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An Analysis of Regulatory Guidelines for the Release of Patients Administered Therapeutic Doses of Radioactive Iodine

by

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Committee Approval

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List of Abbreviations/Symbols

ACR	American College of Radiology
ACS	American Cancer Society
AEC	Atomic Energy Commission
ATA	American Thyroid Association
ATC	Anaplastic Thyroid Cancer
ATSDR	Agency for Toxic Substances and Disease Registry
BTF	British Thyroid Foundation
CFR	Code of Federal Regulations
D (∞)	Dose to Total Decay
D(t)	Accumulated Exposure at time t, in rem
DOE	Department of Energy
DTC	Differentiated Thyroid Cancer
E	Occupancy Factor
E_{MAX}	Maximum Energy
EPA	Environmental Protection Agency
ERDA	Energy Research and Development Administration
F_1	Uptake Fraction - Extrathyroidal Component
F_2	Uptake Fraction - Thyroidal Component
FDA	Food and Drug Administration
GBq	gigabecquerel
HPS	Health Physics Society
I	Iodine
I-131	Iodine - 131

ICRP	International Commission on Radiological Protection
mrem	millirem
mSv	millisievert
MTC	Medullary Thyroid Cancer
mU/L	milliunit per liter
Na ^{131}I	Sodium Iodide
NCRP	National Council on Radiation Protection and Measurements
NIS	Sodium-iodide symporter
NRC	Nuclear Regulatory Commission
RAI	Radioactive Iodine
RG	Regulatory Guide
T_{1EFF}	Effective Half-Life - Extrathyroidal Component
T_{2EFF}	Effective Half-Life - Thyroidal Component
T3	Triiodothyronine
T4	Thyroxine
T_b	Biological Half-Life
T_E	Effective Half-Life
TEDE	Total Effective Dose Equivalent
T_P	Physical Half-Life
TSH	Thyroid-Stimulating Hormone
TT/NT	total/near-total thyroidectomy
WHO	World Health Organization
Xe	Xenon

Abstract

The Nuclear Regulatory Commission has a series of guidelines with differing criteria for the safe release of patients who have been administered unsealed byproduct material or implants containing byproduct material. These criteria were evaluated to see if there were significant differences in patient release times using the different criteria.

Regulatory Guide 8.39 Revision 1 provides the following three release criteria under which a patient can be released from a hospital under federal regulation: 1) Release of Patients Based on the Administered Activity, 2) Release of Patients Based on the Measured Dose Rate, and 3) Release of Patients Based on Patient-Specific Dose Calculations. The results of this study showed all patients failed criteria one at the time of release. The second criteria allowed for the immediate release of four out of eighteen patients evaluated. The third criterion allowed for the immediate release of all patients. These results show that depending on which criteria was used, patient release times from the hospital can vary. If a patient is released too soon there could be a greater radiation exposure risk to the general public, however if the patient is released too late, there could be unnecessary financial stress to the patient for the additional time spent in the hospital.

Keywords: Regulatory Guidelines, patient release, administered activity, dose rate, patient-specific calculations, iodine-131

Chapter 1: Introduction

The *Code of Federal Regulations* (CFR) contains 50 titles all of which are initially published in the Federal Register. The titles are divided into chapters, parts, and subparts (National Archives and Records Administration, n.d.). Title 10 of the *Code of Federal Regulations* contains four volumes that discuss energy-related topics and is produced by the Nuclear Regulatory Commission (NRC). These regulations are divided into Parts 1-199. The Medical Use of Byproduct Material can be found in 10 CFR 35 (*Title 10 of the Code of Federal Regulations*, 2023).

The regulation of radioactive materials for medical use began in 1946 under the Atomic Energy Commission (AEC) and continued until the Energy Reorganizing Act of 1974. The Energy Reorganizing Act of 1974 converted the AEC into the Nuclear Regulatory Commission (NRC) and the Energy Research and Development Administration (ERDA), which was later to become the Department of Energy (DOE) (United States Nuclear Regulatory Commission [U.S. NRC], 2021a).

The NRC or agreement states have regulatory authority over all nuclear medical use except for one microcurie of carbon-14 urea for in vivo studies. The NRC determined that when in capsule form, one microcurie carbon-14 urea possesses an insignificant radiation risk; therefore, radiation safety is not a concern. This allows better distribution and use of the drugs for individuals (United States Food and Drug Administration [U.S. FDA], 1998). The new ruling was implemented after a petition (Docket No. PRM-35-12) was issued by Tri-Med Specialties Inc (Tri-Med) in August 1994. In the petition, Tri-Med cited evidence that up to 10% of the U.S. population suffers from ulcers, which can be caused by the bacteria *Helicobacter pylori* (H. Pylori). *H. pylori* does not have a high mortality rate, but it can cause great suffering. Before this new ruling, the diagnosis of *H. pylori* required an invasive endoscopic biopsy of the stomach lining (U.S. NRC, 1997). Carbon-14 urea, in comparison, is a radiopharmaceutical taken in

pill form. If *H. pylori* are present in a patient, the bacteria will break down the capsule, and the carbon-14 is detected on exhalation with a liquid scintillation counter (Kolekar et al., 2016).

All other "internal or external administrations of byproduct material or the radiation therefrom to human patients or human researcher subjects must be done in accordance with the medical use license (or authorization) issued pursuant to NRC's regulations in 10 CFR Part 35" (United States Nuclear Regulatory Commission [U.S. NRC], 2020b). Subpart C, General Technical Requirements, of 10 CFR 35.75 "Release of Individuals Containing Unsealed Byproduct Material or Implants Containing Byproduct Material" details the criteria needed for a licensee to be able to release a patient who was administered radioactive material (United States Nuclear Regulatory Commission [U.S. NRC], 2017).

The NRC also publishes Regulatory Guides (RGs) to help the public and licensees understand the process that hospital staff can use to maintain compliance with the regulations, explain techniques used for actual or possible events, and help guide hospital/clinical staff in following the regulations (U.S. NRC, 2020b). Regulatory Guide 8.39 Revision 1, "Release of Patients Administered Radioactive Material," is one instance used with 10 CFR 35.75. The guideline uses the following three parameters when evaluating patients for release:

1. Administered Activity
2. Measured Dose Rate
3. Patient-Specific Dose Calculations (U.S. NRC, 2020b).

1.1 Problem Statement

Administered activity and measured dose rate were the only two patient release criteria used prior to 1997 (Reiman, 2004). The administered activity criteria are specific for individual radionuclides. For example, for Iodine-131, the maximum administered activity for immediate release must be less than 33 millicuries. Additionally, the dose rate emitted from the patient needs to be less than 1 mrem per hour at one meter or 5 mrem per hour at one meter with written instructions (U.S. NRC, 2020a).

The NRC added the third criterion of the patient-specific dose calculation (Equation 1) in 1997, to ensure public safety and that no individual would receive greater than 0.5 rem (5 mSv) of radiation exposure from a treated patient (U.S. NRC, 2020a).

$$D(t) = \frac{34.6\Gamma Q_0 T_p(E)\left(1 - e^{-\frac{0.693t}{T_p}}\right)}{r^2} \qquad \text{(Equation 1)}$$

Where:

D(t) = accumulated exposure at time t, in rem

34.6 = conversion factor of 24 hours per day times the total integration of decay (1.44)

Γ = exposure rate constant for a point source, in R/mCi x 1 hr at 1 cm

Q_o = initial activity at the start of the time interval, mCi

T_p = Physical half-life, in days

E = Occupancy factor that accounts for different occupancy times and distances when an individual is near a patient

r = Distance in centimeters (this value is typically 100 cm)

t = Exposure time in days (U.S. NRC, 2020a).

The combination of a patient's characteristic under 10 CFR 35.75 need to be such that at least one of these three criteria are met in order for the patient to be released from the hospital (U.S. NRC, 2020a).

Radioactive Iodine-131 (I-131) is the most frequently used radioisotope of iodine for radiation therapy and is used in treating hyperthyroidism and thyroid cancer. Upon administration of I-131, the patient becomes a radioactive source. Typical doses to treat hyperthyroidism are between 1 and 30 mCi. However, anywhere between 30 and 300 mCi may be used for thyroid cancer treatment. As a consequence of the NRC rules, most patients before 1997 had to be treated as inpatients following the

administration of I-131 (Smith & Burpee, 2021).

Current standards allow patients to be released when they agree to follow written and oral instructions specified by the patient-specific dose calculation criteria. If the patient does not follow the provided instructions, then there is a risk to the family, caregivers and/or general public of receiving an exposure higher than the recommended 0.5 rem (5 mSv). Some in the nuclear medicine community find this approach to be too relaxed. There is some speculation that this could cause a threat to the public (Smith & Burpee, 2021). Conversely, other practitioners argue that the measured dose rate criteria are too conservative and could result in unnecessary hospital stays.

1.2 Objective

This study compared individuals who have been administered therapeutic doses of iodine-131 (I131) post-total or near-total thyroidectomy for thyroid cancer treatment. The activity administered to treat thyroid carcinoma using I-131 is typically higher than the first release criteria of 33 mCi allows and, therefore only compares the second and third criteria.

Information about administered activity and measured dose rate before the patient's release following I-131 administration for thyroid cancer was gathered from the radiation safety team at a local Idaho hospital[1]. This data was used to run the patient-specific dose calculations. Using the measured dose rate and the calculated patient-specific calculation, the anticipated dose and dose rate caused by radiation emitted from the patient as a function of time was calculated to determine when the patient could be safely released. This release time was compared between the two criteria. The mean release time for the two patient release criteria was compared using the students t-test. The students t-test was used to evaluate the hypotheses and determine if there was a "significant difference between the means of two groups" (*Hayes*, 2021).

[1] Data was collected with compliance with the hospital's human use committee.

1.3 Hypothesis Testing

The patient release times calculated by using the patient-specific dose calculation and the measured dose-rate criteria was used to evaluate any difference in release times between the two methods. Hypotheses statements for this question were as follows:

H_0: The patient-specific dose calculation and the measured dose-rate criteria will result in the same release times for patients administered therapeutic doses of Iodine-131.

H_a: The patient-specific dose calculation and the measured dose-rate criteria will result in different release times for patients administered therapeutic doses of Iodine-131.

Decision Rule: The null hypothesis is rejected if the critical value is greater than 2.110 (student's t-test: $t(17) = 2.110$, $p = 0.05$).

Chapter 2: Literature Review

2.1 Radiopharmaceuticals

According to the United States Nuclear Regulatory Commission (NRC), one-third of all individuals admitted to a hospital are given a radiopharmaceutical (U.S. NRC, 2020b). Radiopharmaceuticals are composed of bioactive molecules combined with radionuclides (Brugarolas et al., 2020) and are used in the nuclear medicine department as diagnostic and therapeutic tools (U.S. NRC, 2020b).

Diagnostic radiopharmaceuticals can be injected, inhaled, or swallowed. Once the radioactive material has entered an individual, it is collected within the area of interest, and emitted photons can be viewed with a gamma camera or using equipment such as a PET-CT device (U.S. NRC, 2020b). Larger doses of radiopharmaceuticals are used for therapeutic purposes (Stabin, 2008).

