalized dosimetry to mitigate REILD risk.[13]

Positive outcome predictors include low tumor volume correlate with reduced PFS [hazard ratio (HR) 1.8; p<0.01].[4,14] In high-risk hepatitis B virus-endemic regions (Asia-Pacific), trials such as SIRveNIB confirm SIRT safety but suggest dosimetry adjustments to minimize hepatic toxicity in chronic carriers.[15] Overall, integration of SIRT into the 2022 BCLC guideline update reflects its cross-stage potential from curative to palliative intent, tailored according to clinical and radiomic parameters.[16] A practical summary of established clinical indications and evidence levels is provided in Table 1.

Oncological efficacy

Recent evidence consolidates SIRT as a highly effective locoregional therapy for unresectable HCC. A 2025 meta-analysis aggregating data from six studies (two RCTs, n=443) demonstrated clear superiority over TACE: OS HR 0.68 [95% confidence interval (CI) 0.55-0.86; p=0.0009], PFS HR 0.54 (95% CI 0.44-0.67; p<0.00001), low heterogeneity (I^2=3-41%), and ORR 52-73% *vs* 41-52%.[17] The phase II TRACE trial (n=140, 2022) further validated these findings, reporting median OS of 27 months with 90Y-glass microspheres vs 18 months with drug-eluting bead transarterial chemoembolization (DEB-TACE) (HR 0.53; p=0.005), especially in HCC ≥8 cm, where tumor control was delayed by 8 months.[18]

In high-risk PVTT subgroups, a 2024 propensity-score-matched NCDB analysis (n=1,608) showed OS of 14.5 months with TARE *vs.* 8.7 months with systemic therapy (HR 0.65; p<0.001), outperforming lenvatinib in tolerability.[19] Downstaging potential is impressive: 40-66% from BCLC B/C to Milan/University of California, San Francisco transplant criteria, with surgical conversion in 20–30%, as documented in a 2023 pooled analysis.[20]

Emerging combinations amplify benefits: SIRT followed by nivolumab (NASIR-HCC, 2025) yielded ORR 60% and PFS 12 months in refractory disease by exploiting tumor antigen release to enhance immunogenic response.[21] Compared with sorafenib, RCTs such as SARAH (n=458) confirmed comparable OS (11 *vs.* 10 months) but prolonged PFS (4.1 *vs.* 2.2 months; HR 0.69) with less health-related quality-of-life (HRQoL) deterioration.[22] In summary, SIRT not only delays progression but enables curative trajectories in otherwise palliative patients, supporting its early integration.[23] A comparative overview of the most relevant oncological outcomes from recent meta-analyses and RCTs is summarized in Table 2.

Safety and toxicity management

A major strength of SIRT is its excellent safety profile, with grade ≥3 adverse events limited to 11-18% *vs.* 25-40% with TACE [odds ratio (OR) 0.60; 95% CI 0.29-1.25; p=0.18], as shown in a 2022 individual patient data meta-analysis (n=2465).[24] Post-embolization syndrome (mild fever and abdominal pain) affects 20-21,22% of patients and resolves outpatient within 48 hours, owing to the absence of macroscopic emboli and preserved portal flow.[25] REILD, a feared hepatic complication, occurs in <5% with body surface area or voxel-based dosimetry, preventable by monitoring post-treatment bilirubin rise (>15% indicates high risk) and limiting activity to <3 GBq in Child-Pugh B cirrhosis.[26]

In decompensated subgroups, acute decompensation is rare (10-15%), reversible with medical support, and periprocedural mortality is <1% in experienced centers.[27] Toxicity management

emphasizes antiemetic and steroid premedication, initial weekly biochemical follow-up, and imaging to detect radio-induced abscesses (incidence <2%).[28] Combinations with immunotherapy require vigilance for cytokine release syndrome, but 2025 trials report comparable safety (OR for grade ≥3 hepatic toxicity 0.45; p=0.12).[21] Overall, SIRT reduces hospitalization duration (1-2 *vs.* 3-5 days with TACE) and better preserves HRQoL, making it attractive for frail patients.[29] Direct toxicity profile comparison between SIRT and TACE based on the most updated aggregated data is shown in Table 3.

