

Radiopharmaceutical Therapy and Dosimetry



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Chapter 1

Current FDA-Approved RPTs and Their Uses

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1.1 Introduction

This chapter will provide a brief introduction of the currently FDA-approved *radio-pharmaceutical therapies* (RPT). The goal is to provide a quick reference guide for currently available FDA-approved RPTs, their uses, and basic treatment information, such as typical prescriptions, administration route, and radiation safety precautions that are specific to the RPT. Greater safety recommendations as pertaining to regulatory aspects, release criteria and waste management are provided in chapters 2, 5, and 6, respectively. As more RPTs are approved, we recommend the reader studies the appropriate literature and follows manufacturer and local regulatory guidelines for each drug/isotope.

1.2 Iodine-131 Sodium Iodide

Sodium iodide-131 ([¹³¹I]NaI) or radioiodine-131 is a white non-metallic solid that is soluble in water. Sodium iodide-131, in liquid or capsule form, can be used for the management and treatment of hyperthyroidism and *differentiated thyroid carcinomas* (DTC) as the thyroid and most thyroid cancers naturally take up iodine in the sodium iodide symporters present in the cell membrane plasma of thyroid tissue. Some key recommendations are provided below. For more detailed recommendations, please refer to SNMMI Practice Guideline for ¹³¹I Therapy for Thyroid Disease (Silberstein et al. 2012).

1.2.1 Treatment of Hyperthyroidism

Indication

In 1941, Saul Hertz pioneered the use and administration of radioactive material for medicinal purposes when *radioactive iodine ablation* (RAI) was first used to treat Grave's disease, a common cause of hyperthyroidism. RAI remains a treatment option for hyperthyroidism today. The thyroid preferentially takes up iodine when used as ¹³¹I (Abraham 2010; RSNA 2022).

Imaging and Diagnosis

Diagnosis and categorization of hyperthyroidism consists of analysis of *thyroid-stimulating hormone level* (TSH) as well as diagnostic scans of radioiodine uptake (1–4 mCi or 3.7–15 MBq), as measured either by probes or planar imaging. For these, ¹²³I is typically used, as the half-life is shorter (13.3 h); ¹²³I decays via electron cap-

ture, so no energetic electrons are emitted, and there is an 83% branching ratio for a 159-keV photon.

Typical Prescription

The initial required dosage is 4–10 mCi (148–370 MBq) by mouth, but for toxic nodular goiters and other serious thyroid conditions, larger dosages may be required (Medscape). In particular, ablative dosages typically run in the 10–30 mCi range (Radswiki).

Route of Administration

Sodium iodine-131 is available as a stabilized aqueous solution or a solid capsule that can be administered orally. Due to radiation safety concerns as described below, the capsule form is preferred over the liquid form. Once absorbed by the gastrointestinal tract, the $[^{131}I]$ NaI is redistributed to concentrate in the thyroid (Mandel 2003).

1.2.2 Treatment of Carcinoma of the Thyroid

Indication

Sodium iodine-131 is effective for treating well-differentiated thyroid carcinomas. About 90 percent of thyroid cancers are well-differentiated, which selectively take up radioactive iodine (Palot et al. 2022). Patients are classified in three main categories: low risk, intermediate-risk, and high-risk categories (Palot et al. 2022). More details on treating these three categories with [¹³¹I]NaI are provided by Silberstein et al. (2012). A low-iodine diet should be followed for 10–14 days prior to administration, and a high level of TSH present in the system improves the uptake to the thyroid or thyroid disease. Often recombinant human TSH is administered to the patient prior to the [¹³¹I]NaI.

Typical Prescription

Prescription values for the different disease stages are a subject of debate. Typical prescriptions for thyroid carcinoma are 100–150 mCi (3700–5550 MBq) and 50 mCi (1850 MBq) for post-operative ablation of normal thyroid tissue, while 200 mCi (7400 MBq) is a standard value for disseminated disease. As with hyperthyroidism, diagnosis of thyroid cancer may include blood level of TSH as well as imaging methods that include radioactive iodine uptake. Activity uptake of ¹²³I may inform the prescribed therapeutic activity of ¹³¹I. In some cases, ¹²⁴I may be used for diagnostic or pretherapeutic imaging, as it has a better sensitivity and quantitative interpretation (Bockisch et al. 2006; Jentzen et al. 2010; Hobbs et al. 2009). Iodine-124 is a b⁺ emitter (24% branching ratio) with a half-life of 4.18 d, which allows for PET imaging and multi-timepoint analysis for better pharmacokinetic extrapolation to the ¹³¹I halflife (FDA-3; Radswiki).

1.2.3 Production and Decay Scheme

Iodine-131 decays by β^- emission (~90% of local irradiation) and associated gamma emission (~10% of local irradiation), with a physical half-life of 8.04 days (UW Hos-

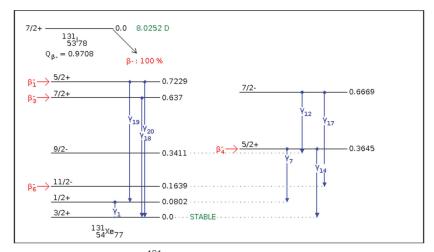


Figure 1.1 Decay scheme for ¹³¹I. Transitional energies are shown in MeV. (Figure from Medical Internal Radiation Dose.)

pitals and Clinics). The maximum energy of beta particles is 0.61 MeV, with an average energy of 0.192 MeV. There is an 82% branching ratio for 364-keV gamma rays that allows for imaging via *single photon computed tomography* (SPECT) but can also present radiation safety concerns. The full decay scheme is presented in Figure 1.1.

Most of the medicinal ¹³¹I is produced by bombarding ¹³⁰Te in powder form with neutrons in a nuclear facility. Several methods for extracting the ¹³¹I exist. Iodine-131 may also be produced in nuclear reactors as a by-product of ²³⁵U fission:

$${}^{130}_{52}Te(n,\gamma) {}^{131}_{52}Te \to {}^{131}_{53}I.$$
(1.1)

1.2.4 Precautions

Radiation Safety

As with all radioactive products, appropriate *personal protective equipment* (PPE) should be utilized for both staff and the patient. Specifically, maximum precautions should be taken to avoid spills, drips, and splatters when dealing with the liquid form of [¹³¹I]NaI, Liquid [¹³¹I]NaI is highly volatile in air and at high risk of localizing within staff members' thyroids when inhaled (Radswiki et al.). The use of a charcoal filter is recommended to reduce the amount of volatile ¹³¹I, which can escape the container. It is also recommended that thyroid bioassays of staff be taken to assess the amount of ¹³¹I that could be absorbed from this volatile iodine. As with all RPTs, be sure to survey the entire area thoroughly when releasing a room/area.

