As a standard practice, the use of radioactive materials has been widely used when treating many diseases. In recent years advances in biotechnology and labeling techniques have broadened the application of these materials. Candidates selected for radiopharmaceutical therapy may be treated on an outpatient basis or hospitalized following administration to ensure the exposure to their family members, associates at work, medical staff and the
general public are ALARA. To maintain compliance with 10 CFR 35.75(a), licensees may release patients immediately following the administration of a radiopharmaceutical if the administered activity is no greater than the amount listed in NUREG 1556, Appendix U, Table U.1 or if it can be shown that members of the general public will not receive a dose greater than 5 mSv during a calendar year. If either of these conditions can’t be met licensees are required to hospitalize patients until the second condition can be met. In cases where holding an individual in isolation may be detrimental to the patient it is advantageous, for the sake of the patient’s health, to conduct specific patient calculations to release the individual at the earliest opportunity. However, the methods provided by the NRC for conducting patient-specific calculations do not adequately model the patient in terms of geometry and biokinetics. Therefore, a method of demonstrating that a patient is eligible for release without holding the individual in isolation beyond a reasonable time period was developed. The method includes a model for computing patient specific calculations and determining the time requirements for patient specific instructions to be given to the patient following release.
Release of Patients Following the Administration of Radiopharmaceuticals

by
Eric J. Munger

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APPROVED:

______________________________

Major Professor, representing Radiation Health Physics

______________________________

Head of the Department of Nuclear Engineering and Radiation Health Physics

______________________________

Dean of the Graduate School

I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

______________________________

Eric J. Munger, Author
ACKNOWLEDGMENTS

With humility and gratitude I acknowledge my indebtedness:

To my wife Maureen, for her patients and understanding during our years together.

To the patients who agreed to participate in the protocol from which the data for this research was gathered.

To all my mentors and advisors from whom I have learned the principles of Radiological Health Physics.
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CHAPTER 1

INTRODUCTION

Since 1950 it has become standard practice to use radioiodine ($^{131}$I) when treating thyroid cancer patients to ablate normal thyroid remnants after total thyroidectomy or to treat patients with persistent or recurrent disease (Herv’e, 2008). Over the years procedures using radioiodine have come to represent about 90% of all therapies in Nuclear Medicine (ICRP-94, 2004). Candidates selected for radioiodine therapy may be treated on an outpatient basis or hospitalized following administration to minimize the dose to their family members, associates at work, medical staff and the general public.

To determining the need for hospitalization and maintain compliance licensees are required to comply with the US Nuclear Regulatory Commission polices set forth in 10 CFR 35.75. In addition, licensees working in agreement states must check with their state regulators for additional restriction concerning applicable release criteria.

As stated in 10 CFR 35.75(a), licensees may release patients immediately following the administration of a radiopharmaceutical if the administered activity is no greater than the amount listed in NUREG 1556, Appendix U, Table U.1. For administrations involving $^{131}$I the administered activity can be no greater than 33 mCi (1.2 GBq) (CFR 35.75). The activity based default values
were obtained by applying an equation from NCRP Report No. 37 to calculate the dose to persons from the released patient. (NCRP – 37, 1970) Using this equation, with the $^{131}$I physical half-life (8.04 days), an occupancy factor of 0.25 at 1 m, and assuming an unshielded point source, an administered activity of 33 mCi (1.2 GBq) $\text{Na}^{131}\text{I}$ will result in an dose of 500 mrem to the person maximally exposed to the patient following release. (NUREG 1556)

When a patient’s administered activity is greater than the activity based default value listed in NUREG 1556 for the specific radionuclide, the patient must be hospitalized and maintained in isolation. The must stay there until they have met the measured dose rate based default release requirement before they can be released. For example, using this method a licensee may release an isolated patient following treatment using $^{131}$I when the measured dose rate at 1 meter is no greater than 7 mrem/h (0.07 mSv/h). Additionally, 10 CFR 35.75(b) requires that released patients be given instructions, including written instructions, on how to maintain doses to other individuals ALARA following release if the measured dose rate at the time of release exceeds that amount listed in NUREG 1556, Appendix U, Table U.1, Column 2. For $^{131}$I this value is 2 mrem/h (0.02 mSv/h) (NUREG 1556).

When patients are hospitalized until they reach release limit they are often isolated for extended periods of time. This isolation is often at increased cost.
and potential detriment to the patient. Additionally, since the instructions
given to the patient following release are often standardized, patients are
typically given all encompassing instructions that are not easy to follow. This
could result in a patient ignoring the given instructions due to an assumption
that the given instruction are of minimal concern. Conversely, the patient may
further isolate themselves from family and friends due to an unrealistic fear
that they may present a danger to others.

An alternative to the method described above is to release patients based on
patient-specific calculations that take into account many specific patient
parameters. To do so in accordance with 10 CFR 35.75(a), licensees must first
calculate the maximum expected dose to an individual exposed to the patient
following release. If this dose is not likely to exceed 500mrem (5 mSv) the
patient may be given written instruction for guidance and released. Using
patient-specific calculations licensees may choose to treat patients on an
outpatient bases even if they have been administered greater than 33 mCi (1.2
GBq) $^{131}$I. Licensees may release patients by taking into account patient-specific
parameters provided a record of the basis for the release maintained for three
years as required by 10 CFR 35.75(c).

