

# What's New in Y-90?

Technical and procedural innovations in Y-90 radioembolization including existing and investigational next-generation technologies.

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**Y**trium-90 (Y-90) transarterial radioembolization (TARE), also known as selective internal radiation therapy (SIRT), has been used for the treatment of primary and secondary liver cancer for decades. This therapy has greatly advanced since the seminal publications on the clinical, technical, and procedural aspects of Y-90 therapy.<sup>1-3</sup> Numerous subsequent studies have confirmed the safety and efficacy of Y-90 therapy, resulting in significant growth in its use. Multidisciplinary recognition of the value of Y-90 therapy is highlighted by its inclusion in the National Comprehensive Cancer Network guidelines as a category 2A recommended therapy for colon and rectal cancer liver metastases.<sup>4</sup> This, as well as a key institution's multidisciplinary team's decision to choose Y-90 as first-line therapy for hepatocellular carcinoma (HCC),<sup>5</sup> should lead to continued growth and adoption. This article describes technical and procedural innovations in Y-90 radioembolization and introduces promising next-generation investigational technologies for this well-established and effective therapy.

## **RADIATION SEGMENTECTOMY/LOBECTOMY AND SAME-DAY THERAPY**

Y-90 TARE has been historically considered a palliative therapy option for patients with unresectable liver malignancies deemed unsuitable for other locoregional therapies; however, more recent publications have explored the prospect of developing TARE techniques with curative intent. Radiation segmentectomy delivers enough radiation to ablate an entire vascular territory, resulting in radionecrosis of tumor and liver tissue, analogous to surgical resection.<sup>6</sup> Administering this ablative dose can thus destroy all tumor in the treated volume and provide a margin of tissue destruction surrounding the tumor akin to surgical resection. Additionally, adjacent satellite lesions not visible on imaging as well as any micro- or macrovascular invasion in the volume can be adequately treated.

Published recommendations for radioembolization now include Y-90 ablation techniques in treatment

algorithms,<sup>7</sup> and these procedures continue to gain clinical adoption as subsequent studies have demonstrated long time to progression (TTP) and meaningful long-term overall survival (OS) rates for patients with limited tumor burden and preserved hepatic function.<sup>8</sup> The PREMIERE trial, a prospective randomized trial of glass microsphere radioembolization versus conventional transarterial chemoembolization (cTACE) with doxorubicin for patients with unresectable, nonablatable (percutaneously) HCC, helped introduce segmental (rather than lobar) radioembolization treatments.<sup>9</sup> This study revealed a TTP > 26 months for radioembolization compared with 6.8 months for cTACE. This work supporting the benefits of segmental radioembolization over segmental cTACE was corroborated by a retrospective, propensity-matched analysis<sup>10</sup> and has led to more widespread application of segmental radioembolization, especially in the bridge to liver transplant setting. Two separate radiology-pathology correlative studies revealed high rates of complete pathologic necrosis at explantation when the segmental radiation dose based on volume of perfusion exceeded 190 Gy.<sup>11,12</sup>

Radiation segmentectomy also lends itself to same-day radioembolization—mapping angiography, lung shunt evaluation, and radioembolization performed in the same session.<sup>13</sup> This paradigm-changing approach makes radioembolization more competitive to other intra-arterial embolotherapies, is convenient for patients, and helps reduce health care costs.

An atrophy-hypertrophy complex was noted when radioembolization was performed in a lobar fashion for patients with unilobar disease where, over time, the treated hepatic lobe atrophies and there is compensatory hypertrophy of the untreated contralateral hepatic lobe.<sup>14</sup> This concept is now being employed to facilitate hepatic resection for select patients presenting with inadequate future liver remnants. As an alternative to portal vein embolization, radiation lobectomy allows for synchronous cancer treatment during the

