Prescribed Activity of ^{131}I Therapy in Differentiated Thyroid Cancer

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One of the most discussed controversies in the management of patients with well-differentiated thyroid cancer (DTC) is selection of the activity for ^{131}I therapy.

One of the problems is that prima facie evidence (i.e., first-look evidence) may lead to incorrect conclusions or implications because the data are not adequately scrutinized. Such data are usually rebutted, but when they are not rebutted, many authors and readers will interpret or simply accept the data as sufficient proof of their opinion or hypothesis. The objectives of this commentary are two-fold: first, to rebut two articles implying or concluding that the motto "less is more" is correct for the activity of ^{131}I therapy for patients who have DTC and either are at intermediate risk for recurrence or have distant metastasis and, second, to demonstrate how individuals subsequently accept prima facie evidence to either make their decision or promulgate their opinion.

Given the space allocated to a commentary, this is not an extensive review of the literature presenting the arguments for and against a lower or higher prescribed ^{131}I activity for the treatment of intermediate-risk patients or distant metastasis. Rather, this is a wake-up call for authors, readers, and practitioners to assess publications with heightened critical scrutiny and not accept prima facie evidence as sufficient proof, even in the face of otherwise well-intentioned people who may press for the unquestioned acceptance of such evidence.

INTERMEDIATE-RISK PATIENTS: LOW ^{131}I ACTIVITY VERSUS HIGH ^{131}I ACTIVITY

Castagna et al. (*1*) evaluated the effectiveness of 1.11–1.85 GBq (30–50 mCi) versus at least 3.7 GBq (100 mCi) of ^{131}I for the treatment of 225 patients who had DTC and were classified as being at intermediate-risk. In that study, the authors evaluated patients for remission, recurrent disease, biochemical disease, persistent disease, and death. Table 1 shows a distillation of the data. The rates of recurrent disease, biochemical disease, metastasis, persistent disease, or death were not statistically different, and Castagna et al. concluded, "Our study provides the first evidence that in DTC patients at intermediate risk, high [^{131}I] activities at ablation [e.g., adjuvant treatment] have no major advantage over low activities." From the authors' prima facie evidence and conclusion, are the authors implying that 1.11–1.85 GBq of ^{131}I is just as effective as 3.7 GBq or more, which seems reasonable on a first look at the data? However, the same conclusion also demonstrates the authors' a priori bias. Using the same data, one could also interpret 1.11–1.85 GBq as being just as ineffective as 3.7 GBq or more. The rates of recurrence, persistent disease, and death as shown in Table 1 are less than satisfactory. One could conclude from their data that neither 1.11–1.85 GBq nor 3.7 GBq or more delivers enough of an absorbed radiation dose to have a tumoricidal effect on the remaining thyroid cancer and that an even higher prescribed activity should be considered. In other words, sometimes "less is less."

Many other authors have subsequently referenced this article in support of promulgating the "less ^{131}I is more" approach to adjuvant treatment (*2–9*). However, as observed in an earlier editorial (*10*), we all need to proceed more slowly, scrutinize more carefully the validity of results, and not prematurely accept, let alone "sloganize," prima facie evidence as sufficient proof of anything. The article of Castagna et al. is a wake-up call—not that we should be considering using less ^{131}I for adjuvant treatment in patients with intermediate-risk disease but that we should be considering using more. We should wake up to the discomfort of having settled for less than a full logical analysis of the findings of Castagna et al., especially as the same findings could logically lead to the consideration of using more ^{131}I activity for these patients rather than less.

TREATMENT OF DISTANT METASTASIS: EMPIRIC ACTIVITY VERSUS DOSIMETRICALLY GUIDED ACTIVITY

In the current issue of *The Journal of Nuclear Medicine,* Deandreis et al. (*11*) compare the use of empiric activity, at Gustave Roussy (GR), versus whole-body/blood clearance (WB/BC) dosimetry-guided activity, at Memorial Sloan Kettering Cancer Center (MSKCC), for the ^{131}I treatment of patients with metastatic DTC. The authors conclude that "Routine use of WB/BC dosimetry without lesional dosimetry provided no [overall survival] advantage when compared with empiric fixed RAI [radioactive iodine] activity in the management of thyroid cancer patients with RAI-avid distant metastases." These authors are arguing that an absence of evidence is evidence of an absence. However, this argument requires an excellent prospective, noninferiority, randomized study evaluating typically the one parameter of interest and controlling all other confounding factors. The study of Deandreis et al. is not such a study. In their study, an absence of evidence is not evidence of an

