^{131}I Dosimetry and Thyroid Stunning

TO THE EDITOR: Dorn et al. have described a dosimetry-guided approach for calculating the largest "safe" dose of ^{131}I for treatment of differentiated thyroid cancer (*1*). With this method, a maximal dose was determined assuming an upper limit of <3 Gy for the absorbed dose to the bone marrow or <30 Gy to the lungs. Their method used an initial tracer dose of 150–400 MBq (4–10.8 mCi) of ^{131}I with serial dosimetric imaging for 4–5 d, followed by administration of the maximal treatment dose of ^{131}I. The authors stated that this approach was intended to achieve "the maximum therapeutic benefit." However, the outcome data presented in Table 4 do not appear to support this claim. From this table, thyroglobulin was >100 in 29 therapy instances. After ^{131}I treatment, 20 of these 29 instances (69%) still had a thyroglobulin level of >100. The average survival of 29 patients who received "curative-intent" therapy was 4.1 y. Even after excluding patients older than 59 y (representing a group with poorer prognosis), average survival of the 10 younger patients was still only 5.2 y. We would be eager to have the authors explain why these outcome considerations support the contention of maximum therapeutic benefit by using this dosimetric approach, compared with that achieved using standardized ^{131}I treatment algorithms.

The authors state in the Discussion, "In our patients, no stunning effect could be objectively demonstrated." They go on to comment that "no decrease in thyroid uptake was seen after dosimetry with a 370-MBq test activity (with estimated absorbed doses as high as 50–100 Gy to the thyroid remnants)." However, the authors have also cited in the Discussion that dose estimates of 300 Gy should be sufficient to fully ablate normal thyroid tissue (their reference 18). It does not seem plausible that doses as large as one third of that estimated to be sufficient to ablate the thyroid would not have been responsible for a substantial stunning effect.

Methodology to assess for stunning was not described by the authors. Therefore, one might presume that such assessment was attempted by subjective comparison of the dosimetric and the posttreatment scans, assuming the latter were obtained (not described in the Materials and Methods). As has been summarized elsewhere by both of us (*2*,*3*), we believe that the potential liability of stunning by diagnostic doses of ^{131}I before administration of the therapeutic dose is real and potentially of concern and that this liability was likely of consequence in the authors' dosimetric procedure.

As has been noted by McMenemin et al. (*4*), qualitative comparison of diagnostic and posttreatment ^{131}I scans may be highly insensitive for the detection of stunning. They described 3 cases in which significant reductions in uptake of the ^{131}I treatment dose, compared with the prior ^{131}I diagnostic dose (14%, 41%, and 60% reduced), were qualitatively inapparent by comparison of the pre- and posttreatment scans. The unreliability of such qualitative comparisons is potentially related to several factors, including the challenge of comparing target-to-background ratios at sites of differentiated thyroid tissue across a large dose range, differences between diagnostic and therapeutic postdose scanning times, and variable-differential washout.

Conversely, the data presented in Table 4 by Dorn et al. permit estimation of potentially significant stunning to thyroid tumor from the diagnostic dose in a substantial proportion of 26 of the therapeutic administrations for which the therapeutic estimates of tumor dosimetry were given. Although the exact diagnostic doses for these patients were not provided, one could assume for the sake of estimation an average of the diagnostic dose range given by the authors (150–400 MBq), equal to 275 MBq (7.5 mCi). By applying a factor equal to the ratio of the average diagnostic dose to the therapeutic dose for each of these 26 patients, the estimated dosimetry from the tracer dose of ^{131}I was 6.4 ± 9 Gy (mean ± SD). Those doses estimated for patients 3, 13, 23, 25, and 28 were 16.6, 18.8, 12.3, 25.1, and 39.6 Gy, respectively. A recent report by Postgård et al. (*5*) described an in vitro porcine thyroid-cell bicameral tissue-culture model that showed a convincing stunning effect by exposure to ^{131}I in the culture medium. A range of ^{131}I exposures from 3 to 80 Gy significantly reduced the subsequent ^{125}I transport from the basal to the apical chamber. The lowest ^{131}I dose tested, 3 Gy, caused a nearly 50% reduction, with a precipitous dose–response falloff for higher-level exposures. With respect to the 26 administrations that could be evaluated from the authors' Table 4, we note that 13 (50%) could be estimated to have received >3 Gy to the thyroid tumor from the average diagnostic dose. This is a conservative quantitative estimate, since 12 of the therapeutic doses listed in Table 4 as ">" a particular Gy value were assumed to equal that value for the purposes of these calculations. Another recent report, by Lees et al. (*6*), described a statistically significant 3-fold increase in additional ^{131}I treatments and a 50% increase in the total cumulative ^{131}I treatment dose required for ablation of the remnant when a 185-MBq dose of ^{131}I was used for the diagnostic scan before radioablation with ^{131}I. This ^{131}I diagnostic dose is approximately one third less than the average diagnostic dose used by the authors. These quantitative considerations would argue that at least some, if not many, of the cases described by the authors could be expected to have had a stunning effect, with consequent reduced fractional uptake of the therapeutic administration caused by the diagnostic dose.

