Individualized treatment of differentiated thyroid cancer: The value of surgery in combination with radioiodine imaging and therapy

A German position paper from Surgery and Nuclear Medicine

Individualisierte Behandlung von differenziertem Schilddrüsenkrebs: Der Wert der Operation in Kombination mit Radiojodbildgebung und -therapie

Ein deutsches Positionspapier aus der Chirurgie und Nuklearmedizin

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ABSTRACT

A consensus statement about indications for post-surgical radioiodine therapy (RIT) in differentiated thyroid cancer patients (DTC) was recently published by the European Thyroid Association (ETA) [1]. This publication discusses indications for RIT on the basis of an individual risk assessment. Many of the conclusions of this consensus statement are well founded and accepted across the disciplines involved. However, especially from the perspective of nuclear medicine, as the discipline responsible for indicating and executing RIT, some of the recommendations may require further clarification with regard to their compatibility with established best practice and national standards of care. Assessment of the indications for RIT is strongly dependent on the weighing up of benefits and risks. On the basis of longstanding clinical experience in nuclear medicine, RIT represents a highly specific precision medicine procedure of proven efficacy with a favorable side-

effect profile. This distinguishes RIT significantly from other adjuvant oncological therapies and has resulted in the establishment of this procedure as a usually well-tolerated, standard safety measure. With regard to its favorable risk/benefit ratio, this procedure should not be unnecessarily restricted, in the interest of offering reassurance to the patients. Both patients' interests and regional/national differences need to be taken into account. We would therefore like to comment on the recent consensus from the perspective of authors and to provide recommendations based on the respective published data.

ZUSAMMENFASSUNG

Die European Thyroid Association (ETA) hat vor Kurzem eine Konsenserklärung zu den Indikationen für eine postoperative Radiojodtherapie (RIT) bei Patienten mit differenziertem Schilddrüsenkrebs (DTC) veröffentlicht [1]. In dieser Veröffentlichung werden die Indikationen für eine RIT auf der Grundlage einer individuellen Risikobewertung erörtert. Viele der Schlussfolgerungen dieser Konsenserklärung sind gut begründet und werden von allen beteiligten Disziplinen akzeptiert. Insbesondere aus der Sicht der Nuklearmedizin, die für die Indikationsstellung und Durchführung der RIT verantwortlich ist, bedürfen einige der Empfehlungen jedoch einer weiteren Klärung im Hinblick auf ihre Vereinbarkeit mit bewährten Verfahren und nationalen Versorgungsstandards. Die Beurteilung der Indikationen für eine RIT ist stark von der Abwägung von Nutzen und Risiken abhängig. Auf der Grundlage der langjährigen klinischen Erfahrung in der Nuklearmedizin stellt die RIT ein hochspezifisches Verfahren der Präzisionsmedizin mit nachgewiesener Wirksamkeit und günstigem Nebenwirkungsprofil dar. Dies unterscheidet die RIT deutlich von anderen adjuvanten onkologischen Therapien und hat dazu geführt, dass sich dieses Verfahren als eine in der Regel gut verträgliche, sichere Standardmaßnahme etabliert hat. In Anbetracht des günstigen Nutzen-Risiko-Verhältnisses sollte dieses Verfahren nicht unnötig eingeschränkt werden, um den Patienten Sicherheit zu geben. Dabei müssen sowohl die Interessen der Patienten als auch regionale/nationale Unterschiede berücksichtigt werden. Wir möchten daher den aktuellen Konsens aus Sicht der Autoren kommentieren und Empfehlungen auf der Basis der jeweils veröffentlichten Daten geben.

Introduction

The treatment of thyroid cancer is a controversial field [2–7]. Data from prospective, evidence-based trials on long-term outcome with/without radioiodine therapy (RIT) are sparse and hard to obtain, because in order to yield clinically relevant results and to demonstrate the benefit of RIT, a follow-up of 10 years or more is generally needed. Thus, guidelines from several countries differ in their advice on how to treat patients with differentiated thyroid carcinoma best [2–7]. Several publications have raised the issue of relevant controversies [8–11]. The multidisciplinary approach to thyroid cancer care has resulted in the implementation of dedicated endocrine tumor boards in many specialized centers, recommending suitable therapy concepts for the individual patient on an interdisciplinary basis. This includes surgery, nuclear medicine, endocrinology, radiation therapy, pathology and other partners. For the development of consensus statements or guidelines, it seems advisable to discuss and also address regional and national differences in thyroid cancer care as well as epidemiological differences in populations worldwide. Any recommendation needs to be discussed with the patient who takes the final decision.

Although few developed countries have a persistent deficiency of iodine intake, Germany is still one of them [12] resulting in a relatively high prevalence of thyroid nodules. Taking into account the frequency of thyroid nodules in different age groups and demographic data, it is estimated that about 15 million persons or more are affected in Germany [9]. Only a small fraction of these nodules is malignant with varying estimations of one malignant nodule in 375 to 1000 benign thyroid nodules. Given the high number of autonomous and other benign thyroid nodules, diagnostic strategies and therapeutic recommendations in Germany differ from those of other countries. As an example, thyroid scintigraphy with pertechnetate is advised for patients with thyroid nodules larger than 1 cm in diameter to identify autonomous nodules as benign findings [14]. Nodules of under 1 cm are usually observed through follow-up examinations. Fine needle aspiration biopsy (FNAB) for nodules of less than 1 cm is recommended neither in Germany [15] nor anywhere else in Europe. Of note, no dramatic increase in papillary thyroid microcarcinomas (PTMC) has been observed in contrast to the steep increase reported in the literature from Asian countries but also – to a lesser extent – from the US [16]. To increase the pretest-likelihood for thyroid cancer, it is considered good practice in Germany to select nodules for FNAB by demonstration of hypofunctionality ("cold nodules") on scintigraphy in combination with suspicious ultrasound features. Regrettably, owing to the high frequency of thyroid nodules and/or the presence of multiple nodules in one patient, FNAB before surgery is frequently not performed in Germany. Yet despite considerable progress in reducing "diagnostic thyroid surgeries", a substantial fraction of operations is carried out mainly to rule out malignancy. A current analysis of a Germany surgery registry showed that among almost 18 000 patients with benign thyroid histology, 68 % had been referred for "exclusion of malignancy", and only 12 % of those had had a previous FNAC [17].

