Practical Dosimetry of ^{131}I in Patients with Thyroid Carcinoma

James C. Sisson, M.D.

Division of Nuclear Medicine, Department of Radiology, University of Michigan Health System, Ann Arbor, MI

Radioiodine treatments of patients with well-differentiated thyroid carcinoma have generally been safe and beneficial. Safety can be ensured while efficacy is increased through practical methods of dosimetry that measure body retention of ^{131}I. Prescriptions for therapeutic ^{131}I can be decreased when the retention level is high and increased when the level is low. Assays of serum free T4 will alert the physician to possible increased radiation to blood and bone marrow, and appreciable concentrations of free T4 are indications to reduce the therapeutic ^{131}I. Carcinomas ≥1 cm in diameter that are not visible on diagnostic scintigraphy are unlikely to respond to the commonly prescribed mCi of ^{131}I. Biologic responses to commonly prescribed levels of therapeutic ^{131}I, as seen in toxic changes of normal tissues and in indices of tumor size, will be the final dosimeters. With lower levels of prescribed diagnostic ^{131}I, stunning should not impair dosimetry. Thus, readily obtained measurements make dosimetry a practical method for improving carcinoma therapy with ^{131}I.

Key Words: dosimetry, thyroid carcinoma, ^{131}I, treatment.

INTRODUCTION

Delivery of selective and tumoricidal radiation to patients with carcinomas is a compelling concept. Treatments of patients with thyroid carcinomas have long been portrayed as examples of this concept in practice. Yet, many well-differentiated thyroid neoplasms in advanced stages have not fully responded to therapies with ^{131}I. Radiation dosimetry has the potential of increasing the effectiveness of radioiodine treatments while preventing or limiting toxicity to normal tissues.

Most of the energies from disintegrations of ^{131}I are deposited within 1 mm from beta particles and therefore are largely confined to the carcinomas that concentrate the radionuclide. Nevertheless, normal body structures must receive some radiation from the ^{131}I that diffuses through the body before excretion, and large amounts of radioiodine can damage organs and tissues. Years ago, from observations of many patients treated with ^{131}I, Benua et al.[1] developed guidelines based on body retention of radioactivity and absorbed radiation to the blood (as a surrogate for radiation to the bone marrow), to prevent toxicity (Table 1). Thomas and colleagues reported that, for most patients, the absorbed blood dose could be inferred from the level of retention of ^{131}I in the body[2] (Table 2), and it appeared that the fraction of radioactivity remaining in a patient at 48 hours would serve as the guideline to prevent toxicity. Exceptions to the blood-body relationships[3] will be discussed below.

Despite the advantages of dosimetry, it is not commonly practiced in the care of patients with thyroid carcinoma. Many physicians find dosimetry methods daunting, and they know that the

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Address reprint requests to James C. Sisson, M.D., Division of Nuclear Medicine, Hospital B1 505G, University of Michigan Health System, Ann Arbor, MI, 48109-0028.

Table 1. Guidelines To Prevent Toxicity From ^{131}I in Treatment of Patients With Thyroid Carcinoma

1. Body retention of ^{131}I at 48 hours should be
    ≤120 mCi (4.4 GBq), but
    ≤80 mCi (3 GBq) in the presence of functioning diffuse lung metastases.

2. Absorbed radiation to blood should be
    ≤200 rad (cGy).

From Benua et. al.[1]

most often prescribed therapies of ^{131}I, 3.7–7.4 GBq (100–200 mCi), are rarely followed by marked toxicity in normal tissues. However, there are a few patients who exhibit relatively high retentions of ^{131}I in their bodies that could not be predicted by knowledge of renal function or of the volumes of tumor. In such patients, 100–200 mCi may pose a risk to normal structures, especially if administered several times. Moreover, although there are no data showing that multiple administrations of moderate amounts of ^{131}I are not efficacious, it would seem that the initial treatment with ^{131}I is likely to have the greatest effect on the carcinoma and, therefore, should be substantial in amount yet still safe.

Measurements of radioactivity in the target tumors would permit a refined dosimetry, but this approach is difficult at best and often impossible because tumor volumes cannot be determined accurately. Still, judgments can be made on the futility of radiopharmaceutical therapy when there is absence of ^{131}I uptake in tumors that are visible by radiographs or by clinical examination.

Thus, dosimetry in patients with well-differentiated thyroid carcinomas can provide information: 1) to ensure safety in normal tissues, 2) to increase efficacy of tumor treatment and 3) to identify futility of ^{131}I therapy for carcinomas in some patients. This report will describe how read-ily obtained information on dosimetry can usefully guide prescriptions of ^{131}I for treatment of patients with thyroid carcinomas.

