Yttrium-90 Radioembolization of Hepatocellular Carcinoma—Performance, Technical Advances, and Future Concepts

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Abstract

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Hepatocellular carcinoma (HCC) is a lethal tumor, claiming over half a million lives per year. Treatment of HCC is commonly performed without curative intent, and palliative options dominate, including catheter-based therapies, namely, transarterial chemoembolization and yttrium-90 (⁹⁰Y) radioembolization. This review will showcase the performance of ⁹⁰Y radioembolization for the treatment of HCC, focusing on recent seminal data and technical advances. In particular, novel radioembolization treatment concepts are discussed and compared with conventional HCC therapy.

Objectives: Upon completion of this article, the reader will be able to discuss how radioembolization challenges established HCC treatment methods, thus offering a powerful alternative therapy for patients with often-limited therapeutic options.

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Hepatocellular carcinoma (HCC) is the most common primary liver tumor and the third most common cause of cancer mortality worldwide, claiming over half a million lives annually.¹ Surveillance programs can achieve an early

diagnosis of HCC; however, only about half of the population at risk receives appropriate screening, resulting in frequent disease presentation without curative options.² More specifically, only approximately 10% of patients receive therapy with curative intent³; thus, the majority of patients are treated with palliative intent. This treatment is often catheter based, namely, transarterial chemoembolization (TACE) and yttrium-90 (⁹⁰Y) radioembolization. TACE has demonstrated improved survival in randomized controlled trials and is the standard of care therapy for appropriately selected patients with unresectable HCC, according to the Barcelona Clinic Liver Cancer (BCLC) staging system.^{4–7} More recently, radioembolization has matured into a recognized treatment option for HCC, receiving regulatory approval and acknowledgment by the most recent National Comprehensive Cancer Network (NCCN) guideline.^{8,9} This overview will highlight recent seminal data, describe technical advances, and discuss combination and future therapy strategies for ⁹⁰Y hepatic radioembolization.

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Level of Evidence

HCC is a radiosensitive tumor.³ Radioembolization delivers high-dose internal radiation to the tumor via the hepatic artery. This technique differs from external beam radiation therapy, where radiosensitivity of normal hepatocytes limits the amount of radiation that can be delivered before the development of radiation-induced liver disease (RILD), especially in patients with cirrhotic livers.^{10–12}

Radioembolization is usually performed with small microspheres loaded with yttrium-90, a β -emitting isotope with short half-life (2.67 days).³ Given the hypervascularity of HCC, ⁹⁰Y microspheres injected into the hepatic artery are preferentially concentrated in the tumor-containing liver relative to the nontumorous organ.¹³ These microspheres emit high-energy, low-penetration radiation (~ 2.5 mm) to the tumor, while sparing much of the background liver parenchyma. There are two commercially available ⁹⁰Y devices: TheraSphere (BTG International, London, United Kingdom) and SIR-Spheres (Sirtex Medical, Sydney, Australia). TheraSphere is a glass microsphere, 20 to 30 μ m size with a high specific activity (2,500 Bq) per sphere. SIR-Spheres are a resin microsphere, 20 to 60 μ m size with a lower specific activity (50 Bq) per sphere.¹³ Despite these technical differences, clinical outcomes to date appear equivalent.³ In distinction to TACE, hepatic artery occlusion is not intended with radioembolization¹⁴; instead, microspheres lodge in the tumor microenvironment and emit lethal β -radiation over about a 2-week period.¹⁵ The lack of macroscopic vessel occlusion limits typical postembolization syndrome, and therapy can be administered as an outpatient.^{10,14}

