Thyroid Remnant Ablation: Questionable Pursuit of an Ill-Defined Goal

James Snyder, Colum Gorman, Paul Scanlon

Mayo Clinic, Rochester, Minnesota

Ablative therapy with I-131 in 30-mCi doses, directed to postsurgical remnants in patients with differentiated thyroid cancer, reduced visible I-131 uptake to zero or nearly zero in 81% of patients but did not protect against tumor recurrence in six of 69 patients who were followed for 2–5 yr. Recurrences developed within 5–37 mo. Effectiveness of 30-mCi doses of I-131 in producing ablation did not correlate with I-131 uptake by the thyroid remnant, surgeon's estimate of remnant size, or delivered dose to the remnant in rads, calculated using reasonable assumptions. These findings emphasize the difficulty of dosimetric measurements and calculations. The value of postsurgical ablative therapy in diminishing morbidity and mortality in patients with differentiated thyroid cancer has not yet been firmly established, and until this is done we advocate a conservative, economical approach to thyroid ablation with 30-mCi treatment doses of I-131 and 1-mCi neck-scanning doses to check on effectiveness of therapy.

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Despite the absence of controlled prospective studies to confirm its efficacy, radioiodine ablation of presumed normal thyroid tissue in patients who have had surgery for papillary and follicular thyroid cancer, has gained wide acceptance. While the fundamental question of whether I-131 ablative therapy improves survival and decreases morbidity in patients with differentiated thyroid cancer remains unanswered, controversy centers on the question of how the term ablation should be defined and what amount of radioiodine should be administered to accomplish it.

In the literature there are tenfold variations in estimates of the amount of radioiodine needed to accomplish ablation (*1–6*), in the number of rads that should be delivered to ensure death of thyroid cells (*7–10*), and in the scanning dose that should be used to detect residual functioning thyroid tissue (*1,2,4,7,11–13*). Complex, expensive, and time-consuming methods have been devised to define precisely how many rads a given dose of radioiodine *will* deliver, while there is no consensus on how many rads *should* be delivered.

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For reprints contact: Dr. Colum Gorman, Endocrinology and Internal Medicine, Mayo Clinic, Rochester, MN 55905.

In an effort to gain the putative benefits of thyroid ablation while minimizing diagnostic and therapeutic whole-body radiation to our patients, we have examined the consequences of empirically administering 30-mCi doses of I-131 to persons who have had subtotal thyroidectomy for thyroid cancer. We have correlated our results with the surgeon's estimate of gland remnant size, pretreatment I-131 uptake, and the calculated thyroid dose in rads, using what we believe are reasonable assumptions. Based on these analyses and our review of the literature, we offer what we believe, in the light of present knowledge, to be a reasoned, if not novel, approach to management of remnant ablation in patients with differentiated thyroid carcinoma.

PATIENTS

Between 1976 and 1979, 69 patients who had surgery for well-differentiated thyroid cancer received radioiodine to ablate the thyroid remnant. Patients ranged in age from 13 to 76 yr. There were 42 females and 27 males. Sixty-two patients had one or more thyroid nodules detected by thyroid palpation. In the remainder, biopsy of cervical nodes led to thyroidectomy. Nineteen patients had palpable cervical adenopathy, but no patient was known to have distant metastases preoperatively.

Fifty-nine patients had their definitive surgical procedure performed at this institution. In 35 cases, total lobectomy on the side of the lesion, with isthmectomy and subtotal thyroidectomy on the side opposite the cancer (subtotal-total) was performed. Thirty-two patients had procedures described as total thyroidectomies, and in two cases lobectomies were carried out leaving a contralateral "normal" lobe. In 32 cases, suspicious nodes were found at operation prompting the surgeon to perform "node-picking" or modified neck dissections, and in 31 instances nodes with carcinomatous involvement were confirmed by pathology. By the surgeon's appraisal, 64 of 69 patients were rendered free of disease. In five of 16 cases in which gross locally invasive disease was encountered, minimal amounts of unresectable cancer tissue were left behind. In most cases the surgeon recorded an estimate in grams of the thyroid remnant as part of the operative report.

