Radioiodine-131 Therapy for Well-Differentiated Thyroid Cancer—A Quantitative Radiation Dosimetric Approach: Outcome and Validation in 85 Patients

Harry R. Maxon III, Emanuela E. Englaro, Stephen R. Thomas, Vicki S. Hertzberg, Jerry D. Hinnefeld, L.S. Chen, H. Smith, Dwight Cummings, and Michael D. Aden

Department of Radiology, Eugene L. Saenger Radioisotope Laboratory and the Division of Medical Physics, Department of Environmental Health, Division of Epidemiology and Biostatistics, University of Cincinnati Medical Center, Cincinnati, Ohio

For almost five decades, ^{131}I treatment of thyroid cancer has been based empirically on administered activity rather than on actual radiation doses delivered. In 1983, we defined radiation dose thresholds for successful treatment. This report is concerned with the subsequent validation of those thresholds in 85 patients. The successful ablation of thyroid remnants occurred after a single initial ^{131}I administration in 84% of inpatients and in 79% of outpatients when treatment was standardized to a radiation dose of at least 30,000 cGy (rad). Administered activities low enough to permit outpatient therapy could be used in 47% of the patients. Lymph node metastases were treated successfully in 74% of patients with a single administration of ^{131}I calculated to deliver at least 8,500 cGy (rad). For athyrotic patients with nodal metastases only, success was achieved in 86% of patients at tumor doses of at least 14,000 cGy (rad). These success rates are equal to or better than those reported with empiric methods of ^{131}I administration. The individualized treatment planning selectively allocates hospitalization and higher exposures to ^{131}I to those patients who require them.

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About 12,000 new cases of thyroid cancer are reported each year in the United States (*1*). Well-differentiated adenocarcinomas of the thyroid account for most of these cases, with papillary carcinoma representing about 80% and non-Hurthle cell follicular carcinoma representing about 15% of all thyroid malignancies. These patients typically are treated initially with some form of surgical thyroidectomy, often followed by ^{131}I therapy. The validation of a radiodosimetric technique for ^{131}I therapy in: (1) the ablation of thyroid remnants and (2) the treatment of metastatic disease is the topic of this report.

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For reprints contact: Harry R. Maxon III, MD, Director, Eugene L. Saenger Radioisotope Laboratory, University of Cincinnati Medical Center, 234 Goodman St., Cincinnati, OH 45267-0577.

Ablation of Thyroid Remnants

The need for ablation of thyroid remnants with ^{131}I after surgical thyroidectomy is controversial (*2,3*), although a variety of arguments for such ablative therapy exist. These include the treatment of residual microscopic foci of papillary cancer in thyroid remnants and removal of residual thyroid tissue as a source of thyroglobulin and of TSH inhibiting thyroid hormone (*2–6*).

Radioiodine-131 has been used for many years to ablate thyroid remnants following thyroid surgery, but a single optimal amount of administered activity has not been established. Because most physicians in the United States work under regulations that require hospitalization of patients at any time that their body burden of ^{131}I exceeds 1,110 MBq (30 mCi), some workers have advocated an empiric administration of slightly less than 1,110 MBq (30 mCi) of ^{131}I for the ablation of thyroid remnants, using decreased radiation exposure to the patient and less costly health care as their reasons (*7,8*). On the other hand, higher administered activities on the order of 3,700 MBq (100 mCi) may provide more predictable ablation of thyroid remnants (*9*). If one classifies patients reported in several studies to have had "successful" ablation of thyroid remnants according to millicuries of administered activity of ^{131}I, then it appears that an average of 53% (104/195) of patients achieved ablation after a single administration of up to 1,110 MBq (30 mCi) (*7,10–15*) as compared with (86%) 248/287 of patients after a single administered activity of 3,700 MBq (100 mCi) or more (*9,14*).

Treatment of Nodal Metastases

Lymph node metastases may be present at the time of initial diagnosis in about 37% of all patients with well-differentiated thyroid cancer and may develop subsequently in about 9% of patients with well differentiated thyroid cancer who are considered to be disease free after their initial treatment (*16*). Several recent studies have indicated that the presence of nodal metastases is associated with a significantly ($p < 0.01$) shorter survival (*17,18*). Up to 80% of recurrent and/or metastatic foci of well-differentiated papillary or follicular carcinoma of the thyroid will concentrate ^{131}I (*16*), but only about 68% of patients with nodal metastases have been shown to experience complete resolution of those metastases after traditional empiric ^{131}I therapy (*19,20*).

