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Techniques in Vascular and Interventional Radiology

Y90 Radioembolization Dosimetry: Concepts for the Interventional Radiologist

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Transarterial radioembolization (TARE) with beta particle emitting microspheres via Yttrium-90 decay has become a fundamental component of the contemporary Interventional Oncology practice. TARE continues to advance as a result of increased utilization, clinical study, technological improvements, and evolving applications. To maximize TARE safety and efficacy, a core understanding of dosimetry is essential. The intent of this overview is to provide the reader with a general survey of radiation physics and biology, device differentiation, patient selection, anatomic assessment, activity administration models, and procedural techniques involved with TARE dosimetry.
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Introduction to Transarterial Radioembolization

The concept of transarterial radioembolization (TARE) is predicated upon the exploitation of tumoral angiogenesis to optimize deposition of radioactive microspheres into tumor vasculature. Through the accumulation of microspheres, as a courier of radioactivity, tumorcidal effects are achieved. This property allows for increased tumor dose, reduced normal parenchymal exposure, and provides unique therapeutic access to tumors amongst locoregional modalities. Despite TARE seeming simple, immense variations in hepatic arterial anatomy, flow dynamics, parenchymal reserve, heterogeneity of tumor arterial supply, properties of currently available devices, and activity principles have resulted in ongoing debates regarding optimal use in practice.

Basics of Radiodosimetry and the Yttrium-90 Microsphere

Yttrium-90 (Y90) microspheres achieve efficacy by providing microscopic brachytherapy and not by imparting a significant embolic effect (Fig. 1). This is supported by animal studies that demonstrate minimal ischemic or hypoxic injury in liver treated with 20-60 um range inert resin microspheres to arterial stasis.[1] Tumoricidal effects are due to near-pure emission of β-particles (free electron emission at an average energy of 933.7 keV), from the radioactive decay of Y90 (half-life = 64.2 h) to stable, nonradioactive, Zirconium-90.[2] About two thirds of the β-particles will travel approximately 2.5 mm in liver tissue (90% of energy will deposited within 5 mm) with a maximum penetration of 11 mm (Fig. 2). Response to radiation is dependent and related to radiobiological effects[3] as well as the relationship between activity (measured in gigabecquerel [GBq]) and dose (measured in Gray [Gy] equivalent to 1 Joule/kilogram).

Radiobiology Principles: The 4R's

There are basic 4 factors are considered in convnetional teachings of therapeutic radiation:

1) Repair: Spontaneous cell death by ionizing radiation is based on the production of unrepairable double-strand DNA breaks. DNA damage occurs primarily through generation of free radicals and highly reactive oxygen species.[4] The majority of ionizing radiation cell damage is generated by sublethal single DNA strand breaks that, when accumulated through prolonged exposure, result in cellular decompensation and apoptosis. The low embolic nature of TARE in the setting of uncompromised

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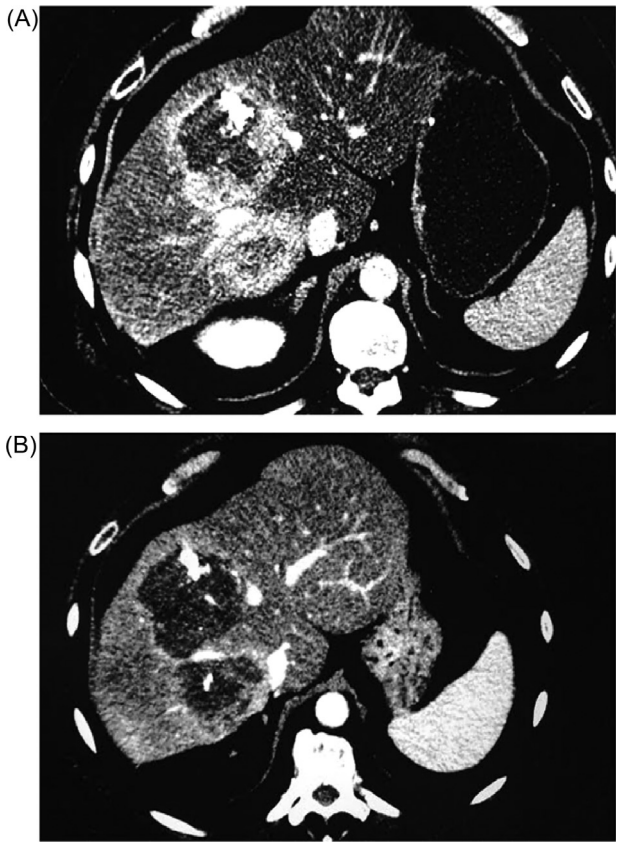


Figure 1 (A) A 61-year-old male patient with recurrent multifocal hepatocellular carcinoma after multiple conventional transarterial chemoembolization (cTACE) treatments demonstrating peripheral viable tumor enhancement within regions of sublethal ischemic and chemotherapy watershed. (B) Postlobar glass microsphere radioembolization showing compete mRECIST response with expected treated liver parenchymal volume loss and contralateral hypertrophy. This illustrates the separate tumoricidal properties of TARE when compared to cTACE.

portal perfusion allows for continued hepatic oxygenation during sustained radiation exposure.

2) Reassortment: Vulnerability to ionizing radiation is dependent upon cell cycle phase. The most sensitive phases are G2 and mitosis with late S-phase being the most resistant. As populations of tumor cells undergo the cell cycle, different regions and cell lines will have variable susceptibility to radiation. The use of TARE optimizes this concept by providing continuous brachytherapy exposure that obviates the need for fractionated therapy.[5]
3) Repopulation: Changes in the rate of repopulation (ie, regrowth and differentiation) may impact tumor genotype, architecture, and may account for aggressive recurrence and nonresponse. TARE helps mitigate this issue by eliminating the need to time and prescribe fractionated radiation therapy that may be susceptible to repopulation effects[6].
4) Reoxygenation: Tumors contain various areas of decreased oxygenation, increased interstitial pressure, and low pH that may alter the ability to generate free oxygen radicals and optimize distribution of radiation within the tumor. TARE may positively affect these phenomena by reducing intratumoral pressure and by facilitating vascular normalization[3].

