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The Nonimpact of Thyroid Stunning: Remnant Ablation Rates in ^{131}I-Scanned and Nonscanned Individuals

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Thyroid stunning has been reported as the temporary impairment of thyroid tissue after a 111-MBq or greater diagnostic ^{131}I dose that decreases the final absorbed dose in ablative therapy. Concerns regarding the reality of stunning have arisen in part due to a flawed study design in prior reports. To assess whether a stunning effect has any impact on therapeutic outcomes, we compared initial treatment ablation rates in patients who received 111- to 185-MBq ^{131}I diagnostic scans (n = 37) before ablative doses of 3700–7400 MBq with ablation rates in patients who did not receive any ^{131}I before the initial treatment dose (n = 63). Ablation rates were 64.9% for scanned patients and 66.7% for nonscanned patients, a nonsignificant difference. Nonscanned patients with metastatic lesions (n = 23) were ablated at a higher rate (78.3%) than scanned patients (n = 9) (66.7%), but the difference was not significant ($P = 0.50$). It is possible that the reported stunning phenomenon, specifically its impact in temporarily impairing tissue, has been overemphasized. (*J Clin Endocrinol Metab* 86: 3507–3511, 2001)

THYROID STUNNING, a phenomenon first recognized in the 1950s (1) that has again recently received attention, refers to the observance of impaired thyroid tissue function after administration of a therapeutic dose of ^{131}I subsequent to a 111-MBq or greater diagnostic dose. Research demonstrates evidence of stunning in posttherapy ^{131}I scans that show less uptake than the diagnostic scan (2–5). By definition, stunning reduces ^{131}I uptake, decreasing the final absorbed dose during ablation (3–5, 6). It has been implied in these studies that stunning diminishes the effectiveness of the ablative dose to an extent that causes lower ablation rates in scanned patients.

Diagnostic radioiodine scanning postthyroidectomy is typically standard practice to determine the amount of residual tissue remaining, the tumor avidity of residual tissue, and the appropriate ^{131}I dosimetry (7, 8). Proponents of the stunning theory advocate using 74 MBq ^{131}I or less as a diagnostic scanning dose. However, our prior research demonstrates that the diagnostic benefit of a 74-MBq or less dose is far smaller than that of a 111- to 370-MBq dose (9). The value of such small diagnostic doses is further called into question by studies indicating that as many as 19% of patients who have no thyroid tumor visualized in diagnostic scans are identified with tumor tissue in 3700-MBq posttherapy scans (9, 10).

Despite an array of research on various aspects of this reported phenomenon, we were prompted to reexamine the stunning issue due to specific flaws in prior study methodologies as well as anomalous results. A majority of reports qualitatively discuss thyroid stunning by comparing postdiagnostic and posttherapy scans. However, several studies only evaluate early (24–72 h) posttherapy scans. In our experience there is a marked difference in the ability to detect iodine-avid tissue when a posttherapy scan is read at 7–10 d, rather than at 2–3 d (9, 11). Therefore, perhaps observations of stunning are merely a product of reading posttherapy scans too early. In addition, there are some discrepancies among studies regarding the time lapse between diagnostic and therapeutic doses that could account for some of the observed stunning effects. Taking into consideration the effective half-life of ^{131}I, increasing the time elapsed between the diagnostic and the therapeutic doses may enhance the ability of the ^{131}I to impair iodine-avid tissue. Thus at many institutions it is common practice to administer a therapeutic dose immediately after obtaining the results of the diagnostic scan. However, several researchers who observed evidence of thyroid stunning prolonged the time interval between diagnostic and therapeutic doses for several days to as much as 6 wk (2, 4, 6, 12).

The significance of a stunning effect lies only in its potential to hinder ablative therapy. Outcomes studies have yielded mixed results. Some findings demonstrated equivalent or nonsignificant differences in ablation rates between patients diagnostically scanned with ^{123}I *vs.* ^{131}I (13, 14). Another group found significantly higher ablation rates in patients who were given 37- *vs.* 111-MBq diagnostic scans (15). Clearly, the issue of whether stunning is a viable physiological phenomenon that impacts outcomes in thyroid cancer radioiodine treatment remains unresolved.