In Germany, about 7000 new cases (5040 women and 2192 men in 2017) of thyroid cancer are diagnosed each year and differentiated thyroid cancer accounts for more than 90 % of all thyroid cancers. The age-standardized mortality of thyroid cancer in Germany, which was initially high in comparison to other countries, approximately halved over the period 1995–2015. According to figures from the USA and Germany for 2015, the mortality of DTC is comparable at about 0.3 cases per 100 000.

However, the USA is one of the few countries worldwide with a mortality of thyroid carcinoma that has increased by about 25 % since the year 2000 [18].

The majority of patients undergoing thyroid surgery in Germany, just as in other iodine-deficient countries, have benign histopathological findings. From intraoperative frozen sections, it has recently been shown that the rate of completion surgeries could be considerably reduced [19]. According to Maneck et al., less than 9465 (15.2 %) out of 62 090 surgical operations assessed revealed a malignancy [20]. In contrast, taking the SEER (Surveillance, Epidemiology, and End Results) data into account, about 36 % of thyroid surgeries in the United States result in a DTC diagnosis, a frequency more than twice as high as that in Germany. Banach et al. published, that preoperative suspicion of thyroid carcinoma was present in 37 % of German but in 84 % of American patients [21].

In 2016, Haugen et al. published the guidelines of the American Thyroid Association (ATA), written predominantly by a group of North American thyroid experts [3]. Though their aim was to give advice on contemporary optimal care of patients with thyroid cancer, the guidelines had to be classified as S2 since neither a systematic literature search nor any evidence tables were available.

With European experts holding different views on this issue, a position paper was published in 2019 contrasting several aspects mainly with respect to the extent of surgery (lobectomy versus thyroidectomy for PTC ≤ 4 cm) and the potential need for completion thyroidectomy [6, 11]. Significant divergence involved ATA 2015's guidance regarding RIT. European panelists favored a wider use of postoperative radioiodine than did ATA 2015. Rationales included the modality's association with favorable patient outcomes and generally limited toxicity, and lack of high-quality evidence supporting a withholding of radioiodine therapy. European panelists also noted that the ATA 2015 risk-stratification system requires information sometimes unavailable in everyday practice [6].

The ATA guidelines introduced a dynamic risk model for recurrence based on histopathologic criteria and molecular analysis such as BRAF mutational status and recommended standard RIT after surgery only in high-risk patients. Low or intermediate risk groups should either not have radioiodine at all or should have radioiodine on a selective basis [3]. However, that recommendation has limited applicability, as it is not entirely clear from where the authors of the ATA guidelines derived the probability of tumor recurrence taken as the basis for their risk model. The issue was aggravated further when the 2022 European Thyroid Association (ETA) consensus statement adopted the ATA risk model without further elaboration and recommended that the decision for postoperative RIT should be taken based on initial prognostic indicators for thyroid cancer related death and risk of recurrence. Of note, the authors state that indeed, despite the inevitable body radiation exposure, the administration of a low activity of RAI has not been demonstrated to present a risk in terms of secondary cancer or leukemia, infertility and untoward pregnancy outcomes or other side effects.

In the following, we modify and comment on the recommendations made in the ETA consensus statement with a special focus on the use of radioiodine. Interdisciplinary evidence-based S3-guidelines for DTC are currently being developed in Germany, with the aim of providing specific guidance tailored to the national situation. These guidelines will provide information in much more detail than the position paper presented here by specialists in surgery and nuclear medicine.

RECOMMENDATION 1 (ETA CONSENSUS STATEMENT)

The decision for post-operative radioiodine therapy should be taken based on initial prognostic indicators for thyroid cancer related death and recurrence, including among others the surgical and pathological report and on the results of serum thyroglobulin measurements and neck ultrasonography obtained after surgery.

MODIFIED RECOMMENDATION 1

The decision to proceed with post-operative RIT should be based on the recommendation of an interdisciplinary tumor board incorporating initial prognostic indicators for thyroid cancer related death and recurrence, including not only the surgical and pathology report, and patient age but also the results of postoperative laboratory and imaging results. The patient should be involved in the decision-making process ("shared decision making").

RIT has many aspects that need to be considered both by the treating doctor and the patient during shared decision making [22]. One aspect is the treatment of occult disease as an adjuvant approach. Here, it is important to note that the frequency of lymph node metastases is quite high in thyroid cancer. On histopathologic workup, lymph node metastases are found in approximately 20–80 % of PTC patients [2, 23] and are increasingly likely to occur in higher T-stage tumors. However, even in PTMC frequencies of lymph node metastases of 35 % and 57 % have been reported [24, 25]. Prophylactic lymph node dissection is the gold standard to exclude metastatic lymph node involvement, but is performed only in certain constellations such as the presence of suspicious lymph nodes or other high risk factors. Furthermore, the probability of complications is higher with this procedure than with (stand-alone) thyroidectomy, and many patients with an incidental finding of thyroid cancer will not have a lymph-node dissection. Both post-therapeutic imaging after administration of RIT and pre-therapeutic imaging using radioactive isotopes of iodine provide a highly sensitive staging in this context and can help to select patients for removal of lymph nodes pre- or post RIT [26].

We do not agree with the authors of the ETA consensus statement that post-surgical nonstimulated Tg levels can be used independently in deciding whether to pursue therapeutic radioiodine administration, especially in patients assigned as low-risk category based on surgical pathology information. Campenni et al. reported in 570 low- and low-intermediate risk DTC patients that post-therapeutic radioiodine imaging including SPECT/CT identified 82 patients (14.4 %) who had metastases, 73 patients of

which (90.2 %) had nonstimulated Tg ≤ 1 ng/ml after surgery. Also, 44 patients (54 %) of 82 metastasized patients had a stimulated Tg ≤ 1 ng/ml [27].

