CONSENSUS STATEMENT

2022 ETA Consensus Statement: What are the indications for post-surgical radioiodine therapy in differentiated thyroid cancer?

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Abstract

Modern use of post-operative radioactive iodine (RAI) treatment for differentiated thyroid cancer (DTC) should be implemented in line with patients’ risk stratification. Although beneficial effects of radioiodine are undisputed in high-risk patients, controversy remains in intermediate-risk and some low-risk patients. Since the last consensus on post-surgical use of RAI in DTC patients, new retrospective data and results of prospective randomized trials have been published, which have allowed the development of a new European Thyroid Association (ETA) statement for the indications of post-surgical RAI therapy in DTC. Questions about which patients are candidates for RAI therapy, which activities of RAI can be used, and which modalities of pre-treatment patient preparation should be used are addressed in the present guidelines.

Introduction

Differentiated thyroid cancer (DTC) accounts for more than 90% of all thyroid cancers. Over the last decades, an increasing incidence of DTC, mainly due to cancers of papillary histology, has been reported in many countries in- and outside of Europe (1, 2). This increase is largely attributable to a better detection of small papillary thyroid carcinomas (PTC), as a result of screening bias (non-selective use of neck ultrasound and fine needle aspiration cytology) (3). Thus, about 70–80% of thyroid carcinomas detected nowadays have PTC with an excellent long-term prognosis for whom overtreatment should be avoided.

Unfortunately, for many years the management of thyroid cancer has been based on retrospective studies which may be biased in many respects. Nowadays, whenever available we should rely on prospective studies which are feasible, as demonstrated by several trials (4, 5, 6, 7).

Definition of RAI therapy

After total thyroidectomy, radioactive iodine (RAI) therapy can be administered to patients with DTC for various indications.
The non-descript colloquial use of the word ‘ablation’ has thus far frustrated a constructive scientific dialogue. While it has generally been recognized that the first administered activity of RAI after thyroidectomy can be used in attempts to destroy (first) presumably benign residual thyroid tissue, (second) suspected but not identified remaining disease, and/or (third) known residual or recurrent disease; a precise nomenclature to describe these three important goals has not been widely accepted (8). In a common proposal between the European Thyroid Association (ETA), American Thyroid Association (ATA), European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI), it is suggested to adopt a nomenclature that uses ‘RAI therapy’ as the broad term that encompasses the three primary goals associated with an administered activity of RAI: (a) remnant ablation, (b) adjuvant treatment or (c) treatment of known disease (9).

In this context, remnant ablation refers to the use of RAI to destroy post-operatively remaining, presumably benign residual thyroid tissue to facilitate follow-up studies (such as serum thyroglobulin and RAI imaging).

Within the context of thyroid cancer care, adjuvant therapies can be defined as I-131 therapy after surgical resection of all known primary tumor tissue and metastatic foci in an effort to destroy subclinical microscopic tumor deposits that may or may not be present. The goals of adjuvant therapy are to improve disease-specific survival and disease-free survival (9).

Treatment of known disease refers to the goal of destroying persistent or recurrent DTC foci with RAI in order to improve progression free, disease-specific and overall survival. It can be given either with curative or palliative intent (9).

After total thyroidectomy, the size of normal, presumably benign remnants is usually small, resulting in very low or frequently even undetectable serum thyroglobulin (Tg) levels (at least in the hands of large volume surgeons) on levothyroxine (LT4) treatment. In these cases, particularly in low-risk patients, the goal of remnant ablation is already achieved following the surgical procedure alone just by the surgical procedure, and thus, there is no rationale to perform RAI ablation (10, 11). Currently, even without post-operative RAI therapy most patients can be followed up with serum Tg on LT4 treatment: an undetectable level is reassuring as well as a low but detectable level. In the latter case, the trend of serum Tg over time should be monitored: a declining or a stable Tg is reassuring, whereas an increase should lead to imaging in order to localize and treat the disease and possibly RAI therapy (8).

It is apparent that remnant ablation is aimed to simplify follow-up in any patient regardless of his/her specific risk, while adjuvant treatment is aimed to reduce disease recurrence and cause-specific mortality (10). Nowadays, the large majority of thyroid cancer patients have a low risk of recurrence after complete surgery and an even smaller risk of thyroid cancer related death, and careful examinations of patients’ outcome suggests that the use of post-surgical RAI ablation may be tailored according to a risk-based approach. This is even more relevant in view of changes in DTC management, preceding a decision on RAI therapy, taking a de-escalating approach with increasing use conservative DTC surgery (lobectomy rather than total thyroidectomy), changes in DTC nomenclature, for example, NIFTP and the concept of ‘active surveillance’ in (very) low-risk PTC (8, 12).

Indeed, despite the inevitable body radiation exposure, the risk of the administration of a low activity of RAI has not been demonstrated in terms of secondary cancer or leukemia, infertility and untoward pregnancy outcomes or other side effects, but, as this is the rule for any treatment modality, expected benefits are warranted to justify its administration (13, 14). In the field of oncology benefits are defined as improvement of overall survival or disease-free survival and quality of life (15).

This European Thyroid Association (ETA) Consensus Statement aims to deliver rational recommendations for the indications of post-operative RAI therapy with its various goals. In particular, we have addressed the issues of which patients are candidates for which form of RAI therapy, which activities of RAI can be used in each scenario and which modalities of preparation should be used. However, this Consensus Statement is mostly based on retrospective studies and biases cannot be excluded, in particular in the selection of patients. In fact, the only way to scientifically compare two treatment modalities and to exclude biases is to perform randomized prospective studies, as such studies are clearly feasible, as already mentioned (4, 5, 6, 7).

