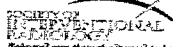


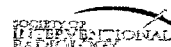
Interventional Radiology: Pathway to Authorized User Status

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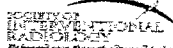
Introduction

- Discuss next steps in evolution of Y90 at NRC guidance level
- Representation
 - Society of Interventional Radiology
 - American Board of Radiology



Review

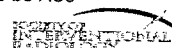
- Yttrium 90 microsphere therapy
 - Available in the USA since 2000
 - TheraSphere (glass), SIR-Spheres (resin)
 - Steady increase in adoption as treatment option (> 5000 patients treated to date)
- Classified as brachytherapy device
 - Status → 35.490
 - Recent addition of 35.390
 - Intent was for IRs to fall under 35.390



Collaborative Efforts

RECOMMENDATIONS FOR RADIOEMBOLIZATION OF HEPATIC MALIGNANCIES USING YTTRIUM-90 MICROSPHERE BRACHYTHERAPY: A CONSENSUS PANEL REPORT FROM THE RADIOEMBOLIZATION BRACHYTHERAPY ONCOLOGY CONSORTIUM

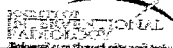
- Consensus statement, International Journal of Radiation Biology and Physics 2006
- Representation by
 - 3 Radiation Oncologists
 - 5 Interventional Radiologists
 - 1 Surgeon
 - 2 Medical Oncologists
 - 1 Nuclear Medicine
- → RO, NM and IR all qualified to be AUs



Collaborative Efforts

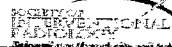
PRACTICE GUIDELINE FOR RADIOEMBOLIZATION WITH MICROSPHERE BRACHYTHERAPY DEVICE (RMBD) FOR TREATMENT OF LIVER MALIGNANCIES

- Consensus statement, ACR Practice Guidelines 2008
- Representation by
 - 4 Radiation Oncologists (ASTRO, ACRO)
 - 4 Interventional Radiologists (SIR, ABR)
 - 6 members of ACR
- ACR Guidelines Radiation Oncology Committee
 - 14 members
- ACR Guidelines Interventional Committee
 - 12 members
- Comments Reconciliation Committee
 - 30 members
- → RO, NM and IR all qualified to be AUs



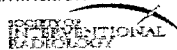
Scope of Issue

- NRC published guidance document
 - Discusses pathway to AU
 - 35.390, 35.490
 - Vendor specific training
- Many states/local RSO/RSC uncertain that IRs fulfill the requirements of 35.390
 - creates confusion
 - impedes ability to gain AU status
 - limits access of patients to therapeutic options



Interventional Radiology Training

- Diagnostic Radiology: 5 years
 - 700-960 clinical hours in nuclear medicine
 - 80 hours didactic (classroom/laboratory training)
- Formal written radiation physics examination
 - Radiation safety/protection/biology/effects on tissue
- Formal written radiology examination
- Formal oral radiology examination



Interventional Radiology Training

Diagnostic Radiology (80 hours under an AU)

- diagnostic radiologic physics, instrumentation, and radiation biology
- patient and medical personnel safety (i.e., radiation protection)
- the chemistry of by-product material for medical use
- biologic and pharmacologic actions of materials administered in diagnostic and therapeutic procedures
- topics in safe handling, administration, and quality control of radionuclide doses used in clinical medicine



Interventional Radiology Training

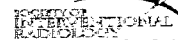
Diagnostic Radiology (80 hours under an AU)

- ordering, receiving, and unpacking radioactive material safely
- performing the related radiation surveys
- safe elution and quality control (QC) of radionuclide generator systems
- calculating, measuring, and safely preparing patient dosages
- calibration and QC of survey meters and dose calibrators
- safe handling and administration of therapeutic doses of unsealed radionuclide sources (i.e., I-131)
- written directives
- response to radiation spills and accidents (containment and decontamination procedures)
- radiation signage and related materials
- using administrative controls to prevent medical events involving the use of unsealed byproduct material



Interventional Radiologists Today: Qualifications for AU

- Perform Y90 safely and effectively
 - institutions with IRs, nonIRs as AUs
- Critical safety and efficacy issue
 - revolve around patient selection for liver directed therapy, safe delivery of treatment using advanced catheterization techniques → realm of IR
- Worked extensively with Y90
 - Courses, workshops, national/international symposia
 - Vast majority of research being performed by IRs
 - Participated in consensus documents
- AUs being proctored and trained by IRs



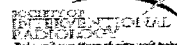
Proposal

- Authorized User Status
 - 35.390 or 35.490
 OR
 - 35.290 (Interventional Radiology) + ABR administered examination (primary clinical certificate in Y90)



Society of Interventional Radiology American Board of Radiology Yttrium 90 AU Course/Workshop

- Number of Hours TBD
- Taught by:
 - Interventional Radiologists
 - Radiation Oncologists
 - Nuclear Medicine Physicians
 - Nuclear Medicine Physicists/Health Physics Experts



Society of Interventional Radiology American Board of Radiology Yttrium 90: Course/Workshop Content Part 1

PATIENT SELECTION AND PREPARATION

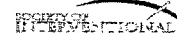
- Identification/screening eligible patients
- vascular mapping and ^{99m}Tc -MAA scanning
- angiographic technique/preparation of hepatic vasculature to administer the therapy
- treatment planning and dosimetry
- radiation safety and monitoring procedures specific to ^{90}Y microsphere dose preparation and administration
- respective technical and clinical aspects unique to the administration of each type of ^{90}Y microsphere therapy
- clinical follow-up and imaging evaluation of patients treated



Society of Interventional Radiology American Board of Radiology Yttrium 90: Course/Workshop Content Part 2

DOSAGE SELECTION AND PREPARATION FOR ^{90}Y

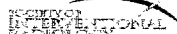
- Radiation physics and instrumentation
- Radiation protection
- Mathematics pertaining to the use and measurement of radioactivity
- Chemistry of byproduct material for medical use
- Radiation biology of beta-isotopes
- Discussion on ordering, receiving, and unpacking radioactive materials safely and performing the related radiation surveys
- Discussion on performing quality control procedures on instruments used to determine the activity of dosages, and performing checks for operation of survey meters
- Discussion on calculating, measuring, and safely preparing patient or human research subject dosages
- Using administrative controls to prevent a medical event involving the use of the beta-isotope
- Using procedures to contain spilled byproduct material safely and using proper decontamination procedures



VENDOR SPECIFIC TRAINING

VENDOR TRAINING

- Sirtex medical-Introductory presentation/discussion, on-site proctors
- MDS Nordion-Introductory presentation/discussion, training course, on-site proctors



Authorized User: Summary

Pathway 1:

35.390/490 + vendor training per NRC guidance

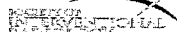
Pathway 2:

35.290 + ABR certificate + vendor training per NRC guidance



Conclusion

- American Board of Radiology
 - Will support an examination for ^{90}Y AU for qualified Interventional Radiologists
 - → primary AU certificate for ^{90}Y
 - Not preclude vendors from onsite support and proctoring as per NRC guidance
- Discussion



REPORT

RECOMMENDATIONS FOR RADIOEMBOLIZATION OF HEPATIC MALIGNANCIES USING YTTRIUM-90 MICROSPHERE BRACHYTHERAPY: A CONSENSUS PANEL REPORT FROM THE RADIOEMBOLIZATION BRACHYTHERAPY ONCOLOGY CONSORTIUM

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 RIAD SALEM, M.D., M.B.A., F.S.I.R.,[‡] RAVI MURTHY, M.D., F.A.C.P.,[§]
 ALEXANDER J. MCEWAN, M.D.,^{||} CHARLES NUTTING, D.O.,[¶] AL BENSON, III, M.D., F.A.C.P.,[‡]
 JOSEPH ESPAT, M.D., M.S., F.A.C.S.,[#] JOSE IGNACIO BILBAO, M.D.,**
 RICKY A. SHARMA, M.D., PH.D.,^{††} JAMES P. THOMAS, M.D., PH.D.,[†]
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 Pamplona, Spain; ^{††}Royal Marsden Hospital, London, UK; and ^{‡‡}University of Texas Southwestern Medical Center, Dallas, TX

Purpose: To standardize the indications, techniques, multimodality treatment approaches, and dosimetry to be used for yttrium-90 (Y90) microsphere hepatic brachytherapy.

Methods and Materials: Members of the Radioembolization Brachytherapy Oncology Consortium met as an independent group of experts in interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology to identify areas of consensus and controversy and to issue clinical guidelines for Y90 microsphere brachytherapy.

Results: A total of 14 recommendations are made with category 2A consensus. Key findings include the following. Sufficient evidence exists to support the safety and effectiveness of Y90 microsphere therapy. A meticulous angiographic technique is required to prevent complications. Resin microsphere prescribed activity is best estimated by the body surface area method. By virtue of their training, certification, and contribution to Y90 microsphere treatment programs, the disciplines of radiation oncology, nuclear medicine, and interventional radiology are all qualified to use Y90 microspheres. The panel strongly advocates the creation of a treatment registry with uniform reporting criteria. Initiation of clinical trials is essential to further define the safety and role of Y90 microspheres in the context of currently available therapies.

Conclusions: Yttrium-90 microsphere therapy is a complex procedure that requires multidisciplinary management for safety and success. Practitioners and cooperative groups are encouraged to use these guidelines to formulate their treatment and dose-reporting policies. © 2007 Elsevier Inc.

Radioembolization, Hepatic neoplasms, Yttrium-90, Microsphere, Brachytherapy.

INTRODUCTION

The key limitation of external beam radiotherapy in the treatment of primary or metastatic liver tumors is the tolerance of normal liver parenchyma to radiation. The dose required to destroy solid tumor, estimated at ≥ 70 Gy, is far greater than the liver tolerance dose of 35 Gy delivered to the whole liver in 1.8 Gy/d fractions (1).

Unlike most organs, the liver has a dual blood supply: the hepatic artery and the portal vein. Observations on vascular supply to hepatic malignancies have demonstrated that metastatic hepatic tumors >3 mm derive 80–100% of their blood supply from the arterial rather than the portal hepatic circulation (2). This fundamental concept is the foundation for the intra-arterial administration of brachytherapy with microspheres embedded with the beta-emitting isotope,

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Acknowledgments—The authors thank Mr. David Carpenter for editorial assistance; and Drs. James Andrews, David Berry, Keith Blanshard, Huan Giap, Thomas Helmberger, W. Scott Helton,

Nasir Khan, Johannes Lammer, David Liu, Val Lewington, Bruno Sangro, James Welsh, and Christoph Johannes Zech for their expert review and valuable suggestions.

Conflict of interest: none.

Received May 8, 2006 and in revised form Nov 1, 2006.
 Accepted for publication Nov 20, 2006.

yttrium-90 (Y90). There are two components to this radioembolization procedure: embolization and brachytherapy. The angiographic endpoints of embolization and stasis and the need to modify the delivery according to angiographic findings under fluoroscopy define the treatment as an embolization procedure. The administration and delivery of radiation with modification of dose based on tumor and target volume define this treatment as a brachytherapy procedure.

At present, more than 3,000 patients have been treated with Y90 microsphere brachytherapy in more than 80 medical centers worldwide. Unfortunately, there are currently no large-scale, prospective clinical trials to guide practitioners on the use of this technology. Therefore it is important to carefully review the available clinical data regarding the indications, techniques, multimodality treatment approaches, and dosimetry used for liver microsphere brachytherapy and formulate guidelines to avoid toxicity and poor tumor response. The optimal management of these patients involves coordinated expertise from a variety of disciplines. The complex overlap of responsibilities and the skills required in Y90 microsphere brachytherapy emphasize the urgent need to establish guidelines for this treatment modality.