Current Study

In 1983, we reported significant relationships between the likelihood of successful ablation of thyroid remnants and/or successful treatment of predominantly nodal metastases and the radiation dose delivered by ^{131}I (*21*). We proposed treatment thresholds derived from this initial experience of 30,000 cGy (rad) for the ablation of thyroid remnants and of 8,000 cGy (rad) for nodal metastases. Snyder and colleagues (*11*) were unable to confirm a dose-response relationship for ^{131}I ablation of thyroid remnants, but the only parameter they actually measured was the percent 24-hr radioiodine uptake in the thyroid remnant. They assumed masses based on the stated surgical procedure, an initial concentration in the region based only on the 24-hr uptake value and a fixed correction factor, and an effective half-time of ^{131}I in the residual tissue of 5 days for all patients. They did not present data on nodal metastases.

The purpose of the current prospective study was to validate the technique of giving ^{131}I treatment based on radiation dose thresholds in a separate population and to compare the results with those reported after empiric administration of ^{131}I.

METHODS

Patient Population

A total of 85 patients treated between January 1978 and July 1990 who had ^{131}I treatment after full quantitative dosimetric studies and who had at least one complete follow-up examination in our clinic are included in this study. Only partial data from a single patient in this study had been reported earlier (*21*).

All patients had undergone a surgical thyroidectomy prior to referral. Their prior thyroidectomies had been considered by their surgeons to be "total" in 49/70 (70%), "near total" in 12/70 (17%) and less than "total" or "near total" in 9/70 (13%). Seventy-five patients had papillary carcinoma of the thyroid, and 10 had follicular carcinoma of the thyroid. All of the cancers were clinically apparent.

Radioiodine-131 therapy prior to referral to us had been given to only 4 of 85 (5%) patients. These four patients were excluded from analysis of outcome for thyroid ablation.

Patient Preparation for ^{131}I Scans

All patients were prepared by having them either wait 6 wk after their surgical thyroidectomy or stop any levothyroxine-containing preparations for 6 wk prior to ^{131}I scans. Substitution of triiodothyronine was permitted during the first 3–4 wk of withdrawal from levothyroxine or after thyroid surgery, but this supplement was stopped 2–3 wk prior to ^{131}I scanning. All patients were asked to follow our standard low iodine diet (*22*) beginning 1 wk prior to the diagnostic ^{131}I study and continuing until the day after the administration of the ^{131}I therapy.

Diagnostic ^{131}I Scans

Our standard format is to repeat ^{131}I scans at yearly intervals until they become negative, then again 2 yr later. If the latter scan is negative, then further scans are obtained only at 5-yr intervals unless clinical or other laboratory data (e.g., serum thyroglobulin, chest x-ray) indicate recurrent thyroid cancer. The mean ($\pm$1 s.d.) time lapsed between the first and the last quantitative ^{131}I study in each patient was 2.6 ± 1.8 yr (range 0.8–10.8 yr). The 85 patients reported here underwent a total of 239 diagnostic radioiodine scans (average 2.8 per patient).

Diagnostic ^{131}I studies were performed after the oral administration of 74 MBq (2 mCi) of ^{131}I. Whole-body scans were done initially with an Ohio Nuclear dual 5-inch rectilinear scanner with 5:1 minification and more recently on a Siemens dual-head body scanner. In addition, 1:1 rectilinear scans of the neck were obtained using a Picker magna scanner. Based on visual analysis of these scans and images, thyroid remnants were considered to be present when discrete ^{131}I uptake was noted in the thyroid bed on the first postoperative study. Abnormal uptake elsewhere in the body on the initial scan or recurring in the thyroid bed after at least one negative scan in that same area was considered to represent metastatic or recurrent cancer.

Selected areas of abnormal uptake were evaluated quantitatively, using computerized analyses of areas of interest obtained from conjugate view gamma camera images, as described previously (*21,23,24*). The sequential scans and images were obtained at 24, 48 and 72 hr after administration of the 74 MBq (2 mCi) diagnostic activity of ^{131}I. The scanning techniques used are standard in our laboratory, so special informed consent was not required for the diagnostic studies.

