Endocrine (2021) 71:378–384
https://doi.org/10.1007/s12020-020-02379-1

ORIGINAL ARTICLE

Risk of structural persistent disease in pediatric patients with low or intermediate risk differentiated thyroid cancer

Michele Klain[1] · Emilia Zampella[1] · Mariarosaria Manganelli[1] · Valeria Gaudieri[1] · Carmela Nappi[1] · Adriana D'Antonio[1] · Leandra Piscopo[1] · Fabio Volpe[1] · Leonardo Pace[2] · Martin Schlumberger[1] · Alberto Cuocolo[1]

Received: 3 April 2020 / Accepted: 1 June 2020 / Published online: 11 June 2020

Abstract

Purpose In pediatric patients with differentiated thyroid cancer (DTC), the risk of recurrence is high and the indication for postoperative ^{131}I administration is still debated. The aim of this study was to assess the outcome in low and intermediate risk pediatric DTC patients.

Methods We retrospectively evaluated 45 pediatric patients with low or intermediate risk DTC, treated with surgery and ^{131}I between 1992 and 2002 and with no detectable antithyroglobulin (Tg) antibodies. Follow-up was performed every 6–12 months with Tg blood level determination and imaging procedures.

Results During follow-up (64 ± 53 months), 15 events occurred (33% cumulative event rate, with an annual event rate of 5% person years). Five of these patients were submitted to additional surgery and all these 15 patients underwent a second ^{131}I treatment course. All patients were alive at the end of the follow-up. Structural persistent disease occurred more frequently in patients at intermediate risk ($p < 0.01$) and in those with Tg values after thyroid hormone withdrawal >10 ng/ml before ^{131}I therapy ($p < 0.01$). At multivariate analysis, only a postoperative thyroid stimulating hormone-stimulated Tg level >10 ng/ml was an independent predictor of persistent disease.

Conclusions In pediatric patients with DTC, postoperative high stimulated Tg values (>10 ng/ml) should be taken into account for deciding the extent of both initial treatment and follow-up.

Keywords Differentiated thyroid carcinoma · ^{131}I therapy · Prognosis · Pediatric patients

Introduction

Differentiated thyroid cancer (DTC) is rare in children, being discovered in 2–3/million children/year in whom it accounts for 21% of all head and neck tumors [1, 2]. Children typically present with advanced disease with large thyroid tumors with frequent extension beyond the thyroid capsule, extensive regional nodal involvement, and distant metastases usually in lungs are more frequently observed than in adult patients [3]. Recurrences are frequent in particular in younger patients [4, 5]. Metastases are usually highly radio-active iodine (RAI) avid with an excellent response to ^{131}I therapy. Overall survival is 98% at 20 years, but cancer related death may occur 30–40 years or even more after initial treatment [6].

According to the American Thyroid Association (ATA) pediatric guidelines [7], postsurgery findings permit the classification of patients as low, intermediate, or high recurrence risk. An improved overall survival and a lower recurrence rate were reported in patients with advanced DTC who received postoperative RAI therapy [7]. However, the role of RAI has not currently been fully clarified in pediatric patients at low or even intermediate risk of recurrence.

The aim of this study was to assess the risk of structural persistent disease in pediatric DTC patients with low and intermediate ATA risk, after an initial treatment with surgery and RAI.

✉ Alberto Cuocolo
cuocolo@unina.it

[1] Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy

[2] Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy

Materials and methods

Study population

We retrospectively evaluated the 69 pediatric DTC patients (age < 18 years) who were referred to our center between 1992 and 2002. All patients underwent a total thyroidectomy, with central and/or lateral neck dissection in 56 (81%) of them. Postoperative histopathological data were collected including tumor histology, tumor size, extrathyroid extension, multifocality, and lymph node involvement. After surgery, and before RAI administration, patients were classified according to the ATA pediatric guidelines as low risk (disease grossly confined to the thyroid with N0 or Nx disease or patients with incidental N1a metastasis), intermediate risk (extensive N1a or minimal N1b disease) or high risk (extensive N1b disease or T4 tumor with gross tumor extension beyond the thyroid capsule, with or without distant metastasis) [7]. In order to consider central (N1a) and lateral (N1b) nodal involvement as extensive, we used the number and size of lymph nodes, for N1a > 5 or >0.2 cm and for N1b > 10 or ≥3 cm, according to the ATA adult guidelines [8, 9]. Before RAI administration, L-thyroxine was discontinued for 20–30 days and until thyroid stimulating hormone (TSH) level increased over 30 mIU/l. At that time, a neck ultrasound was performed, serum thyroglobulin (Tg) and Tg-Antibodies (Tg-Ab) concentrations were measured and ^{131}I was administered. The therapeutic ^{131}I activity was adjusted to the disease stage and ranged from 37 to 111 MBq/Kg body weight. Five to seven days later, a posttherapy whole-body scan (WBS) was performed.