METHODS AND MATERIALS

The Radioembolization Brachytherapy Oncology Consortium (REBOC) is an independent group of experts from the fields of interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology involved with Y90 microsphere therapy. Selected members of the REBOC panel (chair and principal investigator, Dr. Subir Nag) met in Columbus, Ohio on April 6–8, 2006 to identify areas of consensus and controversy and issued clinical guidelines for Y90 microsphere brachytherapy after reviewing all available unpublished and published data. These recommendations were all in Category 2A, with the categories of consensus used by the panel being similar to those used in National Comprehensive Cancer Network guidelines:

- Category 1: There is uniform panel consensus, based on high-level evidence, that the recommendation is appropriate.
- Category 2A: There is uniform panel consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.
- Category 2B: There is nonuniform panel consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.
- Category 3: There is major disagreement among panel members that the recommendation is appropriate.

To safeguard against potential biases arising from conflict of interest, the panel required written disclosure of any potential conflict of interest. To guard against overemphasis of any individual bias or exclusion of expert opinion, members from all involved specialties were included on the panel. Costs associated with developing this report were borne by an unrestricted educational grant from Sirtex Medical (Lane Cove, Australia) and MDS Nordion (Kanata, Ontario, Canada) to the Ohio State University, with Dr. Subir Nag being the principal investigator. These corporate sponsors had no panel membership or review of the text. The

American College of Radiation Oncology, American Brachytherapy Society, Society of Interventional Radiologists, Society of Nuclear Medicine, and the Cardiovascular and Interventional Radiologic Society of Europe had representatives in the panel; however, this report represents the opinions of the individual panel members and does not necessarily imply an official endorsement by the represented societies.

This initial report was sent for review and comments to the sponsoring societies and selected Y90 users who were not part of the panel for broader input. The report was then revised according to the comments of these external reviewers before journal submission. It should be noted that these broad recommendations are intended to be technical and advisory in nature; however, the responsibility for medical decisions ultimately rests with the treating physician. This is a constantly evolving field, and the recommendations are subject to modifications as new data become available.

RESULTS

The deliberations and recommendations of the panel are presented here to guide ongoing clinical practice and future investigations. An executive summary of the recommendations is listed in Table 1.

Y90 glass vs. resin microspheres

Currently two different Y90 microsphere products, glass microspheres and resin microspheres, are available in North America; only the resin type is available worldwide. In the United States, practitioners need to keep in mind that glass Y90 microspheres are approved by the U. S. Food and Drug Administration (FDA) for treatment of unresectable hepatocellular carcinoma under the provisions of a “humanitarian device exemption” (HDE no. H9800006), which includes unique restrictions on the medical use of the device. One of the conditions of approval for a humanitarian device exemption is that there be institutional review board initial review and approval before a humanitarian-use device is used at a facility, as well as continuing review of its use. Resin microspheres have received FDA premarket approval for hepatic metastases from colorectal cancer, concurrent with fluorodeoxyuridine (FUDR). Any other use of resin microspheres is an off-label use and, although it does not need institutional review board approval, the physician performing the treatment should understand their responsibilities in this regard. There has been no direct comparison of the efficacy of the two microsphere products. Similarities and differences between the glass and resin microspheres are outlined in Table 2 (3).

Radioembolization team

The REBOC panel strongly emphasizes that a multidisciplinary team approach, combining the expertise and skill of various specialties, is essential in the management of patients with primary and metastatic liver cancers. The team should include individuals with expertise necessary to (1) assume overall medical management of the cancer patient, (2) perform vascular catheterization, (3) perform and interpret radiologic scans, (4) assume responsibility for the de-

Table 1. Executive summary of the Radioembolization Brachytherapy Oncology Consortium Consensus Panel recommendations

No.	Recommendation
1	The panel believes that there is sufficient evidence to support the safety and effectiveness of yttrium-90 (Y90) microsphere therapy in selected patients.
2	A multidisciplinary team approach combining the expertise and skill of various specialties is essential in the management of patients with primary and metastatic liver cancers. This team approach can be achieved at different institutions by involving various combinations of personnel from the disciplines of interventional radiology, radiation oncology, nuclear medicine, medical physics, hepatology, surgical oncology, medical oncology, and radiation safety, depending on their availability at the local institution.
3	Candidates for radioembolization are patients with unresectable primary or metastatic hepatic disease with liver-dominant tumor burden and a life expectancy >3 months.
4	Absolute contraindications to Y90 microsphere treatment include pretreatment ^{99m}Tc macro-aggregated albumin (MAA) scan demonstrating the potential of >30 Gy radiation exposure to the lung or flow to the gastrointestinal tract that cannot be corrected by catheter techniques. It is important that liver injection of MAA is delivered with flow rates and catheter position that mimic the anticipated Y90 infusion rate and catheter position.
5	Relative contraindications to Y90 microsphere treatment include limited hepatic reserve, irreversibly elevated bilirubin levels, compromised portal vein (unless selective or superselective radioembolization can be performed), and prior radiation therapy involving the liver.
6	Essential pretreatment investigations include cross-sectional imaging with CT or MRI, serum chemistry, and tumor markers. [18]Fluorodeoxyglucose positron emission tomography may be a useful adjunct to determine the site of treatment failure in the presence of hepatic and extrahepatic disease, to rectify the inability to follow tumor markers, and to account for or clarify presence of discordant posttreatment findings on CT and/or MRI.
7	Flow characteristics in the hepatic artery and avoidance of extrahepatic deposition of the microspheres are optimally detected and prevented by percutaneously inserted arterial catheters under fluoroscopy rather than by indwelling intra-arterial catheters.
8	Meticulous angiographic techniques are required for patients under consideration for radioembolization. All extrahepatic vessels originating from the hepatic arteries that supply the gastrointestinal tract should, under most circumstances, be embolized to exclude extrahepatic deposition of the Y90 microspheres.
9	In the presence of bilobar disease, either a single whole liver infusion of Y90 microspheres or sequential unilobar liver treatment is acceptable. Patients with unilobar disease should receive therapy only to the affected lobe.
10	The prescribed activity estimated by the body surface area method for resin microspheres is more consistent with the delivered dose in clinical practice and therefore should be the method of choice. For glass microspheres, the prescribed activity calculation method described by the manufacturer is recommended.
11	It is recognized that there is wide geographic and institutional variation in the regulation of the use of Y90 microspheres. Users should comply with local and national regulations.
12	By virtue of their training, certification, involvement, and contribution to Y90 microsphere treatment programs, the disciplines of radiation oncology, nuclear medicine, and interventional radiology are all qualified to use Y90 microspheres. They need to fulfill the training and experience requirements set in Code of Federal Register 10, Part 35.390 or 35.490.
13	The panel strongly advocates the creation of a treatment registry with uniform reporting criteria.
14	Initiation of clinical trials is essential to further define the safety and role of Y90 microspheres in the context of currently available therapies.

livery of the Y90 microspheres and be the authorized user, and (5) monitor radiation safety. This team approach can be achieved at different institutions by involving various com-

binations of personnel from the disciplines of interventional radiology, radiation oncology, nuclear medicine, medical physics, hepatology, surgical oncology, medical oncology, and radiation safety, depending on their availability at the local institution. A treatment schema is shown in Fig. 1.

Table 2. Properties of resin and glass yttrium-90 microspheres

Parameter	Resin	Glass
Trade name	SIR-Spheres	TheraSpheres
Manufacturer and location	Sirtex Medical, Lane Cove, Australia	MDS Nordion, Kanata, Canada
Diameter	20–60 μ^*	20–30 $\mu^†$
Specific gravity	1.6 g/dL	3.6 g/dL
Activity per particle	50 Bq	2500 Bq
Number of microspheres per 3-GBq vial	40–80 $\times 10^6$	1.2 $\times 10^6$
Material	Resin with bound yttrium	Glass with yttrium in matrix

* SIR-Spheres package insert. Sirtex Medical, Lane Cove, Australia.

† TheraSphere package insert. MDS Nordion, Kanata, Canada.

Indications and patient selection

Success in treatment of tumors in the liver by locoregional therapy, whether bland embolization, chemoembolization, or radioembolization, relies on the presence of appropriate indications to ensure that patients receive safe and effective therapy. Because the nature of primary and secondary hepatic malignancies differs, therapy should be tailored to the disease. The integration of combination therapy with irinotecan, oxaliplatin, and bevacizumab has improved response rates and survival of patients with metastatic colorectal cancer, as demonstrated in large randomized trials (4–6). It is also notable that the responses seen with newer combination regimens sometimes convert patients with un-

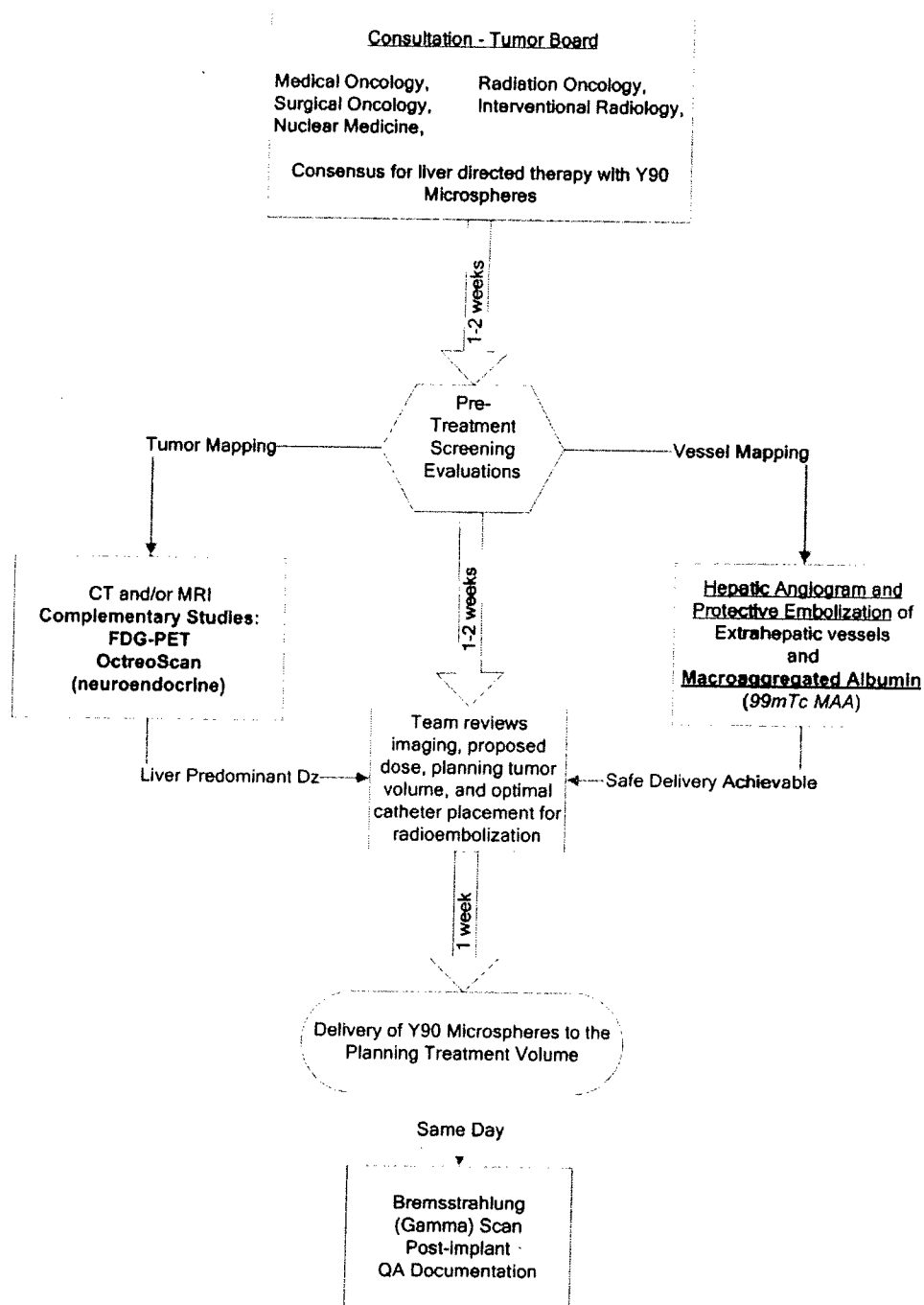


Fig. 1. Treatment algorithm for yttrium-90 microsphere brachytherapy.

resectable liver metastases to resectable status. Similarly, patients with hepatic metastases from other primary sites should be offered standard systemic treatment options with known survival benefit before Y90 treatment. In the case of primary liver tumors, patients should undergo hepatology and transplant evaluations to determine the optimal treatment strategy.

