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Revised 2005 (Res. 21)*

PRACTICE GUIDELINE FOR THE PERFORMANCE OF THERAPY WITH UNSEALED RADIOPHARMACEUTICAL SOURCES

PREAMBLE

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

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

The practice of medicine involves not only the science, but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not assure an accurate diagnosis or a

successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

I. INTRODUCTION

This guideline was revised by the American College of Radiology (ACR), and the American Society for Therapeutic Radiology and Oncology (ASTRO).

It is intended to guide appropriately trained and licensed physicians performing therapy with unsealed radiopharmaceutical sources. Such therapy requires close cooperation and communication between the physicians who are responsible for the clinical management of the patient and those who administer radiopharmaceutical therapy and manage the attendant side effects. Adherence to this guideline should help to maximize the efficacious use of these procedures, maintain safe conditions, and ensure compliance with applicable regulations.

Application of this guideline should be in accordance with the [ACR Technical Standard for Diagnostic Procedures Using Radiopharmaceuticals](#), as that guideline relates to the handling of radiopharmaceuticals, radiation safety, and radiation protection of patients, personnel, and the public. There must also be compliance with applicable laws and regulations.

II. DEFINITION

Therapy with unsealed sources involves administration of radiopharmaceuticals for the treatment of medical conditions.

III. GOAL

The goal of therapy with unsealed radiopharmaceutical sources is to provide either cure or effective palliation of disease while minimizing untoward side effects and complications.

IV. INDICATIONS

Examples of therapy with unsealed radiopharmaceutical sources are:

1. Iodine-131 (sodium iodide) for hyperthyroidism.
2. Iodine-131 (sodium iodide) for therapy of iodine-avid thyroid cancer.
3. Phosphorus-32 (sodium phosphate) for treatment of myeloproliferative disorders such as polycythemia vera and thrombocytosis.
4. Phosphorus-32 (colloidal chromic phosphate) for intracavitary therapy of malignant ascites, malignant pleural effusion, malignant pericardial effusions, and malignant brain cysts.
5. Strontium-89 (strontium chloride) and samarium-153 lexidronam ethylene diaminetetramethylenephosphonic acid (EDTMP) for adjuvant and palliative treatment of painful skeletal metastases when these metastases are radiotracer-avid on a diagnostic bone scan.
6. Yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab, murine monoclonal antibodies that target the CD20 antigen, for treatment of patients with CD20 positive follicular B-cell non-Hodgkin's lymphoma, with or without transformation, that is refractory to rituximab and has relapsed following chemotherapy.

For the pregnant or potentially pregnant patient, see the [ACR Practice Guideline for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation](#).

V. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

The qualifications and responsibilities of physicians and other personnel performing these therapeutic procedures should be in accordance with the ACR Technical Standard for Diagnostic Procedures Using Radiopharmaceuticals and/or the [ACR Practice Guideline for Radiation Oncology](#). In addition, training and experience must be in compliance with the applicable laws and regulations.

VI. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

The written or electronic request for a radiopharmaceutical study should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance and interpretation.

Documentation that satisfies medical necessity includes 1) signs and symptoms and/or 2) relevant history (including known diagnoses). Additional information regarding the specific reason for the examination or a provisional diagnosis would be helpful and may at times be needed to allow for the proper performance and interpretation of the examination.

The request for the examination must be originated by a physician or other appropriately licensed health care provider. The accompanying clinical information should be provided by a physician or other appropriately licensed health care provider familiar with the patient's clinical problem or question and consistent with the state's scope of practice requirements. (ACR Resolution 35, adopted in 2006)

A. General Procedures

1. Clinical evaluation - The initial evaluation of the patient includes history, physical examination, review of pertinent diagnostic studies and reports, and communication with the referring physician and other physicians involved in the patient's care. For the radiopharmaceutical treatments that are potentially marrow-toxic, a complete blood count with differential should be part of the initial evaluation and of each pretreatment examination.
2. Quality management - In order to employ radiopharmaceuticals as unsealed sources for therapy, a "quality management" program must be in place as required by the Nuclear Regulatory Commission (NRC) or agreement state¹ regulations. Key elements of this program are: written directives; duplicative procedures for identifying patients; careful record keeping to ensure correct administered activity; minimization of the possibility of infiltration for agents which are administered intravenously; procedures for minimizing radiation exposure or radiopharmaceutical contamination of personnel, family members of patients, and the public (e.g.,

¹An 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).

alerts regarding possible current or future pregnancy); procedures for containment of radioactivity; and an audit mechanism to ensure compliance with the program.

3. Informed consent - Informed consent must be obtained and documented. See the [ACR Practice Guideline on Informed Consent – Radiation Oncology](#).
4. Treatment - The procedure and follow-up should be performed according to an established system of procedural steps that may be unique for each type of application.
5. Female patients should not be pregnant or breast-feeding at the time radiopharmaceutical therapy is orally, intravenously, or intraperitoneally administered. Pregnancy should be ruled out by a negative human chorionic gonadotropin (hCG) test obtained within 72 hours prior to administration of the radiopharmaceutical or by documented history of hysterectomy or by a postmenopausal state with absence of menstrual bleeding for 2 years, or by premenarche in a child age 10 or younger. Breast-feeding should be completely discontinued prior to the therapy and should not be resumed until it has been determined safe to resume by the physician performing the therapy. After therapeutic doses of iodine-131, the NRC recommends no further breast-feeding until the next pregnancy. Other national regulatory bodies may have similar recommendations. The treating physician should also bear in mind that the immediate post-lactating breast may still concentrate iodine-131 resulting in breast radiation dose.
6. Radiation precautions - Radiation precautions and patient release criteria may be regulated federally by the U.S. Nuclear Regulatory Commission (NRC) in many states, or by the state (with regulations that are closely patterned on the federal regulations and may be more restrictive). The radiation safety officer or health physicist for the local facility can provide information on the applicable regulations. Details on the federal regulations can be obtained at the NRC web site, www.nrc.gov, or by telephone (301-415-7000).