Over the past decade, significant advancements in the science of radioembolization have occurred, together with technical standardization. Radioembolization is now a routine procedure yielding predictable results.³ Numerous well-controlled studies document the safety and tumoricidal effect of ⁹⁰Y microspheres. A 2010 study by Hilgard et al reported the outcome of 108 patients with advanced HCC treated with glass radioembolization.¹⁶ Time to progression (TTP) was 10 months with a median overall survival of 16.4 months, which compares favorably with sorafenib (TTP 5.5 months, survival 10.7 months, SHARP data¹⁷). No lung or visceral toxicity was observed, and the most common adverse event was transient fatigue (61% of patients). The authors concluded that glass radioembolization is a safe and effective treatment for patients with advanced HCC, including those with compromised liver function. A separate single-center prospective 5-year cohort study of 291 patients treated with glass radioembolization was also reported in 2010.¹⁸ The intricate interaction between tumor characteristics and the degree of hepatic dysfunction was highlighted. As expected, survival was negatively impacted by liver dysfunction in patients undergoing radioembolization; survival in Child-Pugh A patients was 17.2 months, but was only 7.7 months in patients with Child-Pugh B disease ($p = 0.002$). Moreover, TTP varied by Child-Pugh stage and the presence of portal vein thrombosis (PVT); Child-Pugh A and B without PVT demonstrated TTP of 15.5 and 13 months, respectively, as

compared with Child-Pugh A and B with PVT, 5.6 and 5.9 months, respectively. This study was the first to describe in granular detail the variant survival and TTP by staging systems.

Survival and prognostic factors were recently reported in a retrospective multicenter European registry of 325 patients with unresectable HCC treated with resin radioembolization.¹⁹ Median overall survival was 12.8 months, and survival was significantly influenced by BCLC stage (BCLC A: 24.4 months, BCLC B: 16.9 months, BCLC C: 10 months). This analysis provides robust evidence of survival achieved with radioembolization, including patients with advanced disease and limited treatment options. Notably, results in this resin radioembolization registry are very comparable to the above-reported outcomes with glass radioembolization, confirming that radiation is the dominant tumoricidal mechanism. Furthermore, the reproducible data achieved among the eight participating centers highlight the technical feasibility of the procedure.³

According to the BCLC guidelines, which are endorsed by both American and European liver societies, TACE is the standard of care therapy for patients with intermediate stage disease.^{20–22} Intermediate stage HCC (BCLC B) encompasses a heterogeneous patient population with variable tumor burden (multinodular) and liver function (Child-Pugh A and B). This results in a wide degree of expected survival (14–45 months) after TACE.²² As such, not all intermediate-stage HCC will derive a similar survival benefit from TACE, and some patients may benefit from other treatment options.²³ Patients with advanced HCC (BCLC C) are similarly heterogeneous when being treated with a single recommended agent, namely, sorafenib. A phase 2 study by Mazzaferro et al reported the efficacy and safety of radioembolization in patients with BCLC intermediate and advanced HCC.²⁴ Median TTP was 11 months, with a median overall survival of 15 months. The authors concluded that radioembolization is a competitive treatment option, with a manageable toxicity profile. This study further validates the reproducible outcomes of radioembolization in select patients, including those with vascular invasion.

There is no randomized trial of radioembolization versus TACE in the treatment of HCC. Instead, several comparative effectiveness trials evaluate radioembolization and TACE with regard to efficacy, downstaging, and quality of life (QoL).

A large comparative effectiveness study published in 2011 matched 122 TACE with 123 ⁹⁰Y radioembolization patients.²⁵ Radioembolization resulted in a significantly longer TTP (13.3 months) versus TACE (8.4 months, $p = 0.046$). However, overall survival of the two techniques was not statistically different (TACE: 17.4 months and radioembolization: 20.5 months, $p = 0.232$), likely due to competing risks of death from HCC and cirrhosis. Post hoc analysis concluded that a sample size of more than 1,000 patients would be needed to establish survival equivalence of radioembolization and TACE.

TACE is a recognized method for downstaging from United Network for Organ Sharing (UNOS) T3 to T2 disease.²⁶ When successful, patients are considered for transplant and granted

a model for end-stage liver disease (MELD) upgrade for HCC. The downstaging efficacy of TACE and radioembolization was retrospectively evaluated in an 86-patient cohort with T3 disease.²⁷ Downstaging to UNOS T2 was achieved in 31% of TACE and 58% of radioembolization patients ($p = 0.023$). The median time to overall progression was 12.8 months for TACE and 33.3 months for radioembolization ($p = 0.005$). As evidenced, radioembolization outperforms TACE for downstage UNOS T3 to T2 disease, thus expanding the pool of patients considered for curative transplantation.

