Ablation of Nonmalignant Thyroid Remnants with Low Doses of Radioactive Iodine: Concise Communication

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Remnants of nonmalignant thyroid tissue are nearly always present after surgery performed for thyroid carcinoma, and their ablation with I-131 is associated with decreased recurrence rates and probably increased survival. The usual dose of I-131 is in the range of 50 to 150 mCi; low-dose therapy (30 mCi) has been controversial. We therefore studied the effects of low-dose therapy in 20 patients. Complete ablation of thyroid tissue, as evidenced by negative neck and total-body scans after 6 to 30 mo, using a 1–1.5-mCi test dose, occurred after a single 30-mCi dose in eight patients (40%) and in one of seven patients who were treated again with the same dose. In three of these patients, a minimally positive scan at 6 mo became negative without further therapy. These results (9/15 successful) compared favorably with those of a single 75-mCi dose (6/9 successful). In 19 of the 20 patients, one or two doses of 30 mCi reduced thyroid iodine uptake to a level much less than that of normal nonthyroid neck tissues; i.e., one that causes no significant interference with the diagnosis or therapy of malignant lesions. We conclude that the use of up to two 30-mCi doses at 6-mo intervals is a reasonable approach to ablation therapy, particularly in young subjects with well-differentiated thyroid cancer. Besides minimizing whole-body and gonadal irradiation exposure, the advantages are greater convenience and reduced expense with a dose that can be given to outpatients. The disadvantages are that about half of the patients will require more treatment, with attendant hypothyroid periods and delay in achieving ablation, and that any tumor in the thyroid remnant may be inadequately irradiated. A long-term, prospective study is needed to evaluate the importance of these factors. The persistence of a positive scan after two 30-mCi doses appears to be an indication for increasing the subsequent dose, as would the detection of I-131 uptake in tumor tissue at any stage. In older patients (>40 yr) and in poorly differentiated thyroid cancer, high-dose therapy (~100 mCi) at the outset may be preferable.

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Radioactive iodine for therapy of thyroid carcinoma represents one of the more specific antineoplastic agents available. Although undifferentiated tumors are typically unresponsive, they are relatively uncommon, and up to 60% of all thyroid carcinomas (80% of differentiated thyroid carcinomas) are treatable with radioactive iodine after removal of nonmalignant thyroid tissue (*1*,*2*). Total thyroid ablation, which almost always requires radioactive iodine treatment in addition to surgical thyroidectomy, is associated with a decreased recurrence

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rate of thyroid carcinoma (*3–5*) and probably increases survival (*3–8*). Doses of I-131 in the range of 50 to 150 mCi are customarily used to ablate thyroid remnants; an initial dose of 75 mCi was most common at our institution before 1977, when a trial of 30-mCi doses was initiated.

Low-dose (30 mCi) therapy was advocated by McCowen et al. (*9*). They compared this dose with higher doses (generally 80–150 mCi) and concluded that the lower dose was nearly equivalent in achieving ablation and allowed a lower total dose to patients who received a low dose initially and a subsequent higher dose when more treatment was necessary. Since the lower dose did not require hospital confinement, according to Nuclear Regulatory Commission regulations, it was also less expensive and inconvenient. In contrast, others (*10,11*) achieved poor results with low-dose I-131.

In our study we used I-131 retention measurements as well as scans to evaluate the efficacy of low-dose ablation therapy in patients who had undergone surgery for thyroid carcinoma, and further treatment was attempted with the same 30-mCi dose when there was no evidence of malignant disease. We also compared these results with those in patients treated initially with 75 mCi.

