Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality assurance procedures for ^{90}Y microsphere brachytherapy in the treatment of hepatic malignancies

William A. Dezarn
Medical Radiation Physics Inc., Milford, Ohio 45150

Jeffery T. Cessna
Physics Laboratory, National Institute of Standards and Technology, Gaithersburg, Maryland 20899

Larry A. DeWerd
Department of Medical Physics, University of Wisconsin-Madison, Madison, Wisconsin 53705

Wenzheng Feng
Heart and Vascular Center, Cardiology and Interventional Radiology, William Beaumont Hospital, Royal Oak, Michigan 48073

Vanessa L. Gates
Division of Interventional Radiology, Department of Radiology, Northwestern Memorial Hospital, Chicago, Illinois 60611

James Halama
Loyola University Medical Center, Maywood, Illinois 60153

Andrew S. Kennedy
Wake Radiology Oncology Services, Cary, North Carolina 27518

Subir Nag
Kaiser Permanente Radiation Oncology, Santa Clara, California 95051

Mehrdad Sarfaraz
Department of Radiation Oncology, Greater Baltimore Medical Center, Baltimore, Maryland 21204

Varun Sehgal
Department of Radiation Oncology, University of California, Irvine Medical Center, Orange, California 92868

Reed Selwyn
Radiology and Radiological Sciences Department, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814

Michael G. Stabin
Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, Tennessee 37232

Bruce R. Thomadsen
Department of Medical Physics, University of Wisconsin-Madison, Madison, Wisconsin 53705

Lawrence E. Williams
Radiology, City of Hope Medical Center, Duarte, California 91010

Riad Salem
Division of Interventional Radiology, Department of Radiology, Northwestern Memorial Hospital, Chicago, Illinois 60611

(Received 8 April 2011; revised 16 June 2011; accepted for publication 17 June 2011; published 1 August 2011)

Yttrium-90 microsphere brachytherapy of the liver exploits the distinctive features of the liver anatomy to treat liver malignancies with beta radiation and is gaining more wide spread clinical use. This report provides a general overview of microsphere liver brachytherapy and assists the treatment team in creating local treatment practices to provide safe and efficient patient treatment. Suggestions for future improvements are incorporated with the basic rationale for the therapy and currently used procedures. Imaging modalities utilized and their respective quality assurance are discussed. General as well as vendor specific delivery procedures are reviewed. The current dosimetry models are reviewed and suggestions for dosimetry advancement are made. Beta activity standards are reviewed and vendor implementation strategies are discussed. Radioactive material licensing and radiation safety are discussed given the unique requirements of microsphere brachytherapy. A general, team-based quality assurance program is reviewed to provide guidance for the

creation of the local procedures. Finally, recommendations are given on how to deliver the current state of the art treatments and directions for future improvements in the therapy. © *2011 American Association of Physicists in Medicine*. [DOI: 10.1118/1.3608909]

Key words: yttrium, microsphere, brachytherapy, radioembolization, liver, dosimetry, imaging

I. INTRODUCTION

Yttrium-90 microsphere brachytherapy of liver cancers takes advantage of the unique vascular system of the liver. In normal liver tissue, approximately 70%–80% of the organ's blood flow is supplied by the portal vein, and the hepatic artery accounts for the rest. This contrasts with both hepatocellular carcinoma (HCC) and metastatic tumors in the liver, which have approximately 80%–100% of their blood flow supplied by the hepatic artery.[1] This difference in perfusion is exploited by microsphere brachytherapy, whereby, radioactive microspheres doped with a beta-emitting radionuclide are used to both embolize and irradiate tumors in the liver by delivering the microspheres through the hepatic artery to selectively target malignant disease.

In contrast, the key limitation in any application of external beam radiation to the liver is the lower tolerance of normal liver parenchyma to radiation compared to the dose required to destroy tumors.[2] The maximum external beam acceptable dose to the whole liver of 35 Gy delivered in 1.8 Gy/day fractions[3] is far below that which is required to destroy solid tumor lesions, estimated at greater than 70 Gy.[4] Therefore, patients selected for conformal external beam radiation therapy must have tumors that are well defined on CT or MR and the ability to treat safely is limited by lesion number, distribution, and location. Microsphere brachytherapy provides an alternative means of treatment for patients.

Treatment with ^{90}Y microspheres is based on cross-sectional images and arteriograms for each patient. The work-up includes triple-phase contrast CT and/or contrast enhanced magnetic resonance (MR) imaging of the liver for assessment of tumor and nontumor volumes, portal vein patency, and extent of extrahepatic disease. Serum chemical analyses evaluate hepatic and renal function and determine the presence and magnitude of elevation of tumor markers. The clinical practice guideline recommendations for ^{90}Y microsphere brachytherapy were recently published by the Radioembolization Brachytherapy Oncology Consortium (REBOC).[5] The procedure entails the injection of embolic particles loaded with a radionuclide using transvascular approaches. There are two components to the procedure:

(1) Embolization: injection of permanent embolic particles and vessel embolization, and
(2) Brachytherapy: delivery of the brachytherapy device (e.g., resin or glass microspheres).

It should be noted that different disciplines use slightly different names for this procedure. From the brachytherapy perspective, the terms microsphere brachytherapy and the microbrachytherapy are used. Here, the emphasis is on the permanent radioactive implant component of the procedure. Interventional radiology uses the term radioembolization which emphasizes the embolization procedures they typically perform. The practitioners of this procedure should be aware of the differences both in discipline and in practical use. The term microsphere brachytherapy will be used in this report.

I.A. Microsphere rationale

The delivery of radioactive microparticles by a patient's vasculature dates back to the 1940s, however, the use of microspheres embedded with a beta-emitting radionuclide, typically ^{90}Y, has only become clinically relevant since the middle-1980s. Kennedy *et al.*[6] provide a comprehensive review of radioactive microsphere development and utilization. As stated earlier, the hepatic artery also preferentially provides tumors with their blood flow. Thus, the hepatic artery provides a natural pathway to tumor cells, while largely missing normal liver cells.

Currently, two ^{90}Y-microsphere products are available commercially worldwide: one is composed of ^{90}Y doped resin (SIR-Spheres®; Sirtex Medical Limited, North Sydney, Australia) and the other incorporates ^{90}Y in a glass matrix (TheraSphere®; Nordion Inc., Ottawa, Canada) (see Table I). Neither type of microsphere demonstrates leaching of ^{90}Y at levels considered potentially important. Erbe and Day[7] present data for glass microspheres while the SIR-Spheres® User Manual notes that trace amounts of radioactivity, 25–50 kBq

TABLE I. Properties of commercially available ^{90}Y microspheres.

Description item	SIR-Spheres®	TheraSphere®
Sphere material	Resin	Glass
Sphere diameter (μm)	20–60	20–30
Activity in single vial (GBq)	3	six sizes: 3, 5, 7, 10, 15, and 20
Number of spheres per vial	40–80 × 10^6	six sizes: 1.2–8 × 10^6
Density (g/cm^3)	1.6	3.29[a]
^{90}Y activation mode	Carrier-free	Reactor
Assumed activity per sphere (Bq)	50	2500
Shelf life	24 h after calibration	12 days after calibration
^{90}Y average decay energy	0.9267 MeV per disintegration	
^{90}Y half-life	2.6684 days	

[a]US Patent 5,302,369.

L^{-1} per GBq delivered, have been detected in patient urine in the past.

Most often, the clinical indication for using microsphere brachytherapy is colon adenocarcinoma metastatic to the liver persisting despite optimal chemotherapy. Patients with primary HCC are also eligible to be treated with microspheres. Clinical experiences in a number of centers have demonstrated the safety, efficacy, and preferred methodological techniques of the microsphere therapy.[5,8–12] However, unlike procedures that use sealed sources common to brachytherapy (^{137}Cs, ^{103}Pd, ^{125}I, etc.), the activity and total number of individual sources cannot be verified uniquely for ^{90}Y microspheres. No standardized methods in microsphere brachytherapy exist for source activity measurement independent of the manufacturers. Only approximate methods exist for location confirmation and actual dosimetry remains elusive. This report presents American Association of Physicists in Medicine (AAPM) recommended methods and standards.

I.B. Liver anatomy

To understand the complexities of microsphere brachytherapy dosimetry requires knowledge of the hepatic vascular physiology and anatomy. The liver is the largest gland of the body with a normal adult mass range of 1.7–3.0 kg. It is wedged-shaped and is situated in the upper right portion of the abdominal cavity under the diaphragm. The liver is divided into two lobes, the right lobe contains about 70% of the liver mass and the left lobe contains about 30% of the liver mass. The hepatic artery and the portal vein provide the liver's blood supply. The hepatic artery normally arrives from the celiac trunk and delivers oxygenated blood, which accounts for approximately 20%–30% of the liver's blood supply. Venous blood is delivered from the gastrointestinal tract to the liver via the hepatic portal vein. Branches of this vein pass between lobules and terminate in the sinusoids. Lobules are hexagonally shaped functional units of the liver and sinusoids are small blood vessels between rows of liver cells. The portal vein supplies the remaining 70%–80% of the liver's blood supply. Blood leaves the liver by entering the central vein in each lobule, which drains into the hepatic vein. The hepatic vein is a conglomeration of short veins originating in each lobe, which ultimately drain into the inferior vena cava.

Various systems exist to describe the segmental anatomy of the liver. One of the most widely used systems is the Couinaud classification.[13] This system divides the liver into eight functionally independent segments. Each segment has its own blood flow and biliary drainage system. The right hepatic vein divides the right hepatic lobe into anterior and posterior segments. The middle hepatic vein is the dividing line between the left and the right lobes. A plane running from the inferior vena cava to the gallbladder fossa can be imagined to create this division. The left hepatic vein divides the left lobe into medial and lateral parts. Finally, the portal vein divides the liver into upper and lower segments.

TABLE II. Indications/contraindications for microsphere brachytherapy.

Indications	Contraindications
Unresectable hepatic primary or metastatic disease	Limited hepatic reserve
Tumor is liver-dominant	Elevated bilirubin (greater than 2 mg/dl)
Life expectancy is at least 3 months	Estimated lung dose greater than 30 Gy
	Uncorrectable extrahepatic deposition

The utility of the Couinaud classification system is that each segment acts as a self contained unit. In a surgical intervention, resection of a given segment can be accomplished without damaging the remaining segments. To maintain a viable liver after surgery, the resection lines should parallel the hepatic veins at the edges of the segments while maintaining the centrally located portal veins, bile ducts, and hepatic arteries of the unresected segments. An analogous process can be achieved by advanced users in microsphere brachytherapy of the liver if the delivery catheter is carefully placed to deliver radioactive microspheres only to the desired segments while leaving the other segments to provide liver function for the patient after treatment.

I.C. Indications/contraindications

Success in treatment of tumors in the liver by loco-regional therapy relies on the presence of appropriate indications that ensure patients receive beneficial evidence-based therapy. Since, each microsphere product has different treatment approval criteria and properties, each patient case should be individually evaluated to determine which product is best suited for the disease presentation. Table II lists some of the most general indications and contraindications for microsphere brachytherapy as detailed in the REBOC report. Please refer to manufacturer documentation for the most current indications and contraindications.

II. IMAGING CONSIDERATIONS

Imaging of liver disease is an important aspect of both diagnosis and following patient response post treatment. The following sections detail some possible imaging protocols for various modalities. As with all patient tracking studies, consistency in the imaging protocol course is exceedingly important. All efforts should be made to image a given patient with the same protocols throughout diagnosis, treatment, and follow-up. Local protocols defining the appropriate imaging modality to use for a given disease presentation should be developed to prevent unnecessary imaging exams. Periodic review of such local protocols should be made to incorporate changes in imaging standards.

The medical images in this section are from the same patient at the same axial plane before microsphere brachytherapy. Exact tumor correlations cannot be made here given the time differences between each image set. These images are a small sample of the available variations but are

TABLE III. Triple-phase CT imaging protocol.

Parameters	Suggested values
Start location	All phases—above diaphragm
End location	All phases—though pelvic brim
Slice thickness	2.5 mm
Slice spacing	2.5 mm
Gantry angle	0°
Contrast injection rate	3–5 ml s^{-1}
Non contrast image set	Prior to any contrast studies
Arterial phase image set	Use CT bolus tracking or 20–25 s delay post contrast injection
Venous phase image set	~70 s delay post contrast injection

intended to illustrate the different information each imaging modality brings to the patient treatment decision making process.

II.A. Computed tomography (CT)

Triple-phase CT provides the fastest and most reproducible imaging of the liver for volume and tumor burden calculation. A triple-phase CT is a protocol for three CT image sets. An initial noncontrast CT image set is followed by IV contrast injection and two more CT image sets time delayed as described in Table III. Proper imaging and volume calculation are essential for dosimetry purposes. When drawing regions of interest and calculating volumes, the middle hepatic vein should be used as the anatomic delineator between the right and the left lobes. If the middle hepatic vein cannot be seen, then the gallbladder fossa and its axis relative to the liver may be used. This technique assumes standard arterial anatomy with single right and left hepatic arteries. If variant anatomy is angiographically observed, for example, an accessory right hepatic artery, then accurate angiographic correlations must be performed when drawing the regions of interest for lobar or segmental volumes. This will increase the accuracy of the volumes obtained.

The pretreatment CT scan is of the abdomen to evaluate liver, stomach, and intestine. Table III outlines a possible CT imaging protocol that assumes the use of a power contrast injector. Figure 1 illustrates the tumor enhancement in the anterior-medial liver region that occurs in the venous phase of a three phase CT data set.

II.B. Positron emission tomography (PET)

Fluorine-18 FDG PET examinations provide physiological data about the tumor and supplement other imaging modalities. A PET study will identify increased metabolic activity related to the ^{18}F-FDG uptake. Since metabolic activity is the intended imaging marker, patient compliance with preimaging fasting protocols is critical.

Whole-body PET scans for liver are typically ordered 1 week before the microsphere brachytherapy procedure. The patient fasts at least 4 h before scanning and should have normal blood glucose levels at the time of FDG injection. Image slices are acquired from the base of brain to the upper thigh 1 h after IV injection of 370–555 MBq (10–15 mCi) of ^{18}F-FDG. Such a scan will typically take 20–30 min. Ideally a PET/CT imaging scanner will be used and both the PET and triple-phase CT imaging for treatment planning can be completed in one session.

