Complications, Sequela and Dosimetry of Iodine-131 Therapy for Thyroid Carcinoma

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Iodine-131 therapy is widely recognized as a valuable adjunct in the management of thyroid cancer (*1,2*). In general, side effects are mild and self-limited and severe complications are rare enough that the benefit of therapy typically outweighs the risk. However, with large doses of ^{131}I, life-threatening sequela such as leukemia, severe bone marrow depression followed by hemorrhagic or infectious complications, and/or radiation pneumonitis/pulmonary fibrosis have been reported, albeit rarely (*3–5*).

We believe it is important to perform careful ^{131}I dosimetric studies prior to therapy for metastatic disease in order to maximize the dose delivered to the tumor sites while limiting the whole-body exposure and minimizing the risks of complications. However, even with such measurements, unexpected problems with ^{131}I clearance may develop and lead to excessive radiation exposure and associated complications.

Reported here is a case where ^{131}I therapy, guided by dosimetric studies, was given for widespread, clinically aggressive, metastatic papillary/follicular thyroid cancer. Unexpected whole-body retention of the ^{131}I resulted in extensive oral candidiasis, severe bone marrow depression, and eventually an episode of gram-negative sepsis.

CASE PRESENTATION

A 70-yr-old white male underwent a total thyroidectomy in 1986 for papillary/follicular carcinoma. He received 138 mCi of ^{131}I postoperatively for ablation of residual thyroid tissue. He was given an additional 150 mCi of ^{131}I in October 1989 for locally recurrent tumor. TSH levels were >30 μU/ml at the time of this and all subsequent ^{131}I therapies and scans. In April 1989, he fractured his right hip in an automobile accident; however, the ^{131}I whole-body scan in October 1989 did not show uptake at the fracture site. In June 1990, he was admitted with nonunion of his right hip fracture. A whole-body ^{131}I scan done at that time showed intense ^{131}I uptake in the hip fracture, very subtle uptake in the cervical neck bed, and no other lesions. Because he had received a therapeutic administration of ^{131}I within the previous year, it was felt that ^{131}I treatment should be postponed. In December 1990, a dosimetric study (described below) and repeat whole-body ^{131}I imaging were performed. The whole-body ^{131}I images of December 1990 showed multiple vertebral metastases along with bilateral lung uptake not seen in June 1990. Chest x-rays showed two small nodules in the left lung and no abnormalities in the right lung.

After dietary restriction of iodine for 1 wk, 5 mCi of ^{131}I-NaI were administered orally. Activity in the blood and urine were followed for 1 wk thereafter using a well-type gamma counter, along with whole body activity using a gamma camera without the collimator, and activity in the hip lesion using anterior and posterior views with the gamma camera. Time-activity curves were then used to determine the cumulative activity in the blood, hip lesion and whole body. From these measurements, it was determined that 40% of the administered activity was retained at 48 hr, and that the blood dose, calculated according to the method of Benua et al. (*3*), was 0.77 rads/mCi administered activity.

The region of increased ^{131}I uptake in the hip, as seen on orthogonal views, was a somewhat irregular volume of approximately 50 to 75 cm^3. The average dose to that region, as determined from the measured cumulative activity and from published dosimetry data (*6,7*), was approximately 50 to 75 rads/mCi administered activity.

Benua et al. (*3*) have established three criteria which determine the maximum activity that may safely be administered: (1) a blood dose of no more than 200 rads, (2) a retained activity of no more than 120 mCi at 48 hr, and (3) in those patients with diffuse lung metastases, a retained activity of no more than 80 mCi at 48 hr.

In our patient, due to the presence of diffuse pulmonary uptake at this time, the limiting criterion was a 48 hr retention of 80 mCi, and the corresponding administered activity was 200 mCi; this administered activity gave a

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predicted dose to the hip lesion of about 10,000 to 15,000 rads. Maxon and colleagues have demonstrated a significantly increased response rate when doses in excess of 8,000 rads are delivered to a metastatic thyroid lesion (*8*). Consequently, an activity of 200 mCi was prescribed and the patient received an actual administered activity of 193 mCi of ^{131}I in December 1990. Radiation survey meter readings following this administration were consistent with the predicted decrease in activity as a function of time.