Under the guidelines of federal code 10 CFR 35.75 and NRC Regulatory Guide 8.39, the patient may be released if the total effective dose equivalent to any other adult who is exposed to the patient is not likely to exceed 0.5 rem (5 mSv), assuming all other regulatory

requirements for patient instructions and record keeping are met. NUREG-1556, Vol 9, “Consolidated Guidance about Materials Licenses; Program-Specific Guidance about Medical Licenses,” describes methods for calculating doses to other individuals and contains tables of activities not likely to cause doses exceeding 5 mSv (0.5 rem).

Most radiation meters measure exposure rates in milliroentgens/hour (mR/hr). For low-linear-energy-transfer-rate radiation (including beta particles and most X-rays and gamma rays), the exposure rate in mR/hr will be equivalent to the dose rate in mrem/hr. Thus, an exposure rate of 7.0 mR/hr at 1 meter is assumed to give a dose rate of 7.0 mrem/hr.

For treatments outside the United States, regulations of the corresponding national regulatory bodies may apply, and all applicable laws and regulations must be followed.

If confinement in a healthcare facility is needed, it is not usually necessary to store body effluents such as urine, stool, or vomitus. For effluent disposal the toilet should be flushed two or three times after each use, to ensure sufficient dilution of radioactivity. Food trays and linens should be stored in the room until monitored and cleared by radiation safety staff. All routine blood work and laboratory specimens should be obtained prior to treatment with the radiopharmaceutical. The patient must stay in the room except in a medical or nonmedical (e.g., fire) emergency, and access by personnel and visitors must be limited. All trash and residual nondisposable items must be monitored after the patient’s release and stored until radiation levels reach the statutory level defined for safe disposal or reuse. Once all known contamination is removed from the room, the room must be surveyed to verify that the radiation levels are sufficiently low to permit its general use. The room may not be used until this survey is performed.

If the admitting physician is different from the physician who administers the radiopharmaceutical, there must be a mechanism to prevent premature discharge or release of the patient from confinement.

B. Iodine-131 (sodium iodide) Therapy for Hyperthyroidism

The basic disease entities treated are: diffuse toxic goiter (Graves’ disease), toxic nodular goiter, and solitary toxic nodule.

1. Diffuse toxic goiter

- a. Patient - A recent radioiodine thyroid uptake should be available (see the [Practice Guideline for the Performance of Thyroid Scintigraphy and Uptake Measurements](#)). The size of the thyroid gland should be estimated, either by palpation or by some other means. Optimally, the patient's system should be free of iodide-containing medications, iodinated contrast agents, exogenous thyroid hormone, and antithyroid medications.
- b. Administered activities - Initial activity of 50 to 200 microcuries (1.85 to 7.4 MBq) per gram of thyroid (after adjusting for current 24-hour radioiodine uptake) is usually administered. Generally the likelihood of residual hyperthyroidism is greater for lower administered activity, and the likelihood of hypothyroidism is greater for higher administered activity. There are also data to support empiric dosing with a "fixed" dose of 6.4 millicuries (240 MBq) or 9.5 millicuries (350 MBq). The limitation of fixed dose administration is that there is little correlation between the millicuries administered to the patient and the dose in cGy delivered to the thyroid gland due to the wide range of radioiodine uptake of hyperthyroid patients. The measurement of radioiodine uptake before radioiodine therapy is necessary even when a fixed dose is planned, to prevent the inappropriate administration of radioactive iodine to a patient with lymphocytic (silent) thyroiditis. Each treating physician, often in consultation with the referring physician, should decide on an appropriate activity to be administered (see section VI.A.6. for radiation precautions).
- c. Side effects/complications - Side effects are rare. Occasional exacerbation of thyrotoxicity may occur, which usually responds to short-term beta blocker medication. Patients may occasionally experience neck pain, tenderness, and/or odynophagia from radiation thyroiditis. Complications are also rare. Hypothyroidism is often considered the expected and desired outcome of successful therapy of Graves' disease or toxic nodular goiter and can occur within 2 months or decades later. Hypothyroidism is treated with carefully monitored hormone replacement therapy.
- d. Prior thioamide therapy - Thioamides (e.g., propylthiouracil and methimazole) inhibit organification of iodide. If radioiodine therapy is administered during the first 2

weeks after discontinuing thioamide, the thyroidal absorbed dose is apt to be diminished due to more rapid iodine turnover. The iodine-131 dosage may need to be increased in these circumstances.

- e. Subsequent therapies - In patients who have not adequately responded to prior iodine-131 therapy, subsequent treatments may be given. A higher activity per gram of gland may be considered. Dose considerations should balance the total activity against the relative risks of residual disease versus hypothyroidism. Repeat therapies are usually not indicated until at least 3 months after a radioiodine treatment to allow the full effect to occur.

