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REVIEW

Reappraisal of the indication for radioiodine thyroid ablation in differentiated thyroid cancer patients

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Abstract Radioactive iodine therapy is administered to patients with differentiated thyroid cancer (DTC) for eradication of thyroid remnant after total thyroidectomy or, in patients with metastatic disease, for curative or palliative treatment. In past years, thyroid remnant ablation was indicated in almost every patient with a diagnosis of DTC. Nowadays, careful revision of patients' outcome has introduced the concept of risk-based selection of patients candidate to thyroid remnant ablation. The present review aims to underline the indications for thyroid remnant ablation and to address methodologies to be employed.

Keywords Radioiodine · Thyroid ablation · Thyroid cancer · Thyroglobulin · rhTSH

Introduction

Differentiated thyroid carcinoma (DTC), including papillary and follicular histotypes and their variants, accounts for more than 90 % of all thyroid cancers. An increasing incidence of DTC over the last decades worldwide has been reported and is mainly due to papillary histotype [1]. Such increase may be attributable to a better detection of small papillary thyroid carcinomas (PTC) as a result of an improved diagnostic accuracy (neck ultrasound and fine needle aspiration cytology) [2].

Currently, about 70–85 % of thyroid carcinomas referred to thyroid cancer centers are PTC with an excellent long-term prognosis intrinsic to their favorable biological properties [3]. Recently, observation without immediate surgery has been proposed for low-risk papillary thyroid microcarcinoma [4].

The aim of this review is to discuss which patients are candidate for ablation and which activities of radioiodine (RAI) (low vs. high activities) and which modalities of preparation [recombinant human TSH administration (rhTSH) vs. hypothyroidism] should be employed.

Postsurgical thyroid remnant ablation

Postsurgical ablation of thyroid remnant with RAI (*remnant ablation*) is aimed to facilitate the early detection of recurrence based on serum thyroglobulin (Tg) measurement and/or RAI whole-body scan (WBS) and to obtain a post-therapy WBS, whose results may change the initial staging by identifying previously undiagnosed disease. In addition, RAI ablation may represent an *adjuvant therapy* by cleaning persistent microscopic foci of cancer, which can be present in the thyroid remnant especially in PTC, which is frequently multifocal, and by destroying small-volume microscopic lymph node metastases (present in up to 80 % of PTC). While the first aim, remnant ablation, is related to follow-up in any patient regardless of his specific risk, the second one, adjuvant therapy, is advocated as a tool to reduce disease recurrence and cause-specific mortality [5], and thus its use must be justified according to a real risk of recurrence.

Risk stratification to asses the need for thyroid remanant ablation

In past years, RAI ablation was indicated in almost every patient with a diagnosis of DTC. Nowadays, careful

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revision of patients' outcome has introduced the concept of risk-based selection of patient candidate to RAI ablation. The individual risk depends on initial prognostic indicators obtained at surgery and on results of serum Tg measurements and neck ultrasonography obtained after surgery [3, 6]. According to these parameters, the American Thyroid Association (ATA) has defined three groups of patients with different risks of recurrence and the benefits of postoperative ^{131}I differ among these groups [3].

ATA high-risk category

DTC patients are defined at high risk if they have: (1) macroscopic invasion of tumor into the perithyroidal soft tissues; (2) incomplete tumor resection; (3) distant metastases; (4) postoperative serum Tg suggestive of distant metastases; (5) pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension; (6) follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion) [3].

The published literature supports ^{131}I ablation for high-risk patients. Disease-specific survival, as well as disease-free survival, is improved after postsurgical ^{131}I therapy in TNM stage III and IV patients [7]. In a meta-analysis of 79 studies, Sakcs et al. [8] concluded that there was sufficient evidence of improved cause-specific survival associated with radioiodine ablation in AJCC TNM stage IV patients. There was also evidence of a benefit for patients aged <45 years with significant extrathyroidal extension or distant metastases. Thus, routine postsurgical ^{131}I treatment with high activity is recommended in high-risk DTC patients.

ATA intermediate-risk category

DTC patients are defined at intermediate risk if they have (1) microscopic invasion of tumor into the perithyroidal soft tissues; (2) RAI-avid metastatic foci in the neck on the first post-treatment WBS; (3) aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma); (4) PTC with vascular invasion; (5) clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension; (6) multifocal papillary microcarcinoma with microscopic invasion of tumor into the perithyroidal soft tissues and BRAFV600E mutation (if known) [3].