One week post-therapy, a whole-body scan was performed which showed multiple lesions in both the appendicular and axial skeleton not seen on the pretherapy images. In June of 1991, the patient returned to the hospital with nontraumatic fractures in the right humerus and left clavicle and continued nonunion of his right hip fracture. A review of the post-therapy ^{131}I images showed metastases at these sites. Repeat ^{131}I imaging showing disappearance of several tumor sites seen in December 1990 and substantially decreased ^{131}I uptake in the right hip. However, there were also several new skeletal lesions. Of importance, the previously seen ^{131}I lung uptake was no longer apparent.

A final ^{131}I therapy was given in August 1991 using the dosimetric measurements obtained in December 1990 as a guide. The serum creatinine level was 1.4 mg/dl with a BUN of 21 mg/dl. These values were unchanged from December 1990. In the absence of pulmonary uptake, 200 rads to the blood became the limiting criterion; this corresponded to an administered activity of 250 mCi. Based on the very aggressive nature of the tumor with ongoing development of metastases and fractures, we felt that the potential benefits of a repeat therapy using this higher administered activity outweighed the risks.

A low iodine diet was initiated 1 wk before and continued for 1 wk after the therapy. The patient was instructed to suck on hard candy every hour and nursing staff and the patient were given directions to push oral fluid intake. The WBC count was 5.6×10^3 cells/mm^3 and the platelet count was 135×10^3 cells/mm^3 prior to therapy. The patient had a longstanding anemia of chronic disease and his hemoglobin level prior to therapy was 9.7% g.

Day 0: 247 mCi of ^{131}I was administered orally.

Day 1 post-therapy: Radiation survey meter readings indicated an 85% retention of ^{131}I. Figure 1 shows retained whole-body ^{131}I activity over the course of the hospitalization. The patient felt well but showed slight confusion and disorientation.

Day 2 post-therapy: The patient reported feeling tired with generalized malaise but he denied nausea, vomiting and salivary gland pain. Survey meter readings showed that activity retained had dropped to 70% (175 mCi). Oral fluid intake was considered inadequate and an intravenous line was started, but the patient became agitated and pulled it out.

Day 3 post-therapy: A second intravenous line was started, but was also pulled out. The patient was disoriented and agitated. Iodine-131 retention was 56% (140 mCi). Since the patient had not had a bowel movement for five days, oral laxatives were given which led to copious amounts of stool later that evening. The patient remained agitated and spread feces and urine around the room.

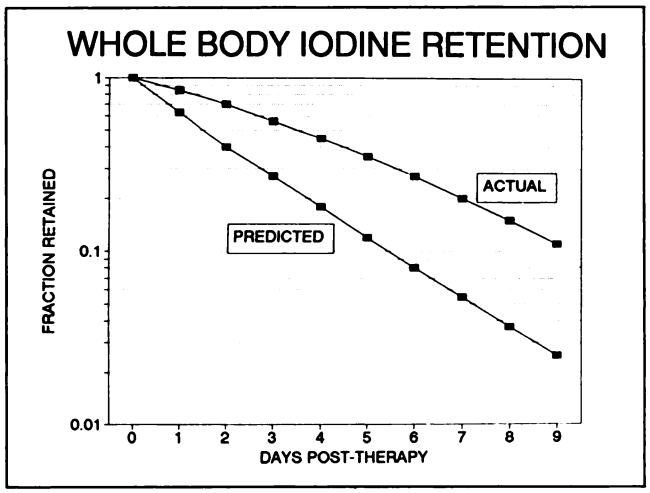

FIGURE 1. Fraction of ^{131}I activity retained as a function of time. It is apparent that the actual whole-body clearance (upper line) of ^{131}I from the therapeutic administration of 250 mCi was substantially slower than the predicted clearance (lower line) based on the dosimetric study.

Day 7 post-therapy: Patient reported burning mouth pain and there were numerous white/grey oral lesions which were erythematous at the bases. He was given viscous lidocaine to swish and swallow and cultures of the lesions were obtained.

Day 9 post-therapy: The patient reported generalized malaise and worsening mouth pain. The oral lesions became extensive, involving almost the entire oral mucosa. Culture results were positive for candida and oral Nystatin was ordered.

The patient was removed from isolation when his whole-body activity reached 8 mCi. Upon removal from isolation his mental status quickly returned to normal.

