ACR–ABS–ACNM–ARS–SIR–SNMMI PRACTICE PARAMETER FOR RADIOEMBOLIZATION OF LIVER MALIGNANCIES

The American College of Radiology, with more than 40,000 members, is the principal organization of radiologists, radiation oncologists, and clinical medical physicists in the United States. The College is a nonprofit professional society whose primary purposes are to advance the science of radiology, improve radiologic services to the patient, study the socioeconomic aspects of the practice of radiology, and encourage continuing education for radiologists, radiation oncologists, medical physicists, and persons practicing in allied professional fields.

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.

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 care[1]. 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 considering 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 variables such as the condition of the patient, limitations of available resources, or advances in knowledge or technology after publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document may consider documenting in the patient record information sufficient to explain the approach taken.

The practice of medicine involves the science, and 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 purpose of this document is to assist practitioners in achieving this objective.

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1 *Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing, 831 N.W.2d 826 (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 Radium Society (ARS), the Society of Interventional Radiology (SIR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

The Nuclear Regulatory Commission (NRC) defines brachytherapy as a medical procedure during which a sealed radioactive source (or sources) is implanted directly into a person being treated for cancer. Radioembolization is the delivery of 20-60 µm radioactive microspheres into the hepatic arterial supply of primary or metastastatic liver tumors . Embolization with brachytherapy microbeads , is also referred to as selective internal (or intra-arterial) radiation therapy (SIRT) and trans arterial radioembolization (TARE). For the purpose of clarity and for the balance of this document, we will use the term radioembolization. Hence, radioembolization is considered a form of brachytherapy by the NRC, even though not all radioactive beads are a sealed source of radiation and have unique physio-chemical properties that affect radiation protection.

Radioembolization takes advantage of the liver's dual blood supply and the fact that tumors larger than 3 mm in diameter receive 80%–90% of their blood supply via the hepatic artery [1,2]. This is in contrast to the hepatic parenchyma which receives 75% of blood flow and significant oxygen from the portal venous circulation. For over 30 years, this difference has been exploited to deliver chemotherapy via intra-arterial pumps, embolic agents to occlude tumoral arteries, and various combinations of both chemotherapy and embolic agents (chemoembolization) to enhance therapeutic effect from synergy of ischemic and antineoplastic effects.

Radioembolization is a more recent addition to the intra-arterial therapeutic armamentarium. The embolizing beads contain yttrium-90 and are radioactive. In this brachytherapy procedure the radioactive source is placed close to or within the target to increase dose to the area of interest while limiting non-target effects. 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 decay results in positron-electron pair production and subsequent annihilation with a branching ratio of 32 ppm, allowing for positron emission tomography (PET) imaging. The beta energy emitted by yttrium-90 decay is approximately 50 Joules per GBq (50 Gy-kg/GBq). One GBq of yttrium-90 uniformly dispersed in 1 kg of tissue delivers an absorbed radiation dose of approximately 50 Gy, assuming 100% absorption of the emitted beta energy.

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

1. Glass microspheres were first approved by the Food and Drug Administration (FDA) in 1999 with a humanitarian device exemption (HDE) followed by full approval in 2021 for use in patients with unresectable (solitary less than or equal to 8cm) hepatocellular carcinoma. The spheres have a median size of 25 µm (range 20-30 µm) and nominal specific activity of 4000 Bq/sphere at time of calibration.
2. Resin microspheres received FDA approval in 2002 for unresectable liver metastases from primary colorectal cancer in conjunction with an intraarterial chemo infusion 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.

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

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

The treatment goal of radioembolization should be tailored to the individual patient characteristics with specific attention to whether the intent, is palliative, curative, or as bridge/ downstaging to surgical resection or liver transplantation. The most common clinical uses of radioembolization are in the treatment of hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, liver-dominant metastatic colorectal cancer (CRC) (particularly chemotherapy resistant) 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].

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

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 is generally liver dominant but is not required to be exclusively within the liver.
2. A performance status that will allow the patient to benefit from such therapy.
3. A life expectancy of at least 3 months.
4. Laboratory data that suggest the procedure can be performed safely [81].