No studies to our knowledge have compared outcomes of ablation after administrating a 111- to 222-MBq scanning ^{131}I dose *vs.* treating without any prior radioiodine scanning. At our institution, the practice of preablation scanning in patients immediately posttotal thyroidectomy with no prior ^{131}I therapy was discontinued in 1994 because benefits of a scan did not outweigh the costs of patient inconvenience at having to undergo two separate radiation protocols as well as concerns over stunning. We regard ablation postthyroidectomy as standard practice in patients at high risk for or known to harbor residual cancer. This change in procedure offered us a unique research opportunity.

The goal of this study was to determine whether the de-

scribed stunning phenomenon has any impact upon initial ablation rates in thyroid cancer patients postthyroidectomy who underwent ^{131}I therapy.

Subjects and Methods

Subjects

During the course of this institutional review board-approved study we retrospectively reviewed records from thyroid cancer patients at Cedars-Sinai Medical Center treated with ^{131}I for ablative therapy of thyroid remnants postthyroidectomy. Patient group 1 (PG1-SCAN) is composed of 37 patients who had 111- to 185-MBq ^{131}I diagnostic scans before their first postthyroidectomy ^{131}I ablative treatment. The second group of patients (PG2-NS; n = 63) did not receive a diagnostic ^{131}I dose before ablative treatment. None of the study patients had received any prior radioiodine therapy. If needed, a therapeutic dose was administered on the same day as or a few days after the scanning dose was read; the time elapsed between administration of the scanning dose and the therapeutic dose was typically 2–5 d.

PG1-SCAN patients were typically treated between 1989 and 1994, although some patients who received pretreatment scans after 1994 (at the request of their endocrinologist) were included in this group. PG2-NS patients were generally treated between 1994–1999. Patients were identified for inclusion in this study through the Cedars-Sinai Medical Center tumor registry (1990–1994) or through a nuclear medicine record of ^{131}I ablative treatment doses administered (1994–1999). Patients consecutively clinically evaluated were studied; excluded patients lacked appropriate follow-up data (*e.g.* failure to complete treatment within 6 months postsurgery or lack of follow-up diagnostic scans). Gender, age, and cancer type statistics for each group are listed in Table 1.

Ablative doses given to patients ranged between 3700–7400 MBq. Nuclear medicine physicians and endocrinologists at our institution have the option of prescribing low (3700 MBq), medium (5550 MBq), or high (>5550 MBq) ablative ^{131}I doses. Patients who exhibited metastases were selected to receive 5550- to 7400-MBq doses due to a significant dose-response correlation in the treatment of these patients (16). (Due to concerns in the early 1990s regarding very high dose radioiodine, no patients in the scanned group were given doses >5550 MBq.) Nevertheless, physicians may follow individualized treatment protocols due to the variability of radiation doses per MBq administered (16) and the success of adjustable radioiodine administration (17). All patients were instructed to follow a low iodine diet beginning 10–14 d before the initial scan, treatment, and follow-up scan.

All posttherapy scans were read at two intervals: 2 and 7–10 d after treatment. None of the patients treated had completely negative posttherapy scans. Further information regarding those scans is not included within the present report for two key reasons. First, our protocol measured ablation through the results of a follow-up diagnostic scan of 111–222 MBq (see below for further details), rendering the specific posttreatment scan results irrelevant. In addition, we believed that any comparison of posttherapy scans with diagnostic scans would be inappropriate due to massive dosage differences. Patients were staged through the examination of surgical and pathology reports and evaluation of posttherapy scans. Disease was stratified as confined to thyroid bed, regional nodes, or distant metastasis.

TABLE 1. Patient statistics

	Scanned (n = 37)	Nonscanned (n = 63)
Gender		
Female	22	43
Male	15	20
Cancer type		
Papillary and papillary-follicular	35	60
Follicular	1	2
Hurthle	1	1
Age (mean ± SD)	40.5 ± 14.0	43.1 ± 13.8

None of the variations between scanned and nonscanned patient groups were statistically significant.