Figure 2 illustrates the PET/CT of the demonstration patient. A slight enhancement can be seen in both images of the anterior-medial region corresponding to the enhancements noted in Fig. 1.

II.C. Magnetic resonance (MR)

MR imaging provides additional soft tissue contrast to supplement the CT image set. Various imaging protocols, such as the ones listed in Table VI, can aid in delineating tumor volumes. Contrast studies with gadolinium (Gd) can provide additional enhancement as needed. Given all of the possible MR imaging protocols, it is even more important to use a consistent imaging protocol set with MR for a particular patient. MR imaging can also be used for organ volume measurement as mentioned in Sec. II A for CT imaging.

Figure 3 displays some of the MR images for the demonstration patient. The anterior-medial lesion that was present on CT and PET can be seen here also. There is additional enhancement in the right-lateral section of the liver for the MR. Further inquiry into the time line of these images would be necessary to determine how this MR image data will influence the treatment plan or assessment of a patient.

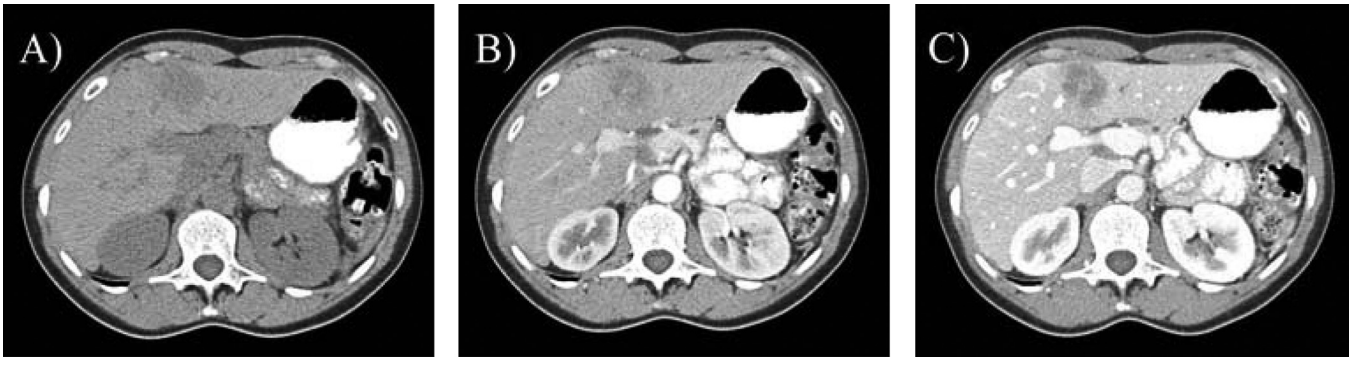

FIG. 1. Representative three phase image set. (A) Noncontrast initial image, (B) arterial phase, and (C) venous phase. Window/level is 380/10 for the three images.

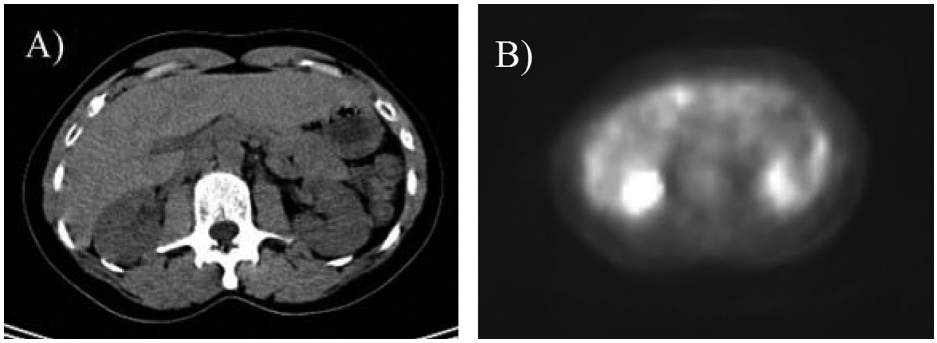

FIG. 2. Representative PET/CT image. (A) CT and (B) ^{18}F-FDG PET image sets.

II.D. Gamma camera imaging

A serious concern in microsphere brachytherapy for hepatic cancers is the possibility of arteriovenous shunting from the arterial deliver point directly to the lungs or other body sites.[14] Once the delivery point has been identified (see Sec. III A), 2–4 mCi (74–148 MBq) of ^{99m}Tc macroaggregated albumin (MAA) are infused into the liver as a surrogate for the ^{90}Y microspheres.

Several manufacturers provide MAA kits where each reconstituted vial of 10 ml solution contains $4–8 \times 10^6$ aggregated albumin particles. 90% or better is between 10 and 90 μm in diameter but no particles exceed 150 μm. Quality control of the radiopharmaceutical labeling process requires that at least 90% of the ^{99m}Tc-pertechnetate be bound to the albumin at the time of preparation and remain bound for 6–12 h depending on the manufacture specifications. The albumin fragments are fragile and their distribution is purely a mechanical process that depends on blood flow through the arterioles and capillaries. Erosion and fragmentation occur making the capillary occlusion within the organs temporary. Some broken particles that are below the size of 10 μm may clear the lung capillary bed and accumulate through the reticuloendothelial system with eventual excretion through the kidneys. Over time, de-labeled ^{99m}Tc will also be visualized in the thyroid, stomach, and kidneys.

TABLE IV. MR imaging protocol descriptions.

Scan name	MR sequence description
STIR	Short T1 inversion recovery
In and opposed phase	In-phase and opposed-phase T1-weighted gradient-echo
TSE T2 FS	Turbo spin echo T2 weighted with fat saturation
HASTE	Half Fourier acquisition single shot turbo spin echo
MRCP	Magnetic resonance cholangiopancreatography
T1 3D VIBE Pre contrast	T1 weighted volumetric interpolated breath hold examination
T1 3D VIBE dynamic	T1 weighted VIBE with Gd contrast given to patient
T1 3D VIBE delayed	T1 weighted VIBE delayed after Gd contrast given to patient

The effective half-life of ^{99m}Tc MAA in the lungs is approximately 4 h.[15] For these reasons, it is recommended that imaging begin within at least 60 min of administration and not to exceed 4 h. Imaging outside of this time window may artificially inflate the lung shunt estimation.

Gamma camera imaging can also provide data regarding the ratio of tumor to normal liver tissue uptake. This data could potentially be appropriate in dose calculations as described in Sec. IV B. Ho *et al.*[16] provide specific details on measuring the tumor to normal liver ratio.

II.D.1. Planar

Whole-body planar imaging is done with a moving, large-field-of-view gamma system with low energy, high resolution, parallel-hole collimators capable of obtaining conjugate anterior and posterior images of the patient. A whole-body scan from the top of the neck to the bottom of the hips is sufficient. A whole-body planar image is illustrated in Fig. 4 with typical scan parameters listed in Table V. Static planar imaging captures the liver and lungs without moving the detectors during image acquisition. Typically one or two static detector positions will cover the desired patient anatomy. Regions-of-interest (ROI) over the whole liver and lungs are drawn directly on the image as seen in Fig. 4. The ROI counts for each region are recorded and the lung shunt is calculated as described in Sec. III B.

II.D.2. Single photon emission computed tomography

SPECT is a three-dimensional (3D) activity image set obtained by rotating gamma detectors around a patient and reconstructing the activity distribution. Table VI gives typical SPECT parameters for microsphere brachytherapy. In SPECT based dosimetry, the ^{99m}Tc MAA particles are used as surrogates for microspheres to assess the microsphere distribution within the liver. However, it should be emphasized that the MAA particles are not exactly the same size as microspheres and are irregular in shape. The assumption of similarity between the microspheres and MAA particle distributions introduces less error into dose calculations than the assumption of uniform activity distribution.

A SPECT image for the demonstration patient is displayed in Fig. 5. ^{99m}Tc MAA uptake is seen in the anterior-

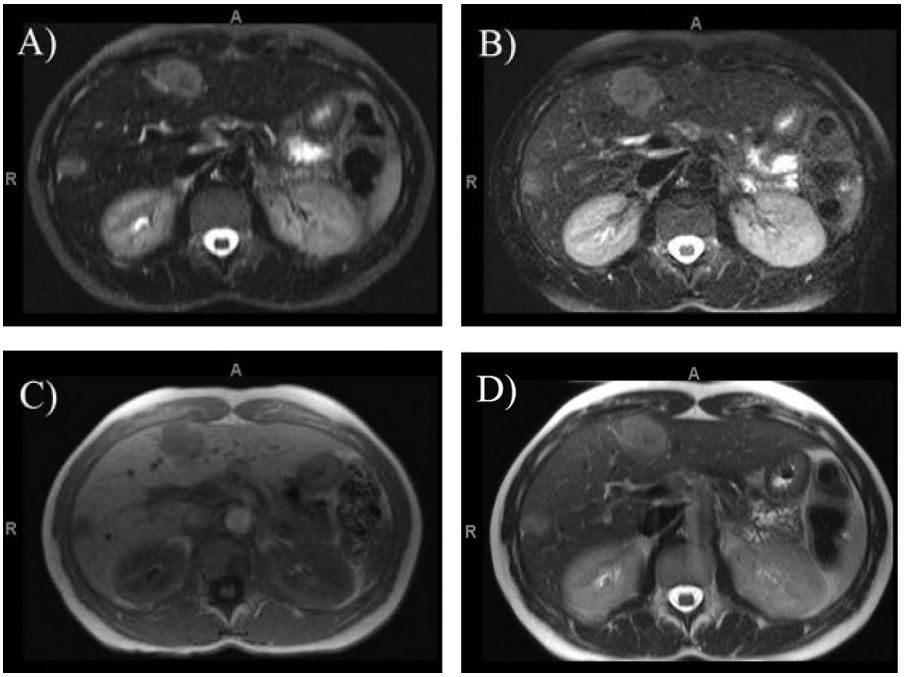

FIG. 3. Subset of possible MR image sets. (A) STIR, (B) TSE T2, (C) in and opposed phase, and (D) HASTE.

medial region similar to where the other imaging modalities displayed the tumor. Software tools that perform three-dimensional registration of image sets can provide geometrical correlations of the activity data with patient anatomy. The uncertainty in the geometrical correlation of the SPECT data as well as photon emission attenuation issues call for the use of SPECT/CT units. Using a SPECT activity distribution correlated with patient anatomy will allow for image-based, patient-specific dosimetry calculation as described in Sec. IV C.

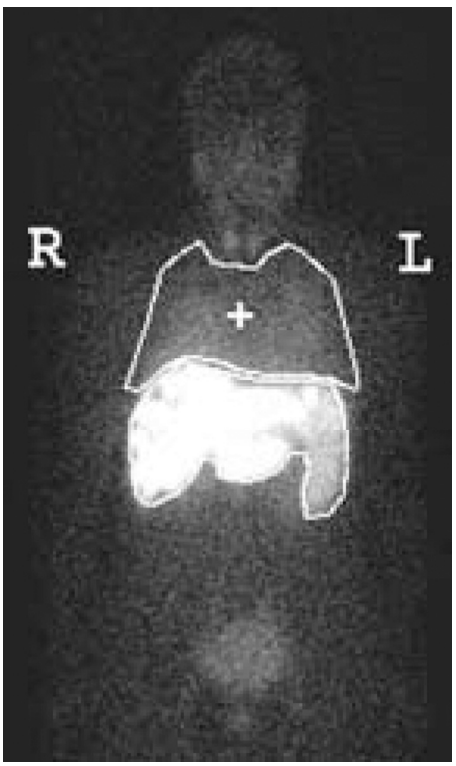

FIG. 4. Planar gamma camera image with ROI drawn.

III. DELIVERY PROCEDURES OF MICROSPHERE PRODUCTS

III.A. Basic angiographic procedure

Once a patient has been selected as a potential candidate for microsphere brachytherapy, an initial angiographic evaluation is performed within two weeks prior to the anticipated treatment date. A catheter is placed percutaneously via patient's femoral artery and is guided to the hepatic artery under fluoroscopy by the interventional radiologist. The catheter is secured in place after verifying its position by digital subtraction angiography (DSA). Fluoroscopic imaging is also required during the microsphere delivery.

There are three main purposes of the angiographic evaluation: (1) guide the delivery catheter positioning, (2) evaluate the pretreatment blood flow, and (3) determine the procedure termination for the resin microspheres. The initial study includes: abdominal aortogram, superior mesenteric and celiac arteriogram, selective right and left hepatic arteriogram.

TABLE V. Whole-body planar imaging protocol, using ^{99m}Tc energy specification.

Parameters	Suggested values
Zoom	As small as needed to image all activity
Counting time	5 min or 1×10^6 counts
Scan speed	20 cm per min
Energy window	15% window on 140 keV peak
Collimator	Low energy

TABLE VI. SPECT imaging protocol for ^{99m}Tc preimplant and ^{90}Y bremsstrahlung postimplant studies.

Parameters	^{99m}Tc	^{90}Y
Acquistion matrix	128 × 128	128 × 128
Azimuth angles	64–128	64–128
Counting time	15–30 s per angle	30 s per angle
Energy window	140 keV/15%	80 keV/30%
Collimator	Low energy	Medium energy

These angiograms should be performed as a minimum and further angiograms may be required depending on the results of these studies, as for example, when aberrant anatomy is noted. Figure 6 illustrates some of the angiograms that should be performed to assess the viability of a patient's treatment. This is done primarily to document the visceral anatomy, identify anatomic variants, and isolate the hepatic circulation by occluding extrahepatic vessels.

To avoid extrahepatic microsphere deposition, prophylactic embolization of all extrahepatic vessels at the time of assessment including the gastroduodenal and right gastric, as well as other extrahepatic vessels, is recommended by most centers. This standardized angiographic approach to the microsphere brachytherapy patient has been previously published.[17] Following embolization of these vessels, the ^{99m}Tc MAA particles are infused with the catheter placed in the proper hepatic artery to assess the magnitude of the pulmonary shunt. Repeat angiograms should be performed before treatment to verify that the arterial anatomy has not changed from the initial assessment.