2. Toxic nodular goiter and solitary toxic nodule

- a. Patient - See section VI.B.1.a.
- b. Administered activity - These conditions tend to be more resistant to radioiodine therapy. Activity of up to 30 or more millicuries (1.1 GBq) for outpatient treatment may be administered provided that the radioiodine uptake is sufficient.
- c. Side effects/complications - See section VI.B.1.c. If a solitary toxic nodule has fully suppressed the function of the remaining thyroid, the risk of resulting hypothyroidism is decreased.
- d. Prior thionamide therapy - The effect of thionamide on the responsiveness of the thyroid to radioiodine therapy is similar to that in diffuse toxic goiter. The treating physician should consider having the patient discontinue the medication to allow for systemic clearance or, if this is not feasible, using an activity in the upper end of the administered activity range.
- e. Treatment failures - Rarely, it may be necessary to administer an activity larger than 33.0 millicuries (1.2 GBq) in which case the patient may need to be confined and placed on radiation precautions (see section VI.A.6.).

C. Iodine-131 (sodium iodide) Therapy for Residual or Metastatic Thyroid Cancer

Iodine-avid thyroid cancers frequently take up radioiodine in the absence of significant amounts of residual normal thyroid tissue. In order to optimize ablative radioiodide therapy for residual or metastatic disease, or in selected cases to facilitate the follow-up for patients with good prognosis, the thyroid remnant should be completely eliminated by surgery and/or radioiodine treatment, if possible.

1. Ablation of thyroid remnant
 - a. Patient - The serum TSH must be elevated, usually to a level in excess of 30 $\mu\text{IU/mL}$, either by withholding oral thyroid hormone to induce endogenous TSH secretion or by injecting recombinant human TSH (rhTSH) to raise the patient's blood level of this hormone before therapy. If the remnant is suspected to be large, thyroid scintigraphy with technetium-99m (pertechnetate) or iodine-123 may be performed to determine how avidly the thyroid remnant is accumulating radioiodine. If the remnant is very small, a whole-body survey with iodine-131 or iodine-123 before ablation may be useful. Documentation of an elevated TSH level as well as adherence to a low iodine diet for 1 to 2 weeks prior to treatment is recommended. Optimally, the patient's system should be free of iodide-containing medications, iodinated contrast agents, exogenous thyroid hormone, and antithyroid medications. No age limits apply. Administration of more than 2 millicuries (74 MBq) of iodine-131 may interfere with subsequent uptake of iodine-131 for several days to several weeks. This "stunning" effect may be minimized by administering the therapeutic dose within 72 hours of the activity administered for the diagnostic radionuclide dosage.
 - b. Administered activities - Activities of 30 to 200 millicuries (1.11 to 7.4 GBq) of iodine-131 (sodium iodide) administered orally are most often used. The lower doses are often used after lobectomy, higher doses after thyroidectomy to ablate the remnant, (e.g., 100 millicuries [3.7 GBq]), or for uptake in nonpalpable lymph nodes post-thyroidectomy. Prior to administration, the patient should be fasting and should abstain from eating for at least 2 hours after taking an oral dose. The patient may need to be placed on radiation precautions (see section VI.A.6. for radiation precautions).
 - c. Side effects/complications -Hypothyroidism, which is usually present prior to iodine-131 therapy as a result of the surgery, is an expected result. Side effects include radiation dysphagia and sialadenitis, both of which are activity related and are self-limited. To prevent sialadenitis, measures should be taken to stimulate saliva flow for 1 to 2 days following therapy, such as recommending administration of a sialogogue or other agent that stimulates the salivary glands. With larger activities or multiple administrations, xerostomia may rarely occur. Patients given 100 millicuries (3.7 GBq) or more may develop mild treatment-related symptoms such as headache, nausea, and vomiting that begin about 4 hours after iodine-131 administration and resolves within 72 hours. Diarrhea has occasionally been noted. A single dose of 50 to 100 millicuries (1.85 to 3.7 GBq) may deliver sufficient radiation to the testes to cause transient testicular failure of uncertain long-term consequence. Sperm banking or discussion of fertility issues should be considered, particularly in young men for whom the cumulative dose is anticipated to be over 100 millicuries (3.7 GBq) or who may need multiple treatments. There is some evidence that female fertility may be decreased after activities in excess of 600 millicuries. Myelosuppression may occur with oral doses of iodine-131 in excess of 150 to 200 millicuries, and dosimetry is suggested when such doses are used, especially in older patients. Leukemogenesis and carcinogenesis (salivary glands, kidney, bladder, gastrointestinal tract) have been described in patients following high dose iodine-131 therapy.
2. Known or suspected residual thyroid cancer
 - a. Patient - See section VI.B.1.a. An elevated thyroglobulin level or a whole body survey performed with iodine-131, iodine-123, or other radiopharmaceuticals that show abnormal concentration of tracer indicates recurrence (see the [Practice Guideline for the Performance of Thyroid Scintigraphy and Uptake Measurements](#)).
 - b. Administered activity - For residual tumor in the thyroid bed, activities of 100 to 150 millicuries (3.7 to 5.55 GBq) are usually administered. Complications, side effects, and radiation precautions are similar to those described in section VI.C.1.c.
3. Distant metastases
 - a. Patient - See Section VI.C.1.a.
 - b. Activities of 100 to over 250 millicuries (3.7 to 9.25 GBq) are usually administered. Complications, side effects, and radiation precautions are similar to those described in sections VI.A.6. and VI.B.1.c. Activity administered can be based on fixed doses, depending on the clinical situation, or based on quantitative iodine-131 dosimetry. Dosimetry calculations of dose to the whole

blood and of total lung activity at 48 hours may be performed when the highest activities are used. When larger activities are administered, bone marrow suppression becomes a concern. There are reports of pulmonary fibrosis and/or pneumonitis resulting from therapy of widespread lung metastases when the administered activity delivers a dose of 600 cGy or more to the lung. Pulmonary function studies should be considered prior to treatment if there are widespread pulmonary metastases.

c. A measurable serum thyroglobulin level indicates functioning thyroid tissue and may be an indication for treatment. In the setting of elevated thyroglobulin and negative iodine-131 or iodine-123 scan, an FDG PET scan with TSH stimulation may be helpful to localize recurrent/metastatic disease that would potentially be amenable to surgical management.