Day 34 post-therapy: The patient reported chills. Rectal temperature was 104.5, and blood pressure was 90/60. The total WBC count was 2.7×10^3 cells/mm^3. The patient was pancultured and was started on Mezlocillin and Gentamicin. The following day results of the urine culture came back positive for *Pseudomonas aeruginosa.*

Day 36 post-therapy: The patient remained febrile (103.6 rectal). Based on urine culture sensitivities, the Gentamicin was discontinued and the patient was started on Ceftazidime. The blood cultures taken on Day 34 came back positive for gram-negative rods. The following day the patient became afebrile.

Day 37 post-therapy: Platelet count reached its lowest level of 11,000 and a platelet transfusion was ordered, but ultimately not given. Platelet count returned to 23,000 spontaneously on Day 39. At no time did he experience a bleeding episode.

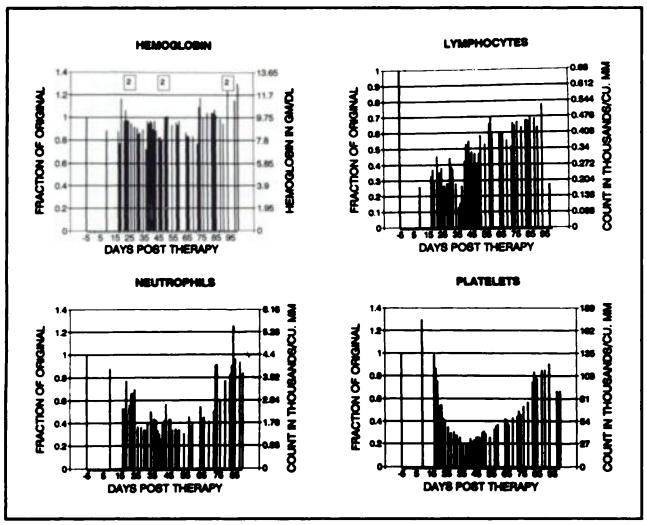

FIGURE 2. Changes in hematologic parameters after therapy. Decreased hemoglobin concentration (upper left) required two units of packed red cells on each of three separate occasions. Lymphocyte concentration (upper right) showed a substantial initial drop within 1 wk of therapy, then gradual return to pretreatment levels. Neutrophil concentration (lower left) showed a maximum decrease between 5 and 8 wk post-therapy. Notice the low neutrophil counts (Days 25–33) just prior to the uroseptic episode (Day 34). The nadir for platelet concentration (lower right) is seen around 5 wk with levels around 20,000/mm^3 and gradual rise to near pre-treatment levels at 3 mo.

Changes in hematologic parameters are shown in Figure 2. The patient showed a gradual decrease in hemoglobin throughout the 3 mo following therapy despite the transfusion of two units of packed red blood cells on three occasions during the post-therapy period. However, as noted, the patient had a significant ongoing anemic disorder prior to the ^{131}I therapy. The platelet levels showed an unexplained increase at Day 9 post-therapy, followed by a sharp fall over the next 28 days. The nadir occurred at 37 to 39 days post-therapy and represented a fall to below 20% of the pre-therapy levels.

There was a rapid decline in lymphocyte count to 25% of the pre-therapy level during the first week with gradual recovery over the ensuing 3 mo. Neutrophil counts showed a more gradual decline, with the lowest absolute count, slightly over 1100 neutrophil/mm^3, occurring at Day 40, and recovery to the pre-therapy range after Day 82. The increase in neutrophil concentration between Days 33 and 38 coincided with the patient's urosepsis. Just prior to the uroseptic episode, the neutrophil count had dropped to 1.5×10^3. Finally, whole-body ^{131}I images obtained 4 mo after the final therapy showed significant regression of the skeletal metastatic disease (Fig 3).

DOSIMETRY

The purpose of a dosimetric study prior to therapy is to obtain information potentially helpful in deciding whether to treat a given patient with ^{131}I, and if so, how much activity to administer. Specifically the information desired is whole body retention of activity at 48 hr after administration, dose to the blood per unit administered activity, and possibly, dose to one or more tumor sites within the body per unit administered activity. We have generally followed the protocol of Benua et al. (*3*) in obtaining and analyzing the data needed to determine dose to the blood and used methods similar to those of Thomas et al. (*9*) to determine dose to the lesion(s). What follows is a more detailed description of the methods used in performing a dosimetric study, including observations and recommendations based on our experience.

