Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-016-3327-3

EDITORIAL

Why the European Association of Nuclear Medicine has declined to endorse the 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer

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Received: 1 February 2016 / Accepted: 2 February 2016

Keywords Thyroid cancer · American Thyroid Association · Management guidelines

Recently the American Thyroid Association (ATA) released the third version of one of the most cited differentiated thyroid cancer (DTC) guidelines under the title "2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer" [1]. Compared to the earlier versions [2, 3], these guidelines are a major departure, as the volume of the text, the number of recommendations and the number of references have increased considerably.

We fully understand the effort involving many hours of work that must have been required for the rigorous screening of the literature to produce the evidence tables and the eventual definitions of the recommendations. The document consists of roughly 73,000 words which make up the 101 recommendations and the explanatory text and comments. In the current ATA guidelines, most of the text appears eminently sensible and represents a significant advance from previous DTC-related guidelines published by the ATA as well as other societies, including the 2008 European Association of Nuclear Medicine (EANM) guidelines on ^{131}I therapy of DTC [4–7]. For instance, we welcome the clear division of indications for initial ^{131}I treatment of DTC patients after total thyroidectomy into ablation, adjuvant therapy and therapy. Furthermore, this change in terminology which we strongly support much more clearly delineates the role of ^{131}I in the care of patients with DTC in other disciplines, especially medical oncology. Considering all the factors that have to be weighed in formulating recommendations this is a huge dedicated effort that has come to fruition.

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Published online: 17 February 2016

Yet when requested by the ATA to endorse these new 2015 guidelines, the Board of the EANM, after due consideration and consultation of the EANM Thyroid Committee, has nonetheless declined to do so.

In this editorial the EANM Board and the Thyroid Committee briefly explain the major issues of the 2015 ATA guidelines which the EANM is concerned about. The guidelines were discussed extensively with members of the 2015 ATA guideline author panel by an interdisciplinary group of European experts at an open meeting under the auspices of the EANM in Berlin on 20 June 2015. It was intended that the comments and views presented during this meeting would be summarized in a document discussing the issues on which European experts speaking for their respective societies and associations do not agree with the 2015 ATA guidelines. Although we understand that a number of the concerns raised within the EANM were also raised within the American nuclear medicine community, we want to explicitly state that in this document we speak only for the EANM, and we would welcome a similar commentary from the Society of Nuclear Medicine and Molecular Imaging representing the views of our American colleagues.

The reasons for declining to endorse these guidelines fall into two categories. In most cases our objections are based on differences in the interpretation of the available evidence, especially where the role of nuclear medicine is concerned. In spite of solid evidence on the clinical efficacy of nuclear medicine in both the diagnostic work-up of nodular thyroid disease and the care of DTC, the 2015 ATA guidelines appear to marginalise the role of nuclear medicine in the care of nodular thyroid disease and DTC. Some of our objections also concern the wording of some parts of the text which differ from our current viewpoint and are mostly based on a cautious, legally motivated choice of words. Our first objection is related to the recommendations regarding the use of thyroid scintigraphy in the initial diagnostic workup of nodular thyroid disease. In recommendations 2B and 2C it is stated:

> B) If the serum TSH is subnormal, a radionuclide (preferably ^{123}I) thyroid scan should be performed. (Strong recommendation, Moderate-quality evidence).
> C) If the serum TSH is normal or elevated, a radionuclide scan should not be performed as the initial imaging evaluation (Strong recommendation, Moderate-quality evidence).