III.B. Lung shunt—^{99m}Tc-MAA

Following the pretreatment angiographic assessment, the treatment location is identified. A catheter is placed in this location and an intraarterially administered ^{99m}Tc MAA injection is used to predict the distribution of the ^{90}Y-microspheres. Whole-body gamma camera imaging of ^{99m}Tc MAA provides data about the shunting of labeled particles to the lungs. The lung shunt ratio is the quotient of the total lung counts (C_{Lung}) to the sum of lung and liver counts (C_{Liver}).

$$L = \frac{C_{Lung}}{C_{Lung} + C_{Liver}} \quad (1)$$

Patients who have considerable shunting of the activity to the lungs, typically greater than 20% shunt value or 16.2 mCi (600 MBq) delivered lung activity, should be disqualified from the use of microsphere brachytherapy due to the possibility of radiation pneumonitis.[14] This activity is determined by assuming a maximum dose of 30 Gy to 1 kg lung mass in Eq. (4). However, activity reduction methods have been suggested[18] to maintain the lung dose below 30 Gy. The use of nonradioactive sphere embolization of the liver to reduce lung shunt, and thus lung dose is also a practiced technique. The use of ^{90}Y-microspheres is also contradicted in patients with deposition to the gastrointestinal tract, unless it can be eliminated by occlusion of suspected arterial branches using angiographic techniques. SPECT imaging of the liver can also provide information regarding the liver treatment volume and preferential uptake of the labeled particles in liver tumors.

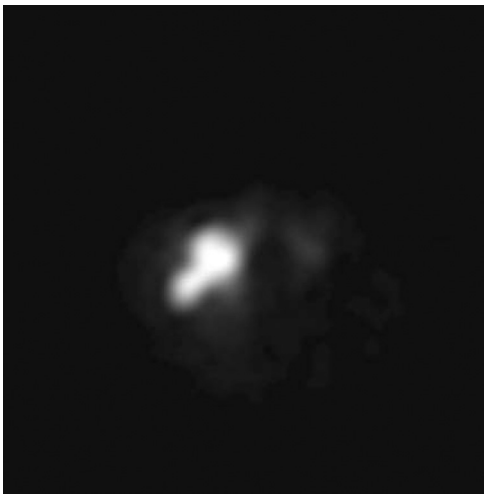

FIG. 5. Representative axial SPECT image.

III.C. SIR-Spheres® specifics

SIR-Spheres® resin microspheres can be implanted via the hepatic artery in one of two ways: (1) an implanted catheter with port, or (2) transfemorally. In current clinical practice, the transfemoral implant is widely used. The dedicated delivery apparatus must be used, providing a safe environment for the implant procedure. Use of the delivery apparatus is mandatory in the United States of America. The US Food and Drug Administration (FDA) approval of SIR-Spheres® can be accessed at their website.[19] SIR-Spheres® are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intrahepatic artery chemotherapy of Floxuridine (FUDR). SIR-Spheres® consist of resin based biocompatible microspheres tagged with ^{90}Y and are considered as a permanent brachytherapy device. SIR-Spheres® are provided in a vial containing approximately 3 GBq of activity in a 5 ml solution of sterile water. SIR-Spheres® must be administered within 24 h after the manufacturer's calibration time stamp. See Table I for detailed data. Additional information regarding patient activity preparations is provided in Sec. VII of this report.

III.D. TheraSphere® specifics

TheraSphere® consists of insoluble glass microspheres, where ^{90}Y is an integral constituent of the glass. TheraSphere® is supplied in 0.6 ml of sterile, pyrogen-free water contained in a 1.0 ml v-bottom vial secured within a 12 mm clear acrylic vial shield. TheraSphere® activity vials are produced weekly by the manufacturer with the activity calibrated for 12:00 EST on Sunday of the specified week. TheraSphere® may be administered up to 12 days following

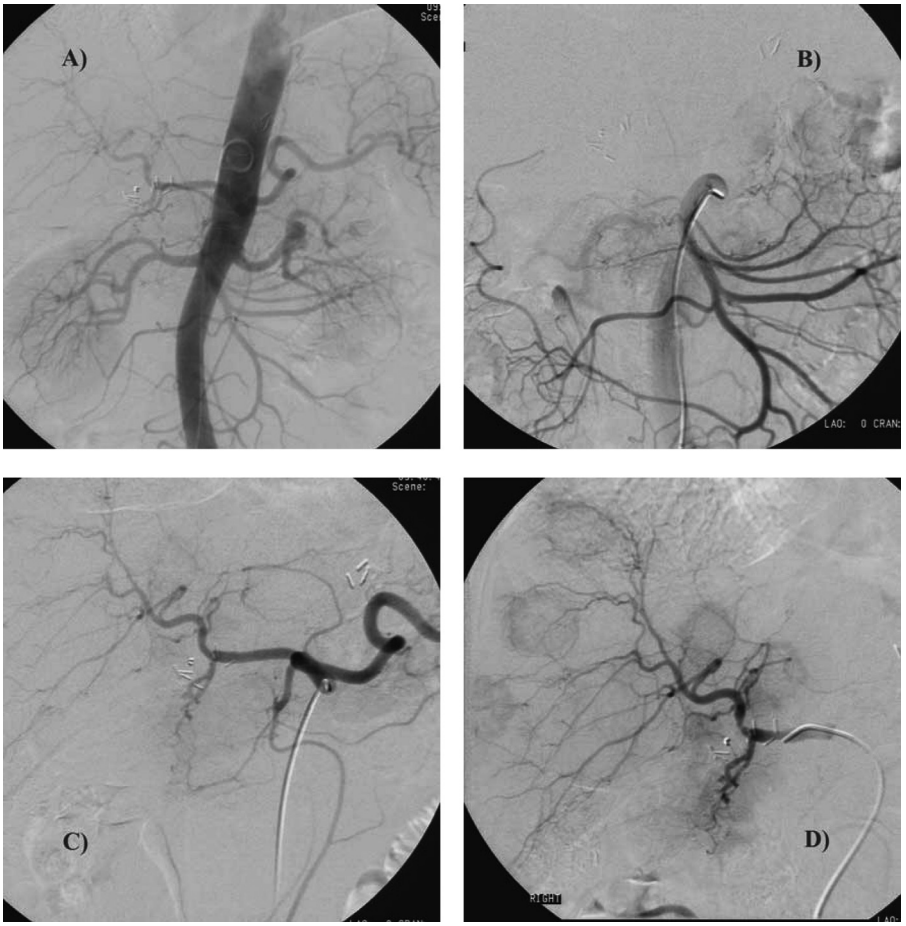

FIG. 6. DSA images taken during assessment of patient. (A) Abdominal aortogram, (B) superior mesenteric angiogram, (C) celiac angiogram, and (D) hepatic and gastroduodenal angiogram, note that some of the hypervascular regions around the tumors can be seen.

the manufacturer's calibration time stamp. TheraSphere® is administered directly from the activity vial using a single use sterile administration set supplied by the manufacturer. See Table I for detailed data.

TheraSphere® is approved in the US under a Humanitarian Device Exemption (HDE) and as such, the US FDA requires Institutional Review Board (IRB) oversight of its use at each institution. The US FDA approval of TheraSphere® can be viewed at their website.[20] US FDA HDE approval only demonstrates that the product can be used safely, but makes no claims about its effectiveness. TheraSphere® is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately position hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion when clinical evaluation warrants the treatment. Please note that this is not an investigational device and is commercially available qualifying for reimbursement through government and private providers. The manufacturer provides a HCC protocol template to facilitate IRB review. A current IRB approval letter covering all the institutional treatments of TheraSphere® is required by the manufacturer.

III.E. Post implant bremsstrahlung confirmation

Planar or SPECT images of the liver can be acquired using ^{90}Y bremsstrahlung to confirm the microsphere deposition in the liver. A typical configuration for imaging bremsstrahlung from ^{90}Y is detailed in Table VI. Given the low count rate of the bremsstrahlung, quantitative assessment is difficult if not impossible. Current usage of the post implant bremsstrahlung SPECT scan is a qualitative assessment of the final location of the microspheres. SPECT imaging is preferred over planar imaging for post implant microsphere deposition assessment because organs adjacent to the liver can be more easily identified. Use of post implant SPECT imaging also allows for documentation that a medical event has not occurred.

IV. ^{90}Y BETA DOSIMETRY

IV.A. Overview

Yttrium-90 is a beta emitter with an average energy of 0.9267 ± 0.0008 MeV and a half-life of 2.6684 ± 0.0013 days.[21] The maximum range of the ^{90}Y beta radiation in water is 11 mm.[22] 90% of the emitted energy is absorbed within a sphere of water with a radius of 5.3 mm.[23] For completeness,

it should be noted that ^{90}Y decays over 99.98% of the time via β^- decay to the ground state of ^{90}Zr. A small fraction of the radionuclide ($\sim$0.01%) β^- decays to the excited 0^+ state of ^{90}Zr, which subsequently decays to the ground state via internal conversion, internal pair production (e^+ e^-), or two-photon deexcitation. The miniscule internal pair production branching ratio[24] is $(31.86 \pm 0.47) \times 10^{-6}$ and might be useful for the nondestructive assay of ^{90}Y.

The average absorbed dose to the liver and tumor is currently estimated by assuming uniform uptake in these source tissues. Measurement of the whole-tissue uptake may be made by a variety of methods including the geometric mean technique.[25] Lung dose may be estimated using the shunting fraction of the activity and again assuming uniform distribution in the pulmonary space. Such dose estimates are averages for whole organs and tumors.

Bremsstrahlung and beta cross-organ doses (e.g., from tumor to liver) can be added to the above procedure if activity data can be obtained in voxel format. With conventional gamma cameras and ^{99m}Tc MAA as the tracer, there are several imaging methods that can provide such information, such as the CT-assisted matrix inversion (CAMI) technique for 2D images and SPECT imaging for 3D images.[26] Given patient-specific 3D voxel activity distributions, ^{90}Y kernels are available to generate the dose to adjacent voxels in both normal tissues and tumor sites. These kernels include bremsstrahlung effects, but do not take into account bone-soft tissue inhomogeneities. The latter could be significant in lung–rib interfaces and would require Monte Carlo radiation transport calculations.

IV.B. Current dosimetry models

The schema developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine is the current dosimetry standard for ^{90}Y microspheres.[27] This schema assumes a uniform distribution of the activity throughout the mass of interest. The dose rate in a generic tissue mass, $\dot{D}$, is given by

$$\dot{D} = k\frac{A}{m}\langle E\rangle, \tag{2}$$

where k is a constant to yield the dose rate in desired units, A is the source activity, m is the mass of tissue in which the radiation is absorbed, and $\langle E\rangle$ is the average energy emitted per nuclear transition. For beta particle decay, it is also assumed that there is no production of bremsstrahlung and all of the decay energy is completely absorbed within the mass. The radioactive source is permanently implanted in the patient with no removal from the region, so the effective half-life is simply the radioactive half-life. The absorbed dose, calculated by integrating the dose rate over all time, is then given by the following:

$$D = \frac{k\langle E\rangle A_0}{m}\int_0^\infty e^{-\ln(2)t/T_{1/2}}dt = k\frac{A_0}{m}\langle E\rangle\frac{T_{1/2}}{\ln(2)}. \tag{3}$$

where A_0 is the activity in the mass of interest and $T_{1/2}$ is the half-life of the radioactive source. The total number of disintegrations, also sometimes referred to as cumulated activity, is equal to $A_0 \times T_{1/2}/\ln(2)$. Assuming that all of the energy of the β^- decay is absorbed in the given tissue, the constant terms can be calculated taking the given physical values and their published statistical uncertainties

$$\begin{aligned} k\langle E\rangle\frac{T_{1/2}}{\ln(2)} &= \left(\frac{0.9267\ \text{MeV}}{\text{dis}}\right)\left(\frac{1.6022\text{x}10^{-13}\text{J}}{\text{MeV}}\right) \\ &\times \left(\frac{\text{Gykg}}{\text{J}}\right)\left(\frac{10^9\ \text{dis}}{\text{sGBq}}\right)\left(\frac{86400\ \text{s}}{\text{day}}\right) \\ &\times \left(\frac{2.6684\ \text{day}}{\ln(2)}\right) \\ &= 49.38 \pm 0.05\frac{\text{Gykg}}{\text{GBq}} \end{aligned}$$

giving

$$D[\text{Gy}] = 49.38\frac{A_0[\text{GBq}]}{m[\text{kg}]}. \tag{4}$$

The radiation absorbed doses to tumor, lung, and normal liver tissue can be further calculated based on a partition model which is described in the following. Assume that all of the administered activity is deposited in the normal liver, tumor, or lungs giving

$$A_{\text{Total}} = A_{\text{NormalLiver}} + A_{\text{Tumor}} + A_{\text{Lung}}. \tag{5}$$

The definition of the lung shunt fraction, L, gives

$$A_{\text{Lung}} = A_{\text{Total}}L. \tag{6}$$

Thus the dose to the lungs is given by

$$D_{\text{Lung}} = 49.38\frac{A_{\text{Total}}}{m_{\text{Lung}}}L. \tag{7}$$

In tumors that can be easily delineated on imaging studies, the tumor-to-liver activity uptake can be estimated from the ^{99m}Tc-MAA study. A ROI is drawn on the anterior and posterior images encompassing the tumor. The same ROI is moved over the normal liver, on a region that exhibited relatively uniform activity uptake. The tumor-to-liver activity uptake ratio is calculated as the tumor-to-liver counts over the corresponding ROIs. Mathematically the tissue/normal activity ratio, T/N, is

$$T/N = (A_{\text{Tumor}}/m_{\text{Tumor}})/(A_{\text{NormalLiver}}/m_{\text{NormalLiver}}). \tag{8}$$

Following some algebra and assuming that the whole liver is the sum of the normal liver and the tumor, the dose to the normal liver can be written as

$$D_{\text{NormalLiver}} = \frac{49.38A_{\text{Total}}(1-L)}{m_{\text{NormalLiver}} + T/N\ m_{\text{Tumor}}}. \tag{9}$$

Similarly the dose to the tumor can be written

$$\begin{aligned} D_{\text{Tumor}} &= \frac{49.38A_{\text{Total}}(1-L)}{\frac{1}{T/N}(m_{\text{NormalLiver}} + T/N\ m_{\text{Tumor}})} \\ &= T/N\ D_{\text{NormalLiver}}. \end{aligned} \tag{10}$$

The lung and normal liver limiting activities can be determined by setting a dose limit and solving the above equations for activity. These equations are called the partition model in some of the literature.[28,29] It should be noted that while these equations describe how to calculate the dose delivered from an administered activity, the vendor has their own methodology for determining the activity to be administered as discussed in Secs. VII B 1 and VII B 2.

