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專題報導

Current Status and Advances in Yttrium-90 Radioembolization for Hepatocellular Carcinoma

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Abstract

Yttrium-90 radioembolization, also known as transarterial radioembolization (TARE), has emerged as a critical locoregional therapy for hepatocellular carcinoma (HCC). This innovative treatment delivers high-dose radiation directly to liver tumors via microspheres, minimizing damage to healthy tissue. TARE is widely used for intermediate-stage HCC as an alternative to transarterial chemoembolization (TACE) and for advanced-stage HCC, particularly in patients with portal vein thrombosis (PVT). Recent advances in personalized dosimetry, such as multi-compartment and voxel-based models, have enhanced treatment precision and safety. Additionally, integrating TARE with systemic therapies, including immune checkpoint inhibitors and VEGF inhibitors, offers promising synergistic effects. Technological innovations in catheterization and imaging, along with the potential of artificial intelligence (AI), are driving further improvements in treatment outcomes. This article reviews the current status and recent advances in Y-90 radioembolization, emphasizing its expanding role in the personalized management of HCC.

Key Words: Yttrium-90 Radioembolization, Embolization, Hepatocellular carcinoma, BCLC

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related mortality worldwide and the second leading cause of death in Taiwan. In many regional and global guidelines, locoregional therapies (LRTs) are the preferred options for managing early and intermediate-stage HCC, while systemic therapy is the recommended first choice for advanced HCC. Regarding the LRTs in real-world practice in Taiwan based on most recent Taiwan Liver Cancer Association (TLCA) management guidelines, various transarterial therapies are available based on the tumor characteristics and the patient's clinical status, including conventional transarterial chemoembolization (cTACE), drug-eluting bead transarterial chemoembolization (DEB-TACE), and transarterial radioembolization with Yttrium 90 (TARE)[1-3]. TARE combines the precision of embolization with the therapeutic effects of radiation by delivering radioactive Y-90

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microspheres directly into the liver's arterial supply to target tumors with high doses of radiation while sparing surrounding healthy tissue, is an advanced locoregional treatment for liver malignancies, including HCC and metastatic liver tumors.

Procedures of Radioembolization

TARE delivers beta radiation directly to the tumor via Yttrium-90 microspheres, causing DNA damage that induces tumor cell death with minimal ischemic effects. The average penetration is approximately 2.5 mm with a maximum depth of up to 10 mm. The half-life of Yttrium-90 is approximately 64.1 hours, and nearly 90% of beta particles are emitted within 7 days after the administration. The radiation effect persists for several weeks to months, ensuring durable tumor control[4]. Two 90Y products are currently commercially available: SIR-Spheres® resin microspheres (Sirtex Medical, Woburn, MA, USA) and TheraSphere® glass microspheres (Boston Scientific, Marlborough, MA, USA). The radioactive microspheres have a size range of 20-60 μm. Glass microspheres have a 50-fold higher particle-specific activity than resin microspheres. Conversely, resin microspheres exhibit higher tumor particle loading capacity, which may influence their distribution within the tumor[5].

TARE typically involves a pretreatment simulation process, which includes hepatic angiography and the injection of technetium-99m macro-aggregated albumin (99mTc-MAA) into the target arteries in an interventional suite. This is followed by 99mTc scintigraphy, using planar imaging and SPECT/CT scans to evaluate the lung shunt fraction (LSF).

Previously, dosimetry for TARE relied on simpler methods like the body surface area (BSA) model and single-compartment model, which assumed uniform radiation distribution. These approaches lacked precision, often leading to suboptimal tumor dosing or increased toxicity. The limitations of these models have driven the shift toward advanced multi-compartment and personalized treatment. Nowadays, the trend in TARE planning involves using the tumor-to-normal liver uptake ratio (T/N ratio) and multi-compartment dosimetry based on the partition model for precise and personalized treatment optimization. Utilizing 99mTc-MAA SPECT/CT, this method divides the target into tumors, healthy liver tissue, and lung compartments. It simulates absorbed doses to optimize activity, ensuring high tumor doses while minimizing exposure to non-target tissues, reducing complications like radiation-induced liver disease (REILD) and radiation pneumonitis, and enabling personalized, precise treatment. A high LSF can result in significant radiation exposure to the lungs, increasing the risk of radiation pneumonitis, which can be fatal. Patients with an LSF exceeding 20% are considered unsuitable candidates for TARE to avoid these severe complications.

