Low-Dose Radioiodine Ablation in Patients with Low-Risk Differentiated Thyroid Cancer

Germán A. Jimenez Londoño^a Ana Maria Garcia Vicente^a Julia Sastre Marcos^b
Francisco Jose Pena Pardo^a Mariano Amo-Salas^c Manuel Moreno Caballero^d
Maria Prado Talavera Rubio^a Beatriz Gonzalez Garcia^a
Niletys Dafne Disotuar Ruiz^a Angel Maria Soriano Castrejón^a

^aNuclear Medicine Department, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; ^bDepartment of Endocrinology, Complejo Hospitalario de Toledo, Toledo, Spain; ^cDepartment of Mathematics, University of Castilla-La Mancha, Ciudad Real, Spain; ^dDepartment of Nuclear Medicine, Hospital Universitario Infanta Cristina Badajoz, Badajoz, Spain

Keywords

Thyroid cancer · Low dose · Radioiodine remnant ablation · AntiTg antibodies · Response

Abstract

Aim: Based on the response criteria of the 2015 American Thyroid Associations guidelines, our objectives were to determine the response rate when using a low dose of 131-I GBq in patients with low-risk differentiated thyroid cancer (LRDTC) and the influence of clinical and analytical variables on the prediction of complete response. **Methods:** We performed a multicentre and longitudinal study, including patients who were operated for LRDTC and who underwent radioiodine remnant ablation with a low-dose of 131-I. All patients were assessed at 6–12 months, and their status was classified as complete (excellent response) or incomplete response (structural incomplete, biochemical incomplete or indeterminate response). Various factors including age, gender, histology, tumour focality and size, stage, time from surgery to treatment, type of thyroid-stimulating hormone (TSH) stimulation, preablation serum thyroglobulin

(pTg), antiTg antibodies (pAntiTgAb) and TSH (pTSH) levels were also analysed in order to predict the complete response rate. **Results:** Of 108 patients, 79.6% achieved complete response and the remaining showed incomplete response (2.9, 5.5 and 12% due to biochemical incomplete, structural incomplete and indeterminate response respectively). Six patients received a new dose of 131-I. Tumour size and pAntiTgAb were the only factors related to therapeutic response ($p = 0.03$ and $p < 0.01$, respectively). However, pAntiTgAb was the only independent factor related to complete response. Patients with complete response showed lower pTg than those with incomplete response (5.1 ± 12.9 vs. 11.2 ± 25 ng/mL) although without statistical significance ($p = 0.14$). There was no significant difference in the response rate depending on the thyrotropin stimulation methods. **Conclusions:** A low dose of 131-I was sufficient for reaching a complete response at 6–12 months of follow-up in the majority of patients with LRDTC. Tumour size and pAntiTgAb variables were related to therapeutic response.

© 2018 European Thyroid Association
Published by S. Karger AG, Basel

Introduction

The incidence of thyroid cancer has increased in many countries during the past decade and this is due mainly to an improvement achieved in detection methods [1, 2]. Most cases are of the differentiated thyroid carcinoma and many patients undergo radioiodine remnant ablation (RRA) to eliminate the residual normal thyroid tissue after total thyroidectomy (TT) or near TT (NTT).

Previous works [3–5] have shown that a low dose of ^{131}I is as effective as a high dose for ablation of thyroid remnants in low and intermediate risk patients. Additionally, the low dose has clinical advantages such as the reduction of side effects and risk of a second primary cancer, but it also influences positively other extra-clinical factors such as the hospital stay and consequently, its financial costs. However, the rate of ablation success has an important variability, especially due to inconsistent definitions of successful ablation and patient selection criteria. Moreover, it has been observed that some elements might be potential prognostic factors for ablation success.