Sodium iodine-131 is typically administered as an outpatient procedure; however, high activities may require an inpatient stay until the patient is considered "releasable" according to regulatory requirements. Even performed as an outpatient procedure, patients and caregivers should exercise appropriate precautions to reduce exposure to themselves and others and provide take-home instructions to patients to protect caregivers and visitors.

Shielding

- Half-Value Layer (HVL / Lead): 0.09 inch = 0.23 cm
- Tenth-Value Layer (TVL / Lead): 0.28 inch = 0.70 cm
- Half-Value Layer (HVL / Water or Tissue) 2.50 inch = 6.30 cm (University of Michigan)

Biological Concerns

The effective half-life (biological + physical) for $[^{131}I]$ NaI for the typical adult is about 5.5 days (about 132 h). There is a faster rate of biological clearance of $[^{131}I]$ NaI for patients who have had surgical resection of their thyroids (Ravichandran et al. 2010). Potential toxicity from ^{131}I administration is bone marrow toxicity or hematotoxicity. Additionally, salivary uptake of radioactive iodine may lead to sialadenitis, dry mouth, and other oral sequelae, and it is a serious quality-of-life concern (Mandel et al. 2003). Metastases in the lungs may lead to concern for pulmonary toxicity (Hobbs et al. 2009).

1.3 Iodine-131 Iobenguane

1.3.1 Treatment

Indication

Iobenguane-iodine-131, commercially known as AZEDRA[®] (Progenics Pharmaceuticals), is indicated for the treatment of pheochromocytoma or paraganglioma. Typical candidates for iobenguane ¹³¹I therapy (CardinalHealth) are adults and children (12+ years old) with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. Pediatrics under 12 years of age have been treated off-label.

Typical Prescription

The recommended planar or SPECT diagnostic/planning dosages for patients:

- Greater than 50 kg: 185 to 222 MBq (5 to 6 mCi)
- 50 kg or less: 3.7 MBq/kg (0.1 mCi/kg)

The recommended therapeutic dosages for patients (up to 2 cycles):

- Greater than 62.5 kg: 18,500 MBq (500 mCi)
- 62.5 kg or less: 296 MBq/kg (8 mCi/kg)

If needed, Azedra therapeutic dosages can be adjusted based on absorbed dose estimated from the diagnostic/planning SPECT scan (FDA-2).

Route of Administration

Iobenguane I-131 is administered intravenously. It is provided as a clear solution in a vial with concentrations of 555 MBq/mL (15 mCi/ml) at *time of calibration* (TOC).

1.3.2 Precautions

Radiation Safety

Due to the high activities of ¹³¹I that these patients receive, patients are typically not considered "releasable" and are kept as radioactive inpatients (3–5 days). Staff who are caring for the patient during the inpatient stay should be trained in handling radioactive patients, including appropriate use of PPE, shielding, and wearing radiation monitoring badges. Pediatric patients typically also require careful monitoring with video surveillance, bladder catheterization, and anesthesia for some younger patients. Also, pediatric patients have a higher risk of long-term radiation effects/toxicity than adults (FDA-2).

Biological Concerns

The mean biological clearance for Azedra (iobenguane-¹³¹I) is reported as $62 \pm 24 \text{ mL/hr/kg}$ by the manufacturer, in a unit that is difficult to interpret, and the mean terminal blood half-life is 35 ± 14 hours (FDA-2). The primary toxicity concerns are for hematological toxicity, both acute and out of concern for myeloplastic syndrome. Activity should be adjusted downwards or the treatment discontinued as a function of platelet and neutrophil counts. Renal toxicity is also a concern from the clearance of the activity through the kidneys, as is salivary gland toxicity or hypothyroidism from any free ¹³¹I. Patients take iodine tablets prior to therapy to saturate the thyroid and salivary glands in iodine and lower the risk of such toxicities.

Azedra is the only FDA-approved RPT that recommends dosimetry with the goal of limiting the amount of activity prescribed as a function of the projected absorbed doses for the dose-limiting normal organs. The recommendation is to perform organ-level dosimetry from 3 planar images and adjust as a function of the given absorbed dose limits provided (12 Gy, 16.5 Gy, 18 Gy, 31 Gy, and 40 Gy for the bone marrow, lungs, kidneys, liver, and small intestine, respectively). Caveats to the recommended methodology are that SPECT/CT would provide more accurate information and the absorbed dose limits seem to be taken from external beam experience.

1.4 Radium-223 Dichloride

1.4.1 Treatment

Indication

Radium-223 dichloride, [²²³Ra]RaCl₂, commercially known as XOFIGO[®] (Bayer), is a radiopharmaceutical used for the treatment of patients with *castration-resistant*

prostate cancer (mCRPC), specifically those with symptomatic bone metastases and no known visceral metastatic disease. In 2013, Xofigo was the first FDA-approved radionuclide for the treatment of patients with mCRPC (CardinalHealth; Morgan et al. 2021). Other indications may be forthcoming. Radium is in the same chemical family as calcium, thus it localizes to areas of calcium uptake, notably bone formations.

Typical Prescription

The recommended prescription for Xofigo is 55 kBq/kg (1.49 μ Ci/kg), which is given for 6 cycles at 4-week intervals (FDA-4). Because of the concern for myelotoxicity, contra-indications exist for low blood counts, both for the initial cycle as well as for succeeding cycles.

Route of Administration

Xofigo is provided as a clear/colorless solution in a patient-specific syringe. It is administered via slow intravenous injection through a syringe. The line should be primed and flushed with saline before and after administration, respectively (Bayer).