Considerable advances in dosimetry techniques for microsphere brachytherapy and radioimmunotherapy are available but not yet widely accepted. For example, unfortunately, many clinicians still practice radionuclide therapy based on the simple methods, based on standard activity values, or activity administered per unit body weight or surface area, when the evidence shows that radiation-dose based methods provide superior results.[30] Furthermore, the average dose to the whole organ does not adequately characterize the variability of dose within organs undergoing therapy, and dose information should be represented using 3D dose distributions and dose-volume histograms. Imaging of patients to obtain anatomical information may be performed using MR or CT in 3D voxel format, with typical resolutions on the order of 1 mm. SPECT and PET imaging systems can provide 3D voxel representations of activity distributions within patients with resolutions in the range of 4–10 mm. Newer imaging systems combine CT with PET or SPECT so that patient anatomy and tracer distribution can be imaged during a single imaging session without repositioning the patient. The use of a validated radiation transport methodology with knowledge of patient anatomy will permit calculation of detailed 3D dose calculations, given valid quantitative PET and SPECT data.

Several efforts to use image data to perform high quality detailed dose calculations include the 3D-ID code from the Memorial Sloan-Kettering Cancer Center,[31] the SIMDOS code from the University of Lund,[32] the RTDS code from the City of Hope Medical Center,[33] the RMDP code from Royal Marsden,[34] and the DOSE3D code.[35] The PEREGRINE Monte Carlo code[36] has also been proposed for three-dimensional, computational dosimetry, and treatment planning in radioimmunotherapy. As an alternative to Monte Carlo calculations, the Attila code has been developed at MD Anderson Center using a deterministic radiation transport code.[37,38] Advances in radioimmunotherapy dosimetry should benefit microsphere brachytherapy.

In early clinical trials using microspheres, due to the difficulty in determining the activity distribution within liver and tumors, radiation absorbed doses were reported with the assumption that administered activity was uniformly distributed throughout the liver. It is evident from the retrospective pathological studies that the tumor to nontumor activity uptake is not uniform. The partition model has been applied to partially address this problem. However, the partition model does not take into account the activity nonuniformity within each partition. Furthermore, the partition model cannot be accurately used for diffused tumors where tumor extent cannot be determined with confidence.

IV.C. Image-based dosimetry

A substantial increase in computing speed has made it possible to implement dosimetry calculations based on volumetric integration. The basic approach to kernel convolution dosimetry is to convolve a 3D *in vivo* activity distribution with a Monte Carlo derived 3D dose kernel. For a homogeneous medium, the dose calculation is conducted using the convolution integral:

$$D(\vec{r}) = \int \tilde{A}(\vec{r}')K(\vec{r} - \vec{r}')d\vec{r}' \tag{11}$$

where $D(\vec{r})$ is the absorbed dose (Gy) in the central voxel, centered at location $\vec{r}$, $\tilde{A}(\vec{r}')$ is the cumulated activity (Bq-s) at location $\vec{r}'$, and $K(\vec{r} - \vec{r}')$ is the spatially invariant dose deposition kernel (Gy Bq^{-1} s^{-1}) between location $\vec{r}$ and source location $\vec{r}'$.

The dose deposited in a voxel centered on $\vec{r}$ is a result of the activity contained within the central voxel as well as the activity contained in the surrounding voxels. The contribution to the central voxel dose from the surrounding voxels is a superposition of the dose distributions due to the activity in each surrounding voxel, using the activity as the weighting function. In general, the convolution method is a blurring function of the activity distribution in the patient.

It is also possible to calculate the dose in Fourier or Hartley space for an additional reduction in calculation time.[39] The fast Fourier transform (FFT) can be used to transform both the activity distribution and the dose kernel for complex multiplication. Use of a fast Hartley transform does not involve complex multiplication; therefore, all the numerical operations are with real numbers. Taking T as the convolution transform operator, either method is given by

$$D(\vec{r}) = T^{-1}[T[A(\vec{r})]T[K(\vec{r})]] \tag{12}$$

Once again, the use of Fourier or Hartley space convolution requires the dose kernel to be spatially invariant, which is a reasonable assumption for a relatively homogenous organ such as the liver.

The incident spectrum for ^{90}Y needed in Monte Carlo dose kernel calculations has been reported in ICRU Report 72[22] and the RADAR website.[40] The Monte Carlo calculations are usually carried out for 10^{10} histories to reduce the statistical uncertainty to below 1.0% in the total dose at 2 mm away from the source. The determination of ^{90}Y beta point dose kernel dates back over 30 yr. Many researchers have generated spherical-scaled dose point kernels in water or tissue using Monte Carlo codes such as ETRAN, ACCEPT, EGSnrcMP, and EGS4/Presta. Kernels generated with different Monte Carlo codes are in excellent agreement with the kernel originally presented by Simpkin *et al.*,[41] which is generally considered the reference standard. Point kernels can also be integrated over a cubic volume to provide dose voxel kernels similar to the voxel S factors.[42]

Sarfaraz *et al.*[43] present an image-based 3D dosimetry for ^{90}Y microspheres. The bremsstrahlung SPECT imaging does

not have adequate resolution for dose distribution calculation. Therefore an MAA-SPECT image, which could be obtained at the same time of lung shunt study, is used for dose calculation. The MAA-SPECT counts per voxels are arbitrary values that depend on many factors including acquisition time and reconstruction algorithm. In addition, there would be some background counts introduced by the reconstruction algorithm in spite of the fact that microspheres are exclusively administered and retained in the liver (except for a few percent lung shunt). Hence, the relative SPECT counts in each voxel of the image is converted to absolute activity by normalizing the total counts minus background to the total ^{90}Y administered activity. The radiation absorbed dose distribution is calculated by convolving the activity distribution obtained from the SPECT images with a dose kernel for ^{90}Y. Isodose lines can be derived from the 3D dose distribution and displayed on the corresponding CT scans registered to the SPECT scans. The dose-volume histogram of the tumor, liver, and other organs can be derived from the calculated dose distribution and the volumes transferred from the CT scan. Research into more sophisticated methods to correct SPECT counts to activity is being conducted and is called quantitative SPECT or QSPECT.[32,44,45] It should be noted that these research systems are not in widespread use at this time and no commercial system exists for microsphere brachytherapy dosimetry.

One caveat must be introduced in a voxel-based strategy. Traditionally, it has been assumed that there is essentially no movement of radioactivity in source tissues. There has been little attempt to measure the kinetics of ^{99m}Tc MAA away from deposition sites due to the degradation of the MAA particles over time. Moreover, the 6 h half-life of ^{99m}Tc may not be useful for long-term follow-up that is relevant to the 64 h half-life of ^{90}Y. If kinetics measurements are possible, the obvious question is the following of individual voxels in the tissues. SPECT/CT and PET/CT scanners could prove useful in this application.

V. MICROSPHERE ACTIVITY MEASUREMENT STANDARDS

V.A. ^{90}Y calibration—international standards

Physical measurement standards for the determination of radioactivity are typically held by a country's National Metrology Institute (NMI). For the United States, the NMI is the National Institute of Standards and Technology (NIST). This standard is most often in the form of a primary measurement method, i.e., a method that relies on first principals instead of a calibration factor for an instrument. Due to the high efficiency of the method, approximately 98% for ^{90}Y, liquid-scintillation (LS) counting is routinely used for activity measurements of beta-emitting radionuclides in solution. Two different methods may be used to determine the efficiency: the CIEMAT/NIST (Centro de Investigaciones Energeticas, Medioambientales y Technologicas) efficiency tracing method[46,47] or the Triple-to-Double Coincidence Ratio method.[48] Both of these methods are used at NIST. Although this method is straight forward, care must be taken to ensure that liquid-scintillation cocktails remain stable over the duration of counting. Typically, expanded uncertainties ($k=2$ or two standard deviations) of less than 1% can be achieved. NIST disseminates the activity standard for ^{90}Y through the yearly production of Standard Reference Materials and through the availability of calibration services.

Comparisons between NMIs are overseen by the International Committee for Weights and Measures (CIPM). For signatories of the Mutual Recognition Arrangement (MRA), these results are tabulated in the Key Comparison Database. The most recent comparison of ^{90}Y was published in 2005.[49] Eight laboratories measured the activity of aliquots of solution distributed by NIST. The standard deviation of the mean of the reported results was 0.05%, well below the individual stated uncertainties, indicating consistency in the Y-90 international standard.

V.B. SIR-Spheres® activity standard

SIR-Spheres® do not have a NIST traceable calibration at the publication of this report; however, activity measurements of ^{90}Y SIR-Spheres® have been performed at The Australian Nuclear Science and Technology Organization (ANSTO) and the Australian Radiopharmaceuticals and Industrials (ARI). ANSTO is the Australian designated laboratory for radioactivity measurements. The clinical data used to support the FDA application was based on an ion chamber calibration that is still in use for the production and release of the products. Each vial of microspheres is calibrated individually within a $\pm 10\%$ range. When new customers start use, the manufacturer provides an activity from the batch report for the first three microsphere vials shipped. This allows the customer to normalize their ion chamber to the same calibration as the manufacturer. Further calibration values can be requested as needed by the user.

It is also noteworthy that activity measurements made using dose calibrators will vary as the distribution of ^{90}Y varies within the dose calibrator and the sample container. For example, an activity measurement made on a sample of settled, ^{90}Y labeled, SIR-Spheres® microspheres will vary considerably from the activity measured using the same quantity of ^{90}Y in an yttrium-chloride solution where the activity is homogeneously distributed throughout the sample container. Similarly, there are geometry dependent variations in activity measurements when different shaped sample containers are used. For this reason, Sirtex recommends to its customers that all activity measurements be made on material in the shipping vial, not the V bottomed v-vial used for patient delivery.

Mo *et al.*[50] detailed another calibration of the activity of SIR-Spheres® independent of the manufacturer and it is briefly described. For the production of SIR-Spheres®, it was necessary to relate measurements made during production to Australian national standards for measurement of ^{90}Y. Calibration factors were determined for four different ionization chamber models using an intermediate geometry of the production and the final geometry. Ionization chamber measurements were made on samples of SIR-Spheres® using the

ionization chambers at ARI. Following these measurements, the microspheres were chemically digested to yield a solution containing only liquid. During the sample digestion, care was taken to account for losses from solution by collection and measurement of the vapors from the reaction. The resulting solution was measured on the ANSTO secondary standard ionization chamber.

While this work established a procedure for activity measurement and quality control of the SIR-Spheres® product, the ionization chamber models used are not routinely used or available in the US. Therefore, the calibration factors determined are not generally useful for US clinical measurements. Also of concern is the fact that the link from measurements at ARI to US national radioactivity measurement standards is based on an ionization chamber measurement of a pure solution of the beta emitter. This measurement has an inherently higher uncertainty than direct liquid-scintillation measurements. The main uncertainty in SIR-Spheres® comes from the volume and homogeneity of the sample. A change in the volume of SIR-Spheres® can affect the activity measurements due to geometry differences. Similarly, the homogeneity of the sample can affect the activity measurements of the sample. Part of SIR-Spheres® training requires the technician to resuspend the SIR-Spheres® prior to measuring the activity. An additional problem comes from the lack of uniformity on the shipping vials. The variations in the thickness of the glass in parts of the vials lead to variations in the penetration of the betas through the glass and into the wall of the chamber.

An independent, nondestructive spectroscopic analysis of SIR-Spheres® at the University of Wisconsin has measured an activity 26% higher than the manufacturer indicated activity.[51] Section V E gives more details on this measurement.

V.C. TheraSphere® activity standard

Nordion participates in the NIST Radioactivity Measurement Assurance Program (NRMAP). Dial settings have been determined for the measurement of TheraSphere® by NIST in commercially available Capintec dose calibrators.[52] NIST maintains a secondary measurement standard for routine calibration of TheraSphere®. Nordion routinely verifies its dose calibrator measurements with NIST, for the full range of available dose sizes.

TheraSphere® user sites are supplied with TheraSphere® dose vial information on vials initially shipped. The measured activity value of the dose vial, referenced to the specified calibration date and time, is provided to the user site. This allows for site specific determination of dose calibrator settings and geometry factors to establish equivalency with Nordion measurements. The site specific factors determined can then be applied to subsequent TheraSphere® activity vials received.

TheraSphere® is supplied with the dose vial contained in a nonremovable acrylic shield. The acrylic shield is an integral part of the safety shielding for the product. User sites will need to use a dose calibrator "dip stick" that will hold the TheraSphere® dose vial in its acrylic shield in a repeatable, fixed position. The highest accuracy of dose calibrator measurements is achieved if all of the microspheres are located at the bottom tip of the dose vial. Prior to dose calibrator measurement, it is recommended to gently rock and tap the acrylic shield to ensure that the microspheres are located at the bottom of the vial. The dose vial should always be measured and maintained upright at all times.

V.D. Vendor to local clinic

Determining the ^{90}Y reference activity for the local clinic is an integral part of the microsphere brachytherapy program. Both vendors will supply reference activity samples to users upon request to establish a local standard. Typically, dose calibrators in the nuclear medicine department are used at a given clinic to verify activity values. Variations in container materials and source position within the dose calibrator can affect the local calibration standard.[50,53,54] In the absence of a well defined local calibration procedure, variations in activity measurements on the order of 10% can occur.[55,56] Given no availability of an Accredited Dosimetry Calibration Laboratory (ADCL) traceable activity standard for microspheres, a fixed geometrical technique for reference activity measurements should be established at the local clinic level and used consistently.