METHODS

Patients with biopsy-proven well-differentiated thyroid carcinoma had partial or near-total thyroidectomy followed after 6 wk by total-body and neck scans, performed 48 hr after 1.0–1.5 mCi diagnostic doses of I-131. They were generally given tri-iodothyronine after surgery until 2 wk before the scan. A laxative, magnesium citrate, was given the night before scanning to reduce nonspecific retention of I-131 by the bowel, and the quantities retained in the neck at 48 hr and in the whole body at 48 and 96 hr were also determined (*12*). A therapeutic dose of 30 mCi I-131 was given when the scan revealed uptake in the thyroid bed. Follow-up scans, which were repeated at 6-mo intervals until negative, were done after 6 wk abstinence from replacement thyroxine and 2 wk abstinence from tri-iodothyronine (*12*). Most patients with positive follow-up scans were treated again with 30 mCi therapy doses, but some with minimally positive scans were not treated again. A few days after a negative or borderline diagnostic scan—or after the therapy dose in the case of a positive scan—patients were started on thyroxine, which was taken until 6 wk before the next follow-up. Radioimmunoassay of serum TSH, thyroxine, tri-iodothyronine, and thyroglobulin was performed during each diagnostic I-131 study. Thyroglobulin (Tg) was kindly assayed by Dr. A. Schneider (*13,14*). For comparison, patients who had received ablation doses of 75 mCi I-131 before the onset of the low-dose study were also evaluated.

During most of the study, a rectilinear dual-probe scanner with 12.7-cm crystals was used, but the last few patients were scanned on a tomographic instrument.* Direct comparison of the two instruments by repeated scanning of one patient showed the newer one to be slightly superior in resolution and sensitivity. Radioactive standards were routinely used, and both instruments very easily detected 1 μCi, or less than 0.1% of the diagnostic dose, in a point source. Scans were blindly reviewed for this study, and a level of twice background was considered positive detection. It was estimated that our scanning methods could detect at least 0.01% of the diagnostic dose distributed in a 1-ml volume within the thyroid bed. Assuming a typical thyroid uptake of about 1% per gram, this amounts to a capability of detecting as little as a few milligrams of normally functioning thyroid tissue. The grading scheme for the scans is given in footnote *c* of Table 1.

The expected radiation exposure to the body from radioiodine was calculated with a computer program, taking advantage of the nonlinear least-squares algorithm available on the National Institutes of Health MLAB system (*15*). The program was based upon the method developed previously by Rall et al. (*16*) and was applied to patients undergoing I-131 therapy for metastatic thyroid cancer at the National Institutes of Health.

RESULTS

Negative scans. The neck retention at 48 hr and the total-body retention at 96 hr were determined in 33 patients who had 46 negative scans (Fig. 1). The average neck retention was 0.30%; (range 0–0.87%, median 0.26%). The average 96-hr total-body retention was 1.82% (range 0.46%–6.16%, median 1.13%). In the case having the highest neck retention, appropriate shielding demonstrated that nearly half was due to nonthyroidal structures such as submandibular salivary tissue. Although such contributions to neck retention are expected

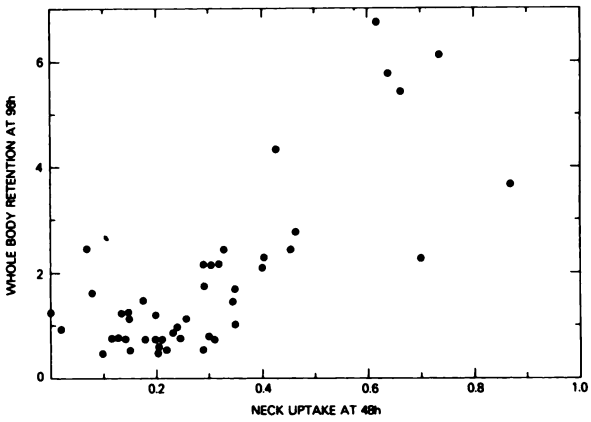

FIG. 1. Total-body retention at 96 hr against neck retention at 48 hr for 46 negative scans in 33 patients.

to be variable, it is likely that all the retention associated with negative scans derives from normal structures. As seen in Fig. 1, the 48-hr neck retention is roughly proportional to the 96-hr total-body retention, especially at higher retention levels.

Treatment with 30-mCi doses. Data for 20 patients are summarized in Tables 1 and 2, and are listed in order of neck retention before the initial I-131 therapy. A consistent decrease of neck uptake was seen with successive treatments in almost all cases (Table 1). If the average normal background of 0.3% is taken into account, it is evident that one or two doses of 30 mCi were sufficient to reduce thyroidal retention nearly to zero in all cases except two. These two patients (Cases 1 and 4) had high neck uptakes at 2 wk off T_3 but were not treated until 4 wk off T_3, at which time the 48-hr neck retention was much lower (probably owing to an increasing rate of iodine release from the thyroid tissue). In patients with initial neck uptake greater than 5%, the serum TSH level increased following the first therapy dose (Table 2), consistent with the decrease in iodine uptake. Thyroid hormone levels (data not shown) were directly correlated with the neck uptake and inversely correlated with the TSH level.

