Prescribed activities of I-131 therapies in differentiated thyroid cancer:

Invited Commentary

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Introduction

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

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: (a) to rebut two articles implying or concluding the motto “less is more” is correct for the activity of I-131 therapy for patients with DTC and either intermediate-risk for recurrence or distant metastasis and (b) 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 lower or higher prescribed I-131 activities for the treatment of intermediate-risk patients or distant metastasis. Rather, this commentary 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 pressures and otherwise good intentions that may press for the unquestioned acceptance of such evidence.

**Intermediate-risk patients: I-131 low activity vs high activity**

Castagna et al. (1) evaluated the effectiveness of 1.11 - 1.85 GBq (30 - 50 mCi) versus > 3.7 GBq (100 mCi) of I-131 for the treatment of 225 patients who had DTC and were classified as intermediate-risk. In this study, the authors evaluated patients for remission, recurrent disease, biochemical disease, persistent disease and death, and Table 1 shows a distillation of the data. The rates of recurrent disease, biochemical disease, metastasis, persistent disease or death for 1.11 - 1.85 GBq (30 - 50 mCi) versus > 3.7 GBq (100 mCi) of I-131 in intermediate-risk patients were not statistically different, and Castagna et al. concluded “Our study provides the first evidence that in patients at intermediate-risk, high [I-131] activities at ablation [e.g. adjuvant treatment] have no major advantage over low activities.”[1] From the authors’ prima facie evidence and conclusion, the implication follows that 1.11 - 1.85 GBq (30 - 50 mCi) of I-131 is equally effective as >3.7 GBq (100 mCi), which seems reasonable on first look at the conclusion.
However, the same conclusion also demonstrates the authors’ apriori bias. Using the same data, one could also interpret that 1.11-1.85 GBq (30-50 mCi) is equally as ineffective as \( \geq 3.7 \text{GBq} \) (100 mCi). 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 (30-50 mCi) nor \( \geq 3.7 \text{GBq} \) (100 mCi) deliver enough radiation absorbed dose to have a tumorcidal effect on the remaining thyroid cancer and that even higher prescribed activities should be considered. In other words, sometimes “less is less.”

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

In a recent issue of this journal, Deandreis et al.\(^\text{11}\) compared 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 I-131 treatment of patients with metastatic DTC, and they concluded “Routine use of WB/BC dosimetry without lesional dosimetry provided no OS [overall survival] advantage when compared to empiric fixed RAI dosing in the management of thyroid cancer patients with RAI\(^{131}\)-avid distant metastases.” These authors are arguing “an absence of evidence IS evidence of an absence.” However, to achieve this one needs an excellent prospective, non-inferiority, randomized study evaluating typically the one parameter of interest and controlling all other confounding factors; Deandreis et al.’s study is not such a study. For their study, “an absence of evidence is **NOT** evidence of an absence.” As the authors’ have acknowledged, their study has limitations including: (1) no comparison of remission rates, (2) “the populations of the two centers are not perfectly matched,” (3) and patient preparation with rhTSH (recombinant human thyrotropin) versus THW (thyroid hormone withdrawal) may have been a confounding factor. But the limitations go beyond being *not perfectly matched.* There is a significant difference in (1) median age at diagnosis of primary tumor (MSKCC=49 y.o.; GR=40 y.o.; \(p =0.03\)), (2) median age at diagnosis of distant metastasis (MSKCC=53 y.o; GR=42 y.o.; \(p <0.01\)), (3) percentage of females (MSKCC 56% ; GR=66%; \(p=0.09\)), (4) presence of macronodular lung metastases (MSKCC=35.6%; GR=21.5%; \(p =0.02\)), (5) additional radiotherapies (MSKCC=34.7%; GR=28.1%) and chemotherapies (MSKCC=10.8%;GR=4.3%), (6) median cumulated I-131 activity (MSKCC=24.2 GBq; GR=14.8 GBq), (7) no measurement of the avidity of I-131 in the
metastases, (8) a large difference in overall exclusion rate of GR 80% (470/701) and MSKCC 22% (34/155), (9) a large difference in exclusion for non- radioiodine avidity of GR % (82/701) and MSKCC 1.3% (2/155), and (9) administration of diagnostic I-131 for dosimetry and pre-therapy scans at MSKCC (i.e., in the earlier years much higher I-131 activity was used than presently and could be a confounding factor with stunning while GR did not perform pre-therapy scanning). Although the authors attempt to correct for confounding factors statistically, they cannot identify all the confounding factors of these two different patient populations from two different institutions, two different countries, and different clinical disease profiles. In fact, based on many of the limitations above as well as GR not preparing patients with low iodine diets, using fractionated treatments, administering lower cumulative I-131 activity, and using less chemotherapy and external radiation therapy, the GR’s patient population may easily have had a better prognosis than the MSKCC’s patient population, and therefore the study’s observation that the outcomes were the same at MSKCC versus GR demonstrated that the dosimetrically-guided I-131 activities, low iodine diet, no fractionation, high cumulative activity, etc. had improved outcomes such that the outcomes of those patients with a worse prognosis were now equal to those patients with a better prognosis who received $\geq 3.7$ GBq (100 mCi). Nevertheless, with all the above 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 Deandreis et al.’s declarative conclusion that “Routine use of WB/BC dosimetry without lesional dosimetry provided no OS advantage when compared to empiric fixed RAI dosing in the management of thyroid cancer patients with RAI-avid distant metastases,” one author has
already promulgated statements in another publication 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,” which implies that one should abandon [whole-body] dosimetry. (12) This author closes his analysis and commentary with the statement, “In the mean time, empiric doses seem to be the way to go.” So, we must ask from an initial retrospective study from two different institutions in two countries with two distinct patient populations where an absence of evidence is not evidence of an absence, one author is already promulgating that WB/BC dosimetry should be abandoned and be abandoned in favor of empiric activity as the way to go. It is concerning that articles like Castagna et al. (1) and Deandreis et al. (11) will be used by many to substantiate their bias. Therefore, as with the Castagna et al. (1)and Deandreis et al. (11) 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 herein have good intentions, which are to have a positive impact on their individual patients as well as the population of patients with DTC. But it is worthy to question the objectives and explore the unintended impact of their publication.