For example, the same container and the same position within the dose calibrator should be used consistently. Using a vendor supplied reference activity vial, dose calibrator settings can be determined by the following simple procedure: (1) vary the dose calibrator calibration value and record the measured activity and (2) graph the measured activity divided by the vendor calibration as a function of calibrator setting. The point that the quotient reaches one is the dose calibrator calibration value to use for the local clinic.

In order to determine the postprocedure residual activity, both microsphere products discuss a method using a survey meter at four compass points around a container holding the items to be measured. Preimplant, an initial reading is taken with only the delivery vial placed in the container. The survey meter response for this measurement is equated with the calibrated activity being delivered to the patient. Following the procedure, the delivery vial and the delivery tubing are placed in the container and measured with the same survey meter. The ratio of the final reading to the initial reading is taken as the fraction of the activity not delivered and subtracted from the patient's activity in the final dosimetry. The accuracy and precision of this method have not been evaluated. Dezarn and Kennedy[56] completed a study to show that measuring post implant residual activity in a dose calibrator is similar to the four compass point method. All the residual activity from a series of microsphere brachytherapy procedures was measured by both methods and found to give consistent results. Given the possible inconsistencies using a survey meter for activity measurements, it is recommended to use a dose calibrator for post implant activity determination.

V.E. New calibration methods for ^{90}Y

Widely used nondestructive assays of ^{90}Y use reentrant ionization chambers or dose calibrators to detect bremsstrahlung or beta radiation directly. The bremsstrahlung production is highly dependent on the source material, its container, and the calibrator chamber wall. The ionization current also depends on the probability of electron detection within the chamber, which varies with electron energy and individual dose calibrator construction. Slight variations in the container wall thickness, solution volume, or location within the well can lead to an increase in the overall assay uncertainty when using the manufacturer supplied calibration factor, which is typically traceable to national standards. Siegel *et al.*[53] and Zimmerman *et al.*[54] determined volumetric corrections and calibration factors for several commercially available dose calibrators for solutions of ^{90}Y (Zevalin®) in a 10 ml syringe. The volume dependence varied from 0.84 to 5.20% over a volume range of 6 ml and the average dial setting varied from 0.89 to 3.60%.

Based on current measurements of microsphere activity, the uncertainties and estimates of geometrical uncertainty in dose delivered can be combined to yield a total dose delivery uncertainty on the order of 20%. One of the largest components of this total is the activity measurement. Thus, an improvement in the calibration methods and the measurement of standards for microspheres would help to greatly reduce the dose uncertainty. New calibration methods may involve branching ratios and even measurements of particulate radiation.

A nondestructive spectroscopic assay[51] can be employed due to a newly updated low uncertainty positron branching ratio of ^{90}Y. The assay is based on the detection of the 511 keV annihilation radiation produced from the positron decay of ^{90}Y. The assay provides precise and relatively geometry independent calibration factors that can be transferred to clinical ionization chambers. Positron emitting impurities such as ^{88}Y should be taken into account by monitoring other photon emissions such as 898 and 1836 keV. Recently, this method was utilized to assay a 3 GBq sample of SIR-Spheres® provided by the manufacturer. The measured activity was (3.81 ± 1.8%) GBq, 26% greater than the manufacturer calibrated activity.

The prescribed activity for SIR-Spheres® is based upon clinical results and ^{90}Y activities obtained by the manufacturer during clinical trials. The manufacturer stated activity should continue to be used until new activity standards and dosimetric implications are studied. End users should continue to use the manufacturer activity standard until NIST or an ADCL can independently provide calibration factors.

VI. RADIOACTIVE MATERIAL LICENSING AND RADIATION SAFETY

VI.A. US NRC and agreement state regulations

The US Nuclear Regulatory Commission (NRC) regulates ^{90}Y microspheres as medical devices since the microspheres do not interact pharmacologically, physiologically, or biochemically within the body. In other words, ^{90}Y microspheres are not metabolized and hence are not radiopharmaceuticals such as ^{131}I Lipiodol, for example. This regulation is codified in 10 CFR 35.1000 "Other Medical Uses of Byproduct Material or Radiation from Byproduct Material." NRC licensing guidance specific to ^{90}Y microspheres can be found at their website.[57] The licensee shall follow all the requirements in 10 CFR Part 35 for brachytherapy sources and manual brachytherapy except where the licensing commitments of 10 CFR 35.1000 provide regulatory relief. NRC agreement states must enforce at least the NRC regulations but may also impose further regulations. When starting a microsphere brachytherapy program in an agreement state, the licensee should contact the local regulatory agency for further possible requirements.

VI.B. Authorized user and authorized medical physicist

A physician must satisfy the training requirements of 10 CFR 35.390 or 10 CFR 35.490 to become an authorized user (AU) of ^{90}Y microspheres. The basic requirements are physicians who have completed residency training programs in radiation therapy or nuclear medicine and are certified by a medical specialty board recognized by the NRC. Interventional radiologists may also apply for AU status for ^{90}Y microspheres by following the procedures in the NRC ^{90}Y microsphere guidance.[57] Medical and health physicists are ineligible to be an AU. Authorized medical physicist (AMP) status is not currently defined for ^{90}Y microspheres. Training requirements of 10 CFR 35 to become an AMP for other procedures can be used as a model to create local departmental physicist training standards for ^{90}Y microspheres. In addition to the requirements of 10 CFR 35, the individual should complete training in the operation of the specific microsphere delivery system and become knowledgeable of safety procedures and clinical use of each type of microsphere. The physician should complete vendor specific training and perform three cases supervised by a vendor trainer or another AU for each type of microsphere for which the physician is seeking AU status.

VI.C. Sealed source inventory and labeling requirements

Leak tests are not required because the activity per microsphere (the sealed source) meets the criteria in 10 CFR 35.67(f); thereby relieving the licensee from the requirements of performing such tests. However, semiannual physical inventory of microspheres aggregates (e.g., vials) is still required by most regulatory agencies. The NRC guidance states that the inventory should include the following information:

1. radionuclide and physical form;
2. unique identification of each vial in which the microspheres are contained;
3. total activity contained in each of the vial(s); and

4. location(s) of the vial(s).

The following additional guidance applies when the radioactive microspheres are placed in vials, syringes, or radiation shields that are not labeled by the manufacturer:

1. Label vials and vial radiation shields with radionuclide and form (e.g., ^{90}Y resin or glass microspheres).
2. Label syringes and syringe radiation shields with the radionuclide, form, and therapeutic procedure (e.g., ^{90}Y resin or glass microspheres, brachytherapy).

VI.D. Written directive

For the purpose of written directives and medical event reporting requirements in the NRC ^{90}Y microsphere guidance,[57] "prescribed dose" means the total dose (rad or Gy). Alternatively, prescribed activity (mCi or GBq) may be used in lieu of prescribed dose. The written directive shall include:

1. patient or human research subject's name;
2. treatment date;
3. signature of the AU for ^{90}Y microspheres;
4. treatment site;
5. radionuclide (including the physical form [^{90}Y microspheres]);
6. prescribed dose or prescribed activity;
7. maximum dose(s)/activity(ies) that would be acceptable to the specified site(s) outside the primary treatment site due to shunting (e.g., lung and gastrointestinal tract)
8. manufacturer;
9. and, if appropriate for the type of microsphere used, the statement "or dose/activity delivered at stasis."

The licensee shall record the administered dose/activity delivered to the primary treatment site and to the other specified site(s). If the administration was terminated because of stasis, then the total dose/activity to the treatment site is the value of the total dose/activity administered when stasis occurred and the administration was terminated. The record should be prepared within 24 h after the completion or termination of the administration and must include the name of the individual who made the assessment, the date, and the signature of an AU for ^{90}Y microspheres, if terminated due to stasis.

Stasis in the context of microsphere brachytherapy means that blood flow through a given region has been stopped.

VI.E. Medical event

A medical event is defined in 10 CFR 35.3045 "Report and notification of a medical event." The elements of this regulation that apply to microsphere brachytherapy are paraphrased here. The actual documentation required will depend on the licensee's Radioactive Material License. Administration of ^{90}Y microspheres must be performed in accordance with the written directive. If stasis is documented as a treatment endpoint in the written directive and reached in a treatment, a medical event has not occurred. Treatment procedures should describe how the total dose to the treatment site, as well as, potential dose to other sites, will be determined before and upon completion of the administration, to confirm that the administration is performed in accordance with the written directive. Moreover, procedures should describe how events that are not the results from intervention of a patient or research subject are reported to regulatory agencies. The reporting requirements of the NRC are described in 10 CFR 35.3045(b)–(g). A ^{90}Y microspheres medical event is defined as the following:

1. the administration of byproduct material results in a dose that exceeds 0.05 Sv (5 rem) effective dose equivalent or 0.5 Sv (50 rem) to an organ or tissue from the use of the wrong radionuclide; or
2. the administration of ^{90}Y-microspheres results in a dose:
   a) that differs from the prescribed dose or the dose that would have resulted from the prescribed activity, as documented in the written directive, by more than 0.05 Sv (5 rem) effective dose equivalent or 0.5 Sv (50 rem) to an organ or tissue, and the total dose-activity administered differs from the prescribed dose/activity, as documented in the written directive, by 20% or more; or
   b) that exceeds 0.05 Sv (5 rem) effective dose equivalent or 0.5 Sv (50 rem) to an organ or tissue from an administration to the wrong individual or human research subject, via the wrong route, or by the wrong mode of treatment; or
   c) to an organ or tissue other than the treatment site that exceeds by 0.5 Sv (50 rem) to an organ or tissue and by 50% or more of the prescribed dose/activity expected to that site from the administration of ^{90}Y microspheres, if carried out as specified in the preadministration portion of the written directive.

VI.F. Instrumentation

The radiation detector used to monitor for contamination must be sensitive to the radiation likely to be encountered. Hand-held survey meters using ionization chambers or Geiger–Müller (GM) tubes that are sensitive to gamma and beta radiation should be used in microsphere brachytherapy procedures. With TheraSphere®, a single microsphere carries approximately 2500 Bq (67 nCi) of ^{90}Y at the calibration time. Most regulations consider the presence of 185 Bq (5 nCi) indicative of contamination. Thus, even a single errant sphere constitutes external contamination. For SIR-Spheres®, at approximately 50 Bq (1.35 nCi) per sphere at the calibration time, four spheres just exceeds the regulatory limit. Thus, very small amounts of material leaking from the delivery system produce sizable contamination. Normally, for this level of contamination, wipe tests would be performed. However, the counting equipment and time would not be available in the interventional radiology room immediately following the procedure, and hand-held survey instruments are used.

VI.G. Procedure room and staff surveys

All personnel participating in the procedure must wear protective equipment including lead apron, scrubs, gloves, gown, face mask, and shoe covers. They also must wear whole-body dosimeters while those with the likelihood of having their hands near the source should also wear extremity dosimeters. The floor of the angiography room should be covered with large water absorbing drapes before the treatment to confine any contamination. Everyone leaving the room during the procedure is scanned for contamination and all contaminated items are collected and disposed of as radiation waste. Following the microsphere brachytherapy procedure, a radiation survey assures that no radioactivity has contaminated the room, waste, or personnel.

The survey procedure follows the same pattern as that would be performed following a radioactive solution treatment. Each person in the room is monitored, surveying their hands (tops and bottoms), their anterior and posterior surfaces and the bottoms of their feet. No one leaves the room before being monitored. All the equipment and surfaces are surveyed, paying particular attention to anything wet or bloody. The surfaces include the floor, which should have been covered. During the survey, either of the personnel or of the materials, the presence of the patient may produce a background reading high enough to mask potential contamination. Both moving away from the patient as much as possible and keeping the surveyor (assumedly still wearing a lead apron) between the patient and the person or material to be surveyed helps reduce the background, usually to levels compatible with detecting contamination.

The background radiation from the patient can be difficult to shield especially around the floor area close to the patient. In such cases, the floor covering can be taken up and the pads measured away from the patient. During the removal, the pads are considered contaminated, so that the tape around the edges holding the pads in place must be removed very carefully and the pads rolled inward from the edges, to contain potential contamination. Likewise, sheets and towels on the patient likely need to be surveyed away from the patient.

Even though, the survey procedures for ^{90}Y microspheres are similar to radioactive solution treatments, the remedial actions for spills or contamination are different. The first response for a radioactive solution spill is to cover the spill with coarse absorbent material such as surgical towels and then to use a plastic-backed, absorbent pad, which would absorb the solution, and presumably the radioactive material with it. With a microsphere spill, the towels can absorb the liquid and trap the microspheres. A contaminated surface usually implies the presence of microspheres. Because microspheres can become trapped in a crevice, such features are particularly challenging. Decontamination sprays and solutions rarely help but on the other hand, foaming products have some chance of lifting the spheres where they could be retrieved. Adhesive tape can also be used to capture microspheres. Cleaning attempts should be repeated until background radioactivity levels are reached. If removal is not possible then the spill should be dried, covered with approximately 1 cm of low Z material, sealed or waterproofed (e.g., with a plastic film), surveyed, and labeled.

VI.H. Radiation safety considerations in patients undergoing transplantation or surgical resection

There will be instances where a patient undergoing ^{90}Y microspheres therapy becomes a surgical candidate for resection or liver transplantation. Although investigators should follow their own institutional guidelines for elapsed time from ^{90}Y treatment to time of surgery or transplantation, this should be balanced against the medical needs of the patient. Monitoring the patient surface dose rate is a typical method to determine what precautions should be followed at the time of surgery. Generally, if the patient's skin surface dose rate that is less than 20 μSv/h, special handling by the surgeon is not required at the time of the procedure.[58] That is, lead gloves, special instruments, and extremity radiation monitors (e.g., ring badge) are not necessary. Radiation safety should be notified for transportation and storage of the explanted specimen. Institutional experience may vary but patients treated with ^{90}Y microspheres typically have surface dose rates less than 20 μSv/h at 30 days regardless of administered activity.