Despite very low thyroidal retention, only five patients had negative neck scans 6 mo after initial 30-mCi therapy (Table 1). Of considerable interest was the finding that three additional patients (Cases 11, 18, 20) who had borderline scans 6 mo after therapy subsequently developed negative follow-up scans after 12 to 24 mo of continued thyroid hormone replacement without further I-131 therapy. One of seven patients whose scans after a second treatment were available also developed a negative scan. One patient's scan (Case 7) became

TABLE 1. NECK UPTAKE AND SCAN BEFORE THERAPY AND 6 MO AFTER SUCCESSIVE 30-mCi OF I-131 [a]

Pt.	Age/Sex	Neck uptake (%)[b] 0	1	2	Neck scan[c] 0	1	2	Comment
1	51F	52.0 (11.3)	19.8 (9.7)	2.2	4+	4+	4+	Pending after third dose.
2	34F	43.8	0.4		4+	2+		Transient radiation thyroiditis; refused second dose.
3	49F	32.1	0.1		4+	0		
4	53F	29.0 (9.9)	2.7 (4.9)	1.1[d]	4+	4+	4+[d]	Negative scan 6 mo after fifth dose of 100 mCi
5	28M	26.3	0.8		4+	3+		Refused second dose.
6	33M	20.0	0.3	0.5	4+	2+	1+	Elected continued observation.
7	30F	16.0	0.7	0.4[e]	4+	4+	3+[e]	
8	48F	ND[f]	0.7 (0.3)	0.5	ND	3+	1+	Pending after third dose.
9	47F	13.5	0.3		4+	0		
10	36F	5.5	0.3		4+	1+		1+ refers to thyroid bed activity. Because of persistent uptake in a lymph node, second dose was 150 mCi.
11	29F	3.0	0.3		4+	2+		Negative scan after 13 mo.
12	28M	2.1	0.25	0.1	4+	3+	0	Cervical lymph-node metastasis (see text).
13	51F	1.6	0.2		4+	0		
14	54M	1.2	0.2		4+	0		
15	58F	0.9	0.3	ND	4+	2+	ND	Refused follow-up scan after second dose.
16	18M	0.7	0.2	0.3	2+	4+	2+	Elected continued observation.
17	56F	0.7	0.3		3+	0		
18	52F	0.7	0.3		2+	1+		Negative scan after 24 mo.
19	50F	0.6	0.5		3+	2+		Elected continued observation.
20	30M	0.3	0.4		3+	1+		Negative scan after 12 mo.

[a] 0 = before therapy; 1 = after 1st therapy; 2 = after 2nd therapy; ND = not done.

[b] Values in parentheses are 4 wk off T_3 and just preceding next therapy dose.

[c] 0 = negative; 1+ = detectable (twice soft-tissue background); 2+ = evident (2 to 3 times background); 3+ = prominent (>3 times background but not most intense uptake); 4+ = most intense uptake.

[d] 3rd and 4th 30-mCi doses gave uptake and scan: 0.7 and 3+, and 0.7 and 2+, respectively.

[e] 3rd and 4th 30-mCi doses gave uptake and scan: 0.4 and 3+, and 0.2 and negative, respectively.

[f] Assumed to be between 16 and 13.5% on basis of extent of partial thyroidectomy.

TABLE 2. SERUM TSH AND Tg BEFORE THERAPY AND 6 MO AFTER SUCCESSIVE 30 mCi OF I-131[a]

Pt.	TSH (μU/ml)			Tg (ng/ml)		
	0	1	2	0	1	2
1	3.9	24	94	42	75	48
	(4.6)	(52)				
2	13	ND		14	4.6	
3	5.9	>50		43	<2	
4	44	66	84[b]	55	11	8.2[b]
	(55)	(83)				
5	16	>50		10	9.9	
6	24	>50	ND	45	<2	4.8
7	4.1	>100	>100[c]	ND	ND	28[c]
8	ND	70	70	ND	14	8.0
		(98)				
9	19	>100		ND	7.3	
10	ND	119		54	24	
11	>100	91		<2	<2	
12	87	>50	126	63	150	172
13	51	>50		2.8	3.5	
14	32	43		2.6	ND	
15	60	48		3.2	ND	
16	>50	ND	ND	<2	4.0	ND
17	76	85		4.6	<2	
18	>100	>100		17	<2	
19	44	53		2.5	<2	
20	>100	>100		5.5	<2	