Applications of TARE

Current role of TARE in BCLC staging system

TARE has gained increasing attention for the treatment of HCC, achieving an overall response rate of over 50% across various BCLC stages[1]. The mechanics of TARE and TACE are quite distinct. Unlike other embolization-based treatments, TARE does not significantly compromise blood flow. This characteristic reduces the risk of post-embolization syndrome and liver function deterioration, offering a more favorable safety profile for patients with advanced liver disease or portal vein thrombosis[6]. Current literature demonstrates comparable clinical outcomes with no significant differences in progression-free survival (PFS) (resin 6.1 mo and glass 5.0 mo)or overall survival (OS) (resin 7.7 mo and glass 7.0 mo) among patients with unresectable hepatocellular carcinoma (uHCC)[7].

The 2022 update of the Barcelona Clinic Liver Cancer (BCLC) treatment algorithm has expanded the role of TARE in managing HCC. This revision

highlights an expanded role for locoregional treatments, notably the inclusion of radioembolization as an option for patients with very early-stage (BCLC-0) and early-stage (BCLC-A) hepatocellular carcinoma (HCC). Patients with solitary tumors ≤8 cm who are ineligible for, or have experienced failure with, resection or ablation may now be considered for radioembolization or transarterial embolization (TAE)[8,9]. TARE is a safe alternative to TACE with a comparable complication profile and survival rates in systematic review and meta-analysis[10]. Contemporary randomized-control trials of PREMIERE[11] and TRACE[12] show improved time to tumor progression when utilizing glass Y90 over cTACE (>26 mo vs. 6.8 mo; p=0.0012) and DEB-TACE (17.1 mo vs. 9.5 mo; p=0.002) respectively. TARE is used in the intermediate stage (BCLC B) of HCC for two primary purposes: 1. As an alternative to TACE: TARE conferred superior tumor control and survival compared with chemoembolization using drug-eluting beads in selected participants with early or intermediate hepatocellular carcinoma in retrospective propensity-matched study[13] and randomized trial[12]. 2. As a downstaging tool: Downstaging has become a critical component of HCC management, allowing patients with more advanced tumors to achieve tumor shrinkage sufficient to meet the criteria for transplantation or surgery (Figure 1). TARE can induce contralateral hypertrophy with a maximal increase of FLR 21%-45% after 3-9 months[14,15].