B. Absolute contraindications include the following:

1. Inability to catheterize the hepatic artery.
2. Fulminant liver failure.
3. Initial mapping angiography, contrast-enhanced cone beam CT, and/or technetium-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy demonstrating clinically unacceptable nontarget deposition that cannot be ameliorated with embolization or delivery adjustment.
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 the acceptable limits specific to each yttrium-90 product
5. Acute hepatic infection.
6. Uncorrectable coagulopathy.

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 biliary of obstruction or Gilbert disease), 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 radio-embolization and should use caution when combining therapies such as with capecitabine [6].
5. Pregnancy, although therapy during pregnancy may possibly be an option in extraordinary circumstances and with multidisciplinary consult and ethical considerations.

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

Core Privileging: This procedure is considered part of or amendable to image-guided core privileging.

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, or for overseeing the administering of, the radioactive product once the interventional radiologist (who may also be the AU) has placed the delivery catheter [7]. 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 [8].
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 [9].
3. Reviewing the hepatic angiogram, cone beam CT (when available), intraprocedure CT (when available), technetium-99m MAA scan, and laboratory reports to make the final determination of eligibility for radioembolization. It should be noted that technetium-99m can be evaluated with either planar or single photon-emission (SPECT)/CT imaging with the caveat that planar imaging overestimates the shunt fraction compared with SPECT due to an inability to correct for tissue attenuation [10].
4. Determining treatment parameters: (a) single or fractionated (staged) treatment, (b) intended activity to be administered, possibly based on intended dose to be delivered, (c)target volume (whole liver, lobar, or segment), and (d) vessel(s) to be used for delivery [81,82]
5. Delivering radioactivity, including monitoring for stasis and/or reflux of microspheres during treatment and terminating the procedure as indicated.
6. Monitoring the patient during the periprocedural period to provide support and clinical management and radiation safety information.
7. Monitoring radiation safety and spill periprocedural events.
8. Following patient after treatment to monitor for side effects, complications, and response to therapy, including radioembolization-induced liver disease that commonly presents with elevated bilirubin, elevated albumin, and development of ascites.
9. Verification of treatment delivery using nuclear medicine imaging as possible in the local practice environment. Posttherapy ytrrium-90 bremsstrahlung 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.

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

A. Interventional Radiologist

Initial Qualifications

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 nontarget vessels, 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. Demonstrate satisfactory training and certification

    a. 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 radioembolization AU physician(s)

    or

    b. 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 radioembolization AU physician(s).

    or

    c. 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 radioembolization AU physician(s).

2. Demonstrate continuing education in accordance with the ACR Practice Parameter for Continuing Medical Education (CME) [11].

3. If acting as AU, be listed as an AU on the radioactive materials license of their 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 Interventional radiologist 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.

Maintenance of Competence

Physicians must perform a sufficient number of overall procedures applicable to the spectrum of core privileges to maintain their skills, with acceptable success and complication rates as laid out in this parameter. Continued competence should depend on participation in a quality improvement program that monitors these rates. Consideration should be given to the physician's lifetime practice experience.

If moderate sedation is used for the procedure, at least one physician who has demonstrated satisfactory training and certification to supervise moderate sedation must be present; alternatively, a credentialed anesthesiologist can provide sedation services.

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

B. Radiation Oncologists

Initial Qualifications

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 external-beam radiation therapy and radiation complications in normal tissues. The radiation oncologist may be the AU at the treating facility, and may be involved in planning the therapy, including assisting in the planning of delivery catheter , placement, may administer the yttrium-90 product, may make the determination of eligibility for radioembolization with the interventional radiologist, 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 their 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. If moderate sedation is used for the procedure, at least one physician must be present who has demonstrated satisfactory training and certification to supervise moderate sedation must be present; alternatively, a credentialed anesthesiologist can provide sedation services.

3. Demonstrate continuing education in accordance with the ACR Practice Parameter for Continuing Medical Education (CME) [11].

4. If acting as AU, be listed as an AU on the radioactive materials license of their 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.

5. 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.

6. 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.

7. 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.

Maintenance of Competence

Radiation oncologists must perform overall procedures to maintain their skills. Continued competence also depends on participation in a quality improvement program. Consideration should be given to the physician's lifetime practice experience.

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

C. Nuclear Medicine Physician

Initial Qualifications

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 assisting in the planning of delivery catheter placement, may administer the yttrium-90 product, 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 yttrium-90 SPECT/CT or PET/CT scan. (See the ACR–SPR Technical Standard for the Use of Radiopharmaceuticals in Diagnostic Procedures [12].)