Serum Tg and TSH were determined by Immunite immunoassay (Siemens Healthcare Diagnostics,) with sensitivities of 0.2 ng/ml and 0.03 mIU/l, respectively. Tg-Ab were detected by Quanta Lite enzyme-linked immunosorbent assay (Inova Diagnostics).

Follow-up

Patients were followed every 6–12 months with serum Tg determinations (on L-thyroxine and in some patients off L-thyroxine therapy) and with imaging procedures as appropriate. Disease status was recorded at each evaluation. Disease-free survival was measured from the date of surgery to the first observation of structural disease persistence [8, 10] or additional therapy (i.e., RAI or surgery). Structural disease persistence was defined by histology or imaging procedures; suspicious nodal abnormalities at neck ultrasonography were confirmed by fine needle aspiration cytology, histology, or the presence of RAI uptake; uptake in the thyroid bed at posttherapy WBS was considered structural disease when it corresponded to abnormal findings at neck ultrasonography and fine needle biopsy [11]. Patients last known to be alive and disease free were censored at the date of last contact.

Statistical analysis

Continuous data are expressed as mean ± standard deviation and categorical data as percentage. Student's two-sample t test and χ^2 test were used to compare the differences in continuous and categorical variables, respectively. Annualized event rate (AER), expressed as % person years was calculated as the cumulative number of events divided by person time at risk. The maximum value of the Youden index J was used as a criterion for selecting the optimum cut-off point for Tg on receiver operating characteristic (ROC) curves [12]. Hazard ratios with 95% confidence intervals (CI) were calculated by univariate and multivariate Cox regression analysis. Variables showing a p value < 0.05 at univariate analysis were considered for multivariate analysis. Disease-free survival analysis was performed using the Kaplan–Meier method and log-rank test. Statistical analysis was performed with Stata 12 software (StataCorp, College Station, TX, USA).

Results

Data from 69 patients aged less than 18 years at initial treatment were recorded. We excluded 15 patients, 8 with positive serum anti-Tg antibody that might induce falsely negative serum Tg determination and 7 who were classified postoperatively as ATA high risk for T4 disease in 2 and for extensive N1b disease in 5. Moreover, among these seven patients three had lung metastases that were known at the time of surgery and four had lung metastases that were discovered at posttherapy WBS.

Of the 54 patients, follow-up was not available in 9 (17%) patients, leaving 45 subjects who formed the basis for the analysis (Table 1). Mean follow-up time was 64 ± 53 months (range 9–205 months). During follow-up, 15 structural events occurred (33% cumulative event rate, with an AER of 5% person years). Five of these patients were submitted to additional surgery for nodal disease evidenced by neck ultrasound in sites previously involved (two with N1a and three with N1b disease at diagnosis). The other ten patients underwent a second RAI treatment course for structural disease in the neck that was located in the thyroid bed in four patients and in both lymph nodes and thyroid bed in the other six (Table 2). At initial posttherapy WBS, one patient had no detectable neck uptake and experienced a lymph node recurrence during follow-up. The other 44 patients had high neck uptake, indicating the presence of large postoperative residues of thyroid tissue. In 38