Furthermore, diagnostic postoperative radioiodine imaging can provide important additional information. In a group of 320 thyroid cancer patients referred for postoperative RIT, Avram et al. showed that diagnostic imaging with ^{131}I including SPECT/CT after thyroid hormone withdrawal (THW) visualized regional metastases in 35 % and distant metastases in 8 % of the cases. TNM stage was changed by this imaging in 4 % of the younger and 25 % of the older patients [25]. In another study by Avram et al., imaging data as well as stimulated thyroglobulin levels measured at the time of diagnostic postoperative ^{131}I imaging provided information that altered the management of the patients in 29 % of cases when compared to the initial strategy based on surgical pathology information and clinical information by itself [28].

Another important aspect of RIT is the psychological impact in terms of assuring patients of their being free of disease with the prospect of retaining a good quality of life in the long term [29, 30]. The data published regarding the outcome of postoperative RIT in low-risk patients (combination of remnant ablation and adjuvant treatment) showed that patients in this category can be reassured of a complete treatment response. They also require a less intense follow-up and fewer imaging procedures [31]. Data published on DTC patients (including those in the low-risk category), who received RIT after surgery, showed that life expectancy is normal in these patients except for those with stage IV disease [32, 33]. Similar data with a sufficiently long follow-up in general but also for Germany specifically are, however, not available for a more restrictive use of radioiodine.

On the other hand, there is broad consensus that risk-adapted treatment of thyroid cancer is a desirable goal and patients should not be exposed to any unnecessary therapeutic procedures. The risk of metastatic spread and recurrence is highly variable in DTC, with most patients having a good prognosis. Patients should be informed and involved in shared decision-making, based not only on histopathology and thyroglobulin results, but also on postoperative radioiodine imaging and the individual need for safety/security [22].

RECOMMENDATION 2 (ETA CONSENSUS STATEMENT)

The use of I-131 therapy as adjuvant treatment or treatment of known disease is indicated for patients in the high risk of recurrence category or with known structural disease. In this setting, high activities (≥ 3700 MBq) of radioiodine are preferred over low activities.

MODIFIED RECOMMENDATION 2

The use of I-131 therapy as adjuvant treatment or treatment of known disease is indicated for patients in the high risk of recurrence category or with known structural disease. In this setting, high activities (≥ 3700 MBq) of radioiodine are preferred over low activities. Individual dosimetry may be considered.

We do agree with the authors of ETA consent in this respect. However, evidence is still lacking on whether a dosimetric approach is superior to a fixed dosing therapy. From a radiobiological point of view, higher activities are preferred over (fractionated) lower activities. Dosimetry with diagnostic postoperative radioiodine imaging helps to avoid exceeding organ-specific dose limits, especially in patients with renal impairment and diffuse lung metastases.

RECOMMENDATION 3 (ETA CONSENSUS STATEMENT)

In the intermediate-risk category*, RIT therapy may be indicated and should be tailored according to individual cases.

*patients with 1) microscopic invasion of tumor into the perithyroidal soft tissues; 2) aggressive histology (e. g., tall cell, hobnail variant, columnar cell carcinoma); 3) PTC with vascular invasion; 4) clinical N1 or > 5 pathologic N1 with all N1 < 3 cm in largest dimension; 5) multifocal papillary microcarcinoma with microscopic invasion of tumor into the perithyroidal soft tissues and BRAFV600E mutation (if known)

MODIFIED RECOMMENDATION 3

In the intermediate-risk category, RIT therapy is indicated.

In our view, there is a clear indication for adjuvant RIT therapy in the ATA intermediate risk group. Evidence from a large retrospective series of patients indicates that there is a benefit for patients, not only in terms of survival but also in terms of recurrence.

In 2008, Sawka et al. published a pilot review article on RIT therapy with a total of 28 publications. With regard to tumor-related mortality, a data pooling of 11 studies revealed a significant reduction from 3.9 % without to 2.5 % with RIT. With regard to recurrence-free survival, 5 studies with the largest number of patients (n = 3474) showed a considerable and significant reduction in risk from 24.2 % without RIT therapy to 12.5 % with RIT therapy. It should be emphasized that patients with a life expectancy of 10 or more years had a definite benefit from radioiodine therapy [34].

From 1998–2006 the National Cancer database, USA, contained 21 870 DTC patients with pT3 N0 M0 or pT1–3 N1 M0. Among 15 418 patients who were treated with radioiodine, there was a reduction in overall mortality by 29 % compared with 6452 patients who were not referred to radioiodine therapy. This advantage in favor of radioiodine therapy was found despite the remarkable fact that the patients who had radioiodine treatment suffered from more advanced disease: In the radioiodine group, 51 % of the patients showed multifocal disease versus 47 % in the non-radioiodine group. Both lymph node metastases (74 % versus 68 %) and R1 resections (19 % versus 15 %) were more frequent in the radioiodine group, respectively. To stress this fact, even despite the less favorable patient population, RIT was able to convert the pre-RIT situation in that group into a decreased post-treatment mortality [35].

Unlike the authors of the ETA consensus, we do not see the role of RIT in BRAF-mutated as controversial – but as clearly indicated. The literature cited by the authors does support their conclusion as well. The cited study by Sabra at al. was performed in 43 patients with DTC who were included because of initially known distant metastases; those authors come to the conclusion that tumor genotype does not influence the response to RIT therapy [36]. However, in the second publication cited where Liu et al. assessed recurrent DTC, the results cannot be readily transferred to the postoperative use of RIT [37]. Even in the setting of recurrent BRAF-mutated DTC (after initial RIT-therapy), 37 % of cases still showed uptake of RIT, indicating a potential benefit from RIT therapy. Besides, there is also published evidence to show that BRAF status does not negatively influence response to RIT therapy [38, 39].

We also disagree that postoperative thyroglobulin levels and neck ultrasound are sufficient to exclude metastatic DTC, especially in the intermediate-risk group (see comment to recommendation 1) [40].

RECOMMENDATION 4 (ETA CONSENSUS STATEMENT)

In low-risk patients§, the benefit of I-131 therapy is a matter of intensive scientific debate and the decision on whether to perform radioiodine therapy should be based on the presence of individual risk modifiers.