Primary liver tumors are known to be associated with a diminished QoL, and disease presentation at an advanced stage means most patients are treated with palliative intent. With a reduced life expectancy, QoL becomes equally as important as overall survival.²⁸ In a prospective study, health-related QoL was compared in patients receiving TACE or ⁹⁰Y radioembolization. Despite the more advanced disease in patients treated with radioembolization, several QoL metrics were significantly better in these patients and overall QoL reached near significant improvement as compared with TACE ($p = 0.055$).

As evidenced in these aforementioned comparative effectiveness trials, radioembolization outperforms TACE in selected patients with regard to TTP, downstaging to transplant, and maintenance of QoL. Some investigators now consider ⁹⁰Y radioembolization a preferred therapy for advanced BCLC B and early BCLC C patients.³

Combination Therapy and Clinical Trials

Catheter-based tumor therapy involves some form of embolization, whether macroembolic in TACE or microembolic in ⁹⁰Y radioembolization. Embolization limits the washout of treatment dose, with subsequent devascularization of an often arterial hypervascular tumor.²⁹ This mechanism causes a hypoxic tumor microenvironment, resulting in upregulation of neo-angiogenic pathways, which threatens to unwind the benefit of embolotherapy. For instance, expression of vascular endothelial growth factor (VEGF) can lead to rebound neovascularization, tumor growth and progression, along with reduced survival.^{30,31} A recent investigation identified increases in several angiogenic cytokines after hepatic resin radioembolization.³² In this small cohort, cytokine changes including a transient increase in VEGF were associated with a worse overall survival rate.

Targeting these neoangiogenic mechanisms of tumor growth is a guiding principle of systemic tumor therapy, particularly for HCC, as it relies on the formation of new blood vessels for progression.^{30,33} Sorafenib is an oral multikinase inhibitor of multiple pathways of angiogenesis, including VEGF.¹⁷ The proven antiangiogenic efficacy of sorafenib, and the scientific rationale of combined transcatheter embolization and systemic antiangiogenic therapies, resulted in several investigative trials.³⁰

Few data are currently available for the combination of radioembolization and sorafenib, as many of these trials are at their early stages. A unique look at this combination is provided by a recent prospective radiological-pathological

analysis of patients treated with the combination of sorafenib and radioembolization as a bridge to transplant.³⁴ This two-arm study correlated the radiologic and pathologic tumor responses of 15 patients randomly assigned to treatment with or without sorafenib. The addition of sorafenib did not augment the radiological or pathological response to radioembolization therapy for HCC. This disappointing result of combination therapy might be explained by small tumor size/burden required for transplant listing. A separate phase II evaluation of radioembolization followed by sorafenib in patients with intermediate and advanced HCC was reported in 2014.³⁵ Adverse events were transient and often managed with sorafenib dose adjustment. Median survival for BCLC stage B was 20.3 months and 8.6 months for BCLC stage C, which is comparable to previously reported data on radioembolization or sorafenib monotherapy. The authors remarked that this study shows the potential efficacy and manageable toxicity of sequential radioembolization/sorafenib in a population of patients with predominantly advanced disease.

Ongoing studies should shed further light on the potential benefit of ⁹⁰Y radioembolization and sorafenib combination therapy. The phase III clinical trial of Intra-arterial TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (STOP-HCC) will examine the effectiveness of glass radioembolization when added to sorafenib. This randomized two-arm trial will compare treatment with glass radioembolization prior to sorafenib in one arm, while patients in the other arm will only receive sorafenib. The primary end point is overall survival. Rather than combination therapy, a randomized phase III trial is examining Sorafenib versus Radioembolization in Advanced Hepatocellular carcinoma (SARAH). This study will determine if radioembolization improves overall survival in advanced HCC compared with BCLC guideline recommended therapy with sorafenib. With these pending clinical trials, the hope of a proven safe and efficacious treatment option, for one of the most common causes of cancer death, maybe on the horizon.

