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REVIEW

Yttrium-90 radioembolization treatment strategies for management of hepatocellular carcinoma

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Abstract

As the third leading cause of cancer-related deaths worldwide, hepatocellular carcinoma (HCC) represents a significant global health challenge. This paper provides an introduction and comprehensive review of transarterial radioembolization (TARE) with Yttrium-90 (Y90), a widely performed transcatheter procedure for HCC patients who are not suitable candidates for surgery. TARE involves the targeted delivery of radioactive microspheres to liver tumors, offering a promising treatment option for managing HCC across various stages of the disease. By evaluating Y90 TARE outcomes across early, intermediate, and advanced stages of HCC, the review aims to present a thorough understanding of its efficacy and safety. Additionally, this paper highlights future research directions focusing on the potential of combination therapies with systemic and immunotherapies, as well as personalized treatments. The exploration of these innovative approaches aims to improve treatment outcomes, reduce adverse events, and provide new therapeutic opportunities for HCC patients. The review underscores the importance of ongoing research and clinical trials to optimize TARE further and integrate it into comprehensive HCC treatment paradigms.

Key Words: Transarterial radioembolization; Hepatocellular carcinoma; Yttrium-90; Radiation segmentectomy; Radiation lobectomy; Portal vein thrombosis; Combination therapies; Downstaging; Curative-intent; Locoregional therapy

Core Tip: This comprehensive review explores Yttrium-90 transarterial radioembolization (TARE) as an effective locoregional therapy for hepatocellular carcinoma across various stages. It compares TARE's advantages over other locoregional treatments and systemic therapies, emphasizing its role in enhancing treatment efficacy and patient outcomes. The potential of TARE in combination with systemic and immunotherapies is highlighted, pointing towards a future of precision medicine through personalized treatments. This comprehensive review aims to elucidate TARE's efficacy, safety, and evolving role in hepatocellular carcinoma management. By addressing emerging findings and new methodologies, we aim to advance the understanding and application of this promising technique in interventional radiology.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignancy of hepatocytes that has a mean five-year survival rate in the United States of 19.6% and is the third leading cause of cancer death worldwide[1-3]. These sobering statistics underscore the urgency of identifying and developing effective treatment strategies for HCC. Historically, HCC therapies include liver transplantation, liver ablation, and liver resection for early-stage HCC, while treatments for intermediate-stage HCC and advanced-stage HCC have been limited to locoregional therapies (LRTs) or systemic therapies focused on the manaement and delay of cancer progression[4-6]. Transarterial radioembolization (TARE) with Yttrium-90 (Y90) is a LRT that has demonstrated effectiveness and safety[7-11]. Research has demonstrated that TARE performs favorably when compared to other LRTs such as transarterial chemoembolization (TACE) and systemic therapies such as sorafenib[12, 13]. More recently, TARE has been included in the updated 2022 Barcelona Clinic Liver Cancer (BCLC) treatment recommendations for HCC when first-line options are not feasible[14].

The objective of this review is to examine the role of TARE in the management of HCC across early, intermediate, and advanced stages of the disease. By evaluating the outcomes associated with TARE, we aim to provide a comprehensive understanding of its efficacy and applications as a treatment modality. This review will also illuminate future research directions with particular emphasis on the potential of TARE combination therapies with systemic and immunotherapies. The prospect of personalized treatments guided by molecular markers is explored, offering a glimpse into the future of precision medicine in the battle against HCC.

TARE

Procedural technique

TARE, also referred to as selective internal radiation therapy, is a complex interventional radiology procedure that delivers radioactive microspheres directly into an artery that perfuses a tumor or tumor-bearing tissue. Commonly, intra-arterial injection of Y90 labeled glass or resin microspheres is used[15,16]. Metastatic hepatic malignancies have been found to derive 80%-100% of their blood supply from the hepatic artery, unlike normal hepatic parenchyma which derives 80% from the portal vein[15]. This unique attribute of hepatic malignancies allows the delivery of internal radiation directly to the tumor, while relatively sparing the surrounding healthy liver parenchyma.

The preparation for TARE involves several steps to minimize risks and ensure that the patient is a suitable candidate [15,17]. First, a preprocedural evaluation is conducted to measure bilirubin, coagulation profiles, and platelet counts. This evaluation is essential for confirming adequate liver function and appropriate blood clot response, which are each important factors to consider in lowering risks of post-TARE liver failure[15]. Notably, recent studies have shown that TARE can still be a viable treatment option even in patients with high bilirubin levels, potentially allowing bridging or downstaging for liver transplant candidates[18]. Following the preprocedural evaluation, an angiogram is performed to map vascular anatomy and locate hepatic tumors[15,17]. A catheter is guided into the hepatic artery through a small incision, typically in the groin, and navigated to the tumor site in the liver. Subsequently, macroaggregated albumin (MAA) is injected into the hepatic artery with follow-up scintigraphy to determine the degree of shunting to the lungs and thepresence of non-target distribution[15]. The simulation angiogram also reveals the location of the extrahepatic arteries originating from the celiac trunk that will need to be avoided, including the cystic artery if the gallbladder is still present[15,17].

During the TARE treatment procedure, a similar process is repeated, including angiography to identify the target vessels. Y90 radioactive beads are then injected at the tumor site[19]. It should be noted that the injected microspheres stay in the liver permanently, and that the radiation emitted slowly decreases over time[19]. Post-procedure, follow-up imaging is performed to assess the tumor's response to treatment[19].

Indications and outcome predictors

TARE is offered for unresectable HCC patients across the early, intermediate, and advanced stages[15]. Several prognostic factors have been identified to predict outcomes following TARE. These include an Eastern Cooperative Oncology Group performance status of 0, hepatic tumor burden < 25%, and an index tumor diameter of < 4 cm[20]. The Child-Pugh classification scheme is also another measure used to evaluate the patient's liver function, which can be helpful in determining if the patient is a suitable candidate for TARE[21]. This classification predicts TARE outcomes by calculating a score based on five clinical measures: Bilirubin, albumin, international normalized ratio, ascites, and encephalopathy. A higher Child-Pugh score correlates with a higher risk of complications from TARE[21].

