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The American College of Radiology will periodically define new practice parameters and technical standards for radiologic practice to help advance the science of radiology and to improve the quality of service to patients throughout the United States. Existing practice parameters and technical standards will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each practice parameter 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 and approval. The practice parameters 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 parameter and technical standard by those entities not providing these services is not authorized.

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ACR–ABS–ACNM–ASTRO–SIR–SNMMI PRACTICE PARAMETER FOR SELECTIVE INTERNAL RADIATION THERAPY (SIRT) OR RADIOEMBOLIZATION FOR TREATMENT OF LIVER MALIGNANCIES

PREAMBLE

This document is an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. Practice Parameters and Technical Standards are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care¹. For these reasons and those set forth below, the American College of Radiology and our collaborating medical specialty societies caution against the use of these documents 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 practitioner in light of all the circumstances presented. Thus, an approach that differs from the guidance in this document, 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 this document when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document 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 the guidance in this document 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 this document is to assist practitioners in achieving this objective.

¹ *Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing*, ___ N.W.2d ___ (Iowa 2013) Iowa Supreme Court refuses to find that the *ACR Technical Standard for Management of the Use of Radiation in Fluoroscopic Procedures* (Revised 2008) sets a national standard for who may perform fluoroscopic procedures in light of the standard's stated purpose that ACR standards are educational tools and not intended to establish a legal standard of care. See also, *Stanley v. McCarver*, 63 P.3d 1076 (Ariz. App. 2003) where in a concurring opinion the Court stated that "published standards or guidelines of specialty medical organizations are useful in determining the duty owed or the standard of care applicable in a given situation" even though ACR standards themselves do not establish the standard of care.

I. INTRODUCTION

The practice parameter was revised collaboratively by the American College of Radiology (ACR), the American Brachytherapy Society (ABS), the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), the Society of Interventional Radiology (SIR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

Radioembolization with a microsphere brachytherapy device, also referred to as selective internal radiation therapy (SIRT) and transarterial radioembolization (TARE), are commonly used terms that describe the same procedure, so for the balance of this document, we will use the term radioembolization.

Radioembolization is the embolization of the hepatic arterial supply of hepatic primary tumors or metastases via delivery of radioactive beta emitters 20 to 60 μm in size. Terms relevant to this practice parameter include intra-arterial therapy and SIRT.

Hepatic arterial therapy takes advantage of the liver's dual blood supply and the fact that tumors larger than 3 mm in diameter receive 80% to 90% of their blood supply from the hepatic artery [1,2]. In contrast, the majority of the normal hepatic parenchyma receives its supply from the portal vein. For over 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 to perform intra-arterial brachytherapy. Brachytherapy is the use of radioisotopes as sealed sources to treat malignancies or benign conditions by means of a radioactive source placed close to or into the tumor. Yttrium-90 is a 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 penetration range in tissue of 11 mm, with a mean path of 2.5 mm and an effective path length of 5.3 mm. Yttrium-90 also emits a positron, with a branching ratio of 32 ppm, allowing for positron emission tomography (PET) imaging. In 1 kg of tissue, 1 GBq of uniformly dispersed yttrium-90 delivers an absorbed radiation dose of approximately 50 Gy.

Currently, two yttrium-90 products are commercially available. Both contain yttrium-90 as the therapeutic radioactive agent.

1. Glass spheres were approved by the Food and Drug Administration (FDA) in 1999 with a humanitarian device exemption (HDE) for use in patients with unresectable hepatocellular carcinoma (HCC). All of the spheres contained within a predetermined activity vial are implanted. The spheres have a median size of 25 μm (range 20-30 μm) and nominal specific activity of 2,500 Bq/sphere at time of calibration.
2. Resin spheres received FDA approval in 2002 for unresectable liver metastases from primary colorectal cancer in conjunction with an intrarterial chemoinfusion pump. The spheres have a median size of 32 μm (range 20-60 μm) and nominal specific activity of 50 Bq/sphere at time of calibration.

The use of brachytherapy requires detailed attention to personnel, equipment, patient, and personnel safety and to continuing staff education. As brachytherapy is performed in a variety of environments, the authorized user (AU), usually an interventional radiologist, radiation oncologist, or nuclear medicine physician, and a Qualified Medical Physicist should apply these practice parameters to individual practices (see section IV.D for the definition of a Qualified Medical Physicist).

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.² Medical use of isotopes for therapeutic procedures must adhere to the constraints set forth by these regulatory agencies. Detailed descriptions

²An 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).

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.

The treatment goal of radioembolization should be tailored to the individual patient, whether it is palliative or a bridge to surgical resection or liver transplantation. The most common clinical utility of radioembolization is in the treatment of HCC and liver-dominant metastatic CRC and neuroendocrine tumors (NETs) (see appendix A). Response to radioembolization is typically assessed with multidetector contrast-enhanced computed tomography (CT) of the liver or with magnetic resonance imaging (MRI) with contrast and, when appropriate, via fluorine-18-2-fluoro-2-deoxy-D-glucose PET/CT (FDG-PET/CT) [3,4].