Risk stratification to assess the need for post-operative RAI administration

Recommendation 1: The decision for post-operative RAI 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 Tg measurements and neck ultrasonography obtained after surgery.

The expected benefit of post-operative RAI therapy depends on the individual risk of the patient (Table 1).

The 8th edition of the TNM classification individualizes patients at low risk of thyroid cancer-related death (<2%) who represent the large majority of DTC patients and a small subgroup of patients (5–10%) for whom the risk is higher (16).

The risk of persistent or recurrent disease is indeed higher than the risk of cancer related death, and the ATA has defined three groups of patients with different risk of recurrence (8):

**ATA high risk (>20%) category** includes patients with: (i) macroscopic invasion of tumor into the perithyroidal soft tissues; (ii) incomplete tumor resection; (iii) distant metastases; (iv) post-operative serum Tg suggestive of distant metastases; (v) pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension; and (vi) follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion). These patients also have a high risk of cancer related death.

**ATA intermediate risk (5–20%) category** includes patients with: (i) microscopic invasion of tumor into the perithyroidal soft tissues; (ii) aggressive histology (e.g. tall cell, hobnail variant, columnar cell carcinoma); (iii) PTC with vascular invasion; (iv) clinical N1 or >5 pathologic N1 with all N1 <3 cm in largest dimension; (v) multifocal papillary microcarcinoma with microscopic invasion of tumor into the perithyroidal soft tissues and BRAFV600E mutation (if known); tumour larger than 1 cm with BRAF v600E mutation could confer an intermediate risk of recurrence but has not been proven yet, based on a prospective study.

**ATA low risk (<5%) category** is defined as: (i) 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); (ii) intrathyroidal encapsulated follicular variant of papillary thyroid cancer or intrathyroidal well-differentiated follicular cancer with capsular or minor vascular invasion (<4 vessels involved); (iii) intrathyroidal papillary microcarcinomas that are either BRAF WT or BRAF mutated (if known). Finally, minimal extrathyroidal extension appears to have little impact on outcome and in the 2017 TNM classification for the risk of thyroid cancer related death is no longer taken into account. Several studies have found no difference in recurrence-free survival between patients with or without minimal extrathyroidal extension and the administration of RAI was not related to survival or recurrence (17, 18, 19).

It is important to note that, regardless of the risk category, the results of post-surgical neck ultrasound performed in the immediate post-operative setting (i.e. 2 weeks to 2 months) and serum Tg measurement obtained at 2 weeks

| Table 1 Tabulated summary of the ETA Consensus Statement. |
|----------------------------------------------------------|
| **Recommendation**                                      |
| RAI therapy should be based on initial prognostic indicators for thyroid cancer-related death and recurrence |
| The use of I-131 therapy as adjuvant treatment or treatment of known disease is indicated in the high-risk group |
| In the intermediate-risk category, RAI therapy may be indicated according to individual risk factors |
| In low-risk patients, RAI therapy should be based on individual risk modifiers |
| Recombinant human TSH is preferred for TSH stimulation |
| Activities of 1110 MBq are equally effective as higher activities for remnant ablation |
| Before RAI therapy diagnostic scan is not routinely required |
| Before RAI therapy any iodine-containing drug should be avoided |
| **Factors to be considered**                            |
| - ATA risk groups: (1) low; (2) intermediate; (3) high |
| - Post-surgical evaluation: (1) neck ultrasound; (2) thyroglobulin |
| - Overall survival and disease-free survival are improved with RAI |
| - Activities >3700 MBq should be considered |
| - The greatest benefit in patients with: (1) advanced age; (2) aggressive histologies; (3) increasing volume of nodal disease; (4) extranodal extension of the tumour; (5) multiple N1; (6) and/or lymph node metastases outside the central neck |
| - Final results of prospective trials expected |
| - RAI treatment not indicated in PTC < 1 cm (uni- or multifocal) |
| - Abnormal neck ultrasound or high Tg may indicate need for RAI therapy |
| - Indicated for all RAI activities |
| - Approved in all risk groups, but metastatic disease |
| - If low-risk patients are referred for thyroid remnant ablation, activity of 1110 MBq should be considered as effective and safer than higher activities |
| - RAI low activities before RAI treatment can induce stunning and reduce treatment effectiveness |
| - Low-iodine diet may be advised |
to 2 months (preferably more than 6 weeks) or more after surgery have a pivotal role in patient selection for RAI therapy \((20, 21, 22, 23)\). Evidence of biopsy proven lymph node metastases and/or unstimulated post-operative Tg values above an institutional cut-off (e.g. >2 ng/mL) should lead to selection for RAI.

Whenever risk factors and patients’ selection for total thyroidectomy and radioiodine are evaluated, wide differences between countries as environmental factors, preclinical care and healthcare should also be considered.

**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 \((\geq 3700 \text{ MBq})\) of radioiodine are preferred over low activities.**

This recommendation is based on the evidence from retrospective or non-controlled prospective studies that both overall survival and disease-free survival, are improved with post-operative radioiodine administration \((24)\). In this situation, RAI administration is clearly intended more as an adjuvant treatment or treatment of known disease rather than for thyroid remnant ablation.

For activity selection, the precise goal needs to be considered. There is no evidence that for adjuvant treatment, more than 3700 MBq will further improve prognosis. For treatment of known disease, there are differing opinions in literature on whether standard activities \(>3700 \text{ MBq}\) or dosimetrically determined activities are of benefit. However, the only large comparative series available \((25)\) does not show any benefit of either dosimetry or activities \(>3700 \text{ MBq}\).