Histologically, 58 were papillary and 11 follicular cancers. Twenty cases showed invasion microscopically. Twenty-nine cases (42%) demonstrated multicentricity.

METHODS

Patients were prepared for scanning by withdrawal from thyroxine for 41 ± 12 days and/or from T_3 for 20 ± 7 days. Low iodine diets, diuretics, or TSH injections were not prescribed. In patients who had TSH and T_4 levels checked before scanning, values were 104 ± 68.9 microunits/ml and 1.5 ± 2.0 μg/ml, respectively. Neck scans with a rectilinear scanner were performed, at 40 cm/min with 0.3-cm line spacing, within 6 wk to 6 mo postoperatively. Neck uptakes were determined with a gamma scintillation detector with a 2- by 2-in. crystal. Radioiodine uptake measurements were performed for 1 min or at least 10,000 counts, and were corrected for background by subtraction of a thigh count. Scans were assessed visually. If, in the opinion of the physician reviewing the scan, a remnant suitable for treatment was present, radioiodine was administered. All patients received their therapeutic radioiodine as outpatients in doses of 29.3 ± 1.5 mCi. Within 3 mo to 1 yr after the ablation attempt, neck and, in most instances, body scans, were performed using dual-mode tomographic scanner at 500 cm/min with 0.3-cm line spacing. Five patients were scanned with 2–3 mCi, 64 with 1 mCi. If no increased uptake was seen in an adequately prepared patient—that is, thyroxine withdrawn for more than 4 wk and T_3 for more than 2 wk—the remnant was considered completely ablated. In some cases when visual inspection of the scan revealed a faint area of increased uptake in an adequately prepared patient, and the measured uptake was less than 1%, the remnant was considered untreatable by 30 mCi of radioiodine and the designation "minimal residual" applied. In all other cases, patients were re-treated with radioiodine, again with an outpatient dose (<30 mCi).

Results of remnant ablation were tabulated and analyzed against uptake, surgeon's estimate of remnant size, and calculated delivered radiation dose, using standard statistical methods.

In patients who had a total lobectomy on the side of the tumor and a subtotal lobectomy on the opposite side, if the surgeon did not make a specific estimate of the grams of thyroid tissue remaining in the neck, a generous estimate of 2.5 g was used. If the surgeon did a less extensive procedure, and stated "lobectomy, medial portion of the other lobe removed" the remnant was estimated to be 7.5 g. If "lobectomy, normal lobe remains" was the notation, an estimate of 10 g was used. Operative reports entitled "total thyroidectomy" were scrutinized for evidence that this was indeed the intent of the surgeon. Those reports with phrases similar to "all visible thyroid tissue removed" were labeled total thyroidectomies (TT) and given mass estimates of 500 mg in dose calculations. All others were reclassified as subtotal-total procedures and given a higher mass estimate. Doses were calculated according to the equation (*14*): $D(\text{rad}) = \frac{\tilde{A}}{m}\Sigma_i\Delta_i\Phi_i = C_0[1.44\ (T_{1/2})\ \text{eff}\ 0.4135 + 0.8041\ \Phi\gamma]$, where $\tilde{A}$(μCi-hr) is the cumulated activity; m (g) is the mass of the lesion, C_0(μCi/g) is the initial radionuclide concentration in the lesion, $(T_{1/2})$ eff (hr) is the effective half-time in the lesion, Δ_i (g·rad/μCi·hr) is the equilibrium dose constant, and Φ_i is the absorbed fraction. Assumptions used included an effective half-time of I-131 of 5 days, an initial concentration in the lesion (μCi/g) equal to the μCi administered in the therapeutic dose times the 24-hr uptake determined with the scanning dose, and $\Phi\gamma = 0.03$. A correction factor of 0.071 times D was added to the dose calculation to account for accumulated activity prior to peak uptake (*15*).

RESULTS

The outcome of remnant ablation with outpatient doses of radioiodine is shown in Table 1. Forty-two of 69

TABLE 1. THYROID-REMNANT ABLATION WITH 29 mCi OF IODINE-131: SUCCESS IN 69 CASES

Status of remnant	Number of doses 1	2	3	Total cases
Complete ablation	42	2	—	44
Minimal residual	14	2	1	17
Treatable remnant remaining*	—	5	3	8

* Additional radioiodine prescribed.