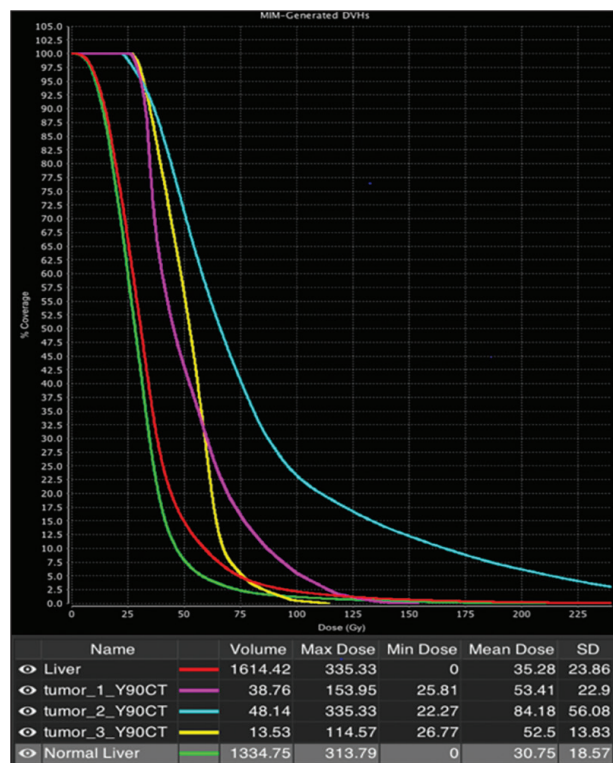
time interval to hypertrophy. A modified radiation lobectomy technique includes a segmental ablation dose (boost) to the targeted tumor with the intent to deliver a complete pathologic response.<sup>15</sup>

## DOSIMETRY: NEW CONCEPTS AND TOOLS

The standard method for dosimetry is the body surface area (BSA) model for resin radiomicrospheres (SIR-Spheres, Sirtex Medical Inc.) and the medical internal radiation dose (MIRD) model for glass radiomicrospheres (TheraSphere, Boston Scientific Corporation). The partition model, which requires a tumor-to-normal (T/N) uptake ratio, is theoretically more accurate and allows for personalized dosimetry because it accounts for tumor avidity. However, the latter assumes uniform distribution of injected activity in the tumor and in the normal liver, which is not the case. Recent advances in dosimetry have been made with the application of dose calculation treatment planning software to radioembolization procedures that allow for voxel-based dosimetry.

A voxel is simply a three-dimensional pixel obtained through positron emission tomography (PET)/CT, single-photon emission CT (SPECT), or SPECT/CT and has a calculated value that can be converted into dose (Gy). There are several dose calculation software systems available including MIM SurePlan LiverY90 (MIM Software Inc.), Planet Dose (DOSIsoft), Simplicit90Y (Mirada Medical/Boston Scientific Corporation), and RapiSphere (Varian Medical Systems, Inc.). These systems allow for automated volume segmentation, measurement of hepatic volumes and tumor volumes, calculation of lung shunts, multimodal image registration, pre- and postimplantation dose calculation, dosimetry comparison, and measurement of treatment response.

Voxel-based dosimetry allows for the creation of a dose-volume histogram, which is the gold standard in radiation oncology for radiation therapy planning and dose measurement (Figure 1). The treatment planning software systems evaluate and measure the distribution of Y-90 radiomicrospheres in different compartments and corresponding doses to different structures. Postimplantation dosimetry with this advanced software provides patient-specific information with respect to actual dose delivered to different tumors, whether there was adequate tumoral coverage, and how much dose was delivered to normal liver tissue. Although technetium-99 macroaggregated albumin (Tc-99m MAA) has limitations, some studies have shown reasonable agreement between Tc-99m MAA SPECT and post-Y-90 PET/CT.<sup>16</sup> Therefore, there is the potential to use treatment planning software for preimplantation