For patients with ATA intermediate-risk DTC, limited risk-group-specific data examining RAI efficacy are available. Sacks et al. [8] found that cause-specific survival was improved in patients with AJCC TNM stage III DTC, which includes patients aged >45 years with primary tumors >4 cm, microscopic extrathyroidal invasion and/or lymph node metastases. It is not clear whether younger patients with lymph node metastases benefit similarly from ^{131}I therapy. In their meta-analysis, Sacks et al. [8] concluded that ^{131}I remnant ablation did not improve survival or recurrence in patients aged <45 years with microscopic central compartment lymph node metastases, whereas benefit was uncertain in the setting of lateral or macroscopic lymph node metastases. More recently, some studies in which only intermediate-risk patients were evaluated, have been published [9–14]. Aggressive variant of PTC, such as diffuse sclerosing (DSV) and tall cell (TCV) variants, has a worse prognosis than classic PTC variant [9, 10]. Recently, it has been reported that aggressive histologic variant (DSV and TCV) was independently associated with reduced overall survival in intermediate-risk PTC patients. Patients with DSV and TCV who did not receive RAI are 4.9 and 2.1 times more likely to die compared with patients who received RAI [9]. The clinical importance of minimal extrathyroidal extension on outcome of PTC is not well established. However, several recent studies reported no significant difference in recurrence or recurrence-free survival between patients with and without minimal extrathyroidal invasion [11–13]. Nixon et al. [12] reported no significant difference in 10-year OS, DSS or RFS between the pT1/pT2 and pT3 groups (OS: 93 vs. 88 %, $p = 0.129$; DSS: 99 vs. 100 %, $p = 0.733$; RFS: 98 vs. 95 %, $p = 0.188$, respectively). In addition, the administration of postoperative RAI in patients with minimal extrathyroidal invasion does not impact on survival or recurrence [12]. However, due to the slow progression of PTC and the short-term nature of these studies, long-term prospective studies should be conducted to confirm the prognostic role of minimal extrathyroidal invasion. After exclusion of aggressive variants, overall survival was better in intermediate-risk patients (lymph node metastases and/or extrathyroidal invasion) treated with RAI [14]. RAI was associated with a 29 % reduction in the risk of death, with a hazard ratio of 0.71. RAI improved overall survival also in patients younger than 45 years (36 % reduction in risk of death with a hazard ratio of 0.64) [14]. However, it is important to note, that in this study the overall survival rate was very high in <45 year DTC patients treated (99 %) or not (98 %) with radioiodine ablation after a median follow-up period of 6.8 years. The absolute risk difference for overall survival would be estimate to be 1 and 4 % in younger (<45 years) and older (≥65 years) DTC patients, respectively. In addition, an important limitation of this study is that the number and the dimension of lymph node metastases were not available [14]. Recent studies reported that macroscopic lymph node metastases and increasing number of lymph node metastases were associated with decreasing overall survival [15, 16]. In PTC, BRAF V600E mutation is associated with increased disease-specific mortality [17] and a significantly higher risk of recurrence than BRAF wild-type tumors (24.9 vs. 12.6 %, $p < 0.00001$)

[18]. The risk of recurrence in BRAF V600E-positive tumors ranged from 11 to 40 % (median 26.5 %), while the risk of recurrence in BRAF wild-type tumors ranged from 2 to 36 % (median 9.5 %) [18]. However, because BRAF V600E mutation is associated with aggressive histologic phenotypes, lymph node metastases and extrathyroidal extension, it is difficult to determine the proportion of risk attributable to the BRAF mutation versus that attributable to the other clinicopathologic features. In a cohort of low-risk patients with intrathyroidal PTC (<4 cm), the overall risk of having structural disease recurrence over 5 years of follow-up was 3 % and BRAF V600E-mutated tumors had a recurrence rate of 8 % compared with only 1 % in BRAF wild-type tumors ($p = 0.003$) [19]. In multivariate analysis, the only significant predictor of persistent disease after 5 years of follow-up was the presence of mutated BRAF [19]. Differently, no association between BRAV600E mutation and recurrent disease has been reported in 203 low-risk DTC patients in multivariate analysis [20]. In a recent meta-analysis, the BRAFV606E mutation was also strongly associated with aggressive clinicopathologic behavior of papillary microcarcinoma, including extrathyroidal extension, lymph node metastases and advanced stage [21]. BRAF V600E-mutated multifocal papillary microcarcinoma with extrathyroidal extension demonstrated a 20 % recurrence rate [22]. However, there are currently no sufficient data to establish whether the presence or absence of BRAFV600E mutation should dictate the need of remnant ablation in PTC.

In conclusion, for patients with *ATA intermediate-risk DTC*, limited risk-group-specific data examining RAI efficacy are available, but existing data suggest that the greatest potential benefit may be observed with adverse thyroid cancer histologies, increasing volume of nodal disease, lymph node metastases outside the central neck and advanced patient age [3]. In the other conditions (i.e., minimal extrathyroidal invasion, microscopic lymph node metastases and intrathyroidal PTC with BRAFV600E mutation), postoperative Tg together with neck ultrasound can be used to select intermediate-risk patients for RAI ablation.