**Recommendation 3: In the intermediate-risk category, RAI therapy may be indicated and should be tailored according to individual cases.**

The greatest benefit of post-operative I-131 therapy may be expected in patients with advanced age, with aggressive histologies, increasing volume of nodal disease, extranodal extension of the tumor, multiple N1 and/or lymph node metastases outside the central neck. In these patients, RAI therapy may be given as an adjuvant treatment.

In patients with minimal extrathyroidal invasion, microscopic or few lymph node metastases and intrathyroidal PTC with BRAFV600E mutation, RAI therapy can be decided based on post-operative Tg and neck ultrasound. Indeed, in this category of patients the benefit of RAI therapy is controversial \((26, 27)\). In addition, we should consider that elderly patients, those with an aggressive histology and those with BRAF mutations frequently do not concentrate radioiodine \((28, 29)\).

Aggressive histologies, such as tall cell variant, columnar and hobnail variant have a lowered likelihood of RAI uptake, and BRAF mutations are found with higher prevalence in these tumors than in classical PTC. As already mentioned, many tumors with aggressive histology, do not express NIS and do not have RAI uptake. This is the basis for redifferentiation protocols and such patients should be preferably offered to enter clinical trials, rather than treated blindly.

Sacks et al. \((30)\) found that cause-specific survival was improved in patients aged >45 years with primary tumors >4 cm, microscopic extrathyroidal invasion, and/or lymph node metastases (UICC/AJCC TNM stage III). It is not clear whether younger patients with lymph node metastases benefit similarly from RAI therapy. In their meta-analysis, Sacks et al. \((30)\) concluded that post-operative I-131 administration did not improve survival or recurrence in patients aged <45 years with microscopic central compartment lymph node metastases, whereas a benefit was uncertain in the setting of lateral or macroscopic lymph node metastases. Aggressive variants of PTC, such as diffuse sclerosing (DSV) and tall cell (TCV) variants, were associated with a reduced overall survival in intermediate-risk PTC patients. Patients with DSV and TCV who did not receive RAI were 4.9 and 2.1 times more likely to die compared to patients who received RAI \((31, 32)\). In addition, in another study after exclusion of aggressive variants, overall survival was better in intermediate-risk patients with lymph node metastases and/or extrathyroidal invasion treated with RAI \((33)\). RAI was associated with a 29% reduction in the risk of death, including patients younger than 45 years (36% reduction in risk of death). The absolute risk difference for overall survival would be estimated at 1% in younger (<45 years) and 4% in older (≥65 years) patients, respectively. At variance \((34)\) both children and adults with MACIS <6 PTC have a <1% chance at 30 years of cause specific mortality.

**Recommendation 4: In low-risk patients, the benefit of I-131 therapy is a matter of intensive scientific debate and the decision on whether to perform RAI therapy should be based on the presence of individual risk modifiers.**

There is controversial discussion among experts on whether post-operative I-131 administration is useful in low-risk patients. In absolute terms, in these patients the risk of disease-specific deaths is less than 1% and that of persistent/recurrent disease is low (2–3%). Thus, the challenge is to identify those patients who should be
treated with RAI and to avoid therapy in patients, who will potentially not benefit from the procedure. It is hard to imagine that retrospective studies can demonstrate any benefit in terms of disease-free survival when the overall risk is as low as 2–3%. As summarized in a meta-analyses by Sawka et al. in 2008 (28) with an update by Verburg in 2020 based on the literature of the past decade (35), the results are not consistent. Some authors report a benefit of applying RAI even to patients with non-metastasized microcarcinomas, whereas other groups find no benefit at all. A tendency for larger groups and longer follow-up duration seems to be loosely associated with showing an advantage of giving RAI – but not consistently across the available reports. Although all authors are studying the same disease and the same therapeutic modality, the variability of the results shows that likely large and important sources of heterogeneity in outcome have thus far neither been identified nor studied sufficiently. An exception to this uncertainty concerns patients with abnormal ultrasound and/or elevated Tg levels (24, 36, 37, 38, 39).

RAI remnant ablation is unlikely to improve the outcome of papillary microcarcinoma (<1 cm, uni- or multi-focal), in absence of other higher-risk features (40, 41) and RAI should not be used in these patients. However, low-risk patients with post-operatively detectable serum Tg, in particular when it is above the institutional cut-off of, for example, 2 ng/mL on l-T4 or >5–10 ng/mL after TSH stimulation or with abnormal ultrasound findings have a higher risk of recurrence, and RAI therapy may be considered, although there is no evidence that it can improve disease-free survival. Currently, two major randomized trials comparing the outcome of low-risk patients receiving post-operative RAI therapy vs no RAI are ongoing in France (ESTIMABL 2) and UK (Ion). The ESTIMABL 2 study randomized 776 low-risk DTC patients to a follow up without adjuvant RAI or to adjuvant treatment with 1110 MBq of I-131 after RAI if TSH stimulation. First results showed that 3 years after randomization the rate of patients without events defined by new RAI administration, surgery or biological abnormalities were similar in both groups (42). Results of the study indicate that there is no need for remnant ablation in this group of DTC patients.

In contrast, the risk of persistent disease is approximately 1.5% when serum Tg is undetectable on l-T4 treatment or <1 ng/mL after TSH stimulation. These patients will potentially not benefit from RAI ablation. In addition, even if no I-131 therapy be given after surgery, clinical recurrences can be treated successfully later on.