The many recent advances in biotechnology and radiolabeling techniques have
broadened the application of radioiodine and other radiolabeled
pharmaceuticals. As a result the distribution and elimination of these radiopharmaceuticals may not be accurately described by the model set forth by the NRC. The goal of this report is to review the methods and applicable regulations set forth by the NRC for establishing a patient’s eligibility for release. Additionally an alternative and dynamic method for calculating the maximum likely dose to an individual exposed to the patient following release is proposed. This method is to be used when patients are treated using a radiopharmaceutical that are not adequately modeled using the method given in the NRS’s Regulatory Guide 1556. In doing so, alternate release methods applicable under specific circumstances will be available for use. By choosing the appropriate method patients can be released as soon as reasonable achievable while maintaining the dose to others as low as reasonably achievable (ALARA).
On January 29, 1997, the NRC published a final rule in the Federal Register on the “Criteria for the Release of Individuals Administered Radioactive Material”, 62 FR 4120 (RIS, 2008). This rule amended the criteria for the release of patient administered radioactive materials in Title 10 of the Code of Federal Regulations (10 CFR), Section 35.75, “Release of Individuals Containing Unsealed Byproduct Material or Implants Containing Byproduct Material”. This rule replaced the activity-based or dose-rate-based release criteria with one based on limiting the total effective dose equivalent (TEDE) to <500 mrem (<5 mSv) for the individual maximally exposed as a result of their time with a patient released after therapeutic administration of radionuclide (NRC, 2008). If an individual’s dose could exceed 100 mrem (1 mSv), (the public dose limit is set forth by 10 CFR 20 in 1991), the patient must be given instructions on how to maintain doses to others ALARA. A regulatory analysis of this criteria concluded that this approach is safe, results in shorter hospital stays, reduces health care costs, and has personal and psychological benefits for the patients and their family members (Schneider, 1996). Additionally, a separate study supported the NRC’s position that the use of this criteria to release patients
would not lead to a member of the general public exceeding the intended dose limits (Grigsby PW, 2000).

The US Nuclear Regulatory Commission, in Regulatory Guide 1556, gives three options for the release of a patient following the administration of radiopharmaceuticals (NUREG-1556, Vol. 9). The release of a patient in accordance with the current regulatory requirement may be based on one of the following:

Option #1) For radiopharmaceuticals administered with activities less than the default criteria for the radionuclide as listed in NUREG 1556, (Appendix U, Table U.2, Column 2) patients may be immediately released and no extensive consideration of the public dose would be required. For $^{131}$I the default is 33 mCi (1.2 GBq). 10 CFR 35.75(b) requires that released patients be given written instructions on how to maintain doses to other individuals ALARA following release if the measured dose rate at the time of release exceeds the value given in NUREG 1556, Appendix U, Table U.1, Column 2.

The activity based default release limits are obtained by assuming that the patient is an unshielded point source and that the only way the administered activity leaves the body is through physical decay. No consideration is made for
biological clearance. Using these assumptions the dose to a member of the general public is calculated using:

\[ D = \frac{34.6 \cdot A \cdot T_{1/2} \cdot \Gamma \cdot E}{100^2} \]

Where:

- \( D \) = Dose to a member of the general public [mrem]
- \( 34.6 \) = conversion factor of 24 h/d times total integration of decay (1.44)
- \( A \) = Administered activity [mCi]
- \( T_{1/2} \) = Physical half-life [h]
- \( \Gamma \) = Exposure rate constant for the specific radioisotope (mrem/h*mCi)
- \( E \) = Occupancy factor at one meter

This calculation is the basis of the activity based default release criterion. For \(^{131}\text{I}\) this calculation results in an activity of 33 mCi (1.2 GBq). This is the worst-case scenario for patient geometry and nuclide elimination because the patient is modeled as an unshielded point source and only physical half-life is accounted for. Additionally, the occupancy factor (E) (the fraction of the day that a member of the public spends one meter away from the patient) is included in the calculation. The NRC assumed the conservative value of 6 hours per day for the occupancy factor. These strict and conservative assumptions are mainly to assure that the dose limit requirements will be met under all
circumstances. Therefore, no further documentation of the release is required when releasing patients that have been given doses below these activity based default release limits. Since the dose to the public depends on the nuclide administered, NUREG 1556 provides nuclide specific activity based default release values for a range of nuclides. If the nuclide under consideration is not listed in NUREG 1556, Appendix U, Table U.2, Column 2 licensees may use the above calculation to establish a nuclide specific activity based default release value.

Option #2) For administered activities greater than the nuclide specific activity based default release value licensees may choose to hospitalize and isolate the patient. Patients must remain in isolation until the measured dose rate at 1 meter from the surface of the patient is no greater than the default release value listed in NUREG 1556, Appendix U, Table U.1, Column 2. For $^{131}I$ the release value is 7 mrem/h (18.1 x 10^-7 C/kg/h). The dose rate based default release criteria for other radionuclides are listed in NUREG 1556, Appendix U, Table U.1, Column 2. When using the default dose rate based limit as the basis for the release of a patient 10 CFR 35.75(c) requires a record be maintained because the release is based on a measurement that takes patient body shielding by tissue into account. Additionally, 10 CFR 35.75(b) requires that released patients be given written instructions on how to maintain doses to
other individuals ALARA. If the measured dose rate at the time of release does not exceed the value listed in NUREG 1556, Appendix U, Table U.2, Column 2 the instruction are not required. For $^{131}$I this value is 2 mrem/h (0.02 mSv/h).

The dose rate base default release values listed in NUREG 1556, Appendix U, Table U.1, Column 2 are calculated in a similar fashion.

$$D = 34.6T_{1/2}ER$$

Where:

- $34.6 = \text{conversion factor of } 24 \text{ h/d times total integration of decay (1.44)}$
- $T_{1/2} = \text{Physical half-life (h)}$
- $E = \text{Occupancy factor at one meter}$
- $R = \text{Dose rate at on meter (mR/h)}$

Here the measured dose rate at one meter is substituted for the exposure rate constant and the activity. This implicitly accounts for patient geometry and patient shielding. It is still conservative because only physical decay is considered as a method of elimination.