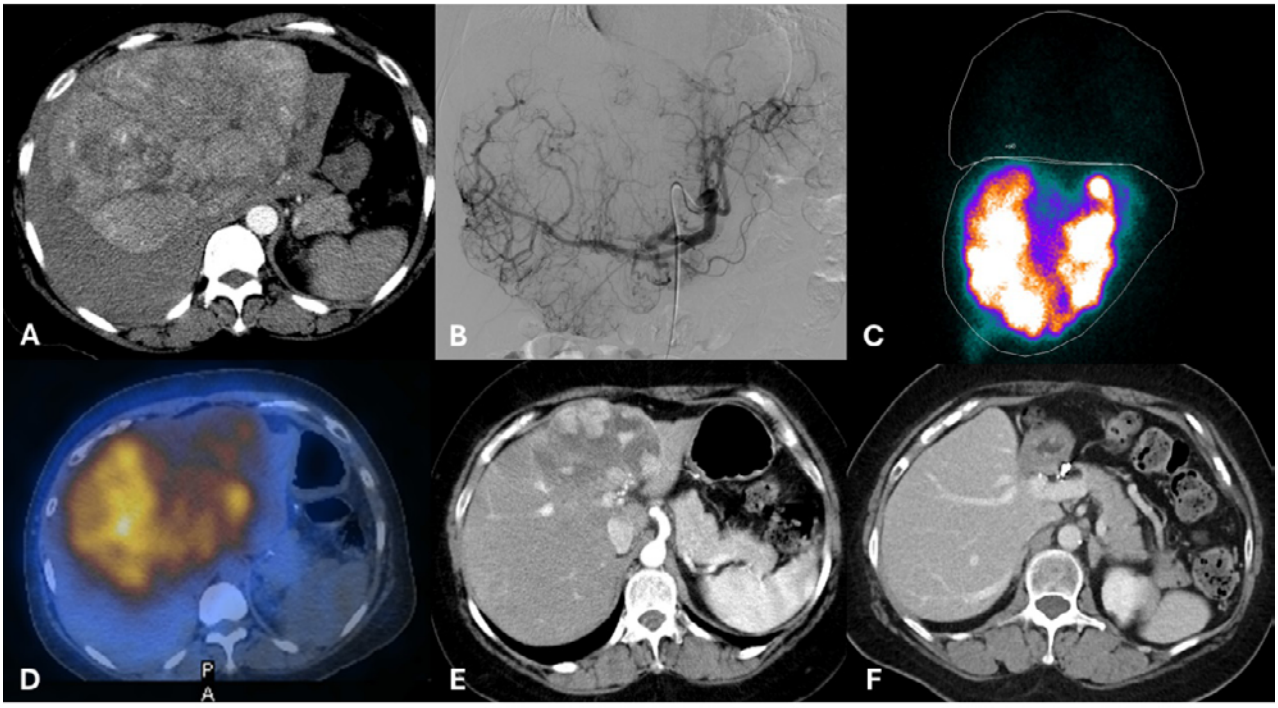

Figure 1. Yttrium-90 TARE for advanced HCC. (A) Axial contrast-enhanced CT of a 48-year-old female with chronic hepatitis B showing an 18cm HCC in the left hepatic lobe with suspected left portal vein invasion. (B) Arterial angiography demonstrates tumor staining with feeding arteries from both the left hepatic artery (LHA) and right hepatic artery (RHA). (C) Pre-treatment Tc-MAA SPECT/CT indicated a lung shunt fraction of 6.8%. (D) Post-Y90 TARE procedure: Resin microspheres delivering a total activity of 4.0 GBq were administered, with 3.3 GBq injected into the RHA and 0.7 GBq into the LHA. The prescribed tumor-absorbed dose was >100 Gy. (E) Six-month follow-up CT showing partial tumor response with residual enhancing viable tumor at the margin. The patient subsequently underwent a left lobectomy, with pathology confirming 70% tumor necrosis and microscopic vascular invasion. (F) After more than 12 years, follow-up CT showed no evidence of disease, demonstrating long-term survival and disease-free status.

The safety profile was confirmed by the P4S study with grade 3 peri/postoperative complications, and any grade of liver failure was experienced by 24 and 7% of patients, respectively[16]. The successful downstage rate ranged from 20%[17] to 34.4%[18] and 77% of tumors can show > 50% pathologic necrosis at surgical resection[15]. Prognostic factors significantly associated with successful downstaging include higher tumor-absorbed radiation doses and low serum AFP levels[17,18].

Personalized Dosimetry

Dosimetry plays a pivotal role in the success of TARE. Glass-based and resin-based TARE differ significantly in their radiobiological characteristics due to differences in microsphere properties. Increasing evidence indicates 90Y dose thresholds for tumor response and treatment-related toxicity. In the past, dosimetry for radioembolization relied heavily on ^{99m}Tc-MAA-based methods to estimate radiation distribution and dose. In the SARAH trial (mainly the BSA method of resin microsphere), a post hoc analysis of the delivered doses based on 99mTc-MAA SPECT/CT showed that OS and disease control were significantly better with a tumor-absorbed dose ≥ 100 Gy[19]. The probability of disease control at 6 months was 72% and 81% with a tumor-absorbed dose of 100 Gy and 120 Gy, respectively. For "ablative" therapy using resin microsphere, a mean absorbed dose to the non-tumoral liver exceeding 70 Gy is proposed for achieving a lobectomy-like effect. A higher mean absorbed dose, potentially exceeding 150 Gy, is recommended for segmentectomy to ensure effective tumor ablation within the targeted liver segment[20]. Regarding the glass microsphere, radiation segmentectomy (RS) was first described in 2011 by Riaz et al.[21], is an approach by which high-dose radiation can be delivered to two or fewer hepatic segments, eradicating the tumor and confining the radiation effect to the segment(s) infused. This threshold dose of 190 Gy was first confirmed using pathologic correlation from transplant explants based on a single-compartment dosimetry model[22]. Thereafter, the DOSISPHERE-01 trial demonstrated that "personalized dosimetry" with a ≥205 Gy tumor dose (TD) significantly improves tumor response and overall survival in patients with advanced HCC compared to standard dosimetry[23]. Moreover, The cutoff tumor dose recognized for a favorable response differed significantly between poorly differentiated HCC (assessed by [^{18}F] FDG PET) and well/moderately differentiated HCC (evaluated by [^{11}C] acetate PET) with thresholds of 262 Gy versus 152/174 Gy, respectively[24]. Recently, the 400 Gy threshold for tumor-absorbed dose established in the LEGACY trial has been shown to result in extensive and complete pathologic necrosis (CPN), associated with durable tumor responses and improved survival outcomes[9,25].