II. INDICATIONS AND CONTRAINDICATIONS

A. Indications for both agents include, but are not limited to, the following:

1. The presence of unresectable or inoperable primary or secondary liver malignancies (particularly CRC and NET metastases). 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.
2. A life expectancy of at least 3 months

B. Absolute contraindications include the following:

1. Inability to catheterize the hepatic artery
2. Fulminant liver failure
3. Initial mapping angiography and/or technetium-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy demonstrating nontarget deposition to the gastrointestinal organs that cannot be corrected by angiographic techniques.
4. Pretreatment hepatic arterial administration with technetium-99m MAA 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. Active hepatic infection
6. Therapy during pregnancy may possibly be an option in extraordinary circumstances and with multidisciplinary consult and considerations.

C. Relative contraindications include the following:

1. Excessive tumor burden in the liver with greater than 50% to 70% of the parenchyma replaced by tumor. In the setting of more extensive tumor burden, treatment can be considered if synthetic hepatic function is preserved.
2. Total bilirubin greater than 2 mg/dL (in the absence of obstructive cause), which indicates severe liver function impairment. Nonobstructive bilirubin elevations may indicate that liver metastases have caused liver impairment to the degree that risks outweigh benefits for this therapy. In contrast, patients with HCC and elevated bilirubin may be treated with radioembolization if a segmental or subsegmental infusion can be performed [5].
3. Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver (clinical judgment by the AU required).
4. Care must be employed when patients are on systemic therapies that may potentiate or may alter the impact of radioembolization and should use caution when combining therapies.

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

Physicians from various medical specialties are involved at different times in the evaluation and management of patients receiving radioembolization. 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 performing the mapping angiogram with or without embolization, planning the delivery of dose, and subsequently placing the delivery catheter.

The AU should provide a written directive for the source administration and is responsible for administering the radioactive product once the interventional radiologist (who may also be the AU) has placed the delivery catheter [6]. The nuclear medicine specialist evaluates the technetium-99m MAA scan to quantify the lung shunt fraction and to evaluate for potential unintended deposition in other gastrointestinal organs. The responsibilities of the multidisciplinary team may include the following:

1. Selecting the patient for radioembolization. This includes history, physical examination, and review of imaging examinations and laboratory reports [7].
2. Obtaining informed consent for radioembolization. Complete explanations of the entire radioembolization process, including necessary imaging, laboratory, and treatment procedures, typical side effects, and potential complications. The team member completing this portion should be the physician coordinating the activities of the entire team [8].
3. Reviewing the hepatic angiogram, technetium-99m MAA scan, and laboratory reports to make the final determination of eligibility for radioembolization.
4. Determining treatment parameters: (a) single or fractionated (staged) treatment, (b) intended activity to be administered, (c) target volume (whole liver, lobar, or segment), and (d) vessel(s) to be used for delivery of activity
5. Delivering radioactivity, including monitoring for stasis and/or reflux of microspheres during treatment and ending the procedure as needed.
6. Monitoring the patient during the periprocedural period to provide support and clinical management and radiation safety information
7. Following patient after the day of treatment to monitor for side effects, complications, and response to therapy
8. Monitoring radiation safety and spill periprocedural events.
9. Verification of treatment delivery using nuclear medicine imaging. Posttherapy yttrium-90 single photon-emission CT (SPECT)/CT or yttrium-90 PET/CT is recommended.
10. Follow-up patients and monitor for radioembolization-induced liver disease that includes elevated bilirubin, elevated albumin, and development of ascites.

A. Interventional Radiologist

Interventional radiologists are the treating physicians who are the experts on locoregional therapy with microsphere embolization and are responsible for placement of the catheter for angiogram, technetium-99m MAA injection, protective embolization of gastric and gastroduodenal artery (GDA) if deemed necessary, and catheter placement for yttrium-90 treatment. The interventional radiologist may also be the AU at the treating facility. This individual should meet the following qualifications:

1. Certification in Radiology, Diagnostic Radiology, or Interventional Radiology/Diagnostic Radiology (IR/DR) by the American Board of Radiology (ABR), the American Osteopathic Board of Radiology, the Royal College of Physicians and Surgeons of Canada, or the Collège des Médecins du Québec and has performed (with supervision) a sufficient number of radioembolization procedures to demonstrate competency as attested by the supervising physician(s)
or
2. Completion of a radiology or interventional residency program and/or interventional/vascular radiology fellowship approved by the Accreditation Council for Graduate Medical Education (ACGME), the Royal College of Physicians and Surgeons of Canada, the Collège des Médecins du Québec, or the American Osteopathic Association (AOA) and has performed (with supervision) a sufficient number of radioembolization procedures to demonstrate competency as attested by the supervising physician(s).
or
3. Completion of an ACGME-approved nonradiology residency or fellowship training and 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 during which the physician was supervised. Documented formal training in the performance of invasive catheter arteriographic procedures must be included. During this training the physician should have performed 50 radioembolization procedures, 25 of

them as primary operator, performing (with supervision) a sufficient number of radioembolization procedures to demonstrate competency as attested by the supervising physician(s).

Maintenance of Competence

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

Interventional radiologists may become AUs. In order to do so, interventional radiologists must meet all of the necessary training requirements as described by the NRC and by their own radiation safety officer (RSO) and state. This includes training in physics as well as completion of the necessary training and proctoring by the yttrium-90 manufacturers.

B. Radiation Oncologists

As well as having training and expertise in the overall management and specific radiation treatment of a wide range of human malignancies, radiation oncologists are experts on liver tolerance to radiation therapy and radiation complications in normal tissues. The radiation oncologist may be the AU at the treating facility, and also may be involved in planning the therapy, including helping to plan where the delivery catheter should be placed, may administer the yttrium-90, may make the final determination of eligibility for radioembolization, may determine treatment parameters, and may monitor for radiation-related complications. The involved radiation oncologist must meet all of the following criteria:

1. Demonstrate satisfactory training and certification
 - a. Satisfactory completion of a residency program in radiation oncology approved by the ACGME, the Royal College of Physicians and Surgeons of Canada, the Collège des Médecins du Québec, or the AOA.