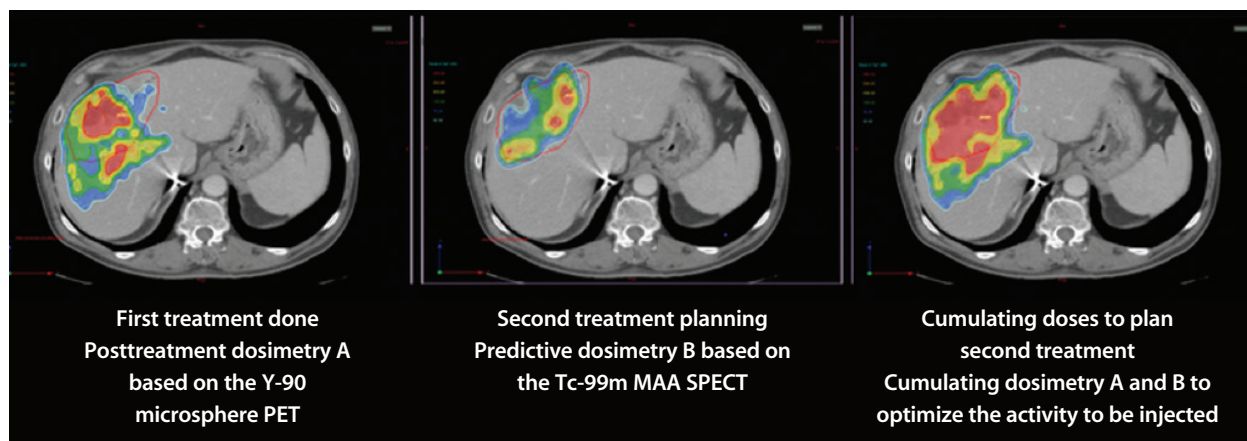


Courtesy of MIM Software Inc.

**Figure 1.** Dose-volume histogram following radioembolization demonstrating radiation dose to volume of three separate tumors and normal hepatic parenchyma. Voxel-based dosimetry is performed on the basis of postprocedure bremsstrahlung SPECT/CT or PET/CT scan.

activity determination. Finally, this technology may be valuable as a decision-making tool in patients undergoing multiple therapies (ie, combination of external beam radiation and Y-90 or multiple Y-90 therapies) to determine cumulative dose to different compartments with the goal of optimizing tumor response and minimizing toxicity to normal liver (Figure 2).

The primary mechanism of action with TARE is related to  $\beta$  radiation emission from the Y-90 microspheres working in unison to create tumoricidal radiation “clouds” and a “crossfire” effect.<sup>17,18</sup> As a result, TARE is driven by the amount and distribution of radioactivity administered and not necessarily the number of microspheres. General recommendations with respect to clinical activity and dose plans have been established by the Radioembolization Brachytherapy Oncology Consortium.<sup>19</sup> The conceptual convergence of two techniques, one providing precise and optimized dose to elicit tumor response considered the “conventional” transarterial radioembolization (C-TARE) technique versus the other intended to radioablate the entire targeted vascular territory (including both the tumor and



Courtesy of DOSSoft.

**Figure 2.** Voxel-based cumulative dosimetry for total dose estimation for multiple treatment planning procedures. Safety of repeat radioembolization, for example, may be determined by using treatment planning software to determine actual dose delivered to both tumor and normal liver from previous therapy. These data may be combined with predictive dosimetry to both compartments on the basis of a Tc-99m MAA SPECT scan to optimize prescribed activity to ensure tumor response while preventing hepatic toxicity.

the liver) considered “ablative” transarterial radioembolization (A-TARE) technique, can be resolved by the concepts of segmentation and targeting of tumor versus liver parenchyma. The discussion of segmentation and partition has conceptually improved the understanding of the relationship between particle deposition, activity, and tissue response. The interrelationship between activity, tissue susceptibility, target/tumor volume, and microsphere distribution that dictates the micro- and macroscopic radiation dose has been previously described.<sup>20</sup> The intent of C-TARE is to target and optimize the deposition of radioactivity to the tumor while minimizing the amount of radiation (ie, dose) to the native liver parenchyma. This stepwise approach to C-TARE is intended to optimize tumor treatment while minimizing the potential for hepatic decompensation and complications related to excessive nontargeted

embolization. With A-TARE, complete ablation and necrosis of the entire vascular territory is desired, dictated by high exposure of radiation to the normal liver in the target region and not limited by optimal dose to the tumor.

With regard to tumor dose thresholds, a study evaluating glass Y-90 C-TARE outcomes for HCC with macrovascular invasion using Tc-99m MAA SPECT-based personalized dosimetry and dose intensification demonstrated improved OS if the tumor dose was > 205 Gy.<sup>21</sup> Ideally, this tumor dose threshold should be considered for both C-TARE and A-TARE using glass Y-90 with the awareness to reduce the tumor dose toward 190 Gy with C-TARE if there is risk of toxicity to the normal liver. Resin Y-90 C-TARE has similar outcomes using BSA dosimetry, resulting in a tumor dose threshold > 100 Gy.<sup>22</sup> For resin A-TARE, a partition