**Preparation for RAI administration**

**Recommendation 5: Recombinant human TSH during l-T4 treatment should be the preferred method of preparation for RAI administration.**

Remnant ablation has historically been performed after prolonged l-T4 withdrawal to increase endogenous thyroid-stimulating hormone (TSH) to levels sufficient to induce robust RAI uptake in thyroid cells. However, this induces hypothyroidism with a major decrease in quality of life, which may last for up to 2–3 months. Empirically, it is estimated that a TSH >30 mU/L is a good cut-off (43), but no comparative study has ever validated this assumption and more recent results seem to contradict this assumption (44). For thyroid hormone withdrawal, two possible approaches are used: (i) switch from l-T4 to triiodothyronine (L-T3) for 2–3 weeks (3, 4) and then stop L-T3 for 2 weeks, or (ii) stop L-T4 for 3–4 weeks without switching to L-T3. Either method will significantly decrease quality of life. Alternatively, induction of a less prominent hypothyroidism (reducing L-T4 half the original dose) has also been proposed (45).

For nearly two decades now, a second method of preparation for RAI therapy has been available: the i.m. administration of exogenous recombinant human TSH (rhTSH) 0.9 mg on 2 consecutive days with RAI administration on the day following the second rhTSH injection. A prospective, multicenter, randomized study demonstrated that remnant ablation with 3700 MBq is equally effective after either rhTSH stimulation or prolonged thyroid hormone withdrawal (46). In another study, remnant ablation rates using 1850 MBq of I-131 were similar with either withdrawal or preparation with rhTSH (47). Recently, two randomized non-inferiority trials comparing low and high activities of radioiodine, each in combination with either rhTSH or thyroid hormone withdrawal (THW), have been published (4, 5). The majority of patients were 'low risk' but some patients at 'intermediate risk' (with lymph node metastases or minimal extrathyroidal invasion) were also included in the British HiLo study (5). The remnant ablation rate was similar in all groups irrespective of the TSH stimulation method used, and the authors concluded that recombinant human thyrotropin is equally effective for preparation for remnant ablation in low-risk patients. In addition, short-term recurrence rates have been found to be similar in patients treated with thyroid hormone withdrawal or rhTSH, both in low (11, 48) and intermediate-risk patients (49, 50). Furthermore the preparation with rhTSH is associated with an unimpaired quality of life (46, 51), and
reduces both the whole body radiation absorbed dose (38, 39) and duration of hospitalization (6, 41, 43, 52). As the use of rhTSH is approved for ‘ablation’, with any RAI activity, both in the United States and Europe, for any patient except those with distant metastases, it is advocated to use rhTSH as the preferred method of patient preparation for I-131 administration in patients that fall within the registration label.

Activity of I-131 to be employed for post-surgical thyroid remnant ablation

Recommendation 6: Activities of 1110 MBq are equally effective as higher activities for ablation of presumably benign thyroid remnants.

Although there is a trend toward higher ablation rates with higher activities in patients with large thyroid remnants as observed in the past, similar rates of successful remnant ablation have been reported using activities ranging from 1110 to 3700 MBq of I-131 (47, 48, 49, 50). A randomized study using preparation with rhTSH showed that ablation rates were comparable with 1850 MBq or 3700 MBq (47). In another prospective, randomized trial in 160 patients, comparing ablation with 1110 MBq and 3700 MBq, the authors found no difference in the ablation rate between activities (49). The two prospective randomized studies in France and England referred to before found no significant difference in the remnant ablation rate using 1110 MBq or 3700 MBq of I-131, either after preparation with thyroid hormone withdrawal or rhTSH (4, 5).

Concerning the issue of the follow up of patients treated with a low activity of I-131, a prospective, randomized study comparing the rate of recurrent disease in low-risk patients ablated with 1110 MBq or 3700 MBq, showed that the rate of persistent disease was similar in both groups over a 10-year follow-up (49). In contrast, a higher DTC-related mortality was recently reported in low-intermediate-risk patients, thus allowing the re-classification of disease stage (57). However, no prospective study has ever determined the cut-off over which interference may actually occur.

Should diagnostic RAI scanning be performed before RAI therapy?

Recommendation 7: Whenever a decision to perform post-operative RAI therapy needs to be taken, a diagnostic scan is not routinely required.

A diagnostic RAI whole body scan (WBS) provides information on the presence of iodine-avid thyroid tissue, both normal and malignant. There is an increasing trend to avoid diagnostic RAI WBS before post-operative I-131 therapy because of its low impact on the decision to treat, and because of concerns regarding I-131-induced stunning of thyroid remnants (53, 54) and metastases (55). The alternative radiopharmaceuticals for staging, I-123 or technetium-99m sestamibi, are not readily or cheaply available (56).

It is recommended to perform a post-therapy WBS within one week after the administration of RAI. This imaging technique is of paramount importance in confirming the presence and the extent of the thyroid remnant and may disclose the presence of unsuspected metastatic foci in 10–26% of high-risk cases (57) and more rarely also in low-intermediate-risk patients, thus allowing the re-classification of disease stage (57). Whenever possible, a single photon emission computed tomography (SPECT)/computed tomography (CT) is to be performed to better define the neck uptake and to distinguish the thyroid remnants from locoregional lymph node metastases (59).

Is a low-iodine diet necessary before RAI administration?

Recommendation 8: A low-iodine diet may be prescribed but its utility is not demonstrated unequivocally. Any iodine-containing drug should be avoided.

Exposure to excessive amounts of stable iodine may influence the uptake of diagnostic or therapeutic activities of RAI. Several centers advocate preparation of the patients with a low-iodine diet (LID) and recommend avoiding excessive iodine exposure (i.e. contrast agent, amiodarone or any other iodine-containing drugs) prior to RAI therapy. However, no prospective study has ever determined the cut-off over which interference may actually occur.