OR

- b. Certification in Radiology by the 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 RCPSC, or the Collège des Médecins du Québec may be considered proof of adequate physician qualifications.
2. Demonstrate continuing education in accordance with the ACR Practice Parameter for Continuing Medical Education (CME) [9].
3. If acting as AU, 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. Demonstrate 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.
5. Have a thorough understanding of each procedure with which the radiation oncologist is involved, ensuring appropriate utilizations 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. Participate in 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.

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, may also be responsible for the technetium-99m MAA injection, may be involved in planning the therapy, including helping to plan where the delivery catheter should be placed, may administer the yttrium-90, may make the final determination of eligibility for radioembolization, may determine treatment parameters, and may monitor for radiation-related complications. The nuclear medicine physician also interprets the postradioembolization PET scan and/or the bremsstrahlung scan. (See the [ACR–SPR Technical Standard for Diagnostic Procedures Using Radiopharmaceuticals](#) [10].)

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 ABR, the American Osteopathic Board of Radiology, the RCPSC, the Collège des Médecins du Québec, the American Board of Nuclear Medicine, and/or the American Osteopathic Board of Nuclear Medicine.

or

b. At a minimum, completion of a general nuclear medicine program approved by the ACGME, the RCPSC, the Collège des Médecins du Québec, or the AOA 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 Parameter for Continuing Medical Education \(CME\)](#) [9].
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 yttrium-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 the nuclear medicine physician 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, 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 strongly 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 by the American Board of Medical Physics (ABMP).

A Qualified Medical Physicist should meet the [ACR Practice Parameter for Continuing Medical Education \(CME\)](#). (ACR Resolution 17, 1996 – revised in 2012, Resolution 42) [9]

The appropriate subfields of medical physics for this standard are Nuclear Medical Physics (including medical physics certification categories of Radiological Physics, Medical Nuclear Physics, and Nuclear Medicine Physics).

Certification by the American Board of Science in Nuclear Medicine in Nuclear Medicine Physics and Instrumentation is also acceptable.

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 (eg, 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.

2. Nuclear medicine technologist

See the [ACR–SPR Technical Standard for Diagnostic Procedures Using Radiopharmaceuticals](#) [10].

F. Nursing Services

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–SIR Practice Parameter for Sedation/ Analgesia](#)) [11].

IV. SPECIFICATIONS OF THE PROCEDURE

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 (eg, carcinoembryonic antigen [CEA], alpha-fetoprotein [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 yttrium-90 radioembolization is to achieve optimal tumor response. CT, MR, and PET-CT are used to evaluate response. Both Response Evaluation Criteria in Solid Tumors (RECIST) criteria and modified RECIST criteria have been used to evaluate imaging response in HCC. RECIST criteria have also been used to evaluate imaging response in metastatic disease [12-15].

C. Obtaining Informed Consent

Consent for the interventional procedure should be obtained by the appropriate health care provider after discussing the procedure in detail with the patient or designated medical power of attorney. The risks and complications of the procedure, as well as the treatment outcomes, should be discussed in detail. The consent for radiation therapy should be obtained by the AU or his or her designee, which could include the interventional radiologist, the nuclear medicine physician, or the radiation oncologist. (See the [ACR Practice Parameter on Informed Consent – Radiation Oncology](#) [8].)

D. Pretreatment Evaluation

Pretreatment planning includes performance of a CT, MR, or PET scan within 30 days of treatment with determination of tumor volume. Other functional imaging may be performed as appropriate and the normal liver volumes.

E. Preliminary Angiographic Evaluation

Once a patient has been selected as a candidate for radioembolization, an initial angiographic evaluation is performed. The proper sequence of vessels to be addressed and evaluated has been previously published [16-18]. This evaluation is done primarily to delineate visceral anatomy, identify anatomic variants, isolate the hepatic circulation, and for consideration of occlusion or embolization of extrahepatic vessels.

Pretreatment visceral arteriography should, at a minimum, include injection of the celiac, superior mesenteric, common and/or proper hepatic, and right and left hepatic arteries. Embolization of the GDA as well as the right gastric or any other gastric arteries can be considered to avoid nontarget microsphere deposition to the gastrointestinal tract. Other vessels that may require similar treatment include the falciform artery, supraduodenal, retroduodenal, left inferior phrenic, accessory left gastric and inferior esophageal arteries. Care should be taken when considering embolization of the arteries perfusing the bowel, as collateralization can occur with time. The consensus for embolization of the cystic artery is still not established. If the cystic artery arises distal to the site of planned delivery, proximal embolization of the cystic artery at the time of yttrium-90 administration, usually with Gelfoam pledgets or coils, has been described. Given the rarity of radiation-induced cholecystitis (<2%) and most of the cases being managed conservatively, some institutes choose not to embolize the cystic artery [19]. Vascular anomalies should be identified, and the relationship of these variants with the tumors should be determined so that all tumors may be treated. These vessels should be recognized and accessed, with consideration for embolization left to the discretion of the operator.

It is important that all hepatic vessels be interrogated during the angiographic assessment of the patient. Only direct catheterization and interrogation of all appropriate vessels would demonstrate remote blood supply to the tumor. 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 yttrium-90 treatment.