RECOMMENDATIONS FOR PRACTICAL DOSIMETRY

Measuring Retention of ^{131}I in the Body

Assays of retention can be readily made in any nuclear medicine laboratory. Patients are seated on a stool 2.5 m from a standard uptake probe aimed at the xiphoid. Determination of a flat field response of the probe will ensure accuracy. Anterior and posterior counts are obtained for 2 minutes each from the seated patient, and appropriate background is subtracted. A geometric mean is calculated for a 100% value 2 hours after ingestion of ^{131}I, and the relative retention is determined 2 days later.

Measurements made in over 80 patients demonstrated that retentions of ^{131}I at 2 days (approximately 48 hours) exhibited a broad range: <5% to 50% of the administered radioactivity (unpublished data). A large proportion of patients fell in the range of 10–25%. A reasonable correlation between retention of diagnostic and of therapeutic ^{131}I was found.

Many physicians will not feel comfortable ad-

Table 2. Relationship Between Blood and Body ^{131}I in Patients With Well-Differentiated Thyroid Carcinoma

Ratio: Radioactivity in Blood/Radioactivity in Body*

Metastases Present (8)	Residual Thyroid Tissue (19)	Scan Negative (23)
0.14±0.04	0.14±0.04	0.17±0.05

From Thomas et. al.[2]
* For the uncommon exceptions to the relationship, see Sisson and Carey[3]

ministering therapeutic quantities of ^{131}I that approach the induction of toxicity, but even with relatively safe amounts of ^{131}I, prescriptions can be modified to increase efficacy. For example, a retention below 10% would be an indication to increase their *usual* prescription of [131]I. On the other hand, a retention may be greater than 25%, and the *usual* prescription could then be decreased to ensure safety.

Estimating Increased Blood Concentrations of [131]I

As noted above and in Table 2, for most patients the absorbed radiation to blood can be inferred from the body retention of ^{131}I, and therefore radioactivity in blood will not modify the amount of therapeutic ^{131}I determined from body retention. However, in a few patients, the carcinomas synthesize compounds that will become labeled with the administered [131]I.[4] Some of these organic molecules, particularly thyroxine, will circulate for days[5] in contrast to radioiodide that rapidly disappears from the blood. In these circumstances the bone marrow receives a disproportionately high level of radiation. Although dosimetry of blood can give an estimate of absorbed radiation, measurements must be carried out for many days and errors can still be appreciable.[3]

A clue to the possibility of increased blood radiation is found in the concentration of serum thyroxine measured in the absence of thyroid hormone medication and usually expressed as free T4 (fT4). With fT4 concentrations <0.25 ng/dl there should be inappreciable levels of ^{131}I labeled compounds that circulate with half-lives longer than a day, but higher concentrations of fT4 should signal caution. After the body retention at 2 days has been determined, therapeutic ^{131}I will be prescribed, but this amount of ^{131}I may be modified using the fT4 value as a guide. Reduce ^{131}I in the treatment by:

> 10–20% for 0.25–1.0 ng/dl,
> 20–40% for 1.0–1.8 ng/dl, and
> 40–60% for >1.8 ng/dl of fT4.

Tumor Dosimetry and the Limitations of Therapy for Carcinoma

Maxon et al. determined that 8000 rad (cGy),[6] and preferably 14000 rad,[7] from ^{131}I treatments were necessary to reduce cervical node metastases of well-differentiated thyroid carcinoma to scintigraphic invisibility; when the absorbed dose of radiation was <4000 rad, none of the metastases disappeared.[8] Such measurements are difficult and often impossible to perform. Still, the results give an indication of levels of radiation that are ineffective.

Although well-differentiated carcinomas concentrate ^{131}I to varying levels, a relationship between scintigraphic visibility of tumors and effective therapy has been worked out in laboratory experiments with phantoms.[9] In a mock tumor of 300 μl, 0.3 μCi of ^{131}I could be detected by a gamma camera in a background of radioactivity simulating that in a patient. Assuming that same concentration of activity would be detectable in a 1000 μl mock, i.e., 1 μCi/ml, then the total in this larger mock would be 0.05% of 2 mCi of ^{131}I administered for diagnosis. From 0.05% of 200 mCi given for therapy, the concentration would be 100 μCi/ml, and, with an effective half life of 3 days that is commonly seen in thyroid carcinomas,[6] the absorbed radiation in this 1 ml target would be approximately 4500–5000 rad. Thus, a tumor of 1 ml (spherical diameter 1.25 cm) that is invisible to scintigraphy after 2 mCi of ^{131}I would concentrate <0.0005 of administered ^{131}I and receive less than 4500 rad from 200 mCi. Probably more modern cameras could detect even smaller concentrations of radioactivity, especially in the low background activity of lungs. Therefore, thyroid carcinomas that are 1 cm and larger by radiographic or clinical measurements but undetectable by a gamma camera would not be eliminated by therapeutic ^{131}I in the range of 200 mCi. Such treatments are likely to be futile.