4. Interactions with other forms of treatment

a. Patients with a high risk of local/regional recurrent disease may be treated with both iodine-131 and external beam irradiation. The use of external beam irradiation prior to or alternating with radioactive iodine treatment has not been shown to be associated with a subsequent reduction in tumor uptake of radioactive iodine. Therefore external beam irradiation, if indicated, need not be delayed. The toxicity, acute and late, is likely to be additive within the field of irradiation.

b. Distant metastatic lesions that are painful or are a threat to life or function may be treated with external beam irradiation or surgery in addition to iodine-131.

D. Strontium-89 and Samarium-153 Lexidronam Therapy for Bone Pain Caused by Skeletal Metastases

1. Patient - Patients with multiple osseous metastases that show increased tracer uptake on bone scintigraphy, who are obtaining diminishing relief from other methods of pain management (e.g., analgesics, external beam irradiation), and whose bone marrow is competent, are candidates for radiopharmaceutical therapy. Patients with disseminated intravascular coagulation (DIC) must be excluded from therapy. Others may be treated after a case-by-case evaluation as adjuvant therapy to delay symptomatic skeletal metastases. Urinary incontinence is not a contraindication to treatment, although the patient or caregiver should be instructed on how

to minimize radiation contamination from spilled urine. For samarium-153 lexidronam and strontium-89, bladder catheterization should be considered for patients incontinent of urine, to minimize the risk of radioactive contamination.

2. Administered activity - For strontium-89 the standard activity is 40 to 60 microcuries (1.48 to 2.22 MBq) per kilogram of body weight, given by intravenous infusion over 1 to 2 minutes. The recommended samarium-153 lexidronam activity is 1.0 millicurie (37.0 MBq) per kilogram of body weight, given intravenously, also over 1 to 2 minutes.

3. Complications - A “flare” phenomenon occurs in some patients, with transient worsening of pain within several days. It may last several days and can be severe, although the pain usually improves when compared to pretreatment level. It may be managed with analgesic or steroidal medication. Extravasation of the radiopharmaceutical should be avoided, and it is imperative to have excellent intravenous access that is functioning properly prior to injection. Bone marrow depression occurs transiently, with a nadir at about 3 to 6 weeks and with recovery in about 3 to 6 additional weeks. Complete blood and platelet counts should be followed routinely for 8 to 12 weeks.

4. Interactions with other forms of treatment

a. Hormone administration need not be discontinued before the administration of radiopharmaceutical therapy, since it does not interfere with the mechanism of action and does not potentiate any side effects.

b. External beam radiation therapy may be used in concert with radiopharmaceutical therapy for local treatment of selected sites, especially those in which pathologic fracture or cord compression might occur.

c. The patient should not have received long-acting myelosuppressive chemotherapy for 6 to 8 weeks and other forms of myelosuppressive chemotherapy for at least 4 weeks prior to radiopharmaceutical administration, also because of potential marrow toxicity.

5. Radiation precautions - There are none for strontium-89. For samarium-153 lexidronam, the patient may be released if the total effective activity equivalent to any other individual who is exposed to the patient is not likely to exceed 0.5 rem (5 millisieverts) per year. If state or facility regulations are more restrictive, these should be followed.

6. Retreatment - Retreatment may be administered because of initial treatment failure or if symptoms recur. Special attention should be paid to recovery of bone marrow and blood counts. Retreatment may be given after adequate bone marrow recovery occurs, which is typically 2 to 3 months.
7. As with all other forms of therapy with unsealed sources, patient management should be coordinated with clinical services and with other involved parties, especially radiation oncology, if external beam irradiation has been employed or is being considered.

E. Phosphorus-32 (sodium phosphate) for Polycythemia Rubra Vera or Thrombocytosis

Phosphorus-32 (sodium phosphate) is approved for treatment of polycythemia vera or thrombocytosis. The diagnosis must be confirmed prior to therapy. The activities may be standard (3.0 millicuries [111 MBq] intravenously) or based on body surface area (2.3 millicuries [85 MBq] per square meter intravenously) but should not usually exceed 5.0 millicuries (185 MBq). Relapse or failure to respond within 12 weeks may require retreatment with dosages up to 7.0 millicuries (259 MBq). Phosphorus-32 should not be given if the platelet count is less than 100,000/microliter or the leukocyte count is less than 3,000/microliter.

F. Phosphorus-32 (colloidal chromic phosphate) for Malignant Ascites or Pleural Effusion

The usual activity for intracavitary therapy is 6 to 12 millicuries (222 to 444 MBq) in the pleural cavity and 10 to 20 millicuries (370 to 740 MBq) in the peritoneum. The ability of the radiopharmaceutical to spread uniformly throughout the affected cavity should be documented using technetium-99m sulfur colloid (see the [ACR Practice Guideline for the Performance of Gastrointestinal Scintigraphy](#)) as an intraperitoneal or intrapleural injection followed by appropriate imaging. The patient should be turned to distribute the imaging agent. After documented dispersal, the patient may be treated. The combination of intraperitoneal phosphorus-32 colloidal chromic phosphate and external irradiation to the pelvis has been reported to be associated with a high incidence of morbidity, particularly bowel obstruction; accordingly, caution must be observed when this combination of therapy is used.