Technical Advances

With gained clinical experience, the usage landscape of radioembolization is changing, including new concepts such as radiation segmentectomy, radiation lobectomy, boosted radioembolization, PET imaging of ⁹⁰Y microspheres, and single-session radioembolization. Although these concepts have not been tested in a diverse multicenter setting, they represent technological evolutions, which lay the foundation for future rigorous evaluation.

Radiation Segmentectomy

Resection and ablation are curative treatment options for HCC ≤ 3 cm in size, according to the BCLC staging system.⁷ Ablation is considered high risk when the lesion is located in close proximity to critical structures.³⁶ Combining microcatheter technology and the localized radiation emission properties of ⁹⁰Y microspheres, highly selective radioembolization (so-called radiation segmentectomy), is a novel

treatment alternative to ablation for high-risk tumor locations (—Fig. 1).

A recent report details the efficacy of radiation segmentectomy in solitary HCC not amenable to ablation or resection.³⁷ Patients in this study were treatment naive with solitary HCCs ≤ 5 cm in diameter. Radiation segmentectomy was defined as ⁹⁰Y microsphere infusion limited to ≤ 2 Couinaud segments. Dosing was achieved by infusing a calculated lobar dose (120–150 Gy) into a segmental tumor-feeding vessel. As such, segmental doses are higher than lobar doses by the ratio of lobar:segmental liver volumes. This methodology minimizes radiation to nontumorous liver parenchyma while delivering ablation-type tumor doses. Among 99 patients with imaging follow-up, complete response was achieved in 47%, partial response in 39%, and stable disease in 12% of patients, by modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Median time to disease progression in all patients was 33.1 months.

In this initial study, about one-third of patients were transplanted after radiation segmentectomy, allowing for radiology–pathology correlation. Pathology revealed 100% and 50 to 99% necrosis in 52 and 48% of tumors, respectively. All cases of partial necrosis (50–99%) exhibited more than 90% necrosis, and thus, radiation segmentectomy resulted in 90 to 100% pathological necrosis in all patients. More complete tumor necrosis was observed when the radiation dose to the segment exceeded 190 Gy ($p = 0.03$), suggesting this level as

a threshold dose for radiation segmentectomy. Median overall survival was 53.4 months, and all adverse events were mild and transient.

Radiation segmentectomy compares favorably with radiofrequency ablation (RFA) for HCC. Median survival for RFA in patients with a single tumor ≤ 5 cm and Child-Pugh A cirrhosis is 61 months, whereas it is 35 months in patients with Child-Pugh B cirrhosis.³⁸ These results are similar to a median survival of 53.4 months with radiation segmentectomy performed in an evenly mixed population of patients with Child-Pugh A and B.³⁷

Achieving complete pathological necrosis with RFA is dependent on lesion size and location. In one study, complete pathologic necrosis was achieved in 65.7% of lesions treated with RFA with a mean lesion size of 2.5 cm.³⁹ These data provide a framework for evaluating a 52% complete pathological necrosis rate for radiation segmentectomy in lesions up to 5 cm in size.³⁷ Radiation segmentectomy not only treats lesions in high-risk locations for ablation, it also avoids the need for transhepatic tumor puncture and the small potential risk of tumor tract seeding. Radiation segmentectomy, like ablation, seeks to eradicate the tumor, along with a margin about the tumor. As such, a sector of the liver is perfused with high-dose ⁹⁰Y microsphere, resulting in a treatment margin analogous to the surgical margin. This concept is supported by the 90 to 100% necrosis observed in all lesions at explant.³⁷

In a similar study, when tumor ⁹⁰Y perfusion is isolated to a single Couinaud segment, segmental radioembolization