Administration of Tracer Dose

When possible we administer the tracer dose on a Monday morning and collect data for seven days thereafter. When this is not possible, we obtain data for at least four days after administration.

We have successfully performed dosimetry studies with administered activities from approximately 0.5 to 10 mCi. An administered activity of 1–2 mCi is adequate for determining whole-body retention, dose to the blood, and dose to sites with high uptake (e.g., a functioning thyroid). An administered activity of 5–10 mCi may be necessary if

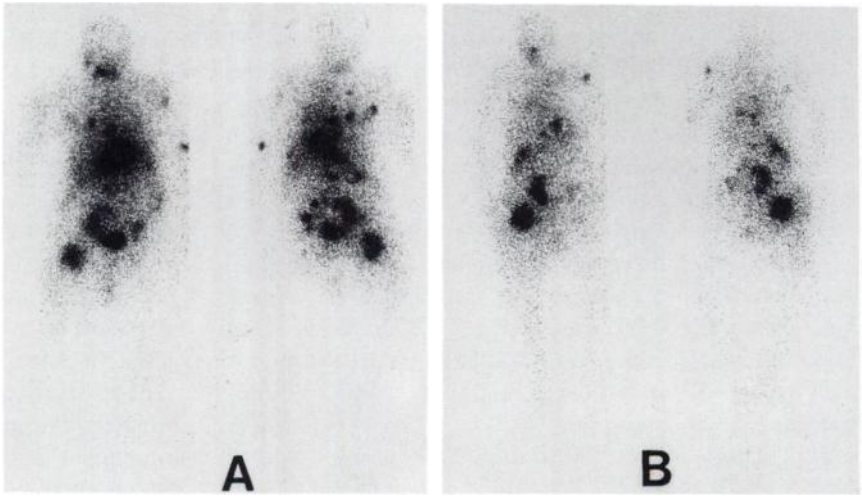

FIGURE 3. Anterior and posterior whole-body images from 8/91 (A). Multiple metastatic lesions are seen in the spine, pelvis and ribs. Also present are lesions in the right proximal femur and distal left humerus. Follow-up whole-body images 4 mo after therapy (B) show either absent or substantially reduced activity in a number of the lesions seen on the pretherapy study. Unfortunately, the hip lesion remained largely unaffected by the therapy. Both sets of images were obtained 48 hr after administration of an 8 mCi dose of ^{131}I.

a whole-body diagnostic scan is to be performed at the same time as the dosimetric study, or if one wishes to determine the dose to sites with lower uptake. It should be taken into consideration, however, that an administered activity of 5–10 mCi may result in a decreased uptake of activity by tumor sites in the subsequent therapy (*1,10*).

Two counting standards are prepared at the time of tracer dose administration, one of approximately 200 μCi for use with the gamma camera, and one of approximately 0.2 μCi for use in the well scintillation counter.

Data Collection

All urine is collected in daily fractions (0–24 hr, 24–48 hr, . . . , 144–168 hr after administration). Blood samples are collected (in 4 ml tubes with anticoagulant) at 4, 24, 48, 72, 96, and 168 hr after administration. The volume of each day's urinary excretion is measured, and 1 ml aliquots of the blood and urine samples are counted in the well counter; background and the well counter standard are also counted.

Total activity in the body is measured immediately after tracer dose administration and again at 24, 48, 72, 96 and 168 hr thereafter by removing the collimator from the gamma camera and aiming the camera at the patient, who is positioned standing approximately 15 ft away; five-minute counts of the patient, background, and the gamma camera standard are obtained. If possible, the counts are made on the same camera each day with the patient and camera in the same position.

Activity in any site(s) of interest is measured at 24, 48, 72, 96 and 168 hr after administration from conjugate images (anterior and posterior) with the gamma camera. Conjugate views of the gamma camera standard in a water or plastic phantom with a thickness similar to that of the patient at the site of interest are also obtained.

Data Reduction

The first step in analyzing the data is to determine activity in the blood, whole body and any site(s) of interest as a function of time. Since all counting is relative to a standard, which decays physically along with the activity in the patient, this initial determination includes only biological changes in activity.

