ORIGINAL ARTICLE

Recombinant human thyrotropin (rhTSH) versus Levo-thyroxine withdrawal in radioiodine therapy of differentiated thyroid cancer patients: differences in abdominal absorbed dose

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Abstract

Purpose In DTC patients, 131-radioiodine therapy has routinely been used for many years for thyroid remnant ablation after thyroid surgery. To date, two different strategies can be used to achieve sufficient TSH stimulation on thyroid remnant: (I) Levo-thyroxine withdrawal or (II) rhTSH stimulation. The aim of our study was to compare the abdominal absorbed dose ratio between differentiated thyroid cancer patients who underwent thyroid remnant ablation after either L-T4 withdrawal or rhTSH stimulation.

Methods We reviewed the records of 63 patients affected by differentiated thyroid cancer. All patients underwent thyroid remnant ablation after either L-T4 withdrawal or rhTSH stimulation.

A post-therapy whole-body scan was obtained 5 days after 131-radioiodine therapy. Qualitative and quantitative image analysis was performed. Quantitative analysis was performed by drawing seven regions of interest on the abdomen (anterior and posterior views) to estimate both the activity ratio (AR) and absorbed dose ratio (DR) obtained in patients treated in hypothyroidism or after rhTSH stimulation.

Results The values of the activity and absorbed dose ratios obtained on each abdomen region (liver, stomach, ascending colon, transverse colon, descending colon, rectum, and small intestine) were always higher in patients treated after L-T4 withdrawal than after rhTSH stimulation with p-values of 0.000, 0.000, 0.001, 0.000, 0.022, 0.007, and 0.002, respectively.

Conclusions DTC patients treated with 131-radioiodine after rhTSH stimulation have lower abdominal radioiodine activity than hypothyroid patients. Our data could be of practical relevance in terms of patient management. The potential impact on rare radioiodine-related gastrointestinal side effects is to be established in specifically designed prospective studies.

Keywords Differentiated thyroid carcinoma · 131-radioiodine therapy · rhTSH stimulation · Levo-thyroxine withdrawal · Radioiodine side effects

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Introduction

Thyroid tumors occur in up to 5% of thyroid nodules. Differentiated thyroid cancer (DTC) is the most common form. In the last few decades, DTC incidence has been increasing with a very large prevalence of papillary thyroid carcinoma (PTC) and small tumors [1–5].

In DTC patients, 131-radioiodine therapy (RaIT) has routinely been used for many years for thyroid remnant ablation (TRA) after thyroid surgery. To date, according to the latest American Thyroid Association (ATA) guidelines [6], TRA is only indicated for high-risk DTC patients. However, the European Association of Nuclear Medicine

Table 1 Demographic and histological data of the patients underwent RaIT with both different strategies and RAI activities

	Male	Female	Mean age	Papillary	Follicular	rhTSH stimulation	Off-LT4	2220 MBq	3700 MBq
Patients (n = 63)	12	51	46,6	57	6	36	27	33	30
Histotype	10*	47*	45,9*	57*	0*	34*	23*	28*	29*
	2†	4†	53,1†	0†	6†	2†	4†	5†	1†
Strategy to perform RaIT	5‡	31‡	47,6‡	34‡	2‡	36‡	0‡	18‡	18‡
	7§	20§	45,2§	23§	4§	0§	27§	15§	12§
Radioiodine activity	4‖	29‖	45,5‖	28‖	5‖	18‖	15‖	33‖	0‖
	8¶	22¶	47,7¶	29¶	1¶	18¶	12¶	0¶	30¶

*Papillary thyroid carcinoma patients, ‡patients treated after rhTSH stimulation, †follicular thyroid carcinoma patients, §patients treated after L-T4 withdrawal, ‖patients treated with 2220 MBq, patients treated with 3700 MBq. RaIT = 131-radioiodine therapy

(EANM) [7] did not endorse ATA guidelines, since the role of nuclear medicine was too marginal.

ATA guidelines [6] do not indicate TRA in many patients, as RaIT would not improve overall survival rate.

Another argument not to indicate TRA has always been the possible side effects (i.e., induced secondary cancer) of ionizing radiation on some organs, such as the stomach and bladder (so-called critical organs) and small bowel [8–11]. However, to date, it is possible to perform TRA using recombinant human TSH (rhTSH) stimulation rather than Levo-thyroxine withdrawal. Indeed, rhTSH stimulation can produce an efficacious treatment maintaining patient quality of life and reducing the side effects due to hypothyroidism induced by LT4-withdrawal, as already reported [12–14].