How can we select intermediate-risk DTC patients for RAI ablation?

Stimulated serum Tg < 2 ng/ml and negative neck ultrasound were associated with very high negative predictive value (~98 %) for biochemical or structural disease 6–12 months after RAI ablation in intermediate-risk DTC patients [23–25]. In ATA low- and intermediate-risk patients who did not receive RAI remnant ablation, a non-stimulated postoperative Tg ≤ 1 ng/ml was also associated with excellent clinical outcomes and recurrence rates <1 % [26]. Several studies have confirmed an increased risk of recurrence in patients who had a postoperative TSH stimulated Tg > 2 ng/ml at the time of ablation [27–30]. In addition, high levels of postoperative stimulated Tg values (>10–30 ng/ml) were associated with poorer survival [23, 31]. Postoperative Tg can also be used to predict the presence of metastatic disease on the post-therapy WBS performed at the time of remnant ablation. Metastatic disease were detected in 12 % of patients with a suppressed Tg < 0.6 ng/ml [32], in 6 % of patients with suppressed Tg < 1.0 ng/ml in another retrospective series [33] and in 7 % of T1-T2, N1 patients with stimulated Tg < 1.0 ng/ml in a different study [34]. However, within the cohort of patients who demonstrated a postsurgical Tg < 0.6 ng/ml, uptake outside the thyroid bed was associated with more aggressive histologies and larger size of metastatic lymph node [32]. Conversely, a postoperative Tg values greater than 5–10 ng/ml increase the likelihood of identifying RAI-avid metastatic disease on the post-therapy WBS (25 % of cases) [32]. It does appear that a postoperative Tg value (either TSH stimulated or non-stimulated) is an important prognostic factor that can be used to guide clinical management. In intermediate-risk patients, postoperative Tg values ≤1 ng/ml are reassuring but do not completely rule out the presence of small-volume RAI-avid metastatic disease at least in patients with aggressive histology or large lymph node metastases. Conversely, a postoperative Tg value >5–10 ng/ml may lead to selection of RAI ablation in ATA intermediate-risk patient that otherwise would not have required RAI ablation (selective use) in order to improve initial staging and facilitate follow-up.

ATA low-risk category

DTC patients are defined at low risk if they have: (1) intrathyroidal PTC without vascular invasion, with or without small-volume lymph node metastases (clinical N0 or ≤5 pathologic N1 micrometastases, <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); and (3) intrathyroidal papillary microcarcinomas that are either BRAF wild type or BRAF mutated [3].

In the low-risk category, RAI ablation is not recommended, because the risk of disease-specific mortality and persistent/recurrent disease is so low, that it is unlikely that may be improved by RAI administration [3, 6]. A retrospective study by Schvartz et al. [35] assessed the effect of ^{131}I on survival in patients with pT1 or pT2 tumors without nodal or distant metastases. After a median follow-up of 10.3 years, there was no difference in overall or disease-free survival between 911 patients who received ^{131}I treatment and 387 patients who did not. Prospective data suggest that

overall and disease-specific mortality are not improved by RAI treatment in stage I and II patients [7, 36]. The risk of persistent disease is even lower in low-risk patients [37, 38]. Rosario et al. [38] evaluated the clinical outcome of 136 patients with intrathyroidal (<2.0 cm) PTC submitted to total thyroidectomy without VI level neck dissection. Over 6.2 years of mean follow-up, a complete clinical remission (defined as stimulated Tg ≤ 1.0 ng/ml, undetectable thyroglobulin antibodies and negative imaging) was observed in 89 % of patients treated with RAI and in 83 % of patients not treated with RAI, without significant difference between the two groups ($p = 0.4$) [38]. More recently, Nixon et al. [39] evaluated 490 patients affected by low-risk DTC. RAI ablation was performed on 178 patients (36 %). There were only four regional recurrences (4/490, 1 %) and two distant recurrences (2/490, 2 %). The 5-year disease-specific survival (DSS) was 100 % and recurrence-free survival (RFS) was 92 % in the total group. Stratifying by RAI ablation, the 5-year regional RFS and distant RFS for patients that did not have RAI ablation were 98 and 100 %, respectively, not significantly different from that observed in patients treated with RAI ablation (100 and 99 %, respectively) [39]. No indication for RAI ablation is reported in ATA guidelines [3] for low-risk patients also in the presence of microscopic lymph node metastases when less than 5 lymph node metastases were involved. Although the rate of microscopic histologic lymph node metastases can be found in as much as 62 % of PTC > 1 cm, the recurrence rate is only 1–6 % [16]. Sugitani et al. [40] demonstrated that the risk of recurrent disease was significantly higher in patients with >5 lymph node metastases (19 %) than in those with <5 lymph node metastases (8 %). RAI remnant ablation is unlikely to improve the outcome of papillary microcarcinoma (<1 cm, uni- or multi-focal), in the absence of other higher-risk features [41, 42].