Whole-body activity is determined from a combination of urinary excretion measurements and total body activity measurements obtained with the gamma camera. We have found that there is considerable redistribution of activity in the first several hours after administration of the tracer dose, largely from deeper to more superficial sites, such that the change in whole-body counts during the first 24 hr generally does not fully reflect the decrease in activity measured by counting the first day's urinary excretion. On the other hand, urinary excretion usually accounts for only about 80%–90% of the administered activity, even when whole-body counting shows that less than 1% of the administered activity remains. Hence, we normally use urinary excretion to determine the decrease in activity over the first 24 hr and whole-body counting to determine the decrease in activity beyond 24 hr. We are considering not collecting urine after the first 24 hr, since we seldom use the counting data. The initial whole-body counting data are also not used in the dosimetry study, but may be useful in interpreting the survey measurements after the subsequent therapy to determine if activity is being eliminated as expected.

Activity in the site(s) of interest is determined, as described by Thomas et al. (*9*), from the geometric mean of net counts per min (after background correction) in a region of interest (usually circular) on the conjugate views. Geometric mean is the square root of the product of the anterior and posterior count rates, and is compared to geometric mean for the gamma camera standard.

Determination of Cumulated Activity

The next step in data analysis is to determine the cumulated activity for the blood, whole body and site(s) of interest. Cumulated activity is the area under the curve when activity is plotted as a function of time, and represents total number of decays which take place until the radionuclide is completely removed by biological and/or physical decay.

Activity (as a fraction of administered activity for the whole body and site(s) of interest, or as a fraction of administered activity per unit volume for the blood) is plotted against time after administration on semi-log graph paper. At this point all activity data have been obtained relative to standards, so that only biological changes in activity, and not physical decay, are plotted. The resultant curves will appear either to fit a straight line (sometimes the case for sites of interest), or to be concave upward (almost always the case for blood and whole-body activity). If the data appear to fit a straight line, we fit such a line visually and determine the initial activity and biological half-life in days. Cumulated activity is the product of initial activity, effective half-life, and the constant 1.443 (1/ln 2), or:

$$\tilde{A} = 1.443\ A_0 t_e,$$

where $\tilde{A}$ is the cumulated activity. A_0 is the initial activity, and t_e is the effective half-life. The effective half-life is determined from the physical and biological half-lives by the equation:

$$1/t_e = 1/t_p + 1/t_b,$$

where t_p is the physical half-life (approximately 8 days) and t_b is the biological half-life.

If the curve is concaved upward, we fit it with two exponential components. First, the last few points are fit to a straight line, and the initial activity and biological half-life in days for that line are determined. The value of this component for each earlier measurement point not used to fit the longer-lived component is subtracted from the original activity value, and the remainders are replotted and fitted with a straight line. The cumulated activities for each component are then calculated as above and

summed. While theoretically one could use more than two components to fit the data, we have not done so in practice.

Dose Calculation

Dose to the blood is calculated as described by Benua et al. (*3*). There are two significant sources causing dose to the blood; beta particles emitted within the blood, and gamma rays emitted anywhere in the body. For purposes of dose calculation, it is assumed that all the energy in the form of beta particles emitted within the blood is absorbed within the blood, and that 40% of the energy emitted as gamma rays is absorbed within the body, with the blood receiving the same average dose from gamma rays as the whole body. Based on these assumptions and the then-current estimates of average beta and gamma energies emitted per decay, Benua et al. (*3*) determined that beta dose to the blood would be equal to cumulated activity for the blood per unit volume multiplied by 10,000 rad-ml/mCi-day, and that gamma dose to the blood would be equal to cumulated activity for the whole body multiplied by 8.16 rad-kg/mCi-day and divided by the patient's body mass. Thus,

$$D_b = 10{,}000\ \tilde{A}_b + 8.16\ \tilde{A}_w/M,$$

where D_b is dose to the blood in rads, $\tilde{A}_b$ is cumulated activity per unit volume for the blood in mCi-days/ml, $\tilde{A}_w$ is cumulated activity for the whole body in mCi-days, and M is the patient's body mass in kg.