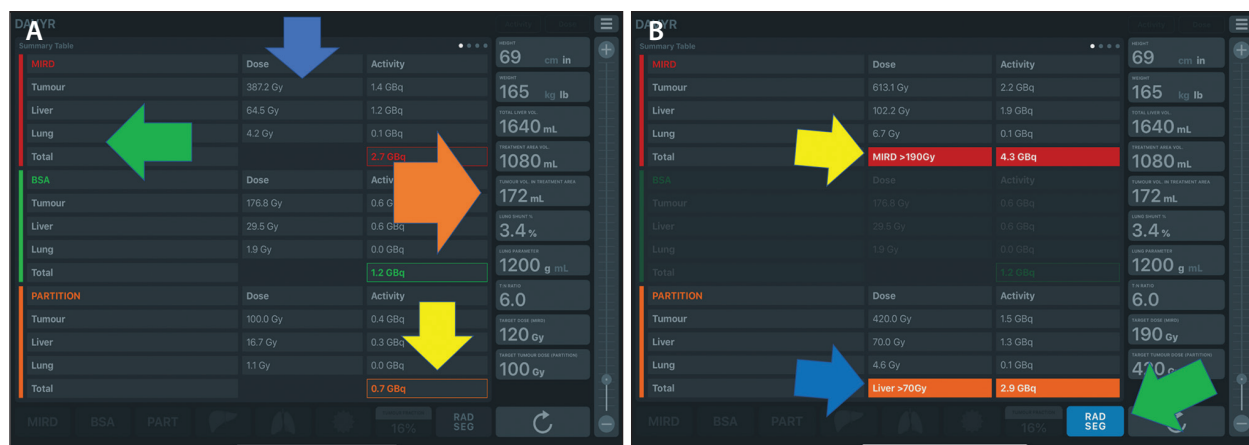
**TABLE 1. DESIRED DOSE THRESHOLDS FOR C-TARE AND A-TARE**

Y-90 Product	C-TARE	A-TARE
Resin (SIR-Spheres)	<ul style="list-style-type: none"> <li>Partition model: &gt; 100 Gy to tumor</li> <li>BSA*</li> </ul>	Partition model: > 70 Gy to liver
Glass (TheraSphere)	<ul style="list-style-type: none"> <li>MIRD model: &gt; 120 Gy to total treatment volume†</li> <li>Partition model: &gt; 205 Gy to tumor</li> </ul>	MIRD model: > 205 Gy to total treatment volume†

Abbreviations: A-TARE, ablative transarterial radioembolization; BSA, body surface area; C-TARE, conventional transarterial radioembolization; MIRD, medical internal radiation dose; Y-90, yttrium-90.

\*BSA model does not provide dosimetric modeling parameters.

†Total treatment volume = tumor volume + nontumoral liver volume in targeted vascular territory.



**Figure 3.** C-TARE dosimetry is easily derived from MIRD, BSA, and partition models using the DAVYR app (A). Initial clinical parameters are entered (orange arrows; iPad screen format illustrated), which then determines overall activity (yellow arrow), as well as the individual compartment distribution (green arrow), resulting in estimated dose to target compartments (blue arrow). A-TARE using the same parameters by activating the “RAD SEG” button (green arrow), the app recalculates MIRD target activity for glass (yellow arrow) and for partition (blue arrow) based on the parameters as outlined in Table 1 (B).

dose > 70 Gy to the target region is desired, inclusive of tumor and normal liver, because 70 Gy is the threshold beyond which destruction of normal liver is anticipated.<sup>7</sup> This strategy is used anecdotally by two authors (Drs. Gandhi and Liu) for resin A-TARE applications. Table 1 summarizes these thresholds.

Greater understanding of the concepts of segmentation, partition, and the relationship between particle deposition, activity, and tissue response can be gained through use of the DAVYR (Dosimetry and Activity Visualizer for Yttrium-90 Radioembolization) app (Figure 3). This free app is available for download on iOS and Android platforms and provides a concise tabulated data set of the currently used techniques and additionally includes an A-TARE calculator (“RAD SEG” button). Once the user enters patient and tumor parameters (height, weight, liver volume, target volume, T/N ratio), the application displays calculated dosimetry for MIRD, BSA, and partition and provides a direct comparison between these models. The tabulated data sets clearly illustrate the relationship between administered radioactivity (GBq) and estimated dose in the respective segment (lung, liver, or tumor), which clarifies a key point: extrahepatic toxicity is a result of deposition of microspheres in nontarget organs (stomach, lung, pancreas), whereas hepatic toxicity is a result of excessive radiation to normal liver parenchyma for which the nonexposed parenchyma is unable to adequately compensate. The user can adjust parameters such as desired target tumor dose to understand the resultant effect on normal liver and lung.