1.4.2 Decay Scheme

Radium-223 (half-life 11.4 days), is primarily an alpha-emitter with a O-value of 5.98 MeV (most alpha-particle energies in the 5.5-5.7 MeV range) and small fractions of gamma emissions (in particular, a 14% branching ratio for 269-keV photons). Alpha particles from RPT have ranges on the order of 50–100 µm, which makes the energy deposition very conformal. However, ²²³Ra also has radioactive daughters, decaying to 219 Rn, which decays via α -decay with a half-life of 4 s and a O-value of 6.95 MeV to ²¹⁵Po. Polonium-215 decays by α -particle decay to ²¹¹Pb with a halflife of 1.78 ms and a Q-value of 7.53 MeV. Lead-211 is a β-emitter with a half-life of 36.1 min and its daughter ²¹¹Bi then provides another α -particle to the decay chain (with a half-life of 2.14 min), either directly to ²⁰⁷Tl or with a 0.3% branching ratio of β -decay to ²¹¹Po, which then decays with an alpha-particle. In all, four alpha-particles are emitted in the decay chain. The full decay scheme is provided in Figure 1.2 over the next several pages (FDA-4). In principle, photons from ²²³Ra and ²¹¹Pb can be imaged for activity quantification; however, due to the low amount of administered therapeutic activity, this has not been feasible until recently (Benabdallah et al. 2021). From a dosimetric standpoint, relocalization of the daughters—in particular the ²¹¹Pb with a 36.1-min half-life—should be considered. Imaging and preclinical studies have shown that for Xofigo, the daughters tend to stay where the parent isotope decays (Henriksen et al. 2003).

Radium-223 is most commonly generated from naturally occurring ²²⁶Ra. The ²²⁶Ra is bombarded with neutrons to form ²²⁷Ra, which decays to ²²⁷Ac, then to ²²⁷Th, which then decays in turn to ²²⁷Ac. Since ²²⁷Ac has a half-life of 21.8 years, once sufficient quantities of ²²⁷Ac have been produced, the ²²³Ra may be eluted from the ²²⁷Ac generator:

$${}^{226}_{88}Ra(n,\gamma) {}^{227}_{88}Ra \to {}^{227}_{89}Ac \to {}^{227}_{90}Th \to {}^{222}_{88}Ra.$$
(1.2)

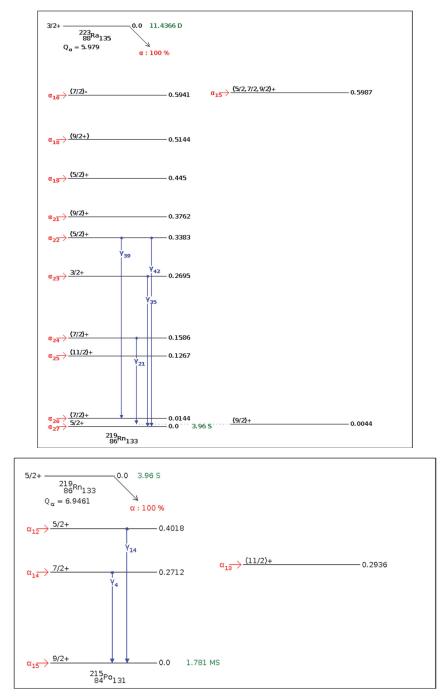
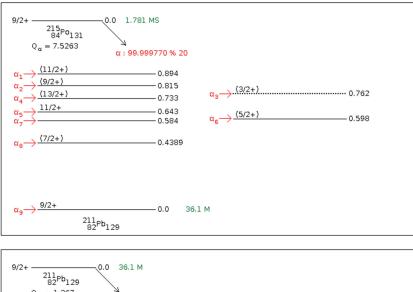


Figure 1.2 Decay scheme for Ra-223 and its daughters (unit: MeV). (Figure from Medical Internal Radiation Dose.)

Current FDA-Approved RPTs and Their Uses



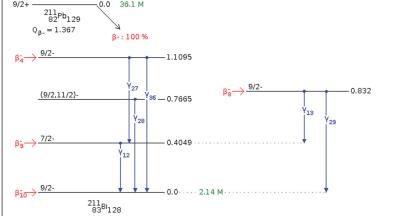


Figure 1.2 (continued)

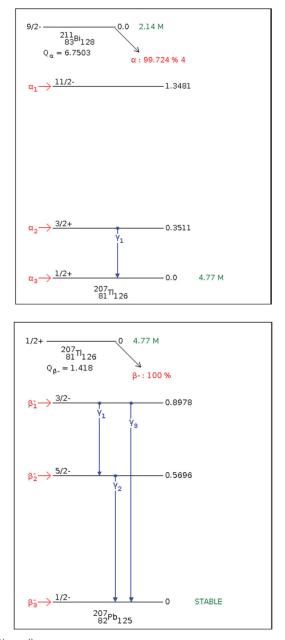


Figure 1.2 (continued)

1.4.3 Precautions

Radiation Safety

Given the low amount of injected material, concerns over caregiver, staff, and general public exposure is negligible. However, care should be taken when handling bodily fluids, especially the feces, as contamination and re-ingestion is the primary concern (FDA-5). For the same reasons, vigilance with regard to spills and potential contamination is required. Even though ²²³Ra has a short range in tissue, it has a high LET and can result in significant toxicity if ingested or if it comes into contact with the skin.

Shielding

Given the low activities and short range of alpha-particles from radium-223 in tissue, Xofigo does not require significant shielding. However, it is still recommended to exercise ALARA precautions when handling this RPT.

Biological Concerns

The primary route of clearance for Xofigo is fecal excretion (Dauer et al. 2014), about half of which clears within 24–48 hours. Patients are recommended to sit while urinating and flush twice after using the restroom.

The most common potential toxicity is bone marrow suppression (FDA-4). Low blood counts will result in the patient being denied the full course of treatment.

1.5 Yttrium-90 Ibritumomab Tiuxetan

1.5.1 Treatment

Indication

Ibritumomab tiuxetan, commercially known as ZEVALIN[®] (Acrotech Biopharma, Inc.), is a CD20-directed radiotherapeutic antibody tagged with ⁹⁰Y. It is used for the treatment of adult patients with relapsed or refractory low-grade or follicular B-cell *non-Hodgkin's lymphoma* (NHL) and previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy (FDA-6; Mondello et al. 2016).

Typical Prescription

The recommended prescription for Zevalin is 0.3–0.4 mCi/kg (11.1–14.8 MBq/kg), depending on platelet counts. Total dosages are typically 777–1110 MBq (21–30 mCi), with a maximum of 1184 MBq (32 mCi) (Kim et al. 2010). Pretreatment diagnostic SPECT imaging with (¹¹¹In)-ibritumomab tuxetan as a surrogate was historically used 1 week before treatment. Indium-111 decays via electron capture with a half-life of 2.8 days and has two imaging photons, one with a 90% branching ratio at 171 keV and another 245 keV with a 94% branching ratio. However, these pretreatment scans are generally not required anymore due to a lack of reported variability between patients' biokinetics of Zevalin (Conti et al. 2005).

Route of Administration

Zevalin is administered intravenously with rituximab (FDA-6).