The therapeutic use of radioactive materials can be divided into three categories: teletherapy, brachytherapy, and therapeutic nuclear medicine. Teletherapy uses a focused beam of radiation to target malignant tumors. Brachytherapy places sealed radioactive sources near or directly inside a tumor and can also be used intravenously to place a source via the arteries inside an irradiation target. High doses of radiopharmaceuticals can be injected or ingested by a patient for therapeutic nuclear medicine (U.S. NRC, 2020b).

2.2 10 CFR 35 “Medical Use of Byproduct Material”

10 CFR 35 gives the requirements that must be met under the authority of a licensee in order to use byproduct material for medical use. Meeting these requirements ensures the protection of radiation workers, the public, patients, and sometimes human research subjects from unnecessary radiation exposure. To aid in the development and employment of 10 CFR 35 criteria, the NRC recommends following the Medical Use Policy Statement. The policy states that the NRC will:

- Protect the safety of radiation workers and the public by controlling radionuclides used in medicine.
- Not interfere with medical decisions affecting patients unless it is essential to maintain the safety of radiation workers and the public.
- Use the regulations mainly to guarantee that the doctor's orders are followed once it has been determined that the benefit outweighs the risk to the patient.
- Consider industry and professional standards for determining reasonable practices for radiation safety (U.S. NRC, 2020c).

Subpart C, General Technical Requirements, of 10 CFR 35.75 is titled "Release of Individuals Containing Unsealed Byproduct Material or Implants Containing Byproduct Material." The NRC states that a patient who was given an unsealed byproduct material or implants containing byproduct material can be released if the radiation emitted by sources in the patient are not likely to produce greater than 5 mSv (0.5 rem) in another individual when oral and written instructions on how to minimize the dose to other people are given and followed. If the total effective dose equivalent (TEDE) received by any other individual around the patient is not likely to be greater than 1 mSv (0.1 rem), then the patient can be released without instructions (U.S. NRC, 2017). If the patient is a nursing mother, and doses could exceed 1 mSv (0.1 rem) to the nursing child, if there were not a break in breast-feeding, the instructions need to include information about the risk to the child if the guidance is not followed. The licensee then also must keep a record of the reason for discharging a nursing patient and a record of what instructions were given to the mother (U.S. NRC, 2017).

2.3 Regulatory Guide 8.39 Revision 1

Regulatory Guide 8.39 Revision 1 “provides methods that are acceptable to the U.S. Nuclear Regulatory Commission (NRC) staff for release of patients who have been administered unsealed

byproduct material or implants that contain radioactive material" (2020). The regulatory guide determined activities and dose rates that allow for the immediate release of patients under the NRC requirements. They also offer instructions for the licensee to give to patients before and after the administration of radioactive material and guidance on what records that must be kept (U.S. NRC, 2020a).

To aid in the determining when patients could be released, Regulatory Guide 8.39 Revision 1 uses Equation 1 and considers "the dose to an individual likely to receive the highest dose from exposure to the patient is taken to be the dose to total decay" (2020). Therefore, the component $\left(1 - e^{\frac{-0.693t}{T_p}}\right)$ from Equation 1 can be set to 1. If the given radionuclide has a physical half-life greater than 1 day, it is assumed that the person to receive the highest dose from exposure to the patient administered the radionuclide would receive 25% of the dose due to decay at a distance of 1 meter (Equation 2). If the physical half-life is less than or equal to 1 day, then the occupancy factor becomes 1 (Equation 3).

$$D(\infty) = \frac{34.6\Gamma Q_0 T_p (0.25)}{(100cm)^2} \qquad \text{(Equation 2)}$$

$$D(\infty) = \frac{34.6\Gamma Q_0 T_p (1)}{(100\ cm)^2} \qquad \text{(Equation 3)}$$

The occupancy factors used in Equations 2 and 3 were adapted from NUREG-1492 (1997), "Regulatory Analysis on Criteria for the Release of Patients Administered Radioactive Material". An occupancy factor of 1 for radionuclides with a half-life of less than 1 day was chosen because the dose delivered will occur over a relatively short time and limiting an individual's exposure to a patient for that duration is not always practical (Schneider & McGuire, 1997).

The decision to use an occupancy factor of 0.25 for radionuclides with a half-life of 1 day or greater was based on the professional judgment of the authors of NUREG-1492 (1997) and from the empirical data they reviewed. Time, distance, and shielding are the cardinal rules to maintain as low as reasonably achievable (ALARA) and are believed by the NUREG-1492 authors' to be standard practices within the United States. A caregiver in charge of an individual administered a radionuclide will, therefore, not spend one hundred percent of their time one meter from the patient during the entire period the patient is radioactive (Schneider & McGuire, 1997).

NUREG-1492 (1997) also referenced two studies that evaluated an occupancy factor of 0.25 for radionuclides with a half-life of one day or greater. A study by Harbert and Wells (1974) showed that an occupancy factor of 0.25 gave conservative estimates of the predicted dose to family members compared to the actual measured dose (Table 1) (Schneider & McGuire, 1997). Buchan and Brindle (1971) evaluated iodine therapy patients and their families who were not given instructions on how to minimize exposure following the administration of a radiopharmaceutical. Their highest recorded reading from a family member was 0.27 rem, well below the 0.5 rem limit. Comparing all the available information, the NUREG-1492 (1997) authors felt using 25 percent was conservative (Schneider & McGuire, 1997).

Table 1: Family Doses from Patients Treated with Iodine-131 for Thyroid Carcinoma

Patient	Total Activity Administered (mCi)	Body Burden at Time of Discharge (mCi)	Measured Doses to Family Members (mrem)	Predicted Dose Based on Occupancy Factor of 25% at 1 meter (mrem)
1	210	25.2	80, 70, 30	386
2	311	26.4	50, 20, 20	404
3	209	18.4	80, 40	282

Source: HA74 (Harbert & Wells, 1974)

If biological elimination is considered and an effective half-life is used in the calculation, the patient-specific calculation (Equation 1) is modified to account for the uptake and retention of the radionuclide within the patient as shown in Equation 8 (U.S.NRC, 2020a).

Equations 2 and 3 calculate the dose from the external exposure to gamma radiation emitted by a source within the patient. These are valid in part because the exposure rate at 1-meter equals ΓQ per 10,000 square centimeters (Equation 4). These equations do not apply to the dose of breastfeeding infants or children who continue to breastfeed (U.S. NRC, 2020a).

$$D = \frac{\Gamma A}{d^2} \qquad \text{(Equation 4)}$$

Where:

Ḋ = exposure rate (R/h)

Γ = gamma ray constant ($\frac{(R)\ (cm^2)}{(hr)(mCi)}$)

A = Activity (mCi)

d^2 = distance (cm)

2.3.1 Criteria 1: Administered Activity

The administered activity criteria are specific for individual radionuclides. Patient release based on administered activity assumes that the internal dose is negligible. Therefore, the total effective dose equivalent (TEDE) becomes "approximately equal" to the external dose limit, which is 5 mSv (0.5 rem) to an individual (U.S. NRC, 2020a). The factors used to determine the values of these activities are the administered activity, physical half-life (T_P), occupancy factors of 0.25 for radionuclides that have a physical half-life greater than 1 day or 1 if the T_P is 1 day or less, and no shielding by tissue. Not considering the biological half-life of that individual removes any consideration of decreased levels within the patient over a period of time which nevertheless clearly effects external dose rates (Siegel et al., 2007), the consequence of this could lead to longer hospitalization.

Column 1 of Table 2 lists different maximum administered activities at which a patient can be immediately released for different radionuclides as given in Regulatory Guide 8.39 Revision 1 (U.S. NRC, 2020a). If the administered activity is greater than those listed, the licensee can release the patient once the activity has decayed to the appropriate value given in Column 1 of Table 2. A record for the reason of release must be kept in this instance since the individual is no longer being released based on administered activity but retained activity (U.S. NRC, 2020a). If a particular radionuclide is not listed in Column 1 of Table 2, Equation 2 or Equation 3 can be used as appropriate to calculate the equivalent activity that would produce 5 mSv (0.5 rem), to a hypothetical individual exposed to the radiation emitted from radioactive material in the patient. (U.S. NRC, 2020a).

TABLE 2. Partial List of Activities and Dose Rates for Authorizing Patient Release as Given in Regulatory Guide 8.9 Revision 1.

Radionuclide	Column 1 Activity at or below which patients may be released (GBq)	(mCi)	Column 2 Dose Rate at 1 meter, at or below which patients may be released (mSv/h)	(mrem/h)
Ag-111	19	520	0.08	8
I-123	6.0	160	0.26	26
I-125 implant	0.33	9	0.01	1
I-131	1.2	33	0.07	7
Sc-47	11	310	0.17	17
Yb-169	0.37	10	0.02	2

2.3.2 Criteria 2 Measured Dose Rate

If the dose rate emitted from the patient is less than 1 mrem per hour at one meter, or 5 mrem per hour at one meter from the surface of the patient with written instructions, patients may be released under the measured dose rate criteria (NRC, 2020). If the administered activity is greater than shown in Column 1 of Table 2, a licensee may still release the patient "as long as the measured dose rate at 1 meter (from the surface of the patient) is no greater than the value in Column 2" of Table 2 for the specific radionuclide used (U.S. NRC, 2020a).

Licensees can calculate the activity leading to a dose rate of 5 mSv (0.5-rem) for a radionuclide not listed in Table 2. A radionuclide with a physical half-life of over 1 day will require the use of Equation 2 to calculate the measured dose rate. If the physical half-life is equal to or less than 1 day, then equation 3 is used (U.S. NRC, 2020a). If the current measured dose rate at 1 meter is less than the calculated dose rate, the patient can be released, but the licensee needs to keep a record of the calculation (U.S. NRC, 2020a).

2.3.3 Criteria 3 Patient-Specific Dose Calculations

A licensee may release a patient who has been administered a dosage higher than the values listed in Column 2 of Table 2 "if dose calculations using patient-specific parameters, which are more realistic than the conservative assumptions used to develop column 2, can be used to demonstrate that the total effective dose equivalent to any individual is not likely to be greater than 5 millisieverts (0.5 rem)" (U.S. NRC, 2020a).

Regulatory Guide 8.39 Revision 1 uses the assumption that 1 Roentgen is equal to 1 Rem for these calculations (U.S. NRC 2020a); which is an oversimplification. The three radiation measurements of concern for the release of patients administered radionuclides are: exposure, absorbed dose, and dose equivalent. Radiation exposure is expressed in Roentgens (R) and measures the air around a photon beam that has energies below 3 MeV (Williams, 1966). Exposure specifically measures how

much ionization is created from the radiation when standard temperature and pressure (STP) conditions are present in 1 cm^3 of dry air that creates 1 electrostatic unit (esu) of charge. The exposure of 1 Roentgen in air is approximately equal to 0.9 rad, while the same exposure equals roughly 0.869 rad in tissue. (Curtis, n.d.).