Comparison with other locoregional and systemic therapies

Compared with TACE, SIRT excels in prolonging TTP by 4-8 months in bilobar or bulky HCC (17.5 *vs.* 9.8 months; mean difference 4.8; 95% CI 1.3-8.3), despite globally comparable OS (-0.55 months), making it ideal for patients with mild functional impairment.[30] RCTs such as SARAH and SIRveNIB (cumulative n=1100) show equivalent OS (11-14 months) but lower fatigue/diarrhea incidence (20-30% *vs.* 10-15%) and HRQoL preservation for an additional 6-9 months.[31] 2024 network meta-analyses equate SIRT to atezolizumab-bevacizumab in unresectable HCC (OS 19 months), yet SIRT prevails in PVTT for hepatic tolerability.[32] From a cost-effectiveness standpoint in the USA, it generates 0.15-0.20 additional quality-adjusted life years (QALYs) *vs.* DEB-TACE with an incremental cost-effectiveness ratio <50,000 USD/QALY, supporting adoption in sustainable healthcare systems.[33]

Discussion

The present narrative review provides an integrated interpretation of the available evidence regarding the role of selective internal radiation therapy in HCC, highlighting its progressive incorporation into personalized, multimodal treatment strategies rather than its use as a universally superior alternative to established locoregional or systemic therapies. Across RCTs, meta-analyses, and large observational cohorts, radioembolization demonstrates OS outcomes comparable to those achieved with TACE or systemic agents, while consistently offering advantages in tumor control, progression-related endpoints, tolerability, and preservation of health-related quality of life in appropriately selected patients.[5,17,18,23]

One of the most relevant aspects emerging from the literature is the apparent discrepancy between outcomes reported in RCTs and those observed in real-world clinical practice. Trials such as SARAH and SIRveNIB enrolled heterogeneous patient populations, frequently characterized by advanced liver dysfunction, extensive tumor burden, or advanced vascular invasion, factors that may have attenuated the potential benefits of locoregional tumor control on OS.[15,31] Conversely, retrospective cohorts, registry-based analyses, and propensity score–matched studies tend to include more carefully selected patients with preserved liver function, limited PVTT, or disease features unsuitable for conventional embolic approaches. In these settings, radioembolization has consistently been associated with improved PFS, prolonged TTP, and higher objective response rates.[17-20,23] This divergence underscores the importance of appropriate patient selection rather than intrinsic limitations of the technique itself.

From a mechanistic standpoint, the favorable clinical profile of radioembolization is supported by its radiobiological characteristics. By delivering high-dose β radiation selectively to tumor tissue while largely preserving portal venous flow, radioembolization minimizes ischemic injury to non-tumoral liver parenchyma, a key determinant of post-treatment hepatic decompensation.[12,24,25] This feature is particularly relevant in patients with borderline liver reserve, in whom embolic strategies may exacerbate liver dysfunction. Advances in personalized and voxel-based dosimetry have further improved the therapeutic index, allowing dose escalation to tumor tissue while maintaining

acceptable exposure to non-tumoral liver and reducing the incidence of radioembolization-induced liver disease.[4,8,9]

Nevertheless, several limitations of the current evidence base must be acknowledged. First, a substantial proportion of the available data derives from retrospective and observational studies, which are inherently subject to selection bias and confounding factors.[12,16,17] However, this limitation is partially mitigated by the consistency of findings across independent cohorts, multicenter registries, and propensity score-matched analyses, which repeatedly demonstrate similar trends in tumor control and safety outcomes.[20,22,23] Second, heterogeneity in dosimetric approaches, microsphere types, and treatment protocols complicates direct comparison across studies. Importantly, recent standardization efforts and the increasing adoption of personalized dosimetry have begun to address this issue, leading to more reproducible and optimized treatment outcomes.[4,7,9]

Another relevant limitation is the evolving systemic treatment landscape, which complicates direct comparisons between radioembolization and systemic therapies evaluated in earlier trials. Many randomized studies were conducted before the widespread adoption of immune checkpoint inhibitors and combination regimens, limiting their applicability to current clinical practice.[22,32,34] At the same time, this rapidly changing context represents an opportunity rather than a drawback, as emerging data suggest potential synergistic effects between radioembolization and immunotherapy, mediated by enhanced tumor antigen release and immune modulation.[21,35]

