

Variations in Radioiodine Therapy in Europe: Decision-Making after Total Thyroidectomy

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Keywords

Radioiodine · Radioiodine therapy · Decision-making · Thyroid cancer

Abstract

The role of radioiodine therapy (RIT) (used as ablation therapy or adjuvant therapy) following total thyroidectomy for differentiated thyroid cancer (DTC) changed. Major revisions of the American Thyroid Association (ATA) Guidelines in 2015 resulted in significant differences in treatment recommendations in comparison to the European Association of Nuclear Medicine (EANM) 2008 guidelines. Recently, we presented the effects on daily practice for RIT among Swiss Nu-

clear Medicine centres. We now performed a study at the European level and hypothesized that there is also considerable variability among European experts. We performed a decision-tree-based analysis of management strategies from all members of the EANM thyroid committee to map current practice among experts. We collected data on whether or not RIT is administered, on which criteria these decisions are based and collected details on treatment activities and patient preparation. Our study shows discrepancies for low-risk DTC, where "follow-up only" is recommended by some experts, while RIT with significant doses is used by other experts. E.g., for pT1b tumours without evidence of metastases, the level of agreement for the use of RIT is as low as 50%. If RIT is administered, activities of I-131 range from

1.1 GBq to 3.0 GBq. In other constellations (e.g., pT1a), experts diverge from current clinical guidelines as up to 75% administer RIT in certain cases. For intermediate and high-risk patients, RIT is generally recommended. However, dosing and treatment preparation (rhTSH vs. thyroid hormone withdrawal) vary distinctly. In comparison to the Swiss study, the general level of agreement is higher among the European experts. The recently proposed approach on the use of RIT, based on integrated post-surgery assessment (Martini article) and results of ongoing prospective randomized studies are likely to reduce uncertainty in approaching RIT treatment. In certain constellations, consensus identified among European experts might be helpful in formulating future guidelines.

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Introduction

For decades, virtually all differentiated thyroid cancers (DTCs) were treated by total thyroidectomy followed by radioiodine therapy (RIT). However, after the latest update 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 DTC, observational studies failed to demonstrate benefits of ablation therapy in low-risk patients [2–6]. The slow growth of DTC often impedes studies investigating a potential benefit of RIT [7]. However, it is these low-risk cancers that mainly account for the increasing overall incidence of thyroid cancer and contribute to the ongoing debate on the use of RIT [8].

The 2008 European Association of Nuclear Medicine (EANM) guideline represented the standard of care for most centres until the publication of the ATA guidelines. Since then, conflicts in recommendations exist in certain situations. E.g., the ATA guidelines state that “post-operative I-131 treatment should not routinely be given to patients who are considered ATA low-risk” [9], which is in contrast to the EANM 2008 guidelines [10]. Furthermore, adjuvant I-131 treatment for primary tumours >4 cm should only be “considered” according to ATA guidelines [9]. EANM guidelines recommend RIT for any DTC >1 cm in diameter as well as DTC <1 cm if additional risk factors such as unfavourable histology or history of radiation exposure are present, thus considering low-risk according to the ATA.

Based on these differences in recommendations for the management of thyroid cancer as well as other controversies in diagnostic procedures, the EANM declined to endorse the ATA guidelines on thyroid cancer [11]. Besides the TNM staging, other prognostic scores exist, including MACIS [12], AGES [13], and AMES [14]. Studies comparing these scoring systems indicate that MACIS is probably the most reliable score [15]. The existence of different scoring systems additionally contributes 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 are routinely used in many centres currently.

With regard to the generally slow progression of DTC, studies need long-term follow-up and large patient cohorts to properly assess the value of RIT. For several stages of DTC, long-term outcome studies are lacking. In the setting of low or uncertain evidence, guidance by the experience of the community may assist treating physicians in daily practice [16]. The clinical decisions to use or not to use RIT can be based on different tumour characteristics or patient associated parameters [17, 18]. Recently, we published the variations in the use of RIT among Swiss centres [19]. Significant differences were demonstrated, e.g., in low-risk DTC patients after thyroidectomy or in patient preparation. In this study, we investigate similarities and differences among European experts.