Option # 3) Alternatively, for administered activities greater than the nuclide specific activity based default release value listed in NUREG 1556, licensees may choose to perform patient-specific calculations and demonstrate that the
likely dose to the maximally exposed individual will be less than 500 mrem (5 mSv) TEDE. If this can be demonstrated the calculations may be used as a basis for the immediate release of the patient. Patients may be released based on patient-specific calculations regardless of the administered activity or dose rate at one meter. 10 CFR 35.75(c) requires a record be maintained if the release is based on calculations that take into account retained activity, an occupancy factor less than 0.25 at 1 meter, effective half-life, or shielding by tissue. When using this method 10 CFR 35.75(b) requires that released patients be given written instructions on how to maintain doses to other individuals ALARA when the measured dose rate at the time of release exceed the value listed in NUREG 1556, Appendix U, Table U.2, Column 2.

The first two options above are based on the conservative assumption that radiopharmaceutical elimination occurs by physical decay. The reliance on the activity and dose rate based default release values as the soul release criteria, while conservative, will often require that patients be isolated for unnecessarily extended periods of time. The isolation period can be significantly reduced or eliminated all together through the use of the third option given in the Regulatory Guide.

The method provided by the NRC for making patient specific calculations that can be used to permit release of patients that have been administered levels of
activity that are greater than the default activity based release values is based on a 2-component, extrathyroidal and intrathyroidal model of pharmacokinetics and allows licensees to take into account occupancy factors, effective half-lives, and uptake fractions. (William K. Tuttle, 2000) The NRC provides a formula that can be used to calculate the dose to the maximally exposed individual to the released patient. This equation is equation B-5 in Regulatory Guide 1556:

\[
D(x) = \frac{34.6 \Gamma Q_0}{(100\text{cm})^2} (E_1 T_P (0.8)(1 - e^{-\frac{\Gamma}{T_P}}) + e^{-\frac{0.693(0.33)}{T_P}} E_2 F_1 T_{1\text{eff}} + e^{-\frac{0.693(0.33)}{T_P}} E_2 F_2 T_{2\text{eff}})
\]

where:

- \(D(\infty)\) = dose to any person exposed to the patient (rem);
- \(\Gamma\) = the exposure rate constant for the radioisotope (R/mCi-hr at 1 m);
- \(Q_0\) = the administered activity (mCi);
- \(E_1\) and \(E_2\) = the occupancy factors for the extrathyroidal and intrathyroidal components, respectively (see Table 1 below);
- \(F_1\) and \(F_2\) = the uptake fractions for the extrathyroidal and intrathyroidal components, respectively (see Table 1 below);
- \(T_P\) = physical half-life of the radioisotope;
• \(T_{1\text{eff}}\) and \(T_{2\text{eff}}\) = effective half-lives (in days) for the extrathyroidal and intrathyroidal components, respectively.

TABLE 1 - UPTAKE FRACTIONS AND EFFECTIVE HALF-LIVES FOR IODINE-131

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>Extrathyroidal component</th>
<th>Thyroidal component</th>
</tr>
</thead>
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<td></td>
<td>Uptake fraction (F_1)</td>
<td>Effective half-life (T_{1\text{eff}}) (day)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>0.20</td>
<td>0.32</td>
</tr>
<tr>
<td>Post-thyroidectomy thyroid cancer</td>
<td>0.95</td>
<td>0.32</td>
</tr>
</tbody>
</table>

When using this equation a licensee may substitute a patient’s specific uptake fractions and effective half-lives for the values given in NUREG 1556, listed in Table 1 when calculating \(D(\infty)\). However, a record must be maintained demonstrating the method used to attain the values that are substituted. The basis for the values provided by the NRC in NUREG 1556 Table 1 is explained in the Regulatory Guide.
The values for the occupancy factor (E), the fraction of time that any other person is considered to be located within 1 meter of the patient, are provided within Regulatory Guide 1556:

1) Use $E = 0.75$ when a physical half-life, an effective half-life, or a specific time period under consideration (e.g., bladder holding time) is no greater than one day.

2) Use $E = 0.25$ when an effective half-life is greater than one day if the patient has been given instructions, such as the following:
   a) Maintain a prudent distance from others for at least the first 2 days;
   b) Sleep alone in a room for at least the first night;
   c) Do not travel by airplane or mass transportation for at least the first day;
   d) No travel on a prolonged auto trip with others for at least the first 2 days;
   e) Have sole use of a bathroom for at least the first 2 days; and
   f) Drink plenty of fluids for at least the first 2 days.

3) Use $E = 0.125$ when an effective half-life is greater than one day if the patient has been given instructions such as the following:
   a) The instructions 1–6 for $E = 0.25$ above;
   b) Live alone for at least the first two days; and
   c) Have few visits by family or friends for at least the first two days.
The exposure rate constant for $^{131}$I is given in the Regulatory Guide 1556.

This value is 0.22 mrem/mCi h ($5.95 \times 10^{-5}$ mSv/MBq) at one meter.