TARE clinical outcomes and current strategies

Several studies have demonstrated the clinical effectiveness of TARE. For example, from 2017 to 2021, a study of 88 patients confirmed its safety and efficacy for lobar HCC treatment, particularly before the adoption of optimized segmentectomy at that institution[11]. Six months post-treatment, outcomes showed 83.3% complete or partial response, 98.3% disease control rate, and 77.3% maintained or were downstaged to Milan criteria[11]. These results indicate successful bridging to transplant and the long-lasting effect with TARE. Post-embolization syndrome was reported in only 5% of patients, supporting previous findings that TARE offers a more tolerable side effect profile and higher quality of life compared to treatments like sorafenib and TACE[11]. The trial also showed notable effectiveness in a complex patient population. Over half of the patients had undergone prior invasive liver treatments and nearly 75% were in BCLC-B or BCLC-C stages, establishing TARE's role in heavily pre-treated patients[11].

Additional prospective studies further support the benefits of TARE, especially when individual predictors, personalized dosimetry, and patient selection are considered. The multicenter European CIRT study analyzed 422 patients to compare dosimetry calculated using the standard body surface area method to the partition model[22]. The partition model utilizes differential tumor-to-nontumoral perfusion to personalize dose estimations. Comparative analysis through an exact matching model reported significantly improved overall survival with the partition model compared to body surface area-based dosing (23.4 *vs* 13.4 months)[22]. The ongoing PROACTIF study, a French post-approval registry with 670 patients, confirms the value of individualized TARE treatments[23]. Interim results showed a median overall survival of 20.8 months, with selective administration providing better outcomes than non-selective (22.8 *vs* 18.5 months)[23]. Improved survival was also observed in patients with unilobar disease and lower albumin-bilirubin grades, reinforcing the advantages of implementing personalized dosimetry and prognosis predictors in current TARE practice[23].

TARE safety and tolerance

While data have shown that TARE is generally well-tolerated, it is not without potential adverse events (AEs). These can include fatigue or mild abdominal pain following the procedure[16]. However, no significant treatment-related complications or treatment-related deaths have been reported from TARE utilization[8]. The high safety profile and limited side effects of TARE can be attributed to the low penetration depth of the high-dose beta radiation emitted during the procedure, which extends only 2.5 mm from the source. This characteristic effectively limits AEs and minimizes unnecessary radiation exposure to surrounding tissues[8].

TARE IN EARLY HCC

Early HCC classification and interventions

The classification of early-stage HCC encompasses very early and early stages, corresponding to the 0 and A stages of the BCLC staging system, respectively. Both stages are characterized by preserved liver function and the absence of macrovascular invasion, extrahepatic spread, or cancer-related symptoms. BCLC-0 is defined by solitary nodules ≤ 2 cm, while BCLC-A involves tumors ≤ 3 cm, which can be solitary or multifocal, with up to three nodules[14].

The 2022 BCLC guidelines prioritize liver transplantation for early and very early HCC tumors[14]. However, many patients become ineligible due to tumor progression or complications while awaiting donor organs. An early intention-to-treat analysis in 1999 identified transplant waiting list dropout as the primary predictor of survival in 87 early HCC cases, with a dropout rate of approximately 15%, despite Spain's distinction for having the highest liver donation rate at the time[24]. Recommended interventions pre-transplant include surgical resection and ablation, but these are limited by specific inclusion criteria which may exclude many HCC patients. The 2012 European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer Clinical Practice Guidelines estimated that only about 20% of HCC patients were eligible for surgical resection due to tumor characteristics and related factors[25,26].

Given the candidacy limitations of transplantation, ablation, and resection, alternative treatments are needed. TARE radiation segmentectomy (RS) has emerged as an effective curative-intent therapy supported by growing clinical evidence[14,27,28]. In 2011, Riaz *et al*[28] initially introduced RS as a selective technique to deliver a potent tumoricidal dose that minimizes collateral injury to healthy liver tissue, thereby confining and eradicating tumors within 1-2 targeted segments[27-29]. Several studies further confirm the safety of high-dosage TARE RS due to its beneficial selectivity and subsequently reduced target liver volume[30,31]. TARE has demonstrated a longer time to disease progression in BCLC-A patients compared to other treatments[32]. The 2022 BCLC guidelines correspondingly recommend TARE for BCLC-A patients facing transplant waiting periods over six months, being one of the treatment options that delay tumor progression alongside ablation and TACE[14]. Further studies have shown TARE's efficacy in managing complications associated with specific disease states and patient factors, highlighting its role in personalized treatment plans for early

HCC.

Early efficacy of early HCC TARE interventions

The introduction of TARE for early-stage HCC was more gradual compared to its use in intermediate or advanced stages, where it was typically a refractory treatment. A seminal multicenter study by Riaz *et al*[28] in 2011 focused on TARE for unresectable HCC tumors, specifically targeting two or fewer liver segments. The study reported a median overall survival (OS) of 26.9 months and a median time-to-progression (TTP) of 13.6 months[28]. However, inconsistent inclusion criteria and adherence to treatment guidelines limited the study, necessitating further research on TARE for early-stage HCC.

Subsequent retrospective reviews over the decade have continued to support TARE's benefits for BCLC 0-A stage tumors[33]. A study by Vouche *et al*[26] showed TARE had a median TTP of 33.1 months, a median time-to-transplantation of 6.3 months, and a median OS of 53.4 months. These results suggest that the outcomes for TARE are comparable to radiofrequency ablation (RFA) and could be preferred in solitary, unresectable HCC ≤ 5 cm. Because ablation curative-intent therapies are typically accepted for tumors ≤ 3 cm, TARE offers alternative advantages of treating tumors up to 8 cm, reducing the risk of unintentional tumor seeding, and preventing liver injury near critical anatomical structures[26, 29].

Comparable efficacy of TARE to standard curative-intent treatments in early HCC

In 2018, Lewandowski *et al*[27] conducted a study that followed 70 patients with preserved liver function over 14 years, demonstrating that TARE produced long-term clinical outcomes comparable to mainstream curative-intent techniques for early-stage HCC. The study revealed similar response rates, tumor control, and survival outcomes to resection, RFA, and transplantation, with longer survival for patients with ≤ 3 cm tumors (BCLC stage 0). Again, this confirms TARE's comparable efficacy to RFA[27].