Materials and Methods

All 9 members of the EANM thyroid committee were asked to participate in this survey. All members agreed to participate; however, as 2 members were working in the same institution, only one of them was included. This resulted in 8 participating experts. They 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 were collected in any available format (free text, Microsoft PowerPoint slides, or personal communication). The responses were collected by the coordinator (F.F.) as previously described [20] and applied in various clinical scenarios [21–26]. Answers were converted into decision trees, which were then revised and improved by bilateral feedback between the study coordinators and each participant. The result 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”). Criteria mentioned by all or most participants were tumour size (“T status”) and lymph node invasion (“lymph node status”).

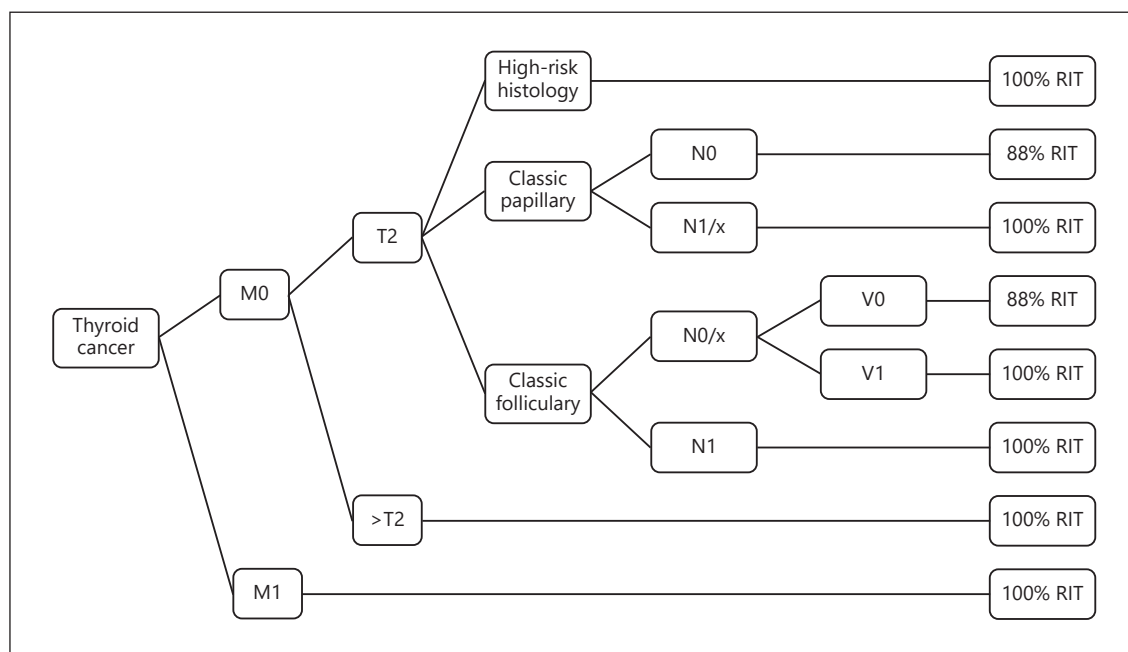


Fig. 1. Majority and full consensus for M1 and M0 \geq T2 (with 2 exceptions). M1, distant metastases; RIT, radioiodine therapy.

Table 1. Overview of the categories and the decision criteria mentioned within this analysis relevant for the decision for or against RIT

T	N	M	R	V	L	Histology	Extension	TG	Anti-TG	B-RAF
T1a	N0	M0	R0	V0	L0	Classic papillary	Intrathyroidal	Negative	Negative	Wild type
T1b	Nx	M1	R1	V1	L1	Classic follicular	Extrathyroidal	Positive	Positive	Mutation
T2	N1					Risk histology				
>T2										

TG, thyroglobulin; RIT, radioiodine therapy.