Following surgery (resection or transplantation), the explanted liver should be placed in a formaldehyde solution for storage in a leak proof container. The container should be refrigerated while in storage. Because the explanted liver may contain radioactive microspheres, the container should be monitored with an energy compensated Geiger–Mueller detector or a portable ionization chamber. If the dose rate at the surface of the container exceeds 50 μSv/h, the container should be placed behind lead shielding for decay-in-storage. While in storage, the explanted liver container should be labeled as radioactive material per local radiation safety guidelines. Institutions should also follow federal and state guidelines for room posting of areas containing radioactive material or designated radiation areas. Once the container has decayed for 60 days, the surface exposure rate will usually be less than 5–10 μSv/h using a portable ionization chamber. At that time, the pathologist may handle the specimen in the grossing lab using their standard, universal precautions, and techniques. If immediate determination of clear surgical margins is required, the volume of tissue handled in analyzing a frozen section is minimal and should not pose a radiation risk to the staff. Hand radiation monitors can be worn to monitor the staff exposure. Once any pathologic analysis is complete, all tissues should be placed in the original storage container and returned to radioactive material storage. All areas where the liver specimen was handled should be surveyed with a radiation detection instrument such as a GM thin window detector. Readings should be less than 1 μSv/h.

VI.I. Radiation safety considerations in case of autopsy, burial or cremation

National Council for Radiation Protection and Measurements (NCRP) Report No. 155 "Management of Radionuclide

Therapy Patients (2006)," provides guidance regarding burial of patients with permanent implants on levels of radioactivity below which no precautions are needed. NCRP Report No.161, "Management of Persons Contaminated with Radionuclides: Handbook (NCRP 2010)," also gives practical guidance to medical and mortuary personnel, although more in the context of dealing with generally contaminated subjects. NCRP reports are generally accepted as appropriate guidance for use in the absence of regulatory requirements. International Commission on Radiological Protection Publication 94 "Release of Patients after Therapy with Unsealed Radionuclides (2005)," provides international guidance on burial, cremation, or the autopsy of patients who have received therapeutic radionuclides.

If an autopsy must be performed on the corpse, special precautions may be required if the activity exceeds the limits set for cremation. However, microsphere brachytherapy with ^{90}Y microspheres usually only involves significant quantities in the liver. Therefore, an autopsy could be performed without the pathologist exceeding the limits for radiation exposures to the general public if the liver can be excised and set aside for radioactive decay. If an autopsy is performed within 34 days of treatment, the physician may want to take the conservative approach and remove the liver or treated tissue prior to performing the autopsy to reduce any extensive exposure (less than 1 h).

For postmortem patients, there would be no radiation safety restrictions on embalming or burial since, it is extremely unlikely that embalmers and funeral workers would receive radiation doses in excess of the public dose limit of 1 mSv per year. In the United States of America, a crematorium may accept a corpse if the radioactivity is less than 74 MBq for all radionuclides (ICRP94). Individual state regulations may prevent cremation based on contaminates introduced during the manufacturing process. For a typical patient that was administered 1.5 GBq of ^{90}Y microspheres, the corpse may have to be stored if death occurred within 12 days of the microsphere brachytherapy treatment. This is a minor consideration that should be decided on a case-by-case basis. As stated above, the conservative approach would be to remove the liver and store it for radioactive decay.

VI.J. Radioactive material storage

At the end of a procedure, there will be at least residual amounts of ^{90}Y microspheres present in transfer tubing, various containers, and various drapes. A physicist should survey everything in the procedure room with an appropriate survey meter. Any contaminated materials should be placed in beta shielded containers and placed in waste storage. The licensee has to hold the radioactive material until the container surface radioactivity cannot be distinguished from background with the radiation survey meter set on its most sensitive scale and no shielding being used. When the radioactive material has reached background levels the licensee will remove or obliterate all radiation labels. Records of all disposals will be kept for 3 yr. The disposal record will include the disposal date, the storage entry date, the radionuclide disposed, the survey instrument used, the background rate used, and the dose rate measured at the surface of each container.

Yttrium-90 can be produced by neutron bombardment of ^{89}Y in a nuclear reactor. In this production modality there are also $(2n,\gamma)$ and $(n,2n)$ reactions occurring that produce ^{91}Y and ^{88}Y, respectively. Depending on the construction of the microsphere, other by-product radionuclides can be generated in reactor production. Long-lived radioactive by-products may not be a problem for microspheres manufactured using carrier free ^{90}Y from a ^{90}Sr generator. While 10 CFR 35.92 allows licensees to store radioactive material with a physical half-life of less than 120 days for decay-in-storage before disposal in ordinary trash, in March 2007, the US NRC issued "NRC Information Notice 2007-10: Yttrium-90 TheraSphere® and SIR-Sphere® Impurities." The purpose of this notice was to notify users that samples of radioactive microspheres were radioactive longer than expected because of ^{88}Y and other long-lived by-products. None of the by-products were at levels high enough to influence the radiation dosage delivered to the patient. The notice recommends performing one of three possible actions: (1) holding the remaining microspheres in decay-in storage in accordance with 10 CFR 35.92, (2) return the microspheres to the manufacturer, or (3) transfer them to an authorized recipient according to 10 CFR 20.2006. The practical side of this information is that decay-in-storage for microspheres may take longer than the 27 days expected for 10 half-life decay. Extra considerations for storage space may be needed. Additional shielding may be necessary if the decay-in-storage location is near nuclear medicine detectors and the storage load is high. The local radiation safety committee must carefully consider all of these issues.

VI.K. Patient release

The patients' tissues usually provide sufficient attenuation of the beta emissions such that patients can be released immediately based on 10 CFR 35.75. In 10 CFR 35.75, an individual containing an implant with byproduct material may be released from institutional care with special written radiation precautions if the individual is not likely to expose another individual to more than 5 mSv (500 mrem) in 1 yr. No written precautions are required if the individual is not likely to expose another individual to more than 1 mSv (100 mrem) in 1 yr. However, patients are advised to avoid contact with the general public for certain periods of time depending on the administered activity. Patients and their family need to be advised to inform future medical professionals of the radioactive implant to minimize the staff radiation exposure during potential future procedures. No restrictions are imposed on the routine nursing care of these patients. As stated earlier, trace amounts of radioactivity have been detected in patient urine after SIR-Spheres® treatments. Double flushing of a standard cistern with the lid closed for 24 h after an implant will generally reduce this activity to acceptable levels.

VII. MICROSPHERE BRACHYTHERAPY QUALITY ASSURANCE

Nag *et al.*[59] recommended a 20% overall deviation from the prescribed dose as a tolerance criterion for most good-quality brachytherapy implants. Brachytherapy implants that could not achieve this tolerance were suggested to consider the following before initiating the therapy: to reposition applicators or sources, adjust the written directive, or abort the procedure. While some of the uncertainties in microsphere brachytherapy are not well quantified, this recommendation for standard brachytherapy is a good starting point for microsphere brachytherapy.

VII.A. Dose calibrator accuracy, consistency, and linearity

Brachytherapy sources are assigned a "calibration" by the manufacturer. It is not uncommon for an institution to accept the manufacturer's calibration. However, it is the responsibility of the institution to verify that this calibration is correct. The institution should periodically compare the manufacturer's stated microsphere activity value with the institution's standard. If the two are within acceptable limits, either the manufacturer's or institution's value may be used. For microsphere brachytherapy this means to compare the activity contained in a vial as stated by the manufacturer with the local activity standard. We recommend that if the institution's verification of source strength on average differs with the manufacturer's calibrated data by more than $\pm 5\%$, the source of the disagreement should be investigated. We further recommend that an unresolved disparity exceeding $\pm 10\%$ for an individual source should be reported to the manufacturer. It is always advisable to ask the manufacturer to review its calibration of the sources to help resolve these discrepancies. With a proper redundancy program to verify that the institution's dosimetry system has not changed with time, there remains a small risk of error when the institution's calibration value is used but differs from the manufacturer's data.

IAEA Report 454 (Ref. 60) gives dose calibrator quality assurance procedures as well as periodic tests and their suggested frequency. Dose calibrator linearity can be tested by a time decay method. Once the initial linearity is established, a shield method can be developed to quickly test linearity. Background readings should be measured regularly in a nuclear medicine laboratory due to the continual receipt of new sources at varying activities for different procedures. The dose calibrator precision should be measured by repeatedly measuring the same source over a short period of time to determine the standard deviation of the sample readings. This value should be measured for all radionuclides used with the dose calibrator, since the precision will not necessarily be the same for different radionuclides. A calibrated long-lived check source traceable to NIST or a NMI should be acquired and periodically measured to assure that the dose calibrator is within the manufacturer's stated accuracy. If the reading falls outside of the stated accuracy, the dose calibrator manufacturer should be contacted for recommended reading corrections or repairs. For microsphere brachytherapy sources, a calibrated microsphere vial should be requested at least every 2 yr to verify the consistency of the local calibration standard. Dose calibrators are not typically returned to an ADCL for periodic recalibration unlike standard brachytherapy dose chambers. Thus, the tests discussed here are even more important to maintain an accurate and consistent local activity standard.

VII.B. Patient activity preparation procedures

For the two products, the source preparation differs considerably. The manufacturers provide complete discussions and step by step procedures for their products, and this section will not repeat such material (since the user should become familiar with the instructions for their system). However, a brief overview does provide some insight into the differences between the systems in use. All procedures include standard radiation protection and aseptic technique where appropriate and necessary.

VII.B.1. SIR-Spheres®

The manufacturer presents three methods for determining SIR-Spheres® prescribed activity:

(1) Body surface area (BSA) method: It is detailed in the following equations:

$$\mathrm{BSA}[\mathrm{m}^2] = 0.20247 \times \mathrm{height}[\mathrm{m}]^{0.725} \times \mathrm{weight}[\mathrm{kg}]^{0.425} \tag{13}$$

$$\mathrm{A}[\mathrm{GBq}] = \mathrm{BSA} - 0.2 + \frac{\text{Tumor Volume}}{\text{Total Liver Volume}} \tag{14}$$

Current prescription activities typically are within the 1.0–2.5 GBq range. This activity can be reduced if hepatic function is compromised. Experienced users will also reduce the BSA activity to deliver if the lung shunt demonstrates that 30 Gy or higher dose will be delivered to the lungs. Users are cautioned that for patients with very large BSA the equation may indicate activities above 3 GBq and they should use discretion.

(2) Empiric method: The method for determining the prescribed activity during the clinical trial, called Empiric method, used a standard activity based on the extent of liver involvement by tumor, modified by the fraction of the activity that deposit in the lung as seen on pretreatment ^{99m}Tc-labeled MAA images. Some practitioners felt that the treatment was better tolerated when treating only one lobe of the liver at a time and an additional factor for modifying the dose was included based on the lobe treated. Equation (15) details how to determine the prescribed activity by the Empiric method, while Table VII gives the factors and their descriptions.

$$\mathrm{A}[\mathrm{GBq}] = \text{Liver Involvement Activity} \times \mathrm{LSM} \times \mathrm{LPM} \tag{15}$$

(3) Partition model: This model solves Eq. (9) for the activity to deliver, limiting the dose to normal liver and the lung, based on Eq. (7).

TABLE VII. Factors for determining the prescribed microsphere activity for SIR-Spheres® using the Empirical method.

Estimated degree of liver involvement	**Standard dosage of Y-90 [GBq]**
>50%	3
25%–50%	2.5
<25%	2
Lung shunting	**Lung shunt modifier (LSM)**
<10%	1.0
10%–15%	0.8
15%–20%	0.6
>20%	Do not proceed
Part of liver	**Liver part modifier (LPM)**
Whole liver	1.0
Right lobe only	0.7
Left lobe only	0.3

Users should note that the empiric method fails to account for the size of the liver or lesions, other than the faction of the liver they occupy, and for patients with particularly small livers consider adjustment.

Modification of the activity projected by each of these models is the subject of current research and involves factors such as prior chemotherapy and tumor volume. None of these models have been based on strong scientific foundations. The ideal activity to deliver and the parameters on which to base it have yet to be determined for any current microsphere product.

Given the calibration of the shipping vial and its nominal 5 ml liquid volume, the volume of the activity required for the prescribed activity can be calculated. Next, the vial is gently agitated, avoiding contact of the solution with the septum. A needle with a filter is inserted to vent the vial while avoiding the fluid. The solution is reagitated and the desired volume is removed with a syringe. The shipping vial is again measured in the well chamber to determine the remaining activity. The difference between the initial and remaining activity in the shipping vial gives the activity in the syringe. If the activity in the syringe is not between 2 and 7% above that prescribed, material is exchanged between the shipping vial and the syringe until this condition is met. Finally, the contents of the syringe are injected into the vented v-vial.

During the filling of the v-vial, the number of punctures of the rubber septum must be kept to a minimum, ideally only the vent and a single hole for the filling. Multiple punctures can lead to loss of septum integrity and subsequent leaking of the radioactive fluid during the delivery to the patient. Punctures should be as near to the thicker edges of the septum as possible and no two punctures should be closer than 2 mm. The manufacturer emphasizes that water, and not saline, must be used with this product. The accidental use of contrast material can cause severe clumping of the microspheres and compromise the delivery distribution.

After filling, the v-vial is placed in the acrylic v-vial holder, the delivery system is assembled, and the lines primed with water. The delivery needle is inserted about 1 cm into the fluid, while the water inlet needle goes to the bottom of the vial. In this system, the inlet water produces a flow that suspends the microspheres in a slurry and a diluted suspension of microspheres leaves the vial toward the patient. The dilution helps prevent clogging of the delivery lines, particularly at connection points. During the delivery, the medical physicist watches for leaking at the septum (often first evidenced by bubbles), for accumulation of microspheres at connections and for the filling of the catheter leading from the delivery box to the patient.

VII.B.2. TheraSphere®

The prescribed activity for TheraSphere® is calculated by solving Eq. (4) for activity, determining the mass of perfused volume to be treated from a CT image set and choosing a dose to be delivered.

$$\mathrm{A(GBq)} = \frac{\mathrm{D[Gy]} \times \mathrm{m[kg]}}{49.38} \tag{16}$$

A typical dose between 100 and 120 Gy is selected for TheraSphere® treatments involving patients with HCC. The target dose for a particular solid tumor is not known but it is currently believed that this dose range balances the response rate with the risk of hepatic fibrosis.