Fig. 1 (a) Arterial phase MRI shows a hypervascular lesion in segment 7 consistent with HCC (arrow). The tumor is subcapsular and subdiaphragmatic making percutaneous ablation challenging; lesion was treated with radiation segmentectomy; segmental dose > 190 Gy. (b) Arterial phase MRI 1 month posttreatment shows a lesion complete response by mRECIST. (c) Four months after radioembolization, there is a continued decrease in size of the lesion and segment 7 with posttreatment geographic enhancement.

yields a complete response in 95% of patients by European Association for the Study of the Liver (EASL) criteria.⁴⁰ Retrospective dose calculations in this study indicated a median dose to the segment of 254 Gy, and a median tumor dose of 536 Gy. No grades 3 to 4 hepatic toxicities were identified in the treatment population, even though 60% of patients had PVT and 20% had a transjugular intrahepatic portosystemic shunt. These data showcase the high local control rate and safety of segmental ⁹⁰Y radioembolization in patients with advanced disease. Taken together, these impressive results should serve as the basis for randomized controlled trials comparing radiation segmentectomy to modern ablation techniques.

Radiation Lobectomy

In contrast to radiation segmentectomy, where lobar radiation doses are delivered in a sublobar fashion, radiation lobectomy describes changes after lobar delivery of therapy. Previous investigations demonstrate ipsilateral atrophy and contralateral hypertrophy after lobar radioembolization, termed *the atrophy–hypertrophy complex* (►Fig. 2).⁴¹ Radiation lobectomy is described in patients with right lobe disease potentially amenable to curative resection, but excluded because of a small future liver remnant (FLR), often expressed as a percent ratio of the whole liver volume. Traditionally, these patients are treated with portal vein embolization

(PVE), resulting in redirection of portal flow with subsequent FLR hypertrophy and surgical resection. The required FLR varies based on underlying liver pathology from approximately 20% (normal) to 40% (cirrhosis).^{42,43} Since many intrahepatic tumors are primarily supplied by the hepatic artery, PVE does not provide local tumor control. Instead pro-angiogenic factors after PVE may lead to tumor progression, including increased chances of contralateral hepatic metastasis.^{44–48} Potential advantages of radiation lobectomy include a single procedure providing local tumor control, with initiation of the atrophy–hypertrophy complex serving as a bridge to resection. Previous investigations reveal a slower rate of portal flow diversion with radiation lobectomy compared with PVE, which may limit pro-angiogenic tumor progression.⁴¹ A biologic test of time, inherent to this slow portal flow diversion, can identify patients best suited for resection.^{3,41}

Vouche et al reported a comprehensive time-dependent analysis of liver volumes following lobar radioembolization.⁴⁹ Eighty-three patients met the inclusion criteria, including isolated right lobe tumor not amenable to immediate resection. Patients were treated with radiation lobectomy, utilizing glass ⁹⁰Y microspheres for right lobe HCC, colorectal cancer (CRC), and cholangiocarcinoma (CC). Changes in liver volumes were assessed with serial follow-up imaging. Liver volumes were calculated assuming a potential extended right

Fig. 2 (a) Arterial phase MRI shows a hypervascular lesion in the anterior right lobe (arrow) with (b) delayed phase washout and capsular enhancement in a patient with underlying cirrhosis, compatible with HCC. Patient was treated with right lobe radioembolization utilizing conventional dosimetry. (c) Arterial phase MRI 4 months posttreatment demonstrates right lobe atrophy with geographic enhancement (arrow) and left lobe hypertrophy (atrophy–hypertrophy complex). Anterior right lobe lesion has decreased in size with residual enhancement; hypovascular lesion in the left lobe is a cyst. Patient underwent right hepatectomy with curative intent.

trisegmentectomy, and the FLR was expressed as a percent ratio (segments 2 + 3 volume/total parenchymal volume). A significant decrease in right lobe volume, together with hypertrophy of the left lobe, was seen 1 month after treatment, resulting in a 7% overall increase in the FLR volume ($p < 0.001$). After more than 9 months, the median percent FLR hypertrophy reach 45% ($p < 0.001$). Similarly, Theysohn et al reported time-dependent changes of cirrhotic liver volumes after lobar radioembolization for HCC.⁵⁰ Six months after right lobe treatment, the left lobe volume increased by 30.8% ($p < 0.01$), confirming compensatory hypertrophy even with underlying cirrhosis. In a recent description of PVE utilizing a foam sclerosant for both primary and secondary liver malignancies, the mean percent increase in FLR was 48.8%, measured approximately 1 month after the procedure.⁵¹ Comparatively, these results highlight the faster kinetics of FLR hypertrophy with PVE.