In conclusion, there is little evidence to suggest that in low-risk patients ^{131}I may improve disease-specific mortality and risk of recurrence, and thus, ^{131}I should not be administered. The overall risk of persistent disease is 3 % and is even lower when serum Tg is undetectable. In this patients category, thyroid ablation may be considered only when serum Tg values are >5–10 ng/ml, when the likelihood of finding foci of radioiodine uptake outside the thyroid bed is significant [27, 43].

Radioiodine dosing and treatment procedures

Preparation for RAI ablation

Remnant ablation has been traditionally performed after thyroid hormone withdrawal to increase endogenous thyroid-stimulating hormone (TSH) to levels sufficient to induce robust RAI uptake in thyroid cells. Empirically, it is estimated that a TSH > 30 mU/l is a good cutoff [44], but no comparative study has ever been done to document this assumption. For thyroid hormone withdrawal, two possible approaches are used: (1) switch from levothyroxine (LT_4) to triiodothyronine (LT_3) for some weeks [3, 5] and then stop LT_3 for 2 weeks, or (2) stop LT_4 for 3–4 weeks without switching to LT_3. A slighter hypothyroidism (reducing LT_4 to one half) has also been proposed [45]. Since several years, the alternative way of preparation for RAI ablation is the administration of rhTSH. A prospective, multicenter, randomized study has, demonstrated that ^{131}I remnant ablation with 100 mCi is equally effective after rhTSH stimulation or thyroid hormone withdrawal [46]. In another study, ablation rates were similar with either withdrawal or preparation with rhTSH using 50 mCi of ^{131}I [47]. Recently, two randomized non-inferiority trials comparing low and high activities of radioiodine, each in combination with either rhTSH or hypothyroidism, have been published [48, 49]. The majority of patients were "low risk," but patients at "intermediate risk" (with lymph node metastases or minimal extrathyroidal invasion) were also included [48, 49]. The ablation rate was similar in the groups despite the thyrotropin stimulation method used, and the authors concluded that the use of rhTSH could be sufficient for the management of low-risk patients. In addition, short-term recurrence rates have been found to be similar in patients prepared with thyroid hormone withdrawal or rhTSH both in low-risk [50, 51] and intermediate-risk patients [52]. The preparation with rhTSH significantly improves quality of life [46, 53] and reduces both whole-body irradiation [54, 55] and hospitalization time [56]. A recent meta-analysis confirmed the above results [57]. Nowadays, the use of rhTSH is approved for remnant ablation, with any ^{131}I activity, in both the USA and Europe.

Activity of ^{131}I to be employed for postsurgical thyroid remnant ablation

Although there is a trend toward higher ablation rates with higher activities, similar rates of successful remnant ablation have been reported using activities ranged from 30 to 100 mCi of ^{131}I [58–60]. A randomized study using preparation with rhTSH showed that ablation rates were comparable between 50 and 100 mCi [61]. A prospective, randomized study performed in 160 patients, comparing ablation with 30 and 100 mCi, after preparation with thyroid hormone withdrawal, found no difference in the ablation rate [62]. Recently, two prospective randomized studies in very large number of patients conducted in France and in the UK found no significant difference in the remnant ablation rate using 30 or 100 mCi of ^{131}I, either after preparation with thyroid

Table 1 Postoperative administration of radioactive iodine (RAI): indication and procedures

Risk class	Indication for remnant ablation	Activity of ^{131}I when indicated	Preparation
Low	Not routinely recommended	30 mCi	rhTSH
Intermediate	May be considered	30 mCi (if low-volume central neck nodal metastases with no other known residual disease are present) 30–150 mCi (if extensive lymph node disease, multiple clinically involved LN or suspected or documented microscopic residual disease are present)	rhTSH
High	Routinely recommended	100–150 mCi	Thyroid hormone withdrawal or rhTSH

hormone withdrawal or rhTSH [48, 49]. It is worth noting that these two studies included not only low-risk patients, but also patients at intermediate risk of recurrence, including those showing minimal extrathyroidal extension of the primary tumor [49] or lymph node metastases [48, 49]. Also in this category, the authors found no difference between low and high RAI activities in terms of ablation success rates. This finding has been confirmed in a retrospective study including only patients at intermediate risk, treated with low or high RAI activities [52]. Concerning the issue of the follow-up of patients treated with low activity of ^{131}I, a prospective, randomized study comparing the rate of recurrent disease in low-risk patients ablated with 30 or 100 mCi showed that in 10 years of follow-up, the rate of persistent disease was similar in both groups [62]. Also in 225 intermediate-risk DTC patients, the final outcome was similar between patients treated with low and high activities of ^{131}I at ablation [52]. On the contrary, it has been recently reported an higher DTC-related mortality in low- and high-risk patients treated with low activities of ^{131}I at ablation ($\leq$2000 MBq) when patients were at least 45 years of age at diagnosis and an higher recurrence rate in older high-risk patients without distant metastases [63].