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TABLE 1
Rate of Recurrent Disease, Persistent Disease, and Death after ^{131}I Therapy in Intermediate-Risk Patients

Population	1.11–1.85 GBq	≥3.7 GBq*	*P*
All patients (n = 225)	24% (20/85)	28% (39/140)	Not significant
T3N0-X (n = 97)	21% (9/43)	20% (11/54)	Not significant
T1–2N1 and T1–2N0 with aggressive histology (n = 54)	21% (4/19)	26% (9/35)	Not significant
T3N1 (n = 74)	30% (7/23)	37% (19/51)	Not significant

*No mean or median was given. Similar results were presented for remission, biochemical disease, and metastatic disease for the first therapy.

absence. As the authors' have acknowledged, their study has limitations, including no comparison of remission rates, imperfect matching of the populations of the two centers, and the possible confounding factor presented by patient preparation with recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal. But the limitations go beyond the lack of perfect matching. There is a significant difference in median age at diagnosis of the primary tumor (MSKCC, 49 y; GR, 40 y [$P = 0.03$]), median age at diagnosis of distant metastasis (MSKCC, 53 y; GR, 42 y [$P < 0.01$]), percentage of female patients (MSKCC, 56%; GR, 66% [$P = 0.09$]), percentage of patients with macronodular lung metastasis (MSKCC, 35.6%; GR, 21.5% [$P = 0.02$]), percentage of patients with additional radiotherapies (MSKCC, 34.7%; GR, 28.1%) and chemotherapies (MSKCC, 10.8%; GR, 4.3%), and median cumulated ^{131}I activity (MSKCC, 24.2 GBq; GR, 14.8 GBq). There is also a lack of measurement of ^{131}I avidity in the metastases, a large difference in overall exclusion rate between GR (80%, 470/701) and MSKCC (22%, 34/155), and a large difference in exclusion for nonradioiodine avidity between GR (11.7%, 82/701) and MSKCC (1.3%, 2/155). In addition, MSKCC administered diagnostic ^{131}I for dosimetry and pretherapy scans (i.e., stunning caused by the much higher ^{131}I activity used in earlier years than presently could be a confounding factor), whereas GR did not perform pretherapy scanning. Although the authors attempt to correct for confounding factors statistically, they cannot identify all the confounding factors of these different patient populations from different institutions and different countries and with different clinical disease profiles. In fact, based on many of the limitations above as well as the fact that GR did not prepare patients with low-iodine diets, used fractionated treatments, administered a lower cumulative ^{131}I activity, and used less chemotherapy and external radiation therapy, the GR patient population may easily have had a better prognosis than the MSKCC patient population. Therefore, the observation that the outcomes were the same at MSKCC as at GR demonstrated that the dosimetrically guided ^{131}I activity, low-iodine diet, lack of fractionation, high cumulative activity, and other factors had improved the outcomes such that those of patients with a worse prognosis were now equal to those of patients with a better prognosis who received at least 3.7 GBq. Nevertheless, in view of all these confounding factors, an absence of evidence is not evidence of an absence, and the results of this study easily represent two different patient populations.

The second objective of this commentary is to demonstrate how individuals subsequently accept prima facie evidence to either make their decision or promulgate their opinion. Drawing from the declarative conclusion of Deandreis et al. that "Routine use of WB/BC dosimetry without lesional dosimetry provided no [overall survival] advantage when compared with empiric fixed RAI activity in the management of thyroid cancer patients with RAI-avid distant metastases," one author has already promulgated statements in another publication (*12*) that "RAI dosimetry does not improve survival as compared with empiric doses of ^{131}I for RAI-avid metastatic thyroid cancer," and "Before abandoning dosimetry based on this study, one must consider another type of dosimetry, that is, lesional dosimetry"—implying that one should abandon WB/BC dosimetry. This author closes his analysis and commentary with the statement, "In the meantime, empiric doses seem to be the way to go." So, in drawing from an initial retrospective study at different institutions in different countries with distinctly different patient populations in which an absence of evidence is not evidence of an absence, one author is already promulgating that WB/BC dosimetry not only should be abandoned but should be abandoned in favor of empiric activity as the way to go. It is concerning that articles such as those of Castagna et al. (*1*) and Deandreis et al. (*11*) will be used by many to substantiate their bias. Therefore, as is the case with those two articles, we need to look past prima facie evidence not merely as a matter of research protocol but because implications illogically drawn from seemingly clear findings can produce potentially enormous negative effects on our patients.