In the Vouche et al study, a significant reduction in median tumor volume and AFP (in patients with HCC) was noted at 3 and 9 months after radiation lobectomy, thus confirming the antitumoral activity of ⁹⁰Y microspheres.⁴⁹ After radiation lobectomy, left lobe tumors developed in 19% of HCC patients, and 25% of CRC and CC patients; this is comparable to literature reports of a 15% recurrence of HCC 1 year after RFA, and a 25% occurrence of CRC metastases in the FLR 3 weeks after PVE.^{52,53}

Radiation lobectomy aids in the identification of patients best suited for surgical resection, by treating the known tumor while simultaneously assessing the regenerative capacity of the liver, as well as introducing a test of time given the slow kinetics of hypertrophy. Future studies comparing long-term outcomes of PVE and radiation lobectomy are warranted.

Boosted Radioembolization

Another novel concept is boosted radioembolization for HCC, where priority is given to tumor dosimetry rather than liver dosimetry. Prior investigations have shown a close correlation with glass microspheres between tumor-absorbed dose and response.^{24,54} Garin et al describe a predicative dosimetry model, based on technetium-99m microaggregated albumin (MAA) single-photon emission computed tomography/computed tomography (SPECT/CT) for treatment intensification, utilizing a previously identified tumor response threshold dose of 205 Gy.^{54,55} Seventy-one patients were retrospectively evaluated, and most patients had BCLC intermediate or advanced stage disease with PVT but without extrahepatic spread. Volumetric analysis was preformed after MAA SPECT/CT to quantify tumor and nontumor liver uptake of radiotracer. In the first 20 patients, conventional glass microsphere dosimetry was utilized with a target liver volume dose of 120 Gy. After the 20th patient, a tumor threshold dose of 205 Gy was ensured by treatment intensification (increasing the injected microsphere activity), while maintaining the nontumor liver dose below 120 Gy. The EASL response rate was 55% in the first 20 patients treated without potential intensification, and 86% in the following 51 patients with intensification intent ($p = 0.001$). Based on MAA SPECT/

CT, median tumor dose was 342 Gy for responding lesions and 191 Gy for nonresponding lesions ($p < 0.001$). Seventeen patients underwent treatment intensification (boosted therapy), representing 33% of the mentioned 51 patient cohort, without increased grade 3 liver toxicity. The median TTP and OS were 5.5 and 11.5 months, respectively, in patients with a tumor dose less than 205 Gy, and 13 and 23.2 months, respectively, in those with a tumor dose more than 205 Gy ($p = 0.0038$ and not significant, respectively).

MAA uptake in PVT was observed in 25 of 26 responding patients, and in only one of six nonresponding patients. Among patients with PVT, the median TTP and overall survival were 4.5 and 5 months, respectively, in patients with a tumor dose less than 205 Gy, and 10 and 21.5 months, respectively, in those with a tumor dose more than 205 Gy ($p = 0.039$ and 0.005).

This study confirms the accuracy of MAA SPECT/CT tumor dosimetry in predicting response, and details the performance of a 205-Gy tumor threshold dose. Interestingly, a prior study found no correlation between liver metastatic lesion vascularity and survival.⁵⁶ Thus, patients with hypervascular tumors, which presumably concentrate ⁹⁰Y microspheres, did not demonstrate a significant survival advantage over patients with hypovascular tumors. Hence, lesion vascularity may not accurately reflect tumor perfusion and deposition of microsphere; perhaps MAA SPECT/CT is a better measure of these characteristics.