Impact of landmark studies on TARE usage in early HCC

Two landmark studies, LEGACY and RASER, further explored TARE's effectiveness in 2021 and 2022 respectively. Refer to Table 1 for a summary of these landmark studies. LEGACY was a retrospective study conducted across three clinical centers that was instrumental in confirming both the specific safety, efficacy, and indication for TARE treatment for early-stage HCC tumors[34]. The study included 162 patients with solitary HCC nodules up to 8 cm, with 45 individuals receiving TARE as neoadjuvant therapy (with transplantation or resection) between 2014 and 2017. LEGACY addressed retrospective limitations by being the first to incorporate a blinded, independent, central review with two independent radiologists evaluating follow-up imaging. Primary endpoints included objective response rate (ORR) and duration of response (DoR) assessed by mRECIST, along with OS. The best ORR was 88.3%, with 62.2% of patients having a DoR greater than six months, and a median OS of 57.9 months[34]. These LEGACY parameters, outcome measures, and standards for therapeutic success were reviewed in accordance with the Food and Drug Administration. Across all 162 patients, the best ORR was 88.3%, with 62.2% having a DoR of greater than 6 months and a median OS of 57.9 months. Higher response rates were also observed in BCLC-A patients compared to the BCLC-C group, with the best ORR increasing to 89.8% and 65.9% of patients showing a DoR over six months. The LEGACY trial left an incredible impact on the TARE technique moving onwards. The Food and Drug Administration set objective standards to determine the success of LEGACY protocol based on target DoR and ORR both by localized mRECIST. The study results surpassed these criteria, granting Premarket Approval of TheraSphere as a novel radiation therapeutic tool. TheraSphere contains millions of glass microspheres that deliver Y90 to hepatic tumors, and it is one of two microsphere delivery options currently available. Furthermore, LEGACY results directly informed the 2022 revision of the BCLC guidelines, which newly incorporated TARE as an available treatment for patients with single nodules up to 8 cm in size[14]. In conclusion, the LEGACY study played a pivotal role in solidifying the clinical significance, safety, efficacy, and future applications of TARE therapy in early-stage as well as advanced HCC tumors.

The RASER trial, a single-arm prospective study, overcame prior limitations of retrospective studies and focused on a cohort with solitary nodules ≤ 3 cm unsuitable for ablation[35]. Twenty-nine eligible adults underwent TARE and were followed for up to 24 months with office visits and imaging evaluations, with mRECIST used to evaluate target tumor response. The trial aimed to demonstrate a 30% improvement in complete response rate compared to other standards like TACE, achieving a remarkable ORR of 100%, with 83% complete response and 17% partial response. The median time to complete response was forty three days, indicating a rapid therapeutic effect, with 90% of patients maintaining a sustained complete response after initial treatment[35]. Along with a median DoR of six hundred and thirty five days, these results highlight the durable impact of TARE. However, it's crucial to acknowledge that 17% of patients received additional therapies during the study, which could have influenced observed outcomes. Disease progression rates at 1 and 2 years were 4% and 12%, respectively. These rates, along with sustained complete response rates, were comparable to those observed in prior thermal ablation trials, affirming the efficacy of TARE relative to established standards of care. 27% of patients receiving liver transplantation also showed 100% complete pathological necrosis (CPN) on pathology results of target lesions, although additional HCC tumors were found in explanted liver tissue. This CPN rate is notably higher than those reported in earlier prospective studies by Lu *et al*[36] and Mazzaferro *et al*[37] with ablation of tumors ≤ 3 cm, which were 83% and 63% respectively. Only one death occurred during the study due to advanced HCC progression and portal invasion, with most side effects being transient or mild. The prospective RASER study provided valuable data on Y90 TARE as a curative-intent treatment for early-stage HCC, including tumor control, safety profile, and long-term clinical outcomes.

Table 1 Landmark studies testing transarterial radioembolization, transarterial chemoembolization, and sorafenib as hepatocellular carcinoma therapies

Ref.	LEGACY[34]	TRACE[40]	PREMIER[50]	RASER[35]	SARAH[69]	SIRveNIB[68]
Publication date	2021	2022	2016	2022	2017	2018
Combination tested	TARE	TARE *vs* TACE	TARE *vs* TACE	TARE	TARE *vs* sorafenib	TARE *vs* sorafenib
Sample size	162	TARE: 38, TACE: 34	TARE: 24, TACE: 21	29	TARE: 237, sorafenib: 222	TARE: 182, sorafenib: 178
ECOG performance status	0: 98 (66.7%), 1: 64 (39.5%)	TARE - 0: 34 (90%), 1: 4 (11%); TACE - 0: 29 (85%), 1: 5 (15%)	NDA	0: 28 (100%)	TARE - 0: 145 (61%), 1: 92 (39%); sorafenib - 0: 139 (63%), 1: 83 (37%)	TARE - 0: 135 (74.2%), 1: 47 (25.8%); sorafenib - 0: 141 (79.2%), 1: 37 (20.8%)
Child-Pugh score	A5: 108 (66.7%); A6: 54 (33.3%)	TARE - A: 36 (95%), B: 2 (5.3%); TACE - A: 29 (85%), B: 5 (15%)	TARE - A: 12 (50%), B7: 6 (25%), B8: 3 (12.5%), B9: 3 (12.5%); TACE - A: 15 (71%), B7: 3 (14%), B8: 2 (10%), B9: 1 (5%)	A5: 14 (48%), A6: 12 (41%), B7: 3 (10%)	TARE - A5+A6: 196 (83%), B7: 39 (16%); sorafenib - A5+A6: 187 (84%), B7: 35 (16%)	TARE - A: 165 (90.7%), B: 14 (7.7%); sorafenib - A: 160 (89.9%), B: 16 (9.0%)
Median overall survival (months)	NDA	TARE: 30.2, TACE: 15.6	TARE: 18.6, TACE: 17.7	NDA	TARE: 8.0, sorafenib: 9.9	TARE: 8.8, sorafenib: 10.0
Median time to progression (months)	NDA	TARE: 17.1, TACE: 9.5	TARE: > 26, TACE: 6.8	NDA	NDA	TARE: 6.1, sorafenib: 5.4
Objective response rate	86.4%	TARE: 88%, TACE: 87%	NDA	90%	TARE: 49%, sorafenib: 66%	NDA
Median duration of response (months)	10.6	NDA	NDA	20.9	NDA	NDA
Median progression free survival (months)	NDA	TARE: 11.8, TACE: 9.1	NDA	NDA	TARE: 4.1, sorafenib: 3.7	TARE: 5.8, sorafenib: 5.1

TARE: Transarterial radioembolization; TACE: Transarterial chemoembolization; NDA: No data available; ECOG: Eastern Cooperative Oncology Group.