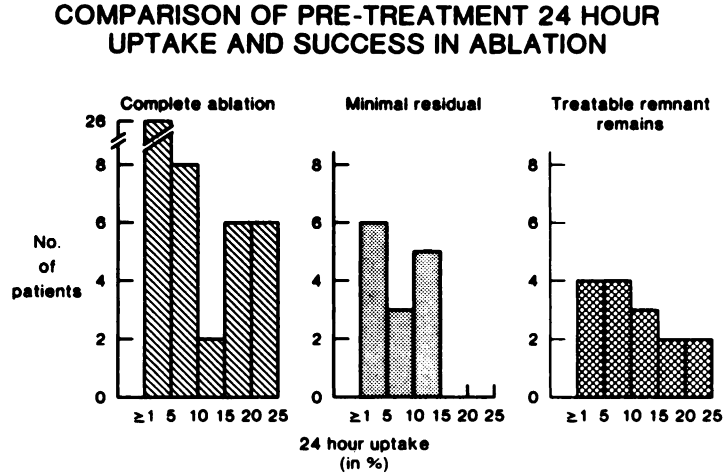

FIG. 1. All patients were given 30 mCi of I-131 immediately after pretreatment uptake. Results are grouped in accordance with whether complete ablation, minimal residual function, or treatable remnant remained on scans made 3–6 mo later. Level of pretreatment uptake did not correlate with results of treatment.

(61%) patients achieved complete ablation after a single dose. An additional 14 (20%) were designated as having minimal residual after a single dose. Therefore, in 56 (81%) of patients a single 30-mCi dose of I-131 caused visible neck uptake of radioiodine to disappear completely or almost completely. Thirteen patients required additional radioiodine. Nine patients received two doses of I-131 and in five patients, a treatable remnant remained. Four patients received three doses of I-131 and none of these was completely ablated. The five patients in whom surgery was not felt "curative" due to unresectable invasive tumor were all completely ablated after a single dose.

For the entire group, the 24-hr radioiodine uptake before the first therapeutic doses of I-131 averaged 7.2% with a range of 1 to 23% (Fig. 1). For patients with complete ablation, minimal residual, and treatable remnant, the mean pretreatment I-131 uptakes were 6.2, 7.6, and 9.6% respectively. There was no significant difference between the groups when the paired t-test was applied.

The comparison of the surgeon's estimate of remnant size with the results after the first dose is presented in Table 2. If a specific estimate was not part of the operative note, an estimate was applied as described in Methods. The term "total thyroidectomy" (TT) as used by our surgeons implies removal of all visible thyroid tissue. Scanning techniques demonstrated that removal of thyroid tissue was never really complete, since small functioning remnants were seen in every instance. There was a significant relationship, by chi-square statistical analysis, between the pretreatment mass estimate and outcome. However, more than 50% of the cells have fewer than five patients; moreover, two of the three cells that contribute the most to the Chi-square statistic have one and four patients respectively within them. Pooling the data would decrease its informative value. Therefore, the relationship between pretreatment mass estimate and outcome is only suggestive.

Table 3 analyzes the outcome in terms of rads delivered. Mass estimates were obtained as stated above. There was no significant relationship evident. Four patients received a calculated dose in excess of 60,000 rads to the remnant, yet these remnants were not ablated. Eight of nine patients whose remnants received less than 30,000 rads had subsequent neck scans that showed no visible uptake.

There were eight local recurrences in this group of patients, occurring within the 2–5 yr follow-up period.

TABLE 2. THYROID-REMNANT ABLATION WITH 29 mCi OF IODINE-131: SUCCESS COMPARED WITH SURGEON'S ESTIMATE OF AMOUNT

Status of remnant	In 69 cases—surgeon's estimate: TT*	≤2.5 g	7.5 g	10 g
Complete ablation	21	18	2	1
Minimal residual	4	9	1	0
Treatable remnant remaining	1	7	4	1

* "Total thyroidectomy."
$chi^2 = 14.4$, $p < 0.05$.