The authors have noted that the initial ^{131}I treatment, "the first strike," has the highest therapeutic effect and that risk–benefit assessment before giving high-dose ^{131}I is essential. We fully agree with these assertions, both of which allude to the importance of assessing the potential liabilities of stunning by the pretreatment diagnostic ^{131}I dose. We believe that the methodology for estimating a maximal safe therapeutic ^{131}I dose incorporating an initial diagnostic ^{131}I dose in the range of that used by the authors most likely would contribute a significant risk of stunning. It is ironic that this effect may in fact offset a significant component of the incremental therapeutic benefit intended by the method. We wonder whether comparable, if not even better, outcomes might have been achieved with substantially lower therapeutic ^{131}I doses had pretreatment exposure to the relatively larger diagnostic ^{131}I doses been avoided. If used, dosimetric approaches for calculating a maximal ^{131}I treatment dose should apply the lowest possible ^{131}I dose to minimize stunning.

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REPLY: I respectfully remind Drs. Gerard and Park that our study was undertaken to demonstrate the safety of dosimetry-guided high-dose radioactive iodine (RAI) therapy. Our data were the first published evidence in 40 y that a bone marrow dose can safely be raised to 1 Gy (300 rad) (*1*,*2*).

We did not discuss methodology to assess stunning because our purpose was not to evaluate the stunning effect. We did, however, state that "no stunning effect could be objectively demonstrated. Additionally, no decrease in thyroid uptake was seen after dosimetry with a 370-MBq test activity (with estimated absorbed doses as high as 50–100 Gy to the thyroid remnants.)" This statement was based on the observation that the posttherapy scans never showed the lack of uptake in metastases that was seen on diagnostic images. However, occasionally we have observed a change in clearance half-life in various metastatic lesions on posttherapy scans. These observations have not specifically been investigated to assess the stunning effect. The success rate of postsurgical RAI ablation in our patient population was close to 100% when successful ablation was defined as $<$1% uptake in the neck on a 1-y follow-up study. Of 278 patients who underwent RAI ablation, 190 (68%) showed no thyroid remnant uptake (mean, 0.2% uptake) on the 1-y whole-body scans and 68 (24%) showed only faint uptake (mean, 0.3% uptake). For 20 (7%), uptake was clearly visible (mean, 0.8% uptake) on the 1-y scans. No impairment of RAI treatment was clinically apparent.

We do believe that diagnostic doses of up to 400 MBq might have a stunning effect in thyroid tumor tissue. Furthermore, the stunning effect might also alter projected dose estimates. The potential impact of stunning on the efficacy of RAI treatment is a subject for controlled clinical studies.

A second issue raised in the letter of Drs. Gerard and Park is the outcome of dosimetry-guided RAI therapy. The "intent" of the dosimetry-guided largest-safe-dose approach is to achieve "the maximum therapeutic benefit." Maximum therapeutic benefit may not necessarily reflect on the clinical endpoints of response (i.e., serum tumor markers, lesion size on anatomic or functional imaging, and survival). In other words, maximum therapeutic benefit may not result in "cure." The reason why Drs. Gerard and Park are baffled about the variable thyroglobulin responses obtained after treatments is related to their overlooking the fact that metastatic thyroid carcinoma is not a uniform disease. It is well known and has recently been well demonstrated by ^{18}F-FDG PET studies that different metastatic sites and lesions differ in metabolic function (*3*). Disparity in the ability of RAI uptake and thyroglobulin production is common. Thus, although maximum radiobiologic effects could be achieved on the radioavid lesions, nonradioavid lesions might still continue to produce thyroglobulin. This phenomenon also explains the RAI treatment failures in patients with advanced metastatic disease. Unfortunately, some of the oncobiologic concepts discussed in regard to the natural course of differentiated thyroid carcinoma and the therapeutic efficacy of RAI will remain speculative because of the protracted course of the disease and difficulties in designing definitive trials. Once again, there is no claim in our article that we have shown dosimetry-guided techniques to have a superior therapeutic benefit over empiric treatments, with the endpoint being survival.

On behalf of all the authors, I thank you for the opportunity to respond to the critique of our article.

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