Side effects and benefits of TARE in early HCC tumors

TARE is a more recent technique than other HCC treatments, and clinical questions remain especially for both early and very early tumor grades. The side effects of TARE therapy for early-stage HCC tumors are a meaningful area of research focus. While investigations of TARE were transitioning from solely palliative in late-stage tumors to a potentially curative therapy for early HCC cases, a 2009 case study drew attention to potential side effects by describing one patient with early-stage HCC who developed gastric radiation enteritis after TARE treatment[38]. The case review introduced the need for prospective studies to elucidate possible risks and side effects. Since that time, several studies involving early-stage HCC tumors continue to demonstrate evidence supporting the safety and efficacy of TARE[26,34,35]. As previously mentioned, RASER along with other trials highlights TARE's effectiveness in achieving CPN and related improvement in outcomes[35,39]. CPN represents the effective elimination of malignant cells and is an important measure of treatment success directly related to positive patient outcomes, and TARE's advantage in achieving this established its use as a curative-intent treatment. Compared to TACE, TARE offers superior tumor control, longer TTP, and greater OS for BCLC-A and BCLC-B patients, enhancing its role in bridging to liver transplantation or downstaging targets[39,40]. TARE also had a similar efficacy to TACE when either was used as a combined therapy with microwave ablation in unresectable, solitary nodules up to 3 cm[32]. These benefits and the potential specificity of TARE to patient factors unaddressed by other treatments have led to its inclusion in recent updates of international guidelines from the European Society for Medical Oncology, BCLC, and more[14,41].

OUTCOMES FOR TARE IN INTERMEDIATE HCC

Intermediate HCC corresponds to a BCLC-B and is defined as being multinodular with preserved liver function, having no cancer-related symptoms, no vascular invasion, and no extrahepatic spread[14]. The 2022 BCLC recommendations further stratified BCLC-B into 3 subgroups dependent on tumor burden and liver function, with different treatment strategies for each subgroup[14]. Patients in the first BCLC-B subgroup have well-defined HCC nodules and are treated with liver transplant if extended liver transplant criteria are met[42]. Patients in the second BCLC-B subgroup cannot receive liver transplants but have preserved portal flow, have defined tumor burden, and are treated with TACE or systemic therapy[14,25,43,44]. Patients in the third BCLC-B subgroup have diffuse, infiltrative, extensive HCC liver

involvement and are treated with systemic therapy[45]. A growing body of literature augments the role of TARE in improving intermediate HCC treatment algorithms, especially as a treatment alternative in situations where TACE is ineffective[46-48]. A growing number of clinical studies suggest that TARE can even be considered as a superior replacement for TACE during second stage BCLC-B due to TARE's more favorable endpoint measures. Recent literature also suggests TARE and TACE used together as a combination therapy for BCLC-B may also be an effective treatment.

TARE as a potential alternative to TACE for second stage BCLC-B

TARE has been considered as an alternative treatment to the more traditional TACE therapy in BCLC-B patients[4,46,47,49]. While TARE has not yet been officially accepted in any official international guidelines, many trials have warranted TARE to be considered as a potential aspect of future HCC treatment algorithms. The 2016 PREMIERE randomized phase 2 study comparing the effects of TACE and TARE in patients diagnosed with BCLC-A or BCLC-B, randomly assigned 179 participants to either TACE or TARE and found that median TTP was significantly increased for the TARE group with > 26 months compared to the TACE group with 6.8 months, demonstrating superior tumor control and survival in TARE treatment[50]. The median OS for TACE and TARE was 17.7 months and 18.6 months respectively and were not significantly different in PREMIERE which corroborates a 2015 study that found similar OS and TTP between TACE and TARE's treatment among BCLC-B patients, despite the fact that there was a larger tumor burden among TARE patients compared to TACE patients[50,51]. A summary of PREMIERE can be found in Table 1. Furthermore, TARE Y90 was better tolerated, associated with fewer hospitalizations, had a superior safety profile, and had fewer treatment sessions than compared to TACE[51]. This further demonstrates the potential of TARE's potential as a suitable or even superior alternative to TACE in intermediate HCC. These findings were further corroborated by the 2022 Treatment of Hepatocellular Carcinoma (TRACE) trial which was a single-center prospective randomized controlled trial comparing the efficacy of TARE *vs* TACE for patients with BCLC-B HCC[40]. A summary of TRACE can be found in Table 1. TRACE found that OS was 30.2 months after TARE and 15.6 after TACE. Patients undergoing TARE had a longer median TTP with 17.1 months compared to TACE with 9.5 months and TARE also had similar safety measures as TACE[40]. Additionally, a 2017 prospective cohort study treating 152 BCLC-B patients with TARE found that the median OS was 25 months which was similar to the median OS of 19.4 months for patients undergoing TACE as reported by the 2018 EASL clinical guidelines, again further supporting TARE's potential promise as a TACE alternative for intermediate HCC[25,52].

TARE in late-stage BCLC-B

It must be emphasized that TARE's promise as a potential replacement for TACE only holds true during the second stage BCLC-B[25]. Guidelines maintain that systemic therapy such as sorafenib is the primary first-line treatment for late-stage BCLC-B and that TACE or TARE should not be performed at this stage[14]. In fact, while TARE has been shown to have a good safety profile and local tumor control, TARE still fails to show an overall survival benefit when compared to sorafenib treatment in late-stage BCLC-B and BCLC-C patients[25]. Studies show that sorafenib alone still has superior OS and TTP outcomes compared to TARE in late-stage BCLC-B[25].