Dose to a lesion site is determined based on cumulated activity for the site, and on the size and shape of the site as determined by either computed tomography or by radionuclide imaging. We calculate dose to the site based on an equilibrium dose constant (average energy emitted per decay) of 9,800 g-rad/mCi-day in the form of nonpenetrating radiation, and 19,300 g-rad/mCi-day in the form of penetrating radiation (*7*). We assume that all the nonpenetrating radiation emitted within the site is absorbed in the site, and that a fraction of the penetrating radiation, depending on size and shape of the site (*6*), is absorbed. Typical values of the absorbed fraction for penetrating radiation (f) are 0.011 for a spherical lesion with a mass of 1 g, 0.025 for a 10-g lesion, 0.039 for a 40-g lesion, and 0.072 for a 100-g lesion (*6*). Thus dose to the lesion, D_l, is given in rads (approximately) by the equation:

$$D_l = 9{,}800\ \tilde{A}_l(1 + 2f)/m,$$

where $\tilde{A}_l$ is the cumulated activity in the lesion in mCi-d, and m is the mass of the lesion in g.

DISCUSSION

We believe, as others have recommended, that careful dosimetric measurements are necessary to optimize therapy in most cases where ^{131}I is used to treat metastatic thyroid carcinoma. The majority of centers using radioiodine in the treatment of metastatic well-differentiated thyroid carcinoma follow a method similar to that recommended by Beierwaltes (*11*), wherein the administered activity is in part based upon the location of metastases. This protocol consists of the following: (1) 150–175 mCi for cervical lymph node metastasis; (2) 175–200 mCi for pulmonary metastasis; and (3) 200 mCi for skeletal metastasis. Such an empirical method is attractive since it is straightforward and avoids lengthy in vivo measurements and calculations, and is supported by extensive experience and well-documented success. Nevertheless, there are patients in whom the whole-body clearance of ^{131}I is sufficiently rapid that therapy doses of greater than 200 mCi may be given safely, thus increasing the potential success of the therapy. Conversely, there are patients in whom the delayed clearance of ^{131}I could lead to excessive and undesirable exposures from administered doses in the 150–200 mCi range. Adjustments in the therapy dose based on dosimetry data compensate for patient-to-patient variations in the rate of iodine clearance. However, even with such measurements, it may not be possible to ensure the expected and adequate clearance of ^{131}I in every patient.

Several studies have indicated that performing dosimetric calculations for specific lesions is useful in assessing the probable response of those lesions to ^{131}I therapy (*8,9, 12,13*). If resources are available, a combined approach is optimal, incorporating dosimetry estimates for specific lesions along with the blood dose and whole-body retention estimates. Maxon et al. (*8,12*) found that treatment of lymph node metastases with ^{131}I was generally successful when the dose delivered to the metastases was at least 8500 rads, and that there was little or no response when the dose delivered was below 3500 rads. Similarly, Kimmig and Hermann (*13*) found no response to ^{131}I therapy for metastatic thyroid cancer when the tumor dose was less than 4000 rads, and an excellent response when the tumor dose was at least 10,000 rads. Maxon et al. (*12*) have pointed out the advantages of using dosimetric studies to standardize tumor dose rather than administered activity. A combined approach, using a dosimetric study to determine both the optimum administered activity based on tumor dose and the limiting activity based on blood dose and whole-body retention, is illustrated in Figure 4. The decision tree shown applies to a patient with a single lymph node metastasis. In other cases, such as the present one, in which the patient had multiple metastases, other decision criteria might determine the activity selected.

A number of measures may be taken in an effort to increase the dose delivered to a metastatic lesion, independent of administered dose. Moreover, it is critical that the same conditions are imposed for both the dosimetric evaluation and the therapy. It is crucial that TSH levels be adequate to ensure high ^{131}I uptake within tumor cells. While disagreement exists over the optimal TSH level for therapy, most agree that levels in excess of 30 μU/ml are likely to be sufficient (*2*). To minimize the symptomatic period of hypothyroidism, T4 should be discontinued and simultaneously T3 initiated and continued for a period of

