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EDITORIAL

The 2015 Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the "evidence-based" refusal to endorse them by EANM due to the "not evidence-based" marginalization of the role of Nuclear Medicine

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In 2007, the American Thyroid Association (ATA) assembled a group of expert clinicians and basic scientists to evaluate published papers and to develop evidence-based guidelines for the diagnosis and management of patients with medullary thyroid carcinoma (MTC). The first ATA guidelines on the management of patients with MTC were published in 2009 [1]. In 2015, ATA released the first revised version of these guidelines [2], in order to assist clinicians of all specialties in the management of these patients.

The ATA Board of Directors selected the Task Force members for elaborating these revised guidelines based on published scientific data in the management of MTC, and included international scientists from the fields of endocrinology, ethics, genetics, medical oncology, molecular biology, nuclear medicine, pathology, paediatrics, radiation oncology, and surgery [2]. Task Force members reviewed relevant articles on MTC by searching MEDLINE/PubMed from January 1980 to April 2014 using specific MTC-related search terms. Task Force members also provided additional relevant articles, book chapters, and other materials. Recommendations were graded using criteria adapted from the United States Preventive Services Task Force Agency for Healthcare Research and Quality as were used in the previous MTC guidelines [1, 2]. After revisions and critical reviews of a series of drafts, the Task Force developed a final document, and the ATA Board of Directors approved the revised set of guidelines [2].

Compared to the earlier version [1], the 2015 revised ATA guidelines on the management of patients with MTC (now consisting of 67 recommendations and related explanatory

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text and comments) in many aspects represents a significant advance and update from previous guidelines on MTC published by the ATA as well as other societies [1, 3].

Nevertheless, when requested by the ATA to endorse the 2015 revised ATA guidelines on MTC, the Board of the European Association of Nuclear Medicine (EANM), after due consideration and consultation of the EANM Thyroid Committee, has declined to do so.

In this editorial the EANM Thyroid Committee will briefly explain the major issues in the 2015 revised ATA guidelines on MTC management, which the EANM is concerned about. Our objections are mainly based on differences in the interpretation of the available scientific evidence about the role of positron emission tomography/computed tomography (PET/CT) with different radiopharmaceuticals, such as fluorine-18 fluorodeoxyglucose (FDG), fluorine-18 dihydroxyphenylalanine (F-DOPA), and somatostatin analogues labelled with gallium-68 in the management of recurrent and/or persistent MTC.

There are some objections and concerns raised within the EANM Thyroid Committee on the revised ATA guidelines with regard to the marginalized role of Nuclear Medicine in the management of MTC. In particular, we are concerned about recommendations 23 and 48 and the explanatory text accompanying these recommendations.

A) In recommendation 23 of the 2015 revised ATA guidelines it is stated:

"Neither FDG-PET/CT nor F-DOPA-PET/CT is recommended to detect the presence of distant metastases. Grade E Recommendation" (according to the rating system used in these guidelines, the grade E recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits) [2]. To support this recommendation, the authors of the revised ATA guidelines state that "FDG-PET/CT and F-DOPA-PET/CT are less sensitive in detecting metastases, compared to other imaging procedures" and cite a single study on the role of imaging methods in recurrent MTC [4].

- First of all in this recommendation the indication of PET/CT imaging in MTC is not specified, i.e., staging or restaging due to increasing serum levels of tumour markers such as calcitonin and/or carcinoembryonic antigen (CEA). In fact, whereas the role of nuclear medicine techniques in preoperative staging of MTC seems limited, on the other hand, an extensive body of evidence in literature clearly supports the role of PET/CT using different radiopharmaceuticals, F-DOPA in particular, in detecting persistent/recurrent MTC [5–12].
- The only cited reference supporting the recommendation 23 [4] concerns an article comparing several non-nuclear medicine imaging modalities with nuclear medicine techniques including bone scintigraphy and FDG-PET/CT in the management of recurrent MTC. However, F-DOPA-PET/CT or somatostatin analogue PET/CT were not considered in this prospective study [4]. Although perhaps we can understand a recommendation against FDG-PET/CT based on this evidence, we fail to comprehend how this evidence can be extrapolated to other (much more sensitive) PET/CT imaging modalities such as F-DOPA-PET/CT.
- This recommendation furthermore represents a 180-degree turn from the 2009 version of the ATA MTC management guidelines, which explicitly recommended especially F-DOPA-PET/CT in recurrent MTC patients with a serum calcitonin value > 150 pg/mL [1]. However, since the publication of the 2009 edition of the ATA guidelines on MTC management, no essential new evidence which might have changed the view against the role F-DOPA-PET/CT has yet emerged. Therefore, again, we fail to comprehend why the ATA MTC guidelines author panel, without having any substantiated reason or scientific evidence, changed its recommendation against such an effective imaging method, i.e., F-DOPA-PET/CT.

B) In recommendation 48 of the revised ATA guidelines it is stated:

"If the postoperative serum calcitonin level exceeds 150 pg/mL, patients should be evaluated by imaging procedures, including: neck ultrasound, chest CT, contrast-enhanced MRI or three-phase contrast-enhanced CT of the liver, and bone scintigraphy, and MRI of the pelvis and axial skeleton. Grade C Recommendation" (according to the rating system used in these guidelines, the grade C recommendation is based on expert opinion) [2].