On the other hand, “the ablation success” has been the main end point for response to RRA. Nevertheless, the disease relapse and disease-specific mortality should be the real endpoints. Thus, different systems have been used to predict the prognosis of patients with thyroid cancer. Recently, the 2015 American Thyroid Association (ATA) guidelines have added a dynamic risk assessment system, which classifies the patient based on the response to initial therapy (excellent, indeterminate, biochemical incomplete and structural incomplete response) using Preablation thyroglobulin (pTg), preablation AntiTg antibodies (pAntiTgAb), ultrasonography (US), diagnostic whole-body scan, PET/CT, CT and/or MRI. This system is based on a dynamics assessment; as a result, it could potentially modify the initial risk estimates (for example, those with an initial high risk could become low risk patients). Therefore, this dynamic system allows a more personalised approach to treatment, follow-up and prognosis [6]. Thus, our objectives were to determine the response rate based on the ATA dynamic risk assessment system, using a low activity radioiodine ablation in patients with low-risk differentiated thyroid cancer (LRDTC) and second, to assess the influence of clinical factors in the therapeutic response.

Methods

A longitudinal and multicentre study, including 5 hospitals, was performed in accordance with the ethical standards prescribed by the Declaration of Helsinki. Additionally, this study

was approved by our institutional Ethics Committee and all patients gave their informed consent for participation in the research study.

Patients

Patients with LRDTC and TT or NTT and both with or without cervical lymph node dissection, referred to our department to receive a low activity ($[30\text{ mCi (1.1 GBq)}]$) for RRA, were consecutively included since November 2013 up to January 2016. Low-risk criteria were defined as follows: (i) pT1a-T3/N0-x/M0 disease stage [7], (ii) macroscopic complete resection of the tumour and (iii) neither aggressive histology (tall cell, columnar cell carcinoma, etc.) nor vascular invasion. Although patients with pT3 initially were included, those with minimal extrathyroidal extension were ultimately excluded for the present analysis. Likewise, patients with suspicion of locoregional or distant metastases on whole body scintigraphy (WBS) after RRA were not included. Patients underwent RRA after thyroid hormone withdrawal (THW) or administration of recombinant human thyroid-stimulating hormone (rhTSH). pTg, pAntiTgAb and preablation TSH (pTSH) levels were measured. Patients were required to have TSH levels $>30\text{ mU/L}$ at the time of RRA.

A WBS was performed 6–8 days after RRA by using a dual-headed-gamma camera equipped with high-energy collimators, obtaining planar images in anterior and posterior views. The WBS speed was 10 cm/min and a 256×512 matrix was used. SPECT/CT of the neck, and in some cases, of other anatomical regions, was performed using a 360° orbit (180° for each head), step and shoot mode, at 35 s per view. Immediately after emission image acquisition, a low-dose CT acquisition (120 kV , 2.5 mA , 15 mm slice thickness) was obtained without changing the patient's position. The WBS was classified as negative (absence of cervical uptake) or positive (thyroid bed uptake).

The following variables were collected: age at diagnosis, gender, histology (papillary, follicular or mixture of both), tumour focality (unifocal or multifocal) and laterality (unilateral or bilateral), primary tumour size (T1, T2, T3) and stage grouping (I, II, III) following the TNM 7th ed [1], time from surgery to RRA (≤ 6 months or > 6 months), type of TSH stimulation (THW or rhTSH administration), pTSH, pTg, pAntiTgAb level (positive $\geq 30\text{ UI/mL}$) and WBS findings (positive or negative).

Response to Therapy

A response-to-therapy assessment was performed between 6 and 12 months after RRA using 4 categories based on ATA guidelines [6]. For statistical purpose, they were grouped into 2 categories: complete response and incomplete response. Thus, a complete response (an excellent response based on ATA guidelines) was defined as a TSH-stimulated Thyroglobulin (Tg) $<1\text{ ng/mL}$ or suppressed Tg $<0.2\text{ ng/mL}$ in the absence of structural or functional evidence of disease (and in the absence of AntiTgAb).

On the other hand, an incomplete response was defined as one of the following:

1. Abnormal suppressed Tg ($\geq 1\text{ ng/mL}$) and/or stimulated Tg values ($\geq 10\text{ ng/mL}$) or rising AntiTgAb with negative imaging, which indicated a biochemical incomplete response.
2. Persistent or newly identified locoregional or distant metastases on US and/or WBS, defined as structural incomplete response (independently of Tg and AntiTgAb).

3. Nonspecific findings on imaging studies (findings that cannot be classified as either benign or malignant), non-stimulated Tg detectable 0.2–1 ng/mL, stimulated Tg detectable 1–10 ng/mL, or AntiTgAb stable or declining in the absence of structural or functional disease, considered indeterminate response.

