Radioembolization for the Treatment of Hepatocellular Carcinoma: The Road to Personalized Dosimetry and Ablative Practice

Cynthia De la Garza-Ramos, MD[1]   Beau B. Toskich, MD[1]

[1] Division of Interventional Radiology, Mayo Clinic Florida, Jacksonville, Florida

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Address for correspondence Beau B. Toskich, MD, Division of Interventional Radiology, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224 (e-mail: Toskich.Beau@mayo.edu).

Abstract

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Radioembolization dosimetry for the treatment of hepatocellular carcinoma has evolved alongside our understanding of best practice for this therapy. At the core of advances in dosimetry are personalized and ablative applications of radioembolization, which have generated paradigm shifts in both safety and efficacy. This review provides a summary of fundamental radioembolization dosimetry concepts and narrates how our approach to treating patients has shifted from conventional to tailored and definitive therapy.

As transarterial radioembolization for the treatment of hepatocellular carcinoma (HCC) continues to advance, radiation dosimetry has emerged as a pivotal element associated with both improved safety and efficacy. At the center of this progress is the jettison of empiric therapy and integration of patient-centered, personalized, radioembolization dosimetry. An improved understanding of parallel factors related to radioembolization dose including radioactive microsphere physics, patient selection, mapping angiography and simulation, device properties, dosimetric methodology, and radiopathologic outcomes has further driven the incorporation of radioembolization into the current standard of care. Alongside these advancements, radioembolization intent has evolved from its sole salvage capacity in former years to its current role as an effective neoadjuvant to surgery and first-line definitive treatment for select patients with HCC. This report will provide a review on radioembolization dosimetry concepts and narrates how our dose optimization shifted from the rigid and empiric therapies of early experience to our current practice of personalized and ablative therapy for the treatment of HCC.

Basic Radioembolization Physics

Unlike external beam photon or charged particle radiotherapy, which generates a homogeneous energy distribution within target tissues from an external source, radioembolization relies on transarterial microsphere brachytherapy deposited within the tumor to exert its therapeutic effect. The most utilized radioembolization isotope is yttrium-90 (Y90), which is a nearly pure β-particle emitter that decays to zirconium-90 with a half-life of 64.1 hours. The β-particle emission energy spectrum is varied with a mean tissue penetration depth of 2.5 mm (highest probability particle) with more than 90% of particles penetrating 5.3 mm and a maximum of 11 mm (lowest probability particle).[1] As transarterially infused Y90 microspheres accumulate preferentially within intrinsically hypervascular tumors via disordered neovascularity, their therapeutic energy distribution will be equally heterogeneous.[2] This property generates a dissimilar radiation dose microenvironment to external beam radiotherapy in its extremes of radioactivity intermixed with more radiation barren regions. Despite this

difference, the increased conformality of radioembolization over external beam radiotherapy allows for higher dose prescription without significant normal tissue complications, which can mitigate the liabilities of dose nonuniformity.

Devices: Glass and Resin Microspheres

The two most commonly utilized Y90 microspheres for the treatment of HCC are fabricated from resin (SIR-Spheres; SIRTeX Medical, Woburn, MA) and glass (TheraSphere; Boston Scientific, Marlborough, MA). Resin microspheres contain surface-bound Y90, with a specific activity of approximately 60 Bq per sphere at calibration, and are Food and Drug Administration (FDA) approved for the treatment of metastatic colorectal carcinoma to the liver. Glass microspheres contain internally fixed Y90 which allows for a greater specific activit of approximately 2,500 Bq/sphere at calibration and are FDA approved for the treatment of unresectable HCC.

Both resin and glass microspheres can be ordered in a variety of particle numbers and specific activities.[3] For a given prescribed activity, resin microspheres can be utilized several days before calibration, which increases specific activity and reduces particle number, while glass microspheres can be utilized on the second week after calibration to similarly reduce specific activity and increase particle number. These dynamics appear to affect radiation dose biology, as both products differ in their reported toxicity dose thresholds. Walrand et al reported that mean fixed liver volume toxic doses (TD50) for glass microspheres are theoretically higher than for resin microspheres, while the TD50 for glass microspheres 8 days after calibration lies in-between the former two.[4] Similarly, animal models have supported that increased microsphere numbers with reduced specific activity are more toxic for a given fixed dose.[5] It has been suggested that resin microspheres administered to the whole liver at the day of calibration—which provide a more uniform dose distribution given higher particle counts per cubic centimeter of liver treated—may generate toxicity above 40 Gy, while a normal tissue threshold of 70 Gy for first week calibration glass microspheres has been similarly reported.[6] Ultimately, hepatic toxicity dose thresholds are challenging to define due to variances in liver function, lack of compartmental dose reporting in the literature, and the percentage of overall liver exposed to radiation during treatment, which is even further complicated by the delayed manifestations of radioembolization adverse events. While less is known regarding the impact of specific activity on treatment efficacy among both devices, there is retropective evidence that their tumor dose (TD) thresholds may differ.[7]