From a clinical and guideline perspective, these considerations support the current positioning of radioembolization as a selective or alternative locoregional option within intermediate-stage disease and in carefully chosen advanced-stage scenarios, rather than as a universal first-line therapy.[10,11,16,36] In particular, radioembolization appears especially valuable in patients with large or bilobar tumors, TACE-refractory disease, or segmental portal vein involvement, where embolic ischemia is less effective or poorly tolerated.[13-15] In early-stage disease not amenable to percutaneous ablation, radiation segmentectomy represents a further strength of this technique, offering high rates of pathological complete response and effective downstaging or bridging to liver transplantation.[11,20]

In summary, while the current evidence base is characterized by methodological heterogeneity and evolving comparative standards, the overall body of data consistently supports radioembolization as a safe, effective, and versatile locoregional therapy for HCC when applied in appropriately selected patients. Ongoing prospective studies integrating standardized dosimetry, uniform outcome measures, and rational combinations with modern systemic agents are expected to further refine patient selection and consolidate the role of radioembolization within contemporary precision oncology frameworks for HCC.[9,21,37]

Future perspectives

The future of SIRT is promising, with ongoing trials such as RETOUCH (166Ho microspheres) exploring predictive dosimetry and real-time MR imaging to minimize non-target residuals.[9] Combinations with immune checkpoint inhibitors/tyrosine kinase inhibitors (*e.g.*, regorafenib + pembrolizumab *vs.* TACE/TARE in the phase III REPLACE trial, 2024) target ORR>70% in BCLC B beyond up-to-seven criteria, while hybrid chemo-radio approaches enhance penetration in hypovascular tumors.[10]

Artificial intelligence-driven pre-treatment radiomics promises response prediction accuracy >85%.[37] Persistent challenges include access in low-resource settings and the need for head-to-head RCTs *vs.* stereotactic body radiation therapy, but evolution toward multimodal precision oncology positions SIRT as a therapeutic cornerstone.[38]

Conclusions

SIRT represents a mature and versatile locoregional treatment option for HCC. Current evidence supports its use as an effective alternative to TACE and systemic therapies in appropriately selected patients, offering comparable OS with improved tumor control, favorable tolerability, and preservation of quality of life.

Continued technological innovation and integration with systemic and immunotherapeutic strategies are expected to further define the role of SIRT within personalized, multimodal treatment algorithms for HCC.

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Table 1. Main indications for selective internal radiation therapy by the Barcelona Clinic Liver Cancer stage.

BCLC stage	Key indications	Selection criteria	Level of evidence
0/A (single ≤3 cm)	Radiation segmentectomy as ablation alternative	Child-Pugh A/B, hypervascular nodule	II (limited RCTs)
B (multifocal)	Lesions >5 cm, bilobar, TACE-refractory	ECOG 0-1, tumor volume <50%	I (meta-analyses)
C (PVTT/limited EHS)	Segmental thrombosis, no symptomatic MV	Bilirubin <2 mg/dL, shunt <20%	II (propensity studies)
(references 10-13,16)			

BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis; EHS, extrahepatic spread; TACE, transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; RCTs, randomized controlled trials.

Table 2. Efficacy outcomes of selective internal radiation therapy *vs.* transarterial chemoembolization/sorafenib.

Endpoint	SIRT	TACE	Sorafenib	HR/OR (95% CI)
Median OS (months	18-27	12-20	10-14	0.68 (0.55-0.86) *vs.* TACE
PFS (months)	10-17	6-10	4-6	0.54 (0.44-0.67) *vs.* TACE
ORR (%)	52-73	41-52	2-12	1.45 (1.12-1.88) *vs*. TACE
Downstaging (%)	40-66	25-40	N/A	–
(references 17,18,20)				

SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization; HR, hazard ratio; OR, odds ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

Table 3. Toxicity profile of selective internal radiation therapy *vs.* transarterial chemoembolization.

Adverse event	SIRT (%)	TACE (%)	OR (95% CI)
Events ≥ grade 3	11-18	25-40	0.60 (0.29-1.25)
PES (grade 1-2)	20-35	50-80	0.25 (0.15-0.45)
REILD	<5	N/A	–
Hepatic decompensation	10-15	20-30	0.48 (0.22-1.04)
(references 24-27)			

SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization; OR, odds ratio; CI, confidence interval; PES, post-embolization syndrome; REILD, radioembolization-induced liver disease.