TARE and TACE as a part of a combination therapy for BCLC-B

An emerging area of study is the potential benefits of a combination therapy using both TARE and TACE techniques in treating BCLC-B. While the literature is still limited, the few studies that focus on this question show promising results. A 2022 study comparing outcomes in BCLC-B patients who received either TARE alone or a combination therapy of TARE followed by TACE found that patients in the combination group had significantly longer OS of 36.8 months compared to 10.6 months in the TARE only group[53]. The combination group also had significantly longer TTP of 14.4 months compared to 5.5 months in the TARE only group[53]. Although this study was limited in its retrospective nature, its encouraging results warrant future prospective studies that further examine combination therapies. A combination therapy of TACE with sorafenib may also prove to be an area of interest for future studies for BCLC-B patients for possible synergistic effects. However, it again should be noted that according to current guidelines, sorafenib is likely more suited for advanced HCC therapy regimens[54].

TARE WITH Y90 IN ADVANCED HCC

According to the BCLC staging system, grade C HCC is classified by the presence of portal invasion and/or extrahepatic spread, alongside preserved liver function (performance status 1-2)[14]. Symptomatic patients are often in the advanced-stage of this disease, and are not responsive to curative treatments such as resection or transplant[55]. Current guidelines recommend initial treatment with combination immunotherapies such as atezolizumab-bevacizumab (atezo-bev) or durvalumab-tremelimumab, which have been demonstrated to be superior to other common forms of therapy. This is then followed by sorafenib, envatinib, or durvalumab alone in cases of contraindications[56-58]. Of note, emerging evidence suggests that envatinib may surpass atezo-bev in efficacy, positioning it as a potential first-line therapy[59]. For post-sorafenib management, second-line treatments include regorafenib, ramucirumab, and cabozantinib, the latter of which is also considered a third-line therapy[60-62]. While TARE using Y90 is recognized as a safe and effective option for advanced-stage HCC, its utility as monotherapy is limited due to the comparative levels of effectiveness of various immunotherapies. As a result, TARE as a standalone approach is not currently included as a standard of treatment for advanced HCC and is unlikely to be included in the foreseeable future. However, when integrated with other treatments, TARE offers valuable potential strategies to personalize treatment regimens and improve patient outcomes. The

following sections will explore these potential regimens and review existing literature on TARE, either alone or in combination with other modalities.

Outcomes of TARE as a monotherapy in advanced HCC

TARE has been validated as an effective option in the setting of advanced HCC[63]. A 2010 study done on 159 European patients found that Y90 radioembolization had similar median OS rates to that of sorafenib, a finding corroborated in a separate 2011 study on 325 European patients, where radioembolization improved OS in patients across various BCLC stages without inducing severe AEs[64,65]. In portal vein thrombosis (PVT) cases, which occur in about 35%-50% of HCC patients, people with BCLC-C also had competitive outcomes to sorafenib[66,67]. This was a significant development especially because TACE failed to show significant survival benefits in advanced HCC and the only available options for treatment have been systemic therapies. However, while TARE has been found to be comparable, it has not been demonstrated to have any major benefits over sorafenib nor has it been shown to work better in combination with sorafenib[68-70]. Given the price of Y90 treatment, sorafenib may be the more cost-effective method in light of their similarities[71].

More recent developments have brought to light the utility of TARE in downstaging advanced HCC. While sorafenib, a systemic treatment, is recognized for extending life expectancy, it does not effectively reduce tumor size[69,72,73]. In an Italian retrospective study, TARE was found to be significantly more effective at downstaging patients, with 10 out of 41 patients treated with TARE achieving curative-intent surgery compared to only 1 out of 24 patients treated with sorafenib [74].

Between TARE and sorafenib, TARE generally shows a more favorable profile in terms of AEs. Fewer patients who are treated with TARE experienced serious AEs compared to those treated with sorafenib- 20.8% *vs* 35.2%, respectively[68]. Additionally, the types of AEs associated with sorafenib, such as fatigue, diarrhea, rash, hand-foot skin reaction, hypertension, weight loss, and rash are more disruptive than symptoms reported in TARE, including fatigue, fever, nausea/vomiting, and abdominal pain[75]. Given that Y90 TARE as an initial advanced HCC therapy has been shown to be non-inferior to sorafenib, the greater safety profile of TARE leaves room for personalized therapies, especially in the setting of palliative care[76]. Another study compared atezo-bev against TARE, showing that both treatments had similar effectiveness with 14.9 months OS and 6.8 months progression free survival (PFS) for atezo-bev *vs* 15.0 months OS and 4.4 months PFS for TARE[77]. Although TARE was not more effective than atezo-bev, this study further suggests TARE can be a viable treatment alternative for certain patients with advanced HCC.

TARE as a combination therapy in advanced HCC

Given the separate mechanisms of action between locoregional TARE and commonly used systemic drugs, combination therapies have been hypothesized to improve outcomes in patients with advanced HCC. However, TARE and sorafenib, one of the most used first-line drugs in treating BCLC-C HCC, have been explored in several studies with mixed outcomes. The SORAMIC trial is one prominent study that investigated this combination, and it did not demonstrate a significant OS benefit with the addition of TARE to sorafenib compared to sorafenib alone for patients with advanced HCC[70]. This same trial does propose that TARE-sorafenib treatment has potential for investigation in non-cirrhotic patients, younger patients, and non-alcoholic HCC patients, leaving open a possibility for the development of personalized therapies.

There have been multiple combination therapies consisting of TARE and another immunotherapy, such as durvalumab, nivolumab, pembrolizumab, and atezolizumab. Reference Table 2 for a summary of TARE combination therapies for advanced HCC. TARE and durvalumab have been safely combined in patients with locally advanced unresectable HCC in a phase I/IIa trial consisting of 23 patients[78]. According to this trial, median PFS was 6.9 months, TTP was 15.2 months while the 18-month OS rate was 58.3%. The efficacy of TARE-durvalumab is encouraging, and the results of this study implicate the need for further large-scale controlled trials. Nivolumab is another immunotherapy that has been tested following TARE administration, and similar to durvalumab, shows promising efficacy along with an acceptable safety profile[79,80]. The NASIR-HCC single-arm study specifically found a PFS of 9 months, a median TTP of 8.8 months, and a median OS of 20.9 months. Very recently, an open-label, single-arm, multicenter pilot study treated patients with pembrolizumab in conjunction with Y90 radioembolization, resulting in a median PFS of 9.95 months, a TTP of 9.95 months, and a median OS of 27.3 months[81]. Atezo-bev, an immunotherapy-antiangiogenic combination with demonstrated superiority over sorafenib was tested in conjunction with TARE duo therapy, resulting in a PFS of 78.8% and 66.7% at 6- and 12-month, respectively. 6-month and 12-month OS rates were 90.0% and 77.1%, respectively [81]. Overall, these studies have each shown that TARE combined with each prospective immunotherapy shows acceptable safety profiles and promising outcomes, warranting the cause of larger comparative studies.