Patient Selection

Patient selection plays a critical role in radioembolization decision-making. Factors taken into consideration include tumor stage and distribution, performance status, hepatic substrate, liver volumetrics, and treatment intent. For example, neoadjuvant radioembolization for initially unresectable patients will be prescribed both radiation dose to the tumor and the hepatic future resection site in an effort to control tumor growth while inducing future liver remnant hypertrophy. Patients with solitary HCC and preserved liver function who are not candidates for resection will commonly receive ablative-intent dosimetry if the tumor is confined to expendable liver. Patients with intermediate-stage disease and tumor multifocality will require an estimation of normal liver radiation exposure to avoid treatment toxicity, while ensuring a minimally effective TD. In the case of compromised liver function, patients may be treated as part of a bridging effort when listed for liver transplantation. All these are illustrations of how radioembolization dose can be tailored to the patient's specific care plan.

Treatment Simulation and Dose Confirmation

Mapping angiography using both cone-beam CT and trans-arterial infusion of 99m-technetium-macroaggregated albumin (99mTc-MAA) as a Y90 microsphere surrogate is the standard-of-care simulation for radioembolization.[8] While the use of 99mTc-MAA as a microsphere surrogate has been controversial given that its deposition is susceptible to catheter position, vasospasm, tumor size and vascularity, and differences in particle shape, there is evidence to support its performance in normal liver dose prediction and in larger tumors.[9–13]

Following radioembolization, particle distribution can be determined by either bremsstrahlung SPECT/CT or higher resolution Y90 PET/CT with which dose volume histograms can be generated to both normal tissue and tumor.[14,15]

Dosimetry Concepts

Basic radiation oncology principles dictate that tumor control probability (TCP) and normal tissue complication probability (NTCP) increase with radiation dose as a sigmoidal function on a dose–response graph. TCP generally occurs at a lower dose than NTCP due to increased susceptibilities to radiation and decreased repair capability within tumor when compared with non-tumoral tissue. The therapeutic index is defined as the distance between the TCP and NTCP sigmoidal curves; the wider apart these are from each other, the higher the probability of tumor response without toxicity. Given the parallel architecture of the liver, and that radioembolization energy originates from within a predetermined volume of perfused tissue (also known as an angiosome), high-dose escalation can be performed with little or no hepatotoxicity when treatments are confined to expendable volumes of liver.[16,17]

Activity administration models are commonly used to prescribe treatment doses and are subject to imputable errors in assumption. The body surface area method assumes both liver treatment volumes and activity distribution; hence, its use is decreasing for the treatment of HCC. The Medical Internal Radiation Dose (MIRD) schema is based on a

single compartment that assumes uniform distribution within the treatment angiosome. The multicompartment or partition model assumes uniform distribution between three main sectors: tumor, normal liver, and lung. Voxel-based dosimetry more closely approximates the heterogeneity of absorbed dose within these compartments, but assumes uniform activity limited to the resolution of its imaging grid. Additionally, the latter two models both rely on particle surrogates that introduce even more assumptions, all of which contribute to the challenges of studying radioembolization dose.

Within the tumor itself, microspheres distribute heterogeneously causing a radiation watershed that has been previously demonstrated with Y90 PET/CT and microscopic absorbed-dose analyses.[18] As such, to increase the TCP while mitigating non-uniform microsphere deposition, either particle number or activity can be increased, which in turn are limited by the capacitance of tumor bed vascular conduit and therapeutic β-particle range, respectively.[19]

The History and Evolution of Dosimetry

For many decades, radiotherapy of liver malignancy was avoided as radiation hepatitis was reported in almost half of patients treated with external beam radiotherapy using nonconformal doses greater than 35 Gy, which was insufficient to control tumor in many cases.[20] This limitation led to the investigation of transarterial brachytherapy, which allowed single-compartment doses above 50 Gy without significant adverse events.[21] The first pilot trials with resin and glass microspheres for the treatment of intrahepatic metastasis and HCC determined that higher tumor vascularity and absorbed dose were associated with improved outcomes.[22,23] A phase I dose escalation study using glass microspheres for the treatment of HCC subsequently demonstrated the safety of liver doses ranging from 50 to 150 Gy.[24]