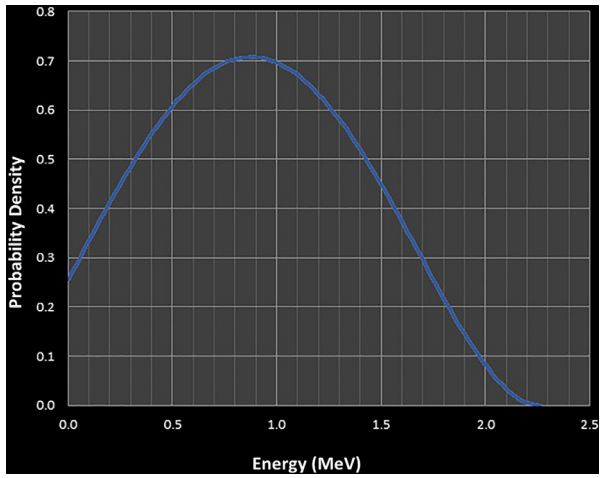


Figure 2 Y90 β-particle energy distribution curve. Approximately two thirds of particles will be just beneath 1.0 MeV and travel 2.5 mm in liver tissue. 90% of energy will be deposited in the 5 mm range. The less frequent high energy events will generate particles that travel 11 mm.

Definitions in TARE Dosimetry

TARE intrinsically targets most tumors as a function of increased vascular density.[7,8] As the source of radiation is bound to each microsphere, radiaiton effects are dependent upon the pattern of their deposition within tumor vasculature. This concept requires the differentiation between administered radioactivity and ultimate tissue exposure when planning a treatment dose as follows:

Dose is the biological effect of radiation measured in Gray (Gy) and is dependent on 4 factors:

1) Activity: Radioactive decay per unit time, commonly referred to in decays per second or Becquerel (Bq). Most TARE activities are administered in the range of billions of decays per second or gigabequerel (GBq).
2) Volume: The amount of tissue in which activity is contained.
3) Distribution: Variations in vascular compartments which affect the geographic deposition of microspheres, resulting in nonuniform patterns of irradiation.
4) Radiation susceptibility: Radiosensitivity and repair capabilities of both tumor and normal parenchyma.

Thus, activity (GBq) is only one factor in determining dose (Gy) and the biological effects of TARE should not be overly simplified by assuming uniform delivery of activity within a target volume.[9]

Device Differentiation

Significant differences exist within the manufacturing, planning, and physical properties of glass and resin microspheres. Although beyond the scope of this article, readers are encouraged to reference a comprehensive review of Y90 microsphere production and regulation.[10] For the purposes

of product differentiation, only factors relating to dosimetry and administration will be discussed.

Two physical properties of glass and resin particles dictate their major differences in administration technique and dosimetric planning: specific gravity and specific activity.

1) Specific gravity (measured in grams per deciliter [g/dL]) refers to particle density. Glass microspheres consist of spherodized aluminum and silicon dioxide glass containing Yttrium-89 (Y89) subjected to neutron bombardment that activates Y89 into Y90. The specific gravity of the glass microsphere is reported as 3.6 g/dL which is approximately 3.4 times the density of whole blood (1.05 g/dL). Resin microspheres consist of a polymer coated with a cross-link cation exchange polystyrene resin ionically bound to Y90. The specific gravity of resin microspheres is reported as 1.6 g/dL, about 1.5 times density of whole blood. Other than affecting administration techniques, variance in specific gravity has not been proven to effect clinical outcome.[10]
2) Specific activity refers to the approximate radioactivity per microsphere calculated by calibrated vial activity divided by an estimated number of microspheres by weight. Glass microspheres are estimated to have 2500 Bq of radioactivity per particle at time of calibration and are typically administered with a radioactivity range of 194-1250 Bq per microsphere for standard decay schedules. Resin microspheres are conventionally delivered the day before administration at an activity of 3.7 Gbq in approximately 40 million microspheres, representing an estimated activity of 75 Bq per microsphere. Specific activity provides a crucial factor in the dose profile of TARE in various applications and will be discussed in the following sections.

Patient Selection

The most critical determinations prior to calculating dosimetry are patient selection and establishing treatment objectives, which can by systematically broken down into the following steps:

1) Performance status: Treatment is typically reserved for individuals with adequate life expectancy to benefit from therapy or as part of a curative regimen, such as a bridge to liver transplantation.
2) Treatment intent: Generally categorized as a neoadjuvant, definitive, salvage, or palliative applications of TARE. Intent must reflect the risk tolerance of the medical team and patient goals throughout the course of their disease.
3) Tumor biology and stage: Hepatic lesion size and number alone may be insufficient characterizations of disease to determine treatment candidacy. Aggressive tumor biology poses a comparable survival hazard that may alter therapeutic trajectory.
4) Hepatic substrate: This represents the functional capability and volumetric reserve of the patient's liver. This is both important in determining the loss of liver function that may be safely sustained and estimating therapeutic benefit in patients with advanced liver disease.

Anatomic Considerations to TARE Dosimetry Conduit

As previously mentioned, TARE is best understood as brachytherapy administered via a series of vascular conduits within a dynamic and continuously changing tumor environment. Analysis can be simplified into microvascular (intratumoral vascular bed) and macrovascular (native arterial supply) conduits that represent the selectable blood supply and intrinsic vascularity of the target lesion, respectively.

