Dosimetrically Determined Prescribed Activity of ^{131}I for the Treatment of Metastatic Differentiated Thyroid Carcinoma

58

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Introduction

Although a favorable prognosis is typically associated with differentiated thyroid carcinoma, this is not necessarily the case for metastatic differentiated thyroid carcinoma (DTC) [1]. Consequently, modifications to the therapeutic approach, particularly with ^{131}I, may be required to achieve better outcomes in patients with metastatic DTC. ^{131}I was first shown to localize in metastatic DTC over half a century ago [2] and has been used extensively since then in the management of these patients [1, 3–5].

However, there is no consensus among clinicians managing these patients regarding what constitutes an appropriate ^{131}I prescribed activity[1] for the treatment of metastatic DTC. Several approaches to select a therapeutic prescribed activity of ^{131}I have been advocated. These can be broadly classified into two groups: (1) "empiric fixed prescribed activity" and (2) "dosimetrically determined prescribed activity." Given the heterogeneity of thyroid cancer patients, the same empiric fixed prescribed activity may not be appropriate for all patients. This chapter reviews the rationale and technique for "dosimetrically determined" prescribed activity of ^{131}I for the treatment of metastatic DTC and discusses (1) the alternatives for selection of a prescribed activity, (2) the two most common approaches for dosimetrically determining ^{131}I prescribed activity, (3) several modifications of these approaches that have been implemented over time, and (4) an overview of the literature regarding the results. The chapter then concludes with general recommendations for patient management regarding the use of dosimetry. This review does not address the use of dosimetrically determined prescribed activity of ^{131}I for the remnant ablation or adjuvant treatment. For definitions and objectives of remnant ablation, adjuvant treatment, and treatment of distant metastases, see Chaps. 33 and 34.

[1]Many authors have used the word "dose" to refer either to the amount of a radiopharmaceutical to be administered for a diagnostic scan, ablation, or treatment in units of Bq (mCi) or to the amount of radiation exposure to an organ or patient in units of cGy (rad). Because this may result in confusion, the authors have used the words "prescribed activity" and "dosage" to refer to the amount of a radiopharmaceutical for diagnostic scan, remnant ablation, adjuvant treatment, and treatment of known metastases while reserving the term "dose" for the radiation exposure.

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Empiric Fixed Prescribed Activity

Many excellent reviews of empiric fixed prescribed activity have been previously published [1, 4, 6–10]. One of the most frequently used and early guidelines for empiric fixed prescribed activities was proposed by Beierwaltes [3] and is summarized in Table 58.1. With this approach, the fixed prescribed activities are typically in the range of 5.55–7.4 GBq (150–200 mCi). However, both smaller and larger prescribed activities have also been proposed and used in practice [11, 12]. Some investigators have used repeated moderate levels of prescribed activities over short time intervals. For example, Schlumberger et al. used an initial prescribed activity of 3.7 GBq (100 mCi) of ^{131}I to treat metastasis of the lung and bone, which might be repeated every 3–6 months. The cumu-

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Table 58.1 Empiric fixed prescribed activity

Regional nodes that cannot be removed by surgery	5.6–6.5 GBq (150–175 mCi)
Pulmonary metastasis	6.5–7.4 GBq (175–200 mCi)
Bone metastasis	7.4 GBq (200 mCi)

Source: Ref. [3]

lative ^{131}I prescribed activity in this group of patients ranged from 2 to 55.5 GBq (54–1,500 mCi), with a mean of 12.5 GBq (339 mCi [±281 mCi]) [11]. Menzel adopted a more aggressive approach, employing an empiric fixed prescribed activity of 11.1 GBq (300 mCi), with intervals as short as 3 months [12]. Further discussion of the spectrum of empiric prescribed activity is discussed in Chap. 56.

"Dosimetrically Determined" Prescribed Activity

Although the simplicity of a set of empiric fixed prescribed activities is appealing and convenient, the wide spectrum of proposed protocols of empiric fixed prescribed activity with no data to show which protocol is better and the persistence of disease in a significant proportion of patients have led to attempts to improve the empiric approach to ^{131}I therapy. The ideal prescribed activity of ^{131}I to treat metastatic DTC is based on the minimum amount of ^{131}I needed to successfully treat the patient's metastases without resulting in unacceptable side effects or risks. Efforts to meet this goal have led to two major approaches, each of which addresses a different aspect of this problem. Benua et al. developed an approach based on determining the maximum activity of ^{131}I that could be administered without causing significant bone marrow suppression [13]. Thomas and Maxon developed a method to evaluate the amount of ^{131}I needed to adequately treat metastatic lymph nodes [14]. This section discusses the two basic approaches of dosimetrically determined prescribed activity and begins with a brief review of the principles involved to better understand the rationale for and the potential greater efficacy of the dosimetric approaches.

Background

Dosimetry

The term *dosimetry* has been used in a variety of contexts. It has been most commonly employed in the area of radiation oncology to describe the methodology and analysis used to calculate a treatment plan designed to deliver a prescribed radiation dose to the patient's tumor using external radiation. Within radiation safety programs and services, it has been used to describe the *monitoring* of the exposure of individuals from internal and external radiation hazards within a working environment. Finally, regarding thyroid cancer therapy with radionuclides, this terminology has been used in two contexts: (1) the calculation of a maximum tolerated activity (MTA) of ^{131}I that can be administered to a given patient, which would not exceed some empirically determined radiation dose to the blood or blood-forming components, and (2) the calculation of the radiation dose that would deliver (or has been delivered) to individually identifiable and quantifiable foci of remnant thyroid tissue or metastatic lesions. The latter conforms more closely with the traditional usage of this term within the radiation oncology community because it applies to the calculation of the dose specifically for the cancer being treated. However, just as in the case of external radiation therapy, it is the radiation dose delivered to the patient's normal tissues that frequently limits the maximum tumor dose. With ^{131}I therapy, the most radiosensitive organ of greatest concern is the patient's bone marrow.

Internal Radiation Dosimetry

When ionizing radiation is absorbed in living tissues, it can cause cellular damage because of the energy that is deposited. Different cell types will respond differently to the same amount of absorbed radiation. Nevertheless, one of the most important parameters used in the assessment of the radiation effects on any particular organ is the amount of energy deposited by the radionuclide in that organ. This calculation has come to be referred to as *internal radiation dosimetry*. When radionuclides were first used for medical purposes, at best, this type of information was fragmented. Consequently, conservative estimates were used to estimate the order of magnitude of the radiation absorbed dose to the body and other critical organs that resulted from the administration of a radionuclide. This radiation absorbed dose (to be distinguished from prescribed activity previously noted) is expressed in units of centigray (rad), which is a measure of the total amount of energy deposited per gram of tissue by all the radiation types emitted by the radionuclide. To perform this calculation, we need to know detailed information about (1) the types of radiation emitted in each disintegration (i.e., charged particles or photons), their relative abundance, and their energy; (2) how many disintegrations occur in each organ; and (3) what fraction of the energy of each radiation type that is released in any given organ is absorbed in another organ (including itself). The nuclear decay data required for the first issue can be found in the physics literature [15] based on experimental measurements performed in the laboratory. The second issue requires detailed knowledge about the uptake and clearance of the radionuclide in various organs within the patient. The third issue requires knowledge not only of the absorption and penetration characteristics of the various radiations emitted but also the size, shape, volume, and geometrical arrangements of the various organs within the patient. Ideally, direct measurements of the

absorbed dose at relevant locations within each patient would be best, but this is nearly impossible. Thus, we are instead restricted to theoretical estimates according to models and measurements performed using standardized humanoid phantoms.

