

Comparison of Outcomes After ^{123}I Versus ^{131}I Preablation Imaging Before Radioiodine Ablation in Differentiated Thyroid Carcinoma

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Detection of residual tissue after thyroidectomy for papillary or follicular thyroid carcinoma may be performed using diagnostic imaging with either ^{123}I or ^{131}I . The former is often preferred to avoid “stunning”—defined as a reduction in uptake of the therapeutic dose of ^{131}I caused by some form of cell damage from the diagnostic dosage of the radionuclide. Stunning could potentially reduce the therapeutic efficacy of ^{131}I given to ablate a postthyroidectomy remnant. This study examines the outcomes of ablative ^{131}I therapy after diagnostic studies with either ^{123}I or ^{131}I to determine if the diagnostic dosages of these radionuclides used in our Thyroid Cancer Center reduce the efficacy of ^{131}I given for remnant ablation. **Methods:** Fifty patients with nonmetastatic papillary or follicular carcinoma of the thyroid received total thyroidectomy; this was followed by thyroid hormone withdrawal to achieve a serum thyroid-stimulating hormone level in excess of 30 $\mu\text{IU/mL}$. They were divided prospectively into 2 groups. Group 1 had diagnostic imaging with 14.8 MBq of ^{123}I followed by thyroid remnant ablation with 3.7 GBq of ^{131}I . Group 2 had empiric ablation with the same 3.7-GBq ^{131}I dosage, but the preceding diagnostic scan was performed with 74 MBq of ^{131}I . Comparisons of equivalence of the 2 population samples and of the postablation outcomes were evaluated by χ^2 analysis. Successful ablation required a negative follow-up thyroid scan 6–8 mo after ablation and also an undetectable serum thyroglobulin level in the absence of antithyroglobulin antibodies. **Results:** There was no significant difference between the 2 groups demographically, in tumor burden or stage, or in the postthyroidectomy ablation rate (group 1, 81%; group 2, 74%; $P > 0.05$). **Conclusion:** If thyroid remnant stunning occurs due to 74 MBq ^{131}I used as a diagnostic agent before ^{131}I ablation, it has no significant clinical correlate, as it yields the same ablation rate as that which occurs after 14.8 MBq of ^{123}I used for imaging.

Key Words: thyroid carcinoma; ablation; stunning; ^{123}I -iodine; ^{131}I -iodine

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Ablation of residual thyroid tissue with ^{131}I after thyroidectomy for papillary or follicular thyroid carcinoma may be accomplished in several ways. An empirically chosen range of therapeutic activities, from 1.1 to 7.4 GBq (30–200 mCi), has been successfully used for many years (1), and expensive preablative dosimetry does not improve the results (2). Diagnostic ^{131}I in dosages in excess of 74 MBq or more has been associated with a decrease in uptake of the subsequent therapeutic dosage of ^{131}I , a phenomenon termed “stunning” (3). Is ^{123}I , which is more expensive than ^{131}I , then preferable for the diagnostic preablative study because of this “stunning” effect? We undertook this study to determine if ablative therapy is more successful when an empiric ablative dosage of 3.7 GBq of ^{131}I is preceded by a diagnostic dosage of 14.8 MBq of ^{123}I or of 74 MBq of ^{131}I , measuring success both by negative whole-body scintigraphy 6–8 mo later and by a serum thyroglobulin (tg) level below the limits of detection at the same time.

MATERIALS AND METHODS

Fifty consecutive patients with histopathologically proven papillary or follicular thyroid carcinoma without detectable distant metastases were studied after total thyroidectomy when a minimal blood level of serum thyroid-stimulating hormone (TSH, thyrotropin) of 30 $\mu\text{IU/mL}$ had been achieved. The patients were randomly assigned to 1 of 2 groups. Group 1 ($n = 26$) received 14.8 ± 0.2 MBq (mean \pm SD) of ^{123}I (as sodium iodide) 24 h before imaging, with ablative therapy given the next day, using 3.7 GBq of ^{131}I (as sodium iodide) if the ^{123}I scan showed only a postthyroidectomy remnant. Group 2 patients ($n = 23$) were dosed with 74.0 ± 0.3 MBq of ^{131}I and scanned at 24, 28, and 72 h; they were then treated at 72 h with the same empiric ablative dosage of 3.7 GBq of ^{131}I if the scan showed a postthyroidectomy remnant without distant metastatic disease. The 72-h delay was required because of a quantitative assessment performed for another study that did not affect the patient’s treatment in any way. Follow-up scintigraphy was performed in the same hypothyroid state 6–8 mo after therapy, using 74 ± 0.3 MBq of ^{131}I . Successful ablation of the initial thyroid remnant was defined as both the absence of visible iodine-concentrating tissue in the thyroid bed and adjacent