Microvascular conduit is subject to great variation, even within the same tumor, and represents one of the major liabilities of any transarterial therapy. It is typically determined by evaluating the enhancement profile, or blood volume, within a lesion per contrast enhanced imaging and by the deposition of technetium macroaggregated albumin (Tc-MAA), though with recognized inconsistency.[11-13] Deficits in microvascular conduit include tumors with poor enhancement or low cellularity, necrosis, high resistance flow and increased interstitial pressure, central shunt formation, capillary attenuation from systemic therapy, or occlusion secondary to previous locoregional treatment. These limitations generate intralesional radiation watershed variations that can compromise dose thresholds and reduce efficacy. Alternatively, tumors with a high saturation of microvascular conduit tend to show improved targeting and treatment outcomes, even with vascular invasion.[14-16] Intralesional radiation watershed can be mitigated either by increasing particle number, which is limited by conduit, or by increasing activity, which is limited by β-particle range.

Macrovascular conduits are ultimately more predictable and can be evaluated with standard angiographic techniques. General assessment includes vessel selectivity, spasticity, flow capacity, perfused tissue flow resistance, and non-target supply. Hepatic parenchymal segmentation of individual macrovascular conduits will influence multiple treatment decisions regarding the number of administration sites, need for intrahepatic redistribution, administered activity and particle number, and catheter selection.

Preferential Flow

Preferential flow results from hydrodynamic properties in vascular systems that generate nonuniform deposition, or compartmentalization, of an embolic substance. Traditional compartments are divided into tumor, liver, and lung moieities. Other examples of less understood compartments include the portal system in the setting of arterial shunting, central portal triad in the setting of high particle infusions, and even lymphatics.[17-20] As preferential flow is the primary mechanism of microsphere distribution, particularly in lobar applications, errors in assessment can lead to poor control of dose allocation. Gross simulation of preferential flow can be achieved by performing angiography with dilute contrast or administering Tc-MAA using syringes and infusion rates that match the administration equipment. Methods to address preferential flow will be discussed in the administration techniques section.

Angiosomal Analysis

Angiosomes, derived from the Greek words angio (vessel) and soma (body), represent the total tissue volume perfused by a given blood vessel. Conventional segmental hepatic angiosomes correspond to the eight well-established portal Couinaud segments. In reality, as a result of anatomic variation and alterations related to tumorigenesis, individual hepatic arterial angiosomes are infinitely variable and may include confounding properties such as partial segmental perfusion, intra and extrahepatic parasitized perfusion, and competitive flow dynamics.

During mapping angiography, angiosomes should be examined for target lesion coverage, relative lesion enhancement, and nontarget perfusion. This is best accomplished with high quality contrast enhanced cone beam CT and Tc-MAA SPECT/CT. Once all angiosomes responsible for tumor supply have been established, each should be inspected for quality of microvascular and macrovascular conduit, preferential flow, and compartmental allocation to better predict dose distribution (Fig. 3).

Once evaluated, 1 of 3 dosimetric decisions should be made for each angiosome based on its impact to tumor and normal liver:

1) No apparent tumor supply. This results in either no treatment or treatment as a neoadjuvant in an effort to hypertrophy liver in preparation for resection.
2) Supply to tumor and nonexpendable liver. This is most accurately treated with the partition method of dosimetry that will be described in the activity administration models section.
3) Supply to tumor only or tumor and expendable liver. To maximize efficacy, this is frequently treated through ablative dosimetry (commonly referred to as radiation segmentectomy and lobectomy), also described in the activity administration models section.

This approach conceptually maximizes the conformality of hepatic radiation by permitting dose flexibility to each angiosome based on its individual contribution to tumor via selective dose intensification.[14,18,21] The long-term fibrotic effects of radioembolization on liver function suggest that sparing parenchyma should remain a primary consideration for the interventionalist, particularly when using TARE as definitive treatment. Angiosomal modification to augment TARE will be discussed in the administration techniques section.