THE PATIENT

I believe that all the authors, physicians, and researchers referenced here have good intentions, which are to have a positive impact on their individual patients and on the entire population of patients with DTC. But it is worthy to question the objectives and explore the unintended impact of the Deandries et al. publication (*11*).

With the good intention of reducing ^{131}I side effects by administering 1.11–1.85 GBq instead of 3.7 GBq or more, are we missing the opportunity to use a higher ^{131}I activity to help reduce recurrence, morbidity, and mortality? What is the objective of showing that in the population of patients with DTC distant metastasis, an empiric activity of at least 3.7 GBq is equal to dosimetrically guided activity? Use of empiric ^{131}I activity for the treatment of DTC distant metastasis is already an accepted practice in the United States and the world. Is the objective to stop institutions from performing dosimetry or reduce their use of it, thereby reducing patient side effects from dosimetrically guided ^{131}I activity? Not only are there strong theoretic arguments for the superiority of WB/BC dosimetrically guided ^{131}I activity based on one of the two fundamentals of radiation therapy (*13*), but studies support benefit from

dosimetrically guided activity (*14–16*). If institutions stop performing dosimetrically guided ^{131}I therapy, patients may lose not only the opportunity to receive the potential benefits from such therapy but also the option to choose their preferred therapy after balancing the potential benefits and risks.

Some good intentions may be negatively affecting our patients.

THE FUTURE

It is very difficult, if not impossible, to perform a well-controlled prospective, noninferiority, randomized study to evaluate empiric activity versus WB/BC dosimetrically guided activity for ^{131}I therapy of metastatic DTC. Although there are many reasons for the difficulty, the most important is the wide spectrum of clinical situations and prognoses in patients with distant metastasis from DTC. Therefore, facilities will continue to administer both empiric and dosimetrically guided ^{131}I activity, and rather than investing time, energy, and resources comparing the two, I encourage us to focus on increasing the uptake of ^{131}I in thyroid cancer cells (e.g., through enhancing agents such as selumetinib and dabrafenib); increasing the residence time of ^{131}I in thyroid cancer cells (e.g., through lithium or stable ^{127}I), which in turn increases the dose taken up by the cancer cells; determining the maximum activity tolerated by the salivary glands and better ways to reduce the absorbed dose (e.g., through montelukast and vitamin E); refining lesional, whole-body, and organ dosimetry with ^{124}I; and obtaining approval of ^{124}I.

SUMMARY

As authors, practitioners, or readers of these studies, we are receiving a wake-up call to be more thoughtful and critical in our assessment of publications in general and our interpretation of these studies in particular. Is 1.11 GBq as effective as, or as ineffective as, 3.7 GBq or more for adjuvant treatment? Does an absence of evidence in two different patient populations equate to evidence of an absence between two treatments?

In the end, everything is about our patients and our commitment to them. Physicians must individually decide what their ^{131}I activity recommendations will be for adjuvant treatment and distant-metastasis treatment in each of their DTC patients. For my patients, I generally recommend an ^{131}I activity approaching 5.55 GBq for adjuvant treatment. For patients with distant metastasis, I explore local treatment options first, and if the decision is to proceed with ^{131}I, I thoroughly discuss with the patient the potential benefits and risks of empiric and dosimetrically guided ^{131}I activity. In addition, and regardless of ^{131}I activity for therapy, I recommend and educate for aggressive preventive management to reduce the frequency and severity of side effects. If I were the patient and initial local treatments were not an option, I would proceed with approximately 5.55 GBq of ^{131}I for adjuvant treatment. For distant metastasis, I would proceed with dosimetrically guided ^{131}I activity with no fractionation of the ^{131}I and adherence to a strict low-iodine diet. Whether to undergo preparation with thyroid hormone withdrawal or recombinant human thyroid-stimulating hormone injections would depend on my clinical situation at the time of treatment.

DISCLOSURE

Douglas Van Nostrand is an advisor to and speaker for Jubliant Draximage, Inc. He receives no compensation for the performance or interpretation of ^{131}I scans or therapy, direct patient care, any of his research efforts, or this commentary. No other potential conflict of interest relevant to this article was reported.

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