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

1. Qualifications and certification
    a. Certification in either Radiology or Diagnostic Radiology with certificate in, Nuclear Radiology, or certification in Nuclear Medicine by 1 of the following organizations: the ABR, the American Osteopathic Board of Radiology, the RCPSC, the Collège des Médecins du Quebec, the American Board of Nuclear Medicine, and/or the American Osteopathic Board of Nuclear Medicine.

    or

    b. At a minimum, completion of a 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.

2. Have documented regular participation in CME specifically related to diagnostic procedures using radiopharmaceuticals, in accordance with the ACR Practice Parameter for Continuing Medical Education (CME) [11].
3. Be listed as an AU on the radioactive materials license of their 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 product 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.

Maintenance of Competence

Nuclear Medicine Physicians must perform overall procedures to maintain their skills. Continued competence also depends on participation in a quality improvement program. Consideration should be given to the physician's lifetime practice experience.

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

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, the American Board of Science in Nuclear Medicine (ABSNM), or the American Board of Medical Physics (ABMP).

A Qualified Medical Physicist should meet the ACR Practice Parameter for Continuing Medical Education (CME). [11]

The appropriate subfield of medical physics for this standard is Nuclear Medical Physics (including medical physics certification categories of Radiological Physics, Medical Nuclear Physics, and Nuclear Medicine Physics). (ACR Resolution 17, adopted in 1996 – revised in 2008, 2012, 2022, Resolution 41f)

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

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

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 the Use of Radiopharmaceuticals in Diagnostic Procedures [12].

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

F. Nursing Services

If the patient is to undergo moderate sedation, a nurse or other appropriately trained individual should monitor the patient as their 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 Minimal and/or Moderate Sedation/Analgesia) [13].

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, alpha-fetoprotein), hemoglobin, hematocrit, creatinine, electrolytes, CA 19-9 and coagulation parameters
4. Review of appropriate anatomic and/or functional imaging studies, such as cross-sectional CT, MR, and PET scans

IV. SPECIFICATIONS OF THE PROCEDURE

B. Establishing Treatment Goals with Patient and Treatment Team

The goal of yttrium-90 radioembolization is to achieve optimal tumor response based on the specific goals of therapy. CT, MR, and PET-CT are used to evaluate response. [14-17 , 84]

IV. SPECIFICATIONS OF THE PROCEDURE

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 their designee, which could include the interventional radiologist, the nuclear medicine physician, or the radiation oncologist. (See the ACR–ARS Practice Parameter on Informed Consent Radiation Oncology [9].)

IV. SPECIFICATIONS OF THE PROCEDURE

D. Pretreatment Evaluation

Pretreatment planning includes performance of a CT, MR, or PET scan within 30-60 days of treatment with determination of tumor volume and liver volume. Other functional imaging may be performed as appropriate.

IV. SPECIFICATIONS OF THE PROCEDURE

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 [18-20]. This evaluation is done primarily to delineate visceral anatomy, identify anatomic variants, isolate the hepatic circulation, and for consideration of occlusion or embolization of vessels that may increase the risk and extent of nontarget embolization.

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, because collaterization 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 of the time of yttrium-90 administration, usually with Gelfoam pledgets or coils, has been described [21]. Given the rarity of radiation-induced cholecystitis (<2%) and that most cases when encountered are managed conservatively, some institutes choose not to embolize the cystic artery [21,22]. Vascular anomalies should be identified, and the relationship of

these variants with the tumor blood supply should be fully characterized to allow all tumor to be appropriately treated. These vessels should be recognized and accessed, with consideration for embolization at the discretion of the operator.

It is important that hepatic vessels be interrogated during the angiographic evaluation. Only direct catheterization and interrogation of all vessels would demonstrate the total blood supply to the tumor. Incomplete angiography may result in failure to treat an accessory supply to the tumor not demonstrated without comprehensive angiographic assessment.

Once the anatomy has been established, selective arteriography is performed in the expected location of the yttrium-90 treatment. If available, cone-beam contrast- enhanced CT, or intraprocedure CT should also be performed at this site to establish that there is sufficient coverage of the area of interest.