G. Yttrium-90 Ibritumomab Tiuxetan and Iodine-131 Tositumomab for Radioimmunotherapy of Non-Hodgkin's Lymphoma

1. Agents
 - a. Yttrium-90 ibritumomab tiuxetan consists of ibritumomab, the murine IgG1 kappa monoclonal antibody from which rituximab was developed, and tiuxetan, which stably chelates 111-In for imaging and 90-Y for therapy. Iodine-131 tositumomab is a murine IgG2a lambda monoclonal antibody covalently linked to iodine-131. Both antibodies are directed against the CD20 antigen which is found on the surface of normal and malignant B lymphocytes.
2. Patient
 - a. Patients with CD20 positive follicular B-cell non-Hodgkin's lymphoma, with or without transformation, including patients who are refractory to rituximab, are candidates for radioimmunotherapy.
 - b. Patients must have two to three diagnostic scans prior to the therapeutic dose delivery in order to verify individual biodistribution. In-111 ibritumomab tiuxetan is used for diagnostic studies prior to treatment with yttrium-90 ibritumomab tiuxetan, and a diagnostic activity of iodine-131 tositumomab is used prior to the therapeutic dose delivery of that radiopharmaceutical. Patients with altered biodistribution as described in sections 3.b and 3.c below should not be treated with these radiopharmaceuticals. The pretreatment scans are also used to calculate the therapeutic dose for iodine-131 tositumomab.
 - c. Patients treated with iodine-131 tositumomab are at risk for hypothyroidism. To reduce this probability, they must be treated with either a saturated solution of potassium iodide (SSKI) four drops orally a day, Lugol's solution 20 drops orally three times a day, or potassium iodide tablets 130 mg orally once a day, starting at least 24 hours prior to initiating the iodine-131 tositumomab dosimetric dose. Thyroid blockade must continue until 2 weeks after administration of the iodine-131 tositumomab therapeutic dose.
3. Dosimetry and assessment of biodistribution
 - a. Pretreatment whole-body dosimetry and/or assessment of biodistribution is required to determine whether the treatment is appropriate for a patient. The assessment is also used to determine the patient-specific activity to be administered in the therapeutic dose step for iodine-131 tositumomab.

- b. Patients being considered for yttrium-90 ibritumomab tiuxetan must be scanned with indium-111 ibritumomab tiuxetan on day 1. The first whole-body planar gamma camera anterior and posterior images are obtained 2 to 24 hours after infusion. The second set is obtained 48 to 72 hours after indium-111 ibritumomab, and if needed, a third image is obtained 90 to 120 hours after infusion. Biodistribution is considered to be altered if the blood pool is not visualized well on the first imaging time point indicating rapid clearance by reticuloendothelial system, which may also appear as diffuse, intense early tracer uptake in the liver and/or spleen. Diffuse, intense tracer uptake in the lung greater than that of the cardiac blood pool on the first image, or more intense than in the liver for the second or third image, is abnormal. On the second or third imaging time points, uptake suggestive of urinary obstruction, or diffuse lung uptake greater than that of the blood pool or intense areas of uptake throughout the normal bowel comparable to the uptake by the liver, represents altered biodistribution.
 - c. Patients treated with iodine-131 tositumomab have total body counts and images obtained by gamma camera scanning on day 0 (within 1 hour of administration, before the patient voids), on day 2 to 4, and on day 6 or 7 if necessary. The biodistribution is evaluated with the same criteria used above. Total body resident times of less than 50 hours or more than 150 hours represent altered biodistribution. The total body residence time is used as a factor in calculation of the dose of iodine-131 tositumomab, which is calculated using a nomogram provided by the manufacturer.
4. Administered activity
- a. For both yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab, administration should occur during a specified period of time after the first diagnostic scan.
 - b. According to manufacturer's instructions, the therapeutic dose of yttrium-90 ibritumomab tiuxetan is administered on days 7 to 9, with day 1 being the day of the first dosimetric scan. Iodine-131 tositumomab administration is recommended to occur on day 7 (up to day 14), with day 0 being the day of the first dosimetric scan.
 - c. Biodistribution of both diagnostic and therapeutic administration is improved by concurrent administration of nonradio-labeled agents, in order to saturate readily accessible CD20 positive sites, including circulating B-cells and cells in the spleen. Biodistribution of radiolabeled ibritumomab tiuxetan is improved with the prior administration of rituximab. Nonradio-labelled tositumomab is used for this purpose with iodine-131 tositumomab administration.
 - d. The therapeutic dose for yttrium-90 ibritumomab tiuxetan, after an infusion of rituximab, is 0.4 mCi/kg (14.8 MBq/kg) for patients with a platelet count > 150,000 and 0.3 mCi/kg (11.1 MBq/kg) for patients with platelet count of 100,000 to 149,000 cells/microliter. The maximum allowable dose of yttrium-90 ibritumomab tiuxetan is 32.0 mCi (1.184 GBq).
 - e. For iodine-131 tositumomab, the administered activity is that calculated to provide a prescribed total body dose of 75 cGy for patients with a platelet count > 150,000 and 65 cGy for patients with platelet count of 100,000 to 149,000 cells/microliter. Patients should not be treated if the platelet count is <100,000 cells/microliter.
5. Complications
- a. Hypersensitivity reactions occur and may be severe. Patients who have received murine proteins should be screened for human antimouse antibodies. Patients who are positive are likely to be at increased risk of anaphylaxis and serious hypersensitivity and may show altered biodistribution of the antibody. Known hypersensitivity to rituximab or murine proteins is considered a contraindication to administration of yttrium-90 ibritumomab tiuxetan. Premedication with acetaminophen and diphenhydramine is recommended and should be considered prior to diagnostic and therapeutic infusions of iodine-131 tositumomab, and should be strongly considered prior to both indium-111 ibritumomab tiuxetan and yttrium-90 ibritumomab tiuxetan. Medications for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and corticosteroids) and equipment for resuscitation should be immediately available.
 - b. The most common serious adverse reactions associated with both yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab are severe or life-threatening cytopenias. With yttrium-90 ibritumomab tiuxetan, approximately 85% of patients are expected to experience grade 3 or 4