To help optimize treatment and tailor to patient requirements, Y-90 manufacturers now offer more treatment options to accommodate clinical need for personalized therapy. Ensuring adequate radiomicrosphere coverage of tumor at an appropriate level of specific activity can optimize tumoricidal dose to the tumor. Users can now choose customized treatments to address varying scenarios, including (1) subsegmental treatment of small volume with a small quantity of radiomicrospheres at standard specific activity; (2) varying volumes with small or high radiomicrosphere quantity at high specific activity for segmentectomy; (3) small, medium, or large quantity at standard activity for general lobar treatment depending on target volume and tumor burden; (4) large quantity at higher specific activity for radiation lobectomy; and (5) numerous intervening combinations to tailor treatment to the specific clinical scenario.

Use of multiple glass Y-90 dose vials at one treatment setting as well as use of second-week, extended-shelf-life doses provide many permutations of quantity and activity and additional flexibility in determining day and time of treatment. Resin Y-90, traditionally provided as a dose vial calibrated to provide 3 GBq on the evening of the treatment day from which the prescribed dose is drawn at the time of administration, is now provided up to 3 days pre-calibration and up to 1 day after calibration. This results in extensive options in desired activity and microsphere quantity at the time of administration, particularly when including the ability to draw a specific dose from the supplied vial. Interventional radiologists can now provide a tailored dose at essentially any day and time desired. Providing a



TABLE 2. YTTRIUM-90 VERSUS HOLMIUM-166 DIAMETER AND  $\beta$  ENERGY SPECIFICATIONS

Specification	Glass Yttrium-90	Resin Yttrium-90	Holmium-166
Median diameter	–	32 $\mu$ m	–
Mean diameter	25 $\mu$ m	–	30 $\mu$ m
Diameter range	20–30 $\mu$ m	20–60 $\mu$ m	30–60 $\mu$ m
Average $\beta$ energy	0.93 MeV	0.93 MeV	0.69 MeV
Maximum $\beta$ energy	2.28 MeV	2.28 MeV	1.81 MeV
Maximum penetration	11 mm	11 mm	7 mm
Half-life	64.1 h	64.1 h	26.8 h

dose vial well before the calibration date and time also allows resin Y-90 to be offered at higher specific activity for A-TARE applications. With regard to specific activity, the long-held view that glass Y-90 has specific activity of 2,500 Bq/sphere versus resin Y-90 at 50 Bq/sphere should be clarified. These values are realistic at the time of calibration for each product; however, the actual day and time of calibration significantly differs between the two devices, resulting in the marked difference. Instead, the focus should be on specific activity at the time of administration, because that is what is clinically relevant. In fact, with the new resin offerings that provide the ability to treat 3 days before the calibration day, the specific activity per microsphere for resin Y-90 starts to approach mid to late second-week specific activity per microsphere for glass Y-90.

### INVESTIGATIONAL IMAGEABLE RADIOMICROSPHERES

Posttherapy implanted Y-90 activity can be evaluated through SPECT/CT detection of bremsstrahlung emission or through Y-90 positron emission through time-of-flight PET/CT. Although SPECT/CT and PET/CT have greatly contributed to our understanding of dose effect to tumor and normal tissue, there are limitations related to resolution, blind spots, and misregistration.<sup>23</sup> Holmium-166 (Ho-166) radiomicrospheres (QuiremSpheres, Terumo Europe), originally developed at Utrecht University, have CE Mark designation in Europe and are an investigational product in the United States. Specifications compared to Y-90 are listed in Table 2.