Scanning techniques

Endogenous TSH stimulation protocols were identical in all cases. If patients were receiving L-T_4, it was discontinued 5–6 wk before scanning. Patients were treated with 25 μg T_3 (Cytomel) twice daily for 4 wk and scanned 2 wk (14–16 d) after T_3 was discontinued. TSH levels were measured 3–6 d before the administration of ^{131}I. All values were either more than 30 mIU/L or would be anticipated to be above that level based upon published TSH doubling times in patients who had undergone thyroidectomy (18). All patients were scanned using a gamma camera device (Marconi Medical Systems/Picker Health Care Products, Cleveland, OH) with a 364-keV rated collimator. During this study two gamma cameras were used, and both used similar collimator specifications. The sensitivities (counts per unit time) of both cameras were also similar. Total body scans were performed at a scan speed of 10 cm/min. Both anterior and posterior views were obtained. Indirect spot views were also obtained for 15 min/view.

The success of ablation was determined by a 111- to 222-MBq ^{131}I dose (mean, 129.5 MBq), and subsequent scans were performed between 4 and 42 months postablative dose (mean, 11.8 months). The patient was considered ablated if the scan was visually negative in the thyroid bed, and there was no iodine-avid tissue seen outside of expected areas (*e.g.* salivary glands). Images were interpreted by two observers without knowledge of the specifics of the surgical findings or the extent of pathology. The films were not independently reviewed for this study.

Statistics

Significance was determined by χ^2 analysis. All statistical analysis was performed using GB-Stat version 6.5 statistical software developed by Dynamic Microsystems, Inc. (Silver Spring, MD) and distributed by Scolari, Sage Publications Software (Thousand Oaks, CA).

Results

Although ablation rates were higher (+1.8%) for nonscanned than scanned patients, this difference was not statistically significant (Table 2). Twenty-four of 37 scanned patients were ablated (64.9%), and 42 of 63 nonscanned patients were ablated (66.7%). There was some variation between ablation rates depending on the dose of ^{131}I administered (Table 3). However, subgroup sample sizes were small, and the differences did not demonstrate a clear dose-response relationship.

The majority of patients with cancers not confined to the thyroid bed had lymph node metastases (Table 4). Nine of the scanned patients (24.3%) had metastatic lesions; 66.7% of these patients were ablated after the first dose, equivalent to overall ablation rates. Twenty-three nonscanned patients (36.5%) exhibited metastases, and 18 of these patients were ablated (78.3%). Although the ablation rate in this group was higher than that in patients with carcinoma confined to the thyroid bed (Table 5), differences were still not significant ($P = 0.50$). However, the number of patients studied in each group is too small to exclude even an important difference.

Discussion

There are marked discrepancies in several prior studies regarding stunning that led us to reinvestigate this issue.

TABLE 2. Scanned (PG1-SCAN) *vs.* nonscanned (PG2-NS) ablation rates

	No. of patients	No. ablated	% Ablation[a]	Significance (*P*)
Scanned	37	24	64.9	0.85
Nonscanned	63	42	66.7	

[a] Ablation is defined here as one scan visually negative in the thyroid bed taken 4–42 months posttreatment.

TABLE 3. Scanned (PG1-SCAN) *vs.* nonscanned (PG2-NS) ablation rates, by dose

Dose	No. of patients	No. ablated	% Ablation	Significance (*P*)
3,700 MBq PG1-SCAN	11	8	72.7%	0.22
3,700 MBq PG2-NS	31	16	51.6%	
5,550 MBq PG1-SCAN	25	16	64.0%	0.28
5,550 MBq PG2-NS	23	18	78.3%	
3,700 + 5,550 MBq PG1-SCAN	36	24	66.7%	0.72
3,700 + 5,550 MBq PG2-NS	54	34	63.0%	
5,550+ MBq PG2-NS	9	8	88.9%	

TABLE 4. Scanned (PG1-SCAN) *vs.* nonscanned (PG2-NS) ablation rates in patients with metastatic lesions

	Patients with metastatic lesions	No. ablated	% Ablation[a]	% of total patients with metastatic lesions
Scanned[b]	9	6	66.7	24.3
Nonscanned[c]	23	18	78.3	36.5

[a] $P = 0.50$.
[b] Metastases to lymph nodes (n = 8); metastases to lung (n = 1).
[c] Metastases to lymph nodes (n = 21); metastases to bone (n = 1); metastases to lung (n = 1).