Classical Dosimetry

The so-called classical dosimetry method was first published in 1948 by Marinelli et al. [16]. This was refined in 1956 by Loevinger et al. [17] and soon became the standard method [18] for calculating the radiation absorbed dose from internal sources. Because charged particles (i.e., β radiation) typically only travel a few millimeters in tissue, it is generally assumed that all the energy carried by this type of radiation is locally absorbed in the organ in which the radioactive decay occurs. In the case of ^{131}I, the maximum range of β particles in tissue [19] is 2.4 mm with most traveling substantially less than this distance. The model developed by Loevinger addressed the more penetrating radiation: the γ emissions. Therefore, the radiation absorbed dose from the two components (penetrating and nonpenetrating) can be expressed as

$$D_{\beta} = 73.8C < E_{\beta} > T_{\mathrm{e}}$$

$$D_{\gamma} = 0.0346C\,\Gamma\,gT_{\mathrm{e}}$$

where C is the initial concentration of the radionuclide in the organ (μCi/g), $<E_{\beta}>$ is the mean energy of the β radiation, Γ is the exposure rate constant specific to ^{131}I, T_{e} is the effective half-life in days, and g is a geometric factor to account for variations in the organ's size, shape, and volume. The constants that appear in these equations are conversion factors, such that the dose is expressed in units of centigray (rad).

Medical Internal Radiation Dose Schema

The medical internal radiation dose (MIRD) methodology was developed by a committee within the Society of Nuclear Medicine and Molecular Imaging to provide a more sophisticated approach for calculating the radiation dose to various organs from radionuclides that are internally deposited and accumulate in other organs. The initial models were released in the mid-1970s [20] and continue to be expanded and refined with the publication of new pamphlets. A review of the basic concepts and recent developments in internal radionuclide radiation dosimetry has been published [21]. This formulation simplified the calculation of radiation absorbed dose to varying organs within the patient by separating biological parameters that describe the uptake and clearance, along with physical decay from the details of energy absorption of the radiation released in each decay. All the absorption characteristics have been lumped into a single quantity: the "S" factor. These "S" factors incorporate (1) the details of the types and energies of the radiations emitted (e.g., how many, how much energy, what type); (2) the size and shape of the organ in which the radionuclide is distributed; (3) the size, shape, and geometrical relationship of any other organ within the patient; and (4) the fraction of energy from each possible emission that would be absorbed in any given organ coming from radiation that originated in any organ. Consequently, this single factor depends on the radionuclide, the organ containing the radionuclide (source), and the organ for which the dose is calculated (target). We can then express the dose to the target organ, D_{t}, as follows:

$D_{\mathrm{t}} = \sum \tilde{A}_{\mathrm{s}} \mathrm{S(t \leftarrow s)}$ where $\tilde{A}_{\mathrm{s}}$ represents the total number of decays that occur for the radionuclide in a given source organ, s. Finally, we sum the dose contributions from all the possible source organs to the target organ, indicated by $\sum$ in this equation, which can include the target organ as one of the source organs.

Dosimetry Approaches

Based on the principles outlined above, Benua et al. [13] developed an approach that set an empirically determined upper limit for the radiation absorbed dose to the patient's blood, whereas Thomas and Maxon [14] calculated the radiation absorbed dose that could be delivered to the lesion. Previous reviews are available [22–24]

Limited Bone Marrow (Benua Approach)

Keldsen et al. noted [25] that even with a relatively conservative empiric fixed prescribed activity of ^{131}I, bone marrow depression still occurs in about one quarter of all patients treated for metastatic thyroid cancer. Unfortunately, the empiric methods do not provide any information to help predict in which patients this would occur. However, the method reported by Benua et al. [13, 26] allows an estimate to be calculated for the radiation absorbed dose that will be delivered to the hematopoietic system from each GBq (or mCi) of ^{131}I administered to a given patient. This is possible because it utilizes information obtained from data collected over the course of 4 days or more following the administration of a tracer prescribed activity of ^{131}I to the patient. Considering the time period when this methodology was first developed, the dosimetry calculations were based on the classical formulations, rather than on MIRD. Furthermore, it should be emphasized that these calculations yield the radiation absorbed dose to the whole blood compartment, not directly to the bone marrow. In their study, a total of 122 administrations in 59 patients were reviewed. However, adequate data were only available to calculate a dose in 85 of these treatments. For this group, the whole blood dose ranged from 45 to 740 cGy (rad) with a mean of 267 cGy (rad), whereas the largest single prescribed activity of ^{131}I was 22.2 GBq (600

mCi). As might be expected, several serious complications and side effects occurred in this group. However, within a patient subgroup (i.e., those that received 200 cGy (rad) or less to the blood), the side effects were not as serious. Based on these observations, a protocol was implemented by Benua and Leeper at the Memorial Sloan Kettering Cancer Center (MSKCC), in which a prescribed activity for ^{131}I treatment was selected that would restrict delivery to no more than 200 cGy (rad) to the blood [27].

Description of the Benua Protocol

Regardless of the dosimetric methodology employed, a common feature is the incorporation of the ^{131}I pharmacokinetics in a given patient into the calculations. Consequently, a tracer prescribed activity of ^{131}I is first administered to the patient, and then the uptake and clearance of this radioiodine is followed for a specified time period. The form of ^{131}I (e.g., liquid or capsule) used for the dosimetry should be the same as that used for the subsequent treatment. In the classical approach, the blood is considered the critical organ, which is irradiated either from the beta particles emitted from the activity circulating in the blood itself or from the gamma emissions originating from activity dispersed throughout the remainder of the body. Therefore, only two compartments need to be monitored for radioactivity: the blood and whole body. The activity in the blood was determined from periodic 5 ml heparinized blood samples, While the activity in the whole body (i.e., the activity remaining in the patient) was monitored redundantly using two independent techniques: 24 h urine collections and whole-body counting using a single uncollimated radiation probe in a fixed geometry with respect to the patient. In this case, the patient-to-detector distance needs to be sufficiently large as to allow the activity from the entire patient while standing to be detected, with nearly the same sensitivity from head to foot. Typically, this requires distances greater than about 3 m. A 12.7 cm diameter NaI(Tl) detector was used originally, but smaller diameter probes could be used with a corresponding increase in the acquisition time to offset the reduction in sensitivity. Benua employed an energy window of ±50 keV centered on the 364-keV γ emission. Although their original investigation followed patients for at least 6 days after the tracer prescribed activity, their protocol has been modified to typically end after 4 days. Thus, a study beginning on Monday would be completed by Friday.

Data Collection

The data collected included the following:

- Blood samples (5 ml, heparinized) at 2, 4, 24, 48, 72, and 96 h
- Whole-body counts at 0, 2, 4, 24, 48, 72, and 96 h
- Total urine collection at 24, 48, 72, and 96 h
- Activity administered to patient as tracer prescribed activity (approximately 37 MBq [1 mCi])

In addition, a standard was prepared at the onset of the procedure of 37 MBq (1 mCi) of ^{131}I to normalize the whole-body counts. This was counted at a distance comparable to that of the patient in a reproducible geometry and was used throughout the 4-day monitoring period. During the initial 4 h period following the ^{131}I administration, the patient is not allowed to urinate or defecate. Under these circumstances, essentially 100 % of the prescribed activity will be contained within the patient at any time during the initial 4 h. The maximum value at 0, 2, or 4 h is then defined to represent the 100 % value, and subsequent daily measurements are normalized to this value using this formula:

$$\text{Retention}(t) = \times \frac{\text{Patientcounts}(t)}{\text{Standardcounts}(t)} \times \frac{\text{Standardcounts@MaxTime}}{\text{Patientcounts@MaxTime}} \times 100\%$$