TABLE 3. THYROID-REMNANT ABLATION WITH SINGLE DOSE: 29 mCi OF IODINE-131: SUCCESS COMPARED WITH CALCULATED* DELIVERED DOSE

Status of remnant	Rads × 10^{-3} in 67 cases: <40	40–60	>60
Complete ablation	10	11	20
Minimal residual	2	5	6
Treatable remnant remaining	3	6	4

* See methods.
$chi^2 = 2.36$, not significant.

TABLE 4. RECURRENCES IN PATIENTS AFTER SUCCESSFUL THYROID REMNANT ABLATION WITH 29 mCi OF I-131
n = 6

Type of surgery	
Subtotal thyroidectomy	5
Total thyroidectomy	1
Histology	
Papillary	6
Invasive	3
Positive nodes at surgery	5
Considered to be free of disease postop.	5
Nature of the recurrence	
Neck nodes or nodules	5
Extrathyroidal neck uptake on scan	1
Visible I-131 uptake in recurrence	2/3
Time to recurrence*	5–37 mo

* From date of ablative dose.

Two of these patients were found to have recurrences on their first follow-up visit at 4 mo after surgery and before remnant ablation. In one of these cases, the lesion was tested for radioiodine uptake and did not accumulate I-131. Both recurrences were treated by local excision. The other six local recurrences occurred in patients who had previously been demonstrated to have thyroid remnants that were completely ablated. Clinical details of these patients are given in Table 4. The patient whose recurrence was not palpable and was detected only by scan had visible uptake in the lateral neck with a recorded neck uptake of 1% of the dose. He was subsequently treated with 150 mCi of I-131. The other patient whose recurrence demonstrated I-131-concentrating ability had a neck uptake of 2%, with activity localized to a 1.5-cm lymph node. All patients with palpable recurrences were treated by local excision and modified neck dissection. There have been no deaths in this series and no patient has developed distant metastases over the follow-up period of 2–5 yr.

DISCUSSION

There is disagreement as to how to define successful thyroid-remnant ablation when radioiodine is applied for this purpose (*1,2,9,11*). If the term ablation is rigorously used, no thyroid tissue should be demonstrable by any technique whatsoever. The success of radioiodine in ablating thyroid remnants has been examined with scanning doses that range from 1–2 mCi (*1,2,7*) to 10 mCi (*4,11–13*). In theory, smaller and smaller foci of residual thyroid tissue can be displayed by using larger and larger scanning doses of I-131. This premise is supported by studies comparing 2- and 10-mCi diagnostic scans (*11*) and in the occasional patient with a tumor site, visualized on a posttherapeutic scan (after 80–150 mCi of I-131), that was not seen on a diagnostic scan (*3,16*). In practice, however, there is a limit to the size of the scanning dose because of whole-body radiation incident to its use and diminishing benefits anticipated from display of tissue that is minute in quantity, may not be malignant, and will not, in any case, accumulate sufficient I-131 for effective treatment, as recently shown by Ramanna et al. (*17*).

We have therefore chosen scanning doses that will certainly display any thyroid tissue functioning at a level that could permit I-131 therapy. We have taken this level to be an uptake of 0.2% of the administered activity per gram of tissue. This fraction of a neck-scanning dose of 1 mCi is 2 μCi, and our equipment can easily detect such focal accumulations of I-131 in volumes as large as 5 ml. Concentrations as low as 0.5 μCi/g may be visualized, corresponding to only 0.05% of the administered activity. Such focal collections are labeled "minimal residual," and therapeutic radioiodine is not prescribed.

The amount of radioiodine needed to achieve ablation of postthyroidectomy functioning remnants is also a matter of debate, with estimates ranging from less than 30 mCi (*1,2*) to 100–200 mCi (*3–6*). The larger doses may well be appropriate for patients with known metastatic functioning thyroid carcinoma, or for patients who may have had removal of less than one lobe at surgery. We wish to confine our remarks to patients who have had at least a subtotal thyroidectomy. For this group, our experience suggested that 30 mCi may be adequate for remnant ablation and, for the additional reasons of convenience and reduced cost, we have continued to use 30 mCi for the purpose of thyroid remnant ablation in patients without known metastatic disease. Our results as reported herein are in agreement with two other published reports. DeGroot found single doses of 30 mCi of I-131 successful in 15 of 18 (83%) patients (*1*). McCowan, using criteria for ablation that included PBI(I-131) conversion rates of less than 0.005% per liter at seven days, reported successful ablation in 21 of 36 (58%) of patients receiving 30 mCi (*2*). The use of a low-iodine diet for 2–3 wk, diuretics to increase iodide excretion (*18*), or TSH (*19*) injections, might have improved our success rate but were not prescribed.