To illustrate the use of the patient-specific calculation method provided by the NRC assumes that a patient is administered 100 mCi (3700 MBq) Na$^{131}$I for post-thyroidectomy cancer treatment. To calculate the dose to an individual maximally exposed to the patient, $D(\infty)$ we can use the values from the Regulatory Guide for uptake fraction and effective half-life. If the result of this calculation is less than 500 mrem (5 mSv), the patient may be released (based on this patient specific calculation) regardless of the dose rate measured at one meter from the surface of the patient at the time of release. However, if the measured dose rate at one meter from the surface of the patient is greater than 2 mrem/h (0.02 mSv/h) the patient must be given written instruction on how to maintain the dose to others ALARA. In this scenario the calculation would be:

$$D(\infty) = \frac{34.6(2.2)100}{(100cm)^2} (0.75(8.04)0.8(1 - e^{-0.693(0.33)}}{8.04}) +$$

$$+ e^{-0.693(0.33)} 8.04 \cdot 0.25(0.95)0.32 + e^{-0.693(0.33)} 8.04 \cdot 0.25(0.05)7.3$$

$$D(\infty) = 226.7mrem \ (2.267 \ mSv)$$

From this result it can be demonstrated that patients who undergo post-thyroidectomy cancer therapy may be treated on an outpatient basis, i.e. not
held at the hospital under confinement, if the administered activity is less than 220.5 mCi $^{131}$I (8158 MBq) and appropriate documentation of patient-specific instructions and calculations are maintained.

$$\frac{2.267 mSv}{5 mSv} = \frac{100 mCi}{Q_{\text{max}}} \rightarrow Q_{\text{max}} = 220.5 mCi$$

Using a similar calculation it can be demonstrated that patients undergoing therapy for hyperthyroidism can be treated on an outpatient basis provided the activity administered is less than 56 mCi $^{131}$I (2072 MBq).

However, it should be understood that because $^{131}$I is primarily excreted in the urine, patients with bladder control problems should be hospitalized to prevent excessive contamination of the home environment. Additionally, patients that require close care should also be hospitalized where trained and monitored staff is available. Therefore, physicists should understand each patient's unique living environment and medical needs when considering the release of a patient regardless of the method chosen as the basis of patient release.

Additionally, licensees should be aware that the regulator requirements for patient release are set forth in 10CFR35.75 as written does not specify how often a licensee may release a patient for whom dose to the public has been calculated to be less than 500 mrem (5 mSv). However, in subsequent
notifications the NRC made it clear that the intent is that the limit is an
annual limit based on the calendar year.

CHAPTER 3

PATIENT SPECIFIC METHOD USING DYNAMIC DATA FOR CALCULATING
EXPECTED RADIATION DOSES TO THE GENERAL PUBLIC

Recent advances in biotechnology and labeling techniques have broadened the
application of radioiodine and other radiolabeled pharmaceuticals.
Additionally, the use of radiopharmaceuticals labeled with $^{131}$I that target
nonthyroid tissue will often require that thyroid uptake be blocked prior to
treatment. Using the method presented by the NRC the effective dose to a
caregiver is calculated by considering the $^{131}$I to be concentrated in a point
source in a patient, without shielding. As a result the distribution and
elimination of administered activity may not be accurately described using a 2-
component pharmacokinetic model as provided by the NRC. The use of a line-
source approximation instead of the point-source model for estimating the dose
to an individual exposed to a patient who has received radioactivity has been
proposed (Siegel JA, Marcus CS, 2002). In addition, computational Monte Carlo
transport techniques using anthropomorphic mathematic phantoms have been
developed for dose calculation (Sparks RB, 1998)( Sherbini SS, 2005). However,
these approaches often do not take into consideration the attenuation and scattering of the radiation by the human body. Therefore, it is necessary to develop a method of conducting patient-specific calculations that model mono-exponential elimination. It is possible to develop a method for rapidly conducting patient-specific dose calculations that can be used to justify the release of patients from historical data. Statistical group data on whole-body retention can be obtained from prior measurements made during patient isolation and release. This methodology of calculating the dose to the public can account for the biokinetics of the specific radiopharmaceutical, shielding of the specific patient and the manner in which the patient is expected to interact with others following release. (Siegel, 2004)

If the patient can't be released under the activity based default release criteria but a patient-specific calculation shows that the estimated dose to the public does not exceed 500 mrem (5 mSv) then the patient may be released. Written documentation of the release must be maintained for three years.

The point source geometry and the assumed absents of biological elimination are unrealistic assumptions in the real world. Licensees are permitted to perform their own calculations that better account for these factors and for different occupancy factors if they can be justified. Some of the factors that may be taken into consideration are:
• Non-point source geometry
• Tissue shielding
• Biological clearance
• Occupancy factors other than 0.25

If Licensees perform their own calculation then they must retain written documentation of the calculation of each patient released using the calculation method for three years.

The most practical method of calculating the dose to the public is to use a measured dose rate based method that implicitly accounts for non-point source patient geometry and tissue shielding as well as takes into account biological elimination.

The radioactivity clearance data gathered from a group of patients may be used as the bases for a release calculation that includes biological elimination.

\[
D(x) = \frac{t_X}{24} \int_{t_{\text{release}}}^{\infty} R(t) dt
\]

Where:

• \( R(t) \) is an equation that describes the dose rate (mR/h) at one meter
• \( t_X / 24 \) = Occupancy factor. A occupancy factor of 0.25 represents 6 h/d
- $t_x$ = Hours per day that the caregiver is expected to spend with the patient.

To develop $R(t)$ the dose rate at one meter is measured at various times following an administration for a group of patients. The data is then fit to a single exponential function and can be used to estimate the effective half-life (Figure 1).

![Dose Rate vs Time](image)

**FIGURE 1 - DOSE RATE VS. TIME**

This will implicitly take into account patient shielding, source geometry, as well as variation in the exposure rate constant for the nuclide used. The general public dose is the area under the dose rate vs. time curve multiplied by the occupancy factor. The occupancy factor can be chosen based on the guidelines provided in the Regulatory Guide 1556. For many radiopharmaceuticals the
biological elimination is described by a single exponential function of time. So an effective half-life can be calculated and substituted for the physical half-life in the previous equations.

This method of calculating the dose to the public considers only the gamma rays emitted from the patient. However, radiopharmaceuticals that are excreted in the urine and other body fluids may contaminate the home environment or surfaces that other members of the public use. Consequently, family members may ingest this contamination and receive an internal dose. This component must be added to the external dose to get the total effective dose.