The rad is used to measure the absorbed dose or amount of energy deposited within a specific material (Equation 5). The rem measures the biological effect the radiation causes on the specific material which it is deposited (Curtis, n.d.). A quality factor is assigned to each radiation type and is multiplied by the absorbed dose to determine the dose equivalent. Photons have a quality factor of 1 and this is where the assumption that 1 rem is equal to 1 rad is created (*Measuring radiation,* 2020).

$$D_{material} = 0.88\, X\, \frac{(\frac{\mu en}{\rho})_{material}}{(\frac{\mu en}{\rho})_{air}} \qquad \text{(Equation 5)}$$

Where:

$D_{material}$ = dose to specific material from photons (rads)

X = exposure (Roentgen)

$(\mu_{en}/\rho)_{material}$ = mass energy absorption coefficient for material at specified energy

$(\mu_{en}/\rho)_{air}$ = mass energy absorption coefficient for air at specified energy

Exposure to a hypothetical third person from a radioactive individual occurs from both external exposure and the potential of inhaling or ingesting radioactive contamination excreted from the patient. The total effective dose equivalent (TEDE) to this hypothetical person considers both sources of exposure. This change was thought by the NRC to better align with their goal of public safety by replacing the dose-rate-based release limit with patient specific characteristics (Siegel et al., 2007). The maximum internal dose exposure can be calculated using Equation 6.

$$Di = Q(10^{-5})(DCF) \quad \text{(Equation 6)}$$

Where:

Di = maximum likely internal committed effective dose equivalent to the individual exposed to the patient in rem

Q = activity administered to the patient in millicuries

1x10 $^{-5}$ = assumed fractional intake

DCF = dose conversion factor used to convert an intake in millicuries to an internal committed effective dose equivalent (U.S. NRC, 2020a). (Federal Guidance Report No. 11 lists the committed dose equivalent per unit intake effective for I-131 is 53 rem/mCi (U.S. EPA, 1988).

Brodsky (1981) developed 1 x 10^{-6} as the fractional activity intake from exposure for radiation workers (both in standard practice and unintentional exposures), and for the general public from accidental airborne releases. It did not consider, however, internal exposure to an individual from a patient given a radioactive byproduct (U.S. NRC, 2020a). To create an acceptable fractional intake, Regulatory Guide 8.39 Revision 1, referenced two studies done on exposure to individuals around patients administered I-131 by Buchanan and Brindle (1971) and Jacobson and Toeroek (1978). The studies showed the internal intake of the individuals was mainly on the order of 1 millionth of the administered activity and was well below doses the individuals received from external exposure. From these studies, a fractional intake of 1 x 10^{-5} was chosen to stay conservative (U.S. NRC, 2020a).

The National Council on Radiation Protection and Measurements (NCRP) also argues that the risk of internal contamination from a patient's excretions that would create a substantial internal exposure is improbable and considers internal dose insignificant for the consideration of patient release (NCRP, 1995). NUREG-1492 (1997) echoes this sentiment and states that internal dose can be ignored in exposure calculations if the internal dose is likely to be less than 10 percent of the external dose since the internal dose would be smaller than the uncertainty calculated for the external dose (Schneider &

McGuire, 1997).

The patient-specific dose calculation is shown in Equation 1 and does not consider possible internal exposure. The occupancy factor for Equation 1 considers multiple aspects of the patient's specific circumstances. It looks, for example, at how long and how far away an individual will be from the patient, whether the physical half-life (T_P) or the patient-specific effective half-life (T_E) is used in the calculation (Equation 1), and whether instructions are given before release. The occupancy factors that should be used in the equation are given in Appendix A.

The effective half-life considers different medical conditions of the patient, for example, if they have hyper- or hypothyroidism (U.S. NRC, 2020a). Equation 7 shows the relationship of physical half-life (T_P) and the biological half-life (T_b) have on the effective half-life (T_E) (Effective Half-Life, n.d.):

$$T_E = \frac{T_p T_b}{T_p + T_b} \quad \text{(Equation 7)}$$

Where:

T_p = Physical Half-Life

T_b= Biological Half-Life

2.3.4: Half-Lives

Knowing an accurate effective half-life is crucial in calculating the elimination rate for individuals administered radioactive materials. The elimination rate is determined by the body's retention of the radionuclide as a function of time. The retention in patients who receive $Na^{131}I$ depends on the thyroid function, the existence of a thyroid, hydration, and renal function (International Commission on Radiological Protection [ICRP], 2004).

Guidelines and recommendations, such as those from NCRP 1970 and U.S. NRC 1997, consider only the radiopharmaceutical's physical half-life (Tp). Using an effective half-life (Teff) (Equation 7) in

place of the physical half-life gives a more accurate representation of how I-131 clears from a patient's body. This allows for a more precise calculation of the radiation dose a treated individual would present to those individuals who may be exposed to the radiation emitted in this situation (Willegaignon et al., 2006).

The biological half-life is the time it takes for half of a radioactive material to be removed from an individual through biological processes (Stabin, 2008). Therefore, to determine the biological half-life, one needs to know the route of administration, uptake, metabolism, clearance, and excretion of that radionuclide from within an individual's body (Yeong et al., 2014).

The biological half-life of iodine has been changed over the years by the ICRP. The biological half-life was listed as 138 days in ICRP 2 (1960). The ICRP decreased this number in 1978 under publication 30 (1979), recommending 120 days and the ICRP 56 (1989) changed the value once again to 80 days. The ICRP has maintained that the fraction of ingested iodine retained in the thyroid is 0.3; however, they do recognize this as a fluid number that can be influenced by the amount of dietary iodine ingested (Kramer et al., 2002). The effective half-life is less than or equal to the shorter half-time (biological or physical) since two processes are contributing to the elemental removal rather than one alone (Stabin, 2008).

ICRP publication 30 (1979), provided the iodine biokinetic model for a healthy person by dividing the body into five compartments. The compartments are composed of the stomach, body fluids, thyroid, whole body, and excretions (Figure 1) (CHEN et al., 2007). Radioactive iodine in a healthy adult is absorbed by the thyroid tissue and is mainly excreted in the urine. Small amounts are excreted through sweat, saliva, feces, and exhaled (ICRP, 2004).

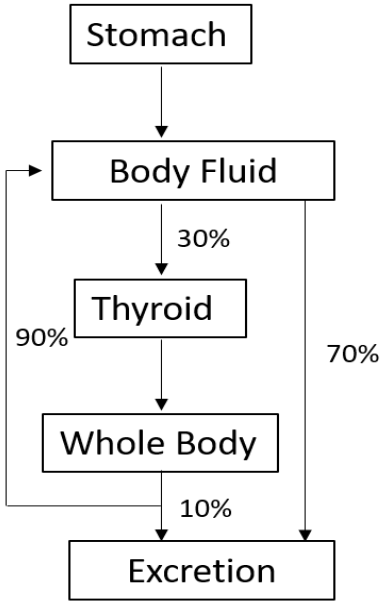

Figure 1. **ICRP-30 Biokinetic Model of Iodine for a Standard Healthy Man**.

After $Na^{131}I$ has been administered to thyroidectomy patients, the principal route of excretion is urine; 80-90% of the activity is excreted within 48 hours, with minimal amounts found in the saliva or feces (ICRP, 2004). Instead of being the dominant uptake organ, the thyroid remnants share iodine retention with the body-fluid compartments (CHEN et al., 2007). Figure 2 shows a typical retention curve for $Na^{131}I$ when administered to different thyroid patients. ICRP 94 (2004) references Driver and Packer's (2001) report of 174 thyroid cancer patients who received $Na^{131}I$, and the discharge of activity that was measured. They found that about 55% of the administered activity was excreted in the first 24-hours post-treatment. The second and third 24-hour periods showed 22% and 6% elimination, respectively. After the first five days, 85% of radioactive iodine was discharged ICRP 94 (ICRP, 2004).

Following a thyroidectomy, only 1 to 5% of the thyroid remains (CHEN et al., 2007). A hyperthyroid patient will clear I-131 faster than a euthyroid adult (Ravichandran et al., 2010). However, ICRP 53 explains that hypothyroid patients will have a lower thyroid uptake but a longer excretion half-time. This creates a larger radiation dose per fraction in a thyroidectomy patient versus a euthyroid patient (ICRP, 1988).

Regulatory Guide 8.39 Revision 1 (2020) states that in post-thyroidectomy patients, the extrathyroidal component has a 95% uptake fraction with an effective half-life of 0.32 days. The thyroidal compartment has an uptake fraction of only 5% with an effective half-life of 7.3 days (U.S. NRC, 2020a).

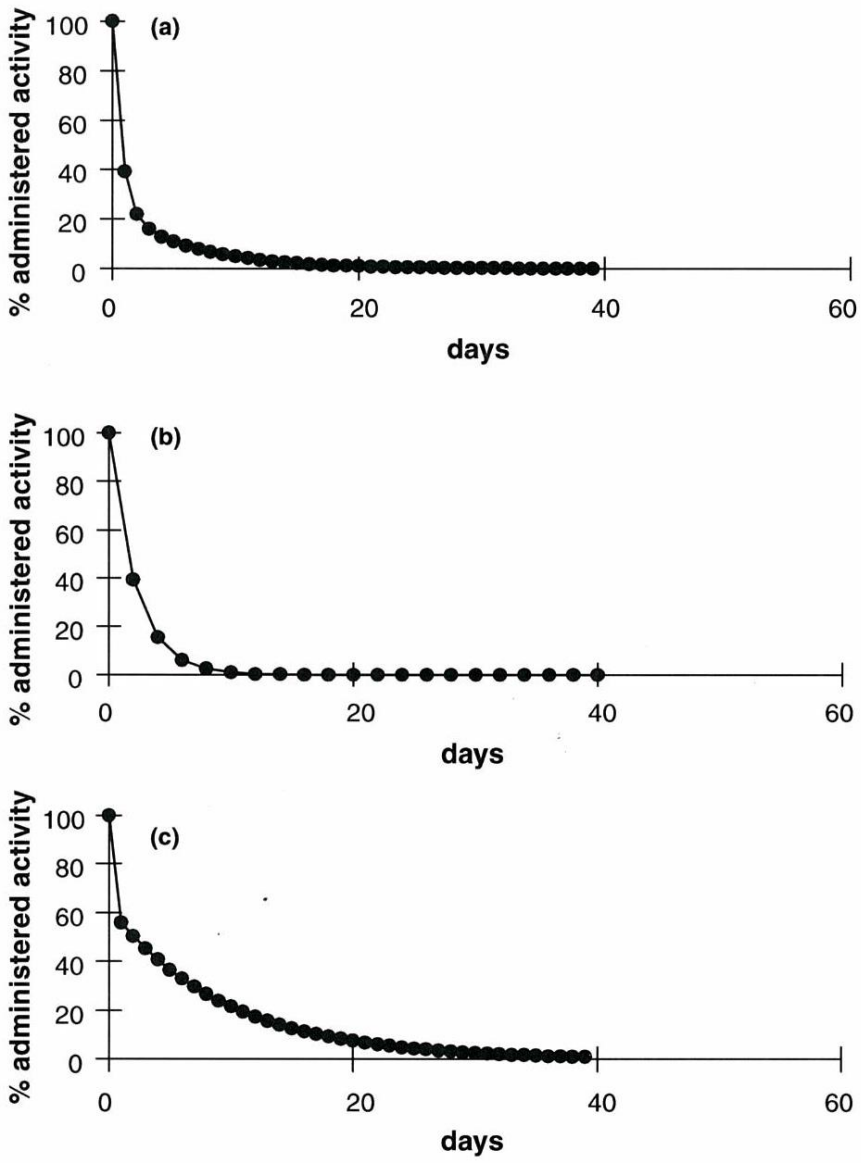

Figure 2. ICRP 94 Retention Curves Post-Administration of Sodium Iodide-131 following (a) cancer therapy, (b) cancer follow-up, and (c) hyperthyroidism (ICRP, 2004).