TABLE 5. Ablation rates for patients with metastatic lesions *vs.* patients with carcinoma confined to the thyroid bed

Dose	Patients with metastatic lesions			Patients with carcinoma confined to thyroid bed		
	Total patients	No. ablated	% Ablation	Total patients	No. ablated	% Ablation
3,700 MBq PG1-SCAN	2	2	100	9	6	66.7
3,700 MBq PG2-NS	3	3	100	28	13	46.4
5,550 MBq PG1-SCAN	7	4	57.1	18	12	66.7
5,550 MBq PG2-NS	13	9	69.2	10	9	90.0
3,700 + 5,550 MBq PG1-SCAN	9	6	66.7	27	18	66.7
3,700 + 5,550 MBq PG2-NS	16	14	87.5	38	22	57.9
5,550+ MBq PG2-NS	7	6	85.7	2	2	100

Park *et al.* (2, 13, 19) published several reports in which postdiagnostic scans were compared with posttherapy scans that were read within 24–72 h of dose administration. Our prior research demonstrates that the image to background ratio in a scan 2–3 d posttherapy hinders the reader's ability to visualize thyroid lesions (11). Scans taken 7–10 d posttherapy reveal substantially more lesions simply due to the improved image to background ratio. Huic *et al.* (3) also observed a reduction in ^{131}I uptake by comparing scans with a 74-MBq ^{131}I diagnostic dose with a subsequent scan with a 4403-MBq therapeutic dose; posttherapy scans were taken only 3 d after the therapeutic dosage. In a more recent study designed to repeat Park's experiments, Cholewinski *et al.* (20) found no evidence of stunning when administering a 185-MBq diagnostic dose, followed by a 5550-MBq therapeutic dose. Again, posttherapy scans were read at 72 h. We cannot predict what differences Huic *et al.*, Park *et al.*, or Cholewinski *et al.* would have observed had the posttherapy scans been read again 4 d later.

Another discrepancy in many of the prior stunning studies is the time lapse between the reading of a scanning dose and the delivery of a therapeutic dose. Our institution appears to be in the majority of hospitals that administer a treatment dose immediately after a 2- or 3-d post-^{131}I diagnostic scan. In fact, our patients are instructed to report to the hospital for their scan prepared to be admitted for treatment should the scan demonstrate residual tissue. This policy exists due to the possibility that there is a time lapse between radiation administration and its effect on the cell. Several studies allow several weeks between diagnostic and therapeutic dose administration or do not control for this variable (6, 14, 21).

Quantitative studies on the topic of stunning are scarce. Yeung *et al.* (21) studied 12 patients with differentiated thyroid cancer (although the extent of thyroid surgery in his subjects was unclear) and determined that the therapeutic dose (mean, 86.5 MBq) yielded a smaller uptake, on the average, than the diagnostic dose. In contrast to several other qualitative studies, Yeung found thyroid stunning at tracer doses of 74 MBq or less. There was no correlation between the size of the tracer dose administered and the percent uptake of the therapeutic dose, demonstrating that other factors (size of lesion and biological variability) are involved. In a similar quantitative study, Jeevanram *et al.* (6) found a negative correlation between the calculated radiation dose delivered to the thyroid bed and the dose predicted by calculations involving initial (diagnostic) radioiodine uptake (diagnostic dose ranging between 3.7–185 MBq). However, Jeevanram also allowed a time lapse of between 10 and 40+ d between the initial diagnostic dose and the treatment dose, which may have negatively impacted the tissue's ability to take up iodine. Despite these findings, neither Yeung nor Jeevanram followed his patients to discover the clinical significance of this decreased uptake.

Leger *et al.* (14) confirmed our findings that patients imaged with 15.17 MBq ^{123}I *vs.* 185 MBq ^{131}I had equivalent outcomes. This group, however, supports the stunning theory because researchers observed a drop in pretreatment uptake values between two ^{131}I diagnostic scans completed

2–3 wk apart. No such drop was evident in patients scanned with ^{123}I, followed by ^{131}I. Despite outcomes similar to our results, one confounding aspect of Leger's work is the 5-wk lapse between diagnostic imaging and treatment. Ledger *et al.* neglected to consider what impact this delay might have had on successful uptake of the therapeutic dose.