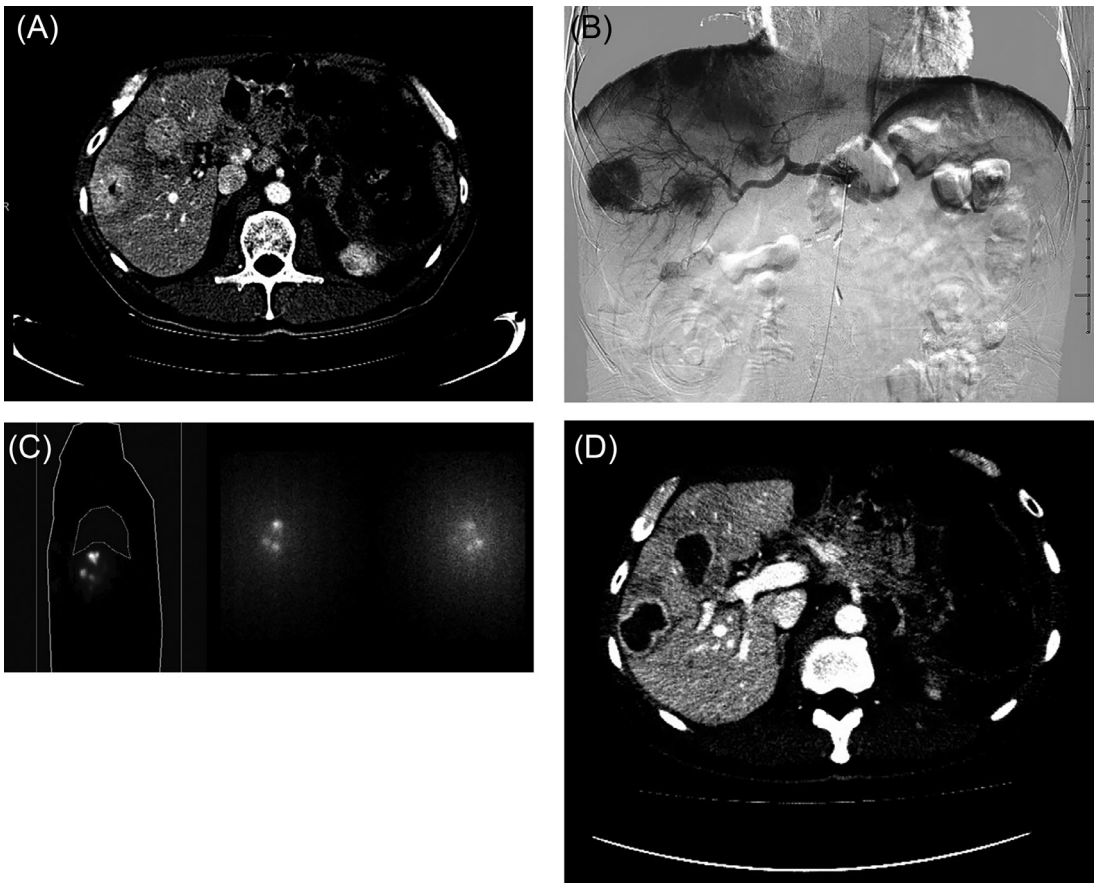


Figure 3 A 68-year-old male post pancreatic resection of high grade neuroendocrine tumor presents with multifocal hepatic metastatic disease that progressed after bland embolization (A). Mapping celiac angiography demonstrates a strong arterial flow preferential to lesions with robust microvascular conduit. Macrovascular conduit is only mildly limited by extrahepatic disease encasing the common hepatic artery origin.* (B) Planar post-Tc-MAA and (C) post-TARE Bremsstrahlung planar scintigraphy confirm the intrinsic tumor dose preferential rendered by its arterial supply (D) A 1-month CT demonstrates mRECIST complete response in all hepatic lesions.

Activity Administration Models

As understanding of the interactions between particle, activity, and conduit has matured, so has dosimetric optimization. The historical approach to dosimetry involved an empirical administration which demonstrated both poor safety and efficacy and has been fundamentally abandoned. The largely adopted activity administration models in current practice include the body surface area (BSA), medical internal radiation dose (MIRD), partition, and ablative methods.

BSA

$$\text{Activity(GBq)} = (\text{BSA} - 0.2) + (\%t/100)$$

where BSA is the body surface area (m^2), and t is the % of liver involved with tumor.

The BSA method, to date, has been the most prospectively studied model due to its implementation in several randomized clinical trials.[22] It is also the most frequent method used in dosing resin microspheres. The BSA method generates a hypothetical volume of liver based on the body surface area with dose modulations for tumor burden, large lung shunt percentage, and poor liver function. The main benefit to the BSA method is a generally well-tolerated toxicity profile. The BSA method is otherwise limited by its lack of anatomic accuracy, disregard of preferential distribution, inability to calculate segmental administrations, and inflexibility to angiosomal demands. As such, some contemporary practices have abandoned the BSA method due to its aforementioned limitations.

MIRD

$$\text{Activity(GBq)} = (D \times m)/50$$

where D is the target dose (Gy), m is mass (kg).

The MIRD method is a common model adopted for glass microsphere administration. It requires volumetric calculation of the targeted hepatic tissue and incorrectly assumes a uniform distribution of activity within the volume. Like BSA, the MIRD method does not differentiate the amount of radiation distributed into the tumor and liver parenchyma. While there is abundant safety data to support MIRD utilization with glass microspheres, the specific activity range of this product can vary by orders of magnitude by demand and the authorized user should be aware of this potential.[23]

Partition

$$\text{Activity} = (D\,x\,T/N \times t\,\text{mass}) + \text{lmass})/49.7 \times (1 - \text{lsf})$$

where D is the dose to tumor (Gy), T/N is the relative uptake of tumor vs normal liver, lmass = liver mass (Hg), and lsf is the lung shunt fraction.

The partition method is technically demanding but theoretically a more accurate dosimetry model as it incorporates preferential distribution to tumor, normal liver, and lung compartments. Dosimetry computational applications may simplify the partition calculation process (Figs. 4 and 5). The partition method allows for dose administration in which either tumor or parenchymal thresholds can be attained as separate enpoints. While appealing at face value, the model is limited by the use of Tc-MAA or contrast agents as a microsphere surrogates and inconsistencies in dose distribution. Based on available SPECT/CT and postadministration PET/CT dosimetry data, Tc-MAA may more reliably predict normal tissue uptake,[11,24] suggesting the partition method may be most effective as a means of preventing liver toxicity. The Tc-MAA distribution can be displayed as dose volume histograms and graphical isodose displays to assist the authorized user in modifying thresholds.

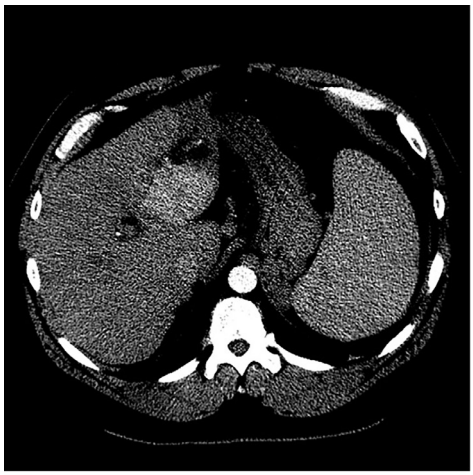
Ablative (Radiation Segmentectomy and Lobectomy)

$$\text{Activity(GBq)} = (> 190\,\text{Gy} \times m)/50$$

where D is the target dose (Gy), m is mass (kg).

