The Significance of I-131 Scan Dose in Patients with Thyroid Cancer: Determination of Ablation: Concise Communication

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Twenty-four patients with differentiated thyroid cancer were studied with diagnostic I-131 neck and chest scans after having undergone bilateral subtotal thyroidectomy and initial I-131 therapy with either 30- or 100-mCi doses. With an endogenous stimulation protocol, follow-up studies were performed with neck and chest scans using 2 and 10 mCi I-131. A 400% increase in sensitivity was found with a 10-mCi dose relative to a 2-mCi dose. Comparison with therapeutic doses of 30 and 100 mCi resulted in further increases in the detection of residual iodine-avid tissue.

We conclude that a 2-mCi or lower dose of I-131 is inadequate in evaluating residual iodine-avid tissue visually in patients with thyroid cancer. The study does not answer the critical question of whether it is necessary to treat a patient presenting a negative 2-mCi but a positive 10-mCi scan. It may be appropriate to define ablation visually as well as clinically, with further studies directed toward determining a treatment rationale in this patient population.

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Iodine-131 has been recommended extensively as a treatment modality for thyroid cancer (*1–8*). Recent reviews indicate the necessity for high doses (30–200 mCi) of I-131 in patients with papillary or follicular carcinoma, with a recommendation that treatment be continued until ablation occurs (*9,10*). Most reports fail to define ablation rigorously, but it is generally accepted to signify absence of iodine-avid tissue on a diagnostic I-131 scan. The doses of I-131 for diagnostic scanning in thyroid-cancer patients range from 200 μCi–5 mCi, with most reports recommending 1–2 mCi.

Because of long-term recurrences, it has been suggested that patients who have had high-dose I-131 treatment for thyroid cancer are best evaluated at 6- or 12-mo intervals with diagnostic I-131 scans (*11*). It is now recommended that the I-131 be administered orally following either withdrawal of exogenous thyroid hormone or a combination of withdrawal of exogenous hormone plus sequential TSH injections (*9,10*). Since subsequent large-dose treatment depends on the detection of residual foci in the thyroid bed or elsewhere, we felt it was important to evaluate the effect of I-131 scan dose on the detection of iodine-avid tissue.

METHODS

Twenty-four patients with surgically proven papillary, follicular, or mixed (papillary-follicular) thyroid cancer were included in this study. All patients had a bilateral subtotal thyroidectomy performed before a therapeutic dose of I-131, given 4–6 wk postoperatively. Follow-up neck and chest scans were obtained within 6–8 mo. If either the 2- or 10-mCi diagnostic follow-up scan was positive, the patient was treated with 30 or 100 mCi of I-131 and scanned again within 5–10 days.

In 21 patients, the initial study was performed with 2 mCi of I-131 and followed with a 10-mCi I-131 scan

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dose immediately after the 2-mCi scan. All studies were done using an endogenous stimulation protocol, with patients off all T-4 preparations for a minimum of 6 wk and T-3 preparations for 10–14 days. Scans were done in all cases 2–6 days after I-131 administration and were repeated at 7–10 days when 30 or 100 mCi of I-131 was given for ablation. A rectilinear scan (5-in. crystal) of the neck and chest was done at a speed of 36 cm/min for 2 mCi I-131 doses and at 36–45 cm/min for 10 mCi or more. Anger camera large-field scintiphotos of neck and chest scans were made in selected cases.

All scans were evaluated by at least two experienced nuclear medicine physicians, with comparisons made between the 2-mCi and 10-mCi scans. A subjective comparison of all abnormal foci was done using relative lesion-to-background activities as the basis for comparison. Chi-squared analysis was performed to compare results of the two levels of activity.

RESULTS

Table 1 summarizes the results for the 21 patients undergoing scan comparisons with 2 and 10 mCi of I-131. The large number of patients and sites in which the 2-mCi scan was negative and the 10-mCi scan positive indicates the lack of sensitivity of the 2-mCi dose in detecting residual iodine-avid tissue. Only four of 21 patients were positive on both the 2- and 10-mCi scans. These findings show a significant difference in the determination of ablation after 10 mCi as compared with 2 mCi of I-131 ($P = 0.001$).