The 8th edition of the AJCC/TNM staging system was used. To preserve comparability, capsular invasion was combined with the extent of the tumour (“extension”), and capsular invasion was classified as extrathyroidal extension. Consensus and disagreement were analysed using the objective consensus methodology [20, 27]. Further decision criteria used were tumour foci, tumour extension, vascular invasion (“V status”), lymphatic invasion (“L status”), residual disease (“R status”), B-RAF mutation, as well as post-operative thyroglobulin (TG) and anti-TG levels.

Criteria mentioned only by 1 participant were excluded from the analysis [28]. Two centres used age and sex for decision-making or to postpone RIT in women in childbearing age. Another centre mentioned prior neck irradiation, while 1 centre decided on diagnostic RI uptake prior to the therapy decision. One centre considered besides the T status [29] the summed up size of all foci in multifocal disease. Furthermore, 1 centre stated as a condition “an advantageous risk situation where the therapy benefit outweighs the potential toxicity,” which was considered a universal criterion and not further represented in the decision analysis.

Centres provided specific treatment activities and recommendations for therapy preparation, i.e., stimulation with rhTSH versus thyroid hormone withdrawal (THW) for different combinations of parameters. For selected tumour stages representing low (pT1b N0 M0 resp. pT2 N0 M0) and high risk (pT3 N1a M0 resp. pT4 N1b M0 and pTx pNx M1 [bone]), the treatment activities were extracted from the decision trees and visualized (Fig. 4).

Results

The 8 participating members of the EANM thyroid committee 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 RIT could be grouped into 9 categories as shown in Table 1.