cytopenia. Cytopenias are influenced by initial bone marrow reserve as evidenced by baseline platelet count. With iodine-131 tositumomab, 71% of 230 patients enrolled in clinical studies experienced grade 3 or 4 cytopenias. The nadir can occur from 1 to more than 3 months after administration, and the duration of cytopenias can be from 3 to 5 weeks. Precautions include not treating patients who have more than 25% of bone marrow involved, or who have poor bone marrow reserve (including but not limited to prior stem-cell or bone marrow transplant, absolute neutrophil count <1,500 cells/microliter, or previous failure of stem cell collection). The dose is modified according to the pretreatment platelet counts. Blood counts are monitored weekly or more frequently as needed until recovery occurs, for at least 10 to 12 weeks. Stem cell support and/or transfusions are provided as necessary, and cases of febrile neutropenia or infection are treated as appropriate.

- c. In patients treated with iodine-131 tositumomab, hypothyroidism occurs approximately 5% of the time despite thyroid protection.

6. Interactions with other forms of treatment

- a. A time interval sufficient to allow for bone marrow recovery after cytotoxic chemotherapy is recommended. Con-comitant use of chemotherapy with yttrium-90 ibritumomab tiuxetan or iodine-131 tositumomab therapy has not been fully evaluated.
- b. Prior to radiopharmaceutical therapy, external beam radiation therapy may be necessary for local treatment of selected sites, especially when life-threatening or function-threatening involvement such as fracture or spinal cord compression exists or is likely to occur without such treatment. Careful consideration must be given to the amount of bone marrow treated, as treatment of a large percentage of the patient's bone marrow is likely to significantly affect the ability to tolerate radioimmunotherapy.

7. Radiation precautions

- a. Lead shielding is used for the storage and handling of radiolabeled indium-111 (a gamma emitter), a required injection before yttrium-90. For yttrium-90 ibritumomab tiuxetan there are no special precautions, beyond the usual care taken to minimize radiation exposure to patients and to medical

personnel, consistent with institutional radiation safety practices and patient management procedures. Yttrium-90 is a pure beta emitter, and safety precautions for medical professionals are universal precautions, with the addition of acrylic shielding for the yttrium-90 ibritumomab tiuxetan. Patients may be released immediately, with basic instructions, after administration of yttrium-90 ibritumomab tiuxetan.

- b. Iodine-131 tositumomab is both a beta and a gamma emitter, and lead shielding is required during storage, preparation, and administration. Under the guidelines of federal code 10 CFR 35.75, the patient may be released if the total effective dose equivalent to any other individual who is exposed to the patient is not likely to exceed 0.5 rem (5 mSv), assuming all other regulatory requirements for patient instructions and record keeping are met. Assessment includes a calculation based on the patient's measured total body residence time (a function of the antibody clearance rate) and dose rate at 1 m, as well as the individual's living and working situation and ability to comply with instructions. If state or facility regulations are more restrictive, they should be followed.

8. As with all other forms of therapy with unsealed sources, patient management should be coordinated with clinical services and with other involved parties, especially medical and radiation oncology.

H. Follow-Up after Treatment

Physicians using unsealed radiopharmaceutical sources for therapy should follow up and manage all patients treated with curative, adjuvant, or palliative intent and document the outcome of therapy, including results of treatment (tumor control, survival, degree of palliation, time to retreatment) and significant sequelae. Patients who are treated with palliative intent may require close follow-up. For patients for whom follow-up is not possible, there should be documentation specifying which physician will be responsible for the patient's ongoing care.

VII. DOCUMENTATION

Reporting should be in accordance with the [ACR Practice Guideline for Communication: Radiation Oncology](#).

VIII. ACR STATEMENT ON THERAPEUTIC USE OF UNSEALED RADIOPHARMACEUTICAL SOURCES

It is the position of the American College of Radiology that both nuclear medicine physicians and radiation oncologists are particularly well qualified by training and experience to administer unsealed radiopharmaceutical sources for treatment and that either can do so independently. Often, the preferred approach is for the nuclear medicine physician and radiation oncologist to work together as a physician team. The approach that is chosen may vary from patient to patient depending on the type of cancer being treated, local expertise, and patient-related issues. Whichever approach is used, it is important that patient selection as well as overall treatment planning and follow-up be performed by physicians with training and expertise in cancer management, basic radiation safety, and radiation physics.

IX. RADIATION SAFETY

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

Facilities, in consultation with the radiation safety officer, 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 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.

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

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

Equipment performance monitoring should be in accordance with the [ACR Technical Standard for Medical](#)

[Nuclear Physics Performance Monitoring of Nuclear Medicine Imaging Equipment](#)².

ACKNOWLEDGEMENTS

This guideline was revised according to the process described in the ACR Practice Guidelines and Technical Standards book by the Guidelines and Standards Committees of the Commissions on Nuclear Medicine and Radiation Oncology in collaboration with the American Society for Therapeutic Radiology and Oncology (ASTRO).