In the first article and with the good intention to reduce I-131 side effects by administering 1.11-1.85 GBq (30-50 mCi) instead of ≥3.7 GBq (100 mCi), are we missing the opportunity to use higher I-131 activities to help reduce recurrence, morbidity, and mortality?
In Deandries et al., what is the objective of showing that an empiric activity of ≥ 3.7 GBq (100 mCi) is equal to dosimetrically-guided activity in the population of patients with DTC distant metastasis? Empiric I-131 activity for the treatment of DTC distant metastases is already an accepted practice in the United States and the world. Is the objective to stop or reduce institutions from performing dosimetry, thereby reducing patient side effects from dosimetrically-guided I-131 activity? Not only are there very strong theoretical arguments for the superiority of WB/BC dosimetrically-guided I-131 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 I-131 therapies, patients may not only lose the opportunity for potential therapeutic benefits from such I-131 activities, they also lose their choice to select the option they desire based on their preference after balancing 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 prospective, well-controlled, non-inferiority, randomized study to evaluate empiric activity versus WB/BC dosimetrically-guided activity for I-131 therapy of patients with metastatic DTC. Although there are many reasons that such a study is difficult, the most important reason is the wide spectrum of clinical situations and prognoses of patients with distant metastases from DTC. Therefore, facilities will continue to administer both empiric and dosimetrically-guided I-131 activities, and rather than invest time, energy and resources studying empiric vs dosimetrically-guided activities, I encourage focusing our future research time, energy, and resources to (1) increasing the uptake of I-131 in thyroid cancer cells such as using enhancing agents (e.g., selumetinib, dabrafenib), (2) increasing the
duration I-131 remains within thyroid cancer cell (residence time) such as with lithium or I-127 (stable iodine), which in turn increases the absorbed dose delivered per millicurie taken up by the cancer cell, (3) determining maximum tolerated activity for salivary glands and better preventive measures to reduce the absorbed dose to the salivary glands (e.g. montekulat, vitamin E), (4) refining lesional, whole-body, and organ dosimetry with I-124, and (5) obtaining approval of I-124.

Summary

In summary, as authors, practitioners, and/or readers of these studies, we are receiving a “wake-up call” that we should be more thoughtful and critical in our assessments of publications in general as well as our interpretations of these studies in particular. Is 1.11 GBq (30 mCi) equally effective or ineffective as > 3.7 GBq (100 mCi) for adjuvant treatment? Is an absence of evidence in two different patient populations, evidence of an absence between two treatments?

In the end, it is about our patients and renewing our commitment to them. Each physician must decide what his/her recommendations are for I-131 activity for each of their patients with DTC for I-131 activity for adjuvant treatment and treatment of distant metastases. For the I-131 activity for my patients for adjuvant treatment, in general I recommend approaching 5.55 GBq (150 mCi) and for my patients with distant metastases, I explore the options of local treatment first, and if the decision is to proceed with I-131 treatment, I present to the patient a thorough discussion of the potential benefits and risks of empiric and dosimetrically-guided I-131 activity. In addition, and regardless of I-131 activity for therapy, I recommend and educate for aggressive preventive management to reduce frequency and severity of side effects. If I was the patient and if initial local treatments are not an option, I would
proceed with ~5.55GBq (150 mCi) of I-131 for adjuvant treatment, and for distant metastases, I would proceed with dosimetrically-guided I-131 activity with no fractionation of the I-131 and adherence to a strict low iodine diet. For preparation with THW or rhTSH injections, this would depend on my clinical situation at the time of treatment.

**Financial Disclosure**

- Advisor to and speaker for Jubliant Draximage, Inc.
- I receive no compensation for the performance/interpretations of I-131 scans/therapies, direct patient care, any of my research efforts, or this commentary.
References


Table 1: Rate of recurrent disease, persistent disease and death after I-131 therapy in intermediate-risk patients.

<table>
<thead>
<tr>
<th></th>
<th>1.11-1.85 GBq (30-50 mCi)</th>
<th>≥3.7 GBq (100 mCi) (no mean or median was given)</th>
<th>p value</th>
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<tbody>
<tr>
<td>All Patients (n=225)</td>
<td>24% (20/85)</td>
<td>28% (39/140)</td>
<td>Not significant</td>
</tr>
<tr>
<td>T3NO-X (n=97)</td>
<td>21% (9/43)</td>
<td>20% (11/54)</td>
<td>Not significant</td>
</tr>
<tr>
<td>T1-2N1 and T1-2NO with aggressive histology (n=54)</td>
<td>21% (4/19)</td>
<td>26% (9/35)</td>
<td>Not significant</td>
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<tr>
<td>T3N1 (n=74)</td>
<td>30% (7/23)</td>
<td>37% (19/51)</td>
<td>Not significant</td>
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