§ patients with 1) intrathyroidal PTC without vascular invasion, with or without small volume lymph node metastases (clinical N0 or ≤ 5 pathologic N1, all < 0.2 cm in largest dimension); 2) intrathyroidal encapsulated follicular variant of papillary thyroid cancer or intrathyroidal well differentiated follicular cancer with capsular or minor vascular invasion (< 4 vessels involved); 3) intrathyroidal papillary microcarcinomas that are either BRAF wild type or BRAF mutated (if known)

MODIFIED RECOMMENDATION 4

In low-risk patients, RIT therapy should be performed in patients at stages pT1b-2, N0–1; in stage pT1a RIT may be performed but under consideration of additional risk modifiers (e. g. multifocality, aggressive histology, BRAF mutation).

Here, we also refer to our comment on recommendation 1. Of note, we do not see a clear dichotomy between ablative and adjuvant RIT therapy, since the therapeutic administration of RIT always has an adjuvant component to treat metastatic disease, as well as a diagnostic intention (resulting in a more adequate tumor staging). Indeed, there has been an intense scientific debate over RIT in low-risk patients. In our view, large patient collectives and long follow-up periods are needed in order to assess the value of RIT in this category in terms of overall survival and recurrence free survival. Currently, there are two ongoing trials assessing the non-inferiority of no radioiodine treatment as compared to low dose RIT in a low-risk population: ESTIMABL2 and ION (NCT01837745 and NCT01398085). First results of ESTIMABL2 have been published. Here, the administration of 1.1 GB I-131 was compared to no RIT. In a first assessment with 3 years of follow-up, no difference in terms of recurrence rate in 776 patients was revealed by this study [41, 42]. Unfortunately, the patients are only followed for 5 years which, for data from the analysis of cancer registries, is too short according to Sawka et al. [34]. In our view, the activity of 1.1 GBq of I-131 is also too low for adjuvant treatment. The use of this activity is even controversial for the purpose of ablation (see comment on recommendation 6). The authors of the ETA consensus themselves state that “a tendency for larger groups and longer follow-up duration seems to be loosely associated with showing an advantage of giving RIT”. In our view, the data from retrospective series with very large patient collectives and a long follow-up are in favor of RIT even in a low-risk population and it is therefore not justified to generally withhold this treatment from these patients. Adam et al. showed that radioiodine therapy led to a significantly improved overall survival in 61 775 patients from the National Cancer Database with PTC diameters of 1.0–2.0 cm and 2.1–4.0 cm [43]. Attributing the average mortality to a value of 1.0, mortality decreased in the RIT group to a value of 0.77 (95 % CI 0.68–0.87) in stage pT1b and to a value of 0.86 (95 % CI 0.76–0.98) in stage pT2. The clinical benefit of RIT therapy was higher than the influence of the extent of the surgical resection.

In an assessment of the Surveillance, Epidemiology, and End Results (SEER) database over the years 1973–2009 with 61 049 patients, the omission of RIT increased disease-specific mortality. For patients in group pT2 N0 M0 and < 45 years of age, there was a significant increase of the hazard ratio for death of 1.3 in patients who had not received RIT ($p < 0.002$) [44]. In another study from Hong Kong with 855 patients recurrent-free survival increased from 82.5 % to 95 % after 10 years when including radioiodine in the therapeutic concept [45].

In addition, as mentioned in the comment to recommendation 1, posttherapeutic radioiodine imaging provides valuable information in terms of a highly specific and sensitive staging tool of great value for assuring the patient.

The authors of the ETA statement also clearly oppose RIT in papillary microcarcinoma (< 1 cm, uni- or multi-focal), in the absence of other higher-risk features. The cited study by Hänscheid et al. does not seem to address this topic at all [46]. The second publication mentioned reflects a joint statement of the ATA, EANM, SNMMI and ETA on controversies, consensus, and collaboration in the use of RIT in differentiated thyroid cancer [3]. A recommendation not to use RIT in tumors smaller than 1 cm is nowhere to be found in this consensus, but instead, it is mentioned that “some authors report a benefit of giving RIT even to patients with non-metastasized microcarcinomas, whereas other groups find no benefit.” In the light of this statement, it would seem justified to discuss not only the benefits but also the potential side effects of RIT in papillary microcarcinoma with the patient in the framework of shared decision-making; risk factors, such as i. e. multifocality, aggressive histology or nonincidental finding [47] should be weighted together with the patient’s expectations. In minimally invasive follicular thyroid cancer without vascular invasion, we see a limited value of RIT irrespective of the size due to

the good prognosis of this entity. However, recurrences were also seen in this group, most likely due to missed vessel infiltration.

The authors of the ETA consensus state that, even if no RIT is given after surgery, recurrences can be treated very successfully later on. However, no respective literature is cited in the consensus paper to support this hypothesis. In addition, and we ourselves are not aware of any larger retrospective or even prospective study in support of this approach.

RECOMMENDATION 5 (ETA CONSENSUS STATEMENT)

Recombinant human TSH during l-T4 treatment should be the preferred method of preparation for RIT administration.

MODIFIED RECOMMENDATION 5

Recombinant human TSH and thyroid hormone withdrawal (THW) can both be used for patient preparation for RIT therapy.

Recombinant human TSH (rhTSH) is an important development for the treatment of patients with thyroid carcinoma reducing symptoms of hypothyroidism and has provided patient benefit in terms of quality of life. Though usually well tolerated, clinical experience shows that some patients complain about muscle pain, fatigue, headache, malaise, sickness and vomiting after injections of rhTSH. The choice of preparation method (THW vs. rhTSH) strongly depends on the regionally pre-established treatment schemes as well as on patient and tumor stage specific factors. Previously published data reveals that in the setting of thyroid remnant ablation, rhTSH and THW stimulation are equivalent, because normal thyroid tissue usually shows a high expression of NIS and no longer intervals of TSH stimulation are necessary to reach an adequate uptake of RAI.