When used in this way, the standard will correct for variations in detector sensitivity from measurement to measurement, as well as for physical decay. Absolute calibrations are not necessary, as the patient is used as his or her reference. The blood and urine samples are counted using scintillation well-detector systems. Because the activity must be established in these samples, it is necessary to make up a calibration standard that can be counted at the same time as the blood samples. This involves the addition of a carefully assayed quantity of ^{131}I (approximately 3.7–7.4 MBq [100–200 μCi]) to a total volume of 500–1,000 ml. Such a small concentration is necessary to avoid saturating the detector. An alternative might be to use a ^{133}Ba rod source that has been cross calibrated against the ^{131}I standard. With its relatively long half-life (10.5 years) and similar γ emissions, ^{133}Ba could serve as a suitable replacement for the prepared ^{131}I standard, which simplifies the protocol. At the conclusion of the data acquisition, 2 ml aliquots of whole blood, diluted or undiluted urine, and the in vitro standard are counted. Using this information, it is possible to calculate the percent of administered dose per liter of whole blood at each timed sample. A zero time point is calculated by dividing the total prescribed activity by the patient's total blood volume. However, a patient-specific blood volume is not determined but is assumed to equal 20 % of the body weight. As indicated in the section on internal radiation dosimetry, one of the factors needed in the dose calculation is the total number of disintegrations that occur in the organ over time. This is reflected in the effective half-life T_e that appears in the first two equations. This formulation assumes that the radionuclide clearance from the organ of interest follows a single exponential curve that can be char-

acterized by the effective half-life. Alternatively, knowing the organ activity as a function of time, and because activity is a measure of disintegrations per second, then the integral (i.e., the area under this curve) is actually a measure of the total number of disintegrations. Therefore, based on this *classical* dosimetry approach, the formula to calculate the radiation absorbed dose to the whole blood follows. The calculation of the area under these two curves is based on a mathematical fit to the data points using a multiple exponential function. Because the data collection is terminated after 4 days, these curves must then be extrapolated to infinity. A conservative estimate is employed by assuming that the clearance following the final measured data point is based simply on the physical decay. Ignoring any biological clearance beyond the last time point results in an overestimate of the area of these tails and, hence, an overestimate in the radiation absorbed dose as well. The radiation absorbed dose to the blood from the beta and gamma components expressed in cGy (rad) per MBq ^{131}I administered is then given as

$$\gamma(\text{cGy / MBq}) = 0.0000141\text{g} \times \left[\frac{1}{Weight(kg)}\right] \times [area\ under\ body\ curve]$$

$$\beta(\text{cGy / MBq}) = 0.00259 \times [area\ under\ blood\ curve]$$

Examples of two patient studies are shown in Fig. 58.1; Fig. 58.1a demonstrates rapid clearance, and Fig. 58.1b shows relatively slow clearance. The *maximum treatment prescribed activity or the maximum tolerated activity* (*MTA*) is then calculated as the activity of ^{131}I that would deliver a combined β and γ dose to the blood component of 200 cGy (200 rad) and is given by

$$\text{Treatment prescribed activity(MBq)} = 200\ \text{cGy} / (\beta[\text{cGy / MBq}] + \gamma[\text{cGy / MBq}])$$

Adjustments to the Original Protocol

To improve reliability and simplify the original dosimetry protocol, several groups have introduced a number of modifications and enhancements; the more significant ones are outlined below, and additional simplified alternatives to full dosimetry are discussed in Chap. 59.

Elimination of the Urine Collection

As previously mentioned, the urine data was used as a redundant method to determine the whole-body activity as a function of time and served as a check of the probe data. The whole-body retention was inferred from the difference between the administered activity and accumulated urine activity. Consequently, there is an inherent problem with this method: any error that may have occurred at one time point is propagated throughout *all* of the following data points as well. Particularly, some potential problems are associated with this measurement, including:

- Incomplete urine collection.
- Loss of iodine through alternative pathways, principally fecal, but also sweat, saliva, respiration, and so on.
- The high concentration of activity in the first 2 days can frequently saturate a well-counter detector, such that an additional 10:1 dilution might be required to avoid dead time counting errors.
- Errors in measuring the volume for each 24 h collection.
- Pipetting errors.

The net effect is that cumulative errors as high as factors of 2–5 in specific cases [28] can occur. Removing the urine collection step, which is a significant burden for many

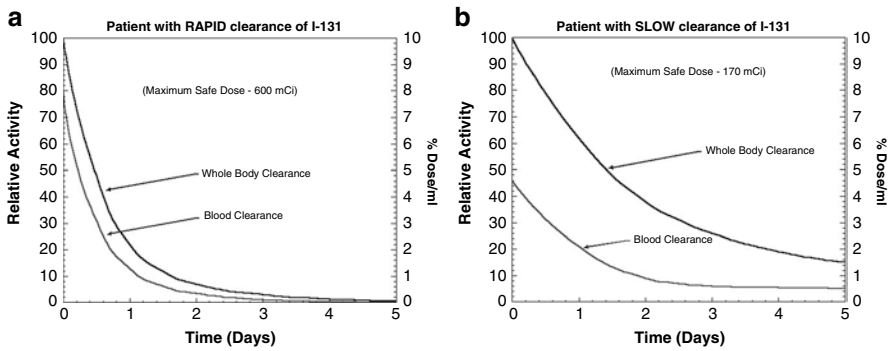

Fig. 58.1 Whole-body and blood clearance curves of ^{131}I for two dosimetry patients. In both cases, the final measured data point was determined at 4 days post-dosing. The classical dosimetry model then uses a conservative assumption of only physical decay, which can be seen as the abrupt change in the slope of the curves at this time point. The patient in **a** has rapid clearance, and little additional area under the extrapolated segment is present, which results in a calculated maximum treatment activity (MTA) of 22.6 GBq (610 mCi) to deliver 200 cGy (rad) to the blood. In contrast, in a patient with slower clearance, such as in **b**, there is a greater area under these curves, which leads to a lower calculated value for the MTA of 10.8 GBq (293 mCi)

patients, substantially reduces the complexity of this protocol by removing all the problems associated with the transport, storage, and handling of large volumes of radioactive body fluids. Furthermore, deleting the urine assay from the protocol also eliminates the possible risk to personnel due to accidental spills and radiation exposure from handling the radioactive urine. Most importantly, this simplification can be accomplished without compromising the objective.

Geometric Mean for Whole-Body Counting

A method of organ and body activity quantitation that has been widely adopted in nuclear medicine incorporates a geometric mean approach. Because the γ rays from ^{131}I are absorbed by varying amounts depending on the depth of the source in the patient, neither an anterior nor a posterior orientation alone is appropriate. This is especially the case as the radionuclide redistributes over time after the absorption from the stomach. Moreover, the geometric mean ($\sqrt{\text{ant} \times \text{post}}$) has been shown to be less sensitive to these variations [29].

Timing and Number of Data Points

Whole-body counting immediately following the ^{131}I tracer administration is generally neither practical nor useful. This is more relevant today when capsules are used instead of liquids for the isotope administration. The activity at this point in time is essentially confined to the stomach in a geometry that does not match the more diffuse body distribution at later times. In addition, a delayed sample at 4 h is inconvenient and may be difficult for the patient to avoid urinating before this measurement can be performed, which would invalidate this sample for normalization purposes. By this time (4 h), there can also be significant accumulation of activity in the bladder that can also bias this measurement. Therefore, a single data point at approximately 2 h after administration of the ^{131}I is usually sufficient for the normalization operation. Although it might seem that there is an insufficient number of time points, it has been shown [30] that a sampling scheme, such as the one outlined above, provides basically the same accuracy as more extensive sampling, at least in the case of radioimmunotherapy. The last data point is also collected at approximately 96 h post-administration of the tracer activity, provided that the whole-body retention at this time is approximately 4 % or less. If not, then an additional measurement may be performed on the following Monday (i.e., day 7).