The regulatory guide provides a mechanism for including this component.

\[ D_I = 10^{-5} A_{\text{release}} C \]

Where:

- \( A_{\text{release}} \) is the retained activity at release (mCi)
- \( C \) is the Dose Conversion Factor (53 rem/mCi for \(^{131}\text{I}\))

For \(^{131}\text{I}\) the ingestion factor, assumed to be 1 part in 100,000, is multiplied by the retained activity at the time of release and by a dose conversion coefficient of 53 mrem/mCi and to obtain the internal dose component. If the internal
component exceeds 10% of the external dose then it must be included in the total.
CHAPTER 4

INITIATION OF PATIENT SPECIFIC METHOD USING DYNAMIC DATA FOR CALCULATING EXPECTED RADIATION DOSES TO OTHERS FROM PATIENTS TREATED FOR THYROID CANCER USING NA-131I USING HISTORICAL DATA

Treatment using radiopharmaceuticals depends on the successful delivery of a high radiation dose to target tissue (Herv‘e, 2008). The radiation doses delivered to normal and neoplastic tissue are frequently estimated during clinical diagnostic studies (Herv‘e, 2008). These estimates are used to determine the optimal activity to be administered (Herv‘e, 2008). Significant side effects can result from excessive radiation doses delivered to nontarget tissues. In thyroid treatments these side effects can include the induction of nausea and vomiting, sialadenitis and xerostomia, loss of taste, bone marrow insufficiency, and late occurrence of extrathyroidal cancer and leukemia (Herv‘e, 2008). Therefore, the radiation dose delivered to target tissues should be optimized while minimizing the radiation dose delivered to nontarget tissues. Furthermore, patients should not be isolated for unnecessarily long times because the physical and physiological effects of isolation may be detrimental to the patients overall health.
To use the method Licensees must first establish a reliable effective half-life for the radiopharmaceutical that’s being administered. The diagnostic procedures used to estimate the radiation dose to the blood and estimate the optimal activity to be administered often include the calculation of an effective half-life for the radionuclide. This effective half-life, if used to calculate the dose to individuals exposed to the patient following release, will not be accurate. This is because the uptake and retention of many radiopharmaceuticals in therapy patients is dependent on several factors that can significantly alter each patient’s effective half-life. For example, induced hypothyroidism following thyroid hormone withdrawal and rhTSH injections changes the radioiodine renal clearance. This leads to a biodistribution of radioiodine that is different from that seen during diagnosis where much lower activity is used. Additionally, individual patient radioiodine uptake may fluctuate depending on the patient’s morphology and metastases.

To establish an effective half-life when initiating the method Licensees must first identify a sufficiently large group of similar patients that can be used to acquire historical data using a retrospective analysis of patient data. In thyroid cancer treatments the intensity of stimulation with thyroid-stimulating hormone (TSH) and uptake of iodine in thyroid cells is directly related to the amount of excess iodine and thyroid cell differentiation (Schlumberger M,
In low-risk patients, all normal and neoplastic thyroid tissue is ablated under hypothyroid conditions with radioiodine after thyroid hormone withdrawal or under euthyroid conditions after injections of recombinant human TSH (rhTSH) (Herv‘e, 2008).

Because the stimulation method (thyroid hormone withdrawal or rhTSH) can affect the whole-body retention of radioiodine, patients can be divided according to the stimulation method used. Recumbent human thyroid stimulating hormone (rhTSH) is a laboratory-made drug that is almost identical to the thyroid stimulating hormone (TSH) normally made by the pituitary gland. The difference in whole-body retention time is mainly due to a delayed urinary excretion of $^{131}$I during hypothyroidism. Patients treated using rhTSH avoid hypothyroidism and rhTSH reduces by about one third the amount of radiation to which the body is exposed (Herv‘e, 2008). Previous dosimetry studies confirm reports on body retention (Hanscheid H, 2006) and on estimated doses to the blood and bone marrow. These studies also indicate that this class of patients the whole-body residence time is shorter for those treated with rhTSH than for those who undergo withdrawal, in whom residence time was longer than the 11.1 hours reported in the ICRP 53 report (ICRP 53, 1987). In a study by Hanscheid et al., patients without metastasis were randomized after thyroidectomy to either the withdrawal group or the rhTSH group, and
residence time in the whole body and in thyroid remnants and absorbed dose to the blood were calculated. Hanscheid et al. concluded that the mean whole-body residence time was shorter in rhTSH patients (17.3 ± 3.9 h and 15.2 ± 3.1 h, respectively) than in withdrawal patients (24.1 ± 7.8 h and 23.0 ± 7.7 h, respectively) (Hanscheid H, 2006).

Historical data can be used to establish an effective half-life that can be used to employ this method for releasing patients following treatment for cancer using Na\(^{131}\)I. For this study data was collected between January 2008 and November 2010 from 60 thyroid cancer patients. Following surgery all patients were treated, after injections of rhTSH with radiiodine at the National Institutes of Health, Bethesda MD. This is called ablation therapy. Initial, release and follow up dose rate measurements were performed as described below. Patients were further separated by administered activity into five groups.

This ablation therapy study was conducted to determine if lithium can enhance the treatment effect of low-dose of \(^{131}\)I following surgery in patients with thyroid cancer. In ablation therapy \(^{131}\)I is used to destroy any thyroid tissue remaining after surgery.

Patients recently diagnosed with papillary or follicular thyroid cancer who had their thyroid gland removed and whose cancer had not spread beyond the
thyroid where eligible for this study. Candidates were screened with a medical history, physical examination, blood tests, thyroid ultrasound and chest x-ray.

Participants were randomly assigned to receive lithium capsules or placebo (look-alike capsules with no active ingredient). They followed a low-iodine diet for two weeks before starting treatment and were then admitted to the NIH Clinical Center for study and treatment for 11 days, during which they remained on the low-iodine diet. Blood samples were collected daily to analyze thyroid hormones, kidney and liver function, lithium concentrations and other tests.