However, recent advancements have shifted toward voxel-based dosimetry, which provides a more precise, three-dimensional evaluation of radiation dose at the voxel level. This approach allows for individualized treatment planning by accurately quantifying dose distribution within the tumor and surrounding tissues, improving therapeutic outcomes and reducing toxicity. Regarding the resin-based TARE, a mean TD of 253 Gy predicted an objective response rate with 92% sensitivity and 83% specificity (AUC = 0.929, $p < 0.001$). A mean TD of 337 Gy predicted a complete response rate with 83% sensitivity and 89% specificity (AUC = 0.845, $p < 0.001$)[26]. Kokabi et al.[27] conducted a comparative study showing that resin-based TARE had a higher incidence of complete response (95% vs 56%, $p = .003$) than glass-based TARE. Patients with HCC treated with resin-based 90Y-TARE received a lower mean TD (308 Gy ± 210 vs 794 Gy ± 523, $p = .0002$) than those treated with glass-based TARE. This can be explained by different levels of particle loading and between resin and glass micro-

spheres (40,172 particles/mL ± 28,039 vs 17,081 particles/mL ± 12,555, p = .0001). This result suggests that higher tumor particle loads at lower mean doses over the entire treatment volume is another key factor.

Combination treatment

Management of advanced HCC with portal vein thrombosis (PVT) is complex and sometimes requires multiple therapeutic options. Sorafenib has been recognized as a standard treatment for advanced-stage HCC, extending survival by approximately 3 months[28]. TARE has emerged as a promising locoregional therapy for advanced HCC. Large-scale retrospective studies of TARE also showed acceptable safety profiles and good results in PVT patients[29-32]. The largest group of 291 PVT patients treated with glass-based Y90 microspheres, reported by Salem and colleagues, showed overall survival of 16.6mo among Child-Pugh A cirrhotics with branch PVT, decreasing to 4.5mo among Child-Pugh B cirrhotics with main PVT[32]. Encouragingly, a cohort study has ever reported a complete regression of PVT in 48.1% of the patients (13 out of 27) who had follow-up imaging available[33]. The efficacy of TARE is being actively explored in combination with other locoregional treatments , systemic therapies, and immunotherapies. Though there have been few studies combined with external beam radiation therapy for portal vein thrombosis, its safety has been demonstrated in clinical evaluations. Dose-volume histogram (DVH) analysis revealed that the fraction of normal liver exposed to more than 30 Gy (V30) when EBRT is performed before TARE[34], or more than 110 Gy (V110) when EBRT is performed after TARE[35], was the strongest predictor of hepatotoxicity.

Two Phase III trials, SARAH[36] and SIRveNIB[37], compared TARE to sorafenib in advanced HCC. Although they failed to show overall survival superiority, TARE achieved higher response rates, highlighting its potential for improved tumor control. In the SIRveNIB trial, among the treated population in the combination group receiving TARE plus sorafenib, the objective response rate (ORR) was 23.1%[37]. This highlights the potential synergistic effect of combining TARE with systemic therapy in improving tumor response.

Recent advances in the treatment have focused on immune checkpoint inhibitors (ICI) and their combination with targeted therapies, offering new hope for patients with advanced or unresectable disease. The IMbrave150 study evaluated patients with BCLC stage B or C disease, where atezolizumab plus bevacizumab (Atezo+Bev) demonstrated an ORR of 30%, showing superior overall and progression-free survival outcomes compared to sorafenib in patients with uHCC[38]. Host immune status and its alterations may be critical in HCC treatment, including TARE. CA Liu et al.[39] recognized high baseline IP-10 level (>200 pg/mL) in peripheral blood as a poor predictor of overall survival. TARE also promotes the recruitment/activation of intra-tumor effector-type immune cells compared to TACE or no preoperative treatment with a significantly higher ratio of CD3+ cells observed in the peri-tumoral area in patients receiving < 100 Gy, whereas a higher ratio of intra-tumoral CD4+ cells was observed in patients receiving > 100 Gy[40]. V Chew et al.[41] demonstrated TARE can activate local immune response through increased expression of CD8+ T cells, CD56+ NK cells, and CD8+ CD56+ NK cells in the tumor microenvironment. The upregulation of genes involved in innate and adaptive immune activation in TARE-treated tumors was also detected.