TARE IN THE SETTING OF PVT

While PVT can result from benign etiologies, it can occur in patients with advanced disease due to portal vein invasion by an aggressive tumor. Once the portal vein is invaded, the BCLC staging system places HCC patients at stage C, at which point patients are candidates for palliative systemic therapy[14]. It is important to note that main portal vein trunk involvement can worsen cancer prognosis through obstruction, which leads to portal hypertension and increased risk for cancer spread[82]. Thus, developing treatment methods for patients with advanced HCC and PVT is crucial to improving survival rates and quality of life. Personalized dosimetry can also enhance TARE treatments of HCC with PVT, with one study yielding an OS of 22.9 months compared to 9.5 months[83-85]. Tailored TARE dosing can therefore expand current

Table 2 Treatments of advanced hepatocellular carcinoma using combination therapies

Ref.	HCRN GI15-225[81]	NASIR-HCC[80]	SOLID[78]	Yu *et al*[96]	SORAMIC[70]
Publication date	2024	2022	2023	2023	2019
Combination tested	TARE + pembrolizumab	TARE + nivolumab	TARE + durvalumab	TARE + atezo-bev	TARE + sorafenib *vs* sorafenib
Sample size	27	42	24	10	216
ECOG performance status	0: 13 (48%), 1: 14 (52%)	0: 38 (90.5%), 1: 4 (9.5%)	0: 20 (83.3%), 1: 4 (16.7%)	0: 4 (40.0%), 1: 4 (40.0%), 2-3: 2 (20.0%)	NDA
Child-Pugh score	A: 26 (96.0%), B7: 1 (4.00%)	A5: 36 (85.7%), A6: 6 (14.3%)	A5: 21 (87.5%), A6: 3 (12.5%)	A: 8 (80.0%), B: 2 (20.0%)	A: 190 (88.0%), B: 26 (12.0%)
Median overall survival (months)	27.3	20.9	NDA	NDA	TARE + sorafenib: 12.1, sorafenib: 11.4
Median time to progression (months)	9.95	8.80	15.2	NDA	NDA
Objective response rate	36.0%	41.50%	83.3%	NDA	NDA
Median duration of response (months)	5.50	7.75	7.2	NDA	NDA
Median progression free survival (months)	9.95	9.0	6.9	NDA	NDA

atezo-bev: Atezolizumab-bevacizumab; TARE: Transarterial radioembolization; TACE: Transarterial chemoembolization; NDA: No data available; ECOG: Eastern Cooperative Oncology Group.

avenues to improve outcomes in especially challenging PVT cases.

TARE in palliative treatment of advanced HCC with PVT

TACE is widely recognized as the gold standard for treating intermediate, unresectable HCC. However, the presence of PVT poses a relative contraindication to TACE due to the heightened risk of hepatic infarction and deterioration of liver function[86]. In this context, TARE emerges as a promising palliative alternative for advanced HCC with PVT, demonstrating improved median survival rates with a comparatively strong safety profile[87]. Particularly, patients with Child-Pugh A liver disease and PVT are especially strong potential candidates for Y90 radioembolization[88]. In a systematic review, Salem *et al*[88] recorded that patients who received TARE and had either branch or main branch PVT had a median survival of 16.6 and 7.7 months respectively. Similar patients using sorafenib had a median survival of 8.9 months, though further comparisons could not be drawn due to a lack of further categorization.

When PVT involves the main portal vein, TARE and systemic therapies are the only options. If the thrombosis involves only a right or left branch, and the tumor is on the opposite side, both TACE and TARE to the contralateral side are viable treatment options. The liver has a dual blood supply from the portal and hepatic arteries, and tumors primarily receive their blood supply from the hepatic arteries. This allows TACE to target the tumor without significantly damaging the liver's overall blood supply. However, when the portal vein is obstructed, performing TACE could lead to liver devascularization. TARE, on the other hand, is a non-ischemic treatment that does not introduce enough particles to cause arterial occlusion, making it a safer alternative in such cases[87].

Moreover, TARE is associated with a favorable safety profile compared to TACE. TACE, which has a greater ischemic effect over TARE, has a higher incidence of post embolization syndrome[89]. This syndrome is a complication that occurs in some patients within 72 hours after transarterial embolization, presenting with fever, nausea, abdominal pain, and fatigue[90]. In fact, out of 32 treatments, 25% of patients had no AEs of any form[91]. The same is true compared to sorafenib. While radioembolization has a similar efficacy to sorafenib, it has a significantly improved sustained health status[92]. Thus, TARE may be a superior option for palliative treatment in advanced HCC with PVT, as it offers a similar efficacy with improved quality of life. Nonetheless, additional research is necessary to definitively ascertain the roles of these treatments in the palliative care of advanced HCC with PVT.

TARE in downstaging advanced HCC with PVT

TARE, along with TACE, hepatic artery infusion chemotherapy, combined chemo-radiotherapy, and stereotactic body radiation therapy are downstaging techniques used in the treatment of intermediate HCC, after which curative treatments, such as liver transplantation, may be used[93]. This same treatment can be useful for select patients who are good candidates based on several factors, including the Japanese Vp classification and Cheng Type classification[93].

The unique features of TARE make it a great candidate for downstaging advanced HCC with PVT, though more studies are needed to compare the efficacy of TARE to other downstaging methods. First, TARE is less likely to induce post-embolization syndrome. As stated, it has been shown to be particularly effective in the presence of PVT and can be delivered with relatively few treatments. In one Italian hospital, 5 out of 24 advanced HCC with PVT patients treated

with TARE were successfully downstaged to surgical curative-intent treatment[94]. These findings correlate with the 6 of 21 patients who were downstaged and treated radically in a separate study, which also found that long term survival post-treatment was 75% at 3 years, a number comparable to survival in patients treated radically in early-stage disease [95]. Given that TARE can rescue advanced HCC to surgery, there is validity for TARE to be used instead of sorafenib in certain patient cases, especially those with a prognostically higher chance of successful downstaging.