At the conclusion of the vascular mapping arteriogram technetium-99m MAA arterial injection is performed through the microcatheter. Scintigraphic imaging of the liver and lungs follows 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 [23,24]. 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 [85].

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

Hepatic arterial scintigraphy with technetium-99m MAA is done for treatment planning and in some cases to detect 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 10–90 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– 5.0 mCi (37-185 MBq).
    ii. Planar images of the thorax and abdomen are obtained immediately in anterior and posterior views. SPECT/CT imaging should be performed where available [85]. For Dual-headed gamma cameras, SPECT imaging with a 128 × 128 matrix with a 3° angle of sampling and 15-20 s per view 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 using the geometric mean (GM). The GM method consists of drawing regions of interest around the whole lung and the whole liver in the anterior and posterior projections and computing the square root of the product of the anterior and posterior counts in each region. The lung shunt fraction is calculated as the ratio of lung GM counts to that of the liver plus lung. 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. Furthermore, the SIR-Spheres package insert only specifies 30 Gy 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 [25,26].

A physician should be available during the immediate postprocedural period to ensure that there is adequate

hemostasis at the puncture site and that the patient is stable prior to transfer to the postprocedural care area.

IV. SPECIFICATIONS OF THE PROCEDURE

F. Variant Mesenteric Anatomy

In 55%–65% of cases, the celiac artery gives rise to the splenic artery, the left gastric artery, and the common hepatic artery (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 [27]. 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.

IV. SPECIFICATIONS OF THE PROCEDURE

G. Radioembolization Treatment Plan

1. A written directive is obtained from the AU before the microsphere dose is ordered. The written directive should include the following information:
    a. Before implantation: treatment site, the radionuclide and type of microspheres (yttrium-90 glass or resin), 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 target, normal liver, 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
        vii. Day of device calibration relative to treatment day of spheres

2. Radioactivity calculation

    Depending on the yttrium-90 product 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 Monte Carlo) may be used in calculating the activity to be administered. Dosimetry is an evolving field, and new computational models are always in development. Currently accepted models for estimating the injected dose are as follows:

a. Glass sphere
    i. The glass microsphere package-insert dosimetry is based on single-compartment uniform uptake MIRD (Medical International Radiation Dose 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

c. There are two methods for calculating the activity as recommended by the manufacturer package-insert:

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 a CT scan.
ii. The partition model facilitates determination of the injected activity into tumor, normal liver, and lung compartments and requires an estimate of the tumor to normal liver activity concentration ratio generated from technetium-99m MAA scintigraphy [28].This method can only be used where the tumor mass or masses are localized as a discrete volume(s) within the liver and delineated as a "volume or volumes of interest" on a technetium-99m MAA SPECT or SPECT/CT study for the determination of uptake concentration and volume.
iii. The technetium-99m MAA SPECT or SPECT/CT study findings should meet criteria to predict adequate distribution of yttrium-90 to meet treatment objectives [28-30].

IV. SPECIFICATIONS OF THE PROCEDURE

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 and capnography should be used in addition to step 2. A registered nurse or other appropriately trained personnel should be present, and their primary responsibility should be to monitor the patient. A record should be kept of medication doses, timed patient vitals, and times of medication 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. Identification of vessels that extend outside the anticipated treatment field (examples may include gastric, duodenal, or esophageal vessels) is critical. Appropriate precautions for vascular exclusions are undertaken at the time (such as distal catheter placement or coil embolization).
6. Posttreatment yttrium-90 bremsstrahlung imaging with SPECT/CT or yttrium- positron imaging with PET/CT may be performed and used for posttreatment assessment of actual in vivo yttrium-90 biodistribution [83,85-87].

IV. SPECIFICATIONS OF THE PROCEDURE

I. Post-procedure 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 postprocedural activity to verify activity administered to the patient [32].
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 interpretation[1] 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 postprocedural 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 maybe excreted in the urine when undergoing radioembolization with resin microspheres, it is advised that for the first 24 hours postprocedural, the patient should use a toilet and not a urinal. The toilet should also be double flushed during this time [25].
4. During the initial postprocedural 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 before discharge.
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 before 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.

[1]The 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.