Table 2 compares the 10-mCi I-131 scan dose with one of 30 mCi in detecting residual iodine-avid tissue. Whereas the difference was not as marked as in the 2–10 mCi comparison (and was not statistically significant), the 10-mCi dose either gave a majority of the detected sites a higher target-to-nontarget ratio, or enabled formerly undetected sites to become visible.

Table 3 is a comparison between the 10-mCi and 100-mCi I-131 scan following therapy. Again we find a slight improvement in the detection of iodine-avid tissue using the higher dose, with 100 mCi revealing two additional sites that were not seen with 10 mCi.

TABLE 1. NECK-CHEST I-131 SCINTIGRAPHY IN DIFFERENTIATED THYROID CARCINOMA: COMPARISON BETWEEN 2- AND 10-mCi STUDIES*

	2 mCi− 10 mCi−	2 mCi < 10 mCi	2 mCi= 10 mCi	2 mCi± 10 mCi+	2 mCi− 10 mCi+
number of patients	5	4	0	3	9
number of sites	—	5	0	3	14

* Symbols: − negative study; ± equivocal; + positive; = visibility equal; < visibility less than.

TABLE 2. NECK-CHEST I-131 SCANNING: 10 mCi COMPARED WITH 30 mCi (SYMBOLS AS IN TABLE 1)

	10 mCi− 30 mCi−	10 mCi< 30 mCi	10 mCi= 30 mCi	10 mCi± 30 mCi+	10 mCi− 30 mCi+
number of patients	0	5	4	0	0
number of sites	0	9	4	0	2

Figure 1 compares scans made with 2, 10, and 100 mCi of I-131 in a patient treated for papillary carcinoma of the thyroid. With 2 mCi the initial interpretation was equivocal, but 10 mCi showed a definitely positive site. On the basis of the latter scan, the patient was treated with 100 mCi of I-131. A new scan with 2-mCi of I-131 was performed 7 mo later, and suggested complete ablation of the iodine-trapping tissue. A 10-mCi dose again, however, showed persistent but reduced activity in the left side of the neck. The patient was treated with 100 mCi of I-131 and scanned again.

Figure 2 presents a patient who showed a single focus of increased activity in the mid neck with the 10 mCi I-131 scan. Following a 100-mCi scan, increased activity was also observed in the right upper part of the neck and in the mediastinum.

Figure 3 illustrates a patient who was inadvertently scanned initially with 10 mCi of I-131 and showed increased activity in the right side of the neck. Seven days later, with the patient still off all thyroid-hormone medication, 2 mCi of I-131 was administered and a new rectilinear scan made. No activity was observed in the neck with the 2-mCi dose. The patient was scanned again one week after administration of 30 mCi of I-131, and the area in the right side of the neck was again shown to be abnormal.

Serum TSH measurements were performed on seven patients before the administration of a 2-mCi scan dose, and again at the time of the 10-mCi scan performed up to 13 days later. There was no significant difference between the two TSH determinations by Student's paired t-test. (Mean TSH before 2 mCi was 147 μU/ml,

TABLE 3. NECK-CHEST I-131 SCANNING: 10 mCi COMPARED WITH 100 mCi (SYMBOLS AS IN TABLE 1)

	10 mCi− 100 mCi−	10 mCi< 100 mCi	10 mCi= 100 mCi	10 mCi± 100 mCi+	10 mCi− 100 mCi+
number of patients	0	5	5	0	0
number of sites	0	6	8	0	2

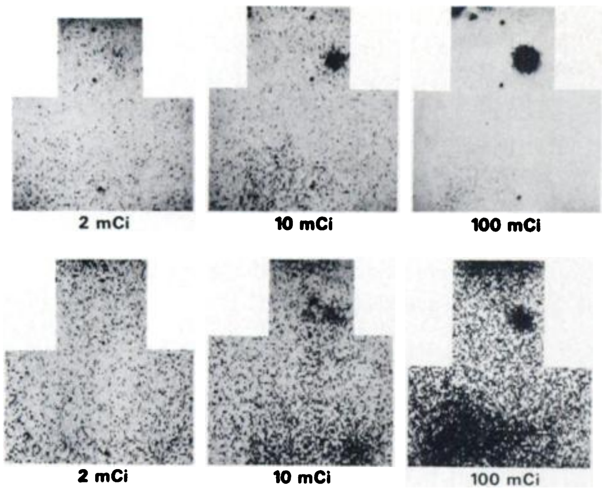

FIG. 1. Scan comparison before (a,b,c) and 7 mo following 100 mCi of I-131 (d,e,f). Note negative 2 mCi study, positive with 10-mCi, in lower set of scans.

and at the time of 10-mCi scan it was 160 μU/ml, $p > 0.1$.)