All patients received levothyroxine to maintain TSH suppressed with an initial TSH goal of 0.1–0.5 mU/L. The evaluation of response to therapy was performed using Tg testing (basal or stimulated) and neck US. In some cases, DxWBS was also performed. The measurement of Tg was performed using immunometric assays calibrated against the international standard CRM 457. The AntiTgAb were assessed in the same sample.

A new dose of ¹³¹I was considered to complete the ablation or treatment of new locoregional or distant metastases.

Statistical Analysis

Quantitative variables were described using the case number, mean and SD. Qualitative variables were reported selecting the case number and percentage. For comparisons of categorical variables between groups, the chi-square was used, as well as the Student *t* test or Mann-Whitney U test for quantitative variables.

We analysed the influence of all the collected clinical and RRA-related variables in the response using a binary multivariate analysis. It was conducted by using the logistic regression method. The OR and CI were calculated. A *p* value not exceeding 0.05 was considered statistically significant.

Results

Patients

A total of 120 patients were initially evaluated. Twelve of them were excluded, 5 due to metastasis on WBS, 6 because of low TSH levels before RRA and 1 patient due to lack of WBS. Our study included 108 patients of which 21 men and 87 women. The mean age (range) was 50.0 ± 13.4 (17–82) years. pTSH levels ranged from 31 to 150 mU/L (mean 106 ± 35.5 mU/L) and pTg span was 0.0–72 ng/mL (mean 5.66 ± 14.3 ng/mL). The remaining demographic and clinical features are summarised in Table 1.

Response to Therapy

Complete response (excellent response) was documented in 86 patients (79.6%). In contrast, 22 patients (20.4%) had incomplete response: 3 due to biochemical incomplete response (2.9%), 6 because of structural incomplete response (5.5%) and 13 with indeterminate response (12%). In the latter group, the criteria were suppressed Tg = 0.5 ng/mL in 1 patient, TSH-stimulated Tg = 2 ng/mL in 1 patient, persistence

Table 1. Patients' clinical characteristics

Parameters	n (%)
Gender (patients)	
Female	87 (80.5)
Male	21 (19.5)
Histology	
Papillary	103 (95.3)
Follicular	5 (4.7)
T stage	
T1a	56 (52)
T1b	34 (31.4)
T2	13 (12)
T3	5 (4.6)
Stage	
I	96 (88.9)
II	8 (7.4)
III	4 (3.7)
Tumor multifocality	
Unifocal	68 (63)
Multifocal	40 (37)
Time from surgery to RAI	
≤6 months	98 (91)
>6 months	10 (9)
Type of TSH stimulation	
Thyroid hormone withdrawal	54 (50)
rhTSH administration	54 (50)
pAntiTgAb	
Positive	13 (12)
Negative	95 (88)
WBS	
Positive	100 (92.6)
Negative	8 (7.4)

RAI, radioiodine remnant ablation; TSH, thyroid-stimulating hormone; rhTSH, recombinant human TSH; pAntiTgAb, preablation serum antiTg antibodies levels; WBS, whole body scintigraphy.

of positive Anti-TgAb in 6 and nonspecific findings on imaging studies in 5. Three patients with previously positive pAntiTgAb showed a normal level during the follow-up. A total of 6 patients received further dose of ¹³¹I ranging from 1.1 to 4.4 GBq (2 because of an increase in the Tg level, 3 due to persistent thyroid remnant on DxWBS and 1 because of lymph node recurrence).

Predicting Factors of Complete Response

In the univariate analysis, the primary tumour size ($\chi^2 = 8.1$, *p* = 0.03) and pAntiTgAb ($\chi^2 = 21.7$, *p* < 0.01) were significantly related with the assessment of response. All the results are detailed in Table 2.