The mass of residual thyroid tissue was calculated using estimates of thickness (determined from the surgeon's operative notes and from discussions with the surgeon) and actual determinations of surface area (based on anterior 1:1 rectilinear scans of the neck). The masses of nodal metastases were calculated from anterior 1:1 rectilinear scans of the neck, assuming spherical or ellipsoidal configurations.

The percent instantaneous uptake in lesions (either residual thyroid or nodes) was calculated by extrapolation back to time zero from actual 24-, 48- and 72-hr measurements, corrected for physical decay and background activity. The effective half-time of ^{131}I in lesions was based on an exponential fit of those same uptake data, assuming only physical decay beyond 72 hr.

Criteria for Success

Given the goals of ablation of thyroid remnants as noted in the introduction, ablation was considered to be successful only when all images and scans were visually negative in the area of the thyroid bed and when the calculated percent instantaneous uptake of ^{131}I in the neck was less than 0.1% of the administered activity. The treatment of nodal metastases was considered to be successful when there was no evidence of nodal metastases on both the physical examination of the patient and on visual examination of the subsequent ^{131}I scans.

Radioiodine-131 Treatments

The actual amount of ^{131}I to be administered was based on delivering at least 30,000 rad to residual thyroid tissue when metastases were not present or at least 8,000 rad to nodal metastases, regardless of the concomitant presence of thyroid remnants.

All patients were asked to sign a specific, detailed "permission for therapy" statement before receiving any ^{131}I therapy. No pregnant or lactating women were treated.

RESULTS

Ablation of Normal Thyroid Remnants

We identified 142 foci of residual thyroid tissue in 70 patients with full quantitative data. It was notable that less than 20% of patients who were considered by their surgeons to have had a "total" thyroidectomy were athyrotic by subsequent ^{131}I scans. The average (± 1 s.d.) administered activity of ^{131}I was 3,212 ± 2,298 MBq (86.8 ± 62.1 mCi) (range 955–9,113 MBq or 25.8–246.3 mCi). Twenty-six of 70 patients (37%) received less than 1,110 MBq (30 mCi), 7/70 (10%) received 1,110–1,665 MBq (30–45 mCi) and the remaining 37/70 (53%) received 1,665 MBq (45 mCi) or more.

The outcomes of the initial ^{131}I ablation of 142 thyroid remnants in 70 patients are shown in Table 1. A total of 81% of the patients and 86% of the thyroid residua were treated successfully with a single ^{131}I administration.

A multivariate logistic regression analysis of outcome in 106 remnants with all variables from 63 patients revealed that the two most important factors in determining success were the mass of residual tissue ($p < 0.001$) and the effective half-time of ^{131}I in that tissue ($p < 0.05$). The instantaneous percent ^{131}I uptake in the residual tissue also was a significant variable by univariate analysis ($p < 0.05$), although it was highly correlated with, and inseparable from, lesion mass ($r = 0.63$, $p < 0.001$).

The effect of the extent of the initial surgical thyroidectomy and of the mass of residual thyroid tissue on outcome is shown in Table 2. The greatest success occurred when a total or near total thyroidectomy had been performed and the mass of residual thyroid tissue to be ablated was less than 2 g.

The effect of the amount of administered activity of ^{131}I on the success of initial ablation also was examined in terms of outpatient administered activities of slightly less than 1,110 MBq (30 mCi) in a single administration or of a combination of slightly less than 1,110 MBq (30 mCi) on Day 1 and 555 MBq (15 mCi) or less on Day 2, given at sequential time intervals so that the patient's whole-body burden of ^{131}I never exceeded 1,110 MBq (30 mCi). When treatment was based on a radiation dose of at least 30,000 cGy (rad) to the residual tissue, the success rates in patients treated with these lower administered activities [77% at < 1,110 MBq (30 mCi) and 79% at < 1,665 MBq (45 mCi)] were not different statistically from those achieved at higher administered activities of ^{131}I (84%–85%) (Table 3). There was no apparent increase in the success rate at radiation doses greater than 30,000 cGy (rad) (Table 4).