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lymph nodes on this follow-up scan and a simultaneous serum tg level below the lower limit of detection in the presence of a negative assay for anti-tg antibodies. Statistical comparisons of groups were made by χ^2 analysis with a P value required to be <0.05 to indicate statistically significant differences. The study was performed under the guidelines of the University of Cincinnati Institutional Review Board.

RESULTS

Fifty patients were entered into the study, with one (from group 2) lost to follow-up. The patients of the 2 groups were found to be statistically comparable in age, sex ratio, ratio of the number of papillary to follicular thyroid carcinomas, tumor burden, and locoregional metastases. None had distant metastases (Table 1). The mean activity of the ablative dosage of ^{131}I was not significantly different between the 2 groups, averaging 3.77 ± 0.11 GBq.

These demographically similar groups had comparable scintigraphic rates of ablation (group 1, 88%; group 2, 91%; $P > 0.05$), but, using our second diagnostic criterion for complete ablation—that the quantitative measurement of serum tg had to be below detectable limits as well (unlike all but one of the studies to be discussed)—decreased our ablative success rate for group 1 to 81% and for group 2 to 74% ($P > 0.05$) (Table 2). Six patients in group 1 (23%) and 4 in group 2 (17%) ($P > 0.05$) had an elevated anti-tg antibody level, invalidating the serum tg test as a criterion of the completeness of ablation for these 10 patients.

DISCUSSION

We have demonstrated that if stunning from ^{131}I occurred in our patients, as much of the relevant literature suggests, this phenomenon did not reduce the yield of complete ablation of thyroid remnants when compared with a statistically similar sample of patients we studied who received ^{123}I as the diagnostic radionuclide. For the detection of residual normal tissue (not thyroid cancer), the ^{123}I scan performed at 24 h is quite sensitive at the dosage we used.

We believe that a preablation radioiodine scan is important for several reasons: (a) about 2% of our patients have had a true total thyroidectomy by both scintigraphic evidence and the absence of measurable serum tg, and it is not justifiable to administer β -emitting radioiodine therapy to patients who do not need it; (b) staging with the preablation iodine dosage may reveal metastatic disease, a finding that

TABLE 2
Outcomes from Using Diagnostic ^{123}I or ^{131}I

Outcome	Group 1 (^{123}I)	Group 2 (^{131}I)
Total patient number	26	23
Complete ablation		
Scan only (%)	23 (88%)	21 (91%)
Scan + tg (%)	21 (81%)	17 (74%)

then requires a higher therapeutic amount of iodine than originally planned; (c) some areas of iodine-concentrating metastatic disease may require special preparations—for example, corticosteroids before treating cerebral metastases.

Several problems became apparent on review of the relevant literature:

- (i) The comparison groups were not always matched for age, sex, type of thyroid cancer, and diagnostic and therapeutic dosages of radioiodine;
- (ii) If stunning was noted, it was usually confirmed only qualitatively, a process which can cause its own problems (4);
- (iii) The great majority of papers in this field have judged the success of ablation solely from visual inspection of a follow-up scan 6 or more months after therapy with ^{131}I ; however, one must also require a negative assay for serum tg to exclude the presence of functioning thyroid tissue.

Stunning, as defined, was first demonstrated in 1951 (5), and this phenomenon has subsequently been reported in numerous papers and summarized in recent reviews (6,7). An inference from the observation of stunning is that the diagnostic dosage has interfered in some way with the trapping or retention of the therapeutic dosage or that the targeted mass has been reduced in volume and, hence, in uptake.