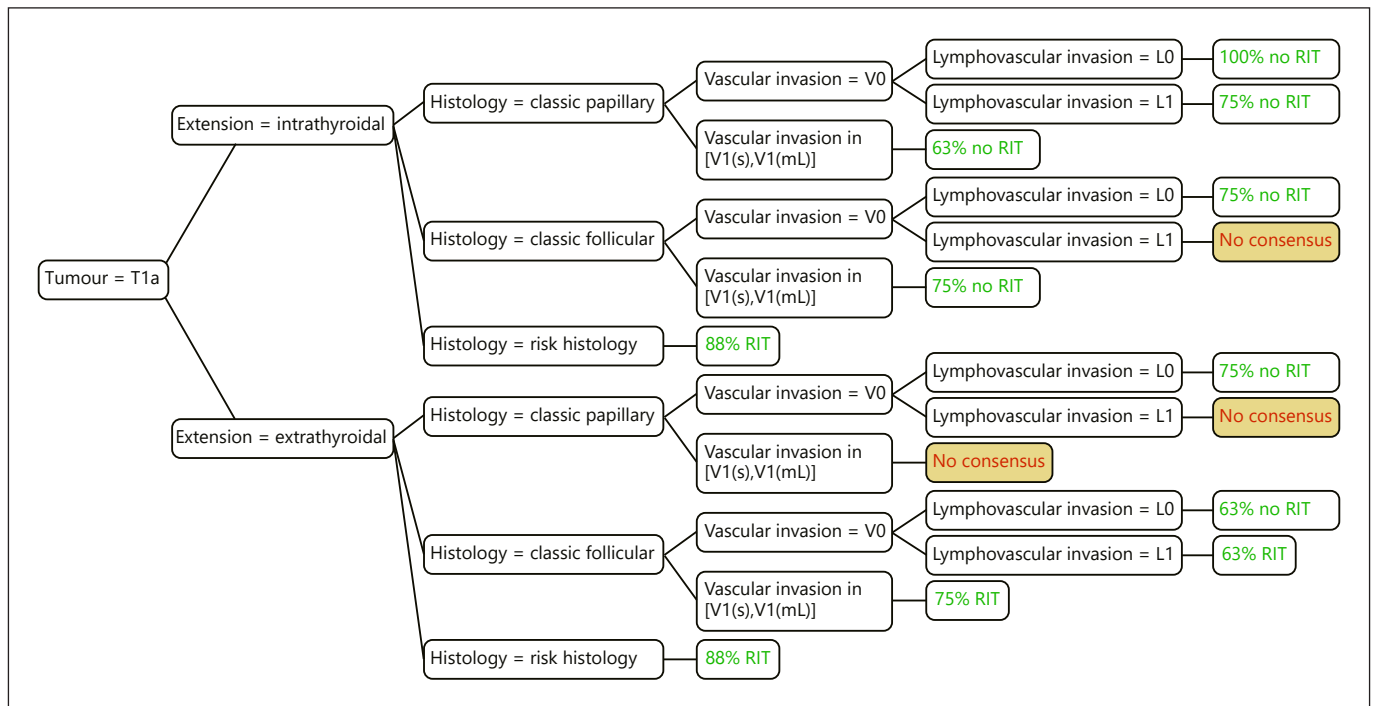


Fig. 2. Illustration of decisions for pT1a unifocal in the absence of the lymph node or distant metastases and negative TG/anti-TG levels as well as wild-type B-RAF. TG, thyroglobulin; RIT, radioiodine therapy.

Our analysis identified tumour characteristics for which all participating experts recommended RIT irrespective of any other attribute of the tumour: distant metastases, >T2 tumours, N1, or residual disease (Fig. 1).

For pT2 tumours with the absence of vascular invasion, 88% of the participating centres recommend RIT, and only 1 centre does not routinely recommend RIT. For vascular invasion, all centres recommend the use of RIT.

A full consensus for omitting RIT was found only for 1 situation: unifocal T1a tumours with classical papillary or follicular histology in the absence of any additional risk factors. If pT1a tumours feature additional characteristics, the recommendations become heterogeneous. For pT1a unifocal intrathyroidal tumours with papillary histology and positive L status, 75% of the experts did not recommend RIT, while for follicular histology, 50% omitted RIT. For positive V status, 63% did not recommend RIT for papillary histology. On the other hand, in V1 75% of experts applied RIT for follicular histology. In case of extrathyroidal disease and in the absence of other risk factors, 7 of 8 experts did not use RIT for papillary histology. Still a majority of 63% recommended RIT for follicular histology independent of L status. However,

75% prefer RIT for positive V status. In case of positive V or L status, no consensus was found for papillary histology (Fig. 2).

For pT1a tumours, one of the participating experts relies on B-RAF mutation status for the decision of recommending or omitting RIT, while 2 centres consider the post-operative TG and anti-TG levels. For T1b tumours with no evidence of metastases, the recommendation towards RIT is predominant, but the level of agreement is low, ranging from 63% to 88%, depending on other factors (Fig. 3).

RIT Activities/rhTSH versus THW

A significant variation in activities used for treatment was found among the experts. All experts recommend risk-adapted strategies. Some use more different amounts of activities than others. Patients classified as ATA low risk may be offered RIT with up to 3,700 MBq I-131 while not being considered for RIT at others centres. In intermediate or high-risk situations, treatment was recommended by all experts. However, activities of I-131 used differed considerably between 2,000 MBq I-131 and 7,400 MBq as shown in Figure 4. For metastatic disease (distant metastases, bone), activities as high as 10,000 MBq I-131