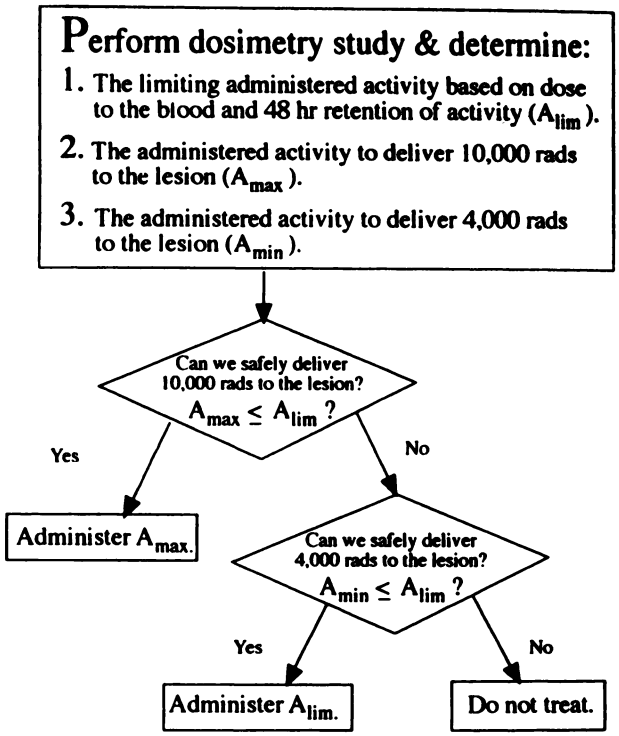

FIGURE 4. Combined dosimetric approach to the treatment of thyroid carcinoma. The figure shows the decision tree we would follow for a patient with a single lymph node metastasis. In this case, we would deliver 10,000 rads to the tumor if and only if this could be done without exceeding the limiting activity as determined by the criteria of Benua et al. (3). Otherwise we would administer the limiting activity, provided that it would deliver at least 4,000 rads.

3–4 wk prior to being withdrawn. Iodine depletion through the use of a low-iodine diet for 7–10 days prior to therapy is also desirable. Several investigators have found substantial increases in the tumor uptake of radioiodine under conditions of reduced iodine intake (*14,15*). The additional use of diuretics to enhance iodine depletion has met with mixed results and is probably not indicated. Lithium carbonate is well known to suppress the release of thyroid hormone from thyroid tissue, and this effect appears to be enhanced in cancerous thyroid tissue (*16*). Ain and colleagues found that serum lithium levels of 0.8–1.2 mmol/liter prolonged the biological half-life of ^{131}I in 10 of 12 thyroid tumors without a significant effect on whole-body exposure (*17*). The effect was greatest for tumors with a biological half-life of less than 6 days, with little advantage when the half-life exceeded 8 days. Therefore, decisions regarding the concomitant use of lithium should be based to some extent upon the measurements of ^{131}I retention in each lesion to be treated.

The dosimetry evaluation used to guide the selection of the final administered activity in this patient was performed 8 mo prior, at the time of the previous therapy. Due to the debilitated condition of the patient (multiple fractures, etc.) and the fact that BUN and creatinine levels had remained unchanged, we decided not to repeat the dosimetry measurements. While such repeat measurements might have been desirable, most probably the results would not have been substantially different. Rather, it is likely that the unanticipated ^{131}I retention in our case was the consequence of both inadequate diuresis from poor hydration and constipation with accumulation of ^{131}I in the stool.

A rough estimate of bone marrow dose for this patient can be made as follows. Based on the dosimetric study, we predicted a blood dose of 192 rads from a 250-mCi therapy. Since the clearance of ^{131}I was considerably slower than predicted, the actual cumulative activity in the whole body was approximately 1.8 times that predicted. The blood dose, if increased proportionately, would be about 345 rads. Calculation of blood dose by more recent methods (*18*) yields a lower estimate, about 0.8 times that obtained by the method of Benua et al. (*3*), or about 280 rads. It has been estimated that the bone marrow dose in thyroid carcinoma patients treated with ^{131}I is around 0.7 times the blood dose (*18,19*). Consequently, we estimate that the actual bone marrow dose was approximately 200 rads. Moreover, the changes in blood cell counts seen in our case (Fig. 2) are similar to those seen after accidental human exposures of 200–300 rads to the marrow (*20*), and include an apparent abortive recovery (temporary rise in neutrophil count) at around 20–25 days post-therapy.

