European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-019-04557-4

ORIGINAL ARTICLE

Variations in radioiodine ablation: decision-making after total thyroidectomy

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Received: 28 May 2019 / Accepted: 25 September 2019
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Abstract

Background The role of radioiodine treatment following total thyroidectomy for differentiated thyroid cancer is changing. The last major revision of the American Thyroid Association (ATA) Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer in 2015 changed treatment recommendations dramatically in comparison with the European Association of Nuclear Medicine (EANM) 2008 guidelines. We hypothesised that there is marked variability between the different treatment regimens used today.

Methods We analysed decision-making in all Swiss hospitals offering radioiodine treatment to map current practice within the community and identify consensus and discrepancies.

Results and Conclusion We demonstrated that for low-risk DTC patients after thyroidectomy, some institutions offered only follow-up, while RIT with significant activities is recommended in others. For intermediate- and high-risk patients, radioiodine treatment is generally recommended. Dosing and treatment preparation (recombinant human thyroid stimulation hormone (rhTSH) vs. thyroid hormone withdrawal (THW)) vary significantly among centres.

Keywords Radioiodine · Thyroidectomy · Treatment · Decision Making

This article is part of the Topical Collection on Oncology – Head and Neck

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Published online: 09 November 2019

Introduction

For decades, total thyroidectomy followed by radioiodine treatment (RIT) has been the standard of care for virtually all differentiated thyroid cancers. However, after the latest updates of the American Thyroid Association (ATA) Management Guidelines for Adult Patients and Children with Thyroid Nodules and Differentiated Thyroid Cancer in 2015, the role of RIT in low-risk thyroid cancer was questioned [1]. While RIT contributes to the excellent overall prognosis of patients diagnosed with differentiated thyroid cancer, observational studies failed to demonstrate benefits of adjuvant RIT in low-risk patients [2–6]. The nature of differentiated thyroid cancer is generally characterized by slow growth hampering the feasibility of studies demonstrating a benefit of radioiodine treatment [7]. Exactly these low-risk cancers account for the increasing overall incidence of thyroid cancer [8].

For many European centres, the 2008 European Association of Nuclear Medicine (EANM) guideline represented a standard of care. With the publication of the ATA guidelines, conflicting recommendations arose; conflicting guidelines are not a rare occurrence [9, 10].

The ATA guidelines state 'post-operative I-131 treatment should not routinely be given to any patient who is considered ATA low risk' [11], which is in contrast to the EANM 2008 guidelines [12]. Furthermore, adjuvant I-131 treatment for primary tumours larger than 4 cm should only be 'considered' according to ATA guidelines [11]. EANM guidelines recommend radioiodine treatment for any DTC larger than 1 cm in diameter as well as DTC smaller than 1 cm if additional risk factors such as unfavourable histology or history of radiation exposure are present, thus considered low risk according to ATA.

Based on these differences in thyroid cancer management and other controversies in the diagnostic procedures, the EANM declined to endorse the ATA guidelines on thyroid cancer [13].

Next to the TNM staging, other prognostic scores exist, including MACIS [14], AGES [15], and AMES [16]. Several studies comparing these scoring systems indicate that MACIS is the most reliable score [17]. The availability of different scoring systems may further contribute to heterogeneous treatment recommendations in clinical routine. Since many scoring systems have been developed over 20 years ago, they do not account for genetic information, which is routinely available nowadays.

With regard to the generally slow progression of DTC, studies with long-term follow-up and large patient cohorts are needed to properly assess the value of radioiodine treatment. For several stages of DTC, long-term outcomes are lacking. In the setting of low or uncertain evidence, guidance by the experience of the community may assist the treating physician in daily practice [18]. Clinical decisions for or against RIT can be based on different tumour characteristics or patient associated parameters [19]. This analysis aims to assess similarities and differences between treatment strategies among Swiss nuclear medicine facilities.

Materials and methods

All Swiss nuclear medicine facilities equipped with a ward to provide in-patient RIT were asked to participate. Nuclear medicine physicians in charge of RIT from each centre were asked to answer the following question: 'Which is your treatment strategy / decision for patients with thyroid cancer after (near) total thyroidectomy?' The treatment recommendations for RIT treatment were collected in any available format (Free text, Microsoft PowerPoint slides or verbal conversation). The survey was carried out from April until October 2018. The responses were collected by the coordinator (OM), as described by Panje et al. [20] and others applying this methodology in various clinical scenarios [9, 21–25]. Answers were converted into decision trees, which were then revised and improved by bilateral feedback between the study coordinators and each participant. The product of this interaction was a decision tree describing decision criteria and their combinations relevant for patient selection for RIT.