One study of Northern American patients found thyroidectomy patients followed a two-compartment model with an effective half-life of 0.9 days for the extrathyroidal compartment and 5.6 days for the thyroidal compartment. These patients were given diagnostic amounts of I-131 and were not on hormone replacement at the time of the study (H. Kramer et al., 2002).

Other studies found similar results including Willeganignon et al. (2006) who calculated the average effective half-life of 0.48 days +/- $8.3x10^{-4}$ days. Two other studies calculated the average effective half-life of I-131 to be 0.6 days (Ravichandren et al., 2010; CHEN et al., 2007). These publications seem to support the recommendations provided in Regulatory Guide 8.39 Revision 1.

2.3.5 Patient Specific Equation for Patients Administered I-131

Regulatory Guide 8.39 Revision 1 discusses patient-specific calculations relative to iodine-131. The exposure rate constant (Γ) given for I-131 is 2.2 R/mCi-h at 1 cm, and the physical half-life is 8.04 days. Regulatory Guide 8.39 also gives "acceptable" values of fractional uptake and effective half-life for both the extrathyroidal and thyroidal components (Table 3). The fractional uptake for I-131 for a post-thyroidectomy patient being treated for cancer was recommended by a U.S. NRC medical visiting fellow, Dr. M. Pollycove, M.D. The effective half-life for the extrathyroidal and thyroidal components was gathered from ICRP No. 53, "Radiation Dose to Patients from Radiopharmaceutical" (U.S. NRC, 2020a).

Table 3. Uptake Fractions and Effective Half-Lives for I-131 Treatments from Regulatory Guide 8.39 Revision 1 (2020)

Medical Condition	Extrathyroidal Component		Thyroidal Component	
	Uptake Fraction (F1)	Effective Half-Life T_{1eff} (day)	Uptake Fraction (F2)	Effective Half-Life $T2_{eff}$ (day)
Hyperthyroidism	0.20	0.32	0.80	5.2
Post-thyroidectomy for Thyroid Cancer	0.95	0.32	0.05	7.3

It is important to also consider the absorption rate from the stomach to the blood and retention in the bladder to rigorously calculated dose. To prevent an underestimated amount, Regulatory Guide 8.39 Revision 1, assumes 80% of the administered I-131 is removed by the body within the first 8 hours following administration when using the physical half-life and ignoring biological clearance (Equation 8).

The patient-specific calculation now has three parts for administered I-131.

1. Dose for the first 8 hours using the physical half-life.
2. Dose from extrathyroidal component from 8 hours to total decay using the effective half-life (T_{1eff})
3. Dose from thyroidal component for 8 hours to total decay using effective half-life (T_{2eff})

(Equation 8)

$$D(\infty) = \frac{34.6\Gamma Q_0}{(100cm)^2}\left\{E_1 T_p (0.8)\left(1 - e^{-\frac{0.693(0.33)}{T_p}}\right) + e^{-\frac{0.693(0.33)}{T_p}} E_2 F_1 T_{1eff} + e^{-\frac{0.693(0.33)}{T_p}} E_2 F_2 T_{2eff}\right\}$$

Where:

F_1 = extrathyroidal uptake fraction

F_2= thyroidal uptake fraction

E_1= occupancy factor for the first 8 hours

E_2 = occupancy factor from 8 hours to total decay

2.4 Thyroid Gland

2.4.1 Anatomy of the Thyroid Gland

The thyroid gland is part of the body's endocrine system and is located anterior to the trachea below the larynx (ICRP, 1975). The name thyroid comes from the Greek words, thyreos meaning shield, and eidos meaning form, to represent it's shield like shape (Fancy et al., 2010). The thyroid consists of two ideally symmetrical lobes on either side of the trachea and is connected by an isthmus (Kapral &

Khot, 2022). Each thyroid lobe typically stretches superiorly to and inferiorly from the levels of the fifth cervical vertebrae to the first thoracic vertebra. The isthmus band's thickness differs between individuals (ICRP, 1975) and runs from the second to the third tracheal ring (Allen & Fingeret, 2021).

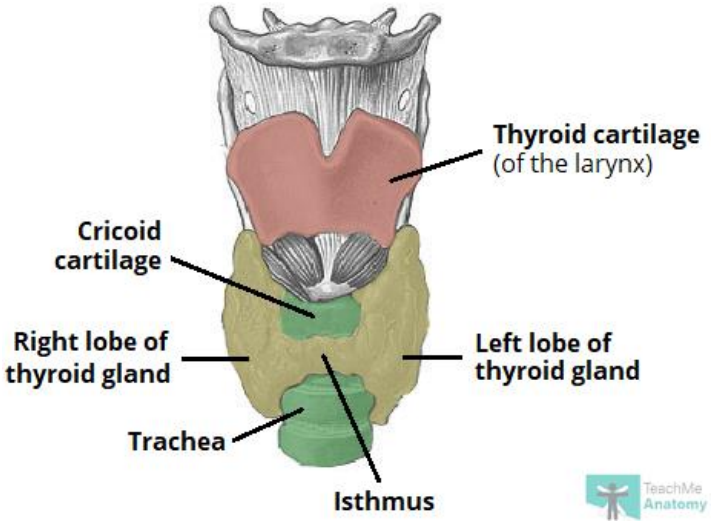

Figure 3. **Thyroid Anatomy (BTF, 2019).**

The size and weight of the thyroid gland are unique to each individual; however, ICRP 23 states that the average dimensions for each lobe of the thyroid gland are 2- cm wide, 5- cm tall, and 1- to 2.5- cm thick. The isthmus for an average adult is 2- cm wide, 2- cm tall, and 0.2- to 0.6- cm wide (ICRP, 1975).

Factors that can affect the weight of the thyroid gland include demographics, geography, and changes in a person's internal or external environment; however, the amount of iodine intake causes the most variation. ICRP 23 explains that an inverse relationship between thyroid weight and iodine uptake by the thyroid gland has been demonstrated. The United States and Western European populations are known for consuming higher levels of dietary iodine and thus 20 grams has been set as the standard thyroid gland weight for those countries by the ICRP. The ICRP however, acknowledges this number's limitations for populations with less iodine consumption (ICRP, 1975).

Each thyroid lobe has an apex and base and is conical in shape. The surface of the lobes is composed of three distinct areas: the lateral, medial, and posterolateral surfaces with an anterior and posterior border. The isthmus is composed of two surfaces and two borders. The anterior and posterior surfaces are bordered by the superior and inferior borders (Khan & Farhana, 2021).

The thyroid lobes are comprised of cuboidal follicular cells that house spherical thyroid follicles (Balasubramanian, 2020). There are between twenty and forty follicles within each lobe (Khan & Farhana, 2021), and it is these follicles that are known as the "structural and functional units of the thyroid glands" (Allen & Fingeret, 2021). The pretracheal fascia attaches to the visceral compartment of the neck that houses the thyroid gland, esophagus, pharynx, and trachea (Allen & Fingeret, 2021). Within this compartment, each thyroid lobe is connected to the trachea by a collection of connective tissue known as the lateral suspensory ligament (Kapral & Khot, 2022). The thyroid gland is highly vascular; blood enters the thyroid from the superior and inferior thyroid arteries and empties through the superior, middle, and inferior thyroid veins (Balasbramanian, 2020). Lymphatic drainage occurs in the isthmus and inferior lateral lobes to the paratracheal and lower deep cervical nodes. The superior lobes drain via the superior peritracheal and cervical nodes (Allen & Fingeret, 2021).

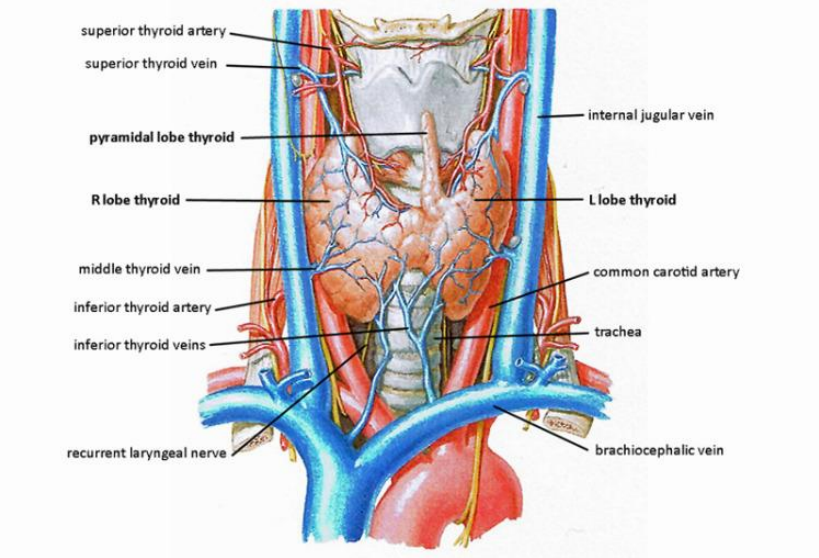

Figure 4. **Thyroid Blood and Lymph Flow (Fleming, n.d.)**

2.4.2 Functions of the Thyroid Gland

The thyroid gland is part of the endocrine system and is responsible for maintaining numerous critical bodily functions, including metabolic and circulatory processes, growth, and development regulation (Khan & Farhana, 2021). The gland produces and circulates the hormones: thyroxine (T4) and triiodothyronine (T3) through the bloodstream (Lee et al., 2016)**.** Calcitonin is also produced and emitted by the thyroid gland (Hall et al., 2021).

Thyroxine contains four iodine atoms, referred to as T4, while triiodothyronine is called T3 for its three iodine atoms (Figure 5). Triiodothyronine is secreted directly from the thyroid gland but is also produced by converting large amounts of thyroxine (T4) found throughout the cells and tissues of the body into T3 (British Thyroid Foundation [BTF], n.d).