DISCUSSION

In 1959 Catz et al. demonstrated, in a limited number of patients, that high-dose (40–100 mCi) I-131 scintigraphy often showed abnormalities not detected using 1–2 mCi of I-131 (*12*). Several variables in this study remained uncontrolled, with patients being scanned while on large doses of exogenous thyroid hormone or receiving varying amounts of TSH for purposes of stimulation. In the current study, we attempted to eliminate the effect of exogenous TSH and/or exogenous thyroid hormone by utilizing an endogenous stimulation technique. Each patient, therefore, was his own control for both the low- and high-dose scans.

Nemec et al. have shown in differentiated thyroid cancer that the distribution of I-131 differed significantly between diagnostic (200–500 μCi) and thyroablative (100 mCi) doses of I-131. In 16% of patients in their study, the therapeutic scan was the only test able to demonstrate the presence of tumor tissue (*13*).

Several studies have indicated that the current protocol of endogenous stimulation (6 wk T-4 withdrawal, 10–14 days T-3 withdrawal) will result in increased TSH levels occurring at the time of diagnostic scans (*14,15*). These studies have indicated that there is a rapid rise in TSH following T-3 withdrawal, but by 11–14 days no further significant increases in TSH levels were observed. Serial TSH determinations in seven of our patients confirmed the lack of a significant increase at the time the 10-mCi scans were performed. Our findings suggest that the effect of increasing dose was the prime reason for detection of metastases and/or residual iodine-trapping tissue and not the additional 4–6 days of delay in performing the high-dose scan, since TSH levels were essentially unchanged.

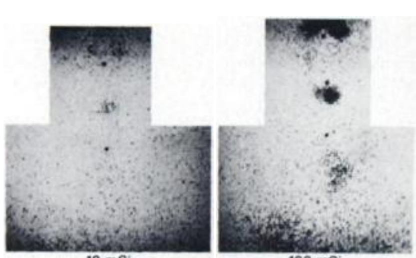

FIG. 2. Patient with differentiated thyroid cancer, showing only increased mid-neck activity on 10-mCi study, while 100-mCi post-therapy scan shows uptake in mid neck, right upper neck, and mediastinum.

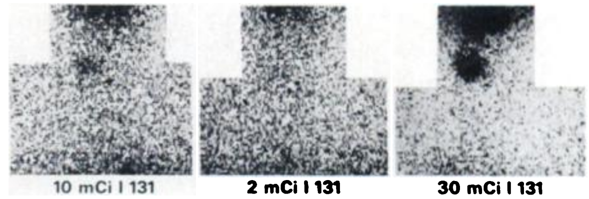

FIG. 3. Patient with mixed (papillary-follicular) thyroid cancer, initially scanned with 10 mCi of I-131, with marked uptake in right side of neck. While still off thyroid, patient was scanned again in 7 days with 2 mCi, and produced a negative scan. Another scan, one week later, with 30 mCi I-131 again showed abnormality in right side of neck.

A 10-mCi dose of I-131 represents a fivefold increase over 2 mCi. If one assumes the percentage uptake to be constant in a given region of iodine-trapping tissue, this should result in a fivefold increase in photon emission. If a 500-μCi dose is compared with a 10-mCi one, the latter would represent a 20-fold increase. Depending upon the sensitivity and resolution of the detection equipment used in making the scan, the fivefold or 20-fold increase in photon emission may be a critical factor in the visual detection of abnormalities.

The data in Table 1 demonstrate that of the 21 patients evaluated using the 2–10 mCi I-131 protocol, the 2-mCi scan would have indicated 14 "cures" and 3 "equivocals." Iodine-131 treatment would therefore have been given to only four patients in this group, since "ablation" would have been considered complete in 17 patients. However, increasing the dose to 10 mCi resulted in a positive test in 16 patients, an increase of 400%. Comparisons with higher scan doses—the 10 with the 30 mCi, or the 10 with the 100 mCi I-131—resulted in the detection of additional sites and somewhat higher target-to-nontarget ratios in the majority of patients.