Among hypothyroidism side effects, constipation due to reduced bowel motility is one of the more frequent and fastidious. In patients treated with 131-radioiodine, it can produce an increase of radiation exposure to the body (in particular the stomach and bowel).

The present retrospective analysis started from our routine clinical observation and was aimed to evaluate the abdominal absorbed dose ratio between differentiated thyroid cancer patients who underwent thyroid remnant ablation after either L-T4 withdrawal or rhTSH stimulation.

Materials and methods

The records of 63 consecutive patients (F = 51, M = 12; F/M ratio = 4.2:1; mean age 46.2 ± 13.4 yrs, range 18–79 yrs, median age: 46) affected by DTC [papillary thyroid carcinoma (PTC), n = 57 (F = 47, M = 10; F/M ratio = 4.7:1); follicular thyroid carcinoma (FTC), n = 6 (F = 4, M = 2; F/M 2:1)] referred to our Nuclear Medicine Unit from January 1, 2017 through December 31, 2017 were reviewed. From the present analysis, we excluded patients who did not meet the following criteria: (I) age ≥ 18 yrs; (II) serum TSH values ≥ 30 µUI/ml at RaIT; (III)—absence of—

locoregional or distant metastases (even if suspected); (IV) absence of any possible disease changing/reducing bowel motility (e.g., irritable bowel syndrome, inflammatory bowel disease).

All patients had undergone (near)-total thyroidectomy and underwent TRA 3 months from thyroid surgery and after either L-T4 withdrawal for 4 weeks (n = 27) or rhTSH stimulation according to standard protocol (n = 36). Thirty-three patients were treated with 2220 MBq (18 after rhTSH stimulation), while 30 patients were treated with 3700 MBq (18 after rhTSH stimulation). Data regarding the enrolled patients are summarized in Table 1.

In all patients, a post-therapy whole body scan (pT-WBS) was obtained 5 days (5d) after RaIT. Whole-body images from head to legs were acquired (scan speed: 5 cm/s) using a double-headed gamma camera (Millennium VG, GE Medical System, Chicago, IL, USA).

Patients took proton pump inhibitors (PPIs) for a week starting on the day of RaIT. In addition, to reduce background activity, patients were required to drink at least 1.5 litres of water and take laxative drugs 2 days before pT-WBS.

Qualitative and quantitative image analysis was always performed by the same experienced nuclear medicine physician (AC). Quantitative analysis was performed by drawing seven region-of-interest (ROI) on the abdomen in both anterior and posterior views, with different shapes and corresponding to the liver (L), stomach (S), ascending colon (AC), transverse colon (TC), descending colon (DC), rectum (R), small intestine (SI). For each region, we evaluated the activity incorporated at pT-WBS as the geometrical mean of anterior–posterior counts, corrected for background (Fig. 1a, b) [15].

We compared the activities in the various districts by calculating the activity ratio (AR) defined as:

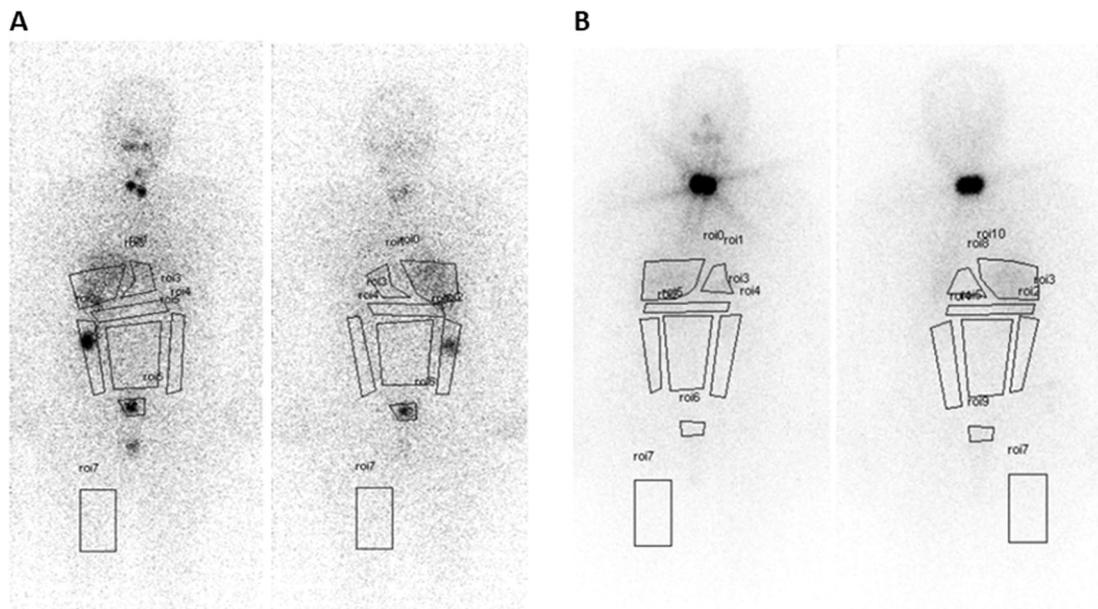$$AR = A_{withdr.}/A_{rhTSH} \tag{1}$$

Fig. 1 a Forty-three-year-old woman, pT2N1bMx-PTC (classic variant) located in the left lobe. Anterior and posterior views of pt-WBS images were obtained 5 days after RaIT (3700 MBq after 5 weeks L-T4 withdrawal). Thyroid remnant was noted, while none locoregional and/or distant 131-radioiodine avid metastases were observed. Regions of interest (ROIs) were painted on the abdomen in both anterior and posterior views. Moderate-to-intense radioiodine uptake were noted on the abdomen, mainly into ROI corresponding to the ascending colon and rectum. **b** Sixty-nine-year-old woman, pT2N0Mx-PTC (classic variant) located in the left lobe. Anterior and posterior views of pT-WBS images were obtained 5 days after RaIT (3700 MBq after rh-TSH stimulation). Thyroid remnant was noted, while none locoregional and/or distant 131-radioiodine avid metastases were observed. ROIs were painted on the abdomen in both anterior and posterior views. Interestingly, low to very-low radioiodine uptake were noted on the abdomen, mainly into ROI corresponding to the small intestine and large bowel

where $A_{withdr.}$ is the activity in the district L-T4 withdrawal regime, and A_{rhTSH} the activity in the rhTSH-stimulation regime. Furthermore, given that, according to the Medical Internal Radiation Dose (MIRD) formalism, the radiation-absorbed dose can be calculated as $D = \tilde{A}S$, where $\tilde{A}$ is the time-integrated activity and S is the S-factor, and considering that in the case of mono-exponential decay kinetics $\tilde{A} = A_0\tau_{eff} = A_0 T_{1/2eff}/ln2$, we estimated the absorbed dose ratio (DR) between the two groups of patients as:

$$DR = A_{withdr.}T_{1/2\,eff\,withdr.} / (A_{rhTSH}T_{1/2\,eff\,rhTSH}) \qquad (2)$$

where the effective half-lives of 15.7 and 10.5 h, respectively, for withdrawal and rhTSH, were used as already described [16].

Statistical analysis

Numerical data are expressed as mean and standard deviation, and the categorical variables as number and percentage.

Examined variables did not present normal distribution as verified by Kolmogorov–Smirnov test; consequently the nonparametric approach was used.

The Wilcoxon test was applied to compare activity (L-T4 withdrawal vs. rTSH) for each district (the liver, stomach, colon, intestine, and rectum), both for 2220 MBq and for 3700 MBq patients, separately and together.

The Mann–Whitney test was applied to evaluate statistical differences between two examined groups (2220 MBq and 3700 MBq patients), for each district.

Statistical analyses were performed using SPSS 20.0 for Window package.

A p-value ≤ 0.050 was considered to be statistically significant.

Results

Thyroid remnant was noted at visual analysis in all patients, but none showed either locoregional or distant 131-radioiodine avid metastases. AR and DR values are reported in Table 2. From the DR and AR values reported, both dose and activity values in L, S, AC, TC, DC, R, and SI regions were always higher in patients treated in L-T4 withdrawal than after rhTSH stimulation with p-values of 0.000, 0.000, 0.001, 0.000, 0.022, 0.007, and 0.002, respectively.