[a] 0 = before therapy; 1 = after 1st therapy; 2 = after 2nd therapy; ND = not done.
[b] 3rd and 4th 30-mCi doses gave TSH and Tg: 71 and <2, and 80 and 2.2, respectively.
[c] 3rd 30-mCi dose gave TSH 76 and Tg < 2. Results after the 4th dose are pending.

negative after a fourth dose of 30 mCi, while another patient (Case 4) did not achieve a negative scan with four doses of 30 mCi, but did following a subsequent treatment with 100 mCi.

As in other studies of the effect of 30-mCi doses (*10*), we found one instance (Case 12) of clearly malignant disease (cervical lymph-node metastasis) that either developed or progressed in the interim between the initial 30-mCi dose and the follow-up scan, despite reduction of retention by the thyroid remnant. Following surgical removal of the metastasis, this patient had a negative follow-up scan but retained a high Tg level of 172 ng/ml (Table 2). As has been reported in other patients (*17,18*), metastatic thyroid tissue that could not be visualized by the whole-body I-131 scan (or by radiograph or Tc-99m bone scan) probably was responsible for the increased Tg level. In another case (Case 10), probable I-131 uptake in a cervical lymph node led to a larger therapeutic dose of I-131 6 mo after the initial low-dose therapy.

The serum Tg levels (Table 2) showed a decrease that accompanied the fall in neck uptake in most cases when the initial uptake was greater than 5%. The scan was generally more sensitive than the Tg assay in disclosing residual thyroid tissue in patients with low neck uptake.

The efficacy of one or two 30-mCi doses in removing detectable normal thyroid tissue is presented in Table 3.

Treatment with 75-mCi doses. Data for nine patients are summarized in Table 4, listed in order of initial 96-hr total-body retention. Although neck retention was not quantitated in these patients, the 96-hr total-body retention should correlate well with thyroidal retention, given that renal iodide clearance (*19*) is rapid ($t_{1/2}$ = 4–14 hr) relative to the rate of iodine release from the thyroid. The half-time for iodine release from small thyroid remnants under increased TSH stimulation is not known, although in two patients we found it to be about 3 days. Though much more rapid than iodine release rates typical of normal thyroid ($t_{1/2}$ = 40 days), these values are still much longer than the renal iodide clearance rate in most patients.

From the average 96-hr body retention associated with negative scans (1.87%) and the data of Table 4, it is clear that 75 mCi I-131 was effective in reducing thyroidal retention nearly to zero in all cases. Five of nine

TABLE 3. OCCURRENCE OF NEGATIVE SCANS AFTER I-131 THERAPY DOSES TO ABLATE THYROID REMNANTS

Dose	Patients treated	Patients evaluated	Negative scans after 6 mo		Total negative scans	
			No.	%	No.	%
1st 30 mCi	20	20	5	25	8	40
2nd 30 mCi	8	7[a]	1	14[b]	1	14[b]
Two 30 mCi	20	15[a]			9	60[b]
75 mCi	9	9	5	55	6[c]	67

[a] Patients not evaluated after two 30-mCi therapy doses are two (Cases 2 and 5) who refused second dose, one (Case 15) who refused testing after second dose, one (Case 10) who received a second dose of 150 mCi because of presence of metastatic disease (nodes), and one (Case 19) in whom further observation was elected after first dose.

[b] Two patients (Cases 6 and 16) had borderline scans after second therapy dose and are being observed without further therapy; if both become negative, total success rate could reach 73%.

[c] Scans of patients 1 and 5 became positive after initial negative scan, probably due to recurrent tumor.

diagnostic scans were negative at initial follow-up, as compared with five of 20 for the 30-mCi dose and nine of 15 after one or two 30-mCi doses (Table 3). One patient developed a negative scan without repeated treatment (Case 8), and in one patient (Case 4) who was not successfully ablated, there was a suspicion that the remaining thyroid tissue was malignant, since uptake clearly in a lymph node was ablated by the initial therapy.