Some authors have emphasized the need for complex and time-consuming quantitative methods as a means to determine accurately how many rads will be delivered to the remnant from a given amount of I-131 (*14*). However, a tenfold variation exists in the published estimates of the radiation dose required for thyroid ablation, with recommendations of 30,000 (*8*), 50,000 (*7*), 75,000–100,000 (*9*), and 300,000 rads (*10*). Therefore, in different hands, the same patient might receive 20 or 200 mCi.

We noted with concern the absence of correlation between results of I-131 therapy and either (a) pre-

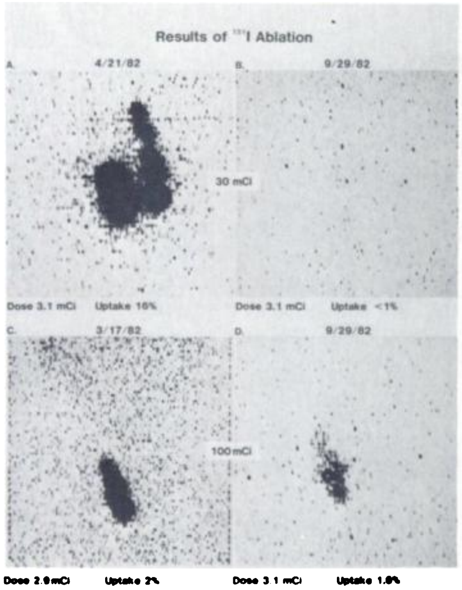

FIG. 2. (A). Preablation scan performed with 3.1 mCi of I-131. (B). Same patient after 30 mCi of I-131. (C). Another patient's preablation scan performed with 2.9 mCi. (D). Same patient after 100 mCi of I-131.

treatment I-131 uptake or (b) the calculated dose in rads to the remnant (Fig. 2). In this we are not alone. Freeburg et al.(*20*) also noted a poor correlation between estimated delivered dose and the histopathologic effects of I-131. McCowan et al. found that doses of 80–100 mCi were not more effective than 30 mCi (*2*). These results highlight the errors inherent in dosimetric calculations and challenge the premises on which pretreatment dose calculations are based. Errors in measuring uptakes less than 5% can be as much as 10–100%. The largest sources of error, however, is in the mass estimate. An error of ±0.5 g can result in a delivered dose that is as little as one-half or as much as two times the calculated amount. Quite different geometry applies to a compact sphere of residual tissue as opposed to multiple thinly spread sheets of tissue, and the potential is great for adding to the already large errors in dose calculation.

We consider it important that among the ablated patients there were six local recurrences within the thyroid bed or neck nodes within 5–37 mo. At least two considerations are raised. One is that some differentiated thyroid cancer does not accumulate I-131 and, therefore, increasing the ablative dose will have no effect on such patients. The second possibility is that a higher ablative dose might have prevented these recurrences. It is sometimes proposed that higher doses of radiation may diminish the theoretical risk of exposing initially "unseen" foci of cancer to a sublethal dose of radiation that might enhance their malignant potential and diminish their propensity to accumulate I-131 (*12*). The problem with the proposal is that there is no dose of I-131 to which it cannot be applied. Until effectiveness of I-131 therapy of thyroid gland remnants has been proven, the doses we have selected have at least the merit of being safe. In the remnants discussed in this paper, we are dealing with presumed normal thyroid tissue—not with proven functioning metastatic cancer, where we emphatically agree with maximal dose therapy.