Patients considered for radioembolization therapy would include those with (1) unresectable hepatic primary or metastatic cancer, (2) liver-dominant tumor burden, and (3) a life expectancy of at least 3 months. In metastatic colorectal

cancer, radioembolization therapy can be given (1) alone after failure of first-line chemotherapy, (2) with FUDR during first-line therapy, or (3) during first- or second-line chemotherapy on a clinical trial.

Contraindications for radioembolization therapy may include (1) pretreatment ^{99m}Tc macro-aggregated albumin (MAA) scan demonstrating the potential of ≥ 30 Gy radiation exposure to the lung or flow to the gastrointestinal tract resulting in extrahepatic deposition of ^{99m}Tc MAA that cannot be corrected by catheter embolization techniques, (2) excessive tumor burden with limited hepatic reserve, (3)

elevated total bilirubin level (>2 mg/dL) in the absence of a reversible cause, and (4) compromised portal vein, unless selective or superselective radioembolization can be performed. Patients with prior radiotherapy involving the liver should be carefully reviewed on a case-by-case basis. It is unclear whether capecitabine chemotherapy treatments represents a contraindication to Y90 treatment.

Investigations and workup

Treatment with Y90 microspheres must be based on cross-sectional images and arteriograms in the individual patient. The workup should include three-phase contrast CT and/or gadolinium-enhanced magnetic resonance imaging of the liver for assessment of tumoral and nontumoral volume, portal vein patency, and extent of extrahepatic disease. Whole body positron emission tomography (PET) can be very helpful. Serum chemical analyses should be performed to evaluate hepatic and renal function and to determine the presence and magnitude of elevation of tumor markers. Patients with irreversible elevations in serum bilirubin should be excluded. In the presence of renal insufficiency, care must be taken to avoid or minimize the use of iodinated contrast material. Pretreatment hepatic artery ^{99m}Tc MAA scan is performed to evaluate hepatopulmonary shunting.

Angiographic evaluation of hepatic vasculature

Once a patient has been selected as a candidate for radioembolization, an initial angiographic evaluation that includes abdominal aortogram, superior mesenteric and celiac arteriogram, and selective right and left hepatic arteriogram is to be performed within 1 h of treatment, primarily to document the visceral anatomy, provide information on perfusional flow characteristics of the targeted vascular territory, identify anatomic variants, and isolate the hepatic circulation by occluding extrahepatic vessels (7). Flow characteristics in the hepatic artery are optimally detected and extrahepatic deposition of the microspheres is prevented by percutaneously inserted arterial catheters under fluoroscopy rather than by the use of indwelling arterial catheters connected to an implanted device. Given the possibility of nontarget deposition of microspheres, this panel recommends the prophylactic embolization of all extrahepatic vessels at the time of MAA assessment, including the gastroduodenal, right gastric, and other extrahepatic vessels, to avoid extrahepatic deposition of microspheres. It is to be noted that these vessels/organs can revascularize quickly, and therefore the embolization should be performed close to the intended time of radioembolization, with a check arteriogram required before radioembolization to ensure that such revascularization has not occurred.

Lobar vs. whole liver treatment/MAA

Depending on the anatomic distribution of tumor, as well institutional preferences, whole liver or unilobar approaches may be considered. For the assessment of lung shunting fraction, unilobar or whole liver injection of MAA may be

performed. Irrespective of the location of MAA injection, it is imperative that the MAA be delivered with flow rates and catheter position that mimic the anticipated Y90 infusion rate. Whole liver or unilobar infusions of Y90 may be considered at the discretion of the treating team, according to tumor characteristics and location. Scintigraphy should be performed within 1 h of injection of MAA to prevent false-positive extrahepatic activity due to free technetium.

Posttreatment radiologic evaluations

The most common change in the CT appearance of the liver after radioembolization is decreased attenuation in the treated hepatic parenchyma and is representative of liver edema, congestion, and microinfarction, a reversible process that is incidental and self-limiting. Early posttreatment CT imaging is often misleading at defining tumor response, owing to the time-dependent, partially reversible attenuation changes. As such, care must be taken to avoid misinterpretation of early imaging as progression of disease (8, 9). Computed tomography imaging may demonstrate Y90-associated effects on adjacent organs, which may include thickening of the duodenum, stomach, and gallbladder. The effects of Y90 microsphere therapy on liver metastases have been compared by CT, magnetic resonance, and PET in small cohort studies. Positron emission tomography imaging may show attenuated metabolic activity, a finding that suggests treatment response that may be discordant with findings on CT images (10). However, PET may be beneficial in monitoring treatment response for selected patients. A postprocedure Bremsstrahlung scan is recommended within 24 h after treatment to evaluate distribution of Y90.

Radiation safety issues

In the United States, Y90 therapy is regulated by the Nuclear Regulatory Commission (<http://www.nrc.gov>) under the Code of Federal Register (CFR) 10, part 35.1000, as a brachytherapy device (not a drug) used for permanent brachytherapy implantation therapy. Each microsphere treatment vial contains millions of spheres, and therefore individual sources cannot be counted or leak tested. They are only to be used under the supervision of an authorized user, who must meet the training and experience requirements for manual brachytherapy (set in CFR 10, part 35.490), as well as the specific vendor training in the use of the microspheres and the microsphere delivery system. For U.S. institutions performing brachytherapy under a broad-scope license, the physician must be authorized by the institutional radionuclide committee. The REBOC panel believes that by virtue of their training, certification, involvement, and contribution to Y90 microsphere treatment programs, the disciplines of radiation oncology, nuclear medicine, and interventional radiology are all qualified to use Y90 microspheres. They would need to fulfill the training and experience requirements set in CFR 10, part 35.390 (for unsealed sources) or 35.490 (for manual brachytherapy), as well as the specific vendor training. As of April

2006, this possible amendment was under discussion at the Nuclear Regulatory Commission.

For Y90 microspheres, the "prescribed dose" means the total dose documented in the written directive. The written directive should include (1) before implantation: the treatment site, the radionuclide (Y90 microspheres), and dose (in gigabecquerels); and (2) after implantation but before completion of the procedure: the radionuclide (Y90 microspheres), treatment site, and the total dose. It is important to consider stopping the radioembolization procedure when there is slowed antegrade flow (before total vascular stasis has been reached) to prevent reflux of microspheres into unintended vessels. This is recognized as an acceptable reason to terminate the delivery of Y90 before the prescribed dose has been delivered. Hence, in addition to the dose, "stopped when there is slowed antegrade flow" should be included in the written directive. If the implantation was terminated because of slowed antegrade flow, then the total dose is the value of the total dose delivered when slowed antegrade flow occurred and the implantation was terminated. The written directive should specify the maximum dose that would be acceptable for a specified site (or sites) outside the primary treatment site to which the microspheres could be shunted (such as the lung and gastrointestinal tract). Procedures should describe measures taken to ensure that the Bremsstrahlung emissions from each patient or human research subject permits his/her release in accordance with local regulations.

Radiation precautions guidelines are as follows.

- Although Y90 is a beta emitter with limited penetration in tissues, it nonetheless represents a source of gamma emission—Bremsstrahlung that can interact with any tissue in the body. Microspheres can cause significant problems if spilled.
- Unlike liquid isotope spills, which can be mopped up, the tiny microspheres can become lodged in crevices from which they are difficult to remove, or they can disperse in the air and be inhaled.
- Pregnant staff and/or pregnant family members should be excluded from procedural or postprocedural care of Y90 patients.
- Infusion personnel must remain behind delivery apparatus containing the dose. Anyone assisting should remain clear of the tubing connected to the catheters.
- The angiographic suite area immediately underneath personnel involved in dose administration should be draped and plastic covers placed over pedals as a precautionary measure in case of spillage.
- Double gloves, double shoe covering, and protective eye-wear are advised for administering staff.
- The delivery catheter should be considered radioactive and disposed of, observing radiation precautions. All other potentially contaminated material (*i.e.*, exit tubing from the dose vial, three-way valve, tube to catheter, needles, gloves, gauzes, hemostat, and drapes) should be

considered radioactive and disposed of, observing radiation precautions, after catheter removal.

- Tubing and syringes to deliver and flush and the catheter sheath are not considered "hot" and therefore do not need special radiation precautions for disposal. However, they should be surveyed for radioactivity before routine disposal.
- All personnel within the angiography suite must have their shoe covers checked for radiation at the end of the procedure and before leaving the suite. The suite must be checked at the end of the procedure after all contaminated waste and the patient have been removed from the room to detect any radiation contamination.
- Special shielding requirements are not necessary for post-procedure nursing care.
- Yttrium-90 resin microspheres may have trace amounts of free Y90 on their surface, which can be excreted in the urine during the first 24 h. Patients are advised to wash their hands after voiding. Men should sit to urinate, and the urinal double-flushed after voiding. These precautions should be undertaken for 24 h after treatment. In contrast, Y90 glass microspheres are not known to have free Y90 in trace amounts in the treatment vial; therefore, no special precautions are necessary for handling of urine of patients treated with Y90 glass microspheres.
- A letter should be given to the patient at discharge confirming they have received radiation internally. Additionally, a wristband indicating the isotope given, date delivered, and a contact number for questions can be helpful. This wristband is to be worn by the patient for 1 week after discharge.

Figure 2 is a copy of the radiation safety instructions given to patients at Ohio State University after discharge from Y90 resin microsphere treatment. As noted, there is no need to make special arrangements for body fluids (urine, stool, blood, or vomit) for glass microsphere patients upon discharge.

Dosimetry

Yttrium-90 is produced by neutron bombardment of ^{89}Y in a commercial reactor, yielding a pure beta emitter with an average energy of 0.94 MeV, tissue penetration of 2.5 mm, and a maximum range of 1.1 cm. One gigabecquerel (27 mCi) of Y90 delivers a total dose of 50 Gy/kg in tissue. No significant amount of Y90 leaches from the sphere (11), and it decays to stable zirconium-90 with a half-life of 2.67 days (64.2 h).