Table 2 Activity ratio (AR) and dose ratio (DR) for two groups of patients in seven abdominal districts

	Liver	Stomach	Ascending Colon	Transverse Colon	Descending Colon	Small Intestine	Rectum	
Patients treated with 3700 MBq (n = 30)	2.84	2.49	3.81	2.38	2.49	3.02	2.77	**AR** L-T4 withdrawal/rhTSH
	4.24	3.73	5.70	3.56	3.72	4.52	4.14	**DR** L-T4 withdrawal/rhTSH
Patients treated with 2220 MBq (n = 33)	2.06	3.18	2.06	1.94	1.49	1.70	2.18	**AR** L-T4 withdrawal/rhTSH
	3.08	4.76	3.08	2.90	2.23	2.54	3.26	**DR** L-T4 withdrawal/rhTSH
All patients (2220 + 3700 MBq) (n = 63)	2.42	2.78	2.91	2.13	1.96	2.33	2.45	**AR** L-T4 withdrawal/rhTSH
	3.62	4.16	4.34	3.19	2.93	3.48	3.66	**DR** L-T4 withdrawal/rhTSH

Average values are reported separately for the two therapeutic activities employed and as overall averages

In particular, AR and DR values calculated for L, S, AC, TC, DC, R, and SI regions were always higher in hypothyroid patients treated with 3700 MBq than in euthyroid patients treated with the same 131-radioiodine activity with p-value of 0.005, 0.037, 0.005, 0.005, 0.022, 0.013, and 0.013, respectively.

Finally, the lowest values of dose and activity for each region were observed in patients treated with 2220 MBq after rhTSH stimulation.

Discussion

According to the latest ATA guidelines [6], TRA is indicated for high-risk DTC patients only. Instead, RaIT is not recommended or only suggested/discouraged in patients affected by low or low-to-intermediate risk cancer, respectively.

As already known, EANM [7] did not endorse ATA guidelines and, more recently, two important points of view on this topic have been published [1, 17]. Luster et al. [17] indicated wider use of postoperative RaIT than ATA guidelines, suggesting modifications to approximately one-third of ATA 2015 recommendations.

ATA guidelines [6] do not indicate TRA in DTC patients with low or low-to-intermediate risk cancer, as RaIT would not improve the overall survival rate. However, this *main reason* is in clear contrast with results reported by Mazzaferri et al. [18] in their important paper (up to date the only prospective paper on this topic) in which they demonstrated how TRA significantly reduced both recurrence and DTC-specific mortality rates. Other authors have accordingly reported [19, 20].

In particular, also in so-called low or low-to-intermediate risk patients, RaIT should be considered as an adjuvant therapy useful to treat both microscopic neoplastic foci in thyroid remnant and unknown metastatic disease [21–23].

The possible side effects of ionizing radiation on organs such as the stomach, bladder, and small bowel have always represented the second reason not to indicate RaIT, mainly in so-called low or low-to-intermediate risk DTC patients [8–11].

However, TRA can now be performed after rhTSH stimulation rather than L-T4 withdrawal. The use of rhTSH stimulation offers at least two main advantages: first, it permits to perform efficacious RaIT in terms of either ablative or adjuvant scope maintaining patient quality of life, as already demonstrated [12–14]; second, the use of rhTSH reduces both absorbed dose to blood (since 131-radioiodine renal clearance is faster than in hypothyroid patients) [24, 25] and radiation exposure to the abdominal organs, since bowel motility is not slowed down. Accordingly, at pT-WBS visual analysis during our routine clinical

observation, we noted that abdominal radioiodine activity was lower in patients treated after rhTSH stimulation than in patients treated after L-T4 withdrawal.

Noteworthy, this *visual observation* was successively confirmed by quantitative analysis, which demonstrated a statistically significant difference in abdominal radioiodine uptake between patients treated after L-T4 withdrawal and those treated after rhTSH stimulation. Remy et al. in their landmark paper [16] reported similar results (in terms of dose estimates) at least regarding the stomach and upper large intestine (even if with a borderline p-value in the latter case). On the contrary, no significant differences were noted for lower large intestine.

However, the authors [16] did not report on which of the seven pT-WBS measurement time points (from $+0.5\,h$ to $+62\,h$) the dose estimates to lower large intestine were evaluated.

In our opinion, the authors did not find any significant differences in terms of dose estimates to lower large intestine between euthyroid and hypothyroid patients as they made this evaluation too early (within $62\,h$) also compared with time point used by us (i.e., 5 days after radioiodine administration or $120\,h$).

In light of this, our study is the first to evaluate the relationship between the strategy to obtain TRA (i.e., L-T4 withdrawal vs. rhTSH stimulation) and abdominal radioiodine activity (in terms of both AR and DR).

However, our study has some evident limitations in addition to the retrospective design. First of all, the limited number of considered patients reduces the statistical power of presented data, thus conferring them a preliminary significance only. Further studies on a larger cohort of patients are needed. In addition, due to our type of study, we did not perform our analysis on serial pT-WBSs performed at different times for each patient, as only a one-point-time pT-WBS (5d) for each patient was available and consequently analyzed.