Ablative dosimetry is a highly promising development in activity administration that adapts the MIRD and partition methods to render a devitalizing dose to both the tumor and normal liver within an angiosome. Ablative applications are most frequently utilized for segmental administrations as definitive radiotherapy for lesions that are poor candidates for resection or thermal ablation (Fig. 6).[25-29] Lobar ablative TARE has been used both as definitive radiotherapy for larger lesions and as a neoadjuvant to resection.[19,30,31] Lobar ablative TARE uniquely generates future liver remnant hypertrophy slower but comparable to portal vein embolization while controlling disease and enabling a biologic test-of-time for patients at high risk for early disease recurrence.[32] It also provides lobe hypertrophy in the setting of portal vein thrombosis with less reported morbidity than the associating liver partition and portal vein ligation for staged hepatectomy procedure.[33] Normal liver function in the setting of an ablated future resection site (FRS) after radiation lobectomy may provide assurance against postoperative liver failure.

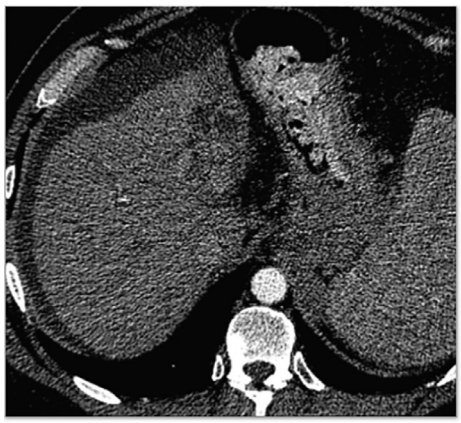
Ablative dosimetry is generally applied to expendable volumes of liver in which such doses are safely tolerated. Greater administered activity results in more decay probabilities that generate higher energy β-particle events that penetrate further in the tumor and improve sublethal dose heterogeneity.[18,34,35] Early radiation segmentectomy radiopathologic data show rates of tumor complete pathologic necrosis in excess of 50%[18,28] and a propensity matched comparison to combination TACE and microwave ablation has suggested noninferiority.[36,37] A 14-year retrospective experience of BCLC 0 and A patients who underwent radiation segmentectomy as sole treatment has recently shown comparable survival rates to resection, radiofrequency ablation, and transplantation for small hepatocellular carcinomas. Being the most recent development, ablative dosimetry lacks the volume of data available for other methods. The principal



(A)

MIRD	DOSE	ACTIVITY
TUMOUR	141.5 Gy	0.7 GBq
LIVER	35.4 Gy	0.1 GBq
LUNG	0.7 Gy	0.0 GBq
TOTAL		0.8 GBq

(B)



(C)

Figure 4 Conventional therapy using MIRD and Partition Model. 43 year old female patient with hepatitis C, radiographic evidence of portal hypertension, and a 6 cm tumor located in segment IV (A). Utilizing MIRD model and glass microspheres, the total volume of treated area (including tumor and liver) was 325cc and targeted to receive 120 Gy, assuming uniform distribution with resultant calculated activity of 0.8 Gbq (B). Three-month postadministration scan demonstrates downstage of tumor to within Milan criteria and subsequent transplant (C). If utilizing the partition model, 0.8 Gbq would have resulted in a tumor target dose of 141.5 Gy (dosimetry screen shot published with permission from the DAVYR app).

detriment to this approach is the potential for irreversible liver injury if hepatic substrate and essential future liver remnant are miscalculated.

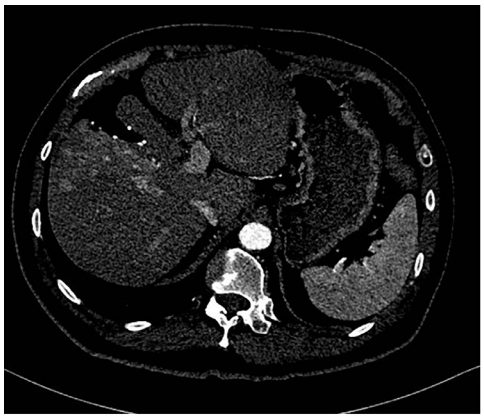
Particle Dynamics

For an assumed dose based on administered activity, TARE is substantially better tolerated than an equivalent external photon or proton radiotherapy prescription due to its integral lack of dose uniformity. Mathematical models have attributed the safety profile of glass beads at higher activities relative to resin as a function of its fewer particles and nonuniform distribution. This property reduces the normal tissue complication probability but may predispose to incomplete lesion dose coverage.[17] Alternatively, greater particle number improves uniformity at the theorhetical expense of greater toxicity risk.[34,38] From a clinical standpoint, underdisribution of radiaiton can be corrected by increasing the particle activity (maximize β-particle penetration) or number of microspheres administered (maximize microvascular conduit saturation). On the other hand, too much dose uniformity may override preferential deposition and increase normal tissue complication probability.