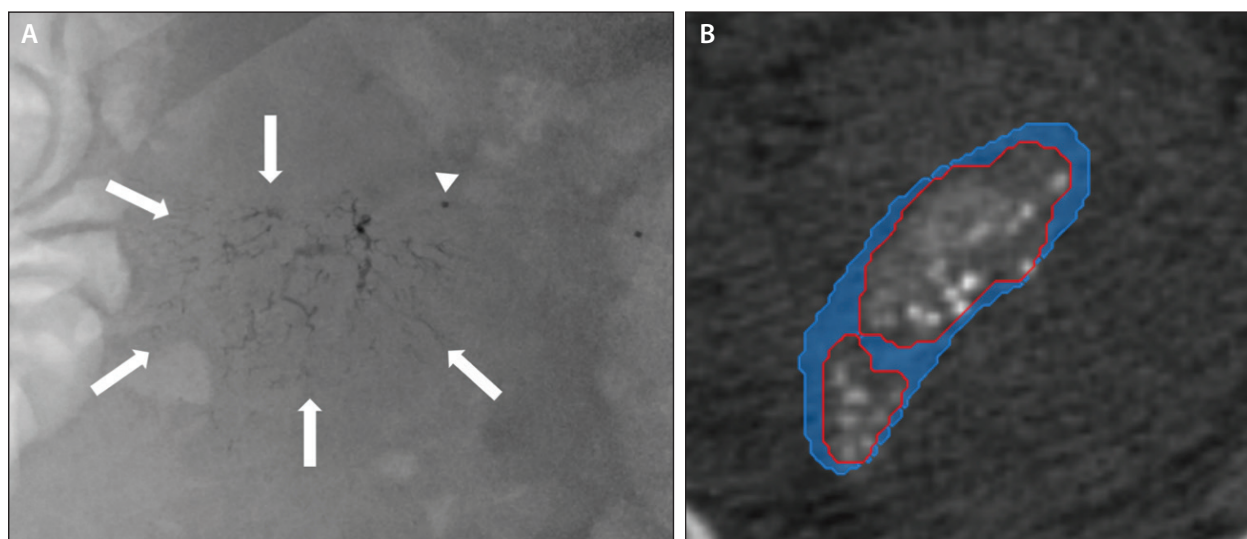


Figure 4. Implanted investigational Y-90 microspheres in swine right renal artery demonstrating strong radiopacity of the implanted microspheres (white arrowheads) (A). No contrast media has been used and all radiopacity visualized is due to microsphere deposition. Microsphere radiopacity can be compared to the radiopaque tip of the microcatheter (white arrowhead). CBCT of swine kidney after investigational radiopaque Y-90 implantation. Modified MIM SurePlan LiverY90 software was used to outline any renal tissue above 210 Hounsfield unit (HU) threshold (red outline) (B). Surrounding normal renal tissue below 210 HU is displayed by the software in comparison to normal renal tissue below the 210 HU threshold (blue fill).

Courtesy of MIM Software and ABK Biomedical Inc.

TABLE 3. MICROCATETER PLATFORMS

Device (Company)	Length	OD/ID	psi Limit	Vessel Diameter
SwiftNinja steerable microcatheter (Merit Medical Systems, Inc.)	125 cm	2.4 F/0.021 inch	1,000	–
Occlusafe temporary occlusion balloon catheter (Terumo Europe)	110, 130, 150 cm	2.8 F/0.017 inch	–	Up to 4 mm
Sniper high-flow microcatheter (Embolic, Inc.)	110, 130, 150 cm	2.9 F/0.029 inch	900	Up to 6 mm
Surefire infusion system (TriSalus Life Sciences)	120, 150 cm	3.2 F/0.021 inch, 3.7 F/0.025 inch	1,200	1.5–3.5 mm, 2–4 mm, 4–6 mm

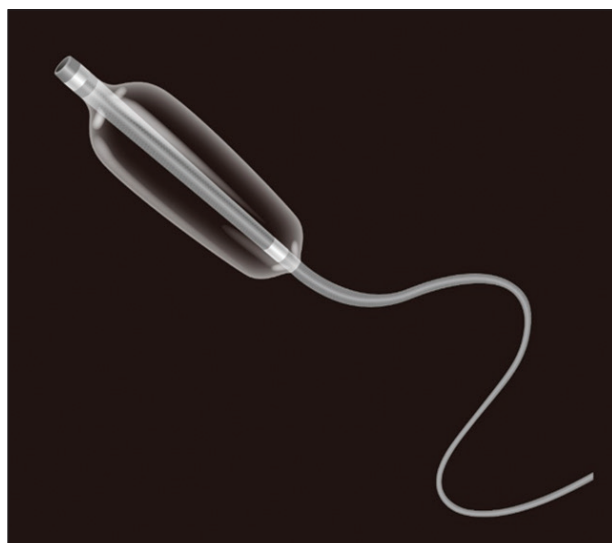
Abbreviations: ID, inner diameter; OD, outer diameter.

