Practical Yttrium-90 Radioembolization Dosimetry for the Treatment of Hepatocellular Carcinoma

Current Y-90 dosimetry concepts driving radioembolization practice for HCC treatment.

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Radioembolization has historically been applied as palliative therapy for patients with advanced hepatocellular carcinoma (HCC). Thus, yttrium-90 (Y-90) microspheres were delivered in lobar, sequential lobar, or whole liver fashion, and dosimetry models were designed to mitigate the risk of radiation-induced liver disease. This approach to radioembolization, which utilized a single palliative intent compartment, inherently limited the potential of transarterial brachytherapy by exposing uninvolved liver to radiation and underdosing tumor. Recent interest and advancements in radioembolization dosimetry, including segmental ablative dosing, partition-model dosimetry, and post–Y-90 imaging analysis, are facilitating a personalized approach to radioembolization that has increased both the safety and efficacy of this therapy. This article reviews current Y-90 dosimetry concepts that are driving radioembolization practice for the treatment of HCC.

PERSONALIZED DOSIMETRY

As radioembolization gained traction in the treatment algorithm for HCC in the previous decade, research into the effect of tumoral and nontumoral radiation dose was conducted to identify predictors of outcomes. In 2012, Garin et al determined that tumor-absorbed dose was the only radioembolization treatment parameter associated with a response and found that a threshold of > 205 Gy per multicompartment medical internal radiation dose (MIRD) improves objective response, progression-free survival (PFS), and overall survival (OS) when compared to tumors that receive less radiation.[1] Furthermore, they determined that 99m technetium-macroaggregated albumin (99mTc-MAA) single-photon emission CT (SPECT) is predictive of glass microsphere therapeutic deposition in advanced tumors, which allowed the authorized user to boost prescribed activities to achieve the > 205 Gy tumor threshold, thereby introducing the concept of personalized dosimetry.[2]

A similar study by Chiesa et al embraced the concept of AHARA (as high as reasonably attainable) in a study that identified that a tumor control probability > 50% requires a mean dose of 250 Gy or 1,000 Gy for small (< 10 g) or large (> 10 g) lesions, respectively.[3] They also found that a mean dose of < 75 Gy to nontumoral parenchyma limits the risk of treatment-related adverse events to < 15%. Subsequently, the same group identified that patients with baseline bilirubin of < 1.1 mg/dL versus > 1.1 mg/dL should receive < 90 Gy and < 50 Gy, respectively, to nontumoral parenchyma when using 4-day decay glass microspheres to avoid a similar toxicity probability.[4]

Recently, Garin et al published DOSISPHERE-01, a phase 2 randomized trial looking at outcomes of personalized dosimetry (target dose to tumor of ≥ 205 Gy based on 99mTc-MAA SPECT) compared with standardized dosimetry (single-compartment 120 Gy) in predominantly (89%) Barcelona Clinic Liver Cancer stage C patients with at least one tumor ≥ 7 cm with or without portal vein invasion.[5] Patients in the personalized dosim-

etry group were found to have an improved objective response rate and OS (26.6 vs 10.7 months; $P = .0096$), as well as a lower incidence of grade 3 or higher adverse events. Although a comparison with results from systemic therapies should be cautioned given patient selection differences between trials, the median OS of 26.6 months seen with personalized dosimetry is currently one of the longest achieved for patients with advanced HCC in a randomized prospective study.

RADIATION LOBECTOMY

The use of unilobar radioembolization led to the observation that radiation fibrosis–induced atrophy of the treated lobe can generate hypertrophy of the contralateral lobe, similar to results achieved by portal vein embolization (PVE). This established the concept of "radiation lobectomy" and prompted research into this technique as a resection neoadjuvant to increase future liver remnant (FLR). Although studies show that the time-to-hypertrophy of radiation lobectomy is generally longer than for PVE (typically 3 months vs 1 month), it provides extensive cytoreduction during the extended hypertrophy period, allowing for a biologic test of time, which theoretically may improve patient selection for resection. This assumes that patients' early progression after radiation lobectomy would have similarly progressed after resection, a notion that has not been prospectively confirmed at this time. Additionally, the ability to devitalize the future resection site (FRS) could obviate the necessity for FLR functional surrogates as the patient is already living without the FRS at the time of resection. The dose to nontumoral parenchyma needed to induce hypertrophy is under investigation, but a minimum threshold of 88 Gy using first-week decay glass microspheres has been suggested with most doses ranging between 100 and 150 Gy.[6] Given the complexities of activity distribution as a function of vascular flow preferential and both microsphere number and specific activity, research is currently underway to identify recommendations for radiation lobectomy best practice.

RADIATION SEGMENTECTOMY

A natural evolution of radioembolization has been the segmental delivery of Y-90 microspheres. A prospective randomized trial of glass microsphere radioembolization versus conventional chemoembolization (cTACE) incorporating this approach yielded time-to-progression (TTP) data significantly favoring those patients undergoing radioembolization (TTP: Y-90 > 26 months vs cTACE, 6.8 months; $P = .0012$).[7] This work was validated by retrospective, propensity score–matched studies from two separate institutions.[8,9] However, the concept of radiation segmentectomy, first described by Riaz et al in 2010, was to deliver high radiation doses to targeted hepatic segments, typically confined to two Couinaud hepatic segments.[10] This approach provides ablative radiation to the tumor and margin, reducing the risk of tumor recurrence while sparing uninvolved hepatic parenchyma.