The first dose–response correlation for HCC was established at doses greater than 120 Gy (overall survival: 55.9 vs. 26.2 weeks) using glass microspheres in a phase I and II study by Lau et al by measuring the delivered radiation dose and tumor-to-normal tissue ratio with a calibrated β probe at laparotomy.[25] Ho et al subsequently demonstrated that laparotomy could be avoided by using the partition model to predict both treatment response and complication rates.[26] These studies initially proposed that radiation hepatitis could be prevented with a maximal nontumoral tissue dose of 70 Gy in patients with cirrhosis, and radiation pneumonitis with a lung dose of less than 30 Gy or less than 50 Gy for single or cumulative treatments, respectively.[25,26]

Radioembolization advancements remained relatively stable until the advent of ablative radioembolization and the introduction of boosted tumor dosimetry. A retrospective, voxel dosimetry analysis performed on 65 tumors from patients with intermediate and advanced HCC in the phase II trial by Mazzaferro et al reported a median TD of 490 Gy in

patients with objective response compared with 275 Gy in nonresponders.[27]

However, much of the initial enthusiasm for radioembolization was tempered by lessons learned from the negative SARAH trial. This phase III randomized controlled trial compared resin microsphere radioembolization using body surface area dosimetry versus sorafenib for advanced, unresectable HCC and found no differences in survival between groups.[28]

Personalized Dosimetry

The concept of personalized dosimetry, defined as a form of partition dosimetry based on 99mTc-MAA uptake in which the predicted TD is boosted above a predetermined threshold, was introduced by Garin et al. In their initial dose–response analysis, a TD greater than 205 Gy based on 99mTc-MAA SPECT/CT was predictive of improved tumor response, progression-free survival, and overall survival when compared with patients who received a TD of less than 205 Gy. Furthermore, TD was the only parameter that correlated with response within their initial investigations.[29]

Personalized dosimetry was subsequently coined in 2015 and found to be effective in additional studies performed on patients with unresectable HCC resulting in a superior median time to progression compared with non-boosted cohorts (11.5 vs. 5.5 months),[30] and in patients with tumor portal vein thrombosis (PVT) demonstrating a median overall survival of 18.2 versus 4.3 months without increasing hepatotoxicity.[31] These outcomes suggested an advantage to personalized dosimetry over those reported for standard dosimetry or sorafenib, and supported the use of 99mTc-MAA in patients with large tumors and PVT.[31,32]

The DOSISPHERE-01 trial was designed to prospectively compare the effect of personalized versus standard dosimetry in a randomized controlled phase II study.[13] Patients with locally advanced, unresectable HC greater than 7 cm were allocated to receive either standard dosimetry, defined as a single-compartment lobar dose 120 ± 20 Gy MIRD, or personalized dosimetry with a TD ≥ 205 Gy using glass microspheres. At least 30% of the liver was to remain free of radiation exposure and all patients had preserved liver function. The trial met its primary endpoint in which the personalized dosimetry group achieved a significantly higher objective response rate in the targeted lesion (71 vs. 36%). It also demonstrated a median overall survival of 26.6 months in the personalized dosimetry group when compared with 10.7 months in the standard dosimetry group, all without a significant difference in toxicity.[13]

Given this promising result, the concept of personalized dosimetry was retrospectively applied to a post hoc analysis of the radioembolization arm of the SARAH trial. Hermann et al described a dose–response and simulation reproducibility relationship as predicted by 99mTc-MAA SPECT/CT, with a significantly longer overall survival in patients who received a TD ≥ 100 Gy with optimal 99mTc-MAA agreement when compared with less than 100 Gy and poor agreement (24.9 vs. 6.7 months).[33] The authors concluded that

increased tumor radiation dose was associated with higher rates of disease control and overall survival, which raises the specter as to whether the SARAH trial would have been positive if designed similarly with DOSISPHERE-01. While a target TD of 120 Gy has been previously established by Lau et al, future studies will be necessary to identify device-specific recommendations for best practice.[34]

In the event of suboptimal tumor arterial supply which would expose large volumes of liver to radioembolization, personalization can be further provided by temporarily attenuating non–tumor-bearing portions of the treatment angiosome. This technique can be accomplished with a variety of devices including gelatin slurry, retractable coils, microvascular plugs, resorbable microspheres, and balloon microcatheters, enabling a more conformal radiation exposure.[35,36]