Indications for activity and for preparation according to ATA risk class

In patients with ATA *low-risk* and ATA *intermediate-risk* DTC without extensive lymph node involvement in whom radioiodine remnant ablation is planned, preparation with rhTSH stimulation is an acceptable alternative to thyroid hormone withdrawal for achieving remnant ablation and a low administered activity of approximately of 30 mCi (1.11 GBq) is generally favored over higher administered activities [3, 6] (Table 1).

In patients with ATA *intermediate-risk* DTC who have extensive lymph node disease (multiple clinically involved LN) in the absence of distant metastases, preparation with rhTSH stimulation may be considered as an alternative to thyroid hormone withdrawal using either low or high RAI activities [3, 6] (Table 1).

In patients with ATA *high-risk* DTC, more data from long-term outcome studies are needed, before rhTSH preparation can be recommended. When RAI is used to treat suspected or documented residual disease in ATA high-risk patients, administered activities of 100–150 mCi are generally recommended [3, 6] (Table 1).

No definitive studies are available in pediatric patients. For every age patients, some authors have suggested to use a lesion dosimetry; others suggest empiric dosages based on the patient's body weight (1 mCi/kg body weight) [64–66]. When available, a ^{124}I PET/CT could be used to perform dosimetry, to tailor treatment, instead of using fixed activities, and to evaluate mean absorbed doses both to target lesions and to nontarget organs (salivary glands) [67].

Should a diagnostic RAI scanning be performed before ablation?

A diagnostic RAI WBS provides information on the presence of iodine-avid thyroid tissue, both normal or tumoral. There is an increasing trend to avoid diagnostic RAI WBS because of its low impact on the decision to ablate and because of concerns over ^{131}I-induced stunning of normal thyroid remnants [68] and distant metastases from thyroid cancer [69, 70]. The alternative radiopharmaceutical for staging, ^{123}I, is not readily available and has a short half-life [71]. More recently, the contribution of preablative ^{131}I scans with SPECT/CT to the postoperative risk stratification in DTC patients has been evaluated [72]. The combination of stimulated serum Tg and imaging data provide information that changes risk stratification in 15 % of patients as compared to recurrence risk estimation based on histopathology and induce modifications in management decision in 31 % of cases [72]. However, only in 7 % of patients changes in management were due to imaging alone, whereas in the majority of cases it was due to contribution of both imaging and Tg information (88 %) or Tg alone (5 %) [72].

Is a low-iodine diet necessary before remnant ablation?

Contamination with stable iodine might theoretically influence the uptake of diagnostic or therapeutic activities of RAI [73]. Based on this assumption, several centers advocate preparation of the patients with a low-iodine diet (LID) and recommend avoiding iodine contamination (intravenous contrast agents, amiodarone or other iodine-containing drugs) prior to RAI therapy. However, no prospective study has ever determined the cutoff at which interference may actually occur.

In a recent systematic review, a LID allowing for ≤50 μg/day of iodine for 1–2 weeks appeared to be associated with an increase in RAI uptake, compared with no LID [74], 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 different levels of urinary iodine on the outcome of thyroid ablation up to urinary iodine levels exceeding 350 μg/day of dietary iodine [75]. In any case, measurement of urinary iodine excretion (when available) before remnant ablation may help in detecting the few cases with significant iodine contamination [6].

Post-therapy WBS after remnant ablation

It is recommended to perform a post-therapy WBS within 1 week after RAI therapy. 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 the cases [76], thus allowing the reclassification of disease stage [77]. Whenever possible, a SPECT-CT can be useful instead of a planar WBS to better define the neck uptake and distinguish the remnant from local lymph node or paratracheal tumor.

Conclusions

In past years, thyroid remnant ablation was indicated in almost every patient with a diagnosis of DTC. Nowadays, careful revision of patients' outcome has introduced the concept or risk-based selection of patients candidate to thyroid remnant ablation. According to this concept, RAI ablation is recommended based on the individual recurrent risk assessed using the ATA stratification system.