On day two of hospitalization, patients had a whole-body scan to determine how much functional thyroid remained after surgery and to rule out spread of the cancer. For the two days before the scan, they received an injection of rhTSH. A capsule containing a small amount of $^{131}$I was administered orally, which was used for imaging the thyroid. The thyroid was imaged after 4 hours and after 24 hours. rhTSH injections were repeated for two more days to prepare for therapy with $^{131}$I. On about day seven of hospitalization, patients took capsules containing the prescribed dose of Na$^{131}$I. For each remaining day of hospitalization patients had additional blood tests to measure the level of radioactivity and scans to evaluate the effectiveness of lithium or placebo and
Na-131I for ablation. On the last day in the hospital, patients stopped taking lithium or placebo and had a repeat scan to make sure that the cancer has not spread outside the thyroid gland.

Written information concerning 131I therapy was given to each patient. When appropriate, instruction on how best to maintain the dose to others ALARA was issued upon release. Group 1 consisted of four patients prescribed 300 mCi (1.11 GBq) Na-131I, administered activity was 300 mCi ± 17.4 mCi (1.11 GBq ± 645 MBq); group 1 patients were hospitalized for 4–5 days in isolation. Group 2 patients consisted of three patients prescribed 200 mCi (7,400 MBq) Na-131I, administered activity was 200 mCi ± 16.2 mCi (7,400 ± 600 MBq); group 2 patients were hospitalized for 3–4 days in isolation rooms. Group 3 patients consisted of 30 patients prescribed 150 mCi (5,550 MBq) Na-131I, administered activity was 150 mCi ± 10.9 mCi (5,550 ± 404 MBq); group 3 patients were hospitalized for 2–3 days in isolation rooms. Group 4 patients consisted of 17 patients prescribed 100 mCi (3,200 MBq) Na-131I, administered activity was 100 mCi ± 8.1 mCi (3,200 ± 300 MBq); group 4 patients were hospitalized for 1–2 days in isolation rooms. Group 5 patients consisted of six patients prescribed 50 mCi (1.85 MBq) Na-131I, administered activity was 50 mCi ± 4.7 mCi (1,850 ± 174 MBq); group 5 patients were hospitalized for one day in
isolation rooms. Abundant hydration treatment was given during isolation to all patients, laxatives were not used. (Protocol Number: 06-DK-0025)

Significant differences between groups were sought to identify variables influencing the effective half-life of radioiodine. Variables such as administered activity, age, sex and number of previous radioiodine treatments were analyzed. No statistical difference of the data distribution was identified based on these variables therefore, all five groups were pooled for analysis.

Variations in the measured exposure rate constant were compared. Because the theoretical exposure rate constant provided by the Regulatory Guide 1556 doesn’t account for photon attenuation by the patient’s body it was generally higher than the observed dose rate constant (figure 2)
Patient measurements were made using a portable scaler meter (Ludlum Model 2241-2) with a scintillation probe (Ludlum Model 44-2). The meter and probe were calibrated annually by A.M. Calibration Services, Rockville MD, with a $^{137}\text{Cs}$ source, Shepherd Model 28-6 #10258-300mCi. Prior to each use of the meter it was checked using a $^{137}\text{Cs}$ source. All measurements were performed using the same meter. Dose rate measurements were collected at one meter and one foot from the surface of each patient. Additionally, patients were asked to stand with their backs against the wall and the meter held 2
meters from the front of the patient at a height of 1 meter off the ground. Six separate 20 second counts were performed for each measurement after $^{131}$I administration. All measurements were performed as close as possible to 2 hour post administration and 21 hours post administration. For patients requiring a longer isolation period additional measurements were conducted every 24 hours following the second measurement, i.e., at 45, 69, 93 and 117 hours post administration as required until the patient reached the dose rate based default release criteria of 7 mrem/h (.07 mSv/h). On average, patients were discharged from the hospital after 1.5 days following their being released from isolation. The time of administration and measurements were recorded along with the estimated initial dose to the nearest nCi. A follow-up measurement was conducted on patients upon returning for further medical attention when practical. Background measurements in the therapy room were made prior to initial dosing, in the therapy room after the patient was released and not in the area, and in areas where follow-up measurements were conducted. Background was subtracted from each measurement.

To fit experimental measurements, mono-phase elimination of the intra-thyroid activity was assumed and the exponential model implemented using initial, release and follow-up measurement values. For data that is missing due to patients not being available for follow-up measurements post release,
exponential modeling was implemented using the initial and release measurement and extrapolated.

For each measurement data set the recorded counts were averaged using the following algorithm:

$$x_{av} = \frac{\sum x}{n}$$

where $\Sigma x$ refers to the sum of all the individual one minute count made at each measurement, and $n$ refers to the total number of one minute counts made during each measurement. The SD, $\sigma$, was calculated using:

$$\sigma_{x} = \sqrt{x_{av}}$$

The background subtracted measurements counts ($C$) was determined by:

$$C \pm SD = (P \pm \sigma_p) - (B \pm \sigma_B) = (P - B) \pm \sqrt{\sigma_p^2 + \sigma_B^2}$$

where $P$ refers to the average patient count and $B$ refers to the average background count from the above equation.

From the measurements made an effective half-life was determined from the exponential curve developed (Figure 3). The effective half-life of $^{131}$I was 0.812 days (19.5 hours). At five days following the initial therapy, dose rates at 1 meter were less than 2 mrem per hour for all patients.
FIGURE 3 – COUNT RATIO VS. TIME

\[ y = e^{0.853x} \]

\[ R^2 = 0.8681 \]
PATIENT INSTRUCTIONS AND RECORD KEEPING

If under the default criteria the patient may be released but written instruction must be provided in accordance with 10 CFR 35.75(b), standardized instructions will suffice.