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²In 2008, this standard was revised and renamed: [ACR Technical Standard for Medical Nuclear Physics Performance Monitoring of Gamma Cameras](#).

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Suggested Reading

1. Bakri YN, Given FT Jr., Peeples WJ, et al. Complications from intraperitoneal radioactive phosphorus in ovarian malignancies. *Gynecol Oncol* 1985;21:294-299.
2. Barbaro D, Boni G, Meucci G, et al. Radioiodine treatment with 30 mCi after recombinant effectiveness for postsurgical remnants ablation. *J Endocrinol Metab* 2003;88:4110-4115.
3. Ben-Josef E, Shamsa F, Williams AO, et al. Radiotherapeutic management of osseous metastases: a survey of current patterns of care. *Int J Radiat Oncol Biol Phys* 1998;40:915-921.
4. Berg G, Lindstedt G, Suurkula M, et al. Radioiodine ablation and therapy in differentiated thyroid cancer under stimulation with recombinant human thyroid stimulating hormone. *J Endocrinol Invest* 2002;25:44-52.
5. *BEXXAR® Prescribing Information*. Glaxo Smith Kline (www.gsk.com) and Corixa Corporation.
6. Brundage MD, Crook JM, Lukka H. Use of strontium-89 in endocrine-refractory prostate cancer metastatic to bone. Provincial Genitourinary Cancer Disease Site Group. *Cancer Prev Control* 1998;2:79-87.
7. Bybel B, Blais M, Vandierendonck R, et al. Radiation safety when a patient dies after therapy. *J Nucl Med Technol* 1998;26:206-207.
8. Cailleux AF, Baudin E, Travagli JP, et al. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? *J Clin Endocrinol Metab* 2000;85:175-178.
9. Cholewinski SP, Yoo KS, Klieger PS, et al. Absence of thyroid stunning after diagnostic whole-body scanning with 185 MBq 131I. *J Nucl Med* 2000;41:1198-1202.
10. Coover LR, Silberstein EB, Kuhn PJ, et al. Therapeutic I-131 in outpatients: a simplified method conforming to the Code of Federal Regulations, title 10, part 35.75. *J Nucl Med* 2000;41:1868-1875.
11. Culver CM, Dworkin HJ. Radiation safety considerations for post-iodine-131 thyroid cancer therapy. *J Nucl Med* 1992;33:1402-1405.
12. Currie JL, Bagne F, Harris C, et al. Radioactive chromic phosphate suspension: studies on distribution, dose absorption, and effective therapeutic radiation in phantoms, dogs, and patients. *Gynecol Oncol* 1981;12:193-218.
13. Grigsby PW, Siegel BA, Baker S, et al. Radiation exposure from outpatient radioactive iodine (131I) therapy for thyroid carcinoma. *JAMA* 2000;283:2272-2274.
14. Grigsby PW, Siegel BA, Bekker S, et al. Preparation of patients with thyroid cancer for 131I scintigraphy or therapy by 1-3 weeks of thyroxine discontinuation. *J Nucl Med* 2004;45:567-570.
15. Harbert JC. *Nuclear Medicine Therapy*. New York, NY: Thieme Medical Publications; 1987.
16. Hermus AR, Huysmans DA. Treatment of benign nodular thyroid disease. *N Engl J Med* 1998;338:1438-1447.
17. Janjan NA. Radiation for bone metastases: conventional techniques and the role of systemic radiopharmaceuticals. *Cancer* 1997;80:1628-1645.
18. Johnson TA, Press OW. Therapy of B-cell lymphomas with monoclonal antibodies and radioimmunoconjugates: the Seattle experience. *Ann Hematol* 2000;79:175-182.
19. Kaminski MS, Estes J, Zasadny KR, et al. Radioimmunotherapy with iodine (131) I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. *Blood* 2000;96:1259-1266.
20. Klassen D, Shelley W, Starreveld A, et al. Early stage ovarian cancer: a randomized clinical trial comparing whole abdominal radiotherapy, melphalan, and intraperitoneal chromic phosphate: a National Cancer Institute of Canada Clinical Trails Group report. *J Clin Oncol* 1988;6:1254-1263.
21. Knox SJ, Goris ML, Trisler K, et al. Yttrium-90-labeled anti-CD20 monoclonal antibody therapy of recurrent B-cell lymphoma. *Clin Cancer Res* 1996;2:457-470.

