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REPORT

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

Andrew Kennedy, M.D., F.A.C.R.O.,* Subir Nag, M.D., F.A.C.R., F.A.C.R.O.,†
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.,†
and Douglas Coldwell, M.D., Ph.D.‡‡

*Wake Radiology Oncology, Cary, NC; †Ohio State University, Columbus, OH; ‡Northwestern University, Chicago, IL; §M. D. Anderson Cancer Center, Houston, TX; ‖Cross Cancer Institute, Edmonton, Alberta, Canada; ¶Swedish Medical Center, Englewood, CO; #University of Illinois, Chicago, IL; **Clínica Universitaria de Navarra, 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.

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,

Reprint requests to: Subir Nag, M.D., Kaiser Permanente Radiation Oncology, 3800 Homestead Road, Santa Clara, CA 95051. Tel: (408) 851-8001; Fax: (408) 851-8010; E-mail: subir.nag@kp.org

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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 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. 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 μ†
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-

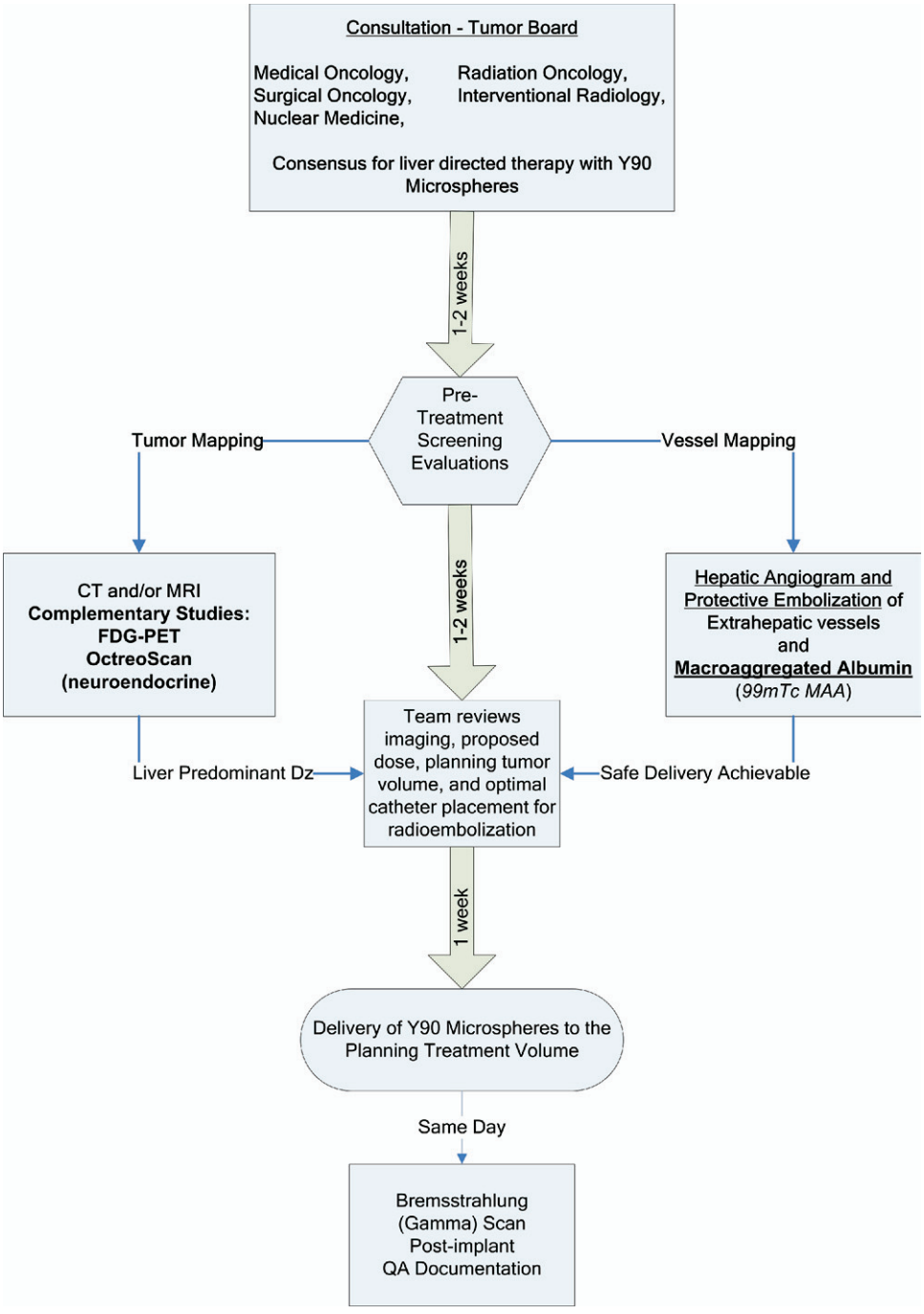

Fig. 1. Treatment algorithm for yttrium-90 microsphere brachytherapy.

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 broadscope 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 eyewear 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 postprocedure 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

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:

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.

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

During normal working hours:

Radiation Medicine:

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 Signature

Date:_____ Date:_____

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:

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

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 ≤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

	First author, year (reference)					
Category	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 aminostransferase	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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