Table 2. Univariate analysis for complete response

Variables	Complete response	In complete response	<i>p</i> value
Age, year			
Continuous value	50.4±13.2	48.3±14.3	0.50
Group			
<45 years	27	10	0.30
≥45 years	59	12	
Gender			1.0
Male	17	4	
Female	69	18	
Histology			0.58
Papillary	83	20	
Follicular	3	2	
T stage			0.03
T1a	47	9	
T1b	23	11	
T2	13	0	
T3	3	2	
Stage			0.43
I	75	21	
II	8	0	
III	3	1	
Tumor multifocality			0.80
Unifocal	55	13	
Multifocal	31	9	
Type of TSH stimulation			0.56
THW	47	7	
rhTSH administration	39	15	
pTSH, mU/L*	105.4±35.2	111.6±37.07	0.46
pTg, ng/mL**	5.1±12.9	11.2±25	0.14
Median	1.6	3.0	
Continuous value			
Group A			0.56
<1	32	4	
≥1	50	9	
Group B			0.55
<1	32	4	
1–10	40	6	
>10	10	3	
Group C			0.28
<10	72	10	
≥10	10	3	
pAcTgAb***			<0.01
Negative	82	13	
Positive	4	9	
WBS†			0.08
Positive	82	18	
Negative	4	4	

* Preablation thyroid-stimulating hormone.

** Preablation serum thyroglobulin levels in patients without antiTg antibodies levels.

*** Preablation serum antiTg antibodies levels.

† WBS.

TSH, thyroid-stimulating hormone; rhTSH, recombinant human TSH; pTSH, preablation TSH; pTg, preablation thyroglobulin; THW, thyroid hormone withdrawal; WBS, whole body scintigraphy.

In a binary multivariate model for incomplete response, negative pAntiTgAb (OR 0.07, 95% CI 0.19–0.20, $p < 0.01$) was identified as the only independent factor related with RRA results.

Discussion

The most important goal of our study was to establish the status of response using low activity radioiodine ablation in patients with LRDTTC based on ATA dynamic risk assessment system. We found that a dose of 1.1 GBq was enough to reach a complete response in 79.8% of patients with LRDTTC.

Given that 2015 ATA dynamic risk assessment system is relatively new [6], most of the studies have used the success rate ablation as surrogate clinical end point for response to 131-I [3–7]. Particularly, 2 large multicentre randomised trials [3, 4] and 1 meta-analysis [5] have shown that low-dose radioiodine (1.1 GBq) is as effective as a high-dose (3.7 GBq) in ablating thyroid remnant in the low and intermediate risk patients. However, some series [3, 4, 8, 9] have reported variable success rates (ranging between 39 and 98%) using a low-dose radioiodine in low/intermediate risk. This can be explained by the variability of inclusion criteria and of success ablation definition. Thus, the definition of success ablation has been based on the combination of different Tg levels, presence or absence of AntiTgAb, WBS findings, and recent US.

Although we used other nomenclature for 131-I response (based on ATA guidelines), our results may be comparable with those of previous studies. Thus, we found that the excellent response represented 79.8% and was lower than that described by some authors [3, 4], mainly due to differences in definition of response criteria. However, it was higher than those found by Qu et al. [8] and Fallahi et al. [9], possibly because of the exclusion of patients with N1a and N1b stage. Nevertheless, we considered that a single low-dose of 131-I is enough to reach a complete response in a high number of patients with LRDTTC.

With regard to 2015 ATA guidelines, the new risk stratification system [6] allows a more personalised approach to treatment, follow-up and prognosis. Thus, based on this system, 86–91% of patients with low risk reach an excellent response, 11–19% exhibit a biochemical incomplete response and 12–29% show an indeterminate response after RRA using different doses [10–12], showing a general disease-specific death risk of <1%

[6]. Qu et al. [8], using a low-dose in low and intermediate risk patients reported an excellent response in 80% and indeterminate response in 20% of their sample. We found similar results using a low dose in low-risk patients.

On the other hand, we identified that negative pAntiTgAb was an independent predicting factor of response after RRA. Our results could be explained for the very low prevalence of positive pAntiTgAb in patients with complete response (4.6%) in comparison with those with incomplete response (40.9%). In the same way, previous studies [13–16] have focused on the value of the AntiTgAb as risk factor of persistent/recurrent disease, although they referred to levels during the follow-up instead of the previous values to RRA, as was our case. In particular, they have found that the onset or rise of antiTgAb or rising titres imply an increased risk of persistent/recurrent disease. In fact, the 2015 ATA guidelines [6] have used the antiTgAb level as factor of response. Additionally, falling levels of antiTgAb could indicate success therapy according to some authors [17, 18]. Spencer et al. [19] suggest that high levels may predict the likelihood of recurrence in patients without Hashimoto thyroiditis. Despite additional factors, as insensitivity and interference from high endogenous Tg concentrations [19–21], the antiTgAb seem to be a potential tumour marker and predictive response factor, since it may reflect viable malignant thyroid tissue.