FUTURE DIRECTIONS

While TARE has emerged as a promising treatment, particularly in the management of HCC, there are several areas where further research and development can realize TARE's full potential. Many aspects of the TARE technique can be potentially expanded or fine-tuned through future clinical trials and include but are not limited to combination therapies with immunotherapy, personalized dosimetry to improve patient outcomes, use of radioembolization TARE radionuclides other than Y90 such as Holmium-166 (Ho-166), and use of TARE in cholangiocarcinoma (CCA).

TARE synergies with immunotherapies and systemics

TARE demonstrates multiple immunologic and inflammatory changes that can offer opportunities for synergistic effects with immunotherapy and other systemic therapies. Previous research studies have found that there are significant increases in interleukin (IL)-1 and IL-6 in patients 3 days after undergoing Y90 radioembolization[96]. It has been shown that rises in IL-1 and IL-6 levels specifically serve important roles for initiating acute-phase inflammatory responses that may provide pro-apoptotic or pro-survival effects[97,98]. Separate studies have also found an increase in IL-8, markers for oxidative stress, and significant increases in factors related to liver regeneration[99]. Granzyme B expression, along with higher infiltration of CD8+ T cells, CD56+ natural killer cells, and $CD8^+$ $CD56^+$ natural killer T cells, demonstrates local immune activation in tumor-infiltrating lymphocytes isolated post Y90 TARE[100].

Analysis of peripheral blood mononuclear cells before and after Y90 radioembolization showed elevated levels of tumor necrosis factor-α on both CD8+ and CD4+ T cells, along with an increased percentage of antigen-presenting cells, indicating systemic immune activation. Moreover, patients who respond favorably to Y90 TARE exhibit a high percentage of CD8+ T cells co-expressing inhibitory receptors programmed death 1 and T cell immunoglobulin and mucin domain 3 along with homing receptors CC chemokine receptor 5 and CXCR6[100]. This specific T cell phenotype indicates that, despite the expression of exhaustion markers, these cells are actively recruited to the tumor site. The immune activation not only supports the direct cytotoxic effects of TARE but also enhances the tumor's immunogenicity, offering opportunities for synergistic effects when combined with immune checkpoint inhibitors that target related pathways[101]. Consequently, the combination of TARE with immunotherapies holds promise for improving therapeutic outcomes by leveraging both local tumor control and systemic immune activation.

Combination therapies with immunotherapy

The field of combination therapies for HCC with TARE is rapidly evolving. Recent studies highlight promising synergies between TARE and various systemic treatments, including immune checkpoint inhibitors and anti-angiogenic agents. Reference Table 2 for a summary of TARE combination therapies for advanced HCC. To confirm these initial findings and determine long-term efficacy, further prospective and comparative studies with larger sample sizes are necessary. Specifically, randomized clinical trials are needed to evaluate the optimal sequence of TARE and atezo-bev administration, as well as the combination of TARE and nivolumab in patients with large or multiple tumors or those with portal vein invasion[80,102]. Similarly, larger studies are essential to assess the benefits of combining pembrolizumab with Y90 radioembolization and to explore the potential advantages of earlier treatment with checkpoint blockade in non-metastatic HCC patients[102]. Additionally, further exploration of combination treatments with TARE and sorafenib is needed, focusing on specific subgroups such as younger patients, non-cirrhotic patients, and those with HCC of non-alcoholic etiology[70]. These future directions underscore the potential of combination therapies to enhance treatment outcomes for HCC patients.

As mentioned, previous combination studies with immunotherapy have shown promise, but are largely limited by small sample sizes and the need for larger, well-designed trials. Thus, a 2023 publication identified patients with advanced HCC that were treated with either combined TARE + immunotherapy or immunotherapy alone, finding that patients treated with a combination of TARE and immunotherapy had an ORR of 30%, with tumor regression observed in 81% of patients[103]. Notably, these researchers found that this combined therapy was associated with improved OS rates compared to immunotherapy alone, nearly doubling the median OS from 9.5 months to 19.8 months. The combination therapy also demonstrated a 50% reduction in mortality hazard compared to immunotherapy alone. These promising results underscore the potential of TARE combined with immunotherapy to significantly improve outcomes for patients with advanced HCC. Ongoing larger clinical trials are expected to further test these findings and help establish optimal treatment protocols for these patients.

Personalized TARE dosimetry to improve patient outcomes

Personalization of the TARE technique continues to significantly evolve in recent years. Potential optimization options, as discussed by Dr. Marnix Lam, include but are not limited to microsphere material, dose distribution and activity prediction models, and alternative radionuclide choice such as Ho-166[104,105]. The toxicity profiles of resin and glass microspheres are notably distinguished by their differences in particle count and distribution. TheraSphere has a lower particle count, higher specific activity, and more heterogenous distribution when compared to resin microspheres known

as SIR-Spheres[105]. A study of lobar radioembolization in healthy pig livers using TheraSphere supported the observation that a higher number of delivered microspheres increases absorbed-dose homogeneity, resulting in larger liver volumes exposed to a potentially cytotoxic dose[106]. Thus, because of its higher particle delivery and homogeneity, SirSpheres can present the same toxicity risk as TheraSphere even when the radiation dosage is reduced by half.