1.5.2 Decay Scheme

Yttrium-90 is a "pure" β -emitter; that is, there are only scarce numbers of associated photons in the decay. Yttrium-90 beta particles have a maximum energy of 2.28 MeV and a range in water of about 11 mm, with a physical half-life of 64.1 hours (2.67 days) (FDA-6). The decay scheme is shown in Figure 1.3.

Yttrium-90 may be produced in several ways: (1) eluted from a 90 Sr source (halflife of 28.1 years), which is produced as a by-product of 235 U fission, or (2) by bombarding stable 89 Y with neutrons:

$${}^{235}_{92}U(n,f){}^{90}_{38}Sr \to {}^{90}_{39}Y$$
(1.3)

$${}^{89}_{39}Y(n,\gamma){}^{90}_{39}Y \tag{1.4}$$

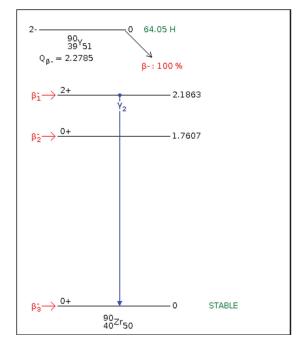


Figure 1.3 Decay scheme for Yttrium-90 (units: MeV). (Figure from Medical Internal Radiation Dose.)

1.5.3 Precautions

Radiation Safety

Even though the range of 90 Y beta particles is short in water/tissue, with very few prompt photons, there is still a broad spectrum of bremsstrahlung photons. Both require appropriate shielding, use of PPE, and the practice of ALARA principles when handling Zevalin both during preparation and when administering to the patient (Jødal et al. 2009).

Shielding

About 1.3 cm of Lucite or acrylic works well to attenuate beta emissions. To shield bremsstrahlung emissions, one can add 3–6 mm of lead on the outside of the primary shielding (Jødal et al. 2009).

Biological Concerns

The mean effective half-life of Zevalin in blood is 27 hours (range 14–44 h). The primary clearance mechanism is urinary excretion, and it accounts for the elimination of about 10% of unbound ⁹⁰Y within the first 12 to 24 hours (Mondello et al. 2016). Common toxicities include neutropenia, leukopenia, thrombocytopenia, anemia, infection, asthenia, musculoskeletal symptoms, and gastrointestinal symptoms. Patients should also not receive live vaccines shortly after receiving Zevalin (Mondello et al. 2016). The major limiting organ for toxicity is the bone marrow. In particular, myelotoxicity may be aggravated by concurrent chemotherapy (Baechler et al. 2010). Studies have been made projecting Zevalin administrations at myeloablative regimens using autologous stem cell support. In these cases, the liver was considered to be the primary organ at risk (Frey et al. 2006; Hobbs et al. 2013).

1.6 Yttrium-90 Microspheres

There are two brands of ⁹⁰Y microspheres available in the United States today: TheraSphere[®] (glass microspheres, Boston Scientific Corporation) and SIR-Spheres[®] (resin microspheres, Sirtex Medical Ltd). Their diameters range from 20 to 60 microns (Bhangoo et al. 2015).

1.6.1 Treatment

Indication

Yttrium-90 microspheres are used to treat primary or metastatic cancer in the liver. Yttrium-90 microsphere radioembolization utilizes the unique physiology of the liver, which has a dual blood supply: the portal vein and hepatic artery. The healthy liver parenchyma receives most of its blood supply from the portal vein, whereas tumors receive nearly all of their blood supply from the hepatic artery. Yttrium-90 microspheres are administered via catheter in interventional radiology through the hepatic artery, embolize within the tumor vasculature, and remain as a permanent implant due to their size. As such, ⁹⁰Y-microspheres are not a typical RPT as they do not re-localize or clear as a function of time, and there are typically up to 10 million particles that carry the activity as opposed to the Avogadro's number of molecules present in most RPTs. TheraSphere is approved for the treatment of unresectable hepatocellular carcinoma, while SIR-Sphere is approved for unresectable metastatic colorectal cancer in the liver (Sirtex; TheraSphere). TheraSphere is also commonly used to treat other liver diseases under humanitarian device exemption. A fraction of the spheres may exit the liver, return to the vasculature, and embolize in the lung. A *lung shunt fraction* (LSF) is determined using surrogate (planar or SPECT) imaging of ^{99m}Tc-MAA (macro aggregated albumin) surrogate. If the LSF is too high or the lung absorbed dose is too high, ⁹⁰Y-microspheres may be contra-indicated. Technetium-99m is a metastable excited state of ⁹⁹Tc which decays by gamma emission with a half-life of 6.0 hours and which emits a 140-keV photon with a 90% branching ratio used for imaging.

Typical Prescription

Prescriptions typically range from 0.3–20 GBq, depending on the brand, tumor size/ burden, lung shunting, etc. TheraSphere activity is determined by prescribing absorbed dose to the treated area according to the mass of the liver or target (Bhangoo et al. 2015; Boston Scientific), generally a lobe or segment. SIR-Sphere activity is determined using either a calculation based on *body surface area* (BSA) or other tumor-to-normal uptake ratio modeling, as described by the manufacturer (Sirtex). Activities for both brands of microspheres are adjusted to account for LSF that is determined during a pretreatment ^{99m}Tc-MAA study (Sirtex; Bhangoo et al. 2015). The pre-therapeutic ^{99m}Tc-MAA may also be used in conjunction with SPECT/CT for more patient-specific dosimetry, where the prescription absorbed dose is now calculated to the normal tissue of the targeted lobe or segment. TheraSphere activities come in ready-to-use, patient-specific vials available in increments of 0.5 GBq from 3 GBq to 20 GBq. SIR-Sphere vials come in standard activities (typically 3 GBq), and patient-specific activities must be drawn and prepared in separate vials.

Route of Administration

Both TheraSphere and SIR-Spheres are administered via an intra-arterial delivery through the hepatic artery or more focused arteries that irradiate a specific lobe or segment(s).

1.6.2 Physical Properties

In spite of the (almost) nonexistent prompt photons, post-treatment imaging of 90 Y microsphere distribution can be performed using PET or SPECT. There is a branching ratio of 32 parts per million internal pair (positron-electron) production in the decay scheme that allows for PET imaging. Similarly, the large number of electrons create a sufficient number of bremsstrahlung photons that allows for SPECT quantification. Since the microspheres remain as a permanent implant, dosimetry calculations are greatly simplified and depend only on the activity and mass of the target.