However, according to Hänscheid et.al., preparation for ablative RIT with THW can lead to higher radiation doses to the blood and the whole body as compared to rhTSH [46]. In this prospective randomized, multicentric international licensing study for rhTSH, THW was performed until a blood level of TSH reached 25 mU/L corresponding to approx. 4 weeks of thyroid hormone withdrawal [46]. In keeping with these results, Bacher et al. showed in a retrospective study in a larger number of patients that an increase in radiation absorbed dose is detectable in patients with an interval of hypothyroidism of 4 or more weeks between surgery and RIT. When a shorter time interval between 18–25 days was chosen, no difference in radiation absorbed dose was seen, though the two preparation regimens were equally effective [49]. In the setting of adjuvant treatment, which is the preferred treatment in many patients, the situation concerning the preferred method for preparation is more complex. The adjuvant aspect of RIT was first acknowledged, after the period during which the registration studies for rhTSH were performed. There is therefore no clear data available in the literature to recommend for or against a specific preparation method, and the registration of rhTSH covers its use in an adjuvant setting.

RECOMMENDATION 6 (ETA CONSENSUS STATEMENT)

Activities of 1110 MBq are equally effective as higher activities for ablation of presumably benign thyroid remnants.

MODIFIED RECOMMENDATION 6

Activities of 1–3.7 GBq may be chosen for ablative/adjuvant treatment, if there is no strong suspicion of residual tumor or of distant metastases. Activities of 1.85–3.7 GBq are favoured under the aspect of adjuvant RIT.

In our opinion, even when labeled as ablative, RIT always has adjuvant aspects, given the high prevalence of lymph node metastases [9, 51]. Even for the goal of ablation, the data does not, in our view, support a clear preference for 1.1 GBq I-131 over higher activities.

Two prospective randomized trials – **HiLo and ESTIMABL** – compared the effectiveness of "radioiodine ablation" with either hypothyroidism or recombinant TSH (rhTSH) using 1.1 GBq (30 mCi) or 3.7 GBq (100 mCi) of radioiodine [48, 50]. They came to the conclusion that the two methods of stimulation are equally effective and stated that 1.1 GBq is not inferior to 3.7 GBq I-131. Both studies included low-risk patients and excluded aggressive histologic subtypes. Of note, neither study questioned the use of radioiodine for the treatment of thyroid cancer.

In the **HiLo** study [48] there was a 6 % lower success rate in the rhTSH group with 1.1 GBq (84.3 %) in comparison to 3.7 GBq (90.2 %) of radioiodine, which resulted in twice as many second radioiodine treatments in the low risk versus high-risk group. A total of 21 patients (9.5 %) receiving low-dose radioiodine were given a subsequent second therapeutic activity, as compared with 9 patients (4.1 %) receiving high-dose radioiodine ($p = 0.02$). Second activities were more than 4 GBq of radioiodine. After a median follow-up of 13 months (with ≥ 24 months of follow-up in 21 % of patients), six cases with recurrence were detected (three in each radioiodine-dose group) according to a combination of results from ultrasonography, fine-needle aspiration, and computed tomography [48].

Another aspect appears noteworthy: In the **HiLo** study ^{99m}Tc-pertechnetate scintigraphy was performed prior to RIT therapy to visualize thyroid remnants and only 2.3 % of patients had a large remnant. This might explain why ablation was successful in 182 of 214 patients (85.0 %) in the group receiving low-dose radioiodine versus 184 of 207 patients (88.9 %) in the group receiving the high therapeutic activity.

In the **ESTIMABL** study [50], persistent disease after surgery was identified in 27/752 patients (3.6 %) through the use of post-ablation total-body scanning (14 patients), post-ablation total-body scanning and neck ultrasonography (8 patients), or neck ultrasonography only (5 patients). It is one of the tasks of nuclear medicine to identify this small group of patients who require advanced therapeutic skills for treatment of persistent disease.

The authors of the ETA consensus correctly cite a recent German publication showing a higher DTC-related mortality in low-and high-risk patients treated with low activities at initial RIT (≤ 2 GBq. I-131) when patients were at least 45 years of age at diagnosis, as well as a higher recurrence rate in older high-risk patients without distant metastases [33]. From our point of view, the treatment activity in this ablative/adjuvant setting should be adapted according to individual risk modifiers including postoperative scintigraphic imaging (see comment on recommendation 1 and 7).

RECOMMENDATION 7 (ETA CONSENSUS STATEMENT)

Whenever a decision to perform post-operative RIT therapy needs to be taken, a diagnostic scan is not routinely required.

MODIFIED RECOMMENDATION 7

A postoperative diagnostic functional scan can be helpful as it has been shown to allow individualized patient management.

We are not certain what the authors of the ETA consensus mean by "Whenever a decision to perform post-operative RIT needs to be taken". A decision, for or against a distinct diagnostic and/or therapeutic approach, has always to be made. However, we assume that the authors are not in favor of a diagnostic functional scan prior to RIT therapy. No statement on how to proceed, if RIT is NOT performed, is to be found anywhere in the consensus.

As mentioned in the comment on recommendation 1, postoperative functional imaging using radioisotopes may change the postoperative clinical management prior to therapeutic RIT administration [51]. Functional imaging is an option to further stratify patients into groups such as those in need of additional lymph node dissection owing to pronounced lymph node involvement, those requiring a higher radioiodine activity, especially in the presence of detectable distant metastases, or those needing lower RIT activities in the case of non-detectable tumor manifestations with minimal thyroid remnants. As mentioned in the ETA consensus, histological information as well as thyroglobulin levels and ultrasound can also be used in this context, although their levels of sensitivity are significantly limited. Moreover, in patients with known persistent disease, diagnostic radioiodine imaging allows subsequent RIT therapy to be tailored through dosimetry. Using $^{123}I/^{124}I$ or even ^{99m}Tc (as used in a major phase III trial [48]), stunning, which is mentioned as a limitation in the consensus, may be reduced or even prevented. Stunning itself is the subject of intense debate. ^{123}I, which avoids this phenomenon, is readily available in Germany and most countries within Europe, as is ^{99m}Tc. In contrast, ^{124}I is limited to just a few specialist centers.

RECOMMENDATION 8 (ETA CONSENSUS STATEMENT)

A low-iodine diet may be prescribed but its utility is not demonstrated unequivocally. Any iodine-containing drug should be avoided.