Radioembolization TARE radionuclides other than Y90 such as Ho-166

A study conducted by Stella *et al*[104], which Dr. Lam was also involved in, further describes the promising advantages of utilizing Ho-166 radionuclides for TARE treatments instead of Y90. Unlike Y90, which faces limitations in single photon emission computed tomography (SPECT) resolution and positron emission tomography sensitivity, Ho-166 can be visualized and monitored in real-time using both magnetic resonance imaging and SPECT at low quantities due to its lanthanide properties[104,105]. This enables the use of the same Ho-166 microspheres for both the scout and therapeutic doses, which improves the accuracy of treatment planning compared to other modalities[104]. In previous studies, workup utilizing MAA labeled with Technetium-99m (99mTc) would typically precede Y90 radioembolization to predict radioactivity distribution. However, the predictive value of planning with 99mTc-MAA for post-treatment Y90 distribution was found to be suboptimal in the SARAH trial and only correlated well in 53% of patients[69,105]. This discrepancy that was observed in almost half of the patients underscores the need for a more reliable scout procedure. A summary of the SARAH study can be found in Table 1. As mentioned before, Ho-166 is consistently utilized in both planning and treatment phases which improves the accuracy of lung-shunt and intra-hepatic distribution estimates[104,105]. Stella *et al*'s study also introduces a novel dual isotope technique that employs Ho-166 for precise tumor targeting while also utilizing 99mTC-stannous phytate to delineate normal liver tissue, offering effective identification of tumor tissue that is distinguished from health liver using SPECT/CT imaging alone[104]. Ho-166 dual isotope protocol has demonstrated efficacy and feasibility in both phantom studies and clinical settings, with further explorations seeking to optimize the Ho-166 and 99mTC ratio and automatic healthy liver segmentation methods[104].

In conclusion, Ho-166 improves treatment outcomes by ensuring highly predictive work-up of the final therapeutic distribution, offering superior imaging capabilities, and improving treatment precision when compared to standard planning modalities. It is evident that tailored dosimetry, which encompasses TARE microspheres, radionuclides, and predictive models, offers many clinical advantages when compared to uniform dosage methods.

CCA treatment with TARE

HCC constitutes the majority of primary hepatobiliary tumors, with CCA being the second most common[107]. CCA is an epithelial cell malignancy that can appear in various locations throughout the biliary tree and has historically been challenging to treat[108]. Research on the effectiveness of LRT for CCA is limited due to limited power of potential studies, which is due to the rarity of CCA as well as the superiority of surgical resection[109]. However, emerging evidence has shown that TARE is effective as a part of treatment algorithms in treating CCA[109].

Due to its difficulty in early detection, higher aggressiveness, and poorer prognosis compared to HCC, the first-line treatment for CCA is typically surgical resection[110]. However, resection may not always be possible due to large tumor size, in which case TARE can be utilized[109]. Studies indicate that TARE is particularly effective in downstaging unresectable CCA to make surgical treatment feasible[111]. Furthermore, research shows that TARE is well-tolerated in CCA treatment[10]. Nevertheless, compared to its use in HCC, there is less evidence supporting TARE in CCA, highlighting the need for future research into TARE as a component of CCA treatment algorithms.

Other considerations

TARE has significantly advanced in treating liver cancer, particularly for cases deemed unresectable. A notable development is TARE RS, which delivers enough radiation to ablate entire vascular territories. This offers curative-intent without the limitations of thermal ablation, such as the heat sink phenomenon and requirement for general anesthesia [112]. The PREMIERE trial further validated the effectiveness of Y90 radioembolization in patients with unresectable, non-ablatable HCC, showing a TTP of over 26 months when compared to 6.8 months for conventional TACE[113]. Its inclusion in the National Comprehensive Cancer Network guidelines for colon and rectal cancer liver metastases underscores its growing clinical acceptance[109].

TARE has also shown future promise in large HCC tumor management, which is an important development given the challenges and limited treatment options of treating large HCCs as opposed to smaller HCC tumors. A study in 2024 contrasted TACE and TARE for HCC tumors exceeding 8 cm and determined that while both TACE and TARE demonstrated similar effectiveness in controlling tumor growth and extending survival rates, TARE experienced fewer complications than the TACE group[114]. In fact, TACE had a 100% post-embolization syndrome rate and 72% severe side effects in comparison to TARE with a 75% post-embolization syndrome rate and 5% severe side effects rate. This same study reported TARE patients had average hospital stays that were 3 days shorter than those of TACE patients. Overall, this study suggests that while TARE and TACE are both viable options for large HCC tumors, TARE has a superior safety profile and reduced recovery time relative to TACE.

Effective patient selection and multidisciplinary collaboration are crucial for optimizing Y90 therapy outcomes, ensuring minimal toxicity and enabling patients to resume normal activities shortly after treatment, unlike the severe post-embolization syndrome often seen with chemoembolization. Essential steps in treatment planning include calculating the target liver mass, mapping tumor-perfusing vessels through angiography, assessing pulmonary shunt, and determining the optimal therapeutic dose[109]. Studies have established safe dosimetry levels and highlighted the importance of precise patient preparation to balance therapeutic benefits against risks to normal liver parenchyma. Both TheraSphere and SIR-Spheres are the primary devices used, each with specific regulatory approvals and indications[109].

Future advancements in Y90 radioembolization lie in expanding its applications beyond liver treatments and combining it with other therapies. Investigational radiopaque microspheres and advanced dosimetry tools, such as voxel-based dosimetry, offer enhanced precision in treatment planning and execution[109]. Combining Y90 with radiosensitizing chemotherapies or other ablative techniques like RFA could further improve outcomes for patients with various types of liver metastases, including those from neuroendocrine tumors[109]. Additionally, expanding Y90's use to extra-hepatic applications, such as treating meningiomas or renal cell carcinomas, represents an exciting frontier, although it requires careful investigation and controlled trials to establish safety and efficacy. As research progresses, integrating Y90 radioembolization into broader oncologic treatment paradigms will likely continue to grow, driven by its minimally invasive nature and significant potential to improve patient quality of life.

CONCLUSION

HCC is a leading cause of cancer death, with many patients presenting with unresectable tumors that necessitate effective treatment strategies. LRTs have emerged as a leader in treating HCC effectively. TARE with Y90 is an evolving LRT that has demonstrated both effectiveness and safety, particularly for unresectable disease, and shows broad applicability across most stages of the BCLC spectrum. Furthermore, TARE allows for good local control, has curative-intent, and provides bridges to transplantation by delivering radioactive microspheres directly to liver tumors or tumor-bearing tissue. Growing evidence has cemented TARE's role in the HCC treatment paradigm across all stages, demonstrating robust efficacy. It has potential for use in combination therapies, as well as in the future of personalized treatments. Ongoing and future work is necessary to verify TARE's clinical applications and to unearth new methods of treatment for patients with HCC and beyond.

FOOTNOTES

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