To allow comparison, the collected decision criteria and recommendations were merged into new comprehensive categories (i.e. 'high-risk histology' representing various variants of DTC with unfavourable prognosis such as 'tall cell' or 'hobnail variant'). The criterion 'lymph node status' was designed to encompass the number of lymph node metastases and/or micro- and macro-metastases, as well as involvement of lymph nodes of the central or lateral compartment figure. Consensus and disagreement were analysed used the objective consensus methodology [20, 26]. Further decision criteria used were positive resection margins ('R status'), vascular invasion ('V status') and lymphovascular invasion ('L status').

Many centres provided specific treatment activities and recommendations for thyroid tissue stimulation (rhTSH) versus thyroid hormone withdrawal (THW) for different combinations of parameters. Though the initial question did not explicitly request information on the applied activities, the majority included those. Therefore, in a second round, this information was collected from all participating centres in order to allow for an analysis. For selected tumour stages representing low (pT1b N0 M0 resp. pT2 N0 M0) and high risk (pT3 N1a M0 resp. pT4 N1b M0), the treatment activities were extracted from the decision trees and visualized (Figs. 1, 2, 3 and 4).

Five of the participating centres mentioned general circumstances and factors that exclude adjuvant RIT per se or generally trigger the recommendation not to offer RIT irrespective of the disease characteristics. These factors consisted of limited life expectancy, other diseases that clearly dominate the patient's overall prognosis (e.g. incurable aggressive malignancies) or absence of patient

consent. These conditions were not included in the decision tree analysis.

Two centres included non-invasive follicular thyroid neoplasms with papillary-like features (NIFTP) in their answers. One centre stated that they recommend RIT for NIFTP with a diameter larger than 4 cm. According to Nikiforov et al., NFTIP is not considered a thyroid cancer [27] and was therefore excluded.

Results

Twelve out of 14 Swiss nuclear medicine facilities provided written, oral or tabular information on their patient selection criteria for adjuvant RIT after total thyroidectomy. The criteria used for the decision for or against adjuvant radioiodine treatment could be grouped into nine categories as shown in Table 1.

Our analysis identified tumour characteristics for which all participating experts recommended RIT irrespectively of any other attribute of the tumour: distant metastases (M1), T3 or T4 tumours and residual disease.

A consensus of 100% for not recommending RIT on the other hand can be reported for only one situation: unifocal T1a tumours with classical papillary of follicular histology in the absence of any additional risk factors. pT1a tumours with additional characteristics show a inhomogeneous pattern of opinions. For pT1a tumours with positive L or V status, still 92% do not recommend RIT. T1a tumours with unfavourable histology or multifocality alone a slight majority of 58% of experts did not recommend RIT. If multifocality and unfavourable histology is combined, no majority consensus exists: 50% recommend RIT while 50% do not.

For T1b tumours with no evidence of metastases, the recommendation towards RIT is predominant, but the level of agreement is low, ranging from 50% (no consensus) to 75%, depending on other factors. One of the participating centres relies for pT1b tumours on B-RAF mutation status for their decision of recommending RIT or not.

For pT2 tumours, 83% of the participating centres recommend RIT. Seventeen percent tailor an individual decision for each patient in the setting of an interdisciplinary board.

The presence of lymph node metastasis results in favouring the use of RIT among nuclear medicine physicians. While 75% participating centres recommend RIT for any lymph node involvement, including a single micrometastasis, 100% consensus for recommending RIT can only be reported if at least 6 micrometastases or 3 or more macro-metastases are present. When only 1–2 macro-metastases are present, just 92% recommend RIT.