MODIFIED RECOMMENDATION 8

A low-iodine diet should be followed for two weeks prior to RIT. Iodine-containing drugs should be avoided.

Avoidance of high stable iodine levels reduces the transport of iodine into thyroid cells significantly, which is important for minimizing interference with RIT uptake. We also consider this diet to be a minor burden for patients in Germany. A study conducted by Pluijmen et al. in 120 patients showed that a low-iodine diet decreased the 24-h urinary iodine excretion by 83 %; at the same time radioiodine uptake in thyroid remnants increased by 65 % ($p < 0.001$) as compared to controls. The efficacy of RIT treatment was found to be better in the low-iodine group with a successful ablation in 65 % compared to 48 % patients in the control arm ($p < 0.001$) [52]

Summary

DTC is the most common endocrine malignancy with an increasing incidence globally over the last 30 years. The standard treatment strategy for DTC patients is a multidisciplinary approach with surgery and RIT as key components of therapy. The authors of this publication aim to provide guidance in a controversial field, based on available literature. Special controversy exists in the use of radioiodine; the authors want to show its clinical usefulness in the intermediate and low-risk groups. A risk-stratified and individualized approach is highly advisable, which should integrate the surgical procedure(s) performed, the results from histopathology, and functional imaging as well as post-operative laboratory values including thyroglobulin levels. Integration of diagnostic functional/radioiodine imaging may be advisable in order to further individualize patient management. Benefits and also risks of RIT have to be weighed against each other. Here, it is important to be aware that RIT is not readily comparable to other systemic treatments in the field of oncology, as it has comparatively few side effects and also has a diagnostic, patient-reassuring component. The results of further prospective trials (ESTIMABL 2, IoN, CLEARAD) are expected. However, due to their limitation in terms of patient numbers, duration of follow-up and potential biases arising from differences in regional iodine supply and national standards of care, the results may be of only limited value for the situation in Germany and potentially for other countries in Europe. In contrast to the US, the disease-specific mortality is decreasing in Germany

and a way needs to be found to decrease treatment intensity without, on the other hand, risking under-treatment. In a field rife with diverging opinions and conflicting study results, shared decision-making with the patient becomes even more important. Further guidance can be expected from the joint EANM/SNMMI practice guidelines on nuclear medicine evaluation and therapy of DTC, soon to be published, as well as the German S3-guidelines on DTC.

Conflict of Interest

Alexander Drzezga:
Research support: Siemens Healthineers, Life Molecular Imaging, GE Healthcare, AVID Radiopharmaceuticals, SOFIE, Eisai
Speaker Honorary/Advisory Boards: Siemens Healthineers, Sanofi, GE Healthcare, Biogen, Novo Nordisk, Invicro, Novartis/AAA
Stock: Siemens Healthineers, Lantheus Holding
Patents: Patent pending for 18F-PSMA7 (PSMA PET imaging tracer).
Ken Herrmann:
Personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, personal fees from Aktis Oncology, personal fees from Theragnostics, personal fees from Pharma15, outside the submitted work.
Michael C Kreißl: Bayer Healthcare: advisory board, event sponsoring; Eisai: advisory board, event sponsoring, talks; Exelixis: advisory bord, talk; GE Healthcare: talks, event sponsoring, research funding; Ipsen: talks, event sponsoring, travel funding, advisory bord; Takeda: talks; SanofiGenzyme: talks, travel, research funding; Siemens: event sponsoring; Curium: event sponsoring.

References

[1] Pacini F, Führer D, Elisai R et al. ETA-Konsenserklärung 2022: Was sind die Indikationen für eine postoperative Radiojodtherapie bei differenziertem Schilddrüsenkrebs? Eur Thyroid J 2022 – im Druck –

[2] Perros P, Boelaert K, Colley S et al. Guidelines for the management of thyroid cancer. Klinische Endokrinologie 2014; 81 (Suppl. 1): 1–122. doi:10.1111/cen.12515

[3] Haugen BR, Alexander EK, Bible KC et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid: official journal of the American Thyroid Association 2016; 26: 1–133. doi:10.1089/thy.2015.0020

[4] Zerdoud S, Giraudet AL, Leboulleux S et al. Radioaktive Jodtherapie, molekulare Bildgebung und Serum-Biomarker bei differenziertem Schilddrüsenkrebs: Leitlinien 2017 der französischen Gesellschaften für Nuklearmedizin, Endokrinologie, Pathologie, Biologie, endokrine Chirurgie und Kopf- und Halschirurgie. Ann Endocrinol (Paris) 2017; 78: 162–175. doi:10.1016/j.ando.2017.04.023

[5] Lamartina L, Grani G, Durante C et al. Follow-up of differentiated thyroid cancer – what should (and what should not) be done. Nature Reviews 2018; 14: 538–551

[6] Luster M, Aktolun C, Amendoeira I et al. European Perspective on 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Proceedings of an Interactive International Symposium Thyroid; 2019; 29: 7–26

[7] Tuttle RM, Ahuja S, Avram AM et al. Controversies, Consensus, and Collaboration in the Use of (131)I Therapy in Differentiated Thyroid Cancer: Eine gemeinsame Erklärung der American Thyroid Association, der European Association of Nuclear Medicine, der Society of Nuclear Medicine and Molecular Imaging und der European Thyroid Association. Thyroid: official journal of the American Thyroid Association 2019; 29: 461–470. doi:10.1089/thy.2018.0597

[8] Dietlein M, Verburg FA, Luster M et al. Man sollte nicht nur lesen, was man glaubt: das fast unlösbare Problem der Erstellung wirklich objektiver, evidenzbasierter Leitlinien für die Behandlung von differenziertem Schilddrüsenkrebs. Europäische Zeitschrift für Nuklearmedizin und molekulare Bildgebung 2011; 38: 793–798. doi:10.1007/s00259-011-1728-x

[9] Schmidt M, Gorges R, Drzezga A et al. A Matter of Controversy: Ist die Radiojodtherapie F avorable in differentiated Thyroid Carcinoma? J Nucl Med 2018; 59: 1195–1201. doi:10.2967/jnumed.117.191338