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Compliance with ethical standards

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

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References

1. Aschebrook-Kilfoy B, Ward MH, Sabra MM et al (2011) Thyroid cancer incidence patterns in the United States by histologic type, 1992–2006. Thyroid 21:125–134
2. Leenhardt L, Bernier MO, Boin-Pineau MH et al (2004) Advances in diagnostic practices affect thyroid cancer incidence in France. Eur J Endocrinol 150:133–139
3. Haugen BR, Alexander EK, Bible KC et al (2016) 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 26(1):1–133
4. Pacini F (2015) Observation for newly diagnosed micro-papillary thyroid cancer: is now the time? J Endocrinol Invest 38:101–102
5. Pacini F, Schlumberger M, Harmer C et al (2005) Post-surgical use of radioiodine (131I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. Eur J Endocrinol 153:651–659
6. Pacini F, Brianzoni E, Durante C et al (2016) Recommendations for post-surgical thyroid ablation in differentiated thyroid cancer: a 2015 position statement of the Italian Society of Endocrinology. J Endocrinol Invest 39:341–347
7. Jonklaas J, Sarlis NJ, Litofsky D et al (2006) Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 16:1229–1242
8. Sacks W, Fung CH, Chang JT et al (2010) 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 20:1235–1245
9. Kazaure HS, Roman SA, Sosa JA (2012) Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. Ann Surg Oncol 19:1874–1880
10. Regalbuto C, Malandrino P, Frasca F et al (2013) The tall cell variant of papillary thyroid carcinoma: clinical and pathological features and outcomes. J Endocrinol Invest 36:249–254
11. Radowsky JS, Howard RS, Burch HB et al (2014) Impact of degree of extrathyroidal extension of disease on papillary thyroid cancer outcome. Thyroid 24:241–244
12. Nixon IJ, Ganly I, Patel S et al (2011) The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. Surgery 150:1242–1249
13. Ahn D, Sohn JH, Jeon JH et al (2014) Clinical impact of microscopic extrathyroidal extension in patients with papillary thyroid microcarcinoma treated with hemithyroidectomy. J Endocrinol Invest 37:167–173
14. Ruel E, Thomas S, Dinan M et al (2015) Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. J Clin Endocrinol Metab 100:1529–1536
15. Adam MA, Pura J, Goffredo P et al (2015) Presence and number of lymph node metastases are associated with compromised