The concept of boosted radioembolization represents continued personalization of HCC radioembolization therapy. MAA SPECT/CT is able to identify tumors that require boosted microsphere dosing to achieve an improved response and survival rate, compared with conventional dosimetry. This technique also helps predict those patients not well suited for radioembolization, therefore excluding them from dangerous or ineffective therapies.⁵⁵ Tumor dosimetry from MAA SPECT/CT enables treatment intensification, resulting in improved outcomes without increased toxicity, especially in patients with PVT (→ Fig. 3). Randomized studies are needed to confirm these retrospective findings and better define the role of treatment intensification.

Positron Emission Tomography Imaging of ⁹⁰Y Microspheres

There are several conventional methods for calculating ⁹⁰Y microsphere doses, and these depend on the type of radioembolization product, namely, resin or glass microspheres. Dosimetry shortcomings exist for both products. Glass microsphere dosimetry utilizes an equation, which requires input of a liver mass and desired dose. This method assumes a uniform distribution of arterially delivered microspheres between the tumor and nontumor compartments, and the known heterogeneous distribution of ⁹⁰Y microspheres is ignored in treatment planning calculations. Consequently, it is likely that the tumor dose is underestimated and the nontumor dose is overestimated.⁵⁷ A detailed understanding of hepatic radiation dose distribution is critical to improving dosing strategies. One such strategy, described earlier, relies on MAA mimicking ⁹⁰Y microsphere distribution.⁵⁵

Fig. 3 (a) Portal venous phase MRI demonstrating a large right lobe infiltrative HCC with right portal vein tumor thrombus. Patient was treated with boosted radioembolization to the right lobe resulting in a tumor dose > 205 Gy. (b) Portal venous phase MRI, 2 years after therapy, shows marked decrease in tumor burden with retraction of portal vein tumor thrombus. Noted is significant right lobe atrophy with left lobe hypertrophy. Patient underwent right trisegmentectomy with portal vein resection/reconstruction. Pathologic assessment of the resection specimen showed no viable tumor.

Recognition of ^{90}Y pair production decay events allows for direct PET imaging of delivered ^{90}Y microspheres, with subsequent formulation of quantitative dose biodistribution maps (**Fig. 4**).^{58–60} This concept of quantitative PET imaging was reported in a cohort of HCC patients treated with glass radioembolization to measure the degree of preferential microsphere uptake by the tumor.⁵⁷

^{90}Y PET/CT and voxel-based S-value methodology were used to create three-dimensional radiation dose maps. Liver parenchyma and liver tumors were contoured on cross-sectional imaging and aligned with these dose maps. A total of 113 tumors were examined; the average intended dose to the target volume was 105 Gy, with an average tumor dose of 173 Gy and an average nontumor parenchymal dose of 93.4 Gy. Consequently, the average tumor-to-parenchymal weighted dose ratio was 2.2.

An optimal tumor radiation dose is largely unknown, yet data from MAA SPECT/CT modeling suggest a response threshold dose of 205 Gy for HCC.⁵⁴ In the present study, there was wide variation in the absorbed tumor dose, with only a weak positive correlation between the intended target volume dose and the absorbed dose in the tumor. Therefore, higher administered activity did not always result in higher

tumor doses. This emphasizes the complexity of hepatic dosimetry with factors such as intrahepatic hemodynamics, arterial branching pattern, and degree of tumor vascularity and size, as potentially influencing dose biodistribution.⁵⁷ Accurate characterization of ^{90}Y dose deposition is important in improving dosing strategies. Dose distribution maps, combined with response assessment, will shed light on optimal tumor dosimetry and guide the development of predictive dosing models.