The finding by Muratet *et al.* (12) that outcomes are significantly different in patients who received a 37-MBq *vs.* a 111-MBq ^{131}I scanning dose before a 3700- MBq therapeutic dose are enigmatic in light of our current results. However, although significantly higher ablation rates were achieved in the group receiving 37 MBq ^{131}I, Muratet appears to have studied only those patients whose cancer was confined to the thyroid bed. This is a surprising omission, as prior research indicates that the stunning effect would tend to impact metastatic lesions more severely than residual thyroid tissue or tumor (4, 7).

When we routinely administered diagnostic scans to patients postthyroidectomy, we observed that surgeries were rarely able to remove all thyroid remnants. We believed that the additional time, expense, and significant patient inconvenience associated with diagnostic scanning were not warranted. We take postablation scans at both 2 and 7 d posttreatment and use this information to observe the presence of distant metastases that were not recognized in surgical pathology reports.

Despite the breadth of studies that discuss stunning, its precise nature and physiological impact are still unclear. According to most definitions, the stunning effect "temporarily" impairs residual thyroid tissue, preventing the uptake of ^{131}I in these damaged cells. We expect to observe a decrease in ablation rates when tissue has been stunned due to a decrease in the ^{131}I dose to the tissue as well as eventual rejuvenation of the stunned tissue. The reported stunning effects may have a greater impact on patients with distant metastases. From this study, which aimed to evaluate the impact of stunning on all patients treated for differentiated thyroid cancer, we cannot ascertain whether stunning had any impact on the treatment success of the three patients with bone or lung metastases. Further research into differences in outcomes between scanned and nonscanned patients being treated for distant metastases is warranted.

A variety of studies have considered the impact of diverse factors on ablation in differentiated thyroid carcinoma, yielding a wide range of ablation rates (15, 16, 22, 23). Many of the differences in results of ablation studies may occur from discrepancies between methods of determining ablation. We routinely use 111–222 MBq for follow-up scans (mean, 148 MBq) and consider the patient to be ablated only if no significant focal accumulation above background activity is visualized in the thyroid bed or in areas where iodine-avid tissue, such as the salivary glands, normally does not reside. Although others also followed this method (23), some investigators used varying amounts of radioiodine for follow-up scans (<111 MBq or unreported doses) and measured successful ablation as less than 1% uptake in the thyroid bed (22), leaving room for the possibility of some minimally visualized uptake. In addition, our prior research has demonstrated a 400% increase in detecting residual tissue after ablative therapy between a 74-MBq and a 370-MBq dose (9). Waxman *et al.* (9) concluded that a 74-MBq ^{131}I dose was inferior in visually evaluating ablation with respect to detectability compared with larger doses. Some researchers determined ablation with total body scans and/or Tg measurements (15). Others determined ablation after reading a 3-d posttherapy scan (20). These different methods of ablation assessment offer different levels of accuracy (24).

Our findings do not enable us to exclude the possibility that large doses of ^{131}I (3700–7400 MBq) worked to obscure a stunning effect. We do not administer ablative doses of radioiodine of less than 3700 MBq due to research indicating that such low doses are not as effective at achieving ablation as one large (3700–7400 MBq) dose (25). (In fact, there is a paucity of definitive evidence that one treatment regimen is more efficacious than the other.) However, for the segment of the medical community that also finds greater effectiveness with high dose radioiodine therapy, this study should demonstrate that regardless of whether the stunning phenomenon exists, its impact relative to large dose therapy is irrelevant.

Although we have discontinued preablative diagnostic scanning, our results show no significant difference in short-term ablation rates between patients who did and did not receive diagnostic doses before treatment. We have only addressed here the potential stunning effect during initial doses of ablative radioiodine. We do not know whether stunning is an important phenomenon in patients who have a delay of weeks to months between the initial scan and subsequent treatment, or in the treatment of persistent or recurrent well differentiated thyroid cancer.

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