We also found that the tumour size was related to response, with better results in microcarcinoma. In fact, due to better prognosis in these patients, the European Association of Nuclear Medicine [22], British Thyroid Association [23] and the most recent ATA guidelines [6] do not recommend RRA in microcarcinoma without risk factors. Thus, there has been an inclination towards managing these patients with a more conservative approach. However, some centres continue using RRA in these patients in order to achieve improved sensitivity of Tg, enabling early recognition of recurrent or metastatic disease. Additionally, there are other risk factors, such as age, tumour multifocality and family history, which could impact the therapeutic approach.

Although pTg did not show statistical significant differences in our study, patients with complete response presented lower pTg than those with incomplete response (5.1 ± 12.9 vs. 11.2 ± 25 ng/mL). Previous studies [24–26] have showed that stimulated Tg level previous to RRA is a useful factor to predict the presence of persistent and

recurrent disease on follow-up with a high negative predictive value using cut-off levels ranging from 1.0 to 18 ng/mL. The meta-analysis by Webb et al. [27] found a 6% likelihood of having persistent disease in patients with preablation Tg value of less than 10 ng/mL. In the same way, previous studies [28–32] have showed that preablation-stimulated Tg is a good predictor of successful ablation using different cut-off points.

The type of TSH stimulation in low-risk patients has been a controversial topic in previous literature. Similar to our results, some authors [3, 4, 33–35] have showed similar success ablations rate with rhTSH and THW. Based on superior short-term quality of life and similar remnant ablation efficacy found in previous studies, ATA considered the rhTSH stimulation an acceptable alternative to THW for achieving remnant ablation, particularly in patients with ATA low-risk and intermediate-risk DTC without extensive lymph node involvement [6]. Likewise, British Thyroid Association [23] recommends the use of rhTSH stimulation for patients with T1–T3, pN0 or Nx or N1, and M0 and R0 (no microscopic residual disease).

Otherwise, some authors [36–38] have found tumour multifocality as an important prognostic factor for disease recurrence/persistence, although the cohort was different from our study since they included patients with intermediate and high risk. Similar to our results (although with different inclusion criteria), others found no association between multifocality and tumour recurrence [39, 40]. Thus, the prognosis of multifocal nature of the disease remains controversial, although the recently developed ATA guidelines [6] have associated a higher risk of tumour recurrence of 4–6% with multifocal disease regardless of the tumour size.

Limitations and Advantages

The weaknesses of our research were the retrospective design and the short time of follow-up for establishing response status. Clearly, a period of time between 6 and 12 months is not enough to make generalizations in thyroid cancer; for this reason, we will reassess these patients in other time points during the follow-up. However, despite this, a clear pattern of complete response was found using low dose of ^{131}I . The measurement of Tg, AntiTgAb and TSH in different centres is apparently the other disadvantage of our study. Nevertheless, all of them were performed according to international standards.

Although previous studies have found that low-dose radioiodine is effective in ablating thyroid remnant in the

low and intermediate risk patients, almost all of them have employed the successful ablation as the surrogate clinical end point. However, we used the ATA dynamic risk assessment system for ¹³¹I response, allowing a better approach to prognosis.

Conclusions

A low dose of ¹³¹I was sufficient for reaching a complete response in the majority of patients with LDTBR at 6–12 months after RRA. Tumour size (T) and pAntiTgAb

were variables related to therapeutic response, the negative pAntiTgAb being the only independent factor on multivariate analysis. On the contrary, there was no significant difference in response rate in the thyrotropin stimulation method.