survival for patients younger than age 45 years with papillary thyroid cancer. J Clin Oncol 33:2370–2375
16. Randolph GW, Duh QY, Heller KS et al (2012) The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 22:1144–1152
17. Xing M, Alzahrani AS, Carson KA et al (2013) Association between BRAFV600E mutation and mortality in patients with papillary thyroid cancer. JAMA 309:1493–1501
18. Tufano RP, Teixeira GV, Bishop J et al (2012) BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. Medicine 91:274–286
19. Elisei R, Viola D, Torregrossa L et al (2012) The BRAF(V600E) mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroid papillary thyroid carcinoma: single-institution results from a large cohort study. J Clin Endocrinol Metab 97:4390–4398
20. Kim TY, Kim WB, Rhee YS et al (2006) The BRAF mutation is useful for prediction of clinical recurrence in low-risk patients with conventional papillary thyroid carcinoma. Clin Endocrinol 65:364–368
21. Li F, Chen G, Sheng C et al (2015) BRAFV600E mutation in papillary thyroid microcarcinoma: a meta-analysis. Endocr Relat Cancer 22:159–168
22. Niemeier LA, Kuffner AH, Song C et al (2012) A combined molecular-pathologic score improves risk stratification of thyroid papillary microcarcinoma. Cancer 118:2069–2077
23. Piccardo A, Arecco F, Puntoni M et al (2013) Focus on high-risk DTC patients: high postoperative serum thyroglobulin level is a strong predictor of disease persistence and is associated to progression-free survival and overall survival. Clin Nucl Med 38:18–24
24. Lee JI, Chung YJ, Cho BY et al (2013) Postoperative-stimulated serum thyroglobulin measured at the time of 131I ablation is useful for the prediction of disease status in patients with differentiated thyroid carcinoma. Surgery 153:828–835
25. Rosario PW, Mineiro Filho AF, Prates BS et al (2012) Postoperative stimulated thyroglobulin of less than 1 ng/mL as a criterion to spare low-risk patients with papillary thyroid cancer from radioactive iodine ablation. Thyroid 22:1140–1143
26. Ibrahimpasic T, Nixon IJ, Palmer FL et al (2012) Undetectable thyroglobulin after total thyroidectomy in patients with low- and intermediate-risk papillary thyroid cancer—is there a need for radioactive iodine therapy? Surgery 152:1096–1105
27. Webb RC, Howard RS, Stojadinovic A et al (2012) The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: a meta-analysis involving 3947 patients. J Clin Endocrinol Metab 97:2754–2763
28. Polachek A, Hirsch D, Tzvetov G et al (2011) Prognostic value of post-thyroidectomy thyroglobulin levels in patients with differentiated thyroid cancer. J Endocrinol Invest 34:855–860
29. Piccardo A, Arecco F, Morbelli S et al (2010) Low thyroglobulin concentrations after thyroidectomy increase the prognostic value of undetectable thyroglobulin levels on levo-thyroxine suppressive treatment in low-risk differentiated thyroid cancer. J Endocrinol Invest 33:83–87
30. Lima N, Cavaliere H, Tomimori E et al (2002) Prognostic value of serial serum thyroglobulin determinations after total thyroidectomy for differentiated thyroid cancer. J Endocrinol Invest 25:110–115
31. Heemstra KA, Liu YY, Stokkel M et al (2007) Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. Clin Endocrinol 66:58–64
32. Robenshtok E, Grewal RK, Fish S et al (2013) A low postoperative nonstimulated serum thyroglobulin level does not exclude the presence of radioactive iodine avid metastatic foci in intermediate-risk differentiated thyroid cancer patients. Thyroid 23:436–442
33. Rosario PW, Furtado MS, Mineiro Filho AF et al (2012) Value of repeat stimulated thyroglobulin testing in patients with differentiated thyroid carcinoma considered to be free of disease in the first year after ablation. Thyroid 22:482–486
34. Nascimento C, Borget I, Al Ghuzlan A et al (2011) Persistent disease and recurrence in differentiated thyroid cancer patients with undetectable postoperative stimulated thyroglobulin level. Endocr Relat Cancer 18:29–40
35. Schvartz C, Bonnetain F, Dabakuyo S et al (2012) Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. J Clin Endocrinol Metab 97:1526–1535
36. Jonklaas J, Cooper DS, Ain KB et al (2010) Radioiodine therapy in patients with stage I differentiated thyroid cancer. Thyroid 20:1423–1424
37. Momesso DP, Vaisman F, Caminha LS et al (2014) Surgical approach and radioactive iodine therapy for small well-differentiated thyroid cancer. J Endocrinol Invest 37:57–64
38. Rosário PW, Borges MA, Valadão MM et al (2007) Is adjuvant therapy useful in patients with papillary carcinoma smaller than 2 cm? Thyroid 17:1225–1228
39. Nixon IJ, Ganly I, Patel SG et al (2013) The results of selective use of radioactive iodine on survival and on recurrence in the management of papillary thyroid cancer, based on Memorial Sloan-Kettering Cancer Center risk group stratification. Thyroid 23:683–694
40. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A (2004) A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. Surgery 135:139–148
41. Hay ID, Hutchinson ME, Gonzalez-Losada T et al (2008) Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery 144:980–987
42. Baudin E, Travagli JP, Ropers J et al (1998) Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. Cancer 83:553–559
43. Melo M, Costa G, Ribeiro C et al (2013) Stimulated thyroglobulin at recombinant human TSH-aided ablation predicts disease-free status one year later. J Clin Endocrinol Metab 98:4364–4372
44. Edmonds CJ, Hayes S, Kermode JC et al (1977) Measurement of serum TSH and thyroid hormones in the management and treatment of thyroid carcinoma with radioiodine. Br J Radiol 50:799–807
45. Marturano I, Russo M, Spadaro A et al (2015) Comparison of conventional L-thyroxine withdrawal and moderate hypothyroidism in preparation for whole-body 131-I scan and thyroglobulin testing. J Endocrinol Invest 38:1017–1022
46. Pacini F, Ladenson PW, Schlumberger M et al (2006) Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 91:926–932
47. Chianelli M, Todino V, Graziano F et al (2006) Low dose (2.0 GBq; 54 mCi) radioiodine postsurgical remnant ablation in thyroid cancer: comparison between hormone withdrawal and use of rhTSH in low risk patients. Eur J Endocrinol 160:431–436
48. Schlumberger M, Catargi B, Borget I et al (2012) Strategies of radioiodine ablation in patients with low-risk thyroid cancer. NEJM 366:1663–1673
49. Mallick U, Harmer C, Yap B et al (2012) Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. NEJM 366:1674–1685