- It is quite surprising that PET imaging or gamma camera imaging using different radiopharmaceuticals is not cited in this recommendation as in the same guidelines it is stated that "FDG-PET/CT and F-DOPA-PET/CT proved superior to conventional imaging procedures in detecting metastases in patients with MTC. F-DOPA-PET/CT had a higher sensitivity, compared to FDG-PET/CT, and seemed more important in assessing extent of the disease. On the other hand, FDG-PET/CT correlated significantly with progressive disease. Survival was significantly lower in FDG-PET/CT-positive patients compared to FDG-

PET/CT-negative patients, and although the same was true for F-DOPA-PET/CT-positive patients compared to those who were negative, the survival in patients with a positive FDG-PET/CT was lower and independent of the F-DOPA-PET/CT result. Therefore, the two studies are complementary with F-DOPA-PET/CT having a higher sensitivity in detecting tumour load, and FDG-PET/CT more accurately identifying patients with progressive disease" [2].

– Despite the stated aim of the ATA Board of Directors to provide "evidence-based" guidelines, any citation of available evidence-based articles, such as meta-analyses on the diagnostic accuracy of PET/CT with different radiopharmaceuticals in recurrent MTC, is lacking in the 2015 revised ATA guidelines on MTC management.

About FDG-PET or PET/CT, a meta-analysis published in 2012, which was not cited in the revised ATA MTC guidelines, showed that the detection rate of FDG-PET or PET/CT in suspected recurrent MTC on a per patient-based analysis is 59 % (95 % confidence interval: 54-63 %) [13]. Therefore, a significant number of recurrent MTC foci, which are suspected based on rising levels of tumour markers, remains unidentified by using FDG-PET/CT. On the other hand, it should be considered that FDG-PET/CT is usually performed in patients with suspected recurrent MTC in whom prior conventional morphological imaging studies already failed to yield any tumour focus. Furthermore, FDG-PET/CT affected the surgical management of patients with recurrent MTC when lesions were detected [13]. As shown in the literature, the diagnostic performance of FDG-PET/CT improves in patients with recurrent MTC having increased serum calcitonin and CEA levels [9, 13]. Also, sensitivity of FDG-PET/CT improves in patients with shorter serum calcitonin and CEA doubling times, confirming the usefulness of this imaging method in patients with more aggressive disease compared to those with comparatively slowly progressive disease [9, 13]. In particular, FDG-PET has a relevant prognostic value as it is able to identify MTC patients with poor survival [14, 15].

About F-DOPA-PET or PET/CT, a meta-analysis published in 2012, which was not cited in the revised ATA guidelines, showed that the detection rate of F-DOPA-PET or PET/CT in suspected recurrent MTC on a per patient-based analysis is 66 % (95 % confidence interval: 58-74 %) [16]. This value increases to 72 % with hybrid PET/CT only [16]. However, a positive F-DOPA-PET/CT might modify the surgical management in a significant number of patients with recurrent MTC [17, 18], because this functional imaging method is often performed in patients with recurrent MTC based on rising tumour marker levels after negative conventional morphological imaging studies [16]. Based on the literature, the overall diagnostic performance of F-DOPA-PET/CT in recurrent MTC seems to be higher than that of FDG-PET/CT and improves in patients with higher serum calcitonin levels and shorter serum calcitonin doubling time, reaching a detection rate of 86 % in recurrent MTC with a calcitonin doubling time lower than 24 months [9, 16]. A further improvement in the detection rate of F-DOPA-PET/CT in MTC could be achieved by early scan acquisition (around 15 minutes after radiopharmaceutical injection) [19, 20].

– The use of somatostatin receptor imaging (in particular somatostatin receptor PET/CT) in patients with MTC is not cited in the revised ATA guidelines. Somatostatin receptor PET/CT using somatostatin analogues labelled with gallium-68 is a valuable diagnostic tool for patients with neuroendocrine tumours (NETs) [21, 22]. The experience with somatostatin receptor PET/CT in recurrent MTC is limited compared to FDG and F-DOPA [9]. Overall, the diagnostic performance of somatostatin receptor PET/CT in recurrent MTC seems to be inferior compared to other NETs (such as lung and gastroenteropancreatic) due to the variable somatostatin receptor expression in MTC [7, 9, 11, 23]. In particular, based on the available literature, the sensitivity of somatostatin receptor PET/CT in patients with recurrent MTC largely varies widely from 25 % to 83 % whereas the specificity is very high [18, 24–29]. As is the case with FDG- and F-DOPA-PET/CT, the detection rate of somatostatin receptor PET/CT in recurrent MTC increases in patients with higher serum calcitonin levels [24]. To date, only one study comparing F-DOPA, FDG, and somatostatin receptor PET/CT in recurrent MTC is available, demonstrating the superior diagnostic accuracy of F-DOPA compared over other PET radiopharmaceuticals in this setting [18]. Nevertheless, compared to FDG- and F-DOPA-PET/CT, somatostatin receptor PET/CT may have an additional role as this method could be useful in pre-selecting metastatic MTC patients for therapy with cold or radiolabelled somatostatin analogues, to potentially treat metastatic lesions which show a high level of expression of somatostatin receptors [30].

In conclusion, in spite of an increasing volume of evidence available in the literature on the usefulness of PET/CT with different radiopharmaceuticals in recurrent MTC [5–13, 16], the 2015 revised ATA MTC guidelines appear to consciously marginalise the role of Nuclear Medicine in this setting, thereby ignoring the emerging role of functional information obtained from highly selective uptake of radiopharmaceuticals in the MTC tissue. As far as the role of Nuclear Medicine is

concerned in this rare tumour entity, compared to previous iteration of these ATA guidelines, the 2015 ATA guidelines on MTC management seem to represent a reversal rather than an advance, even though the body of scientific evidence in the literature has grown considerably since the publication of 2009 ATA MTC guidelines. This reversal of Nuclear Medicine's role is not validated by any published data. Therefore, as a major representative of the Nuclear Medicine community in the world, the EANM decided not to endorse the 2015 ATA guidelines for the management of MTC.

Compliance with ethical standards

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Ethical approval This article does not describe any studies with human participants performed by any of the authors.

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