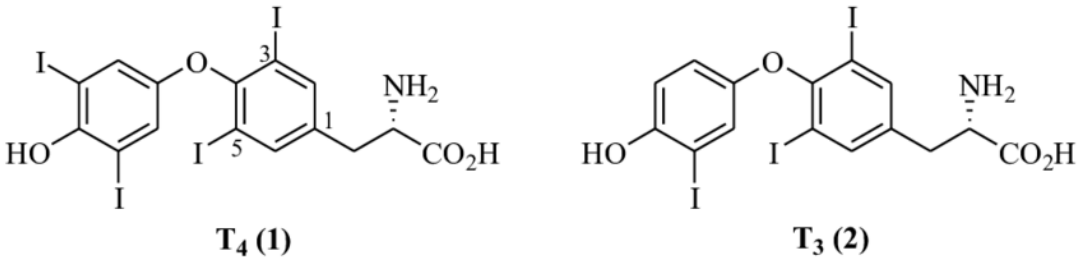

Figure 5. **Thyroxine (T4)(1) and Triiodothyronine (T3)(2) Chemical Structure (S, 2018).**

The pituitary gland is responsible for monitoring the levels of thyroid hormones circulating through the bloodstream. Thyroxine and triiodothyronine increase the body's metabolism by increasing the rate of chemical reactions occurring in most cells (Hall et al., 2021). When the pituitary gland detects higher-than-normal levels of thyroid hormones, it will cease the secretion of thyroid-stimulating hormones (TSH), triggering the thyroid gland to reduce the production and release of T4 and T3. When the pituitary gland detects low thyroid hormone levels circulating through the blood, it secretes (TSH). This hormone activates the thyroid gland to secrete more T4 and T3 hormones (BTF, n.d.).

Calcitonin aids in the control of calcium levels within the body by encouraging calcium and phosphate to deposit in bones and tissues. Calcitonin is found in parafollicular cells or C Cells inside the thyroid follicles. (Khan & Farhana, 2021).

2.4.3 Disorders of the Thyroid Gland

Thyroid disorders can be benign or malignant. Two common benign disorders of the thyroid gland include goiters and nodules. Goiters are observed when the thyroid gland is enlarged. Goiters can be diffuse and affect the entire gland or nodular, and only "one or more" are found in the gland. Thyroid gland nodules can be cancerous, but that occurs only in about 10 to 15% of the cases. Most nodules are fluid or colloid-filled cysts, which tend to be benign. Solid nodules containing a small amount of fluid or colloid are more likely to be cancerous than fluid or colloid-filled cysts, though most solid nodules are not cancerous (American Cancer Society [ACS], 2019).

Hyperthyroidism occurs when too much T3 is released, increasing the metabolism rate of the body's cells (BTF, n.d.). When cells become overworked, a person can develop tachycardia. They could also experience anxiety, irritability, muscle fatigue, and weight loss. The standard type of hyperthyroidism is Graves' Disease, whose symptoms include bulging eyes and a goiter (American Thyroid Association [ATA], n.d.-a).

When not enough T3 is secreted, the cell's metabolism decreases; and the person develops hypothyroidism. When the cells and organs slow down the individual can experience feeling colder, fatigued, depressed, have dry skin and constipation (ATA, n.d.-a).

Thyroid cancer comprises about 1 % of new malignant diseases (Vogiatzi et al., 2015). The American Cancer Society estimated 43,720 new thyroid cancers diagnosis for 2023, with 2,120 deaths from the disease (American Cancer Society [ACS],2023). Thyroid cancer is 2 to 4 times more common in women than in men (Schlumberger, 1998).

Most thyroid gland cancers can be divided into differentiated, medullary, or anaplastic (*Katoh et*

al., 2015). Differentiated thyroid carcinoma (DTC) is the most common type of cancer, making up for 94% of all diagnosed thyroid cancers (Vogiatzi et al., 2015). It arises from the thyroid follicular cells. This cancer has three subcategories: papillary, follicular, and Hurhle cell (American Cancer Society [ACS], 2019).

Papillary differentiated adenocarcinoma accounts for 80% of all thyroid cancers. It usually evolves in one lobe and is slow growing. Even though this type of cancer can spread to the lymph nodes of the neck, there is a high cure rate. Follicular differentiated adenocarcinoma accounts for 10 % of thyroid cancers. While this cancer does not typically spread to the lymphatic system, it can spread to other locations like the lungs and bones. Despite this, there is a good prognosis for Follicular thyroid cancer although not as high as for papillary. Hurtle cell cancer is challenging to find and treat and only accounts for 3% of thyroid cancers (ACS, 2019).

The second type of thyroid cancer, medullary thyroid carcinoma (MTC), comes from the C Cells found in the thyroid gland and accounts for 5 to 10% of all thyroid cancers. Medullary thyroid carcinomas metastasize to the lymph nodes, lungs, liver, or bones (Leboulleux et al., 2004). There are two types of MTCs. Sporadic MTC which accounts for 80% of the MTC cases, is usually found in older adults and is located in one lobe and is not inherited. Familia MTC is discovered in childhood and early adulthood. The familiar connection is strong and this cancer type is likely to be about 20 to 25% can occur in each generation of a family (ACS, 2019).

Finally, anaplastic thyroid carcinoma (ATC) is found in only 2% of thyroid cases but is highly aggressive (Kebebew et al., 2005).

2.5 Iodine

Bernard Courtois discovered the chemical element, Iodine (I) in 1811, in the ashes of seaweed (Fahey & Grant, 2021). Three years later, in 1813, the English chemist, Sir Humphry Davy, received a sample of this new element and gave it the name iodine, derived from the Greek word "ioeides," which

means "violet colored" (Rosenfeld, 2000). Iodine melts at 113 ^{0}C into a deep violet liquid and produces a violet gas once it reaches a boiling point of 184 ^{0}C (van der Krogt, 2010). The French chemist Joseph Louis Gay-Lussac had also been working on the new element and published his findings in 1814, naming the new element "iode." While priority rights became a debate between the two chemists, they both agreed that Courtois was the one who first discovered the element (Rosenfeld, 2000).

Iodine is a nonmetallic element that belongs to the halogen family and is found in Group 7A of the periodic table. Iodine is found naturally in sea water and specific rocks and sediments (Agency for Toxic Substances and Disease Registry [ATSDR], 2004). Iodine is the least abundant stable halogen, with only 0.46 parts per million in the Earth's crustal rock (Straub et al., 1966).

There are thirty-seven known isotopes of Iodine, but Iodine – 127 (I-127) is the only naturally occurring stable isotope (United States Environmental Protection Agency [U.S. EPA], 2023). The only naturally occurring radioactive isotope of Iodine is Iodine-129 (I-129) (Hou et al., 2009). Of the known isotopes, I-129 has the longest half-life of 15.7-million years (Staub et al., 1966). Natural I-129 is considered an extinct radionuclide. However, its daughter product, Xe-129, has been discovered in meteorites; therefore, I-129 is considered primordial (Küpper et al., 2011).

The remaining 35 isotopes of Iodine are anthropogenic (DOE, 1996d; International Isotopes, 2001; USGS, 1998) and have shorter half-lives than I-129. The next most stable isotope following I-129 for example is I-125 which has a half-life of 59 days (Küpper et al., 2011). Iodine-129 and I-131 are produced from nuclear fission (U.S. EPA, 2012).

2.5.1 Iodine – 131

Iodine-131 undergoes isobaric decay emitting a negatron. This beta-emitting isotope decays into stable Xenon (Xe)-131 (Figure 6) (Küpper et al., 2011) and reports a physical half-life of 8.04 days (Aljubeh et al., 2012). It has an atomic number (Z) of 53 and an atomic mass (A) of 131. Beta particles emit a continuous spectrum of energies that range from 0 MeV to the maximum energy of decay (Emax)

(Martin, 2013). Emax represents the highest energy possible for that particle, and for beta emitting radioisotopes, the average energy emitted is around 30 to 40% of Emax (Cember & Johnson, 2008). The energy absorbed from beta decay is related to beta's energy (Martin, 2013).

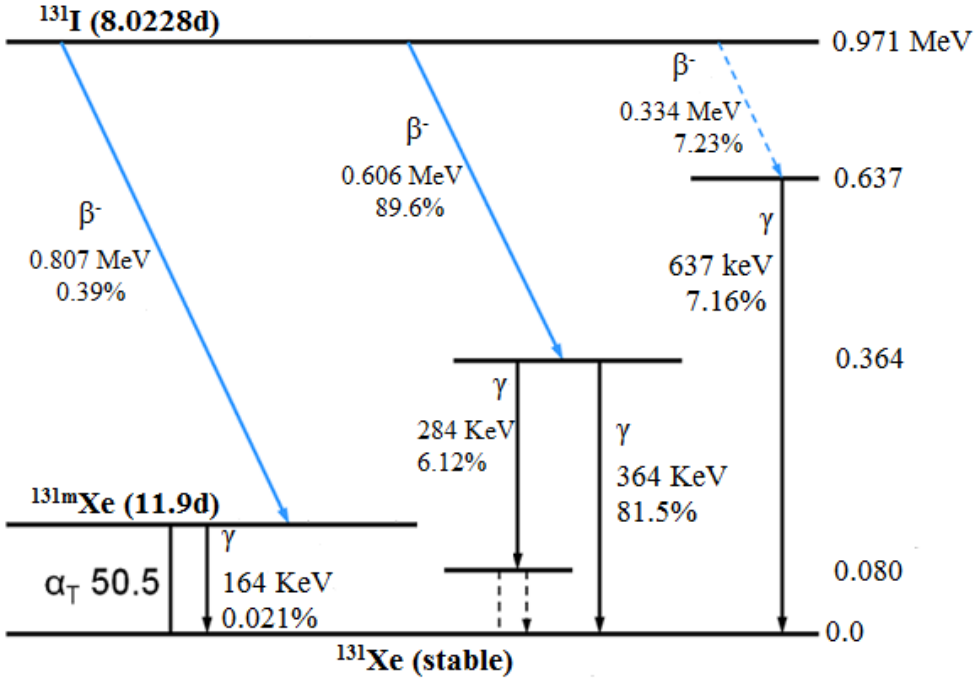

Figure 6. Iodine-131 Decay Scheme (Aljubeh et al., 2012).

Most of the time, I-131 decays into stable Xe-131 in two steps as shown in Equations 9 and 10, and 89.6% of the time, I-131 decays through beta emission with a maximum energy of 0.606 MeV. Following the beta emission, 81.5 % decays again with a gamma emission of 0.364 MeV (Aljubeh et al., 2012).

$$^{131}_{53}I \rightarrow {}^{131}_{54}Xe + \beta^- + \nu_e + 606\ keV \qquad (Equation\ 9)$$

$$^{131}_{54}Xe \rightarrow {}^{131}_{54}Xe + \gamma - rays + 364\ keV \qquad (Equation\ 10)$$

Appendix B shows additional beta/gamma combinations that occur in lower abundance.