The current study does not attempt to define an upper limit of I-131 dose to be used in the evaluation of thyroid cancer. It does suggest, however, that the 2-mCi I-131 scan dose, used in conjunction with available detection equipment, is inadequate in visually evaluating ablation in patients with thyroid cancer.

The study raises a critical question of treatment rationale in patients with a negative 2-mCi and a positive 10-mCi I-131 study. Since this situation implies a relatively low uptake of I-131 within the residual iodinestoring tissue, it is not clear whether, in this subgroup of patients, sufficient radiation can be delivered to accomplish a significant destructive effect.

The 2-mCi negative, 10-mCi positive group may represent a population of patients, described by Krishnamurthy et al. (*11*), who develop long-range recurrences of disease. If this is true, it would be important to recognize patients with residual activity who may not benefit directly from immediate I-131 treatment but who need more frequent follow-up studies. It may be necessary, therefore, to define ablation clinically as well as visually, with the understanding that high-dose I-131 scintigraphy (10–100 mCi of I-131) be used to assess ablation visually while the lower-dose studies (1–2 mCi) would define ablation clinically, indicating tissue with sufficient uptake to warrant high-dose I-131 therapy.

Diagnostic I-131 thyroid imaging with 50–100-μCi tracer doses has demonstrated that thyroid tissue can be visualized easily with as little as 0.25–0.5 μCi/g, corresponding to uptakes of approximately 10% or greater for the average-sized gland. The μCi/g content of a target tissue is an important factor in determining the visibility of that tissue, but there are other variables that can significantly affect visualization of target tissues containing equal μCi/g concentrations, namely, the target-to-background ratios, absolute volume of the target, volume geometry of the target (spherical volume versus an equal flat thin planar volume), and the imaging technique used (*16*).

In treating thyroid cancer, the dose delivered to the tumor depends on the concentration of radioiodine in μCi/g deliverable to the tissue as well as the effective half-life and the radiosensitivity of the tumor. If one assumes that visualization of target tissue is not limited by factors other than the radioiodine concentration, then a relationship can be approximated between the dose necessary for visualization and the treatment dose.

It has been shown by quantitative techniques that visualization of a tumor by a 2-mCi I-131 diagnostic scan may not always be a criterion for successful therapy with 100 mCi of I-131, since the calculated dose delivered to the tumor by 100 mCi can be less than 1500 rads even when the tumor is clearly demonstrated on a 2-mCi scan (*16*).

A 0.5-μCi/g detection level of residual iodine-trapping tissue could theoretically be obtained with a 0.005% uptake per gram when imaging is done with a 10-mCi dose. Assuming a constant uptake in residual tissue, treatment with 100–200 mCi of I-131 would result in a 5–10 μCi/g concentration in the tissue, whereas the desired levels for treatment would be 100 μCi/g or greater. Therefore, visualization by a 10-mCi scan, and not a 2-mCi study, implies a tumor uptake that is quite low, thus reducing the probability that sufficient radiation can be delivered to the tumor using 100–200 mCi of I-131.

The current study clearly indicates that ablation should be defined both visually and clinically. Currently, we are employing both the 2- and 10-mCi I-131 diagnostic scans in the evaluation of patients with differentiated thyroid cancer. Long-term followup is needed to determine whether treatment or nontreatment of a 2-mCi-negative, 10-mCi-positive subgroup is appropriate, as well as to determine whether this group of patients has a higher incidence of recurrent disease when compared with those who are visually ablated.

ACKNOWLEDGMENT

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ERRATUM

In the article entitled "Tricatecholamide Analogs of Enterobactin as Gallium- and Indium-Binding Radiopharmaceuticals," (*J Nucl Med* 22:710–719, 1981) Fig. 3 (p 712) and Fig. 4 (p 713) are incorrect. The correct figures and their captions are shown below.