The two products are produced differently. SIR-spheres are resin microspheres on which 90 Y is attached by ion exchange, then immobilized through precipitation as

a phosphate salt. Theraspheres are created as glass beads containing 89 Y. The beads are then bombarded with neutrons to create the 90 Y as per Equation (1.4).

1.6.3 Precautions

Radiation Safety

As with any RPT, appropriate PPE should be used when preparing for and administering the ⁹⁰Y microspheres. If spilled, the microspheres can bounce and spread readily on surfaces (Medical Physics Consultants, Inc.).

Shielding

For a beta-emitter, the shielding is best provided with a low-atomic-number material such as acrylic. The low-atomic-number shielding reduces the amount of bremsstrahlung radiation. Lead can also help reduce subsequent bremsstrahlung production.

Biological Concerns

Due to biocompatible material of the microspheres, once microspheres are trapped permanently into the liver, they are not metabolized or excreted and, therefore, no biological clearance is expected. Within 12 days of administration, approximately 95% of the radiation from ⁹⁰Y has physically decayed (TheraSphere). Potential adverse events include acute pancreatitis, radiation pneumonitis, acute gastritis, acute cholecystitis, and radioembolization-induced liver disease. Most of these adverse events are the result of nontarget uptake of the ⁹⁰Y microspheres, often fed by extraneous vessels. These extraneous vessels are generally identified and coiled pre-injection during the procedure. Post-treatment imaging with SPECT or PET is highly recommended to verify ⁹⁰Y microsphere distribution (Sirtex; TheraSphere; Boston Scientific).

1.7 Samarium-153 Lexidronam

Samarium-153 lexidronam, commercially known as QUADRAMET[®], is radioactive ¹⁵³Sm chelated with *ethylenediaminetetramethylenephosphonic* acid (EDTMP).

1.7.1 Treatment

Indication

Quadramet is indicated for pain relief from bone metastases, specifically in those patients with confirmed osteoblastic metastatic bone lesions that enhance on ^{99m}Tc-MDP bone scan (Lantheus Medical Imaging). It has been investigated as a curative for several bone cancers (Loeb et al. 2009; Loeb et al. 2010). The chelator mimics the chemistry of calcium, such that it is taken up in bone- forming areas of the body.

Typical Prescription

The recommended dose Quadramet is 1.0 mCi/kg (Lantheus Medical Imaging). Myeloablative regimens have been given up to 30 mCi/kg (Anderson et al. 2002).

Route of Administration

Quadramet is typically administered intravenously over a period of one minute through a secure in-dwelling catheter. Activity is provided in fixed quantities, and the precise activity prescribed to the patient must be drawn into a syringe. The administration is followed with a saline flush (Lantheus Medical Imaging).

1.7.2 Decay Scheme

Samarium-153 is a β^- emitter with a half-life of 46.3 hours and a maximum energy (Q-value) of 808 keV. It has a 103-keV photon with a branching ratio of 30% that is used for imaging. The decay scheme is shown in Figure 1.4.

Samarium-153 is produced from neutron bombardment of samarium oxide of ¹⁵²Sm, the stable isotope of samarium:

$${}^{152}_{62}Sm(n,\gamma){}^{153}_{62}Sm \tag{1.5}$$

1.7.3 Precautions

Radiation Safety

Patients who are candidates for Quadramet may present with incontinence. Please consult with your radiation safety officer and local regulatory guidelines regarding the proper handling and disposal of incontinence pads/diapers, as they will be contaminated with ¹⁵³Sm radioactivity (Lantheus Medical Imaging).

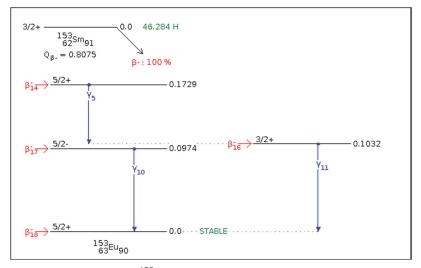


Figure 1.4 Decay scheme for ¹⁵³Sm (unit: MeV). (Figure from Medical Internal Radiation Dose.)

Shielding

The average and maximum beta particle ranges in water respectively are 0.5 mm and 3.0 mm. The specific gamma-ray emission constant for ¹⁵³Sm is 0.46 R/mCi-hr at 1 cm (1.24×10^{-5} mSv/MBq-hr at 1 m). For the lead shielding, the half-value thickness of lead (Pb) for ¹⁵³Sm is approximately 0.10 mm. Quadramet should be stored in a lead-shielded container and frozen until use (Lantheus Medical Imaging).

Biological Concerns

Quadramet is primarily excreted through the urine with approximately 25–50% eliminated through the urine in the first 6 hrs. However, the amount of excreted activity typically decreases with increasing tumor burden (Lantheus Medical Imaging). Quadramet is known to cause bone marrow suppression (Lantheus Medical Imaging) at myelobative regimes, up to 30 mCi/kg. No additional acute toxicities were recorded, although renal toxicity is believed to be of concern (Anderson et al. 2002; Hobbs et al. 2010).

1.8 Lutetium-177 DOTATATE

Lutetium-177 DOTATATE, commercially known as LUTATHERA[®] (Novartis/ Advanced Accelerator Applications), is a peptide receptor radionuclide therapy (PRRT) (FDA-7).

1.8.1 Treatment

Indication

Lutathera is used to treat either metastatic or inoperable somatostatin receptor-positive *gastroenteropancreatic-neuroendocrine tumors* (NETs) in the foregut, midgut, and hindgut (FDA- 7). Gallium-68-DOTATATE PET can be used to identify NET that are somatostatin receptor-positive, and a positive scan is a requirement for therapy (Anderson et al. 2021). PRRT has been used in Europe for over a decade, but has only recently been approved in the United States.

Typical Prescription

Lutathera is prescribed as 200 mCi (7.4 GBq) dosages in 4 cycles spaced 8 weeks apart (FDA- 7).

Route of Administration

Lutathera is injected intravenously either using a gravity infusion technique or using a programmable infusion pump (Maughan et al. 2021). To reduce the chance of renal toxicity, an amino acid solution containing L-lysine and L-arginine are concurrently administered with the Lutathera infusion to allow for faster renal clearance.