Single-Session Radioembolization

Hepatic radioembolization typically involves a two-step process spanning approximately 2 weeks, specifically planning dosimetry with MAA followed by ^{90}Y microsphere administration. Gates et al demonstrated the feasibility of single-session radioembolization on outpatients.⁶¹ In this series, due to travel limitations or rapidly progressive disease, 14 patients were treated with single-session radioembolization. All patients underwent dedicated liver cross-sectional imaging with three-dimensional analysis, allowing for the determination of treatment volume and number of vessels supplying the area of interest. Dose vials were ordered assuming a 10% lung shunt fraction (LSF) for HCC and 5% LSF for metastatic

Fig. 4 (a) Arterial phase CT shows an infiltrative lesion in the right lobe (arrow), which was biopsied given atypical imaging features, and compatible with HCC. This tumor was treated with right lobe radioembolization. (b) ^{90}Y PET/CT fused image on the day of treatment demonstrates ^{90}Y dose biodistribution with preferential microspheres deposition at the lesion periphery.

disease. Given an inherent margin of error associated with this technique, one or two extra dose vials were routinely ordered, at no additional patient cost. A recent report by Gaba et al identified a median LSF of 9% in HCC, and described the imaging tumor characteristics associated with a spectrum of LSFs.⁶² High LSF (> 20%) in HCC was significantly associated with infiltrative tumor morphology, greater than 50% tumor burden, and main portal vein invasion. Avoidance of patients with these tumor characteristics, and hence a likely high LSF, for single-session radioembolizations seems prudent.

On the day of treatment, patients in this study underwent cone-beam CT imaging to determine tumor coverage and assess hepato-enteric communications. A reduced dose of MAA was administered in the hepatic artery supplying the tumor, and only planar scintigraphy was performed for lung shunt determination. All patients were successfully treated in a single session with an average time of 2.7 hours from groin puncture to closure.

Single-session radioembolization is a technical advancement, yielding decreased time between patient evaluation and treatment. This technique relies on detailed angiography and cone-beam CT assessment to identify treatment volumes and hepato-enteric arterial communications, rather than utilizing MAA SPECT/CT for these purposes.⁶¹ In comparing cone-beam CT with nuclear medicine scintigraphy, Louie et al showed that cone-beam CT outperformed scintigraphy for identification of extrahepatic enhancement.⁶³ Correspondingly, detection of the often-minuscule caliber falciform artery was improved with cone-beam CT, over digital subtraction angiography and MAA SPECT/CT.⁶⁴

A reduced dose of MAA was utilized in this protocol because expeditious treatment timing might not allow for the erosion and fragmentation of MAA particles from the tumor microenvironment. The authors speculate that the MAA load is of little consequence as the ⁹⁰Y load contains far more particles. Moreover, the observed response rates in single-session radioembolization parallels outcomes of standard protocol radioembolization. This novel proof of concept report demonstrates the feasibility and safety of single-session radioembolization, which may yield an overall cost savings.⁶¹ The same-day timing of MAA and ⁹⁰Y microsphere delivery emulates a TACE treatment schedule, which is commonly recognized as an advantage of TACE over conventional radioembolization.

Summary

Radioembolization is an evolving technique used in the treatment of HCC, offering new promise to patients with often limited treatment options. It challenges and can sometimes outperform TACE, the BCLC-recommended treatment for intermediate stage HCC, with respect to TTP and QoL.^{25,28} Furthermore, the versatility of radioembolization translates into a potential role in many BCLC disease stages.⁶⁵ In early-stage disease, radiation segmentectomy competes with ablation, achieving comparable rates of complete pathologic necrosis in lesions not amenable to ablation, and without transcapsular tumor

puncture.³⁷ Radiation lobectomy increases the number of patients amenable to curative resection, while the pool of patients eligible for transplantation is increased by more effective tumor downstaging with radioembolization compared with TACE.^{27,49} In advanced stage disease, the dramatic effect on PVT provides a strong rationale for combination with and comparison to treatment with sorafenib.^{3,24} Personalized tumor therapy is now possible with boosted radioembolization and single-session treatment, and continued personalization of tumor therapy will be guided by quantitative ⁹⁰Y PET/CT.^{55,57,61} Pending clinical trials will hopefully replace HCC therapy, guided by opinion and local expertise, with treatment guided by robust data.

Disclosure Statement

C. M. has nothing to disclose. R. L. has served as an advisor for BTG International.

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