In conclusion, DTC patients treated with 131-radioiodine after rhTSH stimulation have lower abdominal radioiodine activity than hypothyroid patients. Our data could be of practical relevance in terms of patient management (i.e., length of hospital stay, health cost, and patient quality of life). The potential impact on rare radioiodine-related gastrointestinal side effects is to be established in specifically designed prospective studies.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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References

1. F. Pacini, F. Basolo, R. Bellantone, G. Boni, M.A. Cannizzaro, M. De Palma, C. Durante, R. Elisei, G. Fadda, A. Frasoldati, L. Fugazzola, R. Guglielmi, C.P. Lombardi, P. Miccoli, E. Papini, G. Pellegriti, L. Pezzullo, A. Pontecorvi, M. Salvatori, E. Seregni, P. Vitti, Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies. J. Endocrinol. Invest. **41**(7), 849–876 (2018)

2. A. Campennì, L. Giovanella, A. Alibrandi, M. Siracusa, R.M. Ruggeri, S. Baldari, BRAF (V600E) mutation in isthmic malignant thyroid nodules. Clin. Endocrinol. **84**(1), 152–153 (2016)

3. A. Campennì, L. Giovanella, M. Siracusa, M.E. Stipo, A. Alibrandi, M. Cucinotta, R.M. Ruggeri, S. Baldari, Is malignant nodule topography an additional risk factor for metastatic disease in low-risk differentiated thyroid cancer? Thyroid **24**(11), 1607–1611 (2014)

4. R. Gallicchio, S. Giacomobono, D. Capacchione, A. Nardelli, F. Barbato, A. Nappi, T. Pellegrino, G. Storto, Should patients with remnants from thyroid microcarcinoma really not be treated with iodine-131 ablation? Endocrine **44**(2), 426–433 (2013)

5. R.M. Tuttle, H. Tala, J. Shah, R. Leboeuf, R. Ghossein, M. Gonen, M. Brokhin, G. Omry, J.A. Fagin, A. Shaha, 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 **20**(12), 1341–1349 (2010)

6. B.R. Haugen, E.K. Alexander, K.C. Bible, G.M. Doherty, S.J. Mandel, Y.E. Nikiforov, F. Pacini, G.W. Randolph, A.M. Sawka, M. Schlumberger, K.G. Schuff, S.I. Sherman, J.A. Sosa, D.L. Steward, R.M. Tuttle, L. Wartofsky, 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**, 1–133 (2015)

7. F.A. Verburg, C. Aktolun, A. Chiti, S. Frangos, L. Giovanella, M. Hoffmann, I. Iakovou, J. Mihailovic, B.J. Krause, W. Langsteger, M. Luster; EANM and the EANM Thyroid Committee, Why the European Association of Nuclear Medicine has declined to endorse the 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Eur. J. Nucl. Med. Mol. Imaging **43**, 1001–1005 (2016)

8. A.M. Sawka, L. Thabane, L. Parlea, I. Ibrahim-Zada, R.W. Tsang, J.D. Brierley, S. Straus, S. Ezzat, D.P. Goldstein, Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid **19**, 451–457 (2009)

9. S. Subramanian, D.P. Goldstein, L. Parlea, L. Thabane, S. Ezzat, I. Ibrahim-Zada, S. Straus, J.D. Brierley, R.W. Tsang, A. Gafni, L. Rotstein, A.M. Sawka, Second primary malignancy risk in thyroid cancer survivors: a systematic review and meta-analysis. Thyroid **17**(12), 1277–1288 (2007)

10. M. Silva-Vieira, S. Carrilho Vaz, S. Esteves, T.C. Ferreira, E. Limbert, L. Salgado, V. Leite, Second primary cancer in patients with differentiated thyroid cancer: does radioiodine play a role? Thyroid 27(8), 1068–1076 (2017)

11. F. de Vathaire, M. Schlumberger, M.J. Delisle, C. Francese, C. Challeton, E. de la Genardiére, F. Meunier, C. Parmentier, C. Hill, H. Sancho-Garnier, Leukaemias and cancers following iodine-131 administration for thyroid cancer. Br. J. Cancer 75(5), 734–739 (1997)

12. A. Campennì, L. Giovanella, S.A. Pignata, M.A. Violi, M. Siracusa, A. Alibrandi, M. Moleti, E. Amato, R.M. Ruggeri, F. Vermiglio, S. Baldari, Thyroid remnant ablation in differentiated thyroid cancer: searching for the most effective radioiodine activity and stimulation strategy in a real-life scenario. Nucl. Med. Commun. 36, 1100–1106 (2015)