At the conclusion of the vascular mapping arteriogram technetium-99m MAA arterial injection is performed: 37 to 185 MBq (1.0-5.0 mCi) of technetium-99m MAA should be injected through the microcatheter for follow-up

imaging of the liver and lungs to determine the degree of shunting to the lungs. Options for MAA injection locations include the (1) site of planned yttrium-90 infusion, (2) lobar artery to the hepatic lobe with greatest risk for elevated lung shunt fraction (eg, vascular invasion or greater tumor burden), or (3) common or proper hepatic artery [20,21]. The shunt fraction obtained is assumed to be representative of the bilobar tumors, and if a lobar injection is performed for bilobar disease, the lung shunt fraction may be a slightly overestimated, which would provide the largest margin of safety with regards to lung dose.

It is important to note that in cases where variant arterial anatomy exists, the technetium-99m MAA administered activity can be fractionated in order to cover the entire liver in one mapping angiogram, if possible. To this purpose, the MAA dose can be split into smaller (eg, 1 or 5 mCi) doses. For example, in cases where there is a replaced right hepatic artery, 2 to 3 mCi of technetium-99m MAA is given in that vessel, whereas the remaining 2 to 3 mCi is given in the left hepatic artery. In cases of a gastrohepatic trunk, 1 to 3 mCi of technetium-99m MAA is injected into the left hepatic artery, and the remainder is injected into the right hepatic artery.

F. Variant Mesenteric Anatomy

In 55% to 65% of cases, the celiac artery gives rise to the splenic artery, the left gastric artery, and the common hepatic artery (CHA). The dorsal pancreatic artery commonly arises from the celiac origin, although it may also arise off the CHA or splenic artery. The CHA 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 or accessory right hepatic artery arising from the superior mesenteric artery (SMA) and a replaced or accessory left hepatic artery arising from the left gastric artery [22]. Other less common variants include a replaced CHA arising from the SMA or bifurcation of a short CHA into 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.

G. Radioembolization Treatment Plan

1. It is recommended that a written directive be obtained from the AU before the microsphere dose administration is ordered. The written directive should include the following information:
 - a. Before implantation: treatment site, the radionuclide and type of spheres (yttrium-90 glass or resin microspheres), planned administered activity, date and time and/or activity ordered and medical end point
 - b. After implantation: the radionuclide (yttrium-90 microspheres), treatment site, and the total administered activity
 - c. In addition, the written directive may include:
 - 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 and the action taken
2. Radioactivity calculation

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 treated (eg, whole liver versus lobar treatment), various models (body surface area (BSA), partition model, single compartment Medical Internal Radiation Dosimetry (MIRD), voxel-based dosimetry) may be used in calculating activity to be administered.

a. Glass sphere

- i. The glass microsphere dosimetry is based on single-compartment MIRD (MIRD committee of the Society of Nuclear Medicine and Molecular Imaging) model. Although sphere distribution is known to be nonuniform, MIRD dosimetry models assume uniform distribution of activity in mass. Activity calculation requires determination of the patient's treatment liver mass and the nominal target dose.

b. Resin sphere

There are two methods for calculating the activity as recommended by the manufacturer:

- i. The 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 partition model is based on the MIRD model and involves implanting the highest possible activity to the tumor while maintaining acceptable radiation doses to radiosensitive tissues, such as lung and normal liver. This method can only be used where the tumor mass or masses are localized as a discrete area or areas within the liver and delineated as a "volume or volumes of interest" on a technetium-99m MAA SPECT or SPECT-CT study.

H. Radioembolization Treatment Delivery

1. Adherence to The Joint Commission's current Universal Protocol for Preventing Wrong Site, Wrong Procedure, Wrong Person Surgery™ is required for procedures in nonoperating room setting, including bedside procedures. The organization should have processes and systems in place for reconciling differences in staff responses during the "time out."
2. All patients should have continuous cardiac monitoring 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 step 2. 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 consists of particles of aggregated human serum albumin with a size range of 10 to 90 μm . 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 to 6.0 mCi (37-222 MBq).
 - ii. Planar images of the abdomen are obtained immediately in the following projections: anterior and posterior, left anterior oblique, and right anterior oblique, left lateral, and right lateral, followed by planar images of the chest and neck (to include the thyroid) in the anterior and posterior projections. SPECT/CT imaging should be performed. When using a single-head, large field-of-view SPECT gamma camera, the following parameters should be used: 64×64 matrix, 6° angle of sampling (60 images in a 360° arc), 20 to 30 seconds per stop. For multiheaded gamma cameras, SPECT imaging with a 128×128 matrix with a 3° angle of sampling (60 images per head for a dual-head camera or 40 images per head for a three-head camera) can be used. The CT as part of SPECT CT should

be of good quality (low noise). There is limited value to using a low-dose CT scan when the liver will be treated to radiation doses that will be orders of magnitude greater.

- b. Identify any extrahepatic radiotracer distribution and calculate the pulmonary shunt fraction by the geometric mean (GM). The GM is performed by drawing a region of interest around the whole lung and the whole liver in the anterior and posterior projections. The square root of the product of the anterior and posterior counts is the GM. Nontarget dose to lung can be calculated based on the lung shunt fraction, and dose reduction may be required to remain under the recommended lung tolerance doses of 30 Gy per treatment and 50 Gy total lifetime lung dose. Furthermore, the SIR-Spheres package insert states that a lung shunt fraction >20% is a contraindication to therapy. A dose reduction should also be considered if the patient has received prior chemotherapy [23,24].
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.