In a recent systematic review, a LID allowing for ≤50 µg/day of iodine for 1–2 weeks prior to RAI administration appeared to be associated with an increase in RAI uptake, compared to no LID (60), but there is conflicting evidence on the impact of LID on the remnant ablation success. In a retrospective study, aimed to compare different levels of urinary iodine excretion on the results of thyroid ablation in patients not prepared with low iodine diet, the authors found no influence of the levels of urinary iodine on the outcome of thyroid ablation up to urinary iodine levels of 350 µg/day (61). In another study (62), a low-iodine diet was associated with a higher rate of remnant ablation.
Measurement of urinary iodine excretion (when available) before RAI therapy may help in detecting the few cases with a significant iodine excess (63).

Conclusions

Careful analysis of patients’ outcome has introduced the concept or risk-based selection of candidates for post-operative I-131 therapy. In accordance with this concept, RAI therapy is recommended based on the individual risk assessment.

Declaration of interest

Daria Handkiewicz-Junak: travel grants from Genzyme-Sanofis. Sophie Leboulleux: Advisory Board membership for Bayer, Lilly and EISAI. Furio Pacini, Dagmar Fuhrer, Rossella Elisei, Markus Luster, Martin Schlumberger and Jan Smit declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this work.

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References

1. Aschebrook-Kilfoy B, Ward MH, Sabra MM & Devesa SS. Thyroid cancer incidence patterns in the United States by histologic type, 1992–2006. Thyroid 2011 21 125–134. (https://doi.org/10.1089/thy.2010.0021)
2. Dal Maso L, Tavilla A, Pacini F, Serraino D, van Dijk BAC, Chiﬁaque MO, Capocaccia R, Laranjinha N, Colonna M, Agius D, et al. Survival of 86,690 patients with thyroid cancer: a population-based study in 29 European countries from EURO-CARE-5. European Journal of Cancer 2017 77 140–152. (https://doi.org/10.1016/j.ejca.2017.02.023)
3. Leenhardt L, Bernier MO, Boin-Pineau MH, Conte Devolx B, Maréchaud R, Riccioli-Pire P, Nocaudie M, Orgiazzi J, Schlumberger M, Wémeau JL, et al. Advances in diagnostic practices affect thyroid cancer incidence in France. European Journal of Endocrinology 2004 150 133–139. (https://doi.org/10.1530/eje.0.1500133)
4. Schlumberger M, Catargi B, Bortegi R, Darde DS, Zerdoud S, Bribi J, Bandet S, Leenhardt L, Bastie D, Schwartz C, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. New England Journal of Medicine 2012 366 1663–1673. (https://doi.org/10.1056/NEJMoa1108586)
5. Mallick U, Harmer C, Yap B, Wadesley J, Clarke S, Mox L, Nicol A, Clark PM, Farrel K, McCready R, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. New England Journal of Medicine 2012 366 1674–1685. (https://doi.org/10.1056/NEJMoa1109589)
6. Bal CS, Kumar A, Chandra P, Dwivedi SN & Pant GS. A prospective clinical trial to assess the efﬁcacy of radioiodine ablation as an alternative to completion thyroidectomy in patients with differentiated thyroid cancer undergoing sub-total thyroidectomy. Acta Oncologica 2006 45 1067–1072. (https://doi.org/10.1080/02841860500418377)
7. Schlumberger M, Leboulleux S, Catargi B, Darde DS, Zerdoud S, Bardet S, Rusu D, Godbert Y, Buffet C, Schwartz C, et al. Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL): 5-year follow-up results of a randomised, phase 3, equivalence trial. Lancet Diabetes and Endocrinology 2018 6 618–626. (https://doi.org/10.1016/S2213-8587(18)30013-X)
8. Haugen BR, Alexander EK, Bibe KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka MJ, Schlumberger M, 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 2016 26 1–133. (https://doi.org/10.1089/thy.2015.0020)
9. van Nostrand D. Selected controversies of radioiodine imaging and therapy in differentiated thyroid cancer. Endocrinology and Metabolism Clinics of North America 2017 46 783–793. (https://doi.org/10.1016/j.ecl.2017.04.007)
10. Pacini F, Schlumberger M, Harmer C, Berg GG, Cohen O, Duntas L, Jamar F, Jarab R, Limbert E, Lind E, et al. Post-surgical use of radioiodine (131I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. European Journal of Endocrinology 2005 153 651–659. (https://doi.org/10.1530/eje.1.02014)
11. Pili T, Brianzoni E, Capocaccia F, Castagna MG, Fattori S, Poggiu A, Rossi G, Ferretti F, Guarino E, Burroni L, et al. A comparison of 1850 (50 mCi) and 3700 MBq (100 mCi) 131-I iodine administered doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. Journal of Clinical Endocrinology and Metabolism 2007 92 3542–3546. (https://doi.org/10.1210/jc.2007-0225)
12. Pitt SC, Yang N, Sauke MC, Marka N, Hanlon B, Long KL, McDow AD, Brito JP & Roman BR. Adoption of active surveillance for very low-risk differentiated thyroid cancer in the United States: a national survey. Journal of Clinical Endocrinology and Metabolism 2021 106 e1728–e1737. (https://doi.org/10.1210/clinem/dgaa942)
13. Teng CJ, Hu YW, Chen SC, Yeh CM, Chiang HL, Chen TJ & Liu CJ. Use of radioactive iodine for thyroid cancer and risk of second primary malignancy: a nationwide population-based study. Journal of the National Cancer Institute 2016 108 djv314. (https://doi.org/10.1093/jnci/djv314)
14. Rubino C, Vathaire F, dottorini ME, Hall P, Schwartz C, Couette JE, Dondon MG, Abbas MT, Langlois C & Schlumberger M. Second primary malignancies in thyroid cancer patients. British Journal of Cancer 2003 89 1638–1644. (https://doi.org/10.1038/sj.bjc.6601319)
15. Delgado A & Goddard AK. Clinical endpoints in oncology – a primer. American Journal of Cancer Research 2011 11 1121–1131. (available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8085844/)
16. Tuttle M, Morris LF, Haugen B, Shah J, Sosa JA & Rhoren E. Thyroid-differentiated and anaplastic carcinoma (Chapter 73). In AJCC Cancer Staging Manual, 8th ed. Eds MB Amin, SB Edge, F Greene, DB Byrd, RK Brookland, MK Washington, CC Compton, KR Hess, DC Sullivan, JM Jessup et al. New York, NY, USA: Springer International Publishing, 2017.
17. Radojevs KS, Howard RS, Burch HB & Stojadinovic A. Impact of degree of extrathyroidal extension of disease on papillary thyroid cancer outcome. Thyroid 2014 24 241–244. (https://doi.org/10.1089/thy.2012.0567)
18. Nixon IJ, Ganly I, Patel S, Palmer FL, Whitten MM, Tuttle RM, Shaha AR & Shah JP. The impact of microscopic extrathyroidal extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. Surgery 2011 150 1242–1249. (https://doi.org/10.1016/j.surg.2011.09.007)
19. Ahn D, Sohn JH, Jeon JH & Jeong JY. Clinical impact of microscopic extrathyroidal extension in patients with papillary thyroid microcarcinoma treated with hemithyroidectomy. Journal of Endocrinological Investigation 2014 37 167–173. (https://doi.org/10.1007/s40638-013-0025-x)
20 Krajewska J, Jarząb M, Czarnecka A, Roskosz J, Kukulis A, Handkiezwicz-Junak D, Puch Z, Wygoda Z, P alice-Cieśl ek Ł, Kropińska A, et al. Ongoing risk stratification for differentiated thyroid cancer (DTC) – stimulated serum thyroglobulin (Tg) before radioiodine (RAI) ablation, the most potent risk factor of cancer recurrence in M0 patients. Endokrynologia Polska 2016 67:2–11. (https://doi.org/10.5603/EP.2016.0001)