Numerous studies indicate that ^{123}I is comparable to ^{131}I in the detection of thyroid remnants after thyroidectomy (8–10). Park et al. studied patients after thyroidectomy with diagnostic dosages of 8.1 MBq of ^{123}I or 111–370 MBq of ^{131}I , with a subsequent ablative dosage of ^{131}I ranging from 3.7 to 7.4 MBq (11). Using the 1-y follow-up scan, without a tg level, these workers reported that total ablation was

TABLE 1
Comparability of 2 Groups

Parameter	Group 1 (^{123}I , $n = 26$)	Group 2 (^{131}I , $n = 23$)
Papillary/follicular carcinoma	22/4	21/2
Presence of anti-tg antibody (%)	6/26 (23%)	4/23 (17%)
Females/males	20/6	17/6
Mean age \pm 1 SD (y)	42.4 ± 14.4	42.9 ± 17.5
Iodine uptake in neck remnant (%)	3.7 ± 2.8	4.1 ± 3.1
No. of patients with visualized neck node metastases on diagnostic scan	3/26	3/23

obtained in 75% of patients receiving ^{123}I before the ablative dosage and 60% in those whose diagnostic tracer was ^{131}I ($P = 0.27$). However, there is no indication what the mean ablative dosages were for these 2 groups and whether they were statistically different from each other. Park et al. did not observe stunning after they reduced the ^{131}I activity administered to 74–111 MBq (11). ^{123}I used in the low dosages that Park et al. and our group administer provides excellent scintigraphic correlation with the ^{131}I scintigraphs performed 7–10 d after ablation.

Several studies have found no evidence of stunning on ablation rate with ^{131}I diagnostic activities of up to 185 MBq. The issue of stunning, and its clinical impact, may be related to the dosage of ^{131}I used. Park et al. noted that qualitatively diagnosed stunning was not a problem at activities of 74–111 MBq (11).

Leger et al. imaged 51 patients after injection with 10–20 MBq (mean, 15.2 MBq) of ^{123}I , 19 of whom also received 185 MBq of ^{131}I on the same day, yielding 93% and 94% ablation rates, respectively, using only scintigraphic evidence (12). Although stunning was documented only qualitatively in the group receiving diagnostic ^{131}I , there was no effect on the outcome (12). Dam et al. used an average therapeutic dosage of ^{131}I of 4.58 ± 0.21 GBq after a diagnostic dosage of 185 MBq, with visual evaluation of decreased uptake (stunning) detected in 19% of patients 7 d after therapy (13). The follow-up ablation rate was 88% in patients whose scans showed no evidence of stunning and 91% ($P > 0.05$) in patients with stunning. However, 26% of patients were lost to follow-up, so information on the therapeutic outcome was available only in 74% (13). Karam et al. also found no difference in ablative outcome, whether a diagnostic dose of 92.5 or 185 MBq of ^{131}I was used, with ablation in 78% and 74% of patients, respectively ($P > 0.05$), although the tg assay was not used (14). Similarly, Morris et al. noted no difference in the success rate of ablation after diagnostic ^{131}I dosages between 111 and 185 MBq given before therapeutic activities of 3.7–7.4 GBq of ^{131}I (65% ablated) as compared with a group that had no diagnostic scans and, thus, no exposure to potentially stunning ^{131}I before treatment (67% ablated) (15).

In contrast to these 4 articles, 2 studies suggest a stunning effect of ^{131}I , in activities of 111–185 MBq, on the outcome of ablation, but both have flaws that raise questions about the authors' conclusions. Muratet et al. retrospectively reviewed 2 patient groups given diagnostic scanning dosages of either 37 or 111 MBq of ^{131}I , which were then treated with 3.7 GBq of ^{131}I (16). Follow-up studies performed 6.1–16.8 mo later revealed successful ablation in 50% of patients who had been scanned with 111 MBq of ^{131}I and 76% success in the group receiving 37 MBq ($P < 0.001$). However, the group receiving the lower dosage was not matched for sex and contained a significantly higher percentage of men (16). In the second such study suggesting an effect of hypothesized stunning on outcome, Lees et al. retrospectively analyzed 3 patient