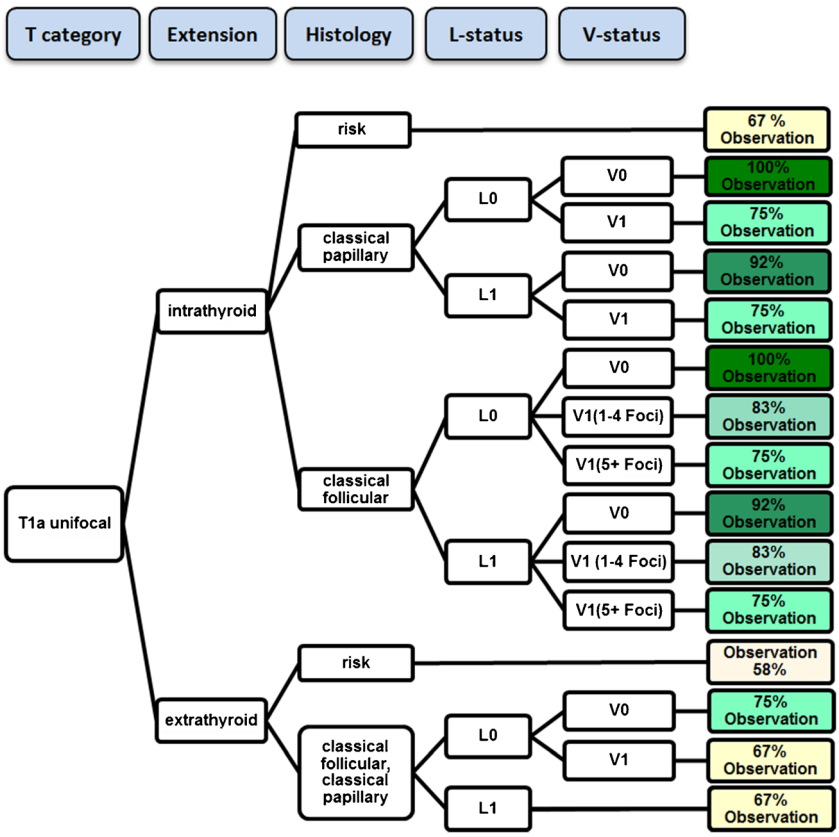

Fig. 1 Illustration of decisions for T1a tumours in the absence of lymph node or distant metastases

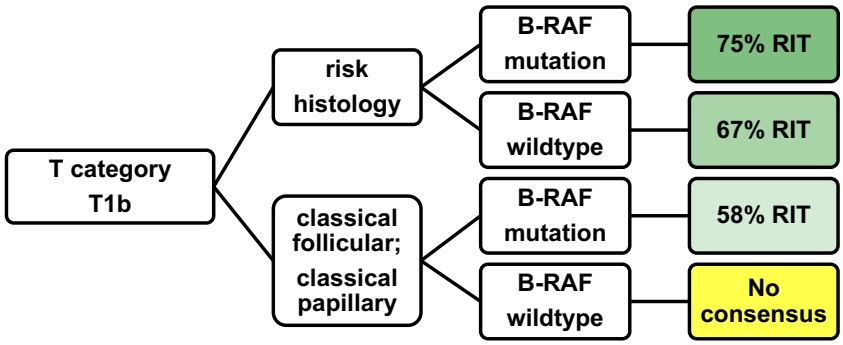

Fig. 2 Majority consensus for DTC of pT1b N0 M0 L0 V0 tumours considering B-RAF status and histology

RIT activities/rhTSH vs. THW

Treatment activities varied significantly among centres. Some centres use the same treatment activities for all radioiodine treatments, while others apply risk-adapted strategies. Patients classified as ATA low risk may be offered a RIT with up to 3700 MBq I-131 while not being considered for adjuvant RIT at others centres. In intermediate- or high-risk situations, treatment was recommended in every centre, but activities of I-131 differ considerably between 2800 MBq I-131 and 7400 MBq as shown in Fig. 4.

The variation of activities administered may reflect that several centres already apply the approach of variation in activities of radioiodine depending on the aim of the RIT: remnant ablation, adjuvant treatment versus treatment of known disease. This variance in RIT activities has recently been consensus recommendation by 'Martinique conference' [28].

TSH stimulation for RIT by rhTSH is recommended by a majority for lower tumour stages. In the situation of pT1b pN0, five out of the seven centres that apply RIT for this tumour stage recommend using rhTSH, while only two centres use thyroid hormone withdrawal (THW). For pT2 pN0 tumours, rhTSH is more common (8 out of 12). For high-risk tumours such as pT4 pN1 tumours, THW slightly outweighs rhTSH (7 centres for THW vs. 5 centres for rhTSH).

Discussion

The similarities and differences worked out by our analysis reflect the contradictions and uncertainties between current guidelines and recent publications.

The factors that trigger consistently the recommendations for the use of RIT by the participating Swiss centres are the presence of metastases, a primary T3 or T4 tumour or residual disease. This is in line with current guidelines. The same applies for the recommendation to refrain from RIT for pT1a tumours without additional risk factors [11, 12, 29].