13. C. Reiners, M. Lassmann, M. Luster, Recombinant human thyrotropin: safety and quality of life evaluation. J. Endocrinol. Invest. 35(6 Suppl), 30–35 (2012)

14. F. Pacini, P.W. Ladenson, M. Schlumberger, A. Driedger, M. Luster, R.T. Kloos, S. Sherman, B. Haugen, C. Corone, E. Molinaro, R. Elisei, C. Ceccarelli, A. Pinchera, R.L. Wahl, S. Leboulleux, M. Ricard, J. Yoo, N.L. Busaidy, E. Delpassand, H. Hanscheid, R. Felbinger, M. Lassmann, C. Reiners, 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(3), 926–932 (2006)

15. J.A. Siegel, S.R. Thomas, J.B. Stubbs, M.G. Stabin, M.T. Hays, K.F. Koral, J.S. Robertson, R.W. Howell, B.W. Wessels, D.R. Fisher, D.A. Weber, A.B. Brill, MIRD pamphlet no. 16: techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. J. Nucl. Med. 40(2), 37S–61S (1999)

16. H. Remy, I. Borget, S. Leboulleux, N. Guilabert, F. Lavielle, J. Garsi, C. Bournaud, S. Gupta, M. Schlumberger, M. Ricard, 131I effective half-life and dosimetry in thyroid cancer patients. J. Nucl. Med. 49, 1445–1450 (2008)

17. M. Luster, C. Aktolun, I. Amendoeira, M. Barczyński, K.C. Bible, L.H. Duntas, R. Elisei, D. Handkiewicz-Junak, M. Hoffmann, B. Jarzab, L. Leenhardt, T.J. Musholt, K. Newbold, I.J. Nixon, J. Smit, M. Sobrinho-Simões, J.A. Sosa, R.M. Tuttle, F. Verburg, L. Wartofsky, D. Führer-Sakel, European perspective on the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Proceedings of an Interactive International Symposium. Thyroid. (2018). https://doi.org/10.1089/thy.2017.0129.

18. E.L. Mazzaferri, S.M. Jhiang, Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am. J. Med. 97, 418–428 (1994)

19. A.M. Sawka, K. Thephamongkhol, M. Brouwers, L. Thabane, G. Browman, H.C. Gerstein, Clinical review 170: a systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J. Clin. Endocrinol. Metab. 89(8), 3668–3676 (2004)

20. E. Ruel, S. Thomas, M. Dinan, J.M. Perkins, S.A. Roman, J.A. Sosa, Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. J. Clin. Endocrinol. Metab. 100(4), 1529–1536 (2015)

21. A. Campennì, S.A. Pignata, S. Baldari, Post-operative radioiodine therapy (RaIT) as adjuvant therapy in low–intermediate risk differentiated thyroid cancer. Clin. Transl. Imaging. (2018). https://doi.org/10.1007/s40336-018-0298-3

22. Y. Luo, Y. Zhao, K. Chen, J. Shen, J. Shi, S. Lu, J. Lei, Z. Li, D. Luo, Clinical analysis of cervical lymph node metastasis risk factors in patients with papillary thyroid microcarcinoma. J. Endocrinol. Invest. (2018). https://doi.org/10.1007/s40618-018-0908-y

23. A. Campennì, L. Giovanella, S.A. Pignata, A. Vento, A. Alibrandi, L. Sturiale, R. Laudicella, A.D. Comis, R. Filice, G. Giuffrida, M.E. Stipo, S. Giovinazzo, F. Trimarchi, R.M. Ruggeri, S. Baldari, Undetectable or low (<1 ng/ml) postsurgical thyroglobulin values do not rule out metastases in early stage differentiated thyroid cancer patients. Oncotarget 9, 17491–17500 (2018)

24. H. Hänscheid, M. Lassmann, M. Luster, S.R. Thomas, F. Pacini, C. Ceccarelli, P.W. Ladenson, R.L. Wahl, M. Schlumberger, M. Ricard, A. Driedger, R.T. Kloos, S.I. Sherman, B.R. Haugen, V. Carriere, C. Corone, C. Reiners, 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 (2006)

25. M. Lassmann, H. Hänscheid, F.A. Verburg, M. Luster, The use of dosimetry in the treatment of differentiated thyroid cancer. Q. J. Nucl. Med. Mol. Imaging 55(2), 107–115 (2011)