groups that received, before remnant ablation with 3.7 GBq of ^{131}I , a diagnostic scan dosage of 185 MBq of ^{131}I , a diagnostic dosage of 740 MBq of ^{123}I , or no diagnostic radioiodine. Visual evidence of complete ablation was present in only 47% of patients receiving ^{131}I , 86% of those receiving ^{123}I , and 83% of the group with no pretherapy exposure to a diagnostic dose of radioiodine. The 3 groups, however, had significant differences between them. The patients who received ^{131}I for both diagnosis and therapy received a statistically larger amount of ^{131}I therapy. The group with no pretherapy diagnostic scan had a mean serum tg of 10.7 ng/mL, whereas the first 2 groups had a far greater tumor burden with significantly higher tg values of 474 and 480 ng/mL, respectively. Follow-up after ablation imaging was performed as early as 3 mo after therapy when cell killing may not have been complete, so scintigraphy at this early time might lead falsely to the assumption of persistent (but mitotically sterile) tumor (17).

Finally, there is a study with the remarkable conclusion that the patients who experienced apparent thyroïdal stunning had a better outcome than those who did not. Bajen et al. found that in 21% of patients studied, the posttherapy scan showed less uptake (stunning) qualitatively than on the diagnostic scans (18). A serum tg level of <3.0 ng/mL was used in this study, along with the radioiodine scan, to determine completeness of ablation. Sixty-two percent of stunned glands and only 37% of nonstunned glands were ablated according to these criteria. In this study, the therapeutic ^{131}I dosage—ranging more widely than in any of the other studies (1.85–7.4 GBq) because patients with distant metastatic disease were included—was given an average of 7.2 wk after the diagnostic activity (185 MBq of ^{131}I). This represents a far greater delay than in any of the other studies, wherein the time between diagnostic and therapeutic dosages of ^{131}I was 1–9 d, except for that of Leger et al., which averaged 34 d with no evidence of an effect of stunning on ablation noted (12). Therefore, it is possible that enough time had passed for a therapeutic effect of the diagnostic activity to be added to the dosage actually given for treatment. The major problem in making any conclusions from the study of Bajen et al. arises from the fact that 23% and 26%, respectively, of the 2 groups had not yet had a follow-up scan (18).

There are also reports of diagnostic dosages of ^{123}I with activities of 185–200 MBq causing the stunning phenomenon (19,20), presumably from Auger electrons emitted by ^{123}I (21). However, despite the stunning phenomenon observed with both radiopharmaceuticals in a range of dosages, complete ablation of postthyroidectomy remnants can usually be successfully achieved.

We chose not to quantitate the uptake of therapeutic ^{131}I given after diagnostic dosages of ^{123}I or ^{131}I because this has been reproducibly done so often previously. Many practices now use recombinant human TSH (rhTSH) routinely for thyroid remnant ablation, but this study began before local insurance companies made rhTSH available to

all patients. However, the lack of rhTSH usage should not have altered the results, because scintigraphy after thyroid hormone withdrawal or after rhTSH stimulation yields equivalent results (22).

Although ^{123}I is frequently used to image patients with thyroid cancer before ablation, ^{131}I remains an important diagnostic radionuclide if one must perform dosimetric studies to determine the largest safe dose that can be given or currently when rhTSH is used. Furthermore, ^{123}I may not always be available in every area performing nuclear medicine, and thus we feel it is important to know an activity of ^{131}I that may be given for diagnostic purposes without sequelae that could affect the therapeutic outcome.

CONCLUSION

This study has demonstrated that a preablative scanning dosage of 74 MBq of ^{131}I yields the same thyroid remnant ablation rate as 14.8 MBq of ^{123}I , confirmed not only by the follow-up scan at 6–8 mo but also by a simultaneous undetectable level of serum tg. This is the first prospective study, to the author's knowledge, of the clinical import of radioiodine-induced stunning with the ^{123}I and ^{131}I groups matched for age, sex ratio, tumor type and stage, and ablation dosage, and with virtually complete (98%) patient follow-up. If one must use ^{131}I for preablative scanning, 74 MBq appears to be an appropriate activity that does not lower the ablation rate as compared with ^{123}I .

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