21 Lamartina L, Granì G, Biffoni M, Giacomelli L, Costante G, Lupo S, Maranghi M, Plasmati K, Sponziello M, Trulli F, et al. Risk stratification of neck lesions detected sonographically during the follow-up of differentiated thyroid cancer. Journal of Clinical Endocrinology and Metabolism 2016 101:3036–3044. (https://doi.org/10.1210/jc.2016-1440)

22 Melo M, Costa G, Ribeiro C, Carrilho F, Martins MJ, Da Rocha AG, Sobrinho-Simões M, Carvalheiro S, Soares F. Stimulated thyroglobulin at recombinant human TSH-aided ablation predicts disease-free status one year later. Journal of Clinical Endocrinology and Metabolism 2013 98:4364–4372. (https://doi.org/10.1210/jc.2013-2267)

23 Rueßmann G, Fish S, Henn LF, Fagin JA & Tuttle RM. Ultrasonographically detected small thyroid bed nodules identified after total thyroidectomy for differentiated thyroid cancer seldom show clinically significant structural progression. Thyroid 2011 21:845–853. (https://doi.org/10.1089/thy.2011.0011)

24 Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen BR, Ladenson PW, Wagner J, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 2006 16:1229–1242. (https://doi.org/10.1089/thy.2006.16.1229)

25 Deandresi D, Rubino C, Tala H, Leboulleux S, Terrot M, Baudin E, Larson S, Fagin JA, Schlumberger M & Tuttle RM. Comparison of empiric versus whole-body/blood clearance dosimetry-based approach to radioactive iodine treatment in patients with metastases from differentiated thyroid cancer. Journal of Nuclear Medicine 2017 58:717–722. (https://doi.org/10.2967/jnumed.116.179606)

26 Saab MM, Dominguez JM, Grevel RK, Larson SM, Ghosein RA, Tuttle RM & Fagin JA. Clinical outcomes and molecular profile of differentiated thyroid cancers with radioiodine-avid distant metastases. Journal of Clinical Endocrinology and Metabolism 2013 98:E829–E836. (https://doi.org/10.1210/jc.2012-3933)

27 Liu J, Liu M, Shen X, Zhu G, Li B & Xing M. The genetic duet of thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. Annals of Surgical Oncology 2012 19:1874–1880. (https://doi.org/10.1245/s10434-011-1219-x)

28 Sawka AM, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A, Straus S & Goldstein DP. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinology and Metabolism Clinics of North America 2008 37:457–480, x. (https://doi.org/10.1016/j.ecl.2008.02.007)

29 Lamartina L, Granì G, D’Antonio C, Borget I, Filetti S & Schlumberger M. Follow-up of differentiated thyroid cancer – what should (and what should not) be done. Nature Reviews: Endocrinology 2018 14:538–551. (https://doi.org/10.1038/s41574-018-0068-3)

30 Sacks W, Fung CH, Chang JT, Waxman A & Braunstein GD. The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a systematic analysis of the peer-reviewed literature from 1966 to April 2008. Thyroid 2010 20:1235–1245. (https://doi.org/10.1089/ thy.2009.0455)

31 Kazaura HS, Roman SA & Sosa JA. Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. Nature Reviews: Endocrinology Oncology 2012 19:1874–1880. (https://doi.org/10.1245/s10434-011-2129-x)

32 Regalbuto C, Malandrino P, Frasca E, Pellegriti G, Le Moël R, Vigneri R & Pezzino V. The tall cell variant of papillary thyroid carcinoma: clinical and pathological features and outcomes. Journal of Endocrinological Investigation 2013 36:249–254. (https://doi.org/10.32758/s515)