Table 1 Baseline characteristics according to the occurrence of events

	All patients ($n = 45$)	Event ($n = 15$)	No event ($n = 30$)	p value
Age (years)	16 ± 2	15 ± 3	16 ± 2	0.18
Age ≤ 14 years, *n* (%)	15 (33)	8 (53)	7 (23)	<0.05
Age > 14 years, *n* (%)	30 (67)	7 (47)	23 (77)	<0.05
Male gender, *n* (%)	13 (29)	5 (33)	8 (27)	0.64
Low risk, *n* (%)	24 (53)	3 (20)	21 (70)	<0.01
Intermediate risk, *n* (%)	21 (47)	12 (80)	9 (30)	<0.01
Papillary type, *n* (%)	43 (96)	13 (87)	30 (100)	0.09
Tumor size >2 cm, *n* (%)[a]	26 (58)	11 (73)	15 (50)	0.13
Neck dissection, *n* (%)	35 (78)	13 (87)	22 (73)	0.31
Lymph node involvement, *n* (%)[b]	34 (76)	13 (87)	21 (70)	0.22
Time interval surgery/RAI therapy (days)	136 ± 150	121 ± 110	143 ± 167	0.64
Administered ^{131}I activity (MBq/Kg)	80 ± 27	84 ± 21	78 ± 29	0.43
Pre-therapy Tg off (ng/ml)	36 ± 70	82 ± 21	13 ± 18	<0.001
Neck uptake at WBS, *n* (%)	44 (98)	14 (93)	30 (100)	0.15

Data are presented as mean ± SD or number and percentage (%)

Tg thyroglobulin, *WBS* posttherapy whole-body scan, *off* off L-thyroxine therapy, before the postoperative administration of ^{131}I

[a]Only one patient had minimal tumor extension beyond the thyroid capsule

[b]% of the patients who underwent an initial lymph node dissection

Table 2 Characteristics of patients with structural events

	Initial treatment		pTNM[a]							Recurrence site	Recurrence treatment		Final clinical status[b]		
	TT	ND	T1	T2	T3	T4	N0	N1a	N1b		ND	RAI therapy	Excellent response	Biochemically incomplete response	Structurally incomplete response
1	+	−	+	−	−	−	+	−	−	TB	−	+	+	−	−
2	+	−	+	−	−	−	+	−	−	TB	−	+	+	−	−
3	+	+	+	−	−	−	−	+	−	LN	+	−	+	−	−
4	+	+	+	−	−	−	−	+	−	LN	+	−	+	−	−
5	+	+	−	+	−	−	−	+	−	TB	−	+	−	+	−
6	+	+	−	+	−	−	−	+	−	TB	−	+	−	+	−
7	+	+	−	+	−	−	−	−	+	LN	+	−	+	−	−
8	+	+	−	+	−	−	−	−	+	LN	+	−	+	−	−
9	+	+	−	+	−	−	−	−	+	TB + LN	−	+	+	−	−
10	+	+	−	+	−	−	−	−	+	TB + LN	−	+	−	+	−
11	+	+	−	−	+	−	−	+	−	TB + LN	−	+	−	+	−
12	+	+	−	−	+	−	−	+	−	TB + LN	−	+	−	+	−
13	+	+	−	−	+	−	−	−	+	TB + LN	−	+	−	+	−
14	+	+	−	−	+	−	−	−	+	LN	+	−	−	+	−
15	+	+	−	−	+[c]	−	−	−	+	TB + LN	−	+	−	−	+

TT total thyroidectomy, *ND* neck dissection, *TB* thyroid bed, *LN* lymph nodes

[a]See Ref. [20]

[b]According to references [8] and [12]

[c]Minimal tumor extension beyond thyroid capsule

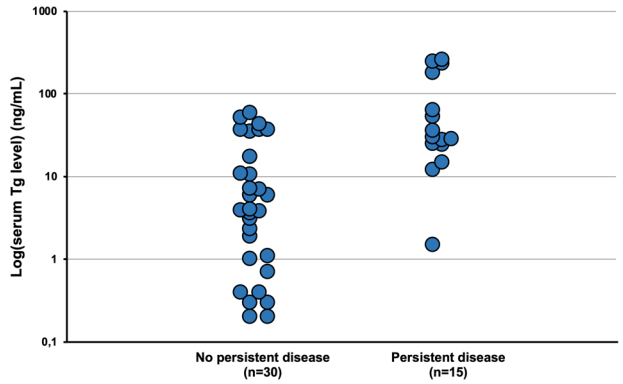

Fig. 1 Postoperative serum Tg level (>10 ng/ml or ≤10 ng/ml) following thyroid hormone withdrawal and before RAI administration according to the risk of structural persistent disease