I. 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 [25].
2. A procedure note must be entered 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, the following: 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. Because a small amount of radioactivity may be excreted in the urine when undergoing radioembolization with resin microspheres, it is advised that for the first 24 hours postprocedure, the patient should use a toilet and not a urinal. The toilet should also be doubled flushed during this time [23].
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.

J. Device Implant

Prior to device implantation, all of the above procedures should have been completed, including review of appropriate studies, diagnostic angiography, MAA scanning, dose 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.

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.

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 from the base catheter is recommended.

For resin microspheres, administration involves the injection of D5W 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 the gastrointestinal 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 super selective placement has been performed.

V. PATIENT AND PERSONNEL SAFETY

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

A. Patient protection measures should include the following:

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 Qualified Medical Physicist to verify independently all brachytherapy parameters to be used in each procedure (source, isotope, and activity calculation, etc) prior to the delivery of radioembolization
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 must be in compliance with state and federal regulations. The AU, Qualified Medical Physicist, and RSO should define the postimplant radiation safety guidelines for patients treated with radioembolization.
6. Personnel in the angiography suite should all be surveyed for possible contamination.
7. The exposure rate from the contaminated waste should be measured to estimate the residual activity. Ninety-degree intervals around the contaminated waste chamber at 25 cm should be used according to the manufacturer’s guidance. These readings should be averaged to determine the final activity.
8. Postprocedure bremsstrahlung planar imaging, SPECT, SPECT/CT, and/or PET/CT, can be used within 24 hours of the conclusion of the procedure to document the placement of the devices and assess for significant extrahepatic shunting.
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 to 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 the following:

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

VI. DOCUMENTATION

Reporting should be in accordance with the [ACR–ASTRO Practice Parameter for Communication: Radiation Oncology](#) [7] or the [ACR–SIR–SPR Practice Parameter for the Reporting and Archiving of Interventional Radiology Procedures](#) [26], with the addition of:

1. Specification of the activity of yttrium-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

VII. RADIATION SAFETY

Radiologists, medical physicists, registered radiologist assistants, radiologic technologists, and all supervising physicians have a responsibility for safety in the workplace by keeping radiation exposure to staff, and to society as a whole, “as low as reasonably achievable” (ALARA) and to assure that radiation doses to individual patients are appropriate, taking into account the possible risk from radiation exposure and the diagnostic image quality necessary to achieve the clinical objective. All personnel that work with ionizing radiation must understand the key principles of occupational and public radiation protection (justification, optimization of protection and application of dose limits) and the principles of proper management of radiation dose to patients (justification, optimization and the use of dose reference levels)

http://www-pub.iaea.org/MTCD/Publications/PDF/Pub1578_web-57265295.pdf.

Facilities and their responsible staff should consult with the radiation safety officer to ensure that there are policies and procedures for the safe handling and administration of radiopharmaceuticals and that they are adhered to in accordance with ALARA. These policies and procedures must comply with all applicable radiation safety regulations and conditions of licensure imposed by the Nuclear Regulatory Commission (NRC) and by state and/or other regulatory agencies. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol.

Nationally developed guidelines, such as the ACR's [Appropriateness Criteria](#)[®], should be used to help choose the most appropriate imaging procedures to prevent unwarranted radiation exposure.

Additional information regarding patient radiation safety in imaging is available at the Image Gently[®] for children (www.imagegently.org) and Image Wisely[®] for adults (www.imagewisely.org) websites. These advocacy and awareness campaigns provide free educational materials for all stakeholders involved in imaging (patients, technologists, referring providers, medical physicists, and radiologists).

Radiation exposures or other dose indices should be measured and patient radiation dose estimated for representative examinations and types of patients by a Qualified Medical Physicist in accordance with the applicable ACR technical standards. Regular auditing of patient dose indices should be performed by comparing the facility's dose information with national benchmarks, such as the ACR Dose Index Registry, the NCRP Report No. 172,

Reference Levels and Achievable Doses in Medical and Dental Imaging: Recommendations for the United States or the Conference of Radiation Control Program Director's National Evaluation of X-ray Trends. (ACR Resolution 17 adopted in 2006 – revised in 2009, 2013, Resolution 52).

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 that 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 benches 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 B for radiation safety discharge instructions.

VIII. EQUIPMENT SPECIFICATIONS

Several technical requirements are necessary to ensure safe and successful diagnostic arteriogram and radioembolization 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 [ACR–SIR–SPR Practice Parameter for the Performance of Arteriography](#) [27].

A gamma camera with a low-energy all-purpose (LEAP) or low-energy high-resolution (LEHR) collimator may be used for the nuclear medicine imaging, of technetium-99m MAA planar or SPECT/CT and medium-energy (ME) or high-energy (HE) collimators for yttrium-90 SPECT/CT as well as PET with time-of-flight (TOF) capabilities.

The activity of yttrium-90 is determined by measurement using an appropriate dose calibrator, such as a pressurized, well-type ionization chamber. The dose calibrator and microsphere manufacturer's instructions regarding calibration for yttrium-90 microsphere 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 versus polycarbonate) of the container holding the source.

IX. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

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 appearing under the heading *Position Statement on QC & Improvement, Safety, Infection Control, and Patient Education* on the ACR website (<https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Quality-Control-and-Improvement>).