Whole-Body Counting Using the γ Camera

As an alternative to using an external probe to measure whole-body retention, a dual detector γ camera system can be used. In this case, the patient is scanned in the whole-body mode in a reproducible geometry while lying supine on the imaging table. This method has been generally accepted for patient-specific whole-body dosimetry of ^{131}I-radiolabeled antibodies [31]. Furthermore, it has been shown to yield results comparable to those obtained using an external probe [32]. This technique has the following features:

- Simultaneous anterior and posterior images using a high-energy collimator.
- Table height, detector radii, scan length, scan speed, and energy window are standardized and reproduced for each data point.
- Scan speed can be relatively rapid (typically 30 cm/min) to complete the data acquisition in approximately 8 min and is comparable to the time required using an external probe.
- Additional scans are performed each day for background and a counting standard (vial containing about 37 MBq [1 mCi] of ^{131}I).
- Total counts in the image or fixed regions of interest encompassing the entire body are used for the calculation of whole-body retention.

Although these images are not used for diagnostic purposes, this approach has the added advantage that if for some reason there is delayed absorption of the tracer in the stomach, then the measurement could be repeated after 4 h. There are other advantages when using this technique over the probe in the dosimetry protocol. This method is easier for patients who are unable to stand for the 5–10 min, which is needed when using a probe. More importantly, it utilizes space and equipment normally found in most nuclear medicine laboratories. In most centers, a radiation probe that can be dedicated to this purpose is not available; hence, a standard thyroid uptake probe is used. These detectors typically have only a 1 in. diameter, and their geometric efficiency is therefore only 1/25 of that of the 5 in. detector used by Benua and Leeper. It is also frequently difficult to locate space where there is an unobstructed area that the probe and patient can be positioned with the required minimum separation of about 3 m. A revised classical blood dosimetry protocol, incorporating the changes discussed above, is summarized in Table 58.2.

Other Modifications

Other modifications and refinements to this dosimetry protocol have also been proposed. Furhang et al. [33] suggested an analytical curve-fitting technique to generate a more realistic extrapolation of the clearance curve beyond the final data point. Another attempt at simplifying this dosimetry protocol [34] suggested the elimination of blood samples. Their investigation examined the accuracy with which the total dose to the blood could be predicted using only the

Table 58.2 Modified classical dosimetry protocol

Whole-body counting (conjugate counting)	2, 24, 48, 72, and 96 h
	Count standard and background
	Normalize data points to 100 % using 2 h value
	Calculate γ component of dose (Gy/MBq) using classical approach
Blood sample (5 ml heparinized)	2, 24, 48, 72, and 96 h
	At conclusion of data collection, make ^{131}I counting standard with concentration of 3.7–7.4 KBq/ml (0.1–0.2 μCi/ml)
	Pipet 1 ml of whole blood from each collection and from standard
	Count duplicate samples in well counter in same run
	Convert blood data into units of % ingested dose/l
	Calculate β component of dose (Gy/MBq) using classical approach

whole-body data. Although there is a strong correlation between these two components, this method assumes that the β and γ doses are in a fixed ratio to each other. Unfortunately, there is a wide range in this value among patients, as shown in the data of Thomas et al. [34], as well as in the study by Robeson et al. [35]. Another area involves the transition from the *classical* model to the MIRD schema. For example, all the β energy released in the blood is assumed to be absorbed in the blood. Because these particles can travel several millimeters, this is likely an overestimation. More sophisticated models that account for the vascular space and geometrical configurations have suggested a value of 0.82 for the absorbed fraction [36]. The recent successes in the use of ^{131}I radioimmunotherapy for B-cell lymphoma have focused considerable attention on patient-specific dosimetry where again the radiation dose to the bone marrow is the limiting factor [37].

Hermanska et al. [38] has suggested using a biphasic model which might approximate complex multicompartmental models better than a monoexponential model. Such a biphasic model incorporates the uptake phase as well as better predicts the slower, long-term clearance phase. However, Hermanska's biphasic model requires more data points than a monoexponential model. Furthermore, the evaluation of the biphasic model was performed in patients who were receiving their first ^{131}I therapy. These patients tend to have more complicated iodine kinetics due to varying amounts of residual normal thyroid tissue compared to post-ablation patients.

Finally, Sisson and Carey [39] has suggested additional empiric modifications of dosimetrically determined prescribed activity in patients who have functioning metastasis with measurable serum thyroxine. For these patients, they have recommended reduction in their therapeutic ^{131}I prescribed activity based on hormone levels. Although further discussion of this is beyond the scope of this chapter, more extensive discussion of other simplified methods of dosimetry is discussed in Chap. 59.

Other Radioiodines for Dosimetry

Although all the discussions in this chapter involve the use of ^{131}I for conducting dosimetry, it is feasible that other radioisotopes of iodine (e.g., ^{123}I and ^{124}I) could also be used for this purpose. The primary reasons that ^{131}I has been used are that (1) it is readily available and relatively inexpensive, (2) it has a physical half-life suited for the required 4–8-day monitoring period, and (3) the γ emission, although somewhat high in energy, is appropriate for imaging with conventional scintillation cameras. Unfortunately, for the radionuclide ^{123}I, the first two requirements are unfavorable. However, a potentially significant advantage of ^{123}I over ^{131}I is that on a per millicurie basis, the radiation dose delivered to a thyroid remnant or metastatic lesion is about 100-fold less. Consequently, potential "stunning" because of the dosimetry procedure prior to treatment would be less concerning. However, the relatively short 13 h half-life of this radionuclide makes it more difficult for a prolonged biokinetic studies. However, it might be feasible to use ^{123}I in a patient for whom it is known that 4 days would be an adequate observation period if the prescribed activity could be increased to about 740 MBq (20 mCi). Of course, with current pricing for ^{123}I, this would be very expensive, even though the radiation dose would still be a fraction of that from a typical amount of activity of 74 MBq (2 mCi) ^{131}I, along with the added benefit of significantly improved image quality on the 24 and 48 h metastatic surveys.

The other potential candidate, ^{124}I, is a positron emitter and could quite possibly become the preferred radioisotope of iodine not only for dosimetry but for part or all of thyroid cancer imaging (see Chap. 103). Unfortunately, it is not approved in the United States by the Food and Drug Administration, and it also has a complicated decay scheme. However, in a study by Eschmann et al. [40], they concluded that ^{124}I, despite its complicated decay scheme, is suitable for the dosimetry of ^{131}I therapy in both benign and malignant thyroid diseases.

Lesion-Based Dosimetry (Maxon Approach)

Calculating a treatment plan based on delivering a prescribed radiation absorbed dose to the tumor is the fundamental tenet of radiotherapy, whereas the classical dosimetry approach of Benua was based on giving the maximum prescribed activity of ^{131}I that was considered safe and therefore more in line with thermotherapeutic strategies. The implicit assumption in the lesion-based dosimetry is that a treatment prescribed activity derived in this manner would achieve the maximum therapeutic effect to any metastatic disease while minimizing

the risk to the patient. Numerous investigations have been performed to determine the radiation absorbed dose that would be delivered to residual thyroid and metastatic tissue, with the objective to correlate the radiation absorbed dose with the therapeutic effect. In order to perform these calculations, it is necessary to measure the uptake and clearance of ^{131}I from identifiable thyroid remnants and/or metastatic lesions. This calculation of lesion dose [41] is generally based on a classical model, which for ^{131}I is given by