Disclosure Statement

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

References

- 1 Stewart B, Wild CP: World cancer report 2014. World: 2015. <http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014> (accessed March 25, 2016).
- 2 Dal Maso L, Tavilla A, Pacini F, Serraino D, van Dijk BAC, Chirlaque MD, et al: Survival of 86,690 patients with thyroid cancer: a population-based study in 29 European countries from EUROCARE-5. *Eur J Cancer* 2017;77:140–152.
- 3 Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, et al: Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 2012;366:1674–1685.
- 4 Schlumberger M, Catargi B, Borget I, Deandreis D, Zerdoud S, Bridji B, et al: Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med* 2012;366:1663–1673.
- 5 Cheng W, Ma C, Fu H, Li J, Chen S, Wu S, et al, et al: Low- or high-dose radioiodine remnant ablation for differentiated thyroid carcinoma: a meta-analysis. *J Clin Endocrinol Metab* 2013;98:1353–1360.
- 6 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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.
- 7 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, et al: *AJCC Cancer Staging Manual* 7th ed. New York, Springer-Verlag, 2010.
- 8 Qu Y, Huang R, Li L. Low- and high-dose radioiodine therapy for low-/intermediate-risk differentiated thyroid cancer: a preliminary clinical trial. *Ann Nucl Med* 2017;31:71–83.
- 9 Fallahi B, Beiki D, Takavar A, Fard-Esfahani A, Ansari Gilani K, Mohsen Saghari et al: Low versus high radioiodine dose in postoperative ablation of residual thyroid tissue in patients with differentiated thyroid carcinoma: a large randomized clinical trial. *Nucl Med Commun* 2012;27:275–282.
- 10 Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al: Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American thyroid association staging system. *Thyroid* 2010;20:1341–1349.
- 11 Castagna MG, Maino F, Cipri C, Pessoa CH, Dias F, Corbo R, et al: Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. *Eur J Endocrinol* 2011;165:441–446.
- 12 Vaisman F, Momesso D, Bulzico DA, Pessoa CH, Dias F, Corbo R, et al: Spontaneous remission in thyroid cancer patients after biochemical incomplete response to initial therapy. *Clin Endocrinol* 2012;77:132–138.
- 13 Seo JH, Lee SW, Ahn BC, Lee J: Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: special emphasis on using (18)F-FDG PET/CT. *Clin Endocrinol (Oxf)* 2010;72:558–563.
- 14 Gorges R, Maniecki M, Jentzen W, Sheu SN, Mann K, Bockisch A, Janssen OE: Development and clinical impact of thyroglobulin antibodies in patients with differentiated thyroid carcinoma during the first 3 years after thyroidectomy. *Eur J Endocrinol* 2005;153:49–55.
- 15 Adil A, Jafri RA, Waqar A, Abbasi SA, Matul H, Asghar AH, Jilani A, Naz I: Frequency and clinical importance of anti-Tg auto-antibodies (ATG). *J Coll Physicians Surg Pak* 2003;13:504–506.
- 16 Chung JK, Park YJ, Kim TY, So Y, Kim SK, Park DJ, Lee DS, Lee MC, Cho BY: Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. *Clin Endocrinol* 2002;57:215–221.
- 17 Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, et al: Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2008;93:4683–4689.
- 18 Spencer C, Fatemi S: Thyroglobulin antibody (TgAb) methods – strengths, pitfalls and clinical utility for monitoring TgAb-positive patients with differentiated thyroid cancer. *Best Pract Res Clin Endocrinol Metab* 2013;27:701–712.
- 19 Latrofa F, Ricci D, Montanelli L, Rocchi R, Piaggi P, Sisti E, et al: Thyroglobulin auto-antibodies in patients with papillary thyroid carcinoma: comparison of different assays and evaluation of causes of discrepancies. *J Clin Endocrinol Metab* 2012;97:3974–3982.
- 20 Taylor KP, Parkington D, Bradbury S, Simpson HL, Jefferies SJ, Halsall DJ: Concordance between thyroglobulin antibody assays. *Ann Clin Biochem* 2011;48:367–369.
- 21 Pickett AJ, Jones M, Evans C: Causes of discordance between thyroglobulin antibody assays. *Ann Clin Biochem* 2012;49:463–467.
- 22 Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJ, et al: Guidelines for radioiodine therapy of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 2008;35:1941–1959.
- 23 Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al; British Thyroid Association: Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)* 2014;81(suppl 1):1–122.