Bone marrow suppression is a serious and potentially life-threatening complication of ^{131}I therapy. Benua et al. (*3*) reported severe and permanent bone marrow suppression in 8 of 59 patients treated with ^{131}I. However, dosimetric evaluations in six of these eight patients suggested that they received in excess of 300 rads to the blood. In using 200 rads to the blood as the upper limit, Leeper et al. (*21*) and Van Nostrand et al. (*22*) found no instances of permanent suppression, although mild, transient decreases in blood cell counts were seen in 90% of the patients in the Van Nostrand series (*22*). Extensive skeletal metastases and prior radioiodine therapy are likely to increase the severity, and duration of marrow suppression. The prior cumulative administered activity of 481 mCi was probably a contributing factor to this patient's significant bone marrow depression, and while the white cell and platelet counts before the final therapy were normal, the marrow reserve capacity may have been depleted.

Although the severe bone marrow depression in this case was transient, dangerously low levels of neutrophils and platelets were seen from 4–6 wk post-therapy. Maximum bone marrow depression typically occurs at about this time in patients given high dose ^{131}I therapy (*1*). The platelet count dropped to around 20,000, representing a level at which the risk of spontaneous bleeding becomes significant. Hemorrhage into a cerebral metastasis, or even the precipitation of cerebral edema, can lead to significant neurological sequelae, even death (*23,24*). Strong consid-

eration should be given to pretreatment with corticosteroids and/or mannitol if ^{131}I therapy is to be undertaken in the presence of cerebral metastases. The neutropenia at 25–33 days probably predisposed to the uroseptic episode requiring aggressive antimicrobial therapy. Infectious complications, particularly with gram negative organisms, are known to be more frequent in neutropenic patients.

Oral candidiasis has been described with head and neck external beam irradiation (*25*). It is possible that small oral mucosal ulcerations due to radiation were precursors to the invasive mucocutaneous candidiasis seen in this patient. The ^{131}I concentration in the oral cavity was probably quite high due to continued salivary secretions and inadequate oral fluid intake. In addition, T-lymphocyte deficiency/dysfunction is known to predispose to mucocutaneous candidiasis (*26*). At the time of peak severity of oral candidiasis, lymphocyte count in our patient was less than 200 cells/mm^3. Total counts less than 1,000 constitute absolute lymphopenia and the degree to which the drop in lymphocyte counts predispose to infection is further modulated by lymphocyte dysfunction (*26*).

Other potential complications of ^{131}I therapy include acute radiation sickness, with headache, nausea, and emesis, as well as sialoadenitis. These typically appear during the first several days after ^{131}I therapy and resolve spontaneously, although sialoadenitis may persist for an extended period of time (*27*). The routine use of hard sour candies can reduce the incidence and severity of sialoadenitis (*2, 22*). Nausea and emesis occur with sufficient frequency to warrant standing orders for anti-emetics. Radiation pneumonitis and pulmonary fibrosis have been reported as a complication of ^{131}I therapy (*3*). However, by restricting the whole-body retention at 48 hr to less than 80 mCi in patients with pulmonary metastases, this complication can usually be avoided (*22,27*).

Maxon and Smith (*1*) have reviewed the literature on leukemia occurring after ^{131}I therapy and found 14 cases from a group of 2,753 patients who received large doses of ^{131}I. To minimize the likelihood of a secondary leukemia, Beierwaltes and coworkers (*11*) advocate a 1 yr interval between therapies and a total cumulative administered activity not to exceed 800 mCi. Concern has been raised that ^{131}I therapy may predispose to the anaplastic transformation of well-differentiated thyroid carcinoma. However, it appears that this occurs no more frequently in those treated with radioiodine than in those who have never received ^{131}I (*28*). Other sequela such as infertility and chromosomal aberrations are discussed in detail in the excellent review on the management and treatment of metastatic thyroid carcinoma by Maxon and Smith (*1*).

Aggressive measures to insure optimal whole-body clearance of ^{131}I after therapy may be required in certain instances. In this patient, retention of stool due to constipation led to the need for laxatives to clear the ^{131}I. Maxon and Smith (*1*) have proposed the use of laxatives in all patients not having at least two stools per day after therapy with ^{131}I. For several reasons, primarily patient noncompliance, oral fluid intake was not adequate in this individual, resulting in a need for intravenous fluid therapy. Unfortunately, the patient's agitated mental state led to his removing the intravenous line on two separate occasions. Strong consideration was given to using sedation and/or restraints so that the intravenous line could be maintained, and, in retrospect, perhaps a more aggressive use of these measures would have been prudent. The confused and agitated state, not uncommon in hospitalized elderly patients (*29*), remitted after he was moved from isolation.

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