of these 44 patients, there was no suspicious finding at initial neck ultrasound; of these 38 patients, 8 had a neck recurrence during follow-up, 4 only in the thyroid bed, and 4 in both the thyroid bed and lymph nodes. The other six patients with neck uptake at initial WBS had suspicious lymph nodes at initial neck ultrasound and two had a neck recurrence in both the thyroid bed and lymph nodes and four had a recurrence only in lymph nodes. No patient had lung uptake at posttherapy WBS. All these 15 patients were alive at the end of the follow-up, 7 with no evidence of disease who were classified as excellent response, 7 with detectable serum Tg on L-T4 treatment (range: 4–17 ng/ml) who were classified as biochemically incomplete response and 1 with persistent structural disease who was classified as structurally incomplete response. Among the 30 patients who had no structural recurrence during follow-up, 26 had an excellent response and 4 a biochemical incomplete response (range of Tg levels: 1.4–2.3 ng/ml).

Predictors of events

The rate of structural events was significantly higher in the 21 patients at intermediate risk compared with those 24 at low risk (cumulative event rate 57% vs. 12% and AER 11% vs. 1.5%, both $p < 0.01$). The risk of recurrence was higher in younger (≤14 years) ($n = 15$) than in older ($n = 30$) patients, but this difference was not statistically significant at univariate analysis (cumulative event rate 53% vs. 23% and AER 8% vs. 3%, both $p = 0.07$). Using ROC curve analysis, TSH-stimulated Tg value >10 ng/ml before postoperative RAI therapy was identified as the best trade-off between sensitivity (93%) and specificity (73%) in predicting the occurrence of events. The 22 patients with a TSH-stimulated Tg > 10 ng/ml (median 37; range 12–260 ng/ml) before the postoperative RAI therapy showed a higher rate of structural events as compared with those 23 with a serum Tg level ≤ 10 ng/ml (median 2; range 0.2–10 ng/ml) (cumulative event rate 64% vs. 13% and AER 15% vs. 0.5%, both $p < 0.01$) (Fig. 1).

Table 3 Univariate and multivariate predictors of structural persistent disease

	Univariate		Multivariate	
	Hazard ratio	*p* value	Hazard ratio	*p* value
Intermediate risk vs. low risk	1.85	<0.01	1.25	0.06
Tg >10 ng/ml vs. <10 ng/ml	3.10	<0.01	2.48	<0.01
Age ≤14 years vs. >14 years	0.93	0.07		

Tg thyroglobulin obtained following thyroid hormone withdrawal before the RAI administration

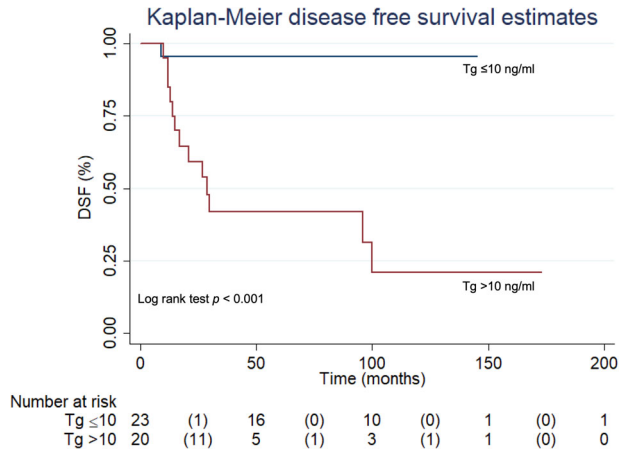

Fig. 2 Disease-free survival by Kaplan–Meier according to the postoperative serum Tg level (>10 ng/ml or ≤10 ng/ml) following TSH stimulation and before RAI administration

At multivariate analysis, the only independent significant prognostic factor of structural recurrence was a serum TSH-stimulated Tg level >10 ng/ml at the time of the postoperative RAI ($p < 0.001$) (Table 3 and Fig. 2). ATA risk category was not independently significant. Figure 3 illustrates a higher risk of structural recurrence in patients with a serum Tg level >10 ng/ml in both ATA risk and age categories (both *p* for trend <0.001).