Nuclear medicine equipment performance monitoring should be in accordance with the [ACR–AAPM Technical Standard for Nuclear Medical Physics Performance Monitoring of Gamma Cameras](#) [28].

The Medical Director of Radiation Oncology, Interventional Radiology, and/or Nuclear Medicine is responsible for the institution and ongoing supervision of continuing quality improvement (CQI) as described in the [ACR–ASTRO Practice Parameter for Radiation Oncology](#) [29]. 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 radioembolization as part of the CQI meeting agenda. Refer to the [ACR–ASTRO Practice Parameter for Radiation Oncology](#) [29] for a detailed description of CQI committee functions.

Medical Event

Medical event must be reported to the regulatory agency (NRC or State), and the AU (or RSO) should follow the published rules and regulations. Common reported events associated with this procedure include, but are not limited to, overdose, wrong site, kinked catheter, defective/cracked catheter, partial obstruction, leaking connection, slow infusion, and reflux to other lobe. Users should be cautious when performing such procedures.

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Collaborative Committee – members represent their societies in the initial and final revision of this technical standard

ACR

Kelvin Kai-Wen Hong, MD, Chair
Don C. Yoo, MD, FACR
Bassem I. Zaki, MD

ABS

Phillip M. Devlin, MD, FACR
Catheryn M. Yashar, MD, FACR

ACNM

Murthy RK Chamarthy, MD
Sonya J. Koo, MD

ASTRO

Andrew S. Kennedy, MD
Zoubir Ouhib, MS, FACR

SIR

Olaguoke Akinwande, MD
Suvranu Ganguli, MD
Siddharth A. Padia, MD
Riad Salem, MD

SNMMI

Lisa Bodei, MD
Shana Elman, MD
Reed G. Selwyn, PhD

Committee on Practice Parameters – Interventional and Cardiovascular Radiology
(ACR Committee responsible for sponsoring the draft through the process)

Clayton K. Trimmer, DO, FACR, FAOCR, FSIR, Chair
Chaitanya Ahuja, MBBS
Drew M. Caplin, MD
Douglas M. Coldwell, MD, PhD
Mandeep S. Dagli, MD
Kevin W. Dickey, MD
Joshua A. Hirsch, MD, FACR, FSIR
Kelvin Hong, MD, FSIR

Elizabeth A. Ignacio, MD, FSIR
Sanjeeva P. Kalva, MD, FSIR
Claire Kaufman, MD
Kenneth F. Layton, MD, FACR
Margaret Hsin-Shung Lee, MD, FACR
John D. Prologo, MD
Sanjit Tewari, MD

Committee on Practice Parameters and Technical Standards – Nuclear Medicine and Molecular Imaging
(ACR Committee responsible for sponsoring the draft through the process)

Kevin P. Banks, MD, Co-Chair
Richard K. J. Brown, MD, FACR, Co-Chair
Alexandru C. Bageac, MD, MBA
Twyla B. Bartel, DO, MBA
Murray D. Becker, MD, PhD, FACR
Erica J. Cohen, DO, MPH
Joanna R. Fair, MD
Erin C. Grady, MD

Edward D. Green, MD
Jeffrey S. Kempf, MD, FACR
Jennifer J. Kwak, MD
Charito Love, MD
Syam P. Reddy, MD
Levi Sokol, MD
Rathan M. Subramaniam, MD, PhD, MPH
Stephanie P. Yen, MD

Committee on Practice Parameters – Radiation Oncology
(ACR Committee responsible for sponsoring the draft through the process)

Alan C. Hartford, MD, PhD, FACR, Chair
Naomi R. Schechter, MD, Vice Chair
Nathan H. J. Bittner, MD
Samuel T. Chao, MD
Chee-Wai Cheng, PhD, FAAPM
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Mark Hurwitz, MD
Lesley A. Jarvis, MD, PhD

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Nikhil Thaker, MD
Paul E. Wallner, DO, FACR
Kristina L. Woodhouse, MD
Ying Xiao, PhD
Sue S. Yom, MD, PhD
Bassem I. Zaki, MD

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Seth A. Rosenthal, MD, FACR, Chair, Commission on Radiation Oncology
Jacqueline Anne Bello, MD, FACR, Chair, Commission on Quality and Safety
Matthew S. Pollack, MD, FACR, Chair, Committee on Practice Parameters and Technical Standards
Mary S. Newell, MD, FACR, Vice Chair, Committee on Practice Parameters and Technical Standards

Comments Reconciliation Committee

K. Elizabeth Hawk, MD, MS, PhD, Chair
Darlene F. Metter, MD, FACR, Co-Chair
Olaguoke Akinwande, MD
Kevin P. Banks, MD
Jacqueline A. Bello, MD, FACR
Lisa Bodei, MD
Richard K. J. Brown, MD, FACR
Murthy RK Chamarthy, MD
Phillip M. Devlin, MD, FACR
Richard Duszak, Jr., MD, FACR
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Alan K. Klitzke, MD, FACNM

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Alan H. Matsumoto, MD, FACR
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Riad Salem, MD
Reed G. Selwyn, PhD
Timothy L. Swan, MD, FACR
Clayton K. Trimmer, DO, FACR, FAOCR, FSIR
Rakesh Varma, MD
Catheryn M. Yashar, MD, FACR
Don C. Yoo, MD, FACR
Bassem I. Zaki, MD