IV. SPECIFICATIONS OF THE PROCEDURE

J. Yttrium-90 Product Management

Before yttrium-90 product administration, all of the above procedures should have been completed, including review of appropriate studies, diagnostic angiography, MAA scanning, dose calculations, and ordering of the yttrium-90 product There should be discussion among team members before patient treatment to address any unique or unusual characteristics that may affect patient safety or outcome.

The yttrium-90 product should be assayed in the dose calibrator to verify the calibration activity of the source. For resin spheres, the appropriate activity should be withdrawn from the source vial and transferred to the treatment vial. Everything that comes in contact with the radioactive source and could be a source of 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 resin microspheres, administration involves the injection of dextrose 5% in Water (D5W) through the treatment vial 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 before the final injection of contrast if super selective placement has been performed.

IV. SPECIFICATIONS OF THE PROCEDURE

K. Post-Treatment Verification

Following treatment administration, post-therapy imaging should be performed for verification where available.. Yttrium-90 SPECT/CT or PET/CT imaging is recommended. This volumetric post-therapy imaging provides verification of planned spatial dose distribution from the treatment and verification of the total activity administered during the treatment, and it facilitates estimation of the integral dose to target lesions as well as normal anatomic structures.

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 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.) before 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 follow state and federal regulations. The AU, Qualified Medical Physicist, and radiation safety officer (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 administration of the yttrium-90 product 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 1–3 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 undergone a radiopharmaceutical treatment Radiation from the yttrium-90 product 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 [8] or the ACR–SIR–SPR Practice Parameter for the Reporting and Archiving of Interventional Radiology Procedures [33], 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. Documentation 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, non-physician radiology providers**,** 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 who work with ionizing radiation must understand the key principles of occupational and public radiation protection (justification, optimization of protection, application of dose constraints and limits) and the principles of proper management of radiation dose to patients (justification, optimization including the use of dose reference levels). https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1775_web.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 in accordance with ALARA principles. 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 applicable state, local, or other relevant regulatory agencies and accrediting bodies, as appropriate. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol, using body habitus or other customized method when such guidance is available.

Nationally developed guidelines, such as the ACR's Appropriateness Criteria®, should be used to help choose the most appropriate imaging procedures to prevent unnecessary radiation exposure.

Additional information regarding patient radiation safety in imaging is available from the following websites – Image Gently® for children (www.imagegently.org) and Image Wisely® for adults (www.imagewisely.org). 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 periodically measured by a Qualified Medical Physicist in accordance with the applicable ACR Technical Standards. Monitoring or regular review of dose indices from patient imaging should be performed by comparing the facility's dose information with national benchmarks, such as the ACR Dose Index Registry and relevant publications relying on its data, applicable ACR Practice Parameters, 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; 2006, 2009, amended 2013, revised 2023 (Res. 2d).

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 in which 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 cervices, becoming practically impossible to remove from benchtops and equipment. Appropriate planning and care can reduce this risk.

Facilities, in consultation with the RSO, should have in place, and should adhere to, policies and procedures for the safe handling and administration of radiopharmaceuticals, in accordance with ALARA, and must comply with all applicable radiation safety regulations and conditions of licensure imposed by the NRC, state, and/or other

regulatory agencies. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol. See Appendix 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 [34].

At a minimum, a gamma camera with a low-energy all-purpose or low-energy high-resolution collimator may be used for the nuclear medicine imaging of technetium-99m MAA planar scintigraphy and SPECT/CT. SPECT/CT with medium-energy or high-energy collimators may be used for yttrium-90 SPECT/CT, whereas PET/CT with time-of-flight capabilities may be used for yttrium-90 PET/CT. Note that due to the low positron branching ratio, 20-30 min/bed PET acquisitions are recommended for post Yttrium-90 PET imaging due to low positron branching ratio.

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 (±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 [35].

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 [36]. 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 [36] 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 another lobe. Users should be cautious when performing such procedures.

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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. The standard of care is surgical resection, but many patients are unable to tolerate major surgery due to liver compromise**.** 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, i.e., transarterial chemoembolization, radioembolization can be utilized effectively [37]. Patients with early stage HCC and well-compensated cirrhosis (Child-Pugh A) respond well to radioembolization as seen in both prospective and retrospective studies [38-49]. 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 [50]. Since this is primarily an outpatient therapy, it is better tolerated than other embolotherapy options for treatment of HCC [50]. 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 [51]. Radioembolization can also be utilized effectively to down stage unresectable HCC, enabling ablative techniques, surgical resection, or transplantation [52].