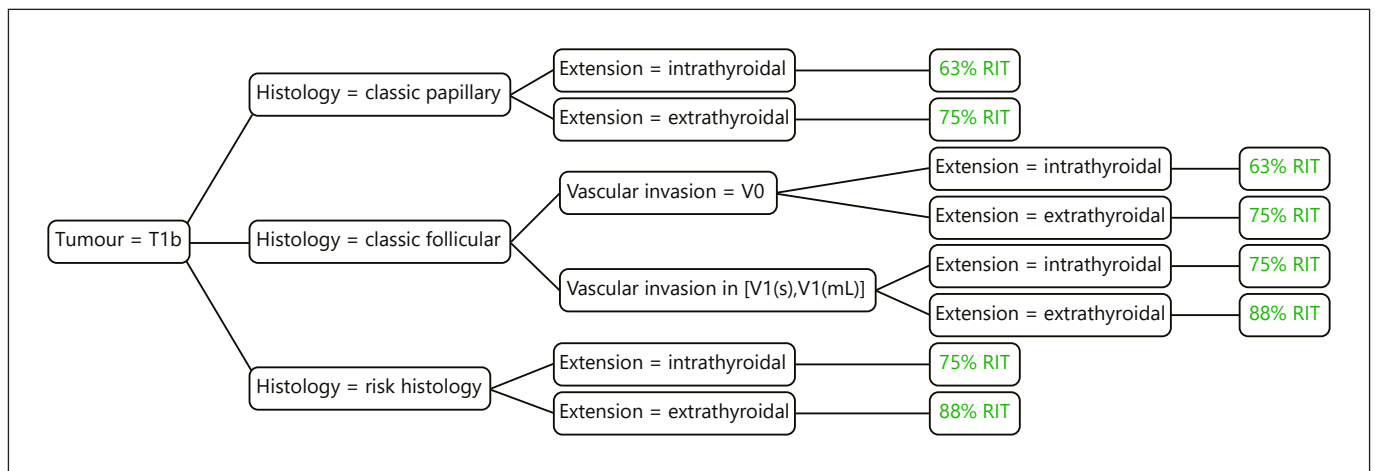


Fig. 3. Majority consensus for pT1b N0 M0. RIT, radioiodine therapy.