It is not made clear in the text why ^{123}I is preferred over ^{99m}Tc-pertechnetate, as in hyperthyroidism usually the much cheaper and much more ubiquitously available ^{99m}Tc-pertechnetate is as diagnostically adequate as ^{123}I, especially in the era of SPECT/CT. Furthermore, the EANM believes that thyroid scintigraphy still has its place in the diagnostic workup of nodular thyroid disease, especially in regions, including a number of EANM member countries, with a known or recently alleviated iodine deficiency. In such populations a normal TSH level cannot rule out thyroid autonomy [8–11]. In their retrospective study, Chami et al. [9] found that 49 % of patients with an autonomously functioning focal thyroid nodule had a normal TSH level. This proportion increased to 71 % among patients in whom thyroid scintigraphy was performed in the workup of a thyroid nodule. Furthermore, the use of thyroid scintigraphy to preselect only the "cold" nodules for cytology can greatly reduce the number of thyroid surgical procedures for benign disease, especially in populations with a high prevalence of iodine deficiency-related nodular thyroid disease [12].

Therefore, we respectfully disagree with our American colleagues, and would like to make it clear that the EANM is of the opinion that a normal TSH level does not preclude the need for thyroid scintigraphy, especially in regions of longstanding insufficient iodine supply. Furthermore, the more expensive and not readily available ^{123}I can be reserved for rare cases, such as large intrathoracic goitres or the diagnosis of Pendred syndrome. Furthermore, the ATA guidelines fail to address the interesting possibilities offered by molecular imaging such as thyroid scintigraphy with ^{99m}Tc-sestamibi for clarification of cytologically unclear findings [13–16]. These topics will be addressed in further detail in the EANM procedural guidelines for thyroid scintigraphy in a joint effort with the Society of Nuclear Medicine and Molecular Imaging which is currently work in progress.

A second major objection to the 2015 ATA guidelines is the indication for ^{131}I therapy in the ablative setting after total thyroidectomy. First, Recommendation 35B states:

> For patients with thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without clinical evidence of any lymph node metastases (cN0), the initial surgical procedure can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low-risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable ^{131}I therapy or to enhance follow-up based upon disease features and/or patient preferences. (Strong Recommendation, Moderate-quality evidence).

While this radical departure from prior, internationally accepted and practised policy with regard to the extent of surgery in patients with a non-microcarcinoma is primarily an issue for our surgical colleagues, nuclear medicine is nonetheless greatly affected by this recommendation. In patients who have undergone lobectomy only, administering a postoperative course of ^{131}I is not a clinically feasible option due to possible complications resulting from large amounts of

remnant thyroid tissue and limited prospects for successful treatment by stricter criteria.

This is also reflected in further recommendations regarding the indication for postoperative ^{131}I. In Recommendation 51A and Table 14 it is stated that: "post-operative I-131 treatment should not routinely be given to any patient who is considered ATA low-risk". This includes both patients with classical unifocal microcarcinoma, in whom it has for a long time been established that ^{131}I ablation offers no advantage, and patients with larger tumour sizes up to 4 cm. In patients with tumours >4 cm without extrathyroidal invasion, ^{131}I therapy should be "considered" with a positive recommendation given only in those patients whose cancer shows additional high-risk characteristics.

For the entire population of patients with DTC exceeding 1 cm in diameter, there is some evidence of the usefulness of postoperative ^{131}I ablation [17]. However, we do agree that not all patients who are treated with ^{131}I will in fact benefit from it, even though we cannot yet reliably identify these patients. We therefore take this opportunity to warn our colleagues that the currently proposed strategy may not yet be based on solid evidence. It is not long since esteemed colleagues Mazzaferri and Jhiang showed in landmark studies [18] that the introduction of postoperative ^{131}I treatment leads to a dramatic decline in both recurrence and DTC-specific mortality rates. There are currently no prospective, controlled studies available that precisely indicate which patients with low-risk DTC may or may not benefit from postoperative ^{131}I therapy. To that end, two well-regarded trials in the UK and France (IoN [19] and ESTIMABL2) comparing ^{131}I ablation and no ablation in patients with lower risk DTC are currently recruiting. A long follow-up of at least 10 years [20] will be needed before these studies are able to provide strong, reliable prospective data on patient outcome. It is known that even treatment with low ^{131}I activities may lead to a worse prognosis in patients with low-risk DTC than treatment with high activities [20], so it is possible that no ^{131}I treatment may lead to an even worse outcome. Therefore we would advise caution in altering long-established and successful practice until sufficient evidence is available indicating that it is safe to omit postoperative ^{131}I treatment – "ablation" or "adjuvant" – in patients with non-microcarcinoma.