For a release based on a licensee’s calculation standardized instructions may not suffice. In these situations specific instructions about the length of time to avoid specific activities may be required. These instructions should address the length of time to avoid the following interactions:

- Children, pregnant women and nursing mothers
- Traveling by public transport
- Spouse or equivalent
- Visitors and coworkers

Additionally, personal hygiene recommendations may be included to guide the patient in their interaction with others and minimize the potential for home contamination.

Note: No radiation safety documentation is required if the patient is released under the activity based default criteria. However, if the patients release is based on a licensee’s calculation, the dose rate at one meter exceeds 2 mrem or
the retained activity is greater than 7mCi (259 mBq) $^{131}$I written instructions must be provided to the patient. A copy of these instructions and any calculation used to justify the release of the patient must be maintained for three years. Written records for patients released based on a licensee’s specific calculation must include:

- Patient ID (NOT Name)
- Retained activity and dose rate at release
- Survey instrument used
- Calculated dose to the general public
- Effective half-life used in the calculations
- Occupancy factors used in the calculations
- Method used to calculate the dose to the public
- Specific patient instruction

Depending on the calculation methods not all the above information will be required.

Additionally, there are many reports of therapy patients setting off alarms at airports, banks and so forth because extremely sensitive equipment is
employed at these locations. To minimize inconvenience and embracement to patients the Society of NM recommends that patients carry a letter of explanation. $^{131}$I patients may set off these alarms for as long as 95 days post therapy (Zukier LS, 2004).

The NRC provides only general guidance for these precautions. However, in general the greater the computed general public dose, the longer the time certain activities should be avoided. The length of time for the restrictions should target a maximum dose of 100 mrem, which is the general public dose limit set forth in 10 CFR 20. The calculations for determining the amount of time necessary for instructions to remain in effect to minimize the radiation dose to sleeping partners, traveling companions, children and pregnant women, and members of the general public can be calculated using the targeted public dose and the calculated effective half time. We can use the same equations from the dynamic method developed above.

Licensees must first conduct a patient interview when generating written instructions regarding radiation safety precautions to maintain doses to other individuals of <500 mrem (5 mSv) and ALARA. The interview must focus on the patient’s living and working conditions, their ability to care for themselves and determine if the patient’s living or working conditions are such that it is
practical to recommend that the patient maintain specific distances while around others.

Common lifestyle behaviors that will increase the dose to others should be identified. Activities such as sleeping with a partner or traveling in a car must be considered because these activities involve long time periods where the patient is very close to the individual that is exposed.

The practicality of expecting patients to abide by the restrictions recommended and degree of confidence that the instructions will be followed must be considered when choosing to release patients based on these calculations. However, the NRC specifically states that it is not the Licensees’ responsibility to enforce the recommendations. (NUREG 1516)

Each instruction should specify how long the patient is to adhere to the specific recommendation. Therefore, prior to releasing patients the instructions must be calculated, written and discussed with the patient and the patient must be given a copy.

Licensees must then measure the dose rate at 1 meter (measured after the therapeutic administration and prior to release) to determine if release restriction apply. If release restrictions apply and a patient specific dose calculation is required Licensees will need to conduct the patient-specific dose
calculation and ensure that the maximally exposed individual will not receive a radiation dose of greater than 500 mrem (5 mSv). Additionally, Licensees will need to calculate the restriction time needed to make recommendation for restrictions following release.
CHAPTER 5

EXAMPLES OF THE APPLICATION OF THE PATIENT SPECIFIC METHOD USING DYNAMIC DATA TO CALCULATE DOSES IN INDIVIDUALS EXPOSED TO PATIENTS TREATED WITH $^{131}$I WHEN PATIENT LIVING CONDITIONS ARE KNOWN

If the patient-specific conditions are well known and it can be expected that the patient can function under minimal supervision Licensees may wish to evaluate dose to a soul caregiver based on an agreed patient exposure time. For this we could use the dynamic method just described to calculate organ and effective doses delivered by patient to the caregiver as well as establish a specific set of instruction for the patient to aid in maintaining the dose to the caregiver ALARA.

To illustrate, a group of specific situations are considered: 1) a patient is released to a caregiver that is simply a resident in the same home as the patient, 2) a patient is released to a caregiver that is a sleeping partner and 3) a patient is accompanied on their trip home and is expected to care for themselves for most of each day.

IRRADIATION SCENARIO # 1
A Patient is administered 200 mCi (7400 MBq) Na\textsuperscript{131}I for cancer. The initial dose rate at one meter from the patient is 25 mrem/h. Based on information gained during an interview prior to the administration it is determined that the patient is to be released to a family member who will provide minimal care. The family member is expected to be the only adult the patient will interact with for a number of days. The family member lives with the patient but is not a sleeping partner and has an infant child. The patient is release after two hours following the administration and has voided prior to release. Assume that the caregiver receives 4.5 hours dose at 1 meter each day following the release. Additionally, when the patient is allowed to resume normal contact with the infant child the patient will have direct contact with the infant for 30 min/day at 10 centimeters and 8 hours of exposure per day at a distance of one meter or greater.

The dose to the caregiver can be calculated using:

\[
D = \frac{t_R}{24} \int_{t_R}^{\infty} R_x e^{-k t} dt
\]

Where:

\( t_R = \text{Hours post therapy that the patient is released.} \)
The case specific calculation for the time when this patient can be released is given by setting $D = 500$ mrem and solving for $t_R$:

$$
 t_R \geq \frac{-1}{k} \ln \left[ \frac{24Dk}{t_X R_o} \right]
$$

$$
 t_R \approx -37.5 \text{ hours}
$$

Since the caregiver is considered the maximally exposed adult the patient can be released under the conditions given and immediately interact with adults.