TABLE 1
Results of Initial ^{131}I Ablative Therapy for 142 Thyroid Remnants in 70 Patients

	Number successful	%Successful
Patients	57/70	81
Foci of residual thyroid	122/142	86

TABLE 2
Effect of Extent of Surgical Thyroidectomy and Mass of Residual Tissue on Outcome in Initial ^{131}I Ablation of Thyroid Remnants

	Successful ablation achieved	
	Patients	Foci of residua
Thyroidectomy		
Total or near total	55/61 (90%)	117/125 (94%)
Other	2/9 (22%)	5/17 (29%)
Significance	p < 0.001	p < 0.001
Mass of Residua		
<2 g	33/35 (94%)	71/74 (96%)
≥2 g	21/31 (68%)	24/36 (67%)
Significance	p < 0.01	p < 0.001

Treatment of ^{131}I Concentrating Lymph Node Metastases

A total of 78 nodal metastases were identified in 23 patients with complete follow-up. Quantitative data were present for 36 of these 78 nodes, with at least one nodal metastasis being quantitatively analyzed in each patient. The mean (± 1 s.d.) administered activity of ^{131}I was 5,798 ± 1,913 MBq (156.7 ± 51.7 mCi) (range 1,077–9,113 MBq or 29.1–246.3 mCi). The calculated radiation dose to the nodal metastases was greater than 8,500 cGy (rad) in all nodes quantified and was greater than 10,000 cGy (rad) in all but three instances. There were no clear cut increases in success rates at higher radiation doses (Table 4).

Successful treatment was achieved with a single ^{131}I administration in 17/23 (74%) patients with nodal metastases and 63/78 (81%) involved lymph nodes (Table 5).

In an attempt to isolate which variables were most important specifically for the therapy of lymph node metastases, we also evaluated outcome following the initial ^{131}I treatment of 29 radioiodine concentrating nodal metastases in 7 patients without any concomitant residual

TABLE 3
Effects of Administered Activity of ^{131}I on Success of Initial Ablation of Thyroid Remnants in 70 Patients

Administered activity mCi (MBq)	Successful	Failed
<30 (1110)	20/26 (77%)	6/26 (23%)
≥30 (1110)	37/44 (84%)	7/44 (16%)
<45 (1665)	26/33 (79%)	7/33 (21%)
≥45 (1665)	31/37 (84%)	6/37 (16%)

TABLE 4
Success of Initial ^{131}I Treatment by Radiation Dose Delivered

	Total dose delivered cGy (rad)		
	≤30,000	30,000–70,000	>70,000
Foci of residua	11/13 (85%)	51/59 (86%)	35/42 (83%)
	8,500–10,000	10,000–50,000	>50,000
Nodal metastases	3/3 (100%)	8/11 (78%)	20/22 (91%)

thyroid tissue or metastases in other locations. A total of 17/29 (59%) nodes were studied with quantitative radiation dosimetry, at least one in each patient. The calculated radiation dose to the nodal metastases was 14,000 cGy (rad) or more in all cases, and the mean (± 1 s.d.) administered activity of ^{131}I was 5,498 ± 1,617 MBq (148.6 ± 43.7 mCi) (range 3,774–7,859 MBq or 102.0–212.4 mCi). The overall success rates were 90% (26/29) for nodal metastases and 86% (6/7) for patients. Neither univariate nor multivariate analyses revealed any distinguishable, discretely important variables, and there was no apparent increase in success rate as radiation doses increased. The absence of increased success at higher doses is not surprising, given the fact that all patients received radiation doses of 14,000 cGy (rad) or more to their metastases.

DISCUSSION

Limitations of Diagnostic Dosimetric Studies

Our initial comparison of whole-body and lesion retention of ^{131}I predicted from pre-therapy diagnostic studies with the retentions observed following ^{131}I therapy suggested good overall agreement, although the data were limited. We noted that our model based on the diagnostic study theoretically could result in about a 10%–15% overestimation of the actual radiation dose (*23*).