Relationship of nonthyroidal radiation dose to administered dose of RaI. The significant potential side effects of radioiodine therapy relate to irradiation of nonthyroid tissues, especially the blood-forming cells, which may undergo leukemic transformation, and the gonads. While potentially leukemogenic cells are localized in the bone marrow, this tissue is widely distributed in the body and thus whole-body irradiation was considered as indicative of leukemic risk. In order to consider maximal risk to reproductive organs, the ovarian dose was estimated, since this is generally somewhat greater than the testicular dose.

The principal factors that determine whole-body radiation exposure from radioiodine are thyroid iodine retention and turnover and renal iodide clearance. After thyroidectomy, renal iodide clearance is the major factor, and estimates of radiation exposure range from 0.3 to 0.5 rad/mCi (*20*). Calculations for N.I.H. patients (*16*) showed a similar range of 0.3 to 0.7 rad/mCi when body retention was less than 5%, while a range of 0.4 to 1.0 rad/mCi was found for patients with higher body retention (5–30%).

Although there have been widely divergent estimates

TABLE 4. RESULTS OF 75-mCi I-131 THERAPY[a]

Pt.	Age/ Sex	Initial: Whole-body uptake at 96 hr (%)	Initial: TSH (μU/ml)	Initial: Neck scan	6 mo after therapy: Whole-body uptake at 96 hr (%)	6 mo after therapy: TSH (μU/ml)	6 mo after therapy: Neck scan	Comment
1	26F	7.9	28.0	4+	0.7	57.1	0	Positive scan 17 mo later.
2	49F	ND[b]	55.7	4+	0.5	68	2+	
3	18F	6.9	ND	4+	0.5	ND	2+	
4	16M	5.2	>50	3+	1.8	465	2+	Residual uptake only in thyroid bed, although initial scan showed uptake in lymph node outside thyroid bed.
5	28F	3.3	76	4+	0.9	>100	0	
6	47F	2.6	14.7	3+	1.8	ND	0	
7	41M	2.3	ND	4+	0.5	ND	0	Positive scan 6 mo later.
8	27F	2.3	>100	4+	1.3	>100	1+	Negative scan after 12 mo.
9	53F	0.4	82	3+	0.7	>50	0	

[a] See footnotes *a* and *c* of Table 1.

[b] Neck uptake at 48 hr was 0.9%.

of ovarian irradiation following radioactive iodine therapy, Robertson and Gorman (*21*) published a nomogram indicating that for thyroid uptake less than 30% there is little dependence of ovarian dose on thyroid release rate. From these considerations, a reasonable maximum dose to the ovary of about 0.4 rad/mCi is expected for low (less than 5%) neck uptakes and about 0.35 rad/mCi at higher (5–30%) uptakes. Profound renal failure would have the effect of increasing these estimates by a factor of about 0.7/0.4 (*21*).

Although 40% of patients respond to a single dose, and thus would not require the exposure related to the second dose, the effect of two 30-mCi doses may be calculated and compared with the effect of a single 75-mCi dose. Assuming that an initial dose of 30 mCi is uniformly successful in reducing a high uptake to a low one, two doses of 30 mCi each produce (maximally) 30 + 0.7(30) = 51 rad for body exposure and 30(0.35) + 30(0.4) = 22.5 rad for ovarian exposure. A single 75-mCi dose results in an estimated maximum of 75 rad to the body and 26 rad to the ovary.

DISCUSSION

We have little information concerning low-dose (30 mCi) ablative therapy for thyroid remnants. One of the first reports of such therapy emphasized its effectiveness relative to a more standard high dose of I-131 (*9*). Although recent reports (*10,11*) have not shown as much success with 30-mCi doses, different and probably more stringent criteria for therapeutic success were used and similar criteria were not applied to determine the comparable effects of higher doses (*10,11*). The present study provides additional data on the effectiveness of the 30-mCi dose. Unlike prior studies, repeated 30-mCi doses have been used.