$\text{Dose(cGy)} = 0.63 C_0 T_{1/2\ \text{lesion}}$ where C_0 is the initial concentration (μCi/g) of ^{131}I in the lesion and $T_{1/2\ \text{lesion}}$ is the effective half-life of the lesion activity in hours. In order to determine the concentration of ^{131}I, how much activity (in absolute units) is contained in the lesion must be known. One way to ascertain this is based on an analysis of selected regions of interest on conjugate view γ camera images. These images are obtained at several time points, measured from the time of administration of the tracer prescribed activity. Typically, these images would be acquired at 24, 48, and 72 h, but later time samples might be necessary if the uptake and clearance are delayed. In addition, transmission images to correct for attenuation in the lesion area, as well as images of a standard for calibration purposes, are necessary. A curve-fitting procedure is then used to establish the assumed single-exponential half-life value and to extrapolate the curve-to-zero time to determine the lesion's initial activity. Another parameter needed to calculate the activity concentration is the lesion mass or volume. Several approaches have been suggested for this determination. For example, Maxon et al. [54] used the nonmagnified anterior images from a rectilinear scanner to determine the lesion dimensions and assumed a spherical or elliptical shape; Koral et al. [42] used both anterior and lateral pinhole camera images with corrections for magnification and an ellipsoidal shape. However, determining the lesion dimensions on a γ camera image has inherent problems. If the projected dimensions of the lesion are small compared to the spatial resolution of the imaging system, then partial volume errors are introduced. In addition, only 2D distances (e.g., the major and minor axes) are measured, and the volume is calculated from a presumed three-dimensional (3D) shape. To overcome some of these limitations, others [43] have used alternative, higher spatial resolution images, such as computed tomography or ultrasound, to determine the mass.

Many investigators have reported the effective half-life of ^{131}I in thyroid metastatic lesions as within a range of about 1–5 days. Thus, a limited number of temporal samples may not accurately predict this curve. Furthermore, in a small sampling of patients studied posttherapy [42], the uptake in the lesion did not achieve its maximum value until 1–3 days post-administration. An assumption of instantaneous uptake therefore results in an overestimate of the radiation absorbed dose. Furthermore, if the dimensions are smaller than about 5 mm (assuming that this could be accurately determined), then the range of the β particles can no longer be neglected in the dose calculation. For example, if ^{131}I is uniformly distributed at the same concentration in small spherical tissues of 0.1 or 1.0 mm in diameter, they would receive a relative radiation absorbed dose of 8.6 % and 56 % [44], respectively, compared to a 5 mm diameter lesion. Consequently, if the concentration of ^{131}I is a constant, then the absorbed dose rate initially increases as the radius of a spherical lesion increases. This curve begins to flatten off at a radius of about 7 mm and is essentially constant for lesions with radii more than 10 mm. Over the range of radii from 1 to 10 mm, there is approximately a threefold increase [45] in the dose rate. In fact, dose rate is a factor that has been generally ignored in ^{131}I therapy. It is well known in external radiation treatment that the dose rate and the total dose have an impact on cell survival. As the dose rate is reduced, more and more of the sublethal cell damage may be repaired during the course of the exposure. Below about 0.6 Gy/h (60 rad/h), there is only a little dose rate effect [46], with the residual cell killing effect from nonrepairable injury associated with the total cumulative radiation absorbed dose. However, these are realistic dose rates for ^{131}I therapy. For example, Schlesinger et al. [47] calculated that for an ^{131}I prescribed activity for treatment of 5.5 GBq (150 mCi) and a lesion uptake of 0.3 % per gram, the initial dose rate would be 1.83 Gy/h. Assuming an effective half-life of 3 days, their data showed that it would take about 5 days to reduce the dose rate to this critical value.

MIRD Dosimetry

Dosimetric approaches have improved significantly over the past 40 years and continue to evolve into more sophisticated methodologies to characterize the transport and absorption of radiation in complex biological systems. Patient-specific models employing Monte Carlo simulations have even been proposed. Indeed, it is generally believed that the MIRD methodology is a more accurate approach to dosimetry than the classical models employed in the Benua and Leeper approach. Using the MIRD methodology, it is possible to estimate the radiation absorbed dose that would be delivered not only to critical organs, such as the bone marrow and lung, but also to the lesion(s) to be treated. However, the latter is considerably more complicated and often not technically feasible if the lesion cannot be visualized with the small prescribed activity of ^{131}I used for the tracer study. Nevertheless, dosimetry-guided ^{131}I therapy for metastatic thyroid cancer has also been reported based on the MIRD methodology by Dorn et al. [48]. This group used the red marrow as the critical target organ, rather than the whole blood, which has been used as a surrogate for the bone marrow in the Benua and Leeper approach. Furthermore, for safety purposes, 3 Gy (300 rad) to the bone marrow or

30 Gy (3,000 rad) to the lungs was selected as their upper limit. Out of all their treatments with a curative intent ($n=41$), only 19 treatments resulted in the bone marrow receiving 3 Gy (300 rad). Based on this approach and the higher safety limit chosen, a single treatment prescribed activity of ^{131}I as high as 38.5 GBq (1,040 mCi) could be given. Although these workers claimed that such a dose limit (i.e., 3 Gy [300 rad]) to the bone marrow is safe and does not result in permanent marrow suppression, the evidence is still somewhat limited to support this conclusion. Note also that the Benua and Leeper model uses 2 Gy (200 rad) to the whole blood, not the bone marrow, as the limit. The actual radiation absorbed dose to the bone marrow is less than that delivered to the whole blood and, at most, is probably about 60–70 % of this value.

OLINDA®, 3D-ID®, and 3D-RD®

More recently, additional reports have been published in attempts to improve dosimetric calculations, and these include OLINDA®, 3D-ID®, and 3D-RD®. A detailed discussion of 3D-ID® and 3D-RD® is available in Chap. 103.

Results

Patient outcomes of ^{131}I treatment for metastatic thyroid carcinoma have been previously reported for (1) empiric fixed prescribed activity [1, 5, 49–52], (2) the Maxon dosimetric approach [14, 53, and 60], and (3) the Benua dosimetric approach [13, 24, 61]. Outcomes of ^{131}I treatments are more extensively discussed in Chaps. 33, 34, 56, 57, 60 and 75. The following is a brief overview of outcomes related to empiric fixed prescribed activity, the Maxon dosimetric approach, and the Benua dosimetric approach.

Maxon and Smith reviewed the literature regarding the effects of ^{131}I on functioning metastatic disease where the ^{131}I prescribed activities used were predominantly empiric fixed activity similar to those in Table 58.1 [5]. Complete resolution was typically defined as no evidence of disease by scan, X-ray, and clinical examination. Thyroglobulin levels were not initially available. For metastasis to the lymph nodes, complete resolution of disease was seen in 68.2 % (58 of 85), "improvement but still evident" disease in 18.8 %, and no apparent effect in 12.5 %. For metastasis to the lung, complete resolution of disease was seen in 45.9 % (134 of 292), "improvement but still evident" disease in 27.7 %, and no apparent effect in 24.5 %. For metastasis to the bone, complete resolution of disease was seen in 6.8 % (16 of 233), "improvement but still evident" disease in 35.6 %, and no apparent effect in 54.2 %. Also examining results after empiric prescribed activity, Schlumberger reported survival rates measured from the time of metastases discovery of 53 % at 5 years, 38 % at 10 year, and 30 % at 15 years. Remission was achieved in only 79 (28 %) of 283 patients once metastases were discovered [11]. Subsequently, Schlumberger indicated (1) a remission rate of 50 % with a 10-year survival rate of 61 % for lung metastasis; (2) a remission rate of 10 % with a 10-year survival rate of 21 % for bone metastasis, and (3) a remission rate of 7 % with a 10-year survival rate of 13 % for lung and bone metastasis [62]. Also using empiric fixed prescribed activity, Menzel reported clinical remission in 14 patients, partial remission in three, stable disease in 16, and progressive disease in 37 [12]. Dinneen found overall survival rates (for all causes) for distant metastasis to be 37 % at 5 years, 24 % at 10 year, and 20% at 15 years [63].