[10] Verburg FA, Aktolun C, Chiti A et al. 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. European journal of nuclear medicine and molecular imaging 2016; 43: 1001–1005. doi:10.1007/s00259-016-3327-3

[11] Luster M, Aktolun C, Amendoeira I et al. European Perspective on 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Proceedings of an Interactive International Symposium. Thyroid: official journal of the American Thyroid Association 2019; 29: 7–26. doi:10.1089/thy.2017.0129

[12] Zimmermann MB, Andersson M. GLOBAL ENDOCRINOLOGY: Global perspectives in endocrinology: coverage of iodized salt programs and iodine status in 2020. Europäische Zeitschrift für Endokrinologie/European Federation of Endocrine Societies 2021; 185: R13–R21. doi:10.1530/EJE-21-0171

[13] Schicha H, Hellmich M, Lehmacher W et al. [Sollten sich alle Patienten mit Schilddrüsenknoten > oder = 1 cm einer Feinnadelaspirationsbiopsie unterziehen?]. Nuklearmedizin 2009; 48: 79–83. doi:10.3413/nukmed-0313

[14] Dietlein M, Eschner W, Grunwald F et al. [Verfahrensrichtlinien zur Radiojodtherapie des differenzierten Schilddrüsenkarzinoms. Version 4]. Nuklearmedizin 2016; 55: 77–89

[15] Feldkamp J, Fuhrer D, Luster M et al. Fine Needle Aspiration in the Investigation of Thyroid Nodules. Deutsches Aerzteblatt international 2016; 113: 353–359. doi:10.3238/arztebl.2016.0353

[16] Vaccarella S, Franceschi S, Bray F et al. Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. The New England Journal of Medicine 2016; 375: 614–617. doi:10.1056/NEJMp1604412

[17] Bartsch DK, Dotzenrath C, Vorlander C et al. Aktuelle Praxis der Chirurgie bei gutartiger Struma – Eine Analyse des prospektiven DGAV StuDoQ|Thyroid-Registers. J Clin Med 2019; 8. doi:10.3390/jcm8040477

[18] WHO/IARC Krebs in fünf Kontinenten. https://ci5.iarc.fr/CI5plus/Default.aspx

[19] Staubitz JI, Elmrich I, Musholt PB et al. Gezielter Einsatz der intraoperativen Schnellschnittanalyse senkt die Häufigkeit der kompletten Thyreoidektomie. BJS Open 2021; 5. doi:10.1093/bjsopen/zraa058

[20] Maneck M, Dotzenrath C, Dralle H et al. [Fallzahlen und Komplikationen nach Schilddrüsenoperationen in Deutschland: eine Analyse der Routinedaten von 48387 AOK-Patienten]. Chirurg 2021; 92: 40–48. doi:10.1007/s00104-020-01191-x

[21] Banach R, Bartes B, Farnell K et al. Results of the Thyroid Cancer Alliance international patient/survivor survey: Psychosoziale/informationelle Unterstützungsbedürfnisse, Behandlungsnebenwirkungen und internationale Unterschiede in der Versorgung. Hormones (Athens) 2013; 12: 428–438. doi:10.1007/BF03401308

[22] Eilsberger F, Luster M, Reiners C. Shared Decision Making for Radioiodine Therapy and the Actual Pattern of Care in Intermediate-Risk Differentiated Thyroid Carcinoma. Front Nucl Med 2022. doi:10.3389/fnume.2021.797522

[23] Pereira JA, Jimeno J, Miquel J et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Chirurgie 2005; 138: 1095–1100, Diskussion 1100-1091 doi:10.1016/j.surg.2005.09.013

[24] Gallicchio R, Giacomobono S, Capacchione D et al. Sollten Patienten mit Resten von Schilddrüsenmikrokarzinomen wirklich nicht mit Jod-131-Ablation behandelt werden? Endocrine 2013; 44: 426–433. doi:10.1007/s12020-013-9935-9

[25] Avram AM, Fig LM, Frey KA et al. Preablation 131-I scans with SPECT/CT in postoperative thyroid cancer patients: what is the impact on staging? The Journal of clinical endocrinology and metabolism 2013; 98: 1163–1171. doi:10.1210/jc.2012-3630

[26] Avram AM, Zukotynski K, Nadel HR et al. Management von differenziertem Schilddrüsenkrebs: Der Standard der Behandlung. J Nucl Med 2021. doi:10.2967/jnumed.121.262402

[27] Campenni A, Giovanella L, Pignata SA et al. Nicht nachweisbare oder niedrige (<1 ng/ml) postoperative Thyreoglobulinwerte schließen Metastasen bei Patienten mit differenziertem Schilddrüsenkrebs im Frühstadium nicht aus. Oncotarget 2018; 9: 17491–17500. doi:10.18632/oncotarget.24766

[28] Avram AM, Esfandiari NH, Wong KK. Preablation 131-I scans with SPECT/CT contribute to thyroid cancer risk stratification and 131-I therapy planning. J Clin Endocrinol Metab 2015; 100: 1895–1902. doi:10.1210/jc.2014-4043

[29] Taieb D, Baumstarck-Barrau K, Sebag F et al. Heat-related quality of life in thyroid cancer patients following radioiodine ablation. Health Qual Life Outcomes 2011; 9: 33. doi:10.1186/1477-7525-9-33

[30] van Velsen EFS, Massolt ET, Heersema H et al. Longitudinal analysis of quality of life in patients treated for differentiated thyroid cancer. European journal of endocrinology/European Federation of Endocrine Societies 2019; 181: 671–679. doi:10.1530/EJE-19-0550

[31] Verburg FA, Mader U, Giovanella L et al. Low or undetectable Basal Thyroglobulin Levels Obviate the Need for Neck Ultrasound in Differentiated Thyroid Cancer Patients After Total Thyroidectomy and (131)I Ablation. Thyroid 2018; 28: 722–728. doi:10.1089/thy.2017.0352