It has not been convincingly shown that I-131 ablation of presumed normal thyroid tissue exerts a beneficial effect on morbidity or mortality of patients with differentiated thyroid cancer. In the widely quoted Mazzaferri study (*21*,*22*), 33 patients with papillary cancer received radioiodine postoperatively for presumably normal residual uptake. Details about their subsequent course are lacking, and so is a comparison with patients who do not receive radioiodine for this purpose but were otherwise similar in clinical characteristics and therapy applied. In the report from Young et al. (*23*) regarding therapy for follicular cancer, the same criticism applies. Additionally, recurrence rates with thyroid hormone suppression only, compared with thyroid hormone plus radioiodine, were not statistically different. Varma and Beierwaltes (*5*) in a retrospective study matched their patients for sex only, a serious flaw considering the known prognostic features of these cancers (*24*,*25*); furthermore, they included in the analysis patients who died in whom it was uncertain that thyroid cancer was indeed the cause of death. Nevertheless, these authors found no benefit from the use of I-131 in patients less than 40 yr of age. Numerous other studies (*4*,*6*,*22*,*26–29*) support the use of radioiodine in the treatment of metastatic disease, but extrapolation to the practice of remnant ablation does not follow.

One of the reasons given in support of the practice of remnant ablation is the high incidence of multicentricity (up to 88%) in patients with thyroid cancer (*30–34*)—42% in this series. However, recurrence rates in patients who have had limited thyroid resection without postoperative I-131 are reported to be only 2.6% and 17% in several large series (*30*,*35–38*). We note that in these series the extent of surgery was generally less than a subtotal thyroidectomy and thyroid hormone was often omitted in the postoperative period—or, if given, confirmation is lacking that TSH suppression was adequate. Although it seems logical that radioiodine, if used for a postthyroidectomy remnant, would decrease the recurrence rate due to multicentric disease, it is not clear that it would be more effective than subtotal or near-total thyroidectomy and confirmed adequate TSH suppression. Furthermore, in a very large series by McConahey et al. (*25*) multicentricity was not shown to be a risk factor influencing survival in patients with papillary thyroid carcinoma. Other clinical or histologic features appear more predictive of the need for total thyroid ablation than does multicentricity. But until such issues are settled by a prospective study, the indications for thyroid remnant ablation will remain in dispute, with some authors recommending its use in most patients (*1,6,7,21*) while others limit its use to subgroups (*29,39*).

We conclude that evidence from the literature is fragmentary and inconclusive that I-131 ablation of thyroid remnants influences morbidity and mortality in patients who have had near-total thyroidectomy for differentiated thyroid cancer. Our own experience is that apparently successful ablation does not prevent recurrence of tumor. We note absence of a consensus as to how many rads should be delivered to ablate thyroid tissue, and our observations highlight the great potential for serious error in dosimetric calculations. We note, too, the endless chase to detect smaller and smaller fragments of thyroid tissue with larger and larger scanning doses of I-131. Until definitive evidence from controlled studies appears, to confirm the efficacy of I-131 ablation of every detectable fragment of thyroid tissue, we feel that the guiding principle should be to keep damage to a minimum while attaining all or most of the claimed benefit of therapy.

Toward this end, treatment doses of 30 mCi of I-131 are convenient and safe, and because they do not require hospitalization, they are economical. They produce complete or almost complete ablation in 81% of the patients who receive them. We plan to continue to use them. In addition, we intend to define ablation operationally as the absence of uptake treatable by a dose of 30 mCi of radioiodine. Treatable uptake as defined in this paper is readily imaged by our equipment when 1 mCi of I-131 is used for neck scans and 3 mCi are used for whole-body scans.

We recognize that our approach is not novel. Nevertheless, when dosimetric measurements and calculations that we believe to be fraught with error, inconvenience, and expense are being advocated, and when ever higher scanning doses are being recommended to confirm attainment of a goal that has not been proven to be beneficial, there is merit in supporting an approach that is conservative, economical, and safe. If the benefits of total ablative therapy are established in a controlled prospective study, a more radical measure may need to be used to ablate and confirm ablation of thyroid remnants. We emphasize that these remarks do not apply to therapy of patients with demonstrated functioning metastatic thyroid cancer, but only to the treatment of functioning remnants of presumed normal thyroid tissue in patients who have had subtotal or near-total thyroidectomy.

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