2.5.2 Iodine in the Body

Iodine is a basic trace element found in the human body that aides in the regulation of body growth and development by synthesizing thyroid hormones (THS) (Leung et al., 2012). The body does not produce iodine, but it enters the body from dietary sources (Health Physics Society [HPS], 2019). Iodine is a naturally occurring element that is found in small amounts in sea water and in certain rocks and sediments (ATSDR, 2004).

A healthy adult body contains up to 20 mg of iodine, with 30% found in the thyroid. It was estimated in 1988 that a third of the global population was iodine deficient (Patrick, 2008). Iodine deficiency most often presents as an enlarged thyroid gland (Rosenfeld, 2000). One symptom of iodine deficiency is hypothyroidism; this affects 5% of the U.S. population (Hatch-McChesney & Lieberman, 2022). Iodine also aids in neurodevelopment (Pehrsson et al., 2016) and is a top cause of preventable mental retardation worldwide (Lee et al., 2016).

A surplus of iodine intake can cause both hyperthyroidism and hypothyroidism. When healthy adults have a larger iodine intake, it can decrease the production of thyroid hormones which in turn increases TSH stimulation (Liu et al., 2019). Extreme amounts of iodine intake are linked with "increased rates of thyroid autoimmunity and other forms of thyroid dysfunction" (Pehrsson et al., 2016).

To ensure proper iodine intake, the World Health Organization (WHO) recommends adults get 150 mg of iodine per day (Küpper et al., 2011). Some people can endure higher levels of iodine without toxic effects but there are also others who have side effects with as little as 1 milligram/day or less (Pennington, 1990). The safe upper limit of iodine intake is set at 1,000 µg (1mg) per day in the United States (Katagiri et al., 2017). Two methods to increase iodine intake are through iodized oil and iodized salt, with salt being the most effective way. When iodine is added to salt, it is done in the form of potassium iodide (KI) or potassium iodate (KIO3) (Küpper et al., 2011). The US Food and Drug Administration (FDA) is responsible for the regulation of the addition of iodine to salt and food (Trumbo,

2016).

When iodine is ingested into the body of a healthy adult, over 90% is absorbed in the stomach and duodenum. The thyroid and kidneys clear iodine from circulation (Küpper et al., 2011). Most of the ingested iodine, 90%, is excreted in the urine (Patrick, 2008). Renal clearance remains fairly constant, but the thyroid clearance can vary significantly depending on iodine intake (Küpper et al., 2011). Around 10% of absorbed iodine is absorbed by the thyroid when there is suitable intake of iodine. When there is a chronic deficiency of intake, this percentage can increase to 80% or higher. Iodine is also found in the blood and the concentration can increase or decrease based on iodine consumption (Küpper et al., 2011).

The thyroid gland aids in removing iodine from the bloodstream but cannot differentiate between stable iodine and radioactive iodine. The thyroid gland will absorb what is required while the remaining iodine is primarily excreted in the urine. Potassium iodide (KI) is a stable iodine salt that saturates the thyroid gland. Once the thyroid gland is saturated, it is limited in the amount of additional iodine the thyroid can absorb. Potassium iodide can be given in pill form to decrease the amount of radioiodine that can be absorbed when an unplanned radiation risk is a concern. It can also be beneficial if given within hours of exposure as the potassium iodide, and radioactive iodine will both be absorbed in the thyroid, helping to decrease the total amount of radioiodine the thyroid gland can absorb. Potassium iodide, however, only protects the thyroid gland within an individual; it does not prevent radioactive iodine from entering an individual or reverse any adverse effects it may have (HPS, 2019).

2.6 Treatment of Thyroid Cancer

Thyroid cancer is the most common endocrine cancer and is the fastest-growing malignancy for men and women in the United States (Carhill & Vassilopoulou-Sellin, 2012). The factors behind the increase in thyroid cancer diagnoses are still being investigated. Some theories suggest that there has been an overdiagnosis of small thyroid nodules due to increased screening capabilities. This is supported

by the fact that growth has been seen among individuals of higher socioeconomic standings and healthcare coverage (Morris et al., 2013). Other theories, however, suggest the increase is linked to previous medical exposure to radiation, increased consumption of iodine and possibly environmental pollutants (Vigneri et al., 2015). An increase in large thyroid tumors, advanced disease at diagnosis and increased mortality reinforces this theory (Aravindan, 2017).

Thyroid cancer is usually treated with surgery followed by radioactive iodine (RAI) ablation when indicated (ATA, n.d.-b). Radioactive iodine ablation is usually considered following total thyroidectomy for intermediate risk differentiated thyroid cancer (DTC) and is recommended for post-total thyroidectomy for high-risk DTC patients (Haugen et al., 2016).

Radioiodine has been used in treating thyroid cancers for over 60 years (Bailey et al., 2014). The goal of RAI following total or near total thyroidectomy (TT/NT) is to ablate any residual thyroid tissue or tumors, helping to decrease the chance of recurrence or metastasis (Zhao et al., 2022). Patients undergoing both treatments have a higher cure rate and lower recurrence rate (Haymart, 2011). Papillary thyroid cancer (PTC) typically involves removal of the tumor and cervical lymph nodes followed by radioiodine ablation. If the tumor is confined within the gland, survival rates are 98%. When there is evidence of regional lymph node spread, the rate then decreases to 58% for distance metastases. Follicular thyroid cancer has a 91% five-year survival rate and an 85% ten-year survival rate (Kreuger & Trommler, 2013).

The efficacy of RAI post-surgical resection depends on how well the patient is prepared, tumor characteristics, and the activity of the administered radioiodine (Yeong et al., 2014).
The optimal administration of I-131 is established by determining a high enough activity to eliminate tumor cells while minimizing excessive whole-body exposure (Khvostunov et al., 2017). RAI doses for thyroid ablation can be delivered in the range of 1 to 5 GBq (Brill et al., 2006). Newly diagnosed DTC patients receive around 1.1 to 3.7 GB1 (30 to 100 mCi) of I-131. This amount is increased for patients

needing subsequent treatment or metastatic disease. This dose typically does not rise above 7.4 GBq (200 mCi) for safety measures (Hänscheid et al., 2006). The IAEA acknowledges administered activities based on standardized versus personalization has been debated over the decades. Guidelines on the varied fixed activities have been published without recommendations (Kreuger & Trommler, 2013).

The dose is calculated based on the thyroid's estimated thyroid mass, fractional uptake, and the biological half-time of I-131 in the thyroid (Brill et al., 2006). Brill et al. states that the primary emphasis should be placed on the thyroid mass and thyroid fractional uptake with minimum consideration on the release of iodine from the blood and thyroid (2006).

A higher TSH level (greater than or equal to 30 mU/L) is thought to increase the sodium iodide symporter (NIS) expression. The symporter is essential for effective iodine uptake in thyroid follicular cells and is what helps radioiodine be an effective tool against thyroid carcinoma. This goal is achieved by ending the use of thyroid hormone replacement medicines prior to treatment to put the patient in a state of hypothyroidism. The medication can then be resumed two days post-RAI. Because food intake can also affect iodine uptake, patients are instructed to avoid large meals 4-hours prior to treatment and 1 hour following treatment (Luster et al., 2008). A low-iodine diet followed prior to the procedure is also beneficial (Pehrsson et al., 2016). Following this diet for one to two weeks depletes the body of iodine, allowing for "optimized RAI uptake in thyroid cells (Sawka et al., 2010).

2.7 Concerns

The United States spends the most money worldwide on healthcare. The U.S. spent $2.9 trillion in 2013. The U.S. spends an annual amount of $125 billion for cancer care specifically (Finnerty et al., 2016). It has been estimated that well-differentiated thyroid cancers have reached $1.6 billion in yearly costs, with initial costs of treatments accounting for 41% of this value. This includes workups, surgery, and radioactive iodine therapy (Biron et al., 2015). With the increase in thyroid malignancy rates, this cost is estimated to reach $3.55 billion by 2030 (Finnerty et al., 2016).

Medical-related expenses are a leading cause of bankruptcies in the United States. Zheng et al. (2001) reported that 43% of thyroid cancer survivors claimed financial difficulties, with 3% of these patients filing for bankruptcy. Only 0.6% of the U.S. population files for bankruptcy. This financial hardship is shared between patients with malignant thyroid disease and patients with benign disease. Performing thyroidectomies as an outpatient procedure has been shown to decrease costs. However, there is an ongoing debate if this decrease in hospital costs is at the expense of increasing the number of the patients' s out of pocket expenses (Zheng et al., 2021). Ramsey et al. suggests that the increase in bankruptcy for thyroid disease specifically could be attributed to the younger age at which individuals are diagnosed. Younger individuals tend to have a higher debt-to-income ratio and the potential to have less quality healthcare coverage (2013).

A study on Brazil's healthcare spending for radioiodine ablation showed that the difference between immediate release and a 2-day hospitalization could decrease the treatment cost by 60 to 86%, depending on the type of facility (public vs. private). Social and human factors can also be impacted by hospitalization (Willegaignon et al., 2006). Grigsby promotes outpatient procedures to decrease the cost of therapy and "psychological strain on patients and their families" (Grigsby, 2000).

The average cost per day in 2020 for an inpatient at a state or local governmental hospital was $2,372. The average daily cost for inpatients at non-profit hospitals was $2,738, and for for-profit hospitals it was $2,149 (Michas, 2022). Idaho specifically reports $1,926 for state and local hospitals, $3,169 for non-profits and $2,795 for for profit hospitals (Chart 1).

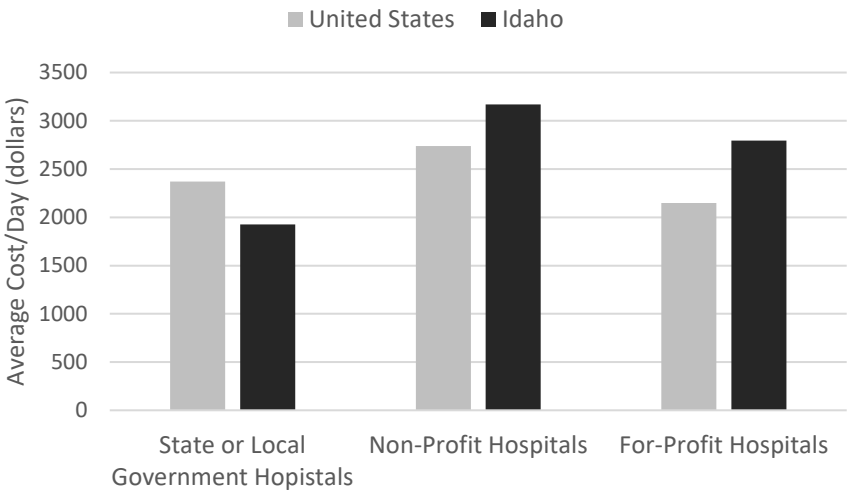

Chart 1. Comparison of the Average Daily Costs for Inpatient Visit between United States and Idaho in 2020.

Patients with a principal thyroid cancer diagnosis averaged 2.3 days in the hospital with $18,739 in average charges. Charges accrued from hospitalization are usually higher than the out-of-pocket cost to the patients. Hospitals have negotiated discounts, and insurance payments have covered part of the cost. However, as expected, more extended hospital stays tend to cause higher average charges (Healthcare Cost & Utilization Project, n.d.).