1.8.2 Decay Scheme

Lutetium-177 is primarily a β^- emitter (0.498 MeV max, 0.133 MeV mean) with a physical half-life of 6.65 days (Medical Internal Radiation Dose; FDA-7; Maughan et

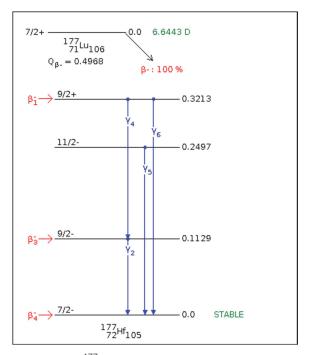


Figure 1.5 Decay scheme for ¹⁷⁷Lu (unit: MeV). (Figure from Medical Internal Radiation Dose.)

al. 2021). There are associated gamma emissions that allow for post-treatment imaging via SPECT (see Figure 1.5), particularly the 208-keV emission with an 11% branching ratio.

The companion diagnostic, 68 Ga, is a β^+ emitter with a 2.9-MeV maximum positron energy and a 67.7-minute half-life. The relatively short half-life of 68 Ga means that although useful as a diagnostic, it cannot be used reliably as a quantitative pretherapeutic for the pharmacokinetics of the therapeutic.

As with a number of other radioactive isotopes used in medicine, ¹⁷⁷Lu is produced from neutron bombardment of the stable isotope of lutetium:

$$\sum_{\gamma_1}^{176} Lu(n,\gamma) \sum_{\gamma_1}^{177} Lu.$$
(1.6)

There may be a small amount of ^{177m}Lu contaminant present in the produced ¹⁷⁷Lu. Studies have shown there to be little dosimetric effect from the contaminant, but regulatory bodies may require inclusion of ^{177m}Lu on the radioactive materials license or careful consideration of waste management with its long half-life (160.4 days).

1.8.3 Precautions

Radiation Safety

Due to long infusion times of the amino acids (3–4 hrs), renal clearance, and the tendency of patients to demonstrate nausea and emesis, the treatment area for Lutathera patients should be appropriately prepared to prevent radiation contamination (Maughan et al. 2021). Patients should also have a dedicated restroom that is restricted to Lutathera only until decontaminated and released to the public/clinical area (Maughan et al. 2021). Be sure to survey the entire area thoroughly when releasing a room/area. Further recommendations on Lutathera treatment are provided by Hope et al. (2019) and Maughan et al. (2021).

Shielding

For maximum energy (497 keV) of emitted beta, the ranges in water and lead are 1.9 mm and 0.3 mm, respectively (Jødal et al. 2009). The gamma constant for ¹⁷⁷Lu is 0.028 mrem/hr per mCi at 1 meter (North Carolina Health Physics Society).

Biological Concerns

The radiation from Lutathera will be detectable in the urine for up to 30 days following administration. Within 4 hr of administration, the distribution of Lutathera goes through the kidneys, tumor lesions, liver, spleen, and, occasionally, the pituitary and thyroid glands. Co-administering with amino acids reduces the median absorbed dose to the kidneys by 47% (34% to 59%) and increases the blood clearance of Lutathera by 36% (Das et al. 2019). While studies have shown that radiation exposure to the general public from patients using public transportation for trips (e.g., by plane) after administration may be below safe thresholds, this does not take into account the danger of contamination during the first few days after administration. Patients should not use public forms of transportation for the first 48 hours.

Acute toxicities include nausea and emesis, typically related to the amino acids that are administered concurrently. Other toxicities may include renal toxicity or hematotoxicty, either as reduced blood cell counts or as the potential for myeloplastic syndrome (FDA- 7).

1.9 Lutetium-177 Vipivotide Tetraxetan

1.9.1 Treatment

Indication

Lutetium-177 vipivotide tetraxetan, commercially known as PLUVICTO[®] (Novartis/ Advanced Accelerator Applications), is a targeted radioligand therapy used to treat adult patients with *prostate-specific membrane antigen* (PSMA)-positive *metastatic castration-resistant prostate cancer* (mCRPC) who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy (CardinalHealth). Before receiving Pluvicto, patients receive a Ga-68 gozetotide (LOCAMETZ) PET scan to help determine eligibility and uptake of the tumors (FDA-1). Common side effects include fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation (FDA-9).

Typical Prescription

Pluvicto is prescribed as 7.4 GBq (200 mCi) in 6 cycles spaced 6 weeks apart (FDA-9).

Route of Administration

Pluvicto is administered intravenously either with a syringe fitted with a syringe shield (with or without syringe pump), gravity infusion-based technique from a vial, or infusion pump-based administration from a vial (FDA-9).

1.9.2 Precautions

Radiation Safety

As with all RPTs, appropriate use of PPE should be utilized when preparing and administering Pluvicto. Patients who are candidates for Pluvicto may present with incontinence. Patients should also have a dedicated restroom that is restricted to Pluvicto only until decontaminated and released to the public/clinical area (Maughan et al. 2021). After treatment administration, be sure to survey the entire area thoroughly when releasing a room/area. Please consult with your radiation safety officer and local regulatory guidelines regarding the proper handling and disposal of incontinence pads/diapers as they will be contaminated with Lu-177 radioactivity.

Biological Concerns

Pluvicto elimination half-life is 41.6 hours and is primarily excreted through the urine (FDA-9). As with Lutathera, patients may be kept in a dedicated room for several hours post-injection while they clear most of their waste into a dedicated bathroom, or they may be released immediately, provided they are given specific instructions and are not using public transportation but will return home quickly.

Organs at risk are similar to those at risk during treatment with Lutathera, but also include the salivary and lacrimal glands, which also express PSMA.

References

- Abraham, P. and S. Acharya (2010). "Current and emerging treatment options for Graves" hyperthyroidism." *Ther. Clin. Risk Manag.* 6:29–40. doi:10.2147/tcrm.s5229.
- Anderson, P. M., G. A. Wiseman, A. Dispenzieri, C. A. Arndt, L. C. Hartmann, W. A. Smithson, et al. (2002). "High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosar-coma and bone metastases." J. Clin. Oncol. 20(1):189–96.
- Anderson, R. C., E. M. Velez, B. Desai, and H. Jadvar (2021). "Management Impact of 68Ga-DOTATATE PET/CT in Neuroendocrine Tumors." *Nucl. Med. Mol. Imaging* 55(1):31–37. doi:10.1007/s13139-020-00677-0.
- Baechler, S.,R. F. Hobbs, H. A. Jacene, F. O. Bochud, R. L. Wahl, and G. Sgouros (2010). "Predicting hematologic toxicity in patients undergoing radioimmunotherapy with 90Y-ibritumomab tiuxetan or 131I-tositumomab." J. Nucl. Med. 51(12):1878–84.