The ablative tumor radiation dose threshold for HCC was initially established with glass microspheres from a multicenter radiology-pathology correlation. This study found that tumors receiving > 190 Gy MIRD, based on the volume of perfusion and single-compartment dosimetry, achieved a statistically higher rate of complete pathologic necrosis (CPN) at explant pathology.[11] This work was replicated in a separate radiology-pathology analysis, with 83% of treated HCC achieving CPN when the > 190 Gy threshold was applied.[12] A recent multicenter analysis by Gabr et al of 45 explants provided a correlation of Y-90–absorbed radiation dose to pathologic necrosis in HCC. There was 86% CPN when the absorbed radiation dose from Y-90 was > 190 Gy, and 100% CPN when the absorbed radiation dose was > 400 Gy, suggesting a new absorbed radiation dose threshold for curative-intent treatment with radiation segmentectomy.[13]

Most recently, a single-institution retrospective analysis of 33 consecutive HCC patients with 37 tumors who received radiation segmentectomy prior to liver transplantation demonstrated an objective response per modified Response Evaluation Criteria in Solid Tumors (mRECIST) of 92% (complete response, 76%) and ≥ 99% pathologic necrosis in 68% (n = 25) of tumors. CPN was present in 53% and 75% of tumors treated with > 190 Gy (n = 18) and > 500 Gy (n = 8) single-compartment MIRD, respectively. No posttransplant tumor recurrences occurred within a median follow-up of 604 days (range, 138-1,223 days). The investigators also found a significantly higher rate of CPN when using glass microsphere–specific activities ≥ 297 Bq versus < 297 Bq ($P = .005$).[14] The concept of radiation segmentectomy as curative intent is based on these high rates of explant CPN and long time-to-treated tumor progression.

A retrospective study on 70 Child-Pugh A patients with solitary HCC up to 5 cm revealed high imaging response rates (90% European Association for the Study of the Liver, 71% World Health Organization), median TTP of 2.4 years, with the target lesion TTP not reached, and median OS of 6.7 years. The 5-year OS for tumors up to 3 cm was 75%.[15] These survival numbers are consistent with those published for other curative-intent therapies, such as thermal ablation. A retrospective propensity score–matching study of radiation segmentec-

tomy versus chemoembolization plus microwave ablation for unresectable solitary HCC up to 3 cm revealed no significant difference in imaging response and progression outcomes between these therapies.[16] A more recent propensity score–matching study evaluated the efficacy of radiation segmentectomy versus percutaneous microwave ablation in patients with solitary unresectable HCC < 4 cm. The study groups revealed similar imaging tumor response rates and OS data, but the treated tumor PFS was prolonged in the radiation segmentectomy group (57.8 vs 38.6 months; $P = .005$, respectively).[17] With these compelling outcomes, radiation segmentectomy appears to expand curative-intent options, although prospective validation is required.

RESIN MICROSPHERE DOSIMETRY

Although most recent dosimetry updates for the treatment of HCC with radioembolization have pertained to glass microspheres, there is an emerging signal for resin microsphere dose optimization, which may improve on previous HCC outcomes attained using traditional body surface area (BSA) methodology. These are welcome advancements that glean lessons from two negative phase 3 randomized controlled trials that used BSA dosimetry (SARAH, SIRveNIB).[18] In a post hoc analysis of patients in the SARAH trial, patients who received a tumor dose of ≥ 100 Gy and had an optimal agreement between pretreatment 99mTc-MAA deposition and posttherapy activity distribution demonstrated a significant improvement in survival (24.9 vs 6.7 months, $P < .001$).[19] Adding to this, in a retrospective analysis of patients with portal vein tumor thrombus who received either conventional dosimetry versus ablative dosimetry (> 100 Gy to the tumor partition vs > 70 Gy to the liver parenchymal partition for the resin microsphere cohort), a significant OS benefit was found in favor of ablative dosimetry (45.3 vs 18.2 months; $P = .003$).[20] When treating bilobar or whole liver volumes, a recent international resin microsphere dosimetry consensus panel has recommended a dose to the normal liver cutoff of 40 Gy, or 30 Gy in patients with poor hepatic substrate. The same panel recommended that segmentectomy doses should be higher than nonablative intent treatments, speculating that > 150 Gy may be considered.[21] Given the inherent differences between glass and resin microspheres, of which specific activity is a predominant

variable, device-specific recommendations for the treatment of HCC will likely be required in future practice.

CONCLUSION

The last decade has seen a veritable industrial revolution in the therapeutic options for HCC. Systemic agents have increased by more than sevenfold, and local therapy modalities have expanded to include external beam radiation therapy, viral oncolytics, and even studies on locally infused chimeric antigen receptor T cells. With the advent of immunotherapy, we are witnessing a paradigm shift away from cytostatic or toxic agents in favor of the patient's own body fighting tumors. With these advancements comes an ever more crowded but patient-centered landscape that will demand increasingly better outcomes from interventional oncologists, in addition to creating opportunities for synergy with other treatments. Radioembolization stands to push the capacity of HCC therapy beyond the previous limitations of thermal ablation and ischemic embolization to include ablative and neoadjuvant applications in otherwise unamenable tumors. Interventional oncology will offer these radioembolization advancements through proper patient selection and optimization of dosimetry by raising tumor dose and lowering normal tissue radiation exposure, a practical and well-established axiom of radiobiology. ■

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