50. Tuttle RM, Brokhin M, Omry G et al (2008) Recombinant human TSH-assisted radioactive iodine remnant ablation achieves short-term clinical recurrence rates similar to those of traditional thyroid hormone withdrawal. J Nucl Med 49:764–770
51. Molinaro E, Giani C, Agate L et al (2013) Patients with differentiated thyroid cancer who underwent radioiodine thyroid remnant ablation with low-activity 131I after either recombinant human TSH or thyroid hormone therapy withdrawal showed the same outcome after a 10-year follow-up. J Clin Endocrinol Metab 98:2693–2700
52. Castagna MG, Cevenini G, Theodoropoulou A et al (2013) Post-surgical thyroid ablation with low or high radioiodine activities results in similar outcomes in intermediate risk differentiated thyroid cancer patients. Eur J Endocrinol 169:23–29
53. Taieb D, Sebag F, Cherenko M et al (2009) Quality of life changes and clinical outcomes in thyroid cancer patients undergoing radioiodine remnant ablation (RRA) with recombinant human TSH (rhTSH): a randomized controlled study. Clin Endocrinol 71:115–123
54. Hanscheid H, Lassmann M, Luster M et al (2006) Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J Nucl Med 47:648–654
55. Frigo A, Dardano A, Danese E et al (2009) Chromosome translocation frequency after radioiodine thyroid remnant ablation: a comparison between recombinant human thyrotropin stimulation and prolonged levothyroxine withdrawal. J Clin Endocrinol Metab 94:3472–3476
56. Borget I, Remy H, Chevalier J et al (2008) Length and cost of hospital stay of radioiodine ablation in thyroid cancer patients: comparison between preparation with thyroid hormone withdrawal and thyrogen. Eur J Nucl Med Mol Imaging 35:1457–1463
57. Tu J, Wang S, Huo Z et al (2014) Recombinant human thyrotropin-aided versus thyroid hormone withdrawal-aided radioiodine treatment for differentiated thyroid cancer after total thyroidectomy: a meta-analysis. Radiother Oncol 110:25–30
58. Bal C, Padhy AK, Jana S et al (1996) Prospective randomized clinical trial to evaluate the optimal dose of 131 I for remnant ablation in patients with differentiated thyroid carcinoma. Cancer 77:2574–2580
59. Tresoldi AS, Sburlati LF, Rodari M et al (2014) Radioiodine ablation with 1,850 MBq in association with rhTSH in patients with differentiated thyroid cancer. J Endocrinol Invest 37:709–714
60. Fang Y, Ding Y, Guo Q et al (2013) Radioiodine therapy for patients with differentiated thyroid cancer after thyroidectomy: direct comparison and network meta-analyses. J Endocrinol Invest 36:896–902
61. Pilli T, Brianzoni E, Capoccetti F et al (2007) A comparison of 1850 (50 mCi) and 3700 MBq (100 mCi) 131-iodine administered doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. J Clin Endocrinol Metab 92:3542–3546
62. Maenpaa HO, Heikkonen J, Vaalavirta L et al (2008) Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PLoS ONE 2(3):e1885
63. Verburg FA, Mader U, Reiners C et al (2014) Long term survival in DTC is worse after low-activity initial post-surgical I-131 therapy in both high and low risk patients. J Clin Endocrinol Metab 99:4487–4496
64. Franzius C, Dietlein M, Biermann M et al (2007) Procedure guideline for radioiodine therapy and 131iodine whole-body scintigraphy in paediatric patients with differentiated thyroid cancer. Nuklearmedizin 46:224–231
65. Jarzab B, Handkiewicz-Junak D, Wloch J (2005) Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. Endocr Relat Cancer 12:773–803
66. Lassmann M, Hanscheid H, Chiesa C et al (2008) EANM dosimetry committee series on standard operational procedures for pretherapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. Eur J Nucl Med Mol Imaging 35:1405–1412
67. Van Nostrand D, Moreau S, Bandaru VV et al (2010) (124)I positron emission tomography versus (131)I planar imaging in the identification of residual thyroid tissue and/or metastasis in patients who have well-differentiated thyroid cancer. Thyroid 20:879–883
68. Muratet JP, Giraud P, Daver A et al (1997) Predicting the efficacy of first iodine-131 treatment in differentiated thyroid carcinoma. J Nucl Med 38:1362–1368
69. Leger AF, Pellan M, Dagousset F et al (2005) 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. Br J Radiol 78:428–432
70. Hilditch TE, Dempsey MF, Bolster AA et al (2002) Self-stunning in thyroid ablation: evidence from comparative studies of diagnostic 131I and 123I. Eur J Nucl Med Mol Imaging 29:783–788
71. Silberstein EB (2007) Comparison of outcomes after (123)I versus (131)I pre ablation imaging before radioiodine ablation in differentiated thyroid carcinoma. J Nucl Med 48:1043–1046
72. Avram AM, Esfandiari NH, Wong KK (2015) Preablation 131-I scans with SPECT/CT contribute to thyroid cancer risk stratification and 131-I therapy planning. J Clin Endocrinol Metab 100:1895–1902
73. Pluijmen MJ, Eustatia-Rutten C, Goslings BM et al (2003) Effects of low-iodide diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma. Clin Endocrinol 58:428–435
74. Sawka AM, Ibrahim-Zada I, Galacgac P et al (2010) Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in well-differentiated thyroid cancer: a systematic review. Thyroid 20:1129–1138
75. Tala Jury HP, Castagna MG, Fioravanti C et al (2010) Lack of association between urinary iodine excretion and successful thyroid ablation in thyroid cancer patients. J Clin Endocrinol Metab 95:230–237
76. Fatourechi V, Hay ID, Mullan BP et al (2000) Are post-therapy radioiodine scans informative and do they influence subsequent therapy of patients with differentiated thyroid cancer? Thyroid 10:573–577
77. Souza Rosario PW, Barroso AL, Rezende LL et al (2004) Post I-131 therapy scanning in patients with thyroid carcinoma metastases: an unnecessary cost or a relevant contribution? Clin Nucl Med 29:795–798