33 Ruel E, Thomas S, Dinan M, Perkins JM, Roman SA & Sosa JA. Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. Journal of Clinical Endocrinology and Metabolism 2015 100:1529–1536. (https://doi.org/10.1210/jc.2014-3432)

34 Hay JD, Johnson TR, Koppolt S, Reinalda MS, Iniguez-Ariza NM, Grant CS, Pitttock ST & Thompson GB. Papillary thyroid carcinoma (PTC) in children and adults: comparison of initial presentation and long-term postoperative outcome in 4432 patients consecutively treated at the Mayo Clinic during eight decades (1936–2015). World Journal of Surgery 2018 42:329–342. (https://doi.org/10.1007/s00268-017-4279-x)

35 Verburg FA, Flux G, Giovanella L, van Nostrand D, Muylle K & Luster M. Differentiated thyroid cancer patients potentially benefitting from postoperative l-131 therapy: a review of the literature of the past decade. European Journal of Nuclear Medicine and Molecular Imaging 2020 47:78–83. (https://doi.org/10.1007/s00259-019-04479-1)

36 Schwartz C, Bonnetain F, Delabre Y, Gauthier M, Ceccarelli C, Volta D, Piaggi P, et al. Patients with differentiated thyroid cancer who underwent radioiodine thyroid remnant ablation with low-activity 131I after either recombinant human TSH or thyroid hormone withdrawal showed the same outcome after a 10-year follow-up. Journal of Clinical Endocrinology and Metabolism 2013 98:2693–2700. (https://doi.org/10.1210/jc.2012-4137)

37 Molinaro E, Gianì C, Agate L, Biagioni A, Pieruzzi L, Bianchi F, Brozzi F, Ceccharelli C, Volta D, Piaggi P, et al. Patients with differentiated thyroid cancer who underwent radioiodine remnant thyroid ablation with low-activity 131I after either recombinant human TSH or thyroid hormone therapy withdrawal showed the same outcome after a 10-year following. European Journal of Endocrinology 2013 169:115–123. (https://doi.org/10.1530/EJE-12-0954)

38 Taieb D, Sebag E, Cherenko M, Bausten-Barrass K, Forcianti C, Farman-Ara B, Mico C, de Vaillant J, Thomas S, Conte-Devolx B, et al. Quality of life changes and clinical outcomes in thyroid cancer patients undergoing radioactive iodine remnant ablation (RAA) with recombinant human TSH (rhTSH): a randomized controlled study. Clinical Endocrinology 2009 71:115–123. (https://doi.org/10.1111/j.1365-2265.2008.03424.x)

39 Tuttle RM, Ahuja S, Avram AM, Bernet VJ, Bourquet P, Daniels GH, Dillehay G, Draganescu C, Flux G, Führer D, et al. Controversies, consensus, and collaboration in the use of (131)I therapy in differentiated thyroid cancer: a joint statement from the American Thyroid Association. Thyroid 2019 29:461–470. (https://doi.org/10.1089/thy.2018.0597)

40 Hanscheid H, Lassmann M, Luster M, Thomas SR, Pacini F, Ceccarelli C, Ladenson PW, Wahl RL, Schlumberger M, Ricard M, et al. Iodine biookinetics and dosimetry in radioidine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. Journal of Nuclear Medicine 2006 47:648–654.

41 Leboulleux S, Bournaud C, Chougnet CN, Zerdoud S, Catargi B, Do Cao C, Kelly A, Barge ML, Dugy I, Vera F, et al. Estimabl2: is there a need for radioiodine ablation in low risk differentiated thyroid cancer (DTC) patients? Results from the French randomized phase III prospective trial on 776 patients (NCT 01837745). Journal of the Endocrine Society 2021 5:Supplement_1:A875. (https://doi.org/10.1210/jendso/bva048.1788)

42 Frigo A, Dardano A, Danese D, Satta MV, Mognetti B, Colato C, Francia G, Bernardi F, Traino C, Monzani F, et al. Chromosome
translocation frequency after radioiodine thyroid remnant ablation: a comparison between recombinant human thyrotropin stimulation and prolonged levothyroxine withdrawal. Journal of Clinical Endocrinology and Metabolism 2009 94 3472–3476. (https://doi.org/10.1210/jc.2008-2830)

44 Edmonds CJ, Hayes S, Kermodje JC & Thompson BD. Measurement of serum TSH and thyroid hormones in the management of treatment of thyroid carcinoma with radioiodine. British Journal of Radiology 1977 50 799–807. (https://doi.org/10.1259/0007-1285-50-599-799)

45 Vrachimis A, Riemann B, Mader U, Reiners C & Verburg FA. Endogenous TSH levels at the time of (131)I ablation do not influence ablation success, recurrence-free survival or differentiated thyroid cancer-related mortality. European Journal of Nuclear Medicine and Molecular Imaging 2016 43 224–231. (https://doi.org/10.1007/s00259-015-3223-2)

46 Marturano I, Russo M, Spadaro A, Latina A, Malandrino P & Regalbuto C. Comparison of conventional L-thyroxine withdrawal and moderate hypothyroidism in preparation for whole-body 131-I scan and thyroglobulin testing. Journal of Endocrinological Investigation 2015 38 1017–1022. (https://doi.org/10.1007/s40618-015-0318-3)

47 Pacini F, Ladenson PW, Schlumberger M, Driedger A, Luster M, Klos RT, Sherman S, Haugen B, Corone C, Molinaro E, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. Journal of Clinical Endocrinology and Metabolism 2006 91 926–932. (https://doi.org/10.1210/jc.2005-1631)