Particle number and activity can be adjusted by choosing the desired number of spheres and allowing for activity to decay to within the target dose range. This allows for instances where fewer particles are needed with greater activity, such as segmental ablative doses, and more particles with less activity, as in palliative lobar doses.[34,39]

Pulmonary Compartment

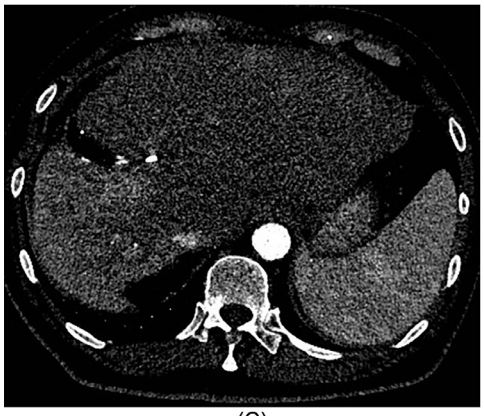
Radiation pneumonitis (RP) is an uncommon, but life-limiting TARE complication. Patients may undergo shunt modification via a low dose radioembolization, bland embolization, hepatic venous outflow obstruction, thermal ablation, vasoactive systemic therapy, or external beam radiotherapy - all in an effort to administer TARE with a reduced risk of RP. The most



(A)

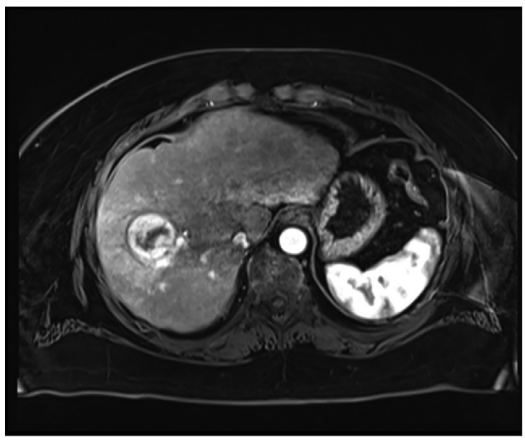
Partition	DOSE	ACTIVI...
TUMO...	315.0...	0.8 GBq
LIVER	70.0 Gy	1.2 GBq
LUNG	1.9 Gy	0.1 GBq
TOTAL		2.0 GBq

(B)

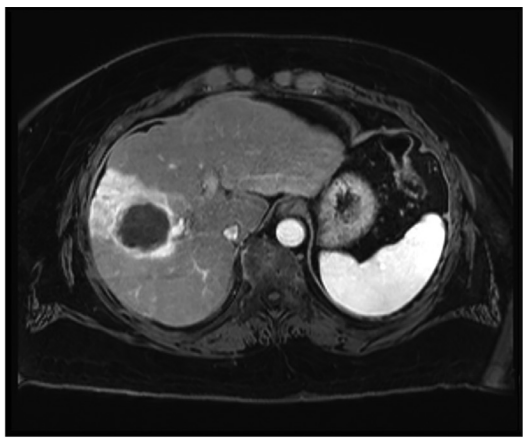


(C)

Figure 5 Radiation lobectomy using the partition model. 54 year old male with hepatitis B, previous mesohepatectomy, who presents with right lobe multifocal HCC and PVT (A). Utilizing partition model and resin microspheres, radiation lobectomy was performed with a target dose to the liver parenchyma of 70 Gy (yellow box), amounting to 2.0 GBq administration (B). Four-month post-TARE scan demonstrates significant atrophy of the right lobe and no residual tumor enhancement (C). Had this patient undergone MIRD based radiation lobectomy target dose of 200 Gy to the total treatment volume, total activity required would be 2.7 GBq (dosimetry screen shot published with permission from the DAVYR app). (Color version of figure is available online.)



(A)



(B)

Figure 6 A 57-year-old male with hepatitis C related cirrhosis and a 5.8 cm hepatocellular carcinoma presents for downstaging to transplant (A). The tumor abuts the right hilum and is a poor ablation candidate secondary both size and location. Patient was treated with outpatient segmental ablative radioembolization (radiation segmentectomy) where both the tumor and normal liver compartments within the angiosome received >190 Gy. A 3-month MRI demonstrates mRECIST complete response without injury to the adjacent portal triad or hepatic decompensation (B). Pateint remained without evidence of disease, 2 years post treatment, at this time of this publicaiton.

commonly accepted lung dose thresholds are 30 Gy for a single session and 50 Gy cumulatively. These guidelines incorrectly assume a uniform dose distribution to the lungs that may not reflect the accurate distribution. This is well illustrated with the reported cases of patients safely exceeding the manufacturer's recommended dose thresholds and patients developing RP within them.[40] Ultimately, the authorized user should be aware of this complication and balance the risk and benefits of treating patients with high lung shunts.

Technical Considerations

Replication

TARE administration is a careful and calculated process that must mimic the vascular environment and technical parameters established during mapping and simulation. Successful administrations rely on minimal to no alteration of conduit during treatment by avoiding spasm, unintended perfusion attenuation, thromboembolic events, or preferential flow that could alter sphere distribution.

Coil Embolization

While coil embolization of nontarget vessels has been generally practiced, the safety benefit of this technique in routine use has not been proven and should be reserved for select cases.[41] Routine embolization of foregut arteries may promote the development of nonselectable hepatoenteric collaterals which could compromise treatment.[42] Consider coil embolization on the day of treatment if a vessel is at risk for this phenomenon or divide the dose to be administered peripherally, away from the at risk vasculature.

Coil redistribution to consolidate tumor supply conduit to a more favorable macrovascular conduit via the recruitment of peribiliary arterial anastomoses has been proven effective.[8,43] However, redistribution may recruit suboptimal or extrahepatic vessel supply, particularly in segmental therapies. There is limited data supporting the feasibility of hepatic TARE via the right inferior phrenic and adrenal artery.[44,47]

Microcatheters

Infusion microcatheter end-hole diameters will affect both laminar flow and the pressure of injection. Larger end-hole microcatheters allow for improved angiographic visualization administration of spheres that will match vessel flow dynamics but have the potential to overwhelm vessel capacity resulting in reflux. Small end-hole catheters offer inferior imaging capability, are susceptible to preferential flow, and may generate nonlaminar microsphere distribution due to end-hole to blood velocity mismatches,[45] but are useful in limiting reflux during injections and in engaging small caliber anatomy. Perhaps of even greater importance, the microcatheter location at the time of administration may significanlty alter particle distribution if an adequate diffusion distance is not provided form the endhole to the receiveing vessel.[48]

Resin Administration

Resin administrations require the user to be highly attuned to hepatic arterial flow states both before and during administration given the higher particle volumes. Flow can be surveyed by intermittently injecting contrast between administered aliquots, by propelling the microspheres with a contrast solution, or by placing a 5 French sheath within the celiac or common hepatic artery central to the microcatheter and coadministering contrast during the infusion. Most users report increased vascular capacitance and decreased in vasospasm by flushing with a 5% dextrose solution rather than sterile water. As stasis can be reached early in smaller volume angiosomes, increased resin particle specific activity can be obtained by administering on or prior to the expected date of calibration.