Ablative Radioembolization

The concept of ablative radioembolization is loosely defined as the prescription of radiation dose in which the entire angiosome is rendered devitalized. This approach behaves more like a delayed anatomic resection rather than palliative-intent radiation, with the ability to administer routine doses in excess of 500 Gy MIRD without major adverse events. The most commonly applied form of ablative radioembolization, commonly referred to as radiation segmentectomy, was first introduced by Riaz et al, where the authors described the selective delivery of ablative dose radioembolization to ≤2 Couinaud liver segments using glass microspheres.[17] The first ablative dose threshold was subsequently established by a multicenter radiopathologic study on unresectable solitary HCC by Vouche et al in which complete pathological necrosis (CPN) correlated with a single-compartment dose greater than 190 Gy MIRD (67 vs. 25%).[37]

In a large retrospective study by Lewandowski et al, long-term outcomes of Barcelona Clinic Liver Cancer (BCLC) stage 0-A patients treated with radiation segmentectomy of greater than 190 Gy MIRD showed comparable results to other curative-intent therapies, with a median time to progression of 2.4 years (95% confidence interval [CI]: 2.1–5.7) and a median overall survival of 6.7 years (95% CI: 3.1–6.7).[38] A more recent explant tissue analysis by Gabr et al described a 100% CPN rate in patients who were treated with ≥400 Gy MIRD.[39] In a validation study, Toskich et al analyzed patients who received radiation segmetectomy as a neoadjuvant to liver transplant using glass microspheres and confirmed that a greater than 500 G was associated with increased rates of CPN, and further identified that a microsphere specific activity ≥297 Bq was an independent predictor of increased tumor necrosis.[40]

The multicenter, retrospective, LEGACY study evaluated response to ablative radioembolization (median dose: 410 Gy to 155 cc of liver) with glass microspheres in unresectable, solitary HCC up to 8 cm.[41] A best response rate (complete and partial response) of 88.3% (CI: 82.4–92.4) was achieved, with a greater than 6-month duration of response in 62.2% (CI: 54.1–69.8%). Three-year overall survival was 86.6% for the entire cohort, and 92.8% in patients in whom radioembolization was neoadjuvant to resection (6.8%, $n = 11$) or liver transplantation (21%, $n = 34$). No local progressions occurred by 24 months, and there was no incidence of radiation-induced liver disease.[41] Notably, tumor size was not found to correlate with CPN in any of the radiopathologic studies of ablative radioembolization, which raises the notion of radiation segmentectomy as a standalone therapy for BCLC stage A disease not amenable to the current guideline recommendations of resection or thermal ablation.

Radiation lobectomy is another form of ablative radioembolization, in which the treatment intent is to gradually ablate the future resection site (such as the right hepatic lobe) in patients who present with inadequate future liver remnant to permit safe resection. First described by Gabr et al for the treatment of HCC, radiation lobectomy is emerging as a promising neoadjuvant to surgical resection as it leads to hypertrophy of the contralateral lobe, although optimal dosimetry remains under investigation at this time.[42–45]

Future Considerations

Tailoring radioembolization dosimetry is an effective strategy to optimize tumor control and improve survival in patients with unresectable HCC. Much of the "blind spot" within this promising therapy lies in the numerous dosimetric assumptions mentioned within this review, particularly those at the near cellular level. Investing in our understanding of microsphere behavior as they are infused into a tumor-bearing vessel and ultimately engage their therapeutic effect within a radiation microdose environment remains a veritable challenge.

The use of concurrent immunotherapy with radioembolization for the treatment of HCC is a potentially promising combination therapy which is currently under investigation. Whether immunotherapy serves as an adjuvant to radioembolization in early-stage disease or the opposite in advanced-stage disease, the role of radiation dose within the dynamic immune environment of the body remains a complex yet captivating concept.[46] While radioembolization has a tremendous capability to present tumor antigens, the effects of brachytherapy-induced lymphopenia on immune potentiation are indeterminate at this time.[47]

Conclusion

In summary, radioembolization is no longer a therapy which permits the empiric administration of radioactive microspheres into an uncertain tumor environment. Tailoring radiation dose via meticulous analyses of both vascular and particle flow properties within tumor and normal liver is necessary for optimizing outcomes. At the core of this approach lies the key notion of personalized dosimetry, where TD can and should be brought to above 205 Gy, and normal tissue should be spared when feasible. If tumor anatomy and hepatic reserve permit, ablative radioembolization has demonstrated some of the best responses and durability within the spectrum of HCC local therapy. Perhaps

of equal significance is the withholding of radioembolization in patients in whom these guiding dosimetry principals cannot be applied.

Conflict of Interest

B.B.T. is an advisor to Boston Scientific, Sirtex Medical, Johnson and Johnson, AstraZeneca, Genentech, Turnstone Biologics, Eisai, and HistoSonics.

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