- 24 Rosario PW, Xavier AC, Calsolari MR: Value of postoperative thyroglobulin and ultrasonography for the indication of ablation and ¹³¹I activity in patients with thyroid cancer and low risk of recurrence. *Thyroid* 2011;21:49–53.
- 25 Pelttari H, Välimäki MJ, Löytyniemi E, Schalin-Jäntti C: Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study. *Eur J Endocrinol* 2010;163:757–763.
- 26 Polachek A, Hirsch D, Tzvetov G, Grozinsky-Glasberg S, Slutski I, Singer J et al: Prognostic value of post-thyroidectomy thyroglobulin levels in patients with differentiated thyroid cancer. *J Endocrinol Invest* 2011;34:855–860.
- 27 Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J, et al: 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* 2012;97:2754–2763.
- 28 Tamilia M, Al-Kahtani N, Rochon L, Hier MP, Payne RJ, Holcroft CA, et al: Serum thyroglobulin predicts thyroid remnant ablation failure with 30 mCi iodine-131 treatment in patients with papillary thyroid carcinoma. *Nucl Med Commun* 2011;32:212–220.
- 29 Kendler DB, Vaisman F, Corbo R, Martins R, Vaisman M: Preablation stimulated thyroglobulin is a good predictor of successful ablation in patients with differentiated thyroid cancer. *Clin Nucl Med* 2012;37:545–549.
- 30 Lee HJ, Rha SY, Jo YS, Kim SM, Ku BJ, Shong M, et al: Predictive value of the preablation serum thyroglobulin level after thyroidectomy is combined with postablation ¹³¹I whole body scintigraphy for successful ablation in patients with differentiated thyroid carcinoma. *Am J Clin Oncol* 2007;30:63–68.
- 31 Heemstra KA, Liu YY, Stokkel M, Kievit J, Corssmit E, Pereira AM, et al: Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. *Clin Endocrinol* 2007;66:58–64.
- 32 Giovannella L, Ceriani L, Suriano S, Ghelfo A, Maffioli M: Thyroglobulin measurement before rhTSH-aided ¹³¹I ablation in detecting metastases from differentiated thyroid carcinoma. *Clin Endocrinol* 2008;69:659–663.
- 33 Rosario PW, Xavier AC: Recombinant human thyroid stimulating hormone in thyroid remnant ablation with 1.1 GBq ¹³¹Iodine in low-risk patients. *Am J Clin Oncol* 2012;35:101–104.
- 34 Barbaro D, Boni G, Meucci G, Simi U, Lapi P, Orsini P, et al: Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. *J Clin Endocrinol Metab* 2003;88:4110–4115.
- 35 Tu J, Wang S, Huo Z, Lin Y, Li X, Wang S: Recombinant human thyrotropin-aided versus thyroid hormone withdrawal-aided radioiodine treatment for differentiated thyroid cancer after total thyroidectomy: a meta-analysis. *Radiother Oncol* 2014;110:25–30.
- 36 Khan M, Syed AA, Khan AI, Hussain SR, Urooj N: Association of tumor size and focality with recurrence/persistence in papillary thyroid cancer patients treated with total thyroidectomy along with radioactive-iodine ablation and TSH suppression. *Updates Surg* 2018;70:121–127.
- 37 Kim HJ, Sohn SY, Jang HW, Kim SW, Chung JH: Multifocality, but not bilaterality, is a predictor of disease recurrence/persistence of papillary thyroid carcinoma. *World J Surg* 2013;376–384.
- 38 Kim KJ, Kim SM, Lee YS, Chung WY, Chang HS, Park CS: Prognostic significance of tumor multifocality in papillary thyroid carcinoma and its relationship with primary tumor size: a retrospective study of 2,309 consecutive patients. *Ann Surg Oncol* 2015;22:125–131.
- 39 Riss JC, Peyrottes I, Chamorey E, Haudebourg J, Sudaka A, Benisvy D, et al: Prognostic impact of tumour multifocality in thyroid papillary microcarcinoma based on a series of 160 cases. *Eur Ann Otorhinolaryngol Head Neck Dis* 2012;175–178.
- 40 Mercante G, Frasoldati A, Pedroni C, Formisano D, Renna L, Piana S, et al: Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. *Thyroid* 2009;19:707–716.