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APPENDIX A

Literature Review

A. Hepatocellular Carcinoma

Treatment of hepatocellular carcinoma (HCC) is a balance between tumor progression and the treatment's detrimental effect on liver reserve. Although single lesions can be treated effectively with ablative techniques such as radiofrequency ablation, with an increase in the number and growth of lesions and the failure of other liver directed therapies, eg, transarterial chemoembolization, radioembolization can be utilized effectively [30]. Patients with early stage HCC and well-compensated cirrhosis (Child-Pugh A) respond well to radioembolization as seen in both prospective and retrospective studies [31-39]. As expected, the more extensive the HCC and the more advanced the cirrhosis, the more survival is impaired. Nevertheless, use of radioembolization in Child-Pugh B and C patients results in survival rates of 6 to 13 months and 4 to 8 months, respectively [43]. Since this is primarily an outpatient therapy, it is better tolerated than other embolotherapy options for treatment of HCC [43]. The invasion of the portal vein by HCC is a contraindication to the use of embolotherapy, except in radioembolization in which the survival of these patients shown promising results [44]. Radioembolization can also be utilized effectively to down stage unresectable HCC, enabling ablative techniques, surgical resection, or transplantation [45].

B. Colorectal Cancer

Colorectal cancer is the third most common cancer diagnosed among both men and women in the United States. The American Cancer Society [46] estimates that approximately 148,810 new cases of colorectal cancer and 49,960 deaths were expected in 2008.

Approximately 72% of new diagnoses are colon cancer and 28% are rectal cancer. The liver is the most frequent site of metastases. An estimated 60% of patients who are diagnosed with colorectal cancer eventually will experience liver disease as a predominant site [47]. Surgical resection is associated with long-term survival in patients with colorectal liver metastases [48]. A median overall survival of 44 months and a 5-year survival rate of 35% [49] are associated with surgical resection of liver confined disease for patients with no evidence of disseminated disease with a resection strategy encompassing all liver disease with adequate remnant liver for recovery and medical fitness for laparotomy. However, patients who have liver metastases amenable to resection account for less than 20% of the population with metastatic liver disease [50]. For the majority of patients without resectable disease, the median overall survival is 22 months and rarely is associated with the survival beyond 5 years [51]. Targeted nonsurgical approaches for liver-confined CRC metastases may offer survival advantages beyond that of systemic therapy alone.

1. Radioembolization for chemorefractory liver metastases:

Radioembolization was evaluated in a cohort of 72 patients with unresectable hepatic colorectal metastases who were treated at a targeted absorbed dose of 120 Gy with a median delivered dose of 118 Gy [52]. The safety and toxicity was assessed using version 3 of the National Cancer Institute Common Terminology

Criteria. Response was assessed radiographically and survival was estimated using the Kaplan-Meier method from the diagnosis of hepatic metastases and first treatment. Treatment-related toxicities included fatigue (61%), nausea (21%), and abdominal pain (25%), with grade 3 and 4 bilirubin toxicities observed in 9 of 72 patients (12.6%). The tumor response rate was 40.3%. The median time to hepatic progression was 15.4 months, and the median response duration was 15 months. Overall survival from the first radioembolization treatment was 14.5 months. Based on substratification analyses, tumor replacement ($\leq 25\%$ versus $>25\%$) was associated with significantly greater median survival (18.7 months versus 5.2 months). The presence of extrahepatic disease was associated negatively with overall survival (7.9 months versus 21 months). Overall survival from the date of initial hepatic metastases was 34.6 months. A subset analysis of patients who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 demonstrated a median survival of 42.8 months and 23.5 months from the time of hepatic metastases and radioembolization treatment, respectively. The data from this study also suggests that patients who have been exposed to fewer than 3 cytotoxic agents may have a better outcome than patients who have received all chemotherapy options prior to radioembolization. Based on the subset analyses of this study, it appears patients with good performance status, no extrahepatic metastases, liver disease limited to $\leq 25\%$ of liver volume, who have not received all available lines of chemotherapy may benefit most from treatment of radioembolization.

Resin microspheres have also been evaluated in the treatment of metastatic colorectal cancer. Radioembolization [53] was associated with mild to moderate toxicity, except for one grade 4 treatment-associated cholecystitis and 2 grade gastric ulcers, using resin microspheres administered as a single session, whole liver treatment in 41 patients with metastatic colorectal cancer refractory to chemotherapy.

2. Radioembolization with chemotherapy in liver metastases:

In a phase III trial [54], 46 patients with unresectable, chemotherapy-refractory liver-limited metastatic CRC were randomly assigned to fluorouracil protracted intravenous infusion 300 mg/m² days 1 through 14 every 3 weeks (Arm A) or to radioembolization plus intravenous FU 225 mg/m² days 1 through 14 and then 300 mg/m² days 1 through 14 every 3 weeks (Arm B) until hepatic progression. Crossover to radioembolization was permitted after progression in the chemotherapy alone arm. Median follow-up was 24.8 months. Median TTLP was 2.1 and 5.5 months in arms A and B, respectively ($P= 0.003$). Grade 3 or 4 toxicities were recorded in 6 patients after FU monotherapy and in one patient after radioembolization plus FU treatment ($P= 0.10$). Twenty-five of 44 patients received further treatment after progression, including 10 patients in arm A who received radioembolization. Median overall survival was 7.3 and 10.0 months in arms A and B, respectively ($P= 0.80$). The conclusion is that radioembolization with 90Y- resin microspheres plus FU is well tolerated and significantly improves TTLP and TTP compared with FU alone for chemotherapy-refractory liver-limited metastatic CRC.