The discrepancies in all other cases in-between illustrate the situation of the ongoing debate in low- and intermediate-risk tumours [7, 30]. While the ATA and NCCN guidelines [31] suggest that ATA low-risk tumours are sufficiently treated by hemi-thyroidectomy, other former [12] and current guidelines [29] recommend radioiodine treatment for certain situations that are considered low risk according to ATA; e.g. pT1b tumours. The great variety of recommendations for pT1b

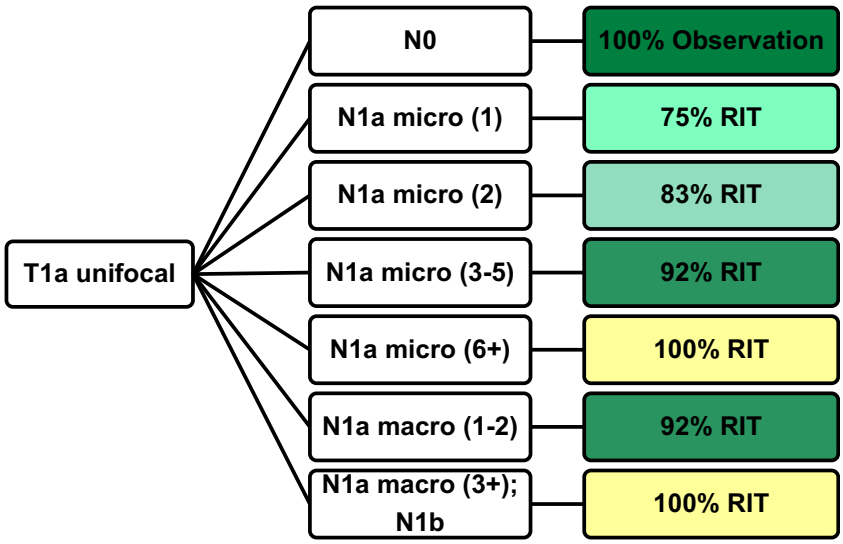

Fig. 3 Influence of N status on the decision for adjuvant RIT. In case of a pT1a tumours without metastases or any other risk factor predisposing for RIT

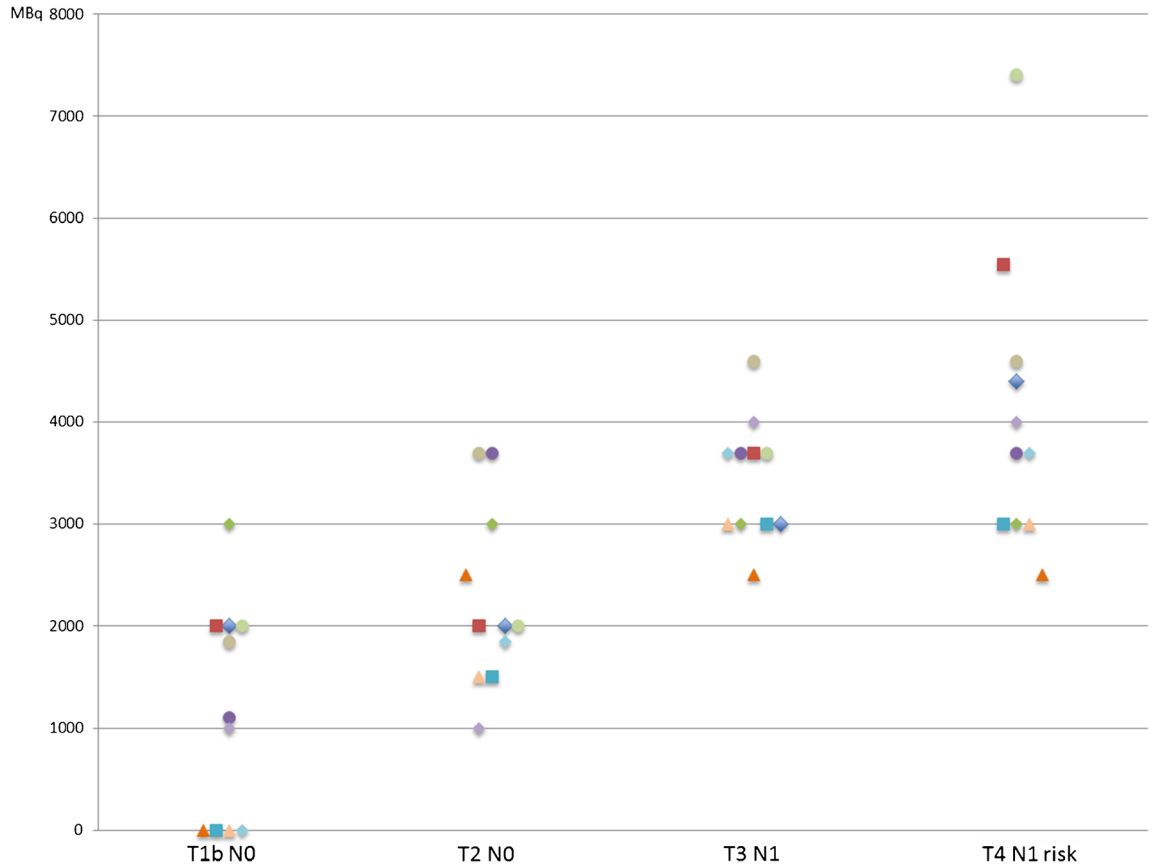

Fig. 4 Four sample tumour stages and the RIA activities of I-131 in MBq recommended by the participants. Centres are represented by coloured markers. The administered activities of I-131 rise with increasing tumour stage in most centres, but still vary significantly