In 1985, Hadjieva (*25*) compared calculated radiation doses based on pre-treatment diagnostic studies with actual doses measured after therapy and determined that about one-third of their patients had an actual dose that was somewhat less than the projected dose due to a shortened effective half-time of ^{131}I after therapy. Hurley and Becker (*26*) subsequently found that the actual mean radiation doses delivered were about 80% of what had been projected in 30 patients whom they treated for ablation of thyroid remnants, primarily due to a more rapid release than expected of ^{131}I at 3–7 days post-therapy. We have considered a 10%–20% error to be intrinsic to our dosimetric methodology and assume that the actual radiation dose delivered to some of our patients was slightly less than that predicted by our diagnostic studies.

TABLE 5
Results of Initial ^{131}I Treatment for 78 Lymph Node Metastases in 23 Patients with Thyroid Cancer

	Number successful	%Successful
Patients	17/23	74
Metastases	63/78	81

Advantages of Dosimetric Approach

As noted earlier, the indications for the ablation of thyroid remnants and/or the treatment of nodal metastases with ^{131}I are somewhat controversial. This study cannot answer those questions, and the controversies only will be resolved by multisite cooperative studies that are yet to be completed. However, once a decision for ^{131}I treatment is made by the attending clinician, the question remains of how much ^{131}I is appropriate for a given individual?

When one considers the average administered activities of ^{131}I that we used either for the initial ablation of remnants (3,212 MBq or 86.8 mCi) or for the initial treatment of nodal metastases (5,798 MBq or 156.7 mCi), then clearly there are no appreciable savings in total exposure to the treated population as a whole as compared with traditional empiric methods of ^{131}I administration. What is different is that the exposure is selectively allocated to individuals, based on the unique characteristics of their case.

In the ablation of thyroid remnants, our dosimetric approach resulted in success rates (81%) comparable to those achieved (86%) after empiric therapy with 3,700 MBq (100 mCi) or more, while avoiding unnecessary exposure and hospitalization in the 47% of our patients who could be treated as outpatients. Although some workers have reported comparable success with empiric administrations of slightly less than 1,110 MBq (30 mCi) (*7*), their results have not been confirmed by others (*13*), and the average response rate to such treatment is low (53%) (*7,10–15*). The quantitative dosimetric approach allows us to identify and separate those individuals who are likely to respond to outpatient therapy with a higher chance of success from those who will require greater administered activities and inpatient treatment.

The charge for our quantitative dosimetric study is about \$150.00 greater than the average charge in the community for a nonquantitative single whole-body radioiodine scan for thyroid cancer. If our patients all were treated empirically with 3,700 MBq (100 mCi) of ^{131}I, they would require an average of 2 days in the hospital at an additional cost of \$640.00 for the room alone. Since our approach gives similar results with only half of the patients requiring hospitalization, there is a net savings of about \$170.00 per patient. Thus, our quantitative approach results in lower overall costs and comparable overall success rates to empiric ablation therapy with 3,700 MBq (100 mCi) of ^{131}I.

In 1983, we reported that when the radiation dose to metastatic lesions was greater than 8,000 cGy (rad), 98% responded to treatment, whereas when the radiation dose was less than 8,000 cGy (rad), only 20% of metastases responded to treatment. None of the eight metastatic lesions receiving less than 3,500 cGy (rad) responded to therapy (*21*). In a separate report that same year, Kimmig and Hermann (*27*) in Heidelberg, Germany, evaluated 15 patients with ^{131}I concentrating metastatic thyroid cancer after complete thyroidectomy. They found that when tumor doses were below 4,000 cGy (rad), no regression was observed, whereas three of four patients with tumor doses above 10,000 cGy (rad) experienced complete disappearance of their metastases. These dosimetric data suggested that a uniformly good response should be possible if a minimal tumor dose of 8,000 to 10,000 cGy (rad) could be achieved.

Our current data confirm that, when only metastatic disease in lymph nodes is present, high success rates on the order of 86% of patients and 90% of involved nodes can be achieved by delivering a radiation dose of at least 14,000 cGy (rad). When nodal metastases are associated either with residual thyroid tissue or with other metastatic foci, then the success rates are about 74% in patients and 81% in involved nodes following a single treatment calculated to deliver at least 8,500 cGy (rad) to the nodal metastases.

The quantitative radiation dosimetric approach to ^{131}I treatment results in predictably high success rates while allowing the assignment of higher ^{131}I exposures and of greater costs to those individuals who require them.

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