Payments for extended hospital stays incurred for patient isolation post radioactive treatment have received pushback from insurers when they are "to pay for extended isolation of patients who do not require medical intervention but only for the sake of reducing exposure to family members and the public (Pickering et al., 2012)". Performing the ablation in an outpatient setting is thought to increase the patient's quality of life and reduce healthcare costs (Kusakabe et al., 2012).

Whether a patient is hospitalized or sent home with instructions, both will affect the patient and require the allocation of expensive resources. The instructions for a patient after leaving the hospital could cause severe disruption of their home and working life. Hospitalizing these patients requires using a more significant number of resources and incurs more expense. Patients who must be hospitalized

following RAI treatment are kept in private isolation rooms. Patients cannot take personal items that would comfort them into the room. They are advised to only take non-important items with them in case contamination occurs, and they must throw the items out (De Klerk, 2000). A review of an article by Al Aamri et al. (2019) stated that a large number of their patients did not like the idea of staying in an isolation room for more than three days, leading to patients refusing treatment. To help in this predicament, they constructed windows following all radiation protection guidelines. Once the window was added to the isolation room, they noted increased agreement for treatment (Al Aamri et al., 2019). The patient has minimal contact with hospital staff, and there were limits on the amount of contact/exposure to family members. Isolation and lack of human contact for a period of time are stressful for patients who are dealing with a severe condition. Patients who are kept in isolation have also reported a greater level of anxiety and depression than those in more general areas of the hospital (Alzahrani, 2021).

As long as the radioactive individual can follow the discharge instructions to minimize radiation exposure and ultimately radiation dose to their family, caregivers, and the general public, it is suggested that not only will there be associated lower health care costs and exposure to hospital personnel, but that the patient and their families will also reap psychological benefits (Venencia et al., 2001). Increased depression and anxiety correlate with hospitalization. Other articles have, however, suggested that the opposite is true of hospitalization (Alzahrani, 2021).

Studies on the mental health of patients and their families from being hospitalized have mainly been associated with ICU costs. However, family members studied by Belayachi revealed that 55.6% of family members experienced anxiety and 41.1% depression following general health care hospitalization. This was associated with more female family members, shared room hospitalization, and the need for more information. Anxiety and depression were more frequently associated with short length of hospital stays and with rural residence of the family. Apparently "short length of visit does not

allow time for the family members to calm their emotional turmoil or to ease their fears, which leads to persistent doubt, fear and, therefore, anxiety. One important task for staff is to facilitate a families' abilities to stay close to their ill family member without a sense of being in the way." With long stays families believe that their loved ones are in the best place with optimal care, regular monitoring, nursing and continuous infusion and therapy. If stays are short, family members may experience fear that the patient is not fully recovered, and uncertainty and pessimism about the future. These are sources of depressive symptoms (Belayachi et al., 2013).

Chapter 3: Materials and Methods

Exposure rate measurements were taken from post-thyroidectomy patients after administering sodium iodide-131 (Na ^{131}I) for thyroid ablation. All the patients were given oral Na ^{131}I in pill form in the nuclear medicine department at a local Idaho hospital. The radiation safety officer (RSO) measured dose rate readings from each patient immediately following the ingestion of Na ^{131}I, 1 meter from the patient at the level of the patient's abdomen.

The health physics department recorded the measured dose rate using a 451P pressurized radiation detector. The administered dose and recorded dose rate at 1 meter were then recorded into an excel spreadsheet maintained by the health physics department. The recorded administered activity and measured dose rate for patients who received greater than 100 mCi of Na ^{131}I were obtained for eighteen patients (Appendix C). The measurements were taken in units of roentgen (R) per hour (h) at 1 meter. The measured exposure rate was converted to rem/h at 1 meter using the same assumptions used in Regulatory Guide 8.39 Revision 1; 1 roentgen equals 1 rem[2].

The administered activity for each patient was compared against the 33 mCi limit set by Regulatory Guide 8.39 Revision 1's first criteria: Release of Patients Based on the Administered Activity (Table 2)**.** Next, the recorded measured dose rate was compared to the second criterion: Release of Patients Based on the Measured Dose Rate which was less than or equivalent to 7 mrem/h at 1 meter for ^{131}I (Table 2).

The last criteria evaluated was Release of Patients Based on Patient-Specific Dose Calculations. The effective half-lives and uptake fractions for post thyroidectomy cancer patients were used for the extrathyroidal and thyroidal component given in Regulatory Guide 8.39, Revision 1 (Table 3). The maximum dose to the most likely exposed individual was calculated in rems (Equation 8). The results

[2] Problems with this assumption are explained in section 2.3.3

from these findings were evaluated to see if they were less than or equal to 0.5 rems determined by the Nuclear Regulatory Commission.

The expected release times for the patients were calculated using the information obtained for the second and third criteria. Activity (A) was set to 7 mrem/h at 1 meter for the data collected for the second criteria and 0.5 rem for the third criteria. The time (t) for the patients to reach these criteria was computed. The difference between the release time for each individual was then applied to a paired t-test to determine if there was a significant difference between the release times using the different criterion.

Chapter 4: Results and Discussion

4.1: Data Analysis

All patients were treated with a minimum of 100 mCi for their thyroid ablation and thus all failed the first release criteria based on administered activity (Table 4).

Table 4. Administered Activity and Pass/Fail for the Immediate Release of Patients Given $Na^{131}I$ Based on Criteria One: Administered Activity

Activity (mCi)	< 33 mCi Criteria
100	fail
130	fail
100	fail
150	fail
186	fail
100	fail
200	fail
200	fail
197	fail
207	fail
191.5	fail
100	fail
192	fail
201	fail
153	fail
201	fail
147	fail
100.4	fail

Using criteria 2, four patients passed for immediate release while the remaining fourteen failed (Table 5).

Table 5. Measured Dose Rate and Pass/Fail for the Immediate Release of Patients Given $Na^{131}I$ based on Criteria 2: Measured Dose

Criteria 2	
mrem/hr @ 1 meter	< 7 mrem/hr @ 1 meter
6.36	Pass
7.56	Fail
4.26	Pass
6.93	Pass
12.5	Fail
2.76	Pass
11.2	Fail
17.5	Fail
19.5	Fail
34.0	Fail
25.0	Fail
8.4	Fail
17.8	Fail
26.0	Fail
16.1	Fail
26.4	Fail
15.5	Fail
11.4	Fail

The dose to total decay was calculated using the patient-specific dose calculation (Equation 8) and these values were compared to the third criteria of a less than or equal to 0.5 rem calculated dose to the person most likely to receive the highest dose. Under this criterion, every patient passed for immediate release (Table 6).

Table 6. Patient-Specific Calculation and Pass/Fail for the Immediate Release of Patients given $Na^{131}I$ based on Criteria Three: Patient-Specific Calculations

Criteria 3	
D (∞) (rem)	< 0.5 rem
0.23	Pass
0.29	Pass
0.23	Pass
0.34	Pass
0.42	Pass
0.23	Pass
0.45	Pass
0.45	Pass
0.45	Pass
0.47	Pass
0.43	Pass
0.23	Pass
0.44	Pass
0.46	Pass
0.35	Pass
0.46	Pass
0.33	Pass
0.23	Pass

Next, the estimated immediate release time was calculated in days or partial days for criterion two and three and the difference was calculated. Any negative numbers in the second column of both tables correspond to the immediate release and were truncated to zero (Table 7) (Chart 2).

Table 7. Comparison of the difference in estimated release time for immediate release using criteria 2 and criteria 3.

Estimated Release Times (d) based on Measured Dose Rate (Criteria 2)	Estimated Release Times (d) based on Patient-Specific Calculations (Criteria 3)	Estimated Release Times (d) based on Patient-Specific Calculations and Truncating negative values to 0 (Criteria 3)	Difference
0.00	-0.38	0	0.00
0.04	-0.26	0	0.04
0.00	-0.38	0	0.00
0.00	-0.19	0	0.00
0.28	-0.08	0	0.28
0.00	-0.38	0	0.00
0.23	-0.05	0	0.23
0.44	-0.05	0	0.44
0.49	-0.05	0	0.49
0.76	-0.03	0	0.76
0.61	-0.07	0	0.61
0.09	-0.38	0	0.09
0.45	-0.07	0	0.45
0.63	-0.04	0	0.63
0.40	-0.18	0	0.40
0.64	-0.04	0	0.64
0.38	-0.20	0	0.38
0.24	-0.38	0	0.24

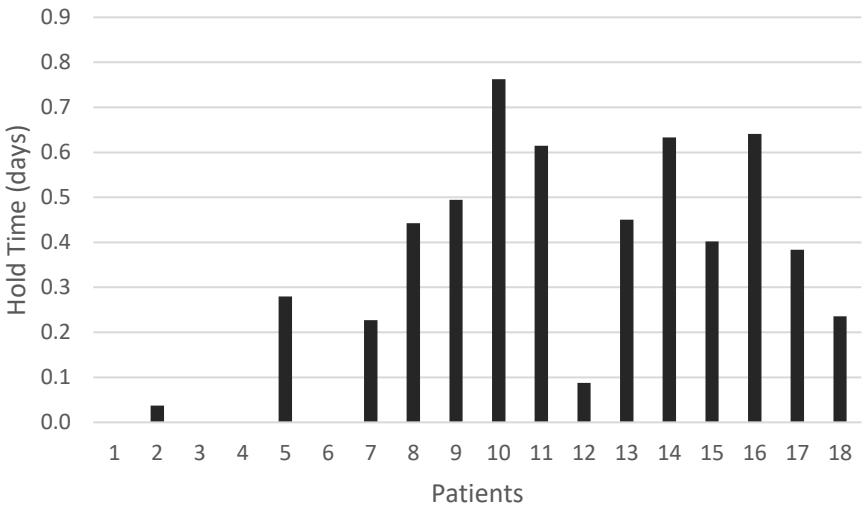

Chart 2: Difference in Estimated Release Times

A paired samples t-test was performed to compare the release times between the measured dose rate criteria (M =[0.3161], SD = [0.2563]) and the patient-specific calculation criteria (M = [0], SD = [0]); $t(17) = 5.2319$, $p = .00007$.

4.2: Discussion

The criteria for release of individuals containing unsealed byproduct material or implants containing byproduct material was evaluated on post-thyroidectomy patients receiving sodium iodine-131 for cancer treatment. A gross evaluation of the data showed that using criteria 1, administered activity, would result in the continued hospitalization of all patients. The second criterion, measured dose rate, allowed for the immediate release of four patients while requiring some type of isolation or hospitalization for the remaining fourteen patients. The final criteria, patient-specific calculation, allowed for the immediate release of all patients. To be in compliance with federal regulations only one of these criteria needed to be met for a patient to be released from a hospital.

The evidence shows that the two criteria do not result in the same patient release times and therefore can give conflicting information for the safe release times for individuals administered unsealed byproduct or implants containing byproduct material.