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 [53] estimates that approximately 153,020 new cases of colorectal cancer and 52,550 deaths were expected in 2023[54].

Approximately 70% of new diagnoses are colon cancer and 30% 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 [55]. Surgical resection is associated with long-term survival in patients with colorectal liver metastases [56]. A median overall survival of 44 months and a 5-year survival rate of 35% [57] 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 [58]. 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 [59]. Targeted nonsurgical approaches for liver-confined CRC metastases may offer survival advantages beyond that of systemic therapy alone.

A. 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 [60]. 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 (=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 =25% of liver volume, who have not received all available lines of chemotherapy may benefit most from treatment of radioembolizaion.

Resin microspheres have also been evaluated in the treatment of metastatic colorectal cancer. Radioembolization [61] 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.

A. Radioembolization with chemotherapy in liver metastases:

A. In a phase III trial [62], 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.
B. In dose escalation studies reporting use of the resin microspheres in combination with oxaliplatin- [63] 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 [64], 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 most patients experiencing mild to moderate transient toxicities.

C. In a phase III trial, 530 chemotherapy naïve patients with liver metastases plus or minus limited extrahepatic metastases were randomized to receive either modified FOLFOX (mFOLFOX6, control) or mFOLFOX6 plus radioembolization plus or minus bevacizumab. The primary study end point was progression-free survival (PFS). Median PFS at any site was similar for control and radioembolization (10.2 versus 10.7 months, respectively; HR 0.93; 95% CI, 0.77 to 1.12; P = .43). By competing risk analysis, the addition of SIRT improved median PFS in the liver from 12.6 (control) to 20.5 months (radioembolization; HR, 0.69; 95% CI, 0.55 to 0.90; P = .002). Grade = 3 adverse events, including recognized radioembolization-related effects, were reported in 73.4% and 85.4% of patients in control versus radioembolization. The conclusion was that the addition of radioembolization to FOLFOX-based first-line chemotherapy in patients with liver-dominant or liver-only metastatic colorectal cancer did not improve PFS at any site but significantly delayed disease progression in the liver [65].

D. Overall, the benefit of radioembolization when added to systemic therapy is not clear. Combined analysis of multiple trials investigating the combination of first line chemotherapy with radioembolization for patients with metastatic colorectal cancer with liver metastases did not demonstrate a survival benefit with the addition of radioembolization [66]. The incidence of progression within the liver in the first 12 months of follow-up was improved with radioembolization; 22% (95% CI 19–26) in the FOLFOX plus radioembolization group vs 39% (35–43) in the FOLFOX alone group. It was noted that patients with colorectal liver metastases from right-sided primaries could benefit more from radioembolization, as this subgroup was associated with improved survival outcomes.

A. Response evaluation:

A. 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].

B.

A. Neuroendocrine Tumors

A. 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 radioembolization has been demonstrated to slow disease progression in patients with NET liver metastases. Based on sound principles, yttrium-90 microsphere radioembolization 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 [15,67-75]. Recently a new form of radiopharmaceutical therapy, peptide-receptor radiation therapy (PRRT) has been established as a standard of care second line therapy for patients with advanced midgut neuroendocrine tumors who have progressed on first-line somatostatin analogue therapy [76]. PRRT consists of a series of infusions of lutetium-177-Dotatate, which binds to neuroendocrine cells and is internalized, delivering the radionuclide directly within tumor cells. Due to the doses received by the liver and other organs during treatment with PRRT, there is concern for increased risk of liver injury from cumulative doses from PRRT and radioembolization. Initial reports have suggested that radioembolization after PRRT is safe [77], but further study is needed to characterize liver constraints in the setting of repeated radiopharmaceutical therapies.

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
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
Wong [78]	**2022**	**170**	**Resin 90Y**	**Observation**	**1.3 (unilobar), 1.9 (bilobar)**	**36**	**nr**	**nr**	**33**	**nr**
Zuckerman [79]	**2019**	**59**	**Resin 90Y (64%) and Glass 90Y (36%)**	**Observation**	**1.71 (Resin), 5.43 (Glass)**	**52.5**	**nr**	**nr**	**31**	**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 [80].

*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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