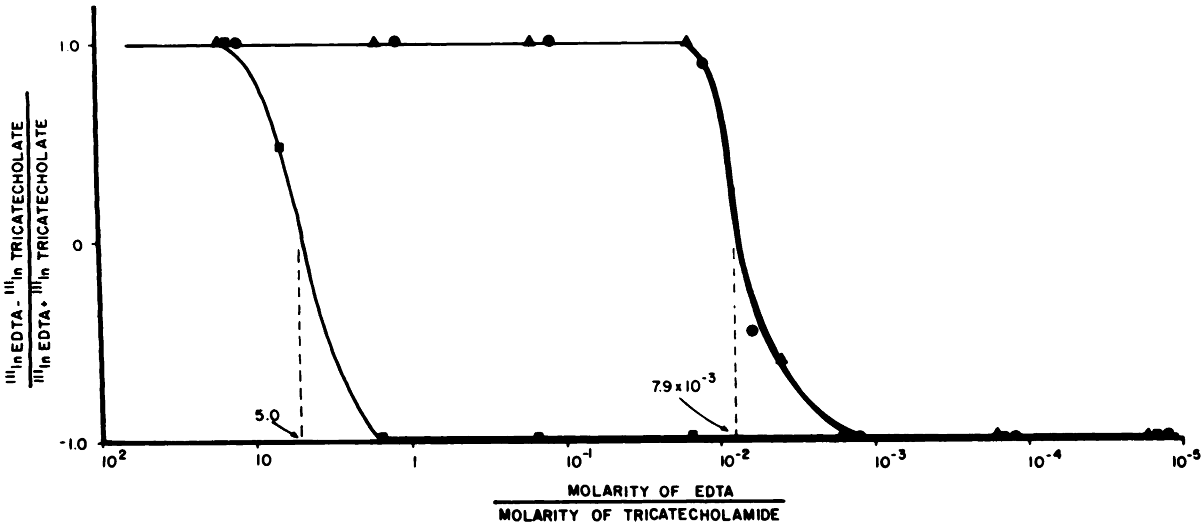

FIG. 3. Variation of In-111 complex concentration as a function of total ligand concentration ratio (in 0.1 *M* citrate, pH 7.0) as determined by Sephadex G-10 gel-permeation chromatography.

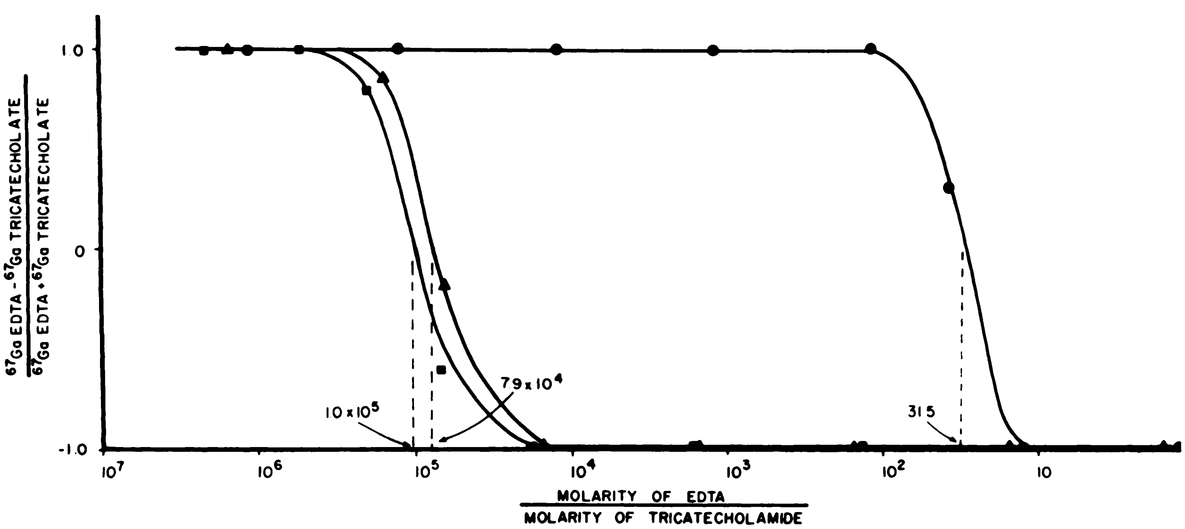

FIG. 4. Variation of Ga-67 complex concentration as a function of total ligand concentration ratio (in 0.1 *M* citrate, pH 7.0) as determined by Sephadex G-10 gel-permeation chromatography.