Based on the Benua dosimetry approach to selecting prescribed activity, Leeper described the status of 70 patients treated at MSKCC for metastatic differentiated thyroid cancer from 1974 to 1981 ([61]; see Table 58.3) and from 1974 to 1984 ([26]; see Table 58.4). This occurred after Benua had implemented several restrictions (see footnotes and Tables 58.3 and 58.4). Benua and Leeper administered an average single therapeutic prescribed activity of ^{131}I of 11.4 GBq (308

Table 58.3 Memorial Sloan Kettering Cancer Center 1974–1981 experience

		Number of ^{131}I treatments						
Status	Number of patients	1	2	3	4	5	6	Average total dose GBq (mCi ^{131}I)
Cured	21	13	6	1	0	0	1	14.7 GBq (463)
Died of disease	17	9	3	3	0	1	1	23.3 GBq (630)
Died of other causes	4	2	2	0	0	0	0	21.0 GBq (568)
Under treatment	19	10	6	1	2	0	0	19.0 GBq (514)
Living with disease; no further treatment	6	5	1	0	0	0	0	17.2 GBq (466)
Lost to follow-up	3	2	1	0	0	0	0	14.0 GBq (379)
Total	70	41	19	5	2	1	2	19.2 GBq (520)

Source: Ref. [61]

After implementation of restriction of maximum (a) 200 cGy (200 rad) total blood radiation, (b) 4.44 GBq (120) mCi of ^{131}I whole-body retention at 48 h, and (c) 2.96 GBq (80 mCi) of ^{131}I whole-body retention at 48 h if pulmonary metastases are present

Table 58.4 Memorial Sloan Kettering Cancer Center 1974–1984 experience

Status	Number of patients
Cured	45
Died of all causes	28
Under treatment	29
Living with disease	9
Status unknown	5
Total	116

Source: Ref. [26]
After implementation of restriction of maximum (a) 200 cGy (200 rad) total blood radiation, (b) 4.44 GBq (120 mCi) of ^{131}I whole-body retention at 48 h, and (c) 2.96 GBq (80 mCi) of ^{131}I whole-body retention at 24 h if pulmonary metastases are present

mCi) with a range of 2.6–24.2 GBq (70–654 mCi). The total cumulative prescribed activity of ^{131}I exceeded 37 GBq (1 Ci) in six patients with the largest being 77.7 GBq (2.1 Ci). In Leeper's group of patients, 19 % were treated with a prescribed activity less than 7.4 GBq (200 mCi). In most cases, each treatment delivered a calculated radiation dose of 200 cGy (200 rad) to the blood. A "cure" was defined as negative roentgenograms, clinical examination, and radioiodine scan. Thyroglobulin assays, albeit relatively insensitive by today's standards, were only used near the end of the above time period. If necessary, treatments were repeated at annual intervals. In 1984, Leeper reported that 58 % of the patients receiving one treatment were "cured." Patients younger than age 40 had a higher "cure" rate (30 of 33, 90 %) than those over age 40 (10 of 23, 43 %).

Using his quantitative, lesional dosimetry approach, Maxon et al. [53] treated 26 patients who collectively had over 67 metastatic lesions. There were 63 lesions in the neck, one in the lung, two in the mediastinum, and one in the bone. One patient had numerous abnormalities in the neck, chest, and abdomen, which were not detailed in the report. Of the 67 lesions in the other 25 patients, 59 responded to ^{131}I. None of the numerous lesions in the 26th patient responded. Based on the location of the abnormalities, the response was 58 of 63 (92 %) in the neck, one of two in the mediastinum, zero of one in the lung, and zero of one in the bone. Maxon reported that the response rate significantly increased in those lesions that received over 8,000 cGy (rad), as determined by his dosimetric approach. Little chance of a response was seen if the radiation dose to the lesion was less than 3,500 cGy (rad). In a subsequent article, Maxon et al. [54] reported successful treatment in 81 % (63 of 78) of lymph node metastases and in 74 % (17 of 23) of overall patients. Notably, some of these patients had residual thyroid tissue in the thyroid bed. The results were achieved after a single ^{131}I administration calculated to deliver a radiation dose to the lesion of at least 8,500 cGy (rad). The mean prescribed activity of ^{131}I in this group was 5.8 ± 1.9 GBq (156.7 ± 51.7 mCi), with a range of 1.8–9.1 GBq (48.6–246.3 mCi). When no residual thyroid tissue was present in the thyroid bed and no distant metastasis was noted, Maxon's treatment success increased to 90 % (26 of 29) of lymph node metastases and 86 % (6 of 7) of patients. This success was seen after a single administration of ^{131}I delivered a radiation exposure of at least 14,000 cGy (rad). The definition of "success" in this case was the absence of evident lymph node metastasis on physical examination and on a 37 MBq (2 mCi) radioiodine scan.

Despite the published outcomes for empiric fixed prescribed activity or prescribed activity determined by either the Maxon or Benua approach, a comparison of those results is difficult. The difficulties lie in the differences in the (1) definition of successful treatment, (2) changing definitions of successful treatment, (3) variability in additional treatment modalities, (4) duration of follow-up, and (5) variability in data collection. In addition, no prospective study comparing the outcomes of empiric prescribed activities to dosimetrically determined prescribed activities has been published. Obtaining adequate statistical samples with reliable follow-up over long time periods is very difficult. To date, only one publication by Klubo et al. [55] has compared dosimetrically determined prescribed activities to empiric fixed prescribed activities, and this report demonstrated a higher efficacy of dosimetrically determined prescribed activity with a similar safety profile compared to the empirical prescribed activity in high-risk patients. However, regardless of the above limitations, we believe that reasonable inferences may be drawn from the data to allow the development of guidelines for the use of dosimetry (see section "Recommendations"). A more extensive discussion of selection of ^{131}I prescribed activity for the treatment of metastatic disease is noted in Chap. 56.

At the time of this publication, the outcomes regarding dosimetry for lesions, whole body, blood, and other organs using ^{124}I are only in the development stage (see Chap. 103).

Strengths and Limitations of the Various Approaches

Empiric Fixed Prescribed Activity

The strengths of using the empiric fixed prescribed activity, such as those of Beierwaltes, are (1) convenience, (2) a long history of use, and (3) a reasonably acceptable rate and severity of complications. A theoretical strength of the higher empiric fixed prescribed activity approach (e.g., protocols using 7.4 GBq (300 mCi) of ^{131}I at 3–6 months' intervals) is improved outcome, but a limitation is the lack of significant data confirming outcomes, as well as the rate and severity of complications. In addition, empiric fixed prescribed activity permits the option of treating recurrent disease as detected

by ^{123}I scans, thyroglobulin blood levels, and/or other imaging modalities without using ^{131}I diagnostically. Avoiding the use of diagnostic ^{131}I eliminates potential reduction of therapeutic ^{131}I uptake because of real or theoretical "stunning" from the diagnostic prescribed activity.

However, empiric fixed prescribed activity has its disadvantages. One major limitation of empiric fixed prescribed activity is the failure to incorporate the individual status of the patient. The ideal ^{131}I prescribed activity to treat metastatic thyroid carcinoma is the lowest possible amount of ^{131}I that still delivers a lethal dose of radiation to the *entire* metastasis while minimizing side effects. Empiric fixed prescribed activities, by their very nature, do not permit the determination of either the minimal ^{131}I that will deliver a lethal radiation absorbed dose or the reasonably safe maximum tolerated activity. In regard to the latter, Leeper [56], Tuttle et al. [57], Kulkarni et al. [58], and Esposito et al. [59] demonstrated that empiric prescribed activity of 11.1 GBq (300 mCi), 7.4 GBq (200 mCi), and even 3.7 GBq (100 mCi) may exceed 200 cGy (rad) to the blood, which may result in increased frequency and severity of complications such as bone marrow suppression and pulmonary inflammation and fibrosis. An additional limitation is that multiple empiric fixed prescribed activities (fractionated radiotherapy) may not be equivalent to the same total ^{131}I prescribed activity calculated by dosimetry administered at one time. As already discussed, dose rate (cGy/h) is also important; thus, multiple smaller prescribed activities may have less therapeutic benefit than the same total prescribed activity administered at one time. Moreover, the first empiric treatment may reduce the effects of the second empiric treatment by reducing the uptake of the ^{131}I by the metastases—one of the arguments used for not even administering diagnostic prescribed activities of ^{131}I because of stunning.