tumours in our survey reflects this discussion. The fact that 'high level of evidence' consists only for two out of 101 ATA 2015 recommendations [7, 11] might contribute to the limited acceptance of the ATA 2015 guidelines in the nuclear medicine community. On the other hand, the publication of 'Martinique's principles' intends to overcome the controversies between the European Association on Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) to the ATA an ETA [28] and may lead to alignment of treatment strategies.

Noteworthy, two out of 12 participating participants did not provide clear recommendations for RIT in T2 tumours. These cases are discussed individually without any standard policy in place.

B-RAF mutation status was mentioned among the factors used in daily routine when deciding whether to recommend radioiodine or not. Though some data indicates that risk is especially pronounced in B-RAF and TERT mutated tumours, TERT mutations were not mentioned by the participants [32].

Table 1 Overview of the categories and the decision criteria mentioned within this survey being relevant for the decision process for or against radioiodine treatment

T	N	M	R	V	L	Histology	Extension	B-RAF-mutation
T1a unifocal	N0	M0	R0	V0	L0	Classic papillary	Intrathyroid	Wildtype
T1a multifocal	N1 micro (n=1)	M1	R1	V1 (foci n≤4)	L1	Classic follicular	extrathyroid	Mutation
T1b	N1 micro (n>1)		R2	V1 (foci n>4)		high risk histology		
T2	N1 macro							
T3	N1a (n≤2)							
T4	N1a (n>2) N1b N1 (n>5)							

Interestingly, post-operative thyroglobulin levels did not play a role in our decision trees, though the measurement of post-operative thyroglobulin is part of the mentioned guidelines. We hypothesise that in daily routine, the decision for or against RIT is made within few days after surgery and post-operative thyroglobulin has not been reassessed yet.

With the recent publication of a consensus statement for low-risk papillary thyroid cancer, discrepancies between Swiss nuclear medicine facilities are likely to be reduced [33] as the publication clearly recommends radioiodine treatment for low-risk primary tumours between 20 and 40 mm. Alignment of treatments might increase in the next years as the results of trials started in 2012 and 2013 are being awaited. The ESTIMABLE2 and Ion trials are investigating the impact of rhTSH-stimulated radioiodine treatment with 1100 MBq for low-risk DTC.

Switzerland provides a good setting for our analysis. The Swiss healthcare system, with insurance that is mandatory for all inhabitants, covers all treatment options for newly diagnosed thyroid cancer. Almost participating centres were public hospitals (11/12). There are 14 hospitals offering RIT for the approx. 8.5 million inhabitants, so treatment is easily accessible. Therefore, we assume that the decision for or against RIT is scarcely influenced by economical or logistical differences between the centres.

One of the limitations of our survey is the restriction of the participants to nuclear medicine physicians. While most participating centres explicitly stated that their treatment recommendations discussed in an interdisciplinary board. This analysis is concerned with the opinions and strategies of the nuclear medicine specialists and does not necessarily reflect a multidisciplinary opinion.

Endocrinologists, surgeons (endocrine surgeons, head-and-neck surgeons, general surgeons) and oncologists are among the treating disciplines for thyroid cancer and usually participate in the decision for or against RIT in the interdisciplinary tumour board. We restricted our survey to nuclear medicine specialists to identify patterns within the nuclear medicine community.

Conclusion

Although the routine use of adjuvant radioiodine treatment for small and intermediate stages of DTC is not recommended by the current ATA guidelines, our survey shows that among nuclear medicine centres in Switzerland, RIT is routinely recommended for selected low-risk stages. This might reflect the missing endorsement of the ATA guidelines by EANM. Our survey reveals great variability in RIT treatment strategies among in Swiss nuclear medicine facilities.

Funding The project was funded by a non-profit grant by Krebsliga Beider Basel as mentioned in the submission portal.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This survey analyses the participating centres for their treatment strategies. This information is derived directly from the clinical experts; individual patient data was not accessed.

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