Biological Responses as Indices of Radiation Effects

Ultimately, the responses of tumors and normal tissues will determine the efficacy and toxicity of ^{131}I therapies. The goals of treatment should be determined beforehand, including not only the scintigraphic changes but also those in clinical, radiographic and biochemical (serum thyroglobulin) expressions of the carcinomas. Progressive disease, especially within the first 6–12 months after therapy is an indicator of failure. Samaan et al. found that most of the benefits in their patients were seen after the first 300 mCi of ^{131}I were given.[10]

The guidelines (Table 1) have served well to prevent major toxicity.[11–13] Still, depression of bone marrow function is a major concern. Cytogenetic analysis of lymphocytes after treat-

ments is a sophisticated assessment of radiation effects[14,15] but not practical in most clinics. However, for patients who are to receive larger and repeated administrations of ^{131}I, it is wise to have a hemogram of platelets, leukocytes and hemoglobin before a treatment and 5–6 weeks later. A major decline in one or more of these blood elements, even though temporary, would signal substantial effects on marrow function. Since radiation effects on tissues are cumulative, future treatments may induce more marked toxicity.

Salivary and lacrimal gland dysfunction arises in 25% or more of patients receiving 100 mCi or more of ^{131}I, and chronic xerostomia will afflict a substantial number.[16,17] It is not clear whether techniques that increase saliva flow, as from chewing gum, lessen these effects, but they are worth considering. Thus, before administering additional ^{131}I, account should be taken of salivary and lacrimal gland responses, at least in terms of symptoms, to prior therapy, and efforts should be made to minimize future impairments.

DRAWBACK TO DOSIMETRY: POSSIBLE STUNNNG

Stunning of thyroid tissues, carcinoma and residual normal gland, is the decrease in concentration of therapeutic ^{131}I in these tissues as a consequence of the effects of a preceding administration of 2–10 mCi of diagnostic [131]I. The evidence for this effect has been: changes in target-to-background patterns on scintigraphic images,[18–21] quantitative decreases in fractional uptake of radioiodine by the tissues,[20,22–24] and lesser responses to the therapies with [131]I.[25,26]

To obviate what has been thought to be stunning, ^{123}I has been suggested as a substitute for [131]I. Compared to ^{131}I, less radiation per mCi will be imparted by ^{123}I, but diagnostic sensitivity for tumors was less with ^{123}I than with [131]I.[25] Moreover, dosimetry is difficult to perform with the rapidly disappearing (half life 13 h) [123]I.

Although fractional concentrations of therapeutic ^{131}I have been found to be smaller than those of diagnostic ^{131}I at the same time points, it is not clear whether this difference is related to the early radiation effects from the diagnostic or the therapeutic [131]I. Probably there is little if any radiation effect imparted by diagnostic ^{131}I of 2 mCi[27] and especially of 1 mCi. Sensitivity can be preserved by increasing the time of data acquisition after the smaller amounts of [131]I. There-fore, unless one is convinced that arbitrary amounts of ^{131}I are optimal for treatments of patients with thyroid carcinoma, the value of dosimetry as described above would seem to outweigh any drawback of stunning.

CONCLUSIONS

The principles of radiation dosimetry have been used to develop practical measurements in patients who are to be treated with ^{131}I for well-differentiated thyroid carcinoma.

The retention of radioiodine in a patient's body is readily assayed in a clinical nuclear medicine laboratory. Based on the retention at 48 hours (2 days) a prescription for therapy with ^{131}I can be made that will be within the guidelines established years ago to avoid toxicity. From knowledge of the wide variation in retention of radioiodine among patients, a *usual* prescription for therapeutic ^{131}I can be modified to give more mCi if retention is low, increasing efficacy, and fewer mCi if retention is high, ensuring safety.

Absorbed radiation to blood has served to predict bone marrow depression from [131]I. In most patients, radiation of blood is correlated with the retention in the body. Cognizance of the free thyroxine concentration will enable modification of the prescription of ^{131}I to keep treatments within the established guidelines for safety.

When carcinomas are 1 cm and larger in diameter but are not visible on scintigraphic image, it is unlikely that the usual amounts of therapeutic ^{131}I will impart effective radiation to the tumors.

Biological responses are the final arbiters of dosimetry. Changes in indices of tumor status—clinical, scintigraphic, radiographic and serum thyroglobulin—reflect efficacy. Post-therapy concentrations of blood elements can portend toxicity.

The lower amounts of diagnostic ^{131}I are unlikely to produce appreciable stunning of the thyroid carcinomas.

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