Discussion

In this retrospective study of pediatric DTC patients with ATA low or intermediate risk of recurrence who were treated with surgery and RAI, the multivariate analysis shows that a serum Tg level off L-thyroxine therapy >10 ng/ml at the time of the postoperative RAI administration is the only independent predictor for structural disease recurrence. Actually, a TSH-stimulated Tg >10 ng/ml has a high

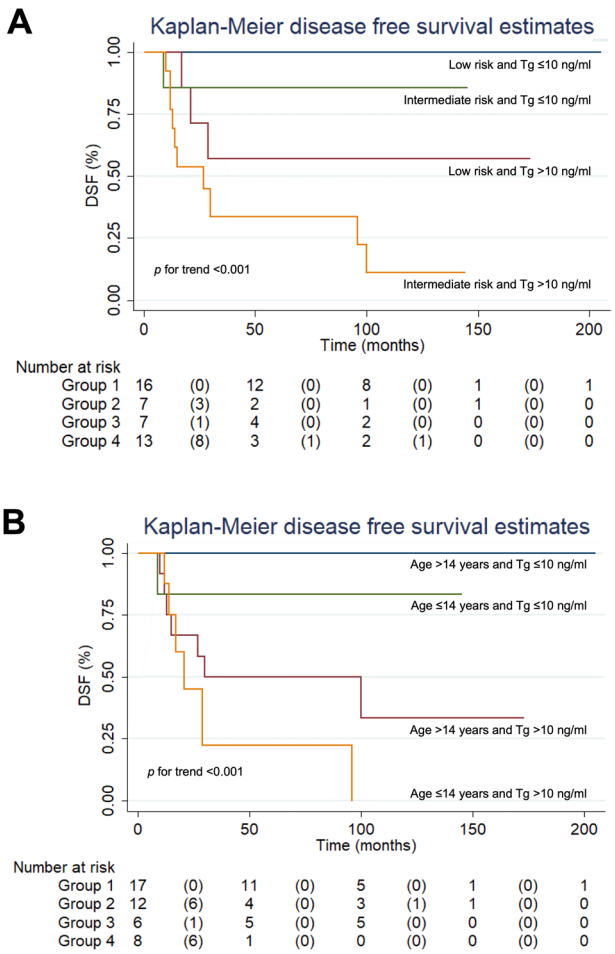

Fig. 3 Disease-free survival curves by Kaplan–Meier according to postoperative serum Tg levels obtained following thyroid hormone withdrawal and ATA risk of recurrence (**a**), and age at diagnosis (**b**)

prognostic impact in both age groups (> or ≤14 years at the time of initial treatment) and ATA risk groups (low or intermediate). Age and risk group categories were not independently significant in the multivariate analysis and this may be related to the relatively small number of patients under study.

In children, a more advanced disease at diagnosis and a higher rate of recurrence as compared with adults indicate the need for lifelong surveillance, but the overall survival is excellent [7].

This high risk of structural recurrence is probably related to the frequent persistence of disease after surgery, that could not be detected on neck ultrasonography due to local postoperative inflammation nor on the posttherapy WBS due to high RAI uptake in the thyroid bed, and at the time of treatment (before 2002), single photon emission computed tomography (SPECT/CT) technology was not available [13].

The high incidence of recurrence in the thyroid bed suggests that the initial resection of the thyroid gland was incomplete as shown by the presence of a high RAI uptake on initial WBS, leaving some foci of thyroid cancer that were not recognized by neck ultrasonography at the time of initial RAI treatment. These foci were not eradicated with RAI treatment and they progressed over time leading to a structural recurrence. It is also noteworthy that all the six patients with suspicious lymph node findings at initial neck ultrasonography experienced a lymph node recurrence during follow-up despite RAI treatment. This strongly suggests in agreement with previous studies [3–8, 14, 15] that complete surgery including a total thyroidectomy leaving small thyroid residues and a complete resection of all metastatic lymph nodes is the best way to decrease the risk of recurrence.

The present study focused on low and intermediate risk patients as assessed postoperatively according to pediatric ATA guidelines, thus excluding high risk patients. A categorization strategy based on the extent of regional disease appears to correlate best with the risk of structural persistent disease. The risk associated with lymph node involvement in the ATA pediatric guidelines [7] is related to central or lateral location of lymph node involvement, but to refine this classification and define extensive lymph node involvement we also used criteria proposed in the adult ATA guidelines, such as the number and size of the metastatic lymph nodes [8, 9]. In fact, the presence of palpable neck lymph nodes at diagnosis is predictive for recurrence, in particular in younger patients (<15 years) [4, 6].