Another important factor in the decision to ablate or not to ablate is the expertise of the surgeon. The 2008 EANM guidelines [5] state: "When thyroid surgery is performed in highly expert hands at selected tertiary referral centres, though, the positive influence of radioiodine ablation may not be apparent". This statement was intended to illustrate that an experienced surgeon performing a large number procedures can perform a truly total thyroidectomy. This has been shown in a recent study in which a surgeon score based on the number of patients referred for postoperative ^{131}I ablation of DTC independently predicted the size of the thyroid remnant [21].

In this regard, and not addressed within the ATA guidelines, it appears that the postoperative serum thyroglobulin (Tg) value as a measure of thyroid remnant volume can be more of a help in identifying patients who may benefit from ^{131}I ablation than in identifying patients who do not require ablation. For example, a postoperative Tg value >5 – 10 ng/mL may lead to initiation of ^{131}I ablation in a patient with low or intermediate risk DTC according to the ATA guidelines who otherwise would not have required ^{131}I treatment (selective use) to improve initial staging and facilitate follow-up. Therefore the selective use of ^{131}I ablation could also be considered in patients with low-risk DTC who received a less than optimal surgery as reflected by the level of Tg. Furthermore serum Tg level after surgery could be used to adjust the initial ^{131}I activity to compensate for larger volumes of remaining benign and/or malignant thyrocytes [22].

Another objection from our association concerns the ATA guidelines' wording of recommendations on the use of recombinant human TSH, which is rather more cautious than the EANM has so far been. Perhaps because of the medicolegal implications, the ATA guidelines, in spite of all the available evidence with regard to equal efficacy and superior patient quality-of-life compared to levothyroxine withdrawal [23–32], are rather hesitant about the use of recombinant human TSH for patient preparation for the initial postoperative course of ^{131}I. The 2008 EANM guidelines [5] designated exogenous stimulation as the "method of choice" for TSH stimulation prior to ^{131}I ablation. In Recommendation 54A of the ATA guidelines it is in contrast stated that "preparation with rhTSH stimulation is an acceptable alternative to thyroid hormone withdrawal" in patients with low-risk DTC according to ATA guidelines. In patients with intermediate-risk DTC (Recommendation 54B) "preparation with rhTSH stimulation may be considered as an alternative to thyroid hormone withdrawal". This choice of words suggests an inferior efficacy of rhTSH, which is in contrast with most currently available evidence in literature.

While the objections described above are our main reasons for declining to endorse the 2015 ATA guidelines, there are of course further disagreements which are of a more detailed nature rather than matters of principle. These include, for example, the precise ^{131}I activities to be given depending on the particular goal of the ^{131}I treatment after surgery, which is still a matter of discussion requiring further study. It remains unclear how to proceed with patients with low-risk disease in accordance with these guidelines: on the one hand in such patients 1,110 MBq is advised for ^{131}I ablation, and on the other hand the same document states elsewhere that such patients do not require ^{131}I ablation at all. Furthermore, there could be discussion of the range of indications for diagnostic whole-body scintigraphy (Recommendations 66 and 67) as well as several other items. However, as with most things in DTC the data in the literature are so limited that a real

evidence-based discussion is almost impossible and any one experience-based opinion may carry as much weight as another.

For future editions of the ATA management guidelines for adult patients with thyroid nodules and DTC, we sincerely offer our support in order to include more experts in nuclear thyroidology and thus create a more balanced set of recommendations which do justice to the role of nuclear medicine in the care of patients with nodular thyroid disease and DTC. Guidelines created in such a manner would indeed gladly be endorsed by the EANM.

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