Although Ho-166 emits a lower level of  $\beta$  energy, has lesser depth of penetration, and a shorter half-life compared with Y-90, it has shown promise in initial clinical trials.<sup>24</sup> Additional study is needed to determine whether Ho-166 can provide long-term outcomes that are comparable to Y-90. Ho-166 does provide diagnostic  $\gamma$  emission that can be imaged with SPECT or SPECT/CT postimplantation. In addition to allowing for more accurate assessment of absorbed dose to tumor and detection of nontarget embolization after treatment, a “scout” dose can be used in lieu of Tc-99m MAA for assessment of a lung shunt and for predictive dosimetry at the time of workup. Ho-166 is also paramagnetic, which allows for quantification in target tissue using magnetic resonance–based R2\* imaging protocols. However, neither Ho-166 nor currently available Y-90 products are clinically radiopaque, which prevents

intraprocedural visualization of microsphere deposition on current C-arm fluoroscopy systems or cone-beam CT (CBCT) used to guide the procedure.

Building on the development of inherently radiopaque bland glass microspheres,<sup>25</sup> an investigational Y-90 product (ABK Biomedical Inc.) has been developed in which radiopacity is an integral feature of Y-90 administration. Preclinical testing has confirmed strong x-ray fluoroscopic and CBCT radiopacity (Figure 4). This technology may provide intraprocedural real-time confirmation of tumor targeting. On an investigational basis, dosimetry software algorithms have been modified and utilized to detect, map, and quantify radiopacity on CBCT (Figure 4B). Use of this software and proprietary calibration phantoms may allow for the ability to quantify the mass of microspheres deposited in tumor tissue at time of treatment, and by using average specific activity, the dose delivered to tumor could potentially be calculated as either critical threshold levels or, ultimately, as total dose delivered to tumor. The deposited microspheres could additionally serve as fiducials to guide complementary treatments such as thermal ablation or external beam radiation.

Courtesy of Terumo Europe.



**Figure 5.** The Occlusafe occlusive microballoon catheter with end-hole balloon allows for complete proximal occlusion during administration. Small internal diameter may present challenges with high-volume particle administration.



Courtesy of Embolic, Inc.

**Figure 6.** The Sniper high-flow microcatheter with end-hole balloon and preshaped tips allow for complete proximal occlusion during administration.

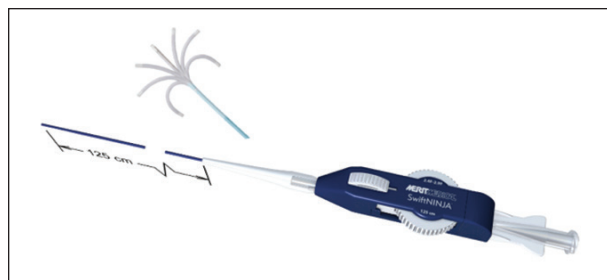
Courtesy of TriSalus Life Sciences



**Figure 7.** The Surefire infusion system with unique basket pin-pull deployment system provides both proximal protection/antireflux, with continued systolic perfusion, allowing for antegrade flow and delivery. High flow (requires > 0.054-inch inner diameter guide or base catheter) and standard internal diameter models (0.038-inch compatible).

### ADVANCEMENTS IN MICROCATHETER SYSTEMS

As our understanding of dosimetry continues to evolve, so have the delivery systems. Recent publica-



Courtesy of Merit Medical Systems, Inc.

**Figure 8.** The SwiftNinja steerable microcatheter is an actively steerable microcatheter through a ratchet wheel, allowing for selection and repositioning without a wire or removal of device. Limited lengths preclude the transradial approach.

tions have demonstrated that alteration of inflow dynamics, through decreases in inflow pressure or occlusion, may result in diversion and optimization of particle deposition in the tumor.<sup>26</sup> Furthermore, steerable microcatheter platforms allow for multi-point administration without the dangers of multiple microcatheters. Due to the advances in design, new generations of microcatheters allow for not only more precise selection for anatomic optimization of payload

delivery but also the ability to alter pressure dynamics to maximize delivery to the tumor (in the case of low vascular capacitance tumors) or maximize exposure to the targeted volume as per A-TARE. Figures 5 through 8 show some of these devices, and their features are summarized in Table 3.

## CONCLUSION

Growing evidence demonstrating positive clinical outcomes with Y-90 radioembolization therapy, the new mindset to achieve cure using Y-90 ablative techniques, recent software and microcatheter developments, and the promising future of investigational imageable radiomicrospheres will further our understanding of Y-90 therapy and ultimately should improve patient outcomes. ■

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