[32] Maier TM, Schober O, Gerss J et al. Differentiated thyroid cancer patients more than 60 years old show paradoxically an increased life expectancy. J Nucl Med 2015; 56: 190–195. doi:10.2967/jnumed.114.150284

[33] Verburg FA, Mader U, Reiners C et al. Long-term survival in differentiated thyroid cancer is worse after low-activity initial post-surgical 131I therapy in both high and low-risk patients. J Clin Endocrinol Metab 2014; 99: 4487–4496. doi:10.1210/jc.2014-1631

[34] Sawka AM, Brierley JD, Tsang RW et al. Eine aktualisierte systematische Übersichtsarbeit und ein Kommentar zur Untersuchung der Wirksamkeit der Ablation von radioaktiven Jodresten bei gut differenziertem Schilddrüsenkrebs. Endocrinol Metab Clin North Am 2008; 37: 457–480, x. doi:10.1016/j.ecl.2008.02.007

[35] Ruel E, Thomas S, Dinan M et al. Adjuvante Therapie mit radioaktivem Jod ist mit einem verbesserten Überleben für Patienten mit papillärem Schilddrüsenkrebs mit mittlerem Risiko verbunden. The Journal of clinical endocrinology and metabolism 2015; 100: 1529–1536. doi:10.1210/jc.2014-4332

[36] Sabra MM, Dominguez JM, Grewal RK et al. Clinical outcomes and molecular profile of differentiated thyroid cancers with radioiodine-avid distant metastases. The Journal of clinical endocrinology and metabolism 2013; 98: E829–E836. doi:10.1210/jc.2012-3933

[37] Liu J, Liu R, Shen X et al. The Genetic Duet of BRAF V600E and TERT Promoter Mutations Robustly Predicts Loss of Radioiodine Avidity in Recurrent Papillary Thyroid Cancer. J Nucl Med 2020; 61: 177–182. doi:10.2967/jnumed.119.227652

[38] Li J, Liang J, Zhao T et al. Noninferior response in BRAF(V600E) mutant nonmetastatic papillary thyroid carcinoma to radioiodine therapy. European journal of nuclear medicine and molecular imaging 2016; 43: 1034–1039. doi:10.1007/s00259-015-3305-1

[39] Li J, Yang T, Zhao T et al. Clinical Outcome of Radioiodine Therapy in Low-intermediate Risk Papillary Thyroid Carcinoma with BRAF(V600E) Mutation. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2016; 38: 346–350. doi:10.3881/j.issn.1000-503X.2016.03.019

[40] Giovanella L, Ceriani L, Trimboli P. Letter to the Editor: "Postoperative Thyroglobulin and Neck Ultrasound in the Risk Restratification and Decision to Perform 131I Ablation". The Journal of clinical endocrinology and metabolism 2017; 102: 1783–1784. doi:10.1210/jc.2017-00206

[41] Leboulleux S, Bournaud C, Chougnet CN et al. Estimabl2: Ist eine Radiojodablation bei Patienten mit differenziertem Schilddrüsenkrebs (DTC) mit niedrigem Risiko erforderlich? Results From the French Randomized Phase III Prospective Trial on 776 Patients (NCT 01837745). Zeitschrift der Endokrinen Gesellschaft 2021; 5: A875–A875. doi:10.1210/jendso/bvab048.1788

[42] Leboulleux S, Bournaud C, Chougnet CN et al. Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer. N Engl J Med 2022; 386: 923–932. doi:10.1056/NEJMoa2111953

[43] Adam MA, Pura J, Gu L et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61 775 patients. Ann Surg 2014; 260 (4): 601–605. doi:10.1097/SLA.0000000000000925

[44] Orosco RK, Hussain T, Brumund KT et al. Analysis of age and disease status as predictors of thyroid cancer-specific mortality using the Surveillance, Epidemiology, and End Results database. Thyroid: official journal of the American Thyroid Association 2015; 25: 125–132. doi:10.1089/thy.2014.0116

[45] Chow SM, Yau S, Kwan CK et al. Local and regional control in patients with papillary thyroid carcinoma: specific indications of external radiotherapy and radioactive iodine according to T and N categories in AJCC 6th edition. Endocr Relat Cancer 2006; 13: 1159–1172. doi:10.1677/erc.1.01320

[46] Hänscheid H, Lassmann M, Luster M et al. Jod-Biokinetik und Dosimetrie in der Radiojodtherapie des Schilddrüsenkrebses: Verfahren und Ergebnisse einer prospektiven internationalen kontrollierten Studie zur Ablation nach rhTSH oder Hormonentzug. J Nucl Med 2006; 47: 648–654

[47] Mehanna H, Al-Maqbili T, Carter B et al. Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21 329 person-years of follow-up. The Journal of clinical endocrinology and metabolism 2014; 99: 2834–2843. doi:10.1210/jc.2013-2118

[48] Mallick U, Harmer C, Yap B et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. The New England Journal of Medicine 2012; 366: 1674–1685. doi:10.1056/NEJMoa1109589

[49] Bacher R, Hohberg M, Dietlein M et al. Thyroid Uptake and Effective Half-Life of Radioiodine in Thyroid Cancer Patients at Radioiodine Therapy and Follow-Up Whole-Body Scintigraphy Either in Hypothyroidism or Under rhTSH. J Nucl Med 2019; 60: 631–637. doi:10.2967/jnumed.118.217638

[50] Schlumberger M, Catargi B, Borget I et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. The New England Journal of Medicine 2012; 366: 1663–1673. doi:10.1056/NEJMoa1108586

[51] Avram AM, Zukotynski K, Nadel HR et al. Management of Differentiated Thyroid Cancer: Der Standard der Behandlung. J Nucl Med 2022; 63: 189–195. doi:10.2967/jnumed.121.262402

[52] Pluijmen MJ, Eustatia-Rutten C, Goslings BM et al. Auswirkungen einer jodidarmen Ernährung auf die postoperative Radiojodidablationstherapie bei Patienten mit differenziertem Schilddrüsenkarzinom. Clin Endocrinol (Oxf) 2003; 58: 428–435. doi:10.1046/j.1365-2265.2003.01735.x

Please note: this article was changed according to the correction from 27.04.2022.