THYROID CANCER

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Not So Fast: Nuclear Medicine Societies Espouse Collaboration while Countering Swing of the ¹³¹I Pendulum in Differentiated Thyroid Cancer

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SUMMARY

Background

There has been discussion in the greater nuclear medicine community regarding some of the recommendations in the 2015 ATA management guidelines for thyroid nodules and thyroid cancer (1) related to ¹³¹I scanning and therapy. In fact, two prominent nuclear medicine organizations, the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI), declined to endorse the guidelines. The EANM subsequently published an editorial discussing their objections to the ATA guidelines (2). A difference in interpretation of available evidence was cited.

In order to promote better understanding of differences in perspective and to reach a more collaborative and consistent, evidence-based set of recommendations, or at least of guiding principles, representatives from the American Thyroid Association (ATA) and the European Thyroid Association (ETA) met with representatives from the EANM and the SNMMI to draft what became known as the Martinique Principles, which are summarized in the current consensus paper (3). The nine principles of

the statement aim to serve five specific goals: (i) support inclusive interdisciplinary cooperation; (ii) define the goals of ¹³¹I ablation as remnant ablation, adjuvant therapy, or treatment of known disease; (iii) emphasize the use of factors beyond clinicopathological staging in postoperative ¹³¹I decision-making; (iv) acknowledge that the published literature is lacking with regard to optimal administered ¹³¹I activity; and (v) seek to improve the current suboptimal definitions of ¹³¹I-refractory disease.

Methods

A 2-day meeting was held in Martinique in January 2018. A panel of 18 senior leaders and subject-matter experts from 8 countries and 4 organizations (the ATA, EANM, SNMMI, and ETA) convened to consider, debate, and exchange ideas regarding the use of ¹³¹I in the management of thyroid cancer.

Results

After much discussion and a review of 60 publications, in addition to expert opinion, the conference participants agreed on a set of nine principles, which are paraphrased as follows:

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1. Optimizing thyroid cancer management requires interdisciplinary cooperation.
2. The goal of ¹³¹I therapy should be specifically defined as (a) remnant (normal thyroid) ablation, (b) adjuvant therapy (for suspected microscopic disease), or (c) treatment of known disease.
3. Proper patient selection for ¹³¹I therapy requires assessment of postoperative disease status (and not simply preoperative staging).
4. Evaluation of postoperative disease status should be standardized in terms of biochemical and structural/imaging data.
5. Proper patient selection for ¹³¹I therapy requires not only assessment of postoperative disease status (Principle 3) but also evaluation of multiple factors, including patient preference, potential side effects, and availability and quality of medical resources.
6. The optimal administered ¹³¹I activity for adjuvant therapy cannot be determined from the available literature (favoring more individualized dosing decisions over those suggested by the 2015 ATA guidelines).
7. Characteristics suggesting that ¹³¹I-refractory behavior should be used to risk-stratify patients for likelihood (or lack thereof) to respond but not to exclude them from consideration for ¹³¹I treatment.
8. ¹³¹I refractory criteria will continue to evolve, especially with progress in evidence-based studies, better standardized imaging, and redifferentiation therapies.
9. Prospective studies are needed to address knowledge and evidence gaps with regard to ¹³¹I therapy.

Conclusions

Defining the optimal use of ¹³¹I in thyroid cancer remains controversial, is subject to interpretation of evidence, and is influenced by many patient and health care delivery variables. Interdisciplinary collaboration will help refine the use of ¹³¹I in the patient-centered care of thyroid cancer.