Glass Administration

Glass administration involves an initial rapid, low volume, uniform pressurized injection to suspend the particles of greater specific gravity followed by a continuous infusion until there is no significant residual vial activity. Due to lower particle counts, stasis is rarely encountered with glass TARE. The lower glass particle counts require the user to be highly attuned to catheter location, preferential flow, and injection rates established during mapping angiography to avoid unintended dose distributions. Coupling the administration line to a microcatheter that has been primed with contrast and visualizing the initial injection behavior with fluoroscopy may help ensure against reflux and aid in matching flow preferentials. Low particle count errors may be addressed by administering larger calibrated activity vials with 8 days of decay or greater (also known as EX administration)[49] to increase particle number or selective catheterization of individual branches and dividing the dose according to the treatment volumes.

Segmental Ablative Administration (Radiation Segmentectomy)

Segmental ablative administration differs from lobar infusion and can be maximized with the following considerations:

1) Selectivity is preferred, provided appropriate compatibility with infusion technique and anticipated particle volume.
2) Ensure no air bubbles are within the administration system as this may result in proximal occlusion of the target vessel.
3) When choosing a lower profile microcatheter for a treatment, consider imaging via a 5 French sheath in a central supplying vessel as previously described for resin administration.
4) Superselective, subsegmental, administrations may occasionally result in focal sphere deposition near the catheter end hole rather than within the target volume and potentially compromise treatment.
5) When using large volume microsphere infusions for segmental applications, increased delivery can be accomplished with pressurized delivery catheters

(antireflux or microballoon) while preventing nontarget delivery. This technique can overcome tumor vascular resistance which theoretically can increase particle deposition.

Lobar Ablative Administration (Radiation Lobectomy)

Lobar ablative applications, as previously mentioned, are used both as a definitive radiotherapy in large, unresectable, hepatic tumors and as a surgical neoadjuvant (Fig. 7). There are 2 points of failure in performing lobar neoadjuvant that require consideration:

1) Too much dose to the tumor and not enough to the parenchyma will accomplish disease control, but inadequate hypertrophy.[31]
2) Too much dose to the parenchyma and not enough to the tumor will result in hypertrophy but inadequate disease control.[15]

Preventing either error is accomplished by identifying the preferential favoring either tumor or normal liver compartments by utilizing partition analysis and ensuring adequate dose correction or administration technique. This typically requires the delivery of greater particle volumes, multiple selective deliveries, or pressurized delivery catheters. Central pressurized catheter delivery can result in inconspicuous extrahepatic perfusion during forced administration and the operator should remain vigilant. Highly dominant tumor sump in large, hypervascular, lesions may require separate segmental administrations to ensure intended dose distribution.

Patients will require a limited operative quarantine to reduce radiation exposure to the surgical and pathology staff, although exact policy is institution specific. Surgical teams must be familiar with operating in the postradioembolization liver, which may generate adhesions in capsular lesions.

Angiosomal Modulation

Angiosomal modulation is utilized to redistribute flow or alter the overall perfusion within an angiosome to both increase TARE dose conformality and facilitate treatment of challenging anatomy, such as poorly selectable vasculature. This is accomplished by occluding the nontarget volume blood supply by using resorbable or permanent bland particles, retractable coils, microballoon catheters, microvascular plugs, iodized oil, or gelatin foam, and administering TARE centrally.[50] This technique is commonly used in central or watershed lesions that would require unnecessary dose deposition the peripheral uninvolved liver. Temporarily occluding a central vessel may result in redistribution to nontargeted vascular territories, thus postocclusion vessel interrogation is recommended (Fig. 8).

Future Considerations

All dosimetry methods are ultimately trying to answer the same question: what will be the true dose? Current technology requires several days for probability modelling, such as Monte Carlo simulations, which are not always practical and cannot consider the near innumerable variables involved with transarterial therapy. To further complicate dose prediction, the current lack of an adequate particle surrogate adds an immense knowledge gap to the calculation of Y90 radiodosimetry. Future experience and computational advancements may improve on both the efficiency of dose allocation and may potentially obviate the necessity for particle simulation. Progress in the correlation of tumor genotype with radiologic phenotype may help guide dose thresholds and concurrent systemic treatment. Of consolation, simulation