In dose escalation studies reporting use of the resin microspheres in combination with oxaliplatin- [55] based chemotherapy, the maximum-tolerated dose of oxaliplatin was 60 mg/m² during the first 3 cycles of chemotherapy. In combination with irinotecan-based chemotherapy [56], the authors concluded that the maximum-tolerated dose of irinotecan was not reached. In both trials, radioembolization treatment was administered within a cycle of chemotherapy with the majority of patients experiencing mild to moderate transient toxicities.

3. Response evaluation:

FDG-PET/CT appears to be an accurate indicator of treatment response [4]. Studies demonstrated a significant difference between the metabolic and the anatomic response after yttrium-90 glass microsphere treatment for unresectable liver metastases in colorectal cancer. FDG-PET imaging is more sensitive than CT in the assessment of early response to resin microspheres, allowing clinicians to proceed with further therapeutic options [3].

C. Neuroendocrine Tumors

NETs, thought to be uncommon, represent the second highest in incidence of gastrointestinal malignancies. There is mounting evidence that NETs have been increasing in incidence and prevalence over last 4 decades. Gastroentero-

pancreatic NETs that arise from cells throughout the gut and pancreas are subclassified based upon the production of hormone-related symptoms (functional versus nonfunctional). The 5-year survival of patients with metastatic disease is less than 40%. The prognosis at presentation for NET is ambiguous, but recent evidence suggests that, along with staging, immunohistochemical and pathological grading are important. Yttrium-90 radioembolotherapy has been demonstrated to retard disease progression in patients with NET liver metastases. Based on sound principles, yttrium-90 microsphere radioembolotherapy offers advantages of low acute and subacute toxicity, and standardized dosing allows interoperator comparison of outcomes. The table below summarizes the peer-reviewed outcomes in NET patients [13,57-65].

Author	Year	Total Patients	Embolotherapy	Study Design	Median Activity/Treatment	CR + PR	Symptom Response%	Tumor Marker Response%	Median Survival (months)	5-year Survival (months)
Granberg	2007	3	Resin 90Y	Observation	1	100	nr	67	15	nr
King	2008	34	IV 5FU+90Y Resin	Phase 4	1.99	50	55	nr	nr	nr
Kennedy	2008	148	Resin 90Y	Observation	1.14	63.2	nr	nr	@36	nr
Rhee	2008	22	Glass 90Y	Observation	nr	54	nr	nr	70	nr
Rhee	2008	20	Resin 90Y	Observation	nr	50	nr	nr	22	nr
Kalinowski	2009	9	Resin 90Y	Phase 4	2.1	66	nr	nr	28	nr
Cao	2009	58	Resin 90Y +/- IV 5FU	Observation	1.8	37	nr	nr	@36	nr
Saxena	2010	48	IV 5FU+90Y Resin	Phase 2	1.94	54	nr	nr	36	nr
Memon	2011	40	Glass 90Y	Observation	1.98	64	84	nr	35	nr
Rajekar	2011	14	Resin 90Y +/- IA 5FU	Observation	nr	nr	100	71	34.4	nr
Paprottka	2012	42	Resin 90Y	Observation	1.63	22.5	95	54.8	25	42%
Memon	2012	40	Glass Y90	Observation	1.98	63.9	84	nr	34.4	nr

APPENDIX B

10 CFR 35.75 authorizes the release of individuals from licensees if the total effective dose equivalent (TEDE) to a member of the public is less than 5 mSv. Written release instructions must be provided if the TEDE to a member of the public is likely to exceed 1 mSv. If the dose to a breast-feeding infant or child could exceed 1 mSv, then breast-feeding interruption guidance and consequences of failure to follow the guidance must be provided. After microsphere administration, dose rates at 1 m have been correlated with administered activity when corrected for by BMI (McCann et al, “Radiation emission from patients treated with selective hepatic radioembolization using yttrium-90 microspheres: Are contact restrictions necessary?”). Patients treated with less than 3 GBq do not require contact restrictions using an occupancy factor of 0.25 (6 hours per day), administered activity, exposure to public at 1 meter, physical half-life, and without considering tissue shielding. Patients who receive greater than 3 GBq may require contact restrictions depending on the situation such that the contact is greater than 6 hrs/day or average distance is less than 1 meter (e.g., caregiver for significant care or extensive travel). The following table, modified from McCann et al, provides threshold dose rates measured at 1 m that will allow patients to be released without contact restrictions (1 mSv) for various situations.

Contact Situation	Occupancy Factor	Distance (m)	Threshold Dose Rate (mSv/hr)
Household member	0.25	1	0.043
Caregiver, sleeping partner, or extensive travel	0.25	0.3	0.004
Caregiver for significant care	0.5	0.3	0.0022
Nursing infant, child or pregnant woman	0.042	0.1	0.0086

It is generally understood that there is very little biological clearance of yttrium-90 and glass microspheres are stable, whereas trace amounts of yttrium can be excreted in urine of patients treated with resin microspheres. Therefore, for the first 24 hours after treatment, patients are instructed to practice good bathroom hygiene by flushing twice and to wash hands very well after the toilet is used [66].

*Practice parameters and technical 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 practice parameters and technical standards published before 1999, the effective date was January 1 following the year in which the practice parameter or technical standard was amended, revised, or approved by the ACR Council.

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