Our results show that a single 30-mCi dose resulted in a negative thyroid scan within 6 mo in 25% of patients. Additional patients whose scans were borderline at 6 mo became negative after 12 to 24 more months on thyroxine, thus increasing the rate of successful initial therapy to 40%. Patients with large remnants seem to be more effectively treated after a 2-wk abstinence from tri-iodothyronine, when thyroid I-131 retention is higher (*12*). Two such cases, in whom an additional 2-wk delay preceded therapy, had the least satisfactory responses to therapy. After a second 30-mCi dose, the negative scans increased to 60%. With two patients showing borderline scans after the second therapy dose, we elected to observe for a longer period without further therapy. If their scans should become negative, the success rate could reach as high as 73%. One or two doses of 30 mCi were sufficient in every case but one to reduce the total neck uptake to a level insignificantly different from that associated with normal nonthyroid neck tissues. This would not be an unreasonable criterion of successful therapy if the only issue were detection of iodine-retaining malignant thyroid tissue, but it is likely that more complete ablation of non-neoplastic thyroid tissue is necessary to afford its reported advantage in terms of decreased recurrences of thyroid carcinoma and increased patient survival (*3–8*). It does seem clear that in patients with recognized metastases in the presence of thyroid remnants (2 of 20 who received 30 mCi doses in this series), the 30-mCi dose is unable to destroy a metastasis completely.

In the small comparison group receiving 75-mCi ablation doses, a single dose, resulting in a negative scan in 67% of patients, was more effective than a single 30-mCi dose but similar to the two 30-mCi doses.

Although our diagnostic tracer method is very sensitive and is capable of detecting 0.01% uptake or less in a 1-ml volume, it is clear that the use of a larger test dose (*22*), or scanning after a therapy dose (*23–25*), will disclose persistent I-131 uptake in some patients we have classified as negative. As discussed by Waxman et al. (*22*), however, the requirement for early therapy in such patients is uncertain at present. Furthermore, our experience in following patients with minimally positive scans indicates that some may become negative without further I-131 therapy. Nevertheless, since 30-mCi is the largest dose usually approved for outpatients, it may be reasonable to combine the therapeutic and diagnostic efficacy of 30-mCi doses for ablation of thyroid remnants.

The benefits of low-dose therapy, in addition to economy and convenience, relate primarily to a reduced total radiation exposure to extrathyroid target organs. While this reduction pertains mainly to the 40% of patients in whom ablation is achieved with a single 30-mCi dose, repeated low-dose exposures, which allow for tissue repair mechanisms to proceed in the interim, may cause less biologic damage than the same total dose delivered at one time. Therefore, even patients requiring two such doses may benefit. The risk of leukemia and ovarian injury after thyroid ablation doses under 150 mCi is unknown, but is probably very small. Pochin (*26*) reported four cases of leukemia in 140 patients who received an average total dose of 735 mCi. Pochin's leukemia cases received 1130–1715 mCi, and other cases gathered from the literature by Brincker et al. (*27*) received 261–1600 mCi. Regarding ovarian injury, Sarkar et al. (*28*) found no evidence of radiation-induced problems in fertility or in the offspring of 33 young adults treated with 80–691 mCi (average 196 mCi) and followed for an average of 19 yr. Despite the lack of evidence of injury below 150 mCi, however, it seems prudent to mitigate radiation exposure by using the minimal effective dose to achieve the desired purpose.

Disadvantages of low-dose therapy are, first, that about half of the patients require more treatment, and thus there are more periods of T_3 withdrawal and hy-

pothyroidism, and a longer time to achieve ablation is required. Second, unrecognized metastases may be inadequately irradiated so that the function of the neoplastic cells but not their growth may be reduced. A long-term, prospective study is needed to evaluate the importance of these factors in the efficacy of low-dose ablation therapy.

Our results suggest that the use of up to two 30-mCi doses at 6-mo intervals, since they result in negative scans in at least 60% of patients, is a reasonable approach to ablation therapy, especially in young subjects with well-differentiated thyroid cancer. In patients over age 40 yr and in poorly differentiated tumors, the more aggressive course of thyroid cancer suggests that high-dose ablation therapy (~100 mCi) may be preferable. Our results also suggest that a minimally positive scan at 6 mo after a therapy dose is an indication for further follow-up rather than immediate further treatment. In patients with persistently positive scans after two 30-mCi doses, the subsequent dose should be increased to 100 mCi in order to increase the chance that the remaining tissue, which might perhaps represent tumor in the thyroid bed, will be destroyed.

FOOTNOTE

* Pho/Con 192, Searle Instruments.

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