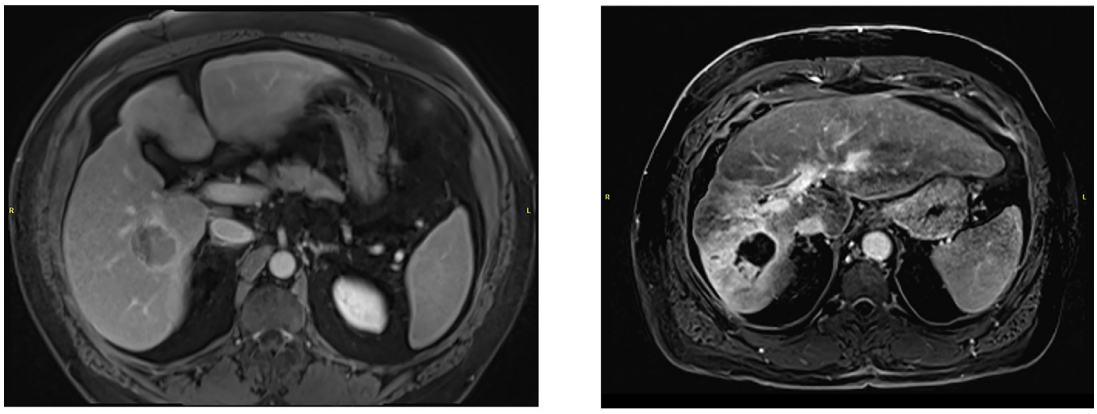


Figure 7 A 71-year-old male with hepatitis C and ALBI grade 1 liver function presents with a 5 CM right hepatic lobe HCC and inadequate future liver remnant (FLR) for resection (A). Ten months after ablative radioembolization of the right hepatic lobe, there is no residual tumor enhancement, the right hepatic lobe (FRS) demonstrates involution with radiation fibrosis, a biologic test of time has been established, and the FLR is within surgical criteria (B). The patient's liver biochemical function remained unchanged throughout treatment.

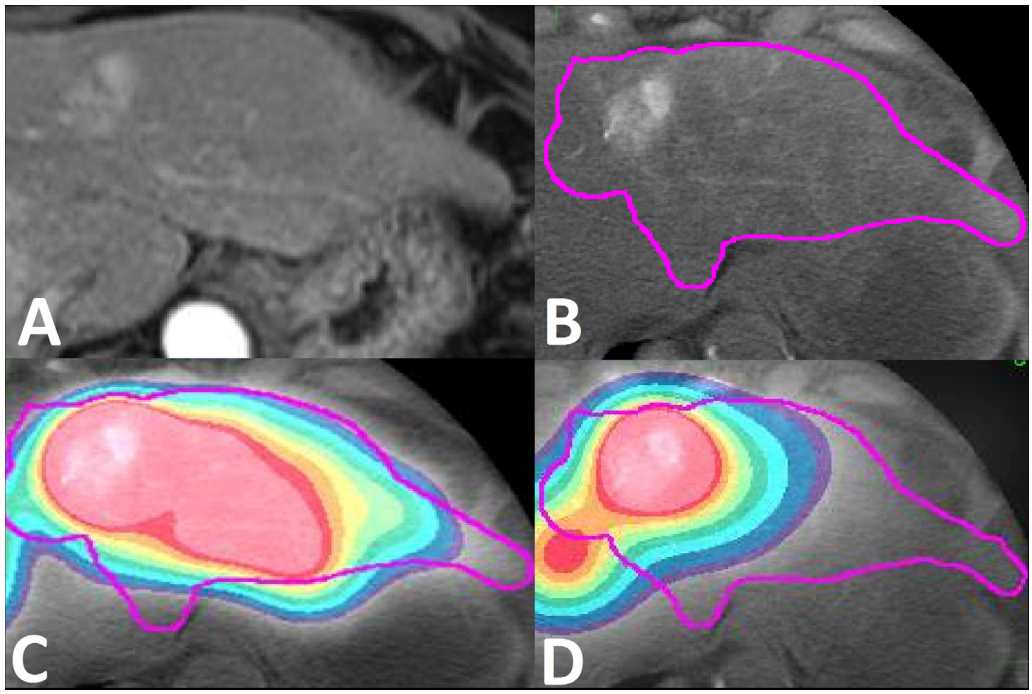


Figure 8 Arterial phase MRI demonstrates a single hepatocellular carcinoma which abuts the central left bile ducts (A). Contrast enhanced cone beam CT demonstrated supply from multiple segment 2 and 3 non-selectable arteries (B). Tc-MAA SPECT-CT shows a relatively large portion of uninvolved liver will be treated if both segments are treated (C). Post TARE with peripheral gelatin slurry administration Bremsstrahlung SPECT-CT demonstrates reduction in in all isodose thresholds increasing tumor dose conformality and sparing uninvolved liver (count threshold: count reduction = 40%:14.7%, 20%:41.1%, and 5%: 7.6%) (D).

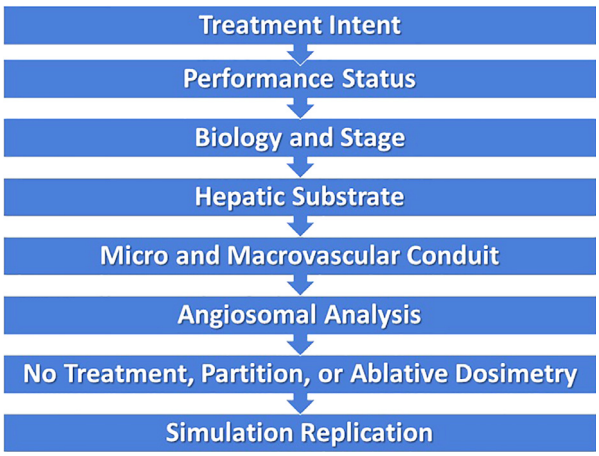


Figure 9 Clinical and technical radiodosimetry workflow.

and administration hurdles are not unique to TARE and are equally confounding in other forms of radiation therapy.[46]

Conclusion

TARE represents a fundamentally unique form of intra-arterial therapy with broad applications that augment therapeutic options in patients with primary and metastatic liver cancer. Rather than an angiographic embolization endpoint, extensive consideration must be made to compartmental deposition of radiation activity. Continual efforts to increase understanding of dose as it relates to patient selection, conduit assessment, and technical aspects of angiosome optimization are essential to advance both safety and efficacy (Fig. 9).

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