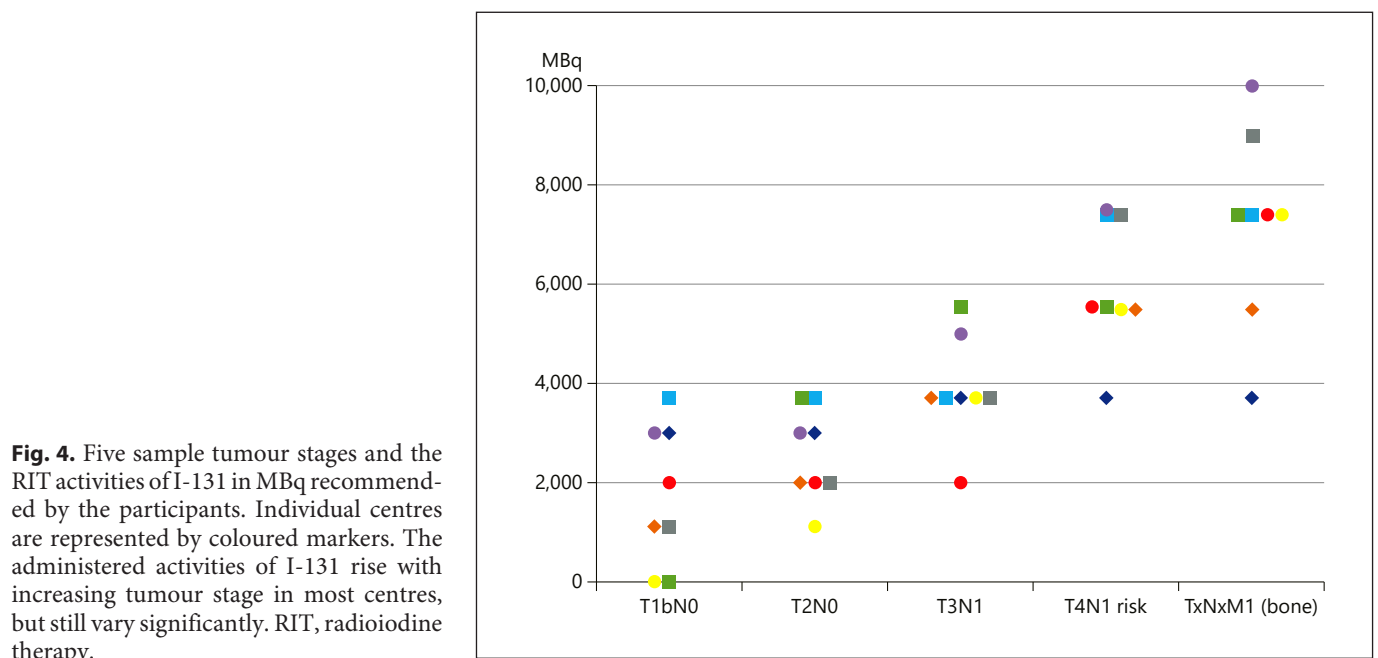


Fig. 4. Five sample tumour stages and the RIT activities of I-131 in MBq recommended by the participants. Individual centres are represented by coloured markers. The administered activities of I-131 rise with increasing tumour stage in most centres, but still vary significantly. RIT, radioiodine therapy.

were recommended by some experts. Three experts applied higher activities specifically in the setting of bone metastases.

The variation of activities administered may reflect that several centres apply the approach of variation in activities of radioiodine depending on the goal of the RIT: remnant ablation and adjuvant treatment versus treatment of known disease. This variance in RIT activities has recently been a consensus recommendation by the “Martinique conference” [30].

The recommendation for therapy preparation varies distinctly. While 3 experts recommend the use of rhTSH, 4 recommend THW. However, 1 expert stated to use THW for economical and not for medical reasons, where the use of THW of rhTSH depends on the type of insurance. While patients with private insurance are prepared with injections of rhTSH, patients with general insurance are prepared by THW.

A higher level of agreement was observed among European experts when compared to a previously published

analysis of Swiss centres [19]. In addition, the range of the activity administered (when RIT is recommended) is lower than in the national Swiss centres. E.g., activities administered for T4N1 risk ranges from 3,700 MBq to 7,400 MBq among European experts, while the Swiss centres apply 2,500 MBq–7,400 MBq.

Discussion

The similarities and differences determined by our analysis reflect the inconsistencies and uncertainties as a result of the current partially contradicting guidelines and recent publications. As already seen in the “Swiss study,” there are certain factors that consistently trigger the use of RIT: the presence of metastases, a primary tumour of pT3, and pT4 or residual disease. To the best of our knowledge, this is in line with all current guidelines. The same applies for the recommendation to refrain from RIT in pT1a tumours without additional risk factors [9, 10, 31].

The discrepancies in the in-between cases illustrate the ongoing debate in low- and intermediate-risk tumours [7, 32]. While the ATA and NCCN guidelines [33] suggest that ATA low-risk tumours are sufficiently treated by hemi-thyroidectomy, other former [10] and current guidelines [31] recommend RIT for certain situations that are considered low-risk according to ATA, e.g., pT1b tumours. The great variety of recommendations for pT1b tumours in our analysis reflects this discussion. The fact that a “high level of evidence” exists only for 2 out of 101 ATA 2015 recommendations [7, 9] might contribute to the limited acceptance of the ATA 2015 guidelines in the nuclear medicine community. On the other hand, the publication of the “Martinique principles” intends to overcome the controversies between the EANM and Society of Nuclear Medicine and Molecular Imaging (SNMMI) to the ATA an ETA [30] and may lead to alignment of treatment strategies.

While in the Swiss study B-RAF mutation status was mentioned among the factors used in daily routine when deciding whether to recommend radioiodine or not, this mutation was not taken into consideration among the European experts. In line with the Swiss centres also, TERT promoter mutations are either not tested routinely or not used in the decision-making process, although some data suggest a higher risk for patients with tumours featuring this mutation [34].