48 Tuttle RM, Brokhin M, Omry G, Martorella AJ, Larson SM, Grewal RK, Pacini F, Ladenson PW, Schlumberger M, Driedger A, Luster M, Klos RT, Sherman S, Haugen B, Corone C, Molinaro E, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: a randomized, double-blind, placebo-controlled trial. Journal of Clinical Endocrinology and Metabolism 2006 91 926–932. (https://doi.org/10.1210/jc.2005-1631)

49 Vanpepa HO, Heikkenen J, Vaalavirta L, Tenhunen M & Joensuu H. Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PLoS ONE 2008 3 e1885. (https://doi.org/10.1371/journal.pone.0001885)

50 Leenhardt L, Leboulleux S, Bournaud C, Zerdoud S, Schwartz C, Ciappuccini R, Kelly A, Morel O, Dygai-Cochet I, Rusu D, et al. Recombinant thyrotropin vs levothyroxine withdrawal in 131I therapy of N1 thyroid cancer: a large matched cohort study (ThyrNod). Journal of Clinical Endocrinology and Metabolism 2019 104 1020–1028. (https://doi.org/10.1210/jc.2018-01589)

51 Elisei R, Schlumberger M, Driedger A, Reiners C, Klos RT, Sherman SI, Haugen B, Corone C, Molinaro E, Grasso L, et al. Follow-up of low-risk differentiated thyroid cancer patients who underwent radioiodine ablation of postsurgical thyroid remnants after either recombinant human thyrotropin or thyroid hormone withdrawal. Journal of Clinical Endocrinology and Metabolism 2009 94 4171–4179. (https://doi.org/10.1210/jc.2009-0869)

52 Bai C, Padhy AK, Jana S, Pant GS & Basu AK. Prospective randomized clinical trial to evaluate the optimal dose of 131 I for remnant ablation in patients with differentiated thyroid carcinoma. Cancer 1999 77 2574–2580. (https://doi.org/10.1002/(SICI)1097-0142(19990615)77:12<2574::AID-CNCR22>3.0.CO;2-O)

53 Verburg FA, Mader U, Reiners C & Hänscheid H. Long-term survival in differentiated thyroid cancer is worse after low-activity initial postsurgical 131I therapy in both high- and low-risk patients. Journal of Clinical Endocrinology and Metabolism 2014 99 4487–4496. (https://doi.org/10.1210/jc.2014-1631)

54 Hilditch TE, Dempsey MF, Bolster AA, McNenemin RM & Reed NS. Self-stunning in thyroid ablation: evidence from comparative studies of diagnostic 131I and 123I. European Journal of Nuclear Medicine and Molecular Imaging 2002 29 783–788. (https://doi.org/10.1007/s00259-002-0785-6)

55 Leger AF, Pellman M, Dagoussset F, Chevalier A, Keller I & Clerc J. A case of stunning of lung and bone metastases of papillary thyroid cancer after a therapeutic dose (3.7 GBq) of 131I and review of the literature: implications for sequential treatments. British Journal of Radiology 2005 78 428–432. (https://doi.org/10.1259/bjr/92548685)

56 Silberstein EB. Comparison of outcomes after (123)I versus (131)I preablative imaging before radioiodine ablation in differentiated thyroid carcinoma. Journal of Nuclear Medicine 2007 48 1043–1046. (https://doi.org/10.2967/jnumed.107.040311)

57 Souza Rosário PW, Barroso AL, Rezende LL, Padrão EL, Fagundes TA, Penna GC & PUTSIC S. Post-I-131 therapy scanning in patients with thyroid carcinoma metastases: an unnecessary cost or a relevant contribution? Clinical Nuclear Medicine 2004 29 795–798. (https://doi.org/10.1097/00003003-200412000-00005)

58 Pacini F, Brianzoni E, Durante C, Elisei R, Ferdeghini M, Fugazza L, Mariotti S & Pellegriti G. Recommendations for post-surgical thyroid ablation in differentiated thyroid cancer: a 2015 position statement of the Italian Society of Endocrinology. Journal of Endocrinological Investigation 2016 39 341–347. (https://doi.org/10.1007/s00259-015-0275-7)

59 Avram AM, Esfandiari NH & Wong KK. Preablative I-131 scans with SPEC/CT contribute to thyroid cancer risk stratification and 131-I therapy planning. Journal of Clinical Endocrinology and Metabolism 2015 100 1895–1902. (https://doi.org/10.1210/jc.2014-4043)

60 Sawka AM, Ibrahim-Zada I, Galagap CG, Tsang RW, Birley JD, Ezzat S & Goldstein DE. Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in well-differentiated thyroid cancer: a systematic review. Thyroid 2010 20 1129–1138. (https://doi.org/10.1089/thy.2010.0055)

61 Tala Jury HP, Castagna MG, Fioravanti C, Cipri C, Brianzoni E & Pacini F. Lack of association between urinary iodine excretion and successful thyroid ablation in thyroid cancer patients. Journal of Clinical Endocrinology and Metabolism 2010 95 230–237. (https://doi.org/10.1210/jc.2010-0624)

62 Pluijmen MJHM, Eustatia-Rutten C, Goslings BM, Stokkel MP, Arias AMP, Diamant M, Romijn JA & Smit JW. Effects of low-iodide diet on postsurgical radiodiode ablation therapy in patients with differentiated thyroid carcinoma. Clinical Endocrinology 2003 58 428–435. (https://doi.org/10.1046/j.1365-2265.2003.01735.x)

63 Borget I, Remy H, Chevalier J, Ricard M, Allyn M, Schlumberger M & Pouvoeurville G de. Length and cost of hospital stay of radioactive iodine ablation in thyroid cancer patients: comparison between preparation with thyroid hormone withdrawal and Thyrogen. European Journal of Nuclear Medicine and Molecular Imaging 2008 35 1457–1463. (https://doi.org/10.1007/s00259-008-0754-9)

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