- Bayer, Inc. (2022). "Product Monograph XOFIGO radium Ra-223 dichloride solution for injection." https://www.bayer.com/sites/default/files/xofigo-pm-en.pdf. Accessed 11/21/2022.
- Benabdallah, N., W. Scheve, N. Dunn, et al. (2021). "Practical considerations for quantitative clinical SPECT/CT imaging of alpha particle emitting radioisotopes." *Theranostics* 11(20):9721–37. Published Sep 27, 2021. doi:10.7150/thno.63860.
- Bhangoo, M. S., D. R. Karnani, P. N. Hein, et al. (2015). "Radioembolization with Yttrium-90 microspheres for patients with unre-sectable hepatocellular carcinoma." J. Gastrointest. Oncol. 6(5):469–78. doi:10.3978/j.issn.2078-6891.2015.056.

Bockisch, A., L. Freudenberg, S. Rosenbaum, and W. Jentzen (2006). "(124)I in PET imaging: impact on quantification, radio-pharmaceutical development and distribution." *Eur. J. Nucl. Med. Mol. Imaging* 33(11):1247–48.

- Boston Scientific (2004). "TheraSphere Package Insert." http://www.therasphere.com/physicians-package-insert/package-insert-eu-en.pdf. Accessed 11/28/2022.
- CardinalHealth (2022). "FDA-approved radiopharmaceuticals." https://www.cardinalhealth.com/content/dam/corp/web/documents/fact-sheet/cardinal-health-fda-approvedradiopharmaceuticals.pdf. Accessed 11/20/2022.
- Conti, P. S., C. White, P. Pieslor, A. Molina, J. Aussie, and P. Foster (2005). "The role of imaging with (111)In-ibritumomab tiuxetan in the ibritumomab tiuxetan (zevalin) regimen: results from a Zevalin Imaging Registry." J. Nucl. Med. 46(11):1812–18.
- Das, S., T. Al-Toubah, G. El-Haddad, and J. Strosberg (2019). "177Lu-DOTATATE for the treatment of gastroenteropancreatic neu-roendocrine tumors." *Expert Rev. Gastroenterol. Hepatol.* 13(11):1023–31. doi:10.1080/17474124.2019.1685381.
- Dauer, L. T., M. J. Williamson, J. Humm, et al. (2014). "Radiation safety considerations for the use of ²²³RaCl₂ DE in men with castration-resistant prostate cancer." *Health Phys.* 106(4):494–504. doi:10.1097/HP.0b013e3182a82b37.
- FDA-1. "FDA approves Pluvicto for metastatic castration-resistant prostate cancer." https:// www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pluvicto-metastatic-castration-resistant-prostate-cancer." Accessed 2/4/2023.
- FDA-2. "Highlights of Prescribing Information: AZEDRA." https://www.accessdata.fda.gov/ drugsatfda_docs/label/2018/209607s000lbl.pdf. Accessed 11/21/2022.
- FDA-3. "Highlights of Prescribing Information: Sodium Iodide I-131 Capsules Therapeutic for oral use." https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016517s016lbl.pdf. Accessed on 11/27/2022.
- FDA-4. "Highlights of Prescribing Information: XOFIGO." https://www.accessdata.fda.gov/ drugsatfda_docs/label/2018/203971s014lbl.pdf. Accessed 11/27/2022.
- FDA-5. "Highlights of Prescribing Information: XOFIGO." https://www.accessdata.fda.gov/ drugsatfda_docs/label/2019/203971s016lbl.pdf. Accessed 11/21/2022.
- FDA-6. "Highlights of Prescribing Information: ZEVALIN." https://www.accessdata.fda.gov/ drugsatfda_docs/label/2013/125019s210s213lbl.pdf. Accessed 11/21/2022.
- FDA-7. "LUTATHERA (lutetium Lu177 dotatate)." https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf. Accessed 11/28/2022.
- FDA-8. "Metastron Strontium-89 Chloride injection." https://www.accessdata.fda.gov/ drugsatfda_docs/label/2013/020134s012lbl.pdf. Accessed 11/28/2022.
- FDA-9. "PLUVICTO (lutetium Lu-177 vipivotide tetraxetan)." https://www.accesdata. fda.gov/drugsatfda_docs/label/2022/215833s000lbl.pdf. Accessed 11/28/2022.
- Frey, E., B. He, G. Sgouros, I. Flinn, and R. Wahl (2006). "Estimation of post-therapy marrow dose rate in myeloablative Y-90 ibri-tumomab tiuxetan therapy." *J. Nucl. Med.* 47(Supplement 1):156P.
- Henriksen, G., D. R. Fisher, J. C. Roeske, O. S. Bruland, and R. H. Larsen (2003). "Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice." *J. Nucl. Med.* 44(2):252–59.
- Hobbs, R. F., R. L. Wahl, E. C. Frey, Y. Kasamon, H. Song, P. Huang, et al. (2013). "Radiobiologic optimization of combination radi-opharmaceutical therapy applied to myeloablative treatment of non-Hodgkin lymphoma." J. Nucl. Med. 54(9):1535–42.
- Hobbs, R. F., R. L. Wahl, M. A. Lodge, M. S. Javadi, S. Y. Cho, D. T. Chien, et al. (2009). "124I PET-based 3D-RD dosimetry for a pedi-atric thyroid cancer patient: real-time treatment planning and methodologic comparison." *J. Nucl. Med.* 50(11):1844–47.
- Hope, T. A., A. Abbott, K. Colucci, et al. (2019). "NANETS/SNMMI Procedure Standard for Somatostatin Receptor-Based Pep-tide Receptor Radionuclide Therapy with 177Lu-DOTATATE." J. Nucl. Med. 60(7):937–43. doi:10.2967/jnumed.118.230607.