COMMENTARY

To understand the basis for this joint statement (3), it helps to be familiar with the key points in the editorial by Verburg et al (2) that was written in response to the publication of the 2015 ATA guidelines, which “appear to marginalise the role of nuclear medicine in the care of nodular thyroid disease and differentiated thyroid cancer (DTC).” The 2015 ATA guidelines do encourage more conservative use of ¹³¹I as compared with prior iterations, based on modern evidence and a greater body of literature about thyroid cancer outcomes as well as duration of expe-

rience with ¹³¹I therapy and its risks and benefits. Members of the EANM object to Recommendation 35b and the “radical departure (consideration of thyroid lobectomy for T>1 cm and <4 cm) from prior, internationally accepted and practised policy with regard to the extent of surgery [total thyroidectomy] in patients with a non-microcarcinoma,” noting that nuclear medicine is greatly affected by this recommendation. Following lobectomy only, ¹³¹I is not a clinically feasible treatment option. Furthermore, even greater objection is expressed

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toward Recommendation 51A and Table 14, which state that: “post-operative I-131 treatment should not routinely be given to any patient who is considered ATA low-risk” (1). Verburg and colleagues emphasize that, in spite of the substantial retrospective literature that was reviewed and cited, there are currently no results from prospective, controlled studies that “precisely indicate which patients with low-risk DTC may or may not benefit from postoperative ¹³¹I therapy.” They discuss two active prospective European trials [IoN (4) and ESTIMABL2 (5)], which are comparing ¹³¹I ablation and no ablation in patients with lower-risk DTC, and they advise caution in altering long-established and successful practices until sufficient evidence is available indicating that “it is safe to omit postoperative ¹³¹I treatment—“ablation” or “adjuvant”—in patients with non-microcarcinoma.”(2)

As for the Martinique Principles, the first principle (interdisciplinary collaboration) is noncontroversial, the second aims at avoiding inconsistent use of the term “ablation” and being more specific in defining the purpose of ¹³¹I use in a given patient, and the third is in complete agreement with the 2015 ATA guidelines (Recommendation 50 states that postoperative disease status should be considered in deciding whether additional treatment may be needed)(1). The fourth principle, that evaluation of postoperative disease status should be standardized, is logical, but the joint statement fails to put forth a clear pathway to accomplishing this goal. It is a universal challenge that the quality and consistency of postoperative imaging (especially ultrasonography and radioiodine scans) and biochemical assays (especially serum thyroglobulin [Tg] and Tg antibody) are highly variable, and the optimal Tg cutoff value warranting further treatment is not well defined. Principle 5, like Principle 3, agrees with the 2015 ATA guidelines’ recommendation for evaluating postoperative disease status and additional

variables to guide further treatment and surveillance (1). Principle 6 is vague, but emphasizes that the optimal dose of ¹³¹I for adjuvant therapy cannot be determined from the available literature, implying that the 2015 ATA guidelines recommendations for specific ¹³¹I doses (Recommendations 55 and 56) are too proscriptive. The 2015 ATA guidelines are also criticized for backing away from a recommendation for remnant ablation or adjuvant therapy in low-risk patients before the results of current prospective studies have been published. Principle 7 is supported by a lengthy defense, emphasizing the many circumstances in which a tumor labeled as ¹³¹I-refractory should still be considered for treatment. The call to risk-stratify tumors or patients as less likely to respond to ¹³¹I serves to keep patients in a pool of potential candidates for ¹³¹I therapy while acknowledging that their disease may be refractory, and ultimately gives greater latitude to those deciding on the dose of ¹³¹I. Principle 8 states that ¹³¹I refractory criteria will continue to evolve, and Principle 9 acknowledges the challenges (6) yet calls for more prospective studies of DTC to close the knowledge and evidence gaps regarding ¹³¹I therapy.

The Martinique Principles, like the 2015 ATA guidelines, emphasize a patient-centered approach to the management of thyroid cancer, avoiding strict rules that prevent flexibility in individualizing therapy, ¹³¹I or other, based on multiple variables.

To paraphrase Steinbrook, “Guidelines [and statements] rely on both evidence and opinion: they are neither infallible nor a substitute for clinical judgment.”(7) Future updates to management guidelines will need to be sensitive to the incorporation of greater nuclear medicine perspective in order to best represent and guide the multidisciplinary and collaborative care of patients with thyroid nodules and thyroid cancer.

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