Hay et al. [3] in a large cohort of papillary thyroid cancer patients (190 children and 4242 adults) found that during the past 40 years the risk of specific mortality was <1% in both children and adults at low risk (MACIS score <6). Differently, significant improvements in mortality rate were observed in high risk patients during the last decades, that may be related to advances in surgery and RAI treatment, but that were not associated with a decreased rate of structural tumor recurrence. In the present study, one-third of patients experienced a structural recurrence but all patients were alive at the end of follow-up and 33 of the 45 patients were considered as excellent response, including 7 of the 15 patients who experienced a neck structural event.

Therefore, the identification of patients at higher risk of recurrence is pivotal. In 109 children older age, total thyroidectomy and RAI had a positive impact on disease-free survival and in a multivariate analysis, radical surgery was the most significant factor for disease-free survival [5, 14]. Younger age was also found as a major predictor of recurrence in pediatric DTC patients [6, 14].

The use of RAI could be restricted to patients in whom the primary tumor and regional nodal metastases have not been completely resected at surgery and this might be indicated by detectable postoperative serum Tg. In "ESTIMABL1" a recent randomized, equivalence trial in 752

adult patients with low-risk thyroid cancer, persistent disease was infrequent after surgery in patients with an undetectable or low postoperative TSH-stimulated Tg level and increases with serum Tg level and in particular when it increases above 10 ng/ml [16], in accordance with previous studies in adults [13, 17, 18]. This was also reported with serum Tg determination on L-T4 treatment and using sensitive serum Tg determination in patients who had not received postoperative RAI [19]. Our data are consistent with these previous reports, which focused on the strong value of Tg in predicting the outcome in DTC patients, even following an apparently complete surgical resection of the disease. In our low or intermediate risk population, no patient had distant metastatic disease at posttherapy WBS or during follow-up. Therefore, the detection of a high serum Tg value could improve the postsurgical risk stratification and indicate RAI treatment. Whether diagnostic WBS should be routinely performed postoperatively in pediatric DTC patients with low serum Tg level needs to be determined by further studies.

Conclusions

Our data suggest that in pediatric patients with DTC, postoperative elevated Tg values (>10 ng/ml) have a high prognostic impact and should lead to more aggressive treatments and closer monitoring, especially in patients with an intermediate risk of recurrence or with a younger age.