Both single and multiple deliveries are safe and widely used, and some related terminology has developed. The intended portion of the liver for treatment is the *planning target volume* (PTV), as defined by the International Commission on Radiation Units and Measurements, which may be a solitary lesion, a segment, a lobe, or both lobes. Treating multiple tumors within the entire liver in a single treatment session is termed a *whole liver delivery*. Treating the entire liver by first treating one lobe and then the other

Radiation Safety Discharge Instructions for Patients with Radioactive Y90 Resin Microspheres for Liver Brachytherapy			
<p>Y90 resin microspheres are radioactive sources that, over time, become inactive. This means that for the next few days there will be a small amount of radioactivity near your liver. This does not represent a significant risk to others. However, to be on the safe side, these precautions and instructions should be followed:</p> <ol style="list-style-type: none"> 1. Patients are advised not to be in close contact (< 1 meter) with others for extended periods of time during the first week after microsphere therapy. 2. If you have to go to a doctor or Emergency Room or need surgery within 3 days of this treatment, notify the medical staff that you have a small amount of radiation in your liver. Your physicians should give you any immediate and necessary medical or surgical treatments without concern for the radiation in the liver. They can call Radiation Medicine or Radiation Safety with any questions regarding the details of the treatment. 3. There is NO need to make special arrangements for body fluids (urine, stool, blood or vomit) for glass microspheres, or after 24 hours if resin microspheres. <p>If you have questions concerning radiation safety, please call the following contacts:</p> <p style="padding-left: 40px;">During normal working hours:</p> <p style="padding-left: 80px;">Radiation Medicine:</p> <p style="padding-left: 80px;">Radiation Safety Officer:</p> <p style="padding-left: 40px;">After hours:</p> <p>I have read and understand the above radiation safety instructions and agree to abide by them.</p> <table style="width: 100%; margin-top: 20px;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>_____ Patient Signature</p> <p>Date: _____</p> </td> <td style="width: 50%; vertical-align: top;"> <p>_____ Radiation Safety Signature</p> <p>Date: _____</p> </td> </tr> </table>		<p>_____ Patient Signature</p> <p>Date: _____</p>	<p>_____ Radiation Safety Signature</p> <p>Date: _____</p>
<p>_____ Patient Signature</p> <p>Date: _____</p>	<p>_____ Radiation Safety Signature</p> <p>Date: _____</p>		

Fig. 2. Radiation safety discharge instructions for patients with radioactive yttrium-90 resin microspheres for liver brachytherapy.

in separate sessions is termed *sequential delivery*; both are described in the literature. Treatment to a single lobe only is termed *lobar delivery*. A 90-day interval before retreatment of the PTV is recommended to allow for adequate hepatic

healing. In sequential treatments, a 30–45-day interval is the generally accepted practice (10, 12, 13).

All patients are to have CT treatment planning with reconstruction of the liver volumes (whole liver, right lobe,

and left lobe). The required activity for treatment of each patient is to be calculated differently according to whether glass or resin microspheres are to be used.

Resin microspheres are received in bulk, and the individual medical centers extract the desired activity from a 3-GBq source vial that arrives on the day of treatment. This process differs from that for glass microspheres; these arrive a few days before the procedure, and the entire vial containing the spheres is delivered to the tumor. When choosing an activity, the significant physical differences between the two spheres must be considered. (1) Activity per microsphere: glass microspheres contain 2,500 Bq per sphere; thus, only 1–2 million spheres are delivered for the typical patient (11). This number of glass spheres is not sufficient to cause significant embolization in the main hepatic arteries. Resin microspheres contain approximately 50 Bq per sphere; thus, an average treatment contains 40–60 million spheres, a number that can cause embolic effects in the arteries (11). (2) Embolic effect on dose delivery: glass microspheres are received in the requested activity, and all of the spheres in the vial are completely infused. The prescribed activity of resin spheres cannot always be infused, owing to slowed antegrade hepatic arterial flow. When delivery of spheres is stopped earlier than planned, the residual activity in the delivery vial is measured and deducted from the activity present at the beginning of the procedure to obtain the amount infused.

Glass Y90 microsphere prescribed activity calculation

The activity determination for glass microspheres is based on a nominal target dose and the patient's liver mass, which is determined from the CT data and assumes uniform distribution of the microsphere throughout liver volume:

$$A \text{ (GBq)}_{\text{glass}} = \frac{D(\text{Gy}) \times M(\text{kg})}{50} \quad (1)$$

In this equation, A is the activity, D the nominal target dose, and M the liver mass for the PTV (*i.e.*, segment, lobe, or whole liver) being treated. For a typical patient with a liver mass of 2 kg, the required activity is 6 GBq to achieve 150 Gy to the target tissue. It is recommended that the cumulative lung dose be kept to <30 Gy to prevent radiation pneumonitis. The target dose for any given solid tumor is not known; however, it is believed that doses of 100–120 Gy balance response rates and hepatic fibrosis risk when glass microspheres are used. Dose is not calculated similarly for resin microspheres, but an equivalent activity for treatment is approximately 1.5–2.0 GBq.

Resin Y90 microsphere prescribed activity calculation

There are two methods for prescribed activity determination provided by the resin microsphere user's manual (Sirtex user's manual, issued March 2002; pages 38–42): (1) the body surface area method (BSA), as outlined below in Eqs. 2 and 3, and (2) the empiric method. However, the

panel strongly recommends the use of the BSA for resin microsphere dose calculation, on the basis of its more favorable toxicity profile, with response and survival outcome similar to the empiric method.

BSA method. The body surface area method is calculated as follows:

$$\text{BSA (m}^2\text{)} = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425} \quad (2)$$

$$\text{Activity (GBq)} = (\text{BSA} - 0.2) + \frac{\text{Tumor volume}}{\text{Total liver volume}} \quad (3)$$

The activity prescribed can be reduced if the hepatic function is compromised. There are not accepted guidelines as to how much to reduce the activity if a patient's liver function or estimated reserve is only just good enough to be a candidate. Generally, more experienced users reduce dose by 30% for patients with poorer liver function but who are still candidates for this approach according to established eligibility criteria.

Empiric method (not recommended). According to the empiric method:

For tumor $\leq 25\%$ of the total mass of the liver by CT scan, use 2 GBq whole liver delivery.

For tumor $> 25\%$ but $< 50\%$ of the liver mass by CT scan, use 2.5 GBq whole liver delivery.

For tumor $> 50\%$ of liver mass by CT scan, use 3 GBq for whole liver delivery.

DISCUSSION

Yttrium-90 microsphere therapy has been studied in prospective clinical trials with encouraging results in Australasia (14–17). Important contributions from these studies have provided invaluable experience, shaping patient selection, treatment technique, and safety issues. Investigators in the United States have had access to Y90 microspheres since 2000 (18–22). Important clinical experiences have established encouraging response and survival data in a modest number of patients in each study. Acceptable toxicity is found in metastatic colorectal patients treated with Y90 for both microsphere types (10, 12, 13, 23). Acute side effects (within 30 days of treatment) are predominately constitutional (fatigue, fever), gastrointestinal (ulcer, nausea, emesis, abdominal pain), or hepatic (biochemical). Late radiation effects (30–90 days) are hepatic, with fibrosis/cirrhosis, ascites, portal hypertension, and development of varices, with permanently elevated liver function tests, termed *radiation-induced liver disease* (24).

Gray *et al.* (25) reported a phase III trial of resin microspheres in chemotherapy-naïve metastatic colorectal disease patients with liver metastases only, who received either

Table 3. Published data on yttrium-90 in hepatocellular carcinoma

First author, year (reference)	No. of patients	Treatment group	Sphere	No. of centers	Toxicity system
Salem, 2005 (13)	43	First line	Glass	1	CTC version 3.0*
Goin, 2005 (35)	121	First line	Glass	5	SWOG
Geschwind, 2004 (29)	80	First line	Glass	4	SWOG
Carr, 2004 (27)	65	First line	Glass	1	N/A
Dancey, 2000 (28)	22	First line	Glass	1	N/A
Lau, 1998 (17)	71	First line	Resin	1	N/A

Abbreviations: SWOG = Southwest Oncology Group; N/A = not available.

* Common Terminology Criteria for Adverse Events, version 3.0; <http://ctep.cancer.gov>; published December 12, 2003.

hepatic artery infusion of FUDR (32 patients) or FUDR plus a single treatment to the whole liver with microspheres (32 patients). In addition to response, time to liver disease progression, and overall survival, quality of life and treatment-related toxicity were measured. The partial and complete tumor response rate was significantly higher for patients who received Y90 in addition to hepatic arterial chemotherapy (44% vs. 17.6%; $p = 0.01$). The median time to progression in the liver was longer for the Y90 patients (15.9 months vs. 9.7 months; $p = 0.04$). Survival was improved for the Y90-treated patients who lived longer than 15 months, with a 5-year survival rate of 3.5% vs. 0. Quality of life was found to be similar for the two groups, as was toxicity.

A retrospective study from 7 U.S. centers by Kennedy *et al.* (12) reported response, toxicity, and overall survival in chemorefractory liver-predominant disease after resin Y90 treatment. More than two thirds of patients responded to treatment, despite a history of heavy chemotherapy treatments. Median survival for responders was 10.5 months, compared with 4.5 months for nonresponders. There were no cases of Grade 4 or 5 toxicity, venoocclusive disease, or radiation-induced liver disease. The most common side effects were fatigue, brief nausea, and transient elevation of liver enzymes. The carcinoembryonic antigen (CEA) response nadir occurred at 12 weeks, as did maximal response on CT scanning.

Yttrium-90 microspheres have been used extensively for the treatment of hepatocellular carcinoma. The acute and late toxicity profile, as well as the identification of high- and low-risk patients for Y90, has been previously reported (26). Safety, tumor response, and survival benefit have been compared with historical controls in reports by several centers (27–29). Surrogate markers for clinical benefits, including tumor marker reduction and quality of life, have also been described (30, 31). Treatment with Y90 as a bridge to transplantation, radiofrequency ablation, or resection has also been studied (32–34).

Substantial data are available on the acute and late side effects of Y90 microspheres in hepatocellular carcinoma patients. It is quite common for patients undergoing Y90 microsphere therapy to experience mild postembolization syndrome on the day of treatment and for up to 3 days after treatment. Symptoms include fatigue, nausea, and abdominal pain. Radioembolization to nontarget organs can also cause other acute damage, resulting in gastrointestinal ulceration, pancreatitis, and radiation pneumonitis. Late toxicity can include radiation-induced liver disease (radiation hepatitis) (26, 31, 35–39). The incidence of nontarget radiation will be minimized if meticulous angiographic and dosimetry techniques are used (40). Fatal radiation pneumonitis has only been reported in 2 cases. Strict adherence to accepted limits on radiation

Table 4. Published details of toxicities (Grade 3–4) of yttrium-90 therapy in hepatocellular carcinoma

Category	First author, year (reference)					
	Salem, 2005 (13)	Goin, 2005 (35)	Dancey, 2000 (28)	Geschwind, 2004 (29)	Carr, 2004 (27)	Lau, 1998 (17)
Gastrointestinal						
Nausea, emesis, pain	12	N/A	4.5	9	15	16.9
Ulcer	0	N/A	13.6	4	0	0
Constitutional						
Weight loss, fatigue, fever	6	27	0	1	N/A	14.1
Liver function						
Bilirubin	14	N/A	22.7	16	17	0
Alkaline phosphatase	0	3	9.1	1	N/A	N/A
Alanine aminotransferase	12	8	22.7	6	70.7	N/A
Aspartate aminotransferase	12	8	22.7	6	N/A	N/A
Ammonia	N/A	3	N/A	N/A	N/A	N/A

Abbreviation: N/A = not available.