The Benua Approach

The strengths of the Benua approach are the (1) patient-specific determination of the maximal tolerated activity (MTA) of ^{131}I, (2) identification of as many as one in five patients whose MTA is less than the empiric fixed prescribed activity, (3) potential to give higher radiation absorbed doses to metastasis at one time rather than multiple treatments with lower empiric prescribed activities which have lower total effective radiation absorbed doses, (4) experience of a long history of use by Benua, Leeper, and Larson at MSKCC, (5) empiric modifications of the original protocol based on observed initial complications, and (6) reasonable complications rates relative to the disease severity after the implementation of those additional modifications.

However, the Benua approach also has several limitations. First, the approach results in increased cost and patient inconvenience. However, we believe this is reasonable and not unlike treatment programs for metastatic disease secondary to other cancers. Second, the approach does not estimate the radiation absorbed dose to the metastasis, and the MTA may be administered without any potential therapeutic effect. Third, the program requires a committed medical staff. Like any treatment program for metastatic disease, the institution must see a reasonable number of patients to establish efficiency and assure quality. Fourth, present dosimetric approaches use ^{131}I diagnostically, which may subsequently reduce uptake of the therapeutic prescribed activity and therefore reduce the radiation absorbed dose delivered to the metastasis (stunning) (see Chaps. 16, 17, and 18). But using a smaller diagnostic prescribed activity, we do not believe this is a problem.

The Maxon Approach

The strength of the Maxon approach, as originally discussed by Maxon, is "[a] more selective exposure to individual patients based upon their individual needs without an increase in radiation exposure to the total patient population and lower overall costs." This could improve the outcome in some patients and avoid complications in those patients who receive no significant benefit from the ^{131}I therapy. However, Maxon's proposed lower overall costs are less because of two factors. First, new Nuclear Regulatory Commission guidelines allow earlier release from hospitals as well as outpatient treatments that reduce costs. Second, more expensive imaging methods may be required to determine the volumes of metastases.

Some technical limitations of the Maxon approach are noted in Table 58.5. Other limitations include the following: (1) increased cost and inconvenience, albeit we again believe that these are also modest and reasonable; (2) no prospective data regarding its use in distant metastasis; and (3) potentially difficult implementation of the approach in distant metastasis.

Another potential disadvantage of the Maxon approach is whether nonvisualization of a lymph node or any distant metastasis on a 74 MBq (2 mCi) ^{131}I scan implies that the metastasis is not treatable with ^{131}I. Again, Maxon indicated that delivery of 8,000 cGy (rad) to the lymph node metastasis was associated with an excellent chance

Table 58.5 Potential problems and limitations of lesion-based dosimetry

A single-exponential model may not accurately reflect the kinetics of the radioiodine in the lesion
Assumption of instantaneous uptake and maximum at time zero
Estimation of the lesion mass
Assumption of uniform distribution of ^{131}I in the lesion
Statistical errors in the measurements
Therapeutic response relative to dose rate
Reduced radiation absorbed dose for a given prescribed activity for lesions <5 mm in diameter

of successful treatment, and doses of less than 3,500 cGy (rad) reduced the chance of effective treatment. However, does this suggest that the necessary cGy (rad) cannot be delivered to a functioning metastasis that is not visualized on a 64 MBq (2 mCi) ^{131}I scan? Arnstein et al. [64] has suggested that significant radiation absorbed dose can still be delivered to lesions even when they are not visualized on scans performed using prescribed activities of ^{131}I of 74 Bq (2 mCi) and even as high as 1.11 GBq (30 mCi). This is one of the arguments for a "blind" ^{131}I therapy when serum thyroglobulin is elevated and the pretherapy radioiodine scan is negative. Clearly, further study is warranted, and ^{124}I may be very useful in these areas of investigation.

General Limitations of All Approaches

A major downfall of all the approaches is the less than optimal definition of "success." This includes not only the criteria for complete remission and partial remission but also the length of follow-up. For example, the criteria for "success" could be merely a normal physical exam and negative radioiodine whole-body survey within less than 3 years of follow-up. These criteria may have been reasonable at the time of the original studies, but it is arguable whether these criteria and the short length of follow-up provide much information about patient outcomes, e.g., the rate of complete remission, partial remission, and length of remission. For example, diagnostic modalities other than physical exam, such as ultrasound of the neck and CT of the chest, were available and have been used since the 1970s. Additional modalities to detect residual disease have become available and were used in the 1980s and 1990s (e.g., serum thyroglobulin assays and magnetic resonance imaging [MRI]). By today's standards, the results of radioiodine whole-body surveys are poor criteria by which to judge success. For example, we now know that the lack of uptake on a 7.4 MBq (2 mCi) radioiodine scan is not necessarily evidence of successful treatment. The size and/or uptake of the metastasis may be too little to be visualized on the radioiodine scan, and/or the metastasis may have dedifferentiated and lost its functional ability to take up iodine. To simply rely on physical exam and a negative radioiodine scan is inadequate as a definition of success. In addition, the described follow-up periods of only several years to assess altered outcomes in a disease that may take significantly longer time periods to recur or progress are problematic. Accordingly, less than optimal definitions of success and short follow-up periods may have overestimated "success" as defined by earlier reports. In addition, the variability of the definitions makes meaningful comparisons unreliable.

However, this should not devalue these approaches but rather encourage us to reevaluate the approaches with more specific definitions of complete and partial remissions that encompass longer-term follow-up periods that are more appropriate for our current practice such as published by Klubo et al. [55].

In summary, many problems exist regarding any dosimetric approach, but physicians and patients should not see these problems as deterrents in using the Maxon and/or Benua approach when appropriate. In addition, third-party insurance payers should not interpret these problematic issues with dosimetric approaches to therapy as their rationale to declare them experimental and thereby deny reimbursement. Rather, dosimetric approaches have been in use as long as empiric approaches, and although no prospective studies assessing outcomes have been reported for dosimetric approaches, neither has prospective studies assessing outcomes have been reported for empiric approaches. Accordingly, we believe any additional cost of these dosimetric approaches over empiric fixed prescribed activity is warranted, at least in patients with metastatic disease (see Chap. 56). The remaining questions or issues regarding dosimetric approaches must be studied and resolved, and then we can move forward and hopefully achieve greater benefit for our patients.