Since the infant child cannot be considered a caregiver the dose to the child should target a TEDE of 100 mrem at the time for release ($t_R$). We can assume that the child doesn’t receive a dose before the restriction period but Licensees must calculate this restriction. The dose to the child is:

$$
 D = \frac{t_X 1}{24} \int_{t_i}^{\infty} R_0 e^{-k t} dt + \frac{t_X 0.1}{24} \left( \frac{1}{r} \right) \int_{t_i}^{\infty} R_0 e^{-k t} dt
$$

Here $r$ is the distance the infant will be from the patient for 30 min/day. Setting the dose ($D$) to 100 and solving for the time in hours until the patient is allowed to resume normal interaction with the infant child ($t_I$):
\[ t_i \geq \frac{-1}{k} \ln \left( \frac{100k}{t_{X1}R_o + t_{X0.1}R_o} \right) \]

\[ t_i \geq 79.8 \text{hours} \]

The patient must be given written instruction giving recommendations on how to maintain the dose to others ALARA. These instructions should include a recommendation to avoid all interactions with the infant child for the four days. A record of the release must be maintained by the Licensee for three years.

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**IRRADIATION SCENARIO # 2**

A Patient is administered 200 mCi (7400 MBq) Na\(^{131}\)I for cancer. The initial dose rate at one meter from the patient is 20 mrem/h (0.2 mSv/h). Based on information gained during an interview prior to the administration it is determined that the patient is to be released to a family member who will provide minimal care. The family member lives with the patient and is a sleeping partner. The patient is released after three hours following the administration and has voided prior to release. Assume that the caregiver receives a dose each day for 6 hours at 1 meter before resuming eight hours each day of normal sleeping at a distance of 0.3 meters.
The dose to the caregiver can be calculated using:

\[
D = \frac{t_x}{24} \int_{t_x}^{\infty} R_o e^{-kt} dt + \frac{t_{x0.3}}{24 r^2} \int_{t_r}^{\infty} R_o e^{-kt} dt
\]

The number of hours the patient and partner must sleep alone is given by \( t_s \):

\[
t_s \geq -\frac{1}{k} \ln \left[ \frac{k}{3R_o} \left( 250 - \frac{0.25R_o}{k} \right) \right]
\]

\( t_s \geq 48.5 \text{ hours} \)

The patient can be released under the conditions given. The patient must be given written instruction giving recommendations on how to maintain the dose to others ALARA and a record of the release must be maintained by the Licensee for three years. The Licensee should advise the patient to sleep alone for the first two nights following the release.

IRRADIATION SCENARIO # 3

During an initial interview a patient express interest in being considered as a candidate for home isolation. The patient’s living environment is adequate. The patient has an adult spouse that has agreed to act as a caregiver each day after work. The caregiver understands that they must sleep in separate rooms for as long as is advised. Once released, the patient plans to be driven home by car
which is approximately one hour from the hospital. The Patient is to receive 350 mCi (12.95 GBq) Na$^{131}$I for cancer and will be eligible to leave in two hours. Can the patient be released following this therapy? The initial dose rate at one meter from the patient is 50 mrem/h (0.5 mSv/h).

Assuming that the patient and caregiver will be interacting approximately six hours per day at an average distance of one meter the dose to the caregiver can be estimated:

$$D = \frac{t_x}{24} \int_{t_s}^{\infty} R_s e^{-kt} \, dt$$

$$D_\infty = \frac{t_x R_o}{24ke^{kt_s}} = 328\text{mrem}$$

However, it is prudent to compute the dose to the caregiver during the drive home. During the drive the patient will be seated one foot from the caregiver. The dose to the caregiver during the one hour drive is estimated to be:

$$D_D = \frac{t_{xc}}{24r^2k} (e^{-kt_s} - e^{-k(t_s+1)}) = 21\text{mrem}$$

Before agreeing to release the patient under these conditions Licensees must consider the potential internal dose to the spouse. Using the method provided by the NRC the internal dose can be estimated to be:
\[ D_I = 10^{-5} A_{\text{release}} C \]

\[ D_I = 185\text{mrem} \]

Since this component is greater than 10% of the external dose they must be added.

\[ TEDE = D_\infty + D_D + D_I = 534\text{mrem} \]

The patient cannot be released.
CHAPTER 6

CONCLUSION

To develop a methodology for releasing patents following radionuclide therapy 60 Candidates were selected for radiopharmaceutical therapy and treated on an inpatient basis. Data was gathered during their hospitalization and during follow-up appointments and used to conduct patient specific release calculation in compliance with 10 CFR 35.75(a). The method developed was based on the dose rates measured in air one meter from each patient. It is also demonstrated that the release equations used can also be used to calculate patient specific time lines to avoid some daily activities. These recommendations can be followed by the patient to maintain the dose to others ALARA.

The method easily accounts for a variety of variables that can affect the dose to others surrounding the patient following release. These variables include; patient body shielding, source geometry and biokinetics when point source geometry doesn’t adequately model the radiopharmaceutical distribution in the body and patient specific variations in the exposure rate constant for the nuclide used.
Using the method developed, licensees may release patients immediately following the administration of a radiopharmaceutical and accurately advise patients on how to maintain the dose to others ALARA. However, licensees must evaluate the specific living conditions that each patient is expected to be released into and some basic dose estimates must be made before the decision to schedule a patient for an outpatient therapy is made.

Using this method for patient release licensees can safely expand their use of outpatient radionuclide therapy and can be expected to greatly reduce costs related to maintaining patients in isolation. Additionally, patients that may suffer detrimental effects due to extended isolation periods can be safely released and cared for by qualified caregivers that might otherwise be required to avoid contact with the patient during the hours of the patient’s greatest need.
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