According to Regulatory Guide 8.39 Revision 1 (2020), the most important thing one can do to help protect the public, caregivers, and family members of an individual who has been given a radionuclide is communication. Current regulations allow the release of patients using only one criterion. Regulatory Guide 8.39 Revision 1 addresses conversations that should occur with the decision-making process of undergoing a medical test or treatment involving a radioisotope and following the radionuclide administration before the patient is released (U.S. NRC, 2020a).

Allowing the patient and their caregivers/families to know ahead of time what kind of practices should be followed to maintain ALARA allows the patients time to reflect and ask clarifying questions before they are released. This also helps the licensee evaluate the patient to determine what kind of environment they are going to and how capable they seem of following directions (U.S. NRC, 2020a).

Items to consider are where the patient will be staying once they are released, whether they can use a private bathroom, sleep in an isolated room, and who is at home with them (i.e., elderly, kids, pregnant people). It is also essential to know how the patient will travel home. Public transportation is generally discouraged, but it is essential to know how long the trip will take and who will be in the vehicle (U.S. NRC, 2020a).

Once a patient is released, they are no longer a concern for the licensee, so it is essential to give simple, easy-to-follow instructions, preferably in the patient's native language. It is also essential to convey how to minimize any contamination and what to do in the case of radioactive contamination (i.e., vomiting). Last would be to ensure the patient and their caregivers understand the timeframe required to follow the given instructions (U.S. NRC, 2020a).

4.2.1 Limitations

No two people are identical, nor do their bodies function in the same manner. Using pre-determined effective half-lives and uptake fractions from Regulatory Guide 8.39 Revision 1 is a limitation of this study. To truly understand the difference between the two criteria, it would be beneficial to know

each patient's individual effective half-life. This could be accomplished by taking multiple measured dose rate readings at differing time intervals so that an accurate, genuinely patient-specific effective half-life could be determined and applied to NRC's 3rd release criteria, patient-specific calculation.

Over 20 million nuclear medicine procedures are done annually in the United States with differing radioisotopes (*Radioisotopes in Medicine* 2023). This study, however, only looks at patients treated with Na ^{131}I for thyroid ablation. It would be valuable to compare these findings to other radionuclides used within the medical community. There were also insignificant studies found evaluating the compliance rate of patients and their caregivers in following the instructions given to minimize exposure after the administration of a radionuclide.

Chapter 5: Conclusion

Release times using criteria 2 and criteria 3 resulted in statistically significant difference in patient release time, and, therefore, the null hypothesis: The patient-specific dose calculation and the measured dose-rate criteria will result in the same release times for patients administered therapeutic doses of Iodine-131, is rejected. The t-value of 5.2319 supports the alternate hypothesis: The patient-specific dose calculation and the measured dose-rate criteria will result in different release times for patients administered therapeutic doses of Iodine-131.

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Appendix

Appendix A: Occupancy Factors to Consider for Patient-Specific Calculations

The selection of an occupancy factor for patient-specific calculations will depend on whether the physical or effective half-life of the radionuclide is used and whether instructions are given to the patient before his or her release. Patient-specific calculations may use the following occupancy factors, E, at
1 meter:

a. E = 0.75 when a physical half-life, an effective half-life, or a specific time period under consideration (e.g., bladder-holding time) is less than or equal to 1 day.

b. E = 0.25 when an effective half-life is greater than 1 day if the patient has been given the following instructions:

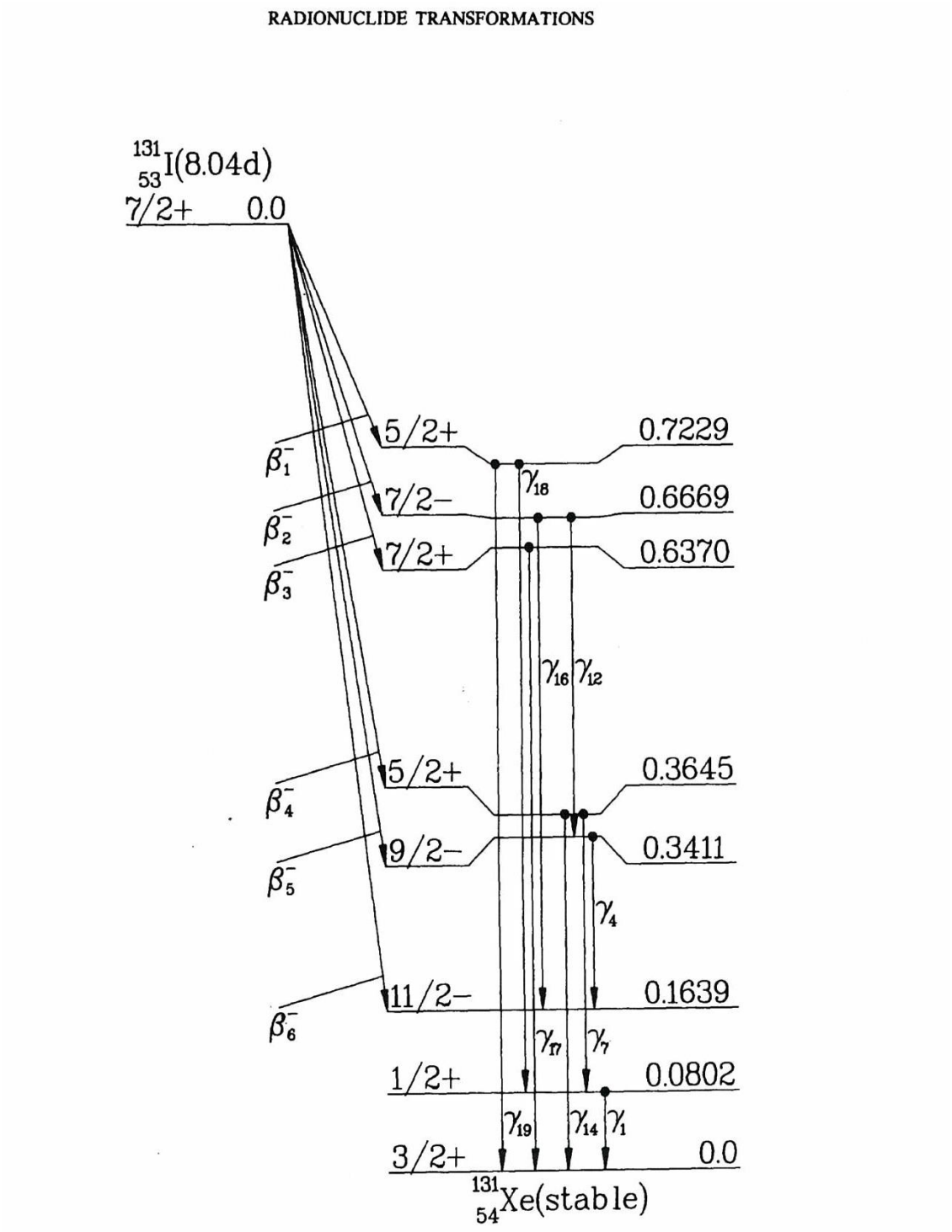
(1) Maintain a prudent distance from others for at least the first 2 days.
(2) Sleep alone in a room for at least the first night.
(3) Do not travel by airplane or public transportation for at least the first day.
(4) Do not travel on a prolonged automobile trip with others for at least the first 2 days.
(5) Have sole use of a bathroom for at least the first 2 days.
(6) Drink plenty of fluids for at least the first 2 days.

c. E = 0.125 when an effective half-life is greater than 1 day if the patient has been given the following instructions:

(1) Follow the instructions for E = 0.25 above.
(2) Live alone for at least the first 2 days.
(3) Have few visits by family or friends for at least the first 2 days.

d. In a two-component model (e.g., uptake of iodine (I)-131 using thyroidal and extrathyroidal components), if the effective half-life associated with one component is less than or equal to
1 day but is greater than 1 day for the other component, it is more justifiable to use the occupancy factor associated with the dominant component for both components.

Appendix B: Iodine-131 Decay Scheme from ICRP 38 (1983)



53-IODINE-131

HALFLIFE = 8.04 DAYS 21-JAN-76
DECAY MODE(S): β^-

RADIATION	y(i) $(Bq-s)^{-1}$	E(i) (MeV)	y(i)×E(i)
β^- 1	2.13E-02	6.935E-02*	1.48E-03
β^- 2	6.20E-03	8.693E-02*	5.39E-04
β^- 3	7.36E-02	9.660E-02*	7.11E-03
β^- 4	8.94E-01	1.915E-01*	1.71E-01
β^- 6	4.20E-03	2.832E-01*	1.19E-03
γ 1	2.62E-02	8.018E-02	2.10E-03
ce-K, γ 1	3.63E-02	4.562E-02	1.66E-03
ce-L_1, γ 1	4.30E-03	7.473E-02	3.21E-04
γ 4	2.65E-03	1.772E-01	4.70E-04
γ 7	6.06E-02	2.843E-01	1.72E-02
ce-K, γ 7	2.48E-03	2.497E-01	6.20E-04
γ 12	2.51E-03	3.258E-01	8.18E-04
γ 14	8.12E-01	3.645E-01	2.96E-01
ce-K, γ 14	1.55E-02	3.299E-01	5.10E-03
ce-L_1, γ 14	1.71E-03	3.590E-01	6.13E-04
γ 16	3.61E-03	5.030E-01	1.82E-03
γ 17	7.27E-02	6.370E-01	4.63E-02
γ 18	2.20E-03	6.427E-01	1.41E-03
γ 19	1.80E-02	7.229E-01	1.30E-02
$K\alpha_1$ X-ray	2.59E-02	2.978E-02	7.72E-04
$K\alpha_2$ X-ray	1.40E-02	2.946E-02	4.12E-04

LISTED X, γ AND $\gamma\pm$ RADIATIONS	3.80E-01
OMITTED X, γ AND $\gamma\pm$ RADIATIONS**	1.09E-03
LISTED β, ce AND Auger RADIATIONS	1.90E-01
OMITTED β, ce AND Auger RADIATIONS**	1.86E-03
LISTED RADIATIONS	5.70E-01
OMITTED RADIATIONS**	2.95E-03

* AVERAGE ENERGY (MeV)
** EACH OMITTED TRANSITION CONTRIBUTES <0.100% TO $\Sigma y(i) \times E(i)$ IN ITS CATEGORY.
XENON-131M DAUGHTER, YIELD 1.11E-02, IS RADIOACTIVE.
XENON-131 DAUGHTER, YIELD 9.889E-01, IS STABLE.

Appendix C: Collected Data

Patient	Activity (mCi)	mR/hr @ 1 meter
1	100	6.36
2	130	7.56
3	100	4.26
4	150	6.93
5	186	12.50
6	100	2.76
7	200	11.20
8	200	17.50
9	197	19.50
10	207	34.00
11	191.5	25.00
12	100	8.40
13	192	17.80
14	201	26.00
15	153	16.10
16	201	26.40
17	147	15.50
18	100.4	11.40