Selecting Empiric vs Dosimetrically Determined Prescribed Activity

Of course, one of the more controversial areas in the management of metastatic DTC is that of using dosimetrically determined vs empirically selected prescribed activities of ^{131}I for the treatment of metastatic DTC. Those who favor an empiric rather than a dosimetric method may argue that until prospective data are published demonstrating that the outcomes of ^{131}I treatments based on dosimetric methods are superior to that using the empiric methods, one should use empiric methods. We agree with empiric methods for the selection of the prescribed activity of ^{131}I for remnant ablation and adjuvant treatment. However, we do not agree with this position when selecting the prescribed activity of ^{131}I for the treatment of known metastases. Rather, we submit that until further data are published demonstrating that the outcomes of ^{131}I treatment with the empiric selected prescribed activities are equal or superior to the dosimetric methods, one should use dosimetric methods. Dosimetric methods are based on—or at least are an attempt to be based on—one or both of the two fundamental principles of radiation therapy planning, namely, "… determining and delivering radiation absorbed dose to the tumor for control as well as determining and minimizing the radiation absorbed dose to the normal tissues." None of the various empiric selected prescribed

activities are based on either one of these fundamental principles of radiation therapy planning. Instead, empiric selected prescribed activities are typically based on an initial proposal by one individual at one facility (see Chap. 56), and ironically no prospective outcome studies are available comparing the many different approaches of empiric selected prescribed activities of ^{131}I for the treatment of metastases of DTC. Further, if one does accept the argument that until additional data are available to demonstrate that dosimetrically determined prescribed activity yields outcomes superior to empirically selected prescribed activity, then how does one select one of the empiric prescribed activities (e.g., 3.7 GBq [100 mCi], 5.55 GBq [150 mCi], 7.4 GBq [200 mCi], or even 11.1 GBq [300 mCi]) when there is no data to demonstrate which of those empiric selected prescribed activities result in superior outcomes? This is inconsistent and illogical. Accordingly and until outcome data are published demonstrating that one empiric selected prescribed activity has any better outcomes to any other empirically selected or dosimetrically determined prescribed activity, the logical choice is to select the method that is at least based on the fundamentals—or at least one of the fundamentals—of radiation therapy planning and not on one or another's individual empiric preference(s).

In addition to the above argument and despite the frequent argument that no article has been published comparing ^{131}I treatments for metastases with empiric selected prescribed activities vs dosimetrically determined, a retrospective study has now been published by Klubo et al. [55]. This study evaluated outcomes and side effects of empirically selected prescribed activity vs dosimetrically determined prescribed activities for ^{131}I treatment of metastases. The study group consisted of 87 patients followed for 51 $\pm$ 35 months. Forty four patients were treated with an empiric prescribed activity, and 43 patients were treated with a dosimetrically determined prescribed activity of ^{131}I. By multivariate analysis, the group administered with the dosimetrically determined prescribed activity were 70 % less likely to progress (odds ratio, 0.29; 95 % confidence interval, 0.087–1.02; $p < 0.052$) and more likely to obtain complete response compared to the group of patients administered with an empiric selected prescribed activity (odds ratio, 8.2; 95 % confidence interval, 1.2–53.5; $p < 0.029$). The advantage of dosimetrically determined prescribed activity was more apparent in the locoregionally advanced group because complete remission was significantly higher in the dosimetrically determined group vs the empiric group (35.7 vs 3.3 %; $p < 0.009$). The rates of partial response, stable disease, and progression-free survival, as well as the frequency of side effects, were not significantly different between the two groups. So, initial data, albeit retrospective, have now been published demonstrating a benefit of ^{131}I treatment for metastases when the prescribed activity has been determined by dosimetry. However, further studies are warranted.

For those who do not perform dosimetry or do not have access to a facility that performs dosimetry, simplified alternative dosimetry methods are available and can be performed in almost any nuclear medicine facility [65, 66]. Further discussion is available in Chap. 59.

Table 58.6 Recommendations for ^{131}I treatment of functioning lung metastasis of differentiated thyroid carcinoma

1. Strongly recommend referral of the patient to a site that performs dosimetry, and if that is not an option, then either perform or refer the patient to a site that performs one of the methods of percent 48 h whole-body retention. Do not exceed a prescribed activity that would either deliver more than 200 cGy (rad) to the blood or result in more than 2.96 GBq (80 mCi) whole-body retention of ^{131}I activity at 48 h[a]
2. If dosimetry or percent 48 h whole-body retention is not available, then select one of the many empiric methods from 3.7 to 11.1 GBq (100–300 mCi). However, if the patient has:
a. Macronodular pulmonary metastases, we recommend caution in exceeding 5.55 GBq (150 mCi), because as many as 10–20 % of patients may exceed 200 Gy to the blood (bone marrow) [56–59] or
b. Diffuse micronodular pulmonary metastases, we recommend caution in exceeding any prescribed activity greater than 3.7 GBq (100 mCi) because the patient is at increased risk of acute radiation pneumonitis and/or radiation pulmonary fibrosis [13]

See Chap. 56

[a]As determined by the Benua and Leeper approach

Table 58.7 Recommendations for ^{131}I treatment of functioning bone distant metastasis

1. Depending on location and number of lesions, recommend consideration of other treatment modalities such as surgical excision, external radiation therapy (e.g., CyberKnife®), radiofrequency ablation, cryotherapy, or embolization, to name several, prior to any ^{131}I treatment. However, ^{131}I treatment may be given before external radiation therapy
2. If ^{131}I treatment is to be administered, then strongly recommend referral of the patient to a site that performs dosimetry, and if that is not an option, then either perform or refer the patient to a site that performs one of the methods of percent 48 h whole-body retention
a. Do not exceed a prescribed activity that would either deliver more than 200 cGy (rad) to the blood or result in more than 4.44 GBq (120 mCi) whole-body retention of ^{131}I activity at 48 h[a]
3. If dosimetry or the simplified methods of percent 48 h whole-body retention are not available, then select one of the many empiric methods from 3.7 to 11.1 GBq (100–300 mCi). Be cautious in selecting 5.55–11.1 GBq (150–300 mCi) because as many as 10–20 % of patients may exceed 200 Gy to the blood (bone marrow) [56–59]

See Chap. 56

[a]As determined by the Benua and Leeper approach

Table 58.8 Recommendations for ^{131}I treatment of functioning brain distant metastasis

1. Depending on location and number of lesions, recommend consideration of surgical excision or external radiation therapy (e.g., gamma knife radiotherapy) prior to or in place of ^{131}I treatment
2. If ^{131}I treatment is to be administered, then strongly recommend referral of the patient to a site that performs dosimetry, and if that is not an option, then either perform or refer the patient to a site that performs one of the methods of percent 48 h whole-body retention
a. Do not exceed a prescribed activity that would either deliver more than 200 cGy (rad) to the blood or result in 4.44 GBq (120 mCi) whole-body retention of ^{131}I activity at 48 h
b. Recommend pre-treatment (i.e., steroids, glycerol, and mannitol) prior to either thyroid hormone withdrawal or administration of recombinant human thyroid stimulating hormone as well as ^{131}I treatment
3. If dosimetry or one of the simplified methods of percent 48 h whole-body retention is not available, then select one of the many empiric methods from 3.7 to 11.1 GBq (100–300 mCi). Be cautious that in selecting 5.55–11.1 GBq (150–300 mCi), as many as 10–20 % of patients may have significant bone marrow suppression [56–59]
See Chap. 56

Recommendations

Our recommendations for the use of dosimetrically determined vs empirically selected prescribed activities to help select ^{131}I prescribed activity for the treatment of metastatic thyroid carcinoma are noted in Tables 58.6, 58.7, and 58.8. Again, the selection of the amount of prescribed activity of ^{131}I is discussed further in multiple other chapters (see Chaps. 56, 59, and 65). We also recognize that many other factors such as the clinical status of the patient, the patient's location, and the patient's own desires may influence the method for the selection of the ^{131}I prescribed activity and even the final ^{131}I prescribed activity determined by any method.

Summary

^{131}I is an important option in the therapeutic armamentarium for metastatic thyroid carcinoma, and dosimetrically determined prescribed activity of ^{131}I for treatment of metastatic DTC is based on—or at least an attempt to be based—on one or both of the two fundamental principles of almost all radiation therapies. More research is needed to compare the long-term outcome and risks of the dosimetric approaches to the empiric approaches as well as to evaluate new approaches, such as patient-specific dosimetry with ^{124}I PET and the 3D internal dosimetry [67] and 3D-RD software developed by Sgouros, Hobbs, and colleagues [68]. However, until further outcome data are available, dosimetrically determined prescribed activities for the ^{131}I treatment of functioning distant metastases is a reasonable alternative, and it is our preferred method.

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