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 patients.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. N.L. Shapiro, N. Bhattacharyya, Population-based outcomes for pediatric thyroid carcinoma. Laryngoscope **115**, 337–340 (2005)
2. S. Dermody, A. Walls, E.H. Jr Harley, Pediatric thyroid cancer: an update from the SEER database 2007-2012. Int. J. Pediatr. Otorhinolaryngol. **89**, 121–126 (2016)
3. I.D. Hay, T.R. Johnson, S. Kaggal, M.S. Reinalda, N.M. Iniguez-Ariza, C.S. Grant, S.T. Pittock, G.B. Thompson, Papillary thyroid carcinoma (PTC) in children and adults: comparison of initial presentation and long-term postoperative outcome in 4432 patients consecutively treated at the Mayo Clinic during eight decades (1936-2015). World J. Surg. **42**, 329–342 (2018)
4. F. Borson-Chazot, S. Causeret, J.C. Lifante, M. Augros, N. Berger, J.L. Peix, Predictive factors for recurrence from a series of 74 children and adolescents with differentiated thyroid cancer. World J. Surg. **28**, 1088–1092 (2004)
5. D. Handkiewicz-Junak, J. Wloch, J. Roskosz, J. Krajewska, A. Kropinska, L. Pomorski, A. Kukulska, A. Prokurat, Z. Wygoda, B. Jarzab, Total thyroidectomy and adjuvant radioiodine treatment independently decrease locoregional recurrence risk in childhood and adolescent differentiated thyroid cancer. J. Nucl. Med. **48**, 879–888 (2007)
6. M. Schlumberger, F. De Vathaire, J.P. Travagli, G. Vassal, J. Lemerle, C. Parmentier, M. Tubiana, Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. J. Clin. Endocrinol. Metab. **65**, 1088–1094 (1987)
7. G.L. Francis, S.G. Waguespack, A.J. Bauer, P. Angelos, S. Benvenga, J.M. Cerutti, C.A. Dinauer, J. Hamilton, I.D. Hay, M. Luster, M.T. Parisi, M. Rachmiel, G.B. Thompson, S. Yamashita; American Thyroid Association Guidelines Task Force., Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid **25**, 716–759 (2015)
8. 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. Schuff, S.I. Sherman, J.A. Sosa, D.L. Steward, M. Tuttle, L. Wartofsky, The American Thyroid Association (ATA) Guidelines Taskforce on thyroid nodules and differentiated thyroid cancer. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid **26**, 1–133 (2016)
9. G.W. Randolph, Q.Y. Duh, K.S. Heller, V.A. LiVolsi, S.J. Mandel, D.L. Steward, R.P. Tufano, R.M. Tuttle, 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 (2012)
10. 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**, 1341–1349 (2010)
11. M. Klain, L. Pace L, E. Zampella, T. Mannarino, S. Limone, E. Mazziotti, G. De Simini, A. Cuocolo, Outcome of patients with differentiated thyroid cancer treated with 131-iodine on the basis of a detectable serum thyroglobulin level after initial treatment. Front. Endocrinol. **10**, 146 (2019)
12. M.D. Ruopp, N.J. Perkins, B.W. Whitcomb, E.F. Schisterman, Youden index and optimal cut-point estimated from observations affected by a lower limit of detection. Biom. J. **50**, 419–430 (2008)
13. R. Ciappuccini, N. Heutte, G. Trzepla, J.P. Rame, D. Vaur, N. Aide, S. Bardet, Postablation (131)I scintigraphy with neck and thorax SPECT-CT and stimulated serum thyroglobulin level predict the outcome of patients with differentiated thyroid cancer. Eur. J. Endocrinol. **164**, 961–969 (2011)
14. B. Jarzab, D. Handkiewicz Junak, J. Włoch, B. Kalemba, J. Roskosz, A. Kukulska, Z. Puch, Multivariate analysis of prognostic factors for differentiated thyroid carcinoma in children. Eur. J. Nucl. Med. **27**, 833–841 (2000)
15. A.J. Alessandri, K.J. Goddard, G.K. Blair, C.J. Fryer, K.R. Schultz, Age is the major determinant of recurrence in pediatric

differentiated thyroid carcinoma. Med. Pediatr. Oncol. **35**, 41–46 (2000)
16. M. Schlumberger, S. Leboulleux, B. Catargi, D. Deandreis, S. Zerdoud, S. Bardet, D. Rusu, Y. Godbert, C. Buffet, C. Schvartz, P. Vera, O. Morel, D. Benisvy, C. Bournaud, M.E. Toubert, A. Kelly, E. Benhamou, I. Borget, ESTIMABL1: favorable outcome after ablation in low risk thyroid cancer patients. Lancet Diabetes Endocrinol. **6**, 618–626 (2018)
17. M. Toubeau, C. Touzery, P. Arveux, G. Chaplain, G. Vaillant, A. Berriolo, J.M. Riedinger, C. Boichot, A. Cochet, F. Brunotte, Predictive value for disease progression of serum thyroglobulin levels measured in the postoperative period and after (131)I ablation therapy in patients with differentiated thyroid cancer. J. Nucl. Med. **45**, 988–994 (2004)
18. T.Y. Kim, W.B. Kim, E.S. Kim, J.S. Ryu, J.S. Yeo, S.C. Kim, S.J. Hong, Y.K. Shong, Serum thyroglobulin levels at the time of 131I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. J. Clin. Endocrinol. Metab. **90**, 1440–1445 (2005)
19. A. Matrone, C. Gambale, P. Piaggi, D. Viola, C. Giani, L. Agate, V. Bottici, F. Bianchi, G. Materazzi, P. Vitti, E. Molinaro, R. Elisei, Postoperative thyroglobulin and neck ultrasound in the risk restratification and decision to perform 131I ablation. J. Clin. Endocrinol. Metab. **102**, 893–902 (2017)
20. J.D. Brierley, M.K. Gospodarowicz, C. Wittekind. *TNM Classification of Malignant Tumours* (John Wiley & Sons, Hoboken, NJ, 2017)