The above findings are consistent with a study of 1,664 patients with advanced hepatocellular carcinoma (HCC) from the National Cancer Database, where combined therapy significantly improved median overall survival (19.8 vs. 9.5 months) and reduced mortality risk by 50% (adjusted hazard

ratio: 0.50, $p < 0.001$)[42]. The safety of the combination therapy has also been studied, showing it to be well-tolerated with a low incidence of severe adverse events (AEs)[43]. These findings highlight the potential of combination therapy for advanced HCC and emphasize the need for further validation in large-scale clinical trials.

Future Perspectives

Artificial Intelligence and Deep Learning

Perspectively, Artificial Intelligence (AI)-driven algorithms hold the potential to enhance dosimetry by accurately predicting radiation dose distribution based on patient-specific anatomical and physiological parameters. This would optimize therapeutic efficacy while minimizing risks to healthy tissues. Moreover, deep learning models can analyze imaging modalities like SPECT/CT or MRI to detect subtle patterns, enhancing the precision of tumor targeting.

Wagstaf e tal.[44] used a deep learning model to predict the treatment response of radiation segmentectomy for a limited number of diseases. This algorithm has the potential to identify patients with treatment failure who may benefit from earlier follow-up or additional treatment. The biodistribution of 90Y microspheres is critical for optimizing treatment outcomes in radioembolization. A study compared SPECT and CT scans, along with the clinical target volume for each patient, which were used as inputs alongside their corresponding post-treatment PET scans. The actual and predicted absorbed doses for the tumor and the entire liver area were analyzed and compared, revealing an average absorbed dose difference of 5.42% ± 19.31% for the tumor and 0.44% ± 1.64% for the liver area[45].

Combining Immunotherapy with TARE

Several ongoing clinical trials focus on objective response rates and investigate the combination of TARE with immunotherapy in intermediate-stage HCC[46]. The STRATUM trial (NCT05377034) compares TARE followed by atezolizumab and bevacizumab to TARE with the placebo. The Phase II ROWAN study (NCT05063565) evaluates TARE followed by durvalumab and tremelimumab. The IMMUWIN trial (NCT04522544) compares TARE with durvalumab and tremelimumab versus TACE combined with the same immunotherapy agents. These studies aim to assess the efficacy and safety of combining TARE with immunotherapy to enhance outcomes in intermediate-stage HCC. The results are highly anticipated to inform future treatment strategies.

Conclusion

This article examines the principles of TARE, its clinical applications, and recent dosimetry and combination therapies advancements. By integrating AI and deep learning into clinical workflows, TARE can be further personalized, improving treatment precision and patient outcomes.

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肝癌釔90放射性栓塞之治療現況與新進展

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摘 要

釔 -90 放射性栓塞術（Yttrium-90 radioembolization），又稱經動脈放射性栓塞術（TARE），已成為肝細胞癌的一項關鍵局部區域治療方法。這種創新療法通過微球將高劑量輻射直接輸送至肝臟腫瘤，最大限度地減少對健康組織的損害。TARE 廣泛應用於中期 HCC 患者，作為經動脈化療栓塞術的替代方案，同時也用於伴隨門靜脈血栓的晚期肝癌患者。近年來，個性化劑量計算的進展，例如多區室模型與基於三維像素的模型，顯著提高了治療的精準性與安全性。此外，將 TARE 與系統性療法結合，包括免疫檢查點抑制劑和標靶藥物，顯示出潛在的協同治療效果。導管技術與影像技術的創新，以及人工智慧（AI）的潛力，正在進一步推動治療效果的改善。本文綜述了釔 -90 放射性栓塞術的現狀與最新進展，並強調其在 HCC 個性化治療中的日益重要角色。