Values are percentages.

dose (<30 Gy) to the lung prevents this complication (41). Radiation-induced liver disease and radiation fibrosis may be long-term sequelae of Y90 treatment. The peer-reviewed publications shown in Tables 3 and 4 describe early and late toxicities encountered with Y90 microspheres.

CONCLUSIONS

Yttrium-90 microsphere therapy is a complex procedure that requires multidisciplinary management for safety and success. The initial results and published literature suggest that there is sufficient evidence to support the safety and effectiveness of Y90 microsphere therapy in selected patients with primary and metastatic liver cancer. However, the role of this therapy must be investigated further to integrate and quantify the benefit when combined with other therapies. Modern combination chemotherapy and targeted

systemic therapy have resulted in prolongation of survival for patients with metastatic colorectal cancer. Limited reports suggest that combination therapy may also increase the number of patients who subsequently can undergo complete surgical resection of liver metastases. These same antineoplastic agents are known radiosensitizers and therefore ideally could be given with Y90 microspheres in an attempt to further control metastatic liver disease and perhaps to increase the potential for surgical resection. Ongoing phase I and II clinical trials investigating combination chemotherapy with concomitant Y90 microsphere treatment should provide important data on the efficacy and toxicity of the combined modality approach and the optimum sequencing of treatments. Performance of clinical trials and creation of a treatment registry with uniform reporting criteria are essential for determining the safety and role of Y90 microspheres in the context of currently available therapies.

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Each practice guideline and technical standard, representing a policy statement by the College, has undergone a thorough consensus process in which it has been subjected to extensive review, requiring the approval of the Commission on Quality and Safety as well as the ACR Board of Chancellors, the ACR Council Steering Committee, and the ACR Council. The practice guidelines and technical standards recognize that the safe and effective use of diagnostic and therapeutic radiology requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline and technical standard by those entities not providing these services is not authorized.

2008 (Res. 2)*

PRACTICE GUIDELINE FOR RADIOEMBOLIZATION WITH MICROSPHERE BRACHYTHERAPY DEVICE (RMBD) FOR TREATMENT OF LIVER MALIGNANCIES

PREAMBLE

These guidelines are an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the American College of Radiology cautions against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. Thus, an approach that differs from the guidelines, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations on available resources, or advances in knowledge or technology subsequent to publication of the guidelines. However, a practitioner who employs an approach substantially different from these guidelines is advised to document in the patient record information sufficient to explain the approach taken.

The practice of medicine involves not only the science, but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict

with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

I. INTRODUCTION

The guideline was developed and written by the American College of Radiology (ACR), the American Society for Therapeutic Radiology and Oncology (ASTRO), and the Society of Interventional Radiology (SIR).

Radioembolization with a microsphere brachytherapy device (RMBD) is the embolization of hepatic primary tumors or metastases by delivering radioactive beta emitters about 25-32 micrometers (μm) in size embolized within the tumors from hepatic arterial blood supply. Terms relevant to this guideline include intra-arterial therapy and selective internal radiation therapy.

Hepatic arterial therapy takes advantage of the liver's dual blood supply and the fact that tumors receive 80%-90% of their blood supply from the hepatic artery once the tumor exceeds 3 mm in diameter. In contrast, the majority of the normal hepatic parenchyma receives its supply from the portal vein. For 30 years, this difference has been exploited to deliver chemotherapy via intra-arterial pumps, embolic agents to occlude the tumoral arteries,

and various combinations of both chemotherapy and embolic agents (chemoembolization) to blend the effects to more fully treat the tumors with both ischemic and antineoplastic effects.

The newest addition to intra-arterial therapies is the use of radioactive particulates using yttrium-90 (Y-90), a pure beta emitting isotope, to perform intra-arterial brachytherapy. Y-90 is a pure beta emitter with a half-life of 64.2 hours (2.67 days). The maximum energy of the emitted beta particles is 2.27 MeV, with an average energy of 0.94 MeV. This corresponds to a maximum range of 1.1 cm in tissue with a mean path of 2.5 mm and an effective path length of 5.3 mm. Y-90 is produced by neutron bombardment of Y-89 and upon beta emission decays to a stable isotope of Zr, (Zr-90). In one kilogram of tissue, 1 GBq of uniformly dispersed Y-90 delivers an absorbed radiation dose of approximately 50 Gy.

Currently 2 commercial products are available. Both contain Y-90 as therapeutic agent.

1. Glass spheres (TheraSphere™, MDS Nordion) were approved by the Food and Drug Administration (FDA) in 1999 as a humanitarian exemption device (HDE). These products are approved for use in patients with unresectable hepatocellular carcinoma (HCC). These microspheres arrive a few days before the implant procedure, and the entire vial containing the spheres is implanted. The spheres have a median size of 25 µm and very high specific activity of 2,500 Bq/sphere.
2. Resin spheres (SIR-Spheres®, Sirtex) received FDA approval in 2002 for premarket approval (PMA) for metastatic unresectable liver tumors from primary colorectal cancer. These microspheres arrive on the day of the implant procedure, and the facility draws the desired activity from the source vial. The spheres have a median size of 32 µm and specific activity of 50 Bq/sphere.

Brachytherapy is the use of radioactive isotopes to treat malignancies or benign conditions by means of a radioactive source placed close to or into the tumor or treatment site. Brachytherapy alone or combined with external beam therapy plays an important role in the management and treatment of patients with cancer.

The use of brachytherapy requires detailed attention to personnel, equipment, patient and personnel safety, and continuing staff education. Since the practice of brachytherapy occurs in a variety of environments, the judgment of the authorized user (AU), usually a radiation oncologist or nuclear medicine physician (or other specialist who has met the training and experience requirements) and a Qualified Medical Physicist (QMP)

should be used to **apply** these guidelines to individual practices (see section IV.D for the definition of a QMP).

The licensing of radioactive sources used in medicine and the safety of the **general** public and health care workers are regulated by the Nuclear Regulatory Commission (NRC) or by agreement states.¹ Medical use of isotopes for therapeutic procedures must adhere to the constraints set forth by these regulatory agencies. Detailed descriptions of NRC licensing and safety issues can be found in the Code of Federal Regulations, Part 20 and Part 35. State requirements for the agreement states are found in the respective state statutes.

While there is some indication that RMBD may increase lifespan, no definitive trials have been performed. Past small randomized trials in patients with metastatic colorectal cancer have demonstrated a survival benefit, but large scale trials have not been performed within the context of modern current chemotherapy. It is unlikely that such trials will ever be performed given the length of time necessary to perform them, and the continuously changing chemotherapeutic options, combined with the inability of many centers to use RMBD because of its complexity and its requirement for multispecialty input.

II. GOALS

The treatment goal of RMBD, whether it is palliative, curative, or a bridge to transplant, should be defined and communicated to patient and treatment team. The use of RMBD is to achieve intrahepatic tumor control. Appropriately selected patients with no or minimal extrahepatic metastases will have an increased disease-free interval and possibly improved survival as a result of hepatic tumor control. RMBD can induce a partial tumor response to allow for subsequent surgical excision or liver transplantation. It has been shown to offer significant palliation not only from local effects of metastases in the liver but also from problematic paraneoplastic syndromes that can be caused from a variety of solid tumors. Response to RMBD is typically assessed with multidetector triple phase contrast enhanced computed tomography (CT) of the liver or with magnetic resonance imaging (MRI) with contrast, and when appropriate to the tumor type, fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). Recent reports suggest that the FDG-PET response is more indicative of the actual tumor response than CT or MRI.

¹ An agreement state is any state with which the U.S. Nuclear Regulatory Commission or the U.S. Atomic Energy Commission has entered into an effective agreement under Subsection 274.b of the Atomic Energy Act of 1954, as amended (73 Stat. 689).

III. INDICATIONS AND CONTRAINDICATIONS

- A. Indications include, but are not limited to:
1. The presence of unresectable and/or medically inoperable primary or secondary liver malignancies. The tumor burden should be liver dominant, not necessarily exclusive to the liver. Patients should also have a performance status that will allow them to benefit from such therapy, i.e., an ECOG performance status of 0 or 1 or KPS of 70 or more.²
 2. A life expectancy of at least 3 months.
- B. Relative Contraindications Include:
1. Excessive tumor burden in the liver with greater than 70% of the parenchyma replaced by tumor (unless synthetic function [prothrombin time and albumin] is maintained).
 2. Portal vein thrombosis without the ability to perform selective infusion (resin based microspheres).
 3. A bilirubin greater than 2 mg/dl (in the absence of obstructive cause) as this indicates irreversible liver function impairment. Nonobstructive bilirubin elevations generally indicate that liver metastases have disease burden beyond the potential benefits that might be achieved by this therapy. In contrast, patients with HCC may be treated with radioembolization if a segmental or subsegmental infusion can be performed.
 4. Pre-treatment hepatic arterial perfusion embolization with technetium-99m macroaggregated albumin (MAA) as a surrogate for the path of the Y-90 containing particles demonstrative of unfavorable (or unacceptable) shunt fraction between the liver and the pulmonary parenchyma. This shunt fraction must not be greater than acceptable limits specific to each brachytherapy device.
 5. Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver (clinical judgment by the radiation oncologist required).
 6. Chemotherapy agents in the preceding 4 weeks not known to be used safely concurrently with RMBD.
 7. If the patient is known to be pregnant, the potential radiation risks to the fetus and the clinical benefits of the procedure required before, during, and after RMBD, and any scatter radiation from the hepatic implant should be considered before proceeding with the study.

- C. Absolute Contraindications Include:
1. Inability to catheterize the hepatic artery.
 2. Frank liver failure.
 3. Technetium-99m MAA hepatic arterial perfusion scintigraphy demonstrates significant reflux to the gastrointestinal organs that cannot be corrected by angiographic techniques such as embolization.

IV. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

Physicians from various medical specialties are involved at different times in the evaluation and management of patients receiving RMBD. Multidisciplinary expertise is essential and includes interventional radiology, radiation oncology, nuclear medicine, medical physics, radiation safety, hepatology, gastroenterology, medical oncology, and surgical oncology. Interventional radiologists are responsible for doing the screening angiogram and then placing the delivery catheter.

The responsibilities of the AU (usually the radiation oncologist) and the QMP (and sometimes with a combination of other specialists responsible for the care of the patient) include:

1. Selection of patient for RMBD, to include history, physical examination, and review of imaging studies and laboratory reports.
2. Obtaining informed consent for RMBD. Complete explanations of the entire RMBD process, including necessary imaging, laboratory and treatment procedures, typical side effects, and potential complications. The team member completing this portion should be the main physician who will coordinate the activities of the entire team.
3. Reviewing the hepatic angiogram, technetium-99m MAA scan, and laboratory reports to make the final determination of eligibility or ineligibility for RMBD.
4. Determining treatment parameters: (a) single or fractionated (staged) treatment, (b) intended activity to be administered, (c) target volume (whole liver, lobar, or segment), (d) vessel(s) to be used for delivery of activity.
5. Delivery of activity. During treatment, the AU should monitor for stasis and/or reflux of microspheres and end the procedure as needed.
6. Monitoring the patient during the periprocedural period to provide support and clinical management and radiation safety information.
7. Follow up of patient after the day of treatment to monitor for side effects, complications, and response to therapy.