22. Kraeber-Bodere F, Campion L, Rousseau C, et al. Treatment of bone metastases of prostate cancer with strontium-89 chloride: efficacy in relation to the degree of bone involvement. *Eur J Nucl Med* 2000;27:1487-1493.
23. Kuzel TM, Rosen ST. Radioimmunotherapy of lymphomas and leukemias. In: Henkin RE, Boles MA, Dillehay GL, et al, eds. *Nuclear Medicine*. Vol. 1. St. Louis, Mo: Mosby-Yearbook Inc; 1996:594.
24. Leslie WD, Ward L, Salamon EA et al. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. *J Clin Endocrinol Metab* 2003;88:978-983.
25. Lugo-Vicente H, Ortiz VN. Pediatric thyroid nodules: insights in management. *Bol Asoc Med P R* 1998;90:74-78.
26. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* 2001;86:1447-1463.
27. McEwan AJ. Use of radionuclides for the palliation of bone metastases. *Semin Radiat Oncol* 2000;10:103-114.
28. Nuclear Regulatory Commission. *Program-Specific Guidance About Medical Use Licenses*. NUREG 1556, Vol 9, 2004; 15:28. Accessible at: www.nrc.gov/reading-rm/doc-collections/nuregs/staff/sr1556/v9.
29. Nygaard B, Hegedus L, Nielsen KG, et al. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. *Clin Endocrinol* 1999;50:197-202.
30. Pacini F, Gasperi M, Fugazzola L, et al. Testicular function in patients with differentiated thyroid carcinoma treated with radioiodine. *J Nucl Med* 1994;35:1418-1422.
31. Park CH. The role of radioisotopes in radiation oncology. *Semin Oncol* 1997;24:639-654.
32. Potter ME, Partridge EE, Shingleton HM, et al. Intraperitoneal chromic phosphate in ovarian cancer: risks and benefits. *Gynecol Oncol* 1989;32:314-318.
33. Press OW, Howeel-Clark J, Anderson S, et al. Retention of B-cell-specific monoclonal antibodies by human lymphoma cells. *Blood* 1994;83:1390-1397.
34. Quilty PM, Kirk D, Bolger JJ, et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994;31:33-40.
35. Robbins RJ, Larson SM, Sinha N, et al. A retrospective review of the effectiveness of recombinant human TSH as a preparation for radioiodine thyroid remnant ablation. *J Nucl Med* 2002;43:1482-1488.
36. Robinson RG, Preston DF, Baxter KG, et al. Clinical experience with strontium-89 in prostatic and breast cancer patients. *Semin Oncol* 1993;20:44-48.
37. Rutar FJ, Augustine SC, Colcher D, et al. Outpatient treatment with (131) I anti-B1 antibody: radiation exposure to family members. *J Nucl Med* 2001;42:907-915.
38. Siegel JA, Kroll S, Regan D, et al. A practical methodology for patient release after tositumomab and (131) I-tositumomab therapy. *J Nucl Med* 2002;43:354-363.
39. Soper JT, Berchuck A, Dodge R, et al. Adjuvant therapy with intraperitoneal chromic phosphate (³²P) in women with early ovarian carcinoma after comprehensive surgical staging. *Obstet Gynecol* 1992;79:993-997.
40. Soper JT, Creasman WT, Clarke-Pearson DL, et al. Intraperitoneal chromic phosphate P32 suspension therapy of malignant peritoneal cytology in endometrial carcinoma. *Am J Obstet Gynecol* 1985;153:191-196.
41. Sullivan DC, Harris CC, Currie JL, et al. Observations on the intraperitoneal distribution of chromic phosphate (³²P) suspension for intraperitoneal therapy. *Radiology* 1983;146:539-541.
42. Tagesson M, Ljungberg M, Strand SE. A Monte-Carlo program converting activity distributions to absorbed dose distributions in a radionuclide treatment planning system. *Acta Oncol* 1996;35:367-372.
43. Tedder TF, Engel P, CD20: a regulator of cell-cycle progression of B lymphocytes. *Immunol Today* 1994;15:450-454.
44. Thrall JH. Endocrine therapy. In: Greenfield LD, Uszler JM, eds. *Nuclear Medicine in Clinical Practice*. Deerfield Beach, Fla: Verlag Chenie International; 1982.
45. Tubiana M, Schlumberger M, Rougier P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer* 1985;55:794-804.
46. Tuttle RM, Becker DV, Hurley JR. Radioiodine treatment of thyroid disease. In: Sandler MP, Coleman RE, Paxton FJ, et al, eds. *Diagnostic Nuclear Medicine*. 4th edition. Philadelphia, Pa: Lippincott Williams; 2003:653-669.
47. Vermiglio F, Violi MA, Finocchiaro MD, et al. Short-term effectiveness of low-dose radioiodine ablative treatment of thyroid remnants after thyroidectomy for differentiated thyroid cancer. *Thyroid* 1999;9:387-391.
48. Wagner HN Jr, Wiseman GA, Marcus CS, et al. Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with (90) Y-labeled anti-CD20 monoclonal antibody. *J Nucl Med* 2002;43:267-272.
49. Wahl RL, Kroll S, Zasadny KR. Patient-specific whole-body dosimetry: principles and a simplified method for clinical implementation. *J Nucl Med* 1998;39:14S-20S.

50. Wiseman GA, Kornmehl E, Leigh B, et al. Radiation dosimetry results and safety correlations from 90Y-ibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-Hodgkin's lymphoma: combined data from four clinical trials. *J Nucl Med* 2003;44:465-474.
51. Wiseman GA, Leigh B, Erwin WD, et al. Radiation dosimetry results for Zevalin radioimmunotherapy of rituximab-refractory non-Hodgkin's lymphoma. *Cancer* 2002;94:1349-1347.
52. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002;20:3262-3269.
53. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer: results of two prospective randomized trials. *N Engl J Med* 1990;322:1021-1027.
54. *Zevalin (ibritumomab tiuxetan) Prescribing Information*. San Diego, Calif: IDEC Pharmaceuticals Corporation; 2002.
55. Zhu X. Radiation safety considerations with yttrium 90 ibritumomab tiuxetan (Zevalin). *Semin Nucl Med* 2004;34:20-23.
56. Zimmer AM. Logistics of radioimmunotherapy with yttrium 90 ibritumomab tiuxetan (Zevalin). *Seminars in Nuclear Medicine* 2004;34:14-19.

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

Development Chronology for this Guideline

1996 (Resolution 11)
Revised 2000 (Resolution 27)
Revised 2005 (Resolution 21)
Amended 2006 (Resolution 35)