The activity for TheraSpheres® is ordered to match the prescribed activity at the time of the procedure. Since, the delivered activity is available in specific incremental units and completely delivered to the patient, the procedure must occur when the activity in the vial has decayed to the prescribed activity. This process ties scheduling of the procedure and ordering the material to the dose to be delivered, within the acceptable margin of error (±10%). The trade off for the more complex scheduling and ordering comes in the simplification in preparation of the dose. Because the shipping vial is the delivery vial with no modification of the received activity, the vial needs only validation of the activity in the clinical site's dose calibrator.

Assembly of the delivery system follows validation of the activity. Saline is used for the fluid rather than water. Because the number of microspheres delivered in this system is small, clogging of either the capillary bed or tubing connections does not typically pose a problem. Thus, the delivery needle begins and remains at the bottom of the v-vial, and almost all of the microspheres tend to flow into the patient within the first few milliliters of the infusion.

VII.C. General imaging and angiography procedures

The American College of Radiology (ACR) Practice Guidelines provide an excellent starting point for imaging QA at their website.[61] In particular, the report "Practice Guideline for Radioembolization with Microsphere Brachytherapy Device (RMBD) for Treatment of Liver Malignancies" details many other ACR Practice Guidelines that cover the entire imaging chain used in microsphere brachytherapy. Two other reports to consider are "ACR Practice Guideline for Performing FDG-PET/CT in Oncology" and "ACR Practice Guideline for the Performance of Magnetic Resonance Imaging (MRI) of the Liver." The AAPM has reports that address the physical QA of the imaging devices

themselves at their website.[62] For example, AAPM Report 15 "Performance Evaluation and Quality Assurance in Digital Subtraction Angiography" and AAPM Report 52 "Quantitation of SPECT Performance" are both directly applicable to microsphere brachytherapy. As always a well defined local QA procedure should be defined and results reported to the microsphere brachytherapy team.

VII.D. Delivery procedures

The SIR-Spheres® administration set consists of a Perspex shield, the activity vial, and inlet and outlet tubing with needles. Standard 10 or 20 cc injection syringes preloaded with sterile water are required to infuse the microspheres into the delivery catheter. Once the catheter is in place and the authorized user is ready for delivery, the catheter is connected to the outlet tubing. Given the very large number of SIR-Spheres® microspheres required to deliver the intended dose, it is not uncommon for the entire vascular bed to become filled with microspheres and an embolic state to be reached. For this reason, fluoroscopic guidance is essential during the infusion. The technique of SIR-Spheres® infusion involves the alternating infusion of sterile water and contrast, never allowing direct SIR-Spheres®-to-contrast contact. This allows the authorized user to adequately monitor the injection and ensure that vascular embolization has not been reached. In cases where unrecognized vascular embolization occurs and microsphere infusion continues, reflux of microspheres and nontarget radiation delivery becomes a distinct possibility. The infusion is complete if either: (1) the entire intended activity has been infused without reaching stasis, or (2) stasis has been reached and only a portion of the activity has been infused. Given the risk of reflux and nontarget radiation, once stasis has been reached, the continued infusion of SIR-Spheres® is not recommended after blood flow stasis has been reached.

The TheraSphere® accessory kit contains reusable components that include an acrylic box, a personal radiation dosimeter (i.e., RADOS RAD-60R), and a beta shield for the Nalgene® waste container. The TheraSphere® Administration Set consists of preassembled single use components that use a 20 cc syringe to infuse saline through the system. The activity vial containing sterile water and the ^{90}Y glass microspheres is infused through a catheter placed in the hepatic vasculature. Once the catheter is positioned at the treatment site and the authorized user verifies the integrity of the delivery system, the catheter is connected to the outlet tubing. Delivery of TheraSphere® is accomplished by pressurizing the syringe such that greater than 20 cc of sterile saline is delivered through the system per minute for a three French microcatheter. The small volume of microspheres contained in a given activity of TheraSphere® (22–216 mg) dictates that the volume of saline required to infuse a vial of TheraSphere® is low; the majority (>90%) of the microspheres will be infused using less than 10 cc of saline. However, complete infusions should use 60 cc of total fluid. Activity delivery is considered complete when greater than 90% of the activity is delivered, although typical administrations exceed 95% delivery. As part of the delivery device quality assurance, the personal dosimeter is positioned at approximately 3 cm from the 1 cm lead shielded container that houses the activity vial. The personal dosimeter provides a visual indicator for microsphere transfer from the dose vial into the patient via the administration system tubing and catheter.

VII.E. Documentation requirements

While the overall documentation for TheraSphere® and SIR-Spheres® brachytherapy are similar, a few notable differences include preprocedure calculations for ordering the activity required for the procedure. Preliminary dose calculations based on the liver volume to be treated and the lung shunt are even more important for TheraSphere® as the product is available in six activity levels with different quantities of microspheres. An error in the preliminary dose calculations for TheraSphere® would lead to the incorrect activity of ^{90}Y microspheres available on the treatment day. This requirement is a little less stringent for the SIR-Spheres® product as it is only available with 3 GBq (81 mCi).

Dose calculations for microsphere brachytherapy require input from interventional radiologist, nuclear medicine physician, and radiation oncologist and acknowledged by the authorized user on the written directive. It is incumbent on the medical physicist to obtain, verify and record this information. It is convenient to develop forms that allow for step by step calculation of the activity to be ordered. Some institutions may decide to develop spreadsheets for dose calculation purposes. While the use of spreadsheets is convenient for routine microsphere dose calculations, it is incumbent on the medical physicist to ensure that the input data and resulting calculations are correct before the activity is ordered and again before administration. Dose calculation considerations for both products have been previously summarized in this report.

Treatment volumes should be determined as accurately as reasonable using appropriate imaging modalities and image segmenting software. A common approach used in several facilities involves importing the images into the local standard radiation oncology treatment planning system and use the contouring tools available to determine the liver volume to be treated. Once the volume has been determined, the information should be recorded and used for preliminary dose calculations. Other pertinent information needed for dose calculations, such as percentage shunting assessed from a ^{99m}Tc-MAA scan, should also be recorded in the form.

On the day of treatment, the microsphere activity verification should be performed using a dose calibrator and recorded in the written directive. The patient should be surveyed prior to the procedure and the baseline reading as well as background reading should be recorded. It is recommended that each site develop a step by step procedural guide for the delivery of microspheres and all the treatment related information documented during the procedure.

VII.F. Coordination of the medical team

The microsphere brachytherapy program is inherently multidisciplinary in nature. Comprehensive documentation at every step of the process is crucial for a well-organized microsphere brachytherapy program. The success of such a program is contingent on clear and unambiguous communication between the different team members involved in patient care.[63]

The medical team for radioactive microsphere brachytherapy implants to the liver ideally consists of an Interventional Radiologist (IR), Radiation Oncologist (RO), Nuclear Medicine Physician (NMP), Medical Physicist (MP), and Radiation Safety Officer (RSO). One person may perform multiple roles, but all of these specialties should be represented in the treatment team. Each discipline brings special insight into this innovative treatment. The IR provides arterial catheter access and patient care during the procedure. The IR and NMP provide expertise in interpreting the patient's nuclear medicine imaging studies. All physicians including RO, NMP, and IR along with the MP provide input in patient care treatment decision making, brachytherapy planning and delivery expertise. The MP and RSO provide radioactive material handling, regulatory compliance and radiation safety expertise. All of these components must be present in a microsphere brachytherapy team to have an effective and safe treatment team.

Most institutions will already have all of the procedures discussed in this report in some form. The greatest challenge for administrating a QA program for microsphere brachytherapy is coordinating these procedures to cover the needs of the local program and fill any remaining gaps.

VIII. SUMMARY AND RECOMMENDATIONS

The following recommendations are for current best practice procedures and future microsphere brachytherapy improvements.

VIII.A. Recommendations for current best practice:

- Implement a rigorous local QA program for ^{90}Y activity measurements. Establish precise and accurate transfer standards and periodic calibration requirements.
- Utilize a team approach to the overall microsphere brachytherapy QA program.
- Develop and maintain a checklist to demonstrate the QA compliance of all elements of the patient imaging and treatment administration chain.
- Measure activity in a dose calibrator with a constant geometry. Survey meter residual activity measurements should be phased out as a site becomes more confident in the dose calibrator method.
- Verify the local clinic dose calibrator settings with a calibrated activity for each microsphere vendor at least every 2 yr. More frequent comparisons can be made until the user is confident in the measurement results.
- Estimate the lung shunt with fresh ^{99m}Tc MAA as soon as possible after preparation to avoid over-estimation. Imaging within the first hour after injection is recommended while imaging after 4 h is highly discouraged.
- For final activity estimates, use the final measured activity as the activity for dose calculations. The final measured activity is the initial activity contained in the delivery vial minus the residual activity remaining in the delivery vial and tubing at the end of the procedure.
- Make efforts to image a given patient with a consistent protocol throughout the course of diagnosis, treatment and follow-up.
- Use post implant SPECT imaging to confirm qualitatively undesirable deposition of microspheres.
- Review QA reports of all imaging modalities used in microsphere brachytherapy to assure consistent and quality imaging. It is understood that imaging studies from institutions outside of the local clinic most likely will not have their QA reports reviewed.
- Carefully conduct initial angiography studies to map the patient-specific vasculature. A subset of the initial angiography study should be repeated before the treatment to ensure consistency with the original assessment.
- Implement staff training since most departments in a medical clinic do not handle therapeutic levels of radioactivity. Frequent reviews should be held to cover staff turnover. Training should include all members of the treatment team as well as ancillary staff that will come into contact with the patient.
- Determine treatment volumes from physician drawn contours on CT or MR images.
- Periodically review decay-in-storage inventories to assure adequate shielding and shelf space.
- To prevent leaks, keep delivery vial septa penetrations as far apart as practical.
- Only conduct treatments outside vendor recommended indications, which is off-label use, under the supervision of an IRB.[64]

VIII.B. Recommendations for future research and improvements:

- The activity calibration of ^{90}Y microspheres needs to be put on equal footing with other brachytherapy sources. The manufacturers of ^{90}Y microspheres should work with NIST or other national standards laboratories and the ADCL system to create a NIST traceable activity standard that can be transferred to the users independent of the manufacturer.
- Once users of ^{90}Y microspheres have an ADCL system to provide calibration services, the users should adopt the same 2 yr calibration cycle as used for other brachytherapy activity standard verifications.
- Research into dose calculation models and the required physical data should be supported for ^{90}Y microspheres with an eventual goal of inclusion in the Radiological Physics Center (RPC) Brachytherapy Source Registry.
- Use of ^{99m}Tc MAA scans in SPECT/CT systems, with voxel-based dose calculation methods (stochastic Monte Carlo and deterministic methods), is recommended for development of liver, tumor, and lung dose distribution data.

- Collect and aggregate patient dose response data, for tumor and normal tissue, to support the future development of NTCP and TCP models. Replace the MIRD-based, BSA, or other empirically prescribed activity methods with careful 3D dose distribution and dose-volume histogram treatment planning.
- At some research institutions, patients receive multiple microsphere brachytherapy treatments or microsphere brachytherapy in addition to external beam treatments or other radioisotope treatments. Careful 3D dose distribution and dose-volume histogram analysis should be applied to these cases to determine the parameters within which multiple therapies can be safely and effectively delivered.
- Implement image-based heterogeneous dose calculations to better account for bone-tissue–lung interfaces and density differences.
- As 3D dosimetry becomes more developed, biological effective dose (BED) and equivalent uniform dose (EUD) models should be utilized for comparison to external beam based liver dosimetry.

ACKNOWLEDGMENTS

The co-authors would like to acknowledge the contributions of Bonnie Hamilton, Nordion Inc., and Steve Jones, Sirtex Medical Limited. They have provided information about the commercially available radioactive microsphere products throughout the writing of this report. The following co-authors have conflict of interest statements: WD has received honoraria from Sirtex Medical. AK is a consultant to and has received honoraria and research grants from Sirtex Medical. RS is a consultant for Nordion and Sirtex Medical.