² ECOG – Eastern Cooperative Oncology Group; KPS – Karnofsky Performance Status

The AU shall write a written directive for the source administration and is responsible for administering the radiation once the interventional radiologist has placed the delivery catheter. The nuclear medicine specialist evaluates the technetium-99m MAA scan for lung shunting. Surgical consultation is helpful in distinguishing patients eligible for tumor resection from those who are better served with other local treatments such as RMBD, radio frequency ablation (RFA), cryotherapy, stereotactic body radiation therapy (SBRT), or other nonsurgical techniques. With RFA, the expertise of the surgeons and interventional radiologists overlaps. The hepatologist or gastroenterologist helps in managing the nonmalignant aspect of the patient's liver disease.

A. Interventional Radiologists

The interventional radiologists are responsible for placement of the catheter for angiogram, technetium-99m MAA injection, protective embolization of gastric and gastroduodenal artery (GDA), and catheter placement for Y-90 treatment. They should meet the following qualifications:

1. Certification in Radiology or Diagnostic Radiology by the American Board of Radiology (ABR), American Osteopathic Board of Radiology, the Royal College of Physicians and Surgeons of Canada, or Le College des Medecins du Quebec and has performed 50 therapeutic embolizations, 25 of them as primary operator with acceptable success and complication rates within the quality assurance threshold rates laid out in this guideline.

or

2. Successful completion of an Accreditation Council for Graduate Medical Education (ACGME) approved radiology residency training program or an American Osteopathic Association (AOA) approved residency program and/or interventional/vascular radiology fellowship, and must have a minimum of 12 months training in a service that is primarily responsible for the performance of percutaneous peripheral, visceral, and neurovascular diagnostic arteriography. Documented formal training in the performance of invasive catheter angiographic procedures must be included. During this training, the physician should have performed 50 therapeutic embolizations, 25 of them as primary operator, and these cases must be documented so that the director of the training program can certify that the physician is proficient in the performance of the procedures, with acceptable success and complication rates within the quality assurance threshold rates laid out in this guideline.

or

3. Successful completion of an ACGME approved nonradiology residency or fellowship training, and must have a minimum of 12 months of training in a service that is primarily responsible for the performance of percutaneous visceral arteriography and vascular/interventional radiology. Documented formal training in the performance of invasive catheter arteriographic procedures must be included. During this training the physician should have performed 50 therapeutic embolizations, 25 of them as primary operator, and these cases must be documented so the director of the training program can certify that the physician is proficient in the performance of the procedures, with acceptable success and complication rates within the quality assurance threshold rates laid out in this guideline.

Maintenance of Competence

Physicians must perform a sufficient number of diagnostic arteriographic and embolization procedures to maintain their skills, with acceptable success and complication rates as laid out in this guideline. Continued competence should depend on participation in a quality improvement program that monitors these rates.

B. Radiation Oncologists

The radiation oncologist is the expert on liver tolerance to radiation therapy and radiation complications in normal tissues. He or she is also the AU in most programs and performs follow up of Y-90 treated patients for detecting any early or late complications. The radiation oncologist should have the following qualifications and certification:

1. Satisfactory completion of an American Council of Graduate Medical Education (ACGME) approved residency program or an American Osteopathic Association (AOA) approved residency program in radiation oncology.

or

2. Certification in Radiology by the American Board of Radiology (ABR) of a physician who confines his or her professional practice to radiation oncology or certification in Radiation Oncology or Therapeutic Radiology by the ABR, the American Osteopathic Board of Radiology, the Royal College of Physicians and Surgeons of Canada, or Le College des Medecins du Quebec may be considered proof of adequate physician qualifications.

and, in addition to certification, education,
and other credentials

3. Completion of the manufacturer's training program, which typically includes a certain number of cases performed under supervision of a proctor provided by the company or under the supervision of an AU who is authorized for the type of microsphere for which the individual is seeking authorization.

The continuing education of a radiation oncologist should be in accordance with the ACR Practice Guideline for Continuing Medical Education (CME).

C. Nuclear Medicine Physician

The nuclear medicine physician is responsible for the technetium-99m MAA scintigraphy including calculation of shunt fraction and may be the AU at the facility. He or she also interprets the positron emission tomography (PET) scan and the bremsstrahlung scan. (see the ACR Technical Standard for Diagnostic Procedures Using Radiopharmaceuticals.)

The physician providing nuclear medicine services must meet all of the following criteria:

1. Qualifications and certification

- a. Certification in either Radiology, Diagnostic Radiology, Nuclear Radiology, or Nuclear Medicine by one of the following organizations: the American Board of Radiology (ABR), the American Osteopathic Board of Radiology, the Royal College of Physicians and Surgeons of Canada, Le College des Medecins du Quebec, the American Board of Nuclear Medicine, and/or the American Osteopathic Board of Nuclear Medicine.
or
- b. At a minimum, completion of a formal Accreditation Council for Graduate Medical Education (ACGME) approved general nuclear medicine program or an American Osteopathic Association (AOA) approved program that must include training in radiation physics, instrumentation, radiochemistry, radiopharmacology, radiation dosimetry, radiation biology, radiation safety and protection, and quality control. In addition, clinical training in general nuclear medicine is required which must cover technical performance, calculation of administered activity, evaluation of images, correlation with other diagnostic modalities, interpretation, and formal reporting. Physicians trained prior to the availability of formal instruction in

nuclear medicine-related sciences may be exempted from this paragraph, provided they have been actively involved in providing nuclear medicine services.

2. Have documented regular participation in continuing medical education (CME) specifically related to diagnostic procedures using radiopharmaceuticals, in accordance with the ACR Practice Guideline for Continuing Medical Education (CME).
3. Be listed as an AU on the radioactive materials license of his or her institution. When required by the NRC or by the state, at least one physician member of the facility must be a participating member of the committee that deals with radiation safety.
4. A physician who will administer Y-90, must have the credentials described in section IV and must complete the manufacturer's training program. This program may include: 1) on-site proctoring or technical support or 2) a training course.
5. Have a thorough understanding of each procedure with which he or she is involved. The physician is further responsible for ensuring appropriate utilization of services, quality of procedures, and all aspects of patient and facility safety and compliance with applicable government and institutional regulations regarding the use of radiopharmaceuticals.
6. Be responsible for developing and maintaining a program of quality control and continued quality improvement (see sections IV and V) or accept responsibility for adhering to such an established program.

D. Qualified Medical Physicist

A Qualified Medical Physicist is an individual who is competent to practice independently one or more of the subfields in medical physics. The American College of Radiology (ACR) considers certification and continuing education and experience in the appropriate subfield(s) to demonstrate that an individual is competent to practice one or more of the subfields in medical physics and to be a Qualified Medical Physicist. The ACR recommends that the individual be certified in the appropriate subfield(s) by the American Board of Radiology (ABR), the Canadian College of Physics in Medicine, or for MRI, by the American Board of Medical Physics (ABMP) in magnetic resonance imaging physics.

The appropriate subfields of medical physics for this standard are Radiological Physics, Medical Nuclear Physics, and Therapeutic Radiological Physics.

A Qualified Medical Physicist should meet the ACR Practice Guideline for Continuing Medical Education (CME). (ACR Resolution 17, 1996 – revised in 2008, Resolution 7)

The Qualified Medical Physicist or other qualified scientist performing services in support of nuclear medicine facilities should meet all of the following criteria:

1. Advanced training directed at the specific area of responsibility (e.g., radiopharmacy, medical physics, health physics, or instrumentation).
2. Licensure, if required by state regulations.
3. Documented regular participation in continuing education in the area of specific involvement to maintain competency.
4. Knowledge of radiation safety and protection and of all rules and regulations applying to the area of practice.

E. Radiologic Technologists

1. Interventional technologist
 - a. Radiologic technologists properly trained in the use of the arteriographic equipment should assist in performing and imaging the procedure. They should be able to demonstrate appropriate knowledge of patient positioning, arteriographic image recording, angiographic contrast injectors, angiographic supplies, and the physiologic monitoring equipment. Certification as a vascular and interventional radiologic technologist is one measure of appropriate training. Technologists should be trained in basic cardiopulmonary resuscitation and in the function of the resuscitation equipment.
 - b. If the patient does not receive moderate sedation, one of the staff members assisting the procedure should be assigned to periodically assess the patient's status. If the patient is to undergo moderate sedation, a nurse or other appropriately trained individual should monitor the patient as his or her primary responsibility. This person should maintain a record of the patient's vital signs, time and dose of medications given, and other pertinent information. Nursing personnel should be qualified to administer moderate sedation (see the ACR Practice Guideline for Adult Sedation/Analgesia).
 - c. Although complications of arteriography only rarely require urgent surgery, these

procedures should be performed in an environment where operative repair can be instituted promptly. This could be performed in an acute-care hospital with adequate surgical, anesthesia, and ancillary support. When these procedures are performed in a free-standing center, detailed protocols for the rapid transport or admission of patient to an acute-care hospital should be formalized in writing.

F. Nuclear Medicine Technologist

See the ACR Standard for Diagnostic Procedures Using Radiopharmaceuticals.

V. SPECIFICATIONS OF THE EXAMINATION

A. Preliminary Angiographic Evaluation

The indications for elective arteriographic studies should be documented as described below. A note should be written summarizing the indications for the study, the pertinent history and physical findings, if available, and the proposed procedure, including:

1. Clinically significant history, including indications for the procedure.
2. Clinically significant physical examination, including an awareness of clinical or medical conditions that may necessitate specific care.
3. Laboratory evaluation if indicated, including liver function tests, appropriate tumor markers (e.g., CEA, AFP), hemoglobin, hematocrit, creatinine, electrolytes, and coagulation parameters.
4. Review of appropriate anatomic and/or functional imaging studies, such as cross-sectional CT, MR, and PET scans.

B. Establishing Treatment Goals with Patient and Treatment Team

The goal of Y-90 RMBD is to achieve intrahepatic tumor control. It is likely that patients with no or minimal extrahepatic metastases (appropriately selected patients) will have increased disease-free and possibly increased overall survival as a result of improved hepatic control. Multidetector triple phase contrast enhanced CT of the liver and PET-CT are used to evaluate response. While Response Evaluation Criteria in Solid Tumors (RECIST) criteria have been used to evaluate response, it has been recently reported that FDG-PET response may be more indicative of the actual tumor response.

C. Obtaining Informed Consent

Consent for the interventional procedure should be obtained by the interventional radiologist after discussing in detail the procedure of visceral arteriography and embolization. The risks and complications of the procedure should be completely and frankly discussed, as well as the treatment outcomes. The consent for radiation therapy should be obtained by the authorized user or his or her designee, which could include the interventional radiologist, the nuclear medicine physician, or the radiation oncologist. (see the ACR Practice Guideline on Informed Consent – Radiation Oncology.)

D. Pretreatment Evaluation

Pretreatment planning includes performance of a CT scan with determination of tumor volume. PET scanning should be performed for PET avid tumors. Other functional imaging may be performed, as appropriate. Pretreatment visceral arteriography should be performed with injection of the celiac, superior mesenteric, left gastric, gastroduodenal, proper hepatic, right and left hepatic arteries. Embolization of the gastroduodenal artery as well as any right gastric or other gastric arteries should be considered to redistribute the flow of blood away from the gastrointestinal tract. Vascular anomalies should be identified and the relationship of these variants with the tumors determined so that all tumors may be treated. At the conclusion of the vascular mapping arteriogram, 1.0-5.0 mCi of technetium-99 MAA should be injected into the catheter for follow-up imaging of the liver and lungs to determine the amount of shunting to the lungs.