Interestingly, in analogy to the Swiss study, post-operative thyroglobulin levels did not play a role in the decision trees, although the measurement of post-operative

thyroglobulin is part of the mentioned guidelines. It is most likely that in daily routine, the decision for or against RIT is made within a few days after surgery, and post-operative thyroglobulin has not been reassessed yet.

It is likely that discrepancies in low-risk papillary thyroid cancer will be reduced in the future as further consensus articles are published [35]. However, it is noteworthy that most of these recommendations are not based on high-level evidence.

Additional evidence might be expected in the next years when the results of trials started in 2012 and 2013 are being awaited. The ESTIMABL2 and IoN trials (ClinicalTrials.gov identifier: NCT01837745 and ClinicalTrials.gov identifier: NCT01398085) are investigating the impact of rhTSH stimulated RIT with 1,100 MBq for low-risk DTC versus no RIT. With regard to patient preparation, the follow-up study of the ESTIMABL1 trial suggests that in patients with low-risk differentiated thyroid carcinoma who underwent RIT, there is no difference in recurrence with a median follow-up of 5 years, independent of the patient preparation (THW vs. rhTSH) [36].

In contrast to a national survey within the Swiss healthcare system providing a setting where universal insurance covers all treatment options for newly diagnosed thyroid cancer, the situation is somewhat different in other European countries. This becomes obvious as, e.g., in 1 centre the insurance status influences the way method of preparation for RIT (THW vs. rhTSH). However, the decision whether to apply RIT or not is – within Europe – probably not economically driven as RIT is a relatively inexpensive therapy.

The study was limited to nuclear medicine physicians. Although the decision whether to apply RIT or not is taken by an interdisciplinary tumour board at most centres, it will be interesting to compare our results with results collected from endocrinologists, surgeons (endocrine surgeons, head-and-neck surgeons, and general surgeons), or oncologists in the next step. We restricted our analysis to nuclear medicine specialists to identify and understand patterns within the nuclear medicine community.

Conclusion

Although the routine use of adjuvant RIT for low- to intermediate-risk DTC is not recommended by the current ATA guidelines, our analysis shows that among European Nuclear Medicine and thyroid experts, RIT is routinely recommended for selected low-risk tumours and most with intermediate risk. This reflects missing consensus be-

tween the ATA and EANM with regard to RIT for low to intermediate DTCs. Our analysis reveals that even between recognized experts in the field, there is variability in RIT treatment strategies for DTC. These findings underline the need for further studies with long-term follow-up and large patient cohorts to properly assess the value of adjuvant RIT in these low- to intermediate-risk DTC patients.

Statement of Ethics

This analyzes the participating centres for their treatment strategies. This information is derived directly from the clinical experts, and individual patient data were not accessed.

Conflict of Interest Statement

F.F., F.G.F., M.O., H.M., I.I., L.M., M.J., O.P.P., V.A., Z.S., and P.P.M. declare that they do not have a conflict of interest to declare related to this manuscript. G.L. received speaker honorarium from Roche Diagnostics, Genzyme-Sanofi, and Brahms GmbH. G.L. is also working as an advisor for Roche Diagnostics and Genzyme-Sanofi. P.M.P. is a section editor in *Oncology*.

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Author Contributions

F.F. is the principal investigator and designed the study, collected and analysed the data, and wrote the final version of the manuscript. F.G.F. evaluated the data, drafted the manuscript, and critically reviewed the final version. M.O. was involved in the data evaluation, co-drafted the manuscript, and critically reviewed the final version. G.L., H.M., I.I., L.M., M.J., P.P., and V.A. provided data for the study and critically reviewed the final version of the manuscript. P.P.M. co-designed the study, helped in evaluating the data, co-wrote the manuscript, and critically reviewed the final version.

Data Availability Statement

All original data are available upon request.

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