[1]C. Breedis and G. Young, "The blood supply of neoplasms in the liver," Am. J. Pathol. **30**, 969–984 (1954).
[2]J. Ingold, G. Reed, and H. Kaplan, "Radiation hepatitis," Am. J. Roentgenol. **93**, 200–208 (1965).
[3]C. C. Pan, B. D. Kavanagh, L. A. Dawson, X. A. Li, S. K. Das, M. Miften, and R. K. T. Haken, "Radiation-associated liver injury," Int. J. Radiat. Oncol. Biol. Phys. **76**, S94–S100 (2010).
[4]L. A. Dawson, C. J. McGinn, D. Normolle, R. K. Ten Haken, S. Walker, W. Ensminger, and T. S. Lawrence, "Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies," J. Clin. Oncol. **18**, 2210–2218 (2000).
[5]A. Kennedy, S. Nag, R. Salem, R. Murthy, A. J. McEwan, C. Nutting, A. Benson, 3rd, J. Espat, J. I. Bilbao, R. A. Sharma, J. P. Thomas, and D. Coldwell, "Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: A consensus panel report from the radioembolization brachytherapy oncology consortium," Int. J. Radiat. Oncol. Biol. Phys. **68**, 13–23 (2007).
[6]A. S. Kennedy, C. Nutting, D. Coldwell, J. Gaiser, and C. Drachenberg, "Pathologic response and microdosimetry of ^{90}Y microspheres in man: Review of four explanted whole livers," Int. J. Radiat. Oncol. Biol. Phys. **60**, 1552–1563 (2004).
[7]E. M. Erbe and D. E. Day, "Chemical durability of Y_2O_3–Al_2O_3–SiO_2 glasses for the in vivo delivery of beta radiation," J. Biomed. Mater. Res. **27**, 1301–1308 (1993).
[8]B. Carr *et al.*, "Hepatic arterial yttrium labeled glass microspheres TheraSphere as treatment for unresectable HCC in 36 patients," *Proceedings of ASCO* Journal of Clinical Oncology, Orlando FL, 2002.
[9]B. Gray, G. Van Hazel, M. Hope, M. Burton, P. Moroz, J. Anderson, and V. Gebski, "Randomised trial of SIR-Spheres plus chemotherapy vs chemotherapy alone for treating patients with liver metastases from primary large bowel cancer," Ann. Oncol. **12**, 1711–1720 (2001).
[10]A. S. Kennedy, W. A. Dezarn, P. McNeillie, D. Coldwell, C. Nutting, D. Carter, R. Murthy, S. Rose, R. R. P. Warner, D. Liu, H. Palmedo, C. Overton, B. Jones, and R. Salem, "Radioembolization for unresectable neuroendocrine hepatic metastases using resin ^{90}Y-microspheres: Early results in 148 patients," Am. J. Clin. Oncol. **31**, 271–279 (2008).
[11]A. S. Kennedy, D. Coldwell, C. Nutting, R. Murthy, D. E. WertmanJr., S. P. Loehr, C. Overton, S. Meranze, J. Niedzwiecki, and S. Sailer, "Resin ^{90}Y-microsphere brachytherapy for unresectable colorectal liver metastases: Modern USA experience," Int. J. Radiat. Oncol. Biol. Phys. **65**, 412–425 (2006).
[12]J. E. Dancey, F. A. Shepherd, K. Paul, K. W. Sniderman, S. Houle, J. Gabrys, A. L. Hendler, and J. E. Goin, "Treatment of nonresectable hepatocellular carcinoma with intrahepatic ^{90}Y-microspheres," J. Nucl. Med. **41**, 1673–1681 (2000).
[13]C. Couinaud, *Le Foie: Études anatomiques et chirurgicales [The Liver: Anatomical and Surgical Studies]* Masson, Paris, France, 1957.
[14]T. W. Leung, W. Y. Lau, S. K. Ho, S. C. Ward, J. H. Chow, M. S. Chan, C. Metreweli, P. J. Johnson, and A. K. C. Li, "Radiation pneumonitis after selective internal radiation treatment with intraarterial ^{90}yttrium-microspheres for inoperable hepatic tumors," Int. J. Radiat. Oncol. Biol. Phys. **33**, 919–924 (1995).
[15]R. Chandra, J. Shamoun, P. Braunstein, and O. L. DuHov, "Clinical evaluation of an instant kit for preparation of ^{99m}Tc-MAA for lung scanning," J. Nucl. Med. **14**, 702–705 (1973).
[16]S. Ho, W. Y. Lau, T. W. Leung, M. Chan, K. W. Chan, W. Y. Lee, P. J. Johnson, and A. K. Li, "Tumour-to-normal uptake ratio of ^{90}Y microspheres in hepatic cancer assessed with ^{99m}Tc macroaggregated albumin," Br. J. Radiol. **70**, 823–828 (1997).
[17]R. J. Lewandowski, K. T. Sato, B. Atassi, R. K. Ryu, A. A. Nemcek, Jr., L. Kulik, J. F. Geschwind, R. Murthy, W. Rilling, D. Liu, L. Bester, J. I. Bilbao, A. S. Kennedy, R. A. Omary, and R. Salem, "Radioembolization with ^{90}Y microspheres: Angiographic and technical considerations," Cardiovasc. Intervent. Radiol. **4**, 571–592 (2007).
[18]J. S. Welsh, A. S. Kennedy, and B. Thomadsen, "Selective Internal Radiation Therapy (SIRT) for liver metastases secondary to colorectal adenocarcinoma," Int. J. Radiat. Oncol. Biol. Phys. **66**, S62–S73 (2006).
[19]http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p990065. Last accessed March 2011.
[20]http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H980006. Last accessed March 2011. This is the original indication. Please see manufacturer for complete current indication as given in the report.
[21]http://www.nucleide.org/DDEP_WG/Nuclides/Y-90_tables.pdf. Last accessed March 2011.
[22]Dosimetry of beta rays and low-energy photons for brachytherapy with sealed sources (Report 72)," J. ICRU 4, (2004).
[23]D. J. Simpkin and T. R. Mackie, "EGS4 Monte Carlo determination of the beta dose kernel in water," Med. Phys. **17**, 179–186 (1990).
[24]R. G. Selwyn, R. J. Nickles, B. R. Thomadsen, L. A. DeWerd, and J. A. Micka, "A new internal pair production branching ratio of ^{90}Y: The development of a non-destructive assay for ^{90}Y and ^{90} Sr," Appl. Radiat. Isot. **65**, 318–327 (2007).
[25]J. A. Siegel, S. R. Thomas, J. B. Stubbs, M. G. Stabin, M. T. Hays, K. F. Koral, J. S. Robertson, R. W. Howell, B. W. Wessels, D. R. Fisher, D. A. Weber, and A. B. Brill, "MIRD pamphlet no. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates," J. Nucl. Med. **40**, 37S–61S (1999).
[26]A. Liu, L. E. Williams, and A. A. Raubitschek, "A CT assisted method for absolute quantitation of internal radioactivity," Med. Phys. **23**, 1919–1928 (1996).
[27]R. Loevinger, T. Budinger, and E. Watson, *MIRD Primer for Absorbed Dose Calculations, Revised Edition* (Society of Nuclear Medicine, New York, 1991).
[28]S. Ho, W. Y. Lau, T. W. Leung, M. Chan, P. J. Johnson, and A. K. Li, "Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer," Eur. J. Nucl. Med. **24**, 293–298 (1997).
[29]S. Ho, W. Y. Lau, T. W. Leung, M. Chan, Y. K. Ngar, P. J. Johnson, and A. K. Li, "Partition model for estimating radiation doses from yttrium-90

microspheres in treating hepatic tumours," Eur. J. Nucl. Med. **23**, 947–952 (1996).
[30]M. G. Stabin, "Update: The case for patient-specific dosimetry in radionuclide therapy," Cancer Biother. Radiopharm. **23**, 273–284 (2008).
[31]K. S. Kolbert, G. Sgouros, A. M. Scott, J. E. Bronstein, R. A. Malane, J. Zhang, H. Kalaigian, S. McNamara, L. Schwartz, and S. M. Larson, "Implementation and evaluation of patient-specific three-dimensional internal dosimetry," J. Nucl. Med. **38**, 301–308 (1997).
[32]Y. K. Dewaraja, S. J. Wilderman, M. Ljungberg, K. F. Koral, K. Zasadny, and M. S. Kaminiski, "Accurate dosimetry in ^{131}I radionuclide therapy using patient-specific, 3-dimensional methods for SPECT reconstruction and absorbed dose calculation," J. Nucl. Med. **46**, 840–849 (2005).
[33]A. Liu, L. E. Williams, G. Lopatin, D. M. Yamauchi, J. Y. C. Wong, and A. A. Raubitschek, "A radionuclide therapy treatment planning and dose estimation system," J. Nucl. Med. **40**, 1151–1153 (1999).
[34]M. J. Guy, G. D. Flux, P. Papavasileiou, M. A. Flower, and R. J. Ott, "RMDP: A dedicated package for ^{131}I SPECT quantification, registration and patient-specific dosimetry," Cancer Biother. Radiopharm. **18**, 61–69 (2003).
[35]I. Clairand, M. Ricard, J. Gouriou, M. Di Paola, and B. Aubert, "DOSE3D: EGS4 Monte Carlo code-based software for internal radionuclide dosimetry," J. Nucl. Med. **40**, 1517–1523 (1999).
[36]J. Lehmann, C. H. Siantar, D. E. Wessol, C. A. Wemple, D. Nigg, J. Cogliati, T. Daly, M. -A. Descalle, T. Flickinger, D. Pletcher, and G. DeNardo, "Monte Carlo treatment planning for molecular targeted radiotherapy within the MINERVA system," Phys. Med. Biol. **50**, 947–958 (2005).
[37]T. Wareing, J. McGhee, J. Morel, and S. Pautz, "Discontinuous finite element $_{SN}$ methods on three-dimensional unstructured grids," Nucl. Sci. Eng. **138**, 256–268 (2001).
[38]J. Mikell, O. Vassiliev, W. Erwin, T. Wareing, and F. Mourtada, "Comparing a grid-based Boltzmann solver with Monte Carlo simulation for voxel-based therapeutic radionuclide dose calculations," Med. Phys. **36**, 2772 (2009).
[39]A. K. Erdi, E. D. Yorke, M. H. Loew, Y. E. Erdi, M. Sarfaraz, and B. W. Wessels, "Use of the fast Hartley transform for three-dimensional dose calculation in radionuclide therapy," Med. Phys. **25**, 2226–2233 (1998).
[40]http://www.doseinfo-radar.com/RADARServices.html. Last accessed March 2011.
[41]D. J. Simpkin, S. J. Cullom, and T. R. Mackie, "The spatial and energy dependence of bremsstrahlung production about beta point sources in H_2O," Med. Phys. **19**, 105–114 (1992).
[42]W. E. Bolch, L. G. Bouchet, J. S. Robertson, B. W. Wessels, J. A. Siegel, R. W. Howell, A. K. Erdi, B. Aydogan, S. Costes, E. E. Watson, A. B. Brill, N. D. Charkes, D. R. Fisher, M. T. Hays, and S. R. Thomas, "MIRD pamphlet no. 17: The dosimetry of nonuniform activity distributions-radionuclide S values at the voxel level. Medical Internal Radiation Dose Committee," J. Nucl. Med. **40**, 11–S36S (1999).
[43]M. Sarfaraz, A. S. Kennedy, M. A. Lodge, X. A. Li, X. Wu, and C. X. Yu, "Radiation absorbed dose distribution in a patient treated with yttrium-90 microspheres for hepatocellular carcinoma," Med. Phys. **31**, 2449–2453 (2004).
[44]G. L. DeNardo, D. J. Macey, S. J. DeNardo, C. G. Zhang, and T. R. Custer, "Quantitative SPECT of uptake of monoclonal antibodies," Semin. Nucl. Med. **19**, 22–32 (1989).
[45]K. F. Koral, Y. Dewaraja, J. Li, Q. Lin, D. D. Regan, K. R. Zasadny, S. G. Rommelfanger, I. R. Francis, M. S. Kaminski, and R. L. Wahl, "Update on hybrid conjugate-view SPECT tumor dosimetry and response in ^{131}I-Tositumomab therapy of previously untreated lymphoma patients," J. Nucl. Med. **44**, 457–464 (2003).
[46]B. E. Zimmerman and R. Collé, "Standardization of ^{63}Ni by $4\pi\beta$ liquid scintillation spectrometry with ^{3}H-standard efficiency tracing," J. Res. Natl. Inst. Stand. Technol. **102**, 455–477 (1997).
[47]K. Kossert and H. Schrader, "Activity standardization by liquid scintillation counting and half-life measurements of ^{90}Y," Appl. Radiat. Isot. **60**, 741–749 (2004).
[48]B. E. Zimmerman, R. Colle, and J. T. Cessna, "Construction and implementation of the NIST triple-to-double coincidence ratio (TDCR) spectrometer," Appl. Radiat. Isot. **60**, 433–438 (2004).
[49]B. E. Zimmerman and G. Ratel, "Report of the CIPM key comparison CCRI(II)-K2.Y-90," Metrologia **42**, 06001 (2005).
[50]L. Mo, B. Avci, D. James, B. Simpson, W. M. Van Wyngaardt, J. T. Cessna, and C. Baldock, "Development of activity standard for ^{90}Y microspheres," Appl. Radiat. Isot. **63**, 193–199 (2005).
[51]R. Selwyn, J. Micka, L. DeWerd, R. Nickles, and B. Thomadsen, "Technical note: The calibration of ^{90}Y-labeled SIR-Spheres® using a nondestructive spectroscopic assay," Med. Phys. **35**, 1278–1279 (2008).
[52]B. M. Coursey, J. M. Calhoun, and J. T. Cessna, "Radioassays of yttrium-90 used in nuclear medicine," Nucl. Med. Biol. **20**, 693–699 (1993).
[53]J. A. Siegel, B. E. Zimmerman, K. Kodimer, M. A. Dell, and W. E. Simon, "Accurate dose calibrator activity measurement of ^{90}Y-ibritumomab tiuxetan," J. Nucl. Med. **45**, 450–454 (2004).
[54]B. E. Zimmerman, J. T. Cessna, and M. A. Millican, "Experimental determination of calibration settings for plastic syringes containing solutions of ^{90}Y using commercial radionuclide calibrators," Appl. Radiat. Isot. **60**, 511–517 (2004).
[55]W. Dezarn and A. Kennedy, "SU-FF-T-380: Significant differences exist across institutions in ^{90}Y activities compared to reference standard," Med. Phys. **34**, 2489 (2007).
[56]W. A. Dezarn and A. S. Kennedy, "Resin ^{90}Y microsphere activity measurements for liver brachytherapy," Med. Phys. **34**, 1896–1900 (2007).
[57]http://www.nrc.gov/materials/miau/med-use-toolkit.html. Last accessed March 2011. Follow links given under heading 'Other Guidance'.
[58]R. Salem and K. G. Thurston, "Radioembolization with ^{90}Yttrium microspheres: A state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part1: Technical and methodologic considerations," J. Vasc. Interv. Radiol. **17**, 1251–1278 (2006).
[59]S. Nag, R. Dobelbower, G. Glasgow, G. Gustafson, N. Syed, B. Thomadsen, and J. F. Williamson, "Inter-society standards for the performance of brachytherapy: A joint report from ABS, ACMP and ACRO," Crit. Rev. Oncol./Hematol. **48**, 1–17 (2003).
[60]IAEA, "Quality assurance for radioactivity measurement in nuclear medicine," International Atomic Energy Agency Technical Report Series No. 454 (2006).
[61]http://acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/toc.aspx. Last accessed March 2011.
[62]http://www.aapm.org/pubs/reports. Last accessed March 2011.
[63]W. A. Dezarn, "Quality assurance issues for therapeutic application of radioactive microspheres," Int. J. Radiat. Oncol. Biol. Phys. **71**, S147–S151 (2008).
[64]B. R. Thomadsen, H. T. Heaton II, S. K. Jani, J. P. Masten, M. E. Napolitano, Z. Ouhib, C. S. Reft, M. J. Rivard, T. T. Robin, M. Subramanian, and O. H. Suleiman, "Off-label use of medical products in radiation therapy: Summary of the report of AAPM task group no. 121," Med. Phys. **37**, 2300–2311 (2010).