E. Preliminary Angiographic Evaluation

Once a patient has been selected as a candidate for RMBD through multidisciplinary collaboration, an initial angiographic evaluation is performed. The proper sequence of vessels to be addressed and evaluated has been previously published. This is done primarily to document the visceral anatomy, identify anatomic variants, and isolate the hepatic circulation by occluding or embolizing extrahepatic vessels.

This will allow identification of variant mesenteric anatomy, as well as the prophylactic embolization of extrahepatic vessels such as the right gastric, gastroduodenal, or falciform artery. Other vessels that may require similar treatment include the supraduodenal, retroduodenal, left inferior phrenic, accessory left gastric, and inferior esophageal. Care should be taken when considering embolization of the gastroduodenal artery (GDA), as accessory hepatic vessels feeding tumor may arise from this artery.

Prophylactic embolization of the above-mentioned vessels essentially functions to convert the hepatic blood flow into one that might be found when a surgically placed hepatic arterial port is placed. Usually, in surgical port placement, the common hepatic artery is skeletonized, the GDA and right gastric are ligated, and any other hepatic-mesenteric or extrahepatic vessels are ligated. This is identical to what is accomplished with the above-described angiographic technique. Furthermore, it is important that all hepatic vessels be interrogated during the angiographic assessment of the patient. Given the propensity of tumors to parasitize blood flow from vessels other than the actual tumor location, only such direct catheterization and interrogation of all vessels would demonstrate this phenomenon. The lack of recognition of this phenomenon may result in incomplete treatment of the target tumor bed.

Once the anatomy has been established, selective arteriography is performed in the expected location of the Y-90 treatment. If possible, the visceral selective catheter may be advanced distally to the desired location; however, if the vessels are small in caliber or demonstrate significant tortuosity, a 3-French microcatheter may be required.

Technetium-99m MAA arterial injection is performed after all vessels have been embolized. In all cases of metastases, injection can often be performed in the proper hepatic artery, given the low incidence of lung shunting in patients with metastatic disease to the liver. In contrast, the approach to the technetium-99m MAA injection in patients with HCC is slightly different. If the patient has bilobar HCC, proper hepatic artery injection of technetium-99m MAA is performed unless gross vascular shunting into the hepatic or portal vein is seen. The shunting fraction obtained is assumed to be representative of the bilobar tumors. In cases of bilobar disease where angiographic shunting is seen, a unilobar injection of technetium-99m MAA is performed and only one lobe is assessed at any one time. A repeat technetium-99m MAA injection is repeated at a later date when the second lobe requires treatment. Alternatively, both lobes can be evaluated during the initial MAA if the intent is to treat both lobes in a single treatment.

It is important to note that in cases where variant arterial anatomy exists, the technetium-99m MAA dose should be fractionated in order to cover the entire liver in one sitting if possible, saving the patient an unnecessary catheterization. For example, in cases where there is a replaced right hepatic artery, 2-3 mCi of technetium-99m MAA is given in that vessel, while the remaining 2-3 mCi is given in the left hepatic artery. In cases of a gastrohepatic trunk, 1-3 mCi of technetium-99m MAA are injected in the left hepatic artery, while the remainder is injected in the right hepatic artery.

Variant Mesenteric Anatomy

In 55%-65% of cases, the celiac artery gives rise to the splenic artery, the left gastric artery, and the common hepatic artery. The dorsal pancreatic artery commonly arises from the celiac origin, although it may also arise off the common hepatic artery (CHA) or splenic artery. The common hepatic artery then gives rise to the GDA and becomes the proper hepatic artery, which divides into the right and left hepatic arteries. When a distinct vessel arising from the right hepatic artery provides flow to segment IV, it is referred to as the middle hepatic artery. In more than 40% of cases, the origin and course of the hepatic arteries vary, as does the vascular distribution of the vessel irrespective of its anticipated course. Vessels supplying one segment may be recruited to provide flow to other anatomic segments. The most common variants include a replaced right hepatic artery, which arises from the superior mesenteric artery (SMA), a replaced common hepatic artery arising from the SMA, or bifurcation of a short common hepatic artery in right and left hepatic arteries. The right and left hepatic arteries may arise separately from the celiac trunk, or directly from the aorta. The caudate lobe most commonly receives its blood supply from a small branch off the left or right hepatic artery. This caudate artery is normally rather diminutive; however, in the setting of tumor, it can become prominent, thereby allowing selective catheterization and treatment. Given that traditional transcatheter arterial chemoembolization (TACE) and other large-particle type therapy involves thick, viscous chemotherapy as well as embolic particles (300-700 micrometers), the use of significantly smaller Y-90 microspheres (20-40 micrometers) is particularly advantageous in this setting of diminutive vasculature.

F. RMBD Treatment Plan

1. It is recommended that a written directive be obtained from the AU before the source is ordered. The written directive will be in the patient chart and should include the following information:
 - a. Before implantation: treatment site, the radionuclide (Y-90 microspheres), dose (activity ordered in gigabecquerels [GBq]) and medical end point (stasis to determine when to terminate implantation).
 - b. After implantation, but before completion of the procedure: the radionuclide (Y-90 microspheres) treatment site and the total dose implanted.
 - c. In addition, the written directive often includes:
 - i. Mass or volume of the target.
 - ii. Location of the target.
 - iii. Lung shunt fraction.

- iv. Dose estimate for lung and gastrointestinal tract.
- v. Approximate time of administration.
- vi. Upon completion of the procedure, any deviations from the written directive.

2. Dosimetry

Depending on the brachytherapy device being used, results of the studies (CT, technetium-99m MAA hepatic arterial scintigraphy, or angiogram) and the volume of liver to be irradiated (e.g., whole liver versus lobar treatment) various dosimetry models may be used in calculating activity to be administered.

a. Glass sphere – Therasphere, MDS Nordion

- i. The glass microsphere dosimetry is based on the MIRD (Medical Internal Radiation Dosimetry committee of the Society of Nuclear Medicine) model. Although sphere distribution is known to be nonuniform, MIRD dosimetry models assume uniform distribution of activity in mass. Activity calculation requires the patient's liver mass and the nominal target dose.
- ii. The partition model is based on the MIRD model and involves implanting the highest possible activity to the tumor while maintaining radiation dose to sensitive tissues such as lung and normal liver at an acceptable level. This method can only be used where the tumor mass is localized in a discrete area within the liver and the tumor can be drawn as an "area of interest" on SPECT (single photon-emission CT) camera image.

b. Resin sphere – SIRsphere, Sirtex

There are 3 methods for calculating the activity as recommended by the manufacturer.

- i. The body surface area (BSA) method uses the manufacturer's formula to calculate the activity to be implanted. This formula requires the patient's height, weight, and percentage of the liver that is replaced by the tumor as calculated from the CT scan.
- ii. The empiric method recommends a standard amount of activity based on estimated percentage of tumor burden in the liver as shown in the table below.

Estimated Tumor Involvement of Liver	Recommended Activity for Treatment
>50%	3 GBq
25%-50%	2.5 GBq
<25%	2 GBq

- iii. The partition model is based on the MIRD model and involves implanting the highest possible activity to the tumor while maintaining radiation dose to sensitive tissues such as lung and normal liver at an acceptable level. This method can only be used where the tumor mass is localized in a discrete area within the liver and the tumor can be drawn as an "area of interest" on SPECT camera image.

While all 3 methods have been mentioned in the literature, the BSA method is preferred and most commonly utilized when resin based microsphere device is used.

G. RMBD Treatment Delivery

1. Adherence to the Joint Commission's Universal Protocol for Preventing Wrong Site, Wrong Procedure, Wrong Person Surgery™ is required for procedures in nonoperating room settings including bedside procedures. "Time out" must be conducted in the location where the procedure will be done, just before starting the procedure and must:
 - Involve the entire operative team.
 - Use active communication.
 - Be briefly documented, such as in a checklist, and include at least:
 - Correct patient identity.
 - Correct side and site.
 - Agreement on the procedure to be done.
 - Correct patient position.
 - Availability of correct implants, and any special equipment or special requirements.

The organization should have processes and systems in place for reconciling differences in staff responses during the "time out."
2. All patients should have cardiac monitoring continuously during the procedure, with intermittent blood pressure monitoring. A record of vital signs should be maintained.
3. All patients should have intravenous access for the administration of fluids and medications as needed.

4. If the patient is to receive moderate sedation, pulse oximetry should be used in addition to 2 above. A registered nurse or other appropriately trained personnel should be present, and his or her primary responsibility should be to monitor the patient. A record should be kept of medication doses and times of administration.
5. The diagnostic angiography portion involves assessment of the vascular anatomy, any arterial variants, patency of the portal venous system, and any other vascular anomalies. In particular, therapy with radioembolization involves the identification of vessels that extend outside the anticipated treatment field (examples might include gastric, duodenal, or esophageal vessels). Appropriate precautions for vascular exclusions are undertaken at the time (such as distal catheter placement or coil embolization).
6. Hepatic arterial scintigraphy with technetium-99m MAA is done for treatment planning and for detecting patients who might be at risk for complications from extrahepatic deposition.
 - a. Perfusion of hepatic tumors
 - i. Technetium-99m MAA (see the ACR Practice Guideline for the Performance of Pulmonary Scintigraphy), consists of particles of aggregated human serum albumin with a size range of 10-90 micrometers. Given intra-arterially via a hepatic artery perfusion catheter, the MAA particles will localize within the liver in a distribution similar to that of the radioembolization microspheres. The usual adult administered activity is 1.0-5.0 millicuries (37-185 MBq).
 - ii. Planar images of the abdomen are obtained immediately in the anterior (with and without external markers), followed by left anterior oblique (LAO), left lateral, and posterior projections, anterior and posterior images of the chest, and anterior images of the neck to include the thyroid. If SPECT imaging is performed, then for single-headed, large-field-of-view SPECT gamma cameras, a 64 x 64 matrix, 6 degree angle of sampling (60 images in a 360 degrees arc), and 20-30 seconds per image are appropriate parameters. Attenuation correction is sufficient. For multiheaded SPECT cameras, a 128 x 128 matrix with a 3 degree angle of sampling (60 images per head for a dual-head camera or 40 images per head for a 3-head camera) can be used.

- b. Any extrahepatic radiotracer distribution is identified, and the pulmonary shunt fraction is calculated. -
7. A physician should be available during the immediate postprocedure period to ensure that there is adequate hemostasis at the puncture site and that the patient is stable prior to transfer to the postprocedure care area.