- IAEA. Manual for Reactor Produced Radioisotopes. IAEA-TECDOC-1340. Vienna: International Atomic Energy Association, 2003.
- Jentzen, W., R. F. Hobbs, A. Stahl, J. Knust, G. Sgouros, and A. Bockisch (2010). "Pre-therapeutic I-124 PET(/CT) dosimetry confirms low average absorbed doses per administered I-131 activity to the salivary glands in radioiodine therapy of differentiated thyroid cancer." *Eur. J. Nucl. Med. Mol. Imaging* 37(5):884–95.
- Jødal, L. (2009). "Beta emitters and radiation protection." *Acta Oncol.* 48(2):308–13. doi:10.1080/02841860802245163.
- Kim, Y. C., Y. H. Kim, S. H. Uhm, et al. (2010). "Radiation safety issues in y-90 microsphere selective hepatic radioembolization therapy: possible radiation exposure from the patients." *Nucl. Med. Mol. Imaging* 44(4):252–60. doi:10.1007/s13139-010-0047-7.
- Lantheus Medical Imaging, Inc. "Quadramet prescribing information." https://www.
- accessdata.fda.gov/drugsatfda_docs/label/2017/020570s008lbl.pdf. Accessed 11/28/2022. Loeb, D. M., E. Garrett-Mayer, R. F. Hobbs, A. R. Prideaux, G. Sgouros, O. Shokek, et al. (2000) "Dese finding study of (152)Sm EDTMB in patients with near programs estab
- (2009). "Dose-finding study of (153)Sm-EDTMP in patients with poor-prognosis osteosarcoma." Cancer 115(11):2514–22.
 Loeb D. M. P. F. Hobbs, A. Okoli, A. P. Chen, S. Cho, S. Sriniyasan, et al. (2010). "Tanden
- Loeb, D. M., R. F. Hobbs, A. Okoli, A. R. Chen, S. Cho, S. Srinivasan, et al. (2010). "Tandem dosing of samarium-153 ethylenedia-mine tetramethylene phosphoric acid with stem cell support for patients with high-risk osteosarcoma." *Cancer* 116(23):5470–78.
- Mandel, S. J. and L. Mandel (2003). "Radioactive iodine and the salivary glands." *Thyroid* 13(3):265–71.
- Maughan, N. M., H. Kim, Y. Hao, et al. (2021). "Initial experience and lessons learned with implementing Lutetium-177-dotatate radiopharmaceutical therapy in a radiation oncology-based program." *Brachytherapy* 20(1):237–47. doi:10.1016/j.brachy.2020.07.004.
- Medical Internal Radiation Dose (MIRD) format from the Evaluated Nuclear Structure Data File (ENSDF). Version available at http://www.nndc.bnl.gov/ensarchivals/. Accessed on 11/27/2022.
- Medical Physics Consultants, Inc. (2020). "Radiation Safety for Yttrium-90 Microsphere Therapy." https://www.mpcphysics.com/wp-content/uploads/Y-90-Microspheres-Radiation-Safety-Inservice-Nuclear-Techs-10-6-2020.pdf. Accessed 11/28/2022.
- Medscape. "Sodium iodide I-131 (rx)." https://reference.medscape.com/drug/hicon-sodiumiodide-i-131-999924. Accessed on 11/16/2022.
- Mondello, P., S. Cuzzocrea, M. Navarra, and M. Mian (2016). "90 Y-ibritumomab tiuxetan: a nearly forgotten opportunity." *Oncotarget* 7(7):7597–609. doi: 10.18632/oncotarget.6531. PMID: 26657116; PMCID: PMC4884941.
- Morgan, R., D. Wermuth, E. Molina, and M. Perraillon (2021). "Utilization and Cost of Radium-223 Dichloride (Xofigo®) for Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPR) in the US Medicare Population." J. Nucl. Med. 62(supplement 1):1309.
- Musolino, S. (2002). Radionuclide and Radiation Protection Data Handbook. Book review. Health Phys. 83(1)136. https://ehs.stanford.edu/reference/sr-89-radionuclide-fact-sheet.
- National Center for Biotechnology Information. PubChem Compound Summary for CID 5388879, Strontium chloride SR-89. https://pubchem.ncbi.nlm.nih.gov/compound/Strontium-chloride-SR-89. Accessed 11/28/2022.
- North Carolina Health Physics Society. "I-131: Nuclide Safety Data Sheet." http://www.hpschapters.org/northcarolina/NSDS/131IPDF.pdf. Accessed 1/18/2023.
- North Carolina Health Physics Society. "Lu-177: Nuclide Safety Data Sheet." http://www.hpschapters.org/northcarolina/NSDS/177LuPDF.pdf. Accessed 1/18/2023.
- Palot Manzil, F. F. and H. Kaur. *Radioactive Iodine For Thyroid Malignancies*. Treasure Island (FL): StatPearls Publishing, 2022. Available from: https://www.ncbi.nlm.nih.gov/books/ NBK580567/.
- RSNA (2022). Radioactive Iodine (I-131) Therapy for Hyperthyroidism. Radiological Society of North America, Inc. (RSNA). https://www.radiologyinfo.org/en/info/radioiodine. Accessed on 11/16/2022.
- Radswiki, T., D. Bell, Y. Weerakkody, et al. Thyroid scintigraphy (I-123). Reference article, Radiopaedia.org. https://doi.org/10.53347/rID-12707. Accessed on 1/19/2023.
- Ravichandran, R., J. Binukumar, and A. A. Saadi (2010). "Estimation of effective half life of clearance of radioactive Iodine (I) in patients treated for hyperthyroidism and carcinoma thyroid." *Indian J. Nucl. Med.* 25(2):49–52. doi:10.4103/0972-3919.72686.

- Silberstein, E. B., A. Alavi, H. R. Balon, et al. (2012). "The SNMMI practice guideline for therapy of thyroid disease with 1311 3.0." J. Nucl. Med. 53(10):1633–51. doi:10.2967/jnumed.112.105148.
- Sirtex (2004). Approved indication, Package Insert (IFU) for SIR-Spheres® User's Manual. Sirtex Medical Limited. https://www.sirtex.com/media/jswdjodw/ifu-005-eu-sir-spheresmicrospheres-ifu-for-eu.pdf. Accessed 11/28/2022.
- Smith, D. S. and M. G. Stabin (2012). "Exposure rate constants and lead shielding values for over 1,100 radionuclides." *Health Phys.* 102(3):271–91. doi:10.1097/hp.0b013e318235153a.
- TheraSphere[™] P200029. https://www.fda.gov/medical-devices/recently-approved-devices/ theraspheretm-p200029. Accessed 11/28/2022.
- University of Michigan. Facilities & Operations Environment, Health, and Safety. "Environmental, Health, and Safety Guideline: I-131." https://ehs.umich.edu/wp-content/uploads/ 2016/04/Iodine-131.pdf. Accessed 11/18/2022.
- UW Hospital & Clinics. Nuclear Medicine Procedure, I-131 Sodium Iodide for Thyroid Cancer Therapies. https://www.radiology.wisc.edu/wp-content/uploads/2017/12/I-131_ Sodium_Iodide_for_Thyroid_Cancer_March_2017.pdf. Accessed on 11/27/2022.