H. Postprocedure Care

1. The room and staff should be surveyed at the end of the procedure, before they come off the floor pad. The area and all trash containers should also be surveyed for contamination. All contaminated materials must be placed in storage. A dose calibrator, or other system recommended by the manufacturer, should be used to determine residual postprocedure activity, in order to verify activity administered to the patient.
2. A procedure note must be written in the patient's chart summarizing the major findings of the study and any immediate complications. This note may be brief if an official interpretation³ is available within a few hours. The immediate note should include at a minimum: indications, operative procedure and imaging findings, date and time, operator(s)/surgeon(s), complications, medications and/or contrast used, and conclusions. However, if the official interpretation is not likely to be on the chart the same day, a more detailed summary of the procedure should be written in the chart at the conclusion of the procedure. In all cases, pertinent findings should be communicated to the referring physician in a timely manner.
3. All patients should be at bed rest and observed in the initial postprocedure period. The length of this period of bed rest will depend on the site and size of the arteriotomy and the patient's medical condition.
4. During the initial postprocedure period, skilled nurses or other appropriately trained personnel should periodically monitor the puncture site and the status of the distal vascular distribution.
5. The patient should be monitored for urinary output, cardiac symptoms, pain, and other indicators of systemic complications that may need to be addressed further.
6. The initial ambulation of the patient must be supervised. Vascular perfusion, puncture-site

stability, and independent patient function and mobility must be ensured.

7. The operating physician or a qualified designee should evaluate the patient after the procedure, and these findings should be summarized in a progress note. If moderate sedation was administered prior to and during the procedure, recovery from moderate sedation must be documented. The physician or designee should be available for continuing care during hospitalization and after discharge. The designee may be another physician, a nurse, or other appropriately qualified and credentialed health care provider.

I. Device Implant

Prior to device implantation all of the above procedures should have been completed including: review of appropriate studies, diagnostic angiography, MAA scanning, dosimetry calculations, and ordering of the brachytherapy device. There should be discussion among team members prior to patient treatment to address any unique or unusual characteristics that may affect patient safety or outcome.

The brachytherapy device should be assayed in the dose calibrator to verify the calibration activity of the source. For resin spheres the appropriate activity should be withdrawn from the source vial and transferred to the treatment vial. Everything that comes in contact with the radioactive source and could cause contamination should be placed in storage. Treatment room preparation should include placement of absorbent pads on the floor where patient/staff contact is anticipated. A "bail out" box should be available. In preparation for implantation the appropriate hepatic artery is accessed, the catheter is placed in the predetermined position and confirmed by angiography, the administration kit is assembled, and the infusion is initiated. Once treatment delivery starts, everything that comes into contact with the patient should stay on the table.

For glass microspheres, administration involves the injection of sterile saline through the treatment vial in order to suspend the microspheres for transcatheter delivery. Following complete administration, a postradioembolization angiogram is recommended.

For resin microspheres, administration involves the injection of sterile water through the treatment vial in order to suspend the microspheres for transcatheter delivery. Intermittent angiography should be performed to evaluate for antegrade flow. Once slowing or stasis is observed, no further activity should be administered. Following complete administration, a postradioembolization angiogram should be performed. However, to avoid dislodging microspheres which can reflux into

³The ACR Medical Legal Committee defines official interpretation as that written report (and any supplements or amendments thereto) that attach to the patient's permanent record. In a health care facility with a privilege delineation system, such a written report is prepared only by a qualified physician who has been granted specific delineated clinical privileges for that purpose by the facility's governing body upon the recommendation of the medical staff.

the GI tract, contrast injection should be performed gently and with a minimum amount of contrast that will still achieve an adequate image of the final vasculature, postimplant. Preferably, the microcatheter should be withdrawn to at least the proper, right or left hepatic artery prior to the final injection of contrast if superselective placement has been performed.

VI. PATIENT AND PERSONNEL SAFETY

Patient protection measures include those related to medical safety and radiation protection.

A. Patient protection measures should include:

1. A radiation exposure-monitoring program, as required by the Nuclear Regulatory Commission (NRC) and agreement states.
2. Charting systems and forms for documenting all aspects of the treatment, including the prescription, definition and delivery of treatment parameters, and summaries of brachytherapy. In addition, any previous interventions such as chemotherapy, external beam radiation therapy, and surgeries should be documented.
3. A physics program for ensuring accurate dose delivery to the patient.
4. A check system for the AU and QMP to verify independently all brachytherapy parameters to be used in each procedure (source, isotope and activity calculation, etc.) prior to the delivery of RMBD.
5. Patients should be provided with written descriptions of the radiation protection guidelines, including, but not limited to, discussion of potential limitations of patient contact with minors and pregnant women. This description should be in compliance with state and federal regulations. The AU, QMP, and radiation safety officer (RSO) should define the postimplant radiation safety guidelines for patients treated with RMBD.
6. Personnel in the angiography suite should all be surveyed for possible contamination.
7. All contaminated waste should be surveyed for activity by measuring the activity at 90-degree intervals around the contaminated waste chamber at 25 cm or according to the manufacturer's guidance. These readings should be averaged to determine the final activity.
8. Postprocedure bremsstrahlung planar imaging should be performed within 24 hours of the conclusion of the procedure, to document the placement of the devices.
9. Patients should be seen immediately following the procedure and at intervals consistent with good medical practice.

10. Imaging follow-up should be obtained at 1-3 months following the procedure to determine the effectiveness of the procedure.

It is recommended that patients be given a document on discharge stating that they have received a radioactive medical implant. Radiation from the implant can trigger sensitive security alarms in airports and public buildings. Appropriate hospital/clinic contact information for security personnel should be provided on such documents.

B. Personnel safety measures should include:

1. A radiation exposure-monitoring program, as required by the institution's radioactive materials license.
2. Appropriate safety equipment for storage of the sources.

VII. DOCUMENTATION

Reporting should be in accordance with the ACR Practice Guideline for Communication: Radiation Oncology or the Practice Guideline for the Reporting and Archiving of Interventional Radiology Procedures, with the addition of:

1. Specification of the activity of Y-90.
2. Target volume: whole liver, right or left lobe, or segment.
3. Final activity delivered.
4. Any evidence of target embolization.
5. Any evidence of nontarget embolization.
6. Condition of patient on discharge.
7. Follow-up clinical visits planned.
8. Follow-up laboratory/radiological examinations.
9. Final disposition of patient.

VIII. RADIATION SAFETY

Radiologists, medical physicists, radiologic technologists, and all supervising physicians have a responsibility to minimize radiation dose to individual patients, staff, and to society as a whole, while maintaining the necessary diagnostic image quality. This concept is known as "as low as reasonably achievable (ALARA)."

Facilities, in consultation with the medical physicist, should have in place and should adhere to policies and procedures, in accordance with ALARA, to vary examination protocols to take into account patient body habitus, such as height and/or weight, body mass index or lateral width. The dose reduction devices that are available on imaging equipment should be active; if not, manual techniques should be used to moderate the exposure while maintaining the necessary diagnostic image quality. Patient radiation doses should be periodically measured by a medical physicist in

accordance with the appropriate ACR Technical Standard. (ACR Resolution 17, adopted in 2006)

The manufacturer-provided acrylic shielding effectively blocks the beta radiation and does not generate significant bremsstrahlung. Although the NRC classifies microspheres as sealed sources, in general they should be handled more like unsealed radiopharmaceutical sources. One area where particular care should be exerted is in the prevention and rapid cleanup of any spills. Unlike solutions of unsealed radiopharmaceuticals, which dry in place after a spill, the microspheres can roll about and blow around after drying, thereby presenting a somewhat different hazard. Additionally, the microspheres can wedge themselves into tiny cracks and crevices, becoming practically impossible to remove from benchtops and equipment. Appropriate planning and care can reduce this risk.

Facilities, in consultation with the RSO, should have in place and should adhere to policies and procedures for the safe handling and administration of radiopharmaceuticals, in accordance with ALARA, and must comply with all applicable radiation safety regulations and conditions of licensure imposed by the NRC, state, and/or other regulatory agencies. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol.

See Appendix A for radiation safety discharge instructions.

IX. EQUIPMENT SPECIFICATIONS

Several technical requirements are necessary to ensure safe and successful diagnostic arteriogram and RBMD procedures. These include adequate equipment, institutional facilities, physiologic monitoring equipment (including intravascular pressure measurement systems), and appropriately trained and qualified personnel.

For specific requirements for the arteriographic procedures, see the Practice Guideline for the Performance of Diagnostic Arteriography in Adults.

A gamma camera with a low-energy all-purpose (LEAP) or low-energy high-resolution collimator may be used for the nuclear medicine imaging.

The activity of Y-90 is determined by measurement using an appropriate dose calibrator, such as an ion chamber. The dose calibrator manufacturer's instructions regarding calibration for Y-90 sources should be followed.

Adjustments to the dose calibrator settings or a correction factor may be necessary to bring the measurement from the ion chamber to an acceptable level ($\pm 10\%$ of the manufacturer-supplied measurement). These settings or

correction factor should then be the standard used for activity measurements of microspheres. Other factors that can influence the activity measurements include the shape and material (glass versus plastic tubing vs. polycarbonate) of the container holding the source.

X. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION CONCERNS

Policies and procedures related to quality, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control and Improvement, Safety, Infection Control, and Patient Education Concerns appearing elsewhere in the ACR Practice Guidelines and Technical Standards book.

Nuclear medicine equipment performance monitoring should be in accordance with the ACR Technical Standard for Medical Nuclear Physics Performance Monitoring of Gamma Cameras.

The Medical Director of Radiation Oncology is responsible for the institution and ongoing supervision of continuing quality improvement (CQI) as described in the ACR Practice Guideline for Radiation Oncology. It is the responsibility of the director to identify problems, see that actions are taken, and evaluate the effectiveness of the actions. The director will designate appropriate personnel to constitute the CQI committee that will review RMBD as part of the CQI meeting agenda. Refer to the ACR Practice Guideline for Radiation Oncology for a detailed description of CQI committee functions.

ACKNOWLEDGEMENTS

This guideline was developed according to the process described in the ACR Practice Guidelines and Technical Standards book by the ACR Guidelines and Standards Committee of the Commission on Interventional Radiology and Radiation Oncology in collaboration with the American Society for Therapeutic Radiology and Oncology (ASTRO) and the Society of Interventional Radiology (SIR).

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APPENDIX A

Radiation Safety Discharge Instructions for Patients with Radioactive Y-90 Spheres for Liver Brachytherapy

Y-90 microspheres are radioactive sources that, over time, become inactive. This means that for the next few days there will be a small amount of radioactivity near your liver. This does not represent a significant risk to others. However, to be on the safe side, these precautions and instructions should be followed:

1. Try not to be within 3 feet of others for the next 3 days, especially children (e.g., anyone under 18 years old) or pregnant women.
2. If you have to go to a doctor or emergency room or need surgery within 3 days of this treatment, notify the medical staff that you have a small amount of radiation in your liver. Your physicians should give you any immediate and necessary medical or surgical treatments without concern for the radiation in the liver. They can

- call Radiation Medicine or Radiation Safety with any questions regarding the details of the treatment.
3. There is no risk of allergic reaction and no restrictions on any study protocol except that you cannot receive chemotherapy for 1 month.
4. There is NO need to make special arrangements for body fluids (urine, stool, blood, or vomit).

If you have any questions concerning radiation safety, please call the following contacts:

During normal working hours: _____

Radiation Oncologist/Interventional Radiologist: _____

Radiation Safety Officer: _____

After hours: _____

I have read and understand the above radiation safety instructions and agree to abide by them.

Patient Signature

Radiation Safety Officer Signature

DATE

DATE

*Guidelines and standards are published annually with an effective date of October 1 in the year in which amended, revised, or approved by the ACR Council. For guidelines and standards published before 1999, the effective date was January 1 following the year in which the guideline or standard was amended, revised, or approved by the ACR Council.

Development Chronology for this Guideline
2008 (Resolution 2)