

Pediatric differentiated thyroid carcinoma in the Netherlands: a nationwide follow-up study

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Introduction: Treatment for differentiated thyroid carcinoma (DTC) in pediatric patients is based mainly on evidence from adult series due to lack of data from pediatric cohorts. Our objective was to evaluate presentation, treatment-related complications, and long-term outcome in patients with pediatric DTC in the Netherlands.

Patients and methods: In this nationwide study, presentation, complications and outcome of patients with pediatric DTC (age at diagnosis ≤ 18 years) treated in the Netherlands between 1970 and 2013 were assessed using medical records.

Results: We identified 170 patients. Overall survival was 99.4% after median follow-up of 13.5 (range 0.3–44.7) years. Extensive follow-up data were available for 105 patients (83.8% women), treated in 39 hospitals. Median age at diagnosis was 15.6 (range 5.8–18.9) years. At initial diagnosis, 43.8% of the patients had cervical lymph node metastases; 13.3% had distant metastases. All patients underwent total thyroidectomy. Radioiodine was administered to 97.1%, with a median

cumulative activity of 5.66 (range 0.74–35.15) GBq. Lifelong postoperative complications (permanent hypoparathyroidism and/or recurrent laryngeal nerve injury) were present in 32.4% of the patients. At last known follow-up, 8.6% of the patients had persistent disease and 7.6% experienced a recurrence. TSH suppression was not associated with recurrences (OR 2.00, 95% CI 0.78 to 5.17, $P = 0.152$).

Conclusions: Survival of pediatric DTC is excellent. Therefore, minimizing treatment-related morbidity takes major priority. Our study shows a frequent occurrence of lifelong postoperative complications. Adverse effects may be reduced by centralization of care, which is crucial for children with DTC.

Differentiated thyroid carcinoma (DTC), which comprises papillary (PTC) and follicular thyroid carcinoma (FTC), is a rare disease during childhood. Age-standardized incidence rates for children 0–4 years of age are 0.4 per 100,000, and up to 1.5 per 100,000 for adolescents aged 15–19 years (1). However, DTC is the most common pediatric endocrine malignancy and its incidence is increasing (1–3). The prognosis in children has been reported to be excellent with 15-year survival rates > 95% (3). Due to sparse pediatric data, however, thyroid cancer care for pediatric patients is based predominantly on evidence from adult series. This year, the American Thyroid Association (ATA) published their first guidelines for children with DTC, thereby providing a thorough overview of the available literature (4).

The initial treatment for children with DTC generally consists of a (near) total thyroidectomy with or without lymph node dissection, although for patients with minimally invasive FTC ≤ 4 cm and lacking other adverse risk factors, a less aggressive treatment has recently been recommended (4, 5). Complication rates of thyroid surgery in children have been reported to be higher than those in adults (6). In most cases, surgery is followed by ablation therapy with radioactive iodine (^{131}I) to destroy residual tumor foci and to facilitate disease monitoring by follow-up scans and measurement of serum thyroglobulin (Tg). However, nowadays ^{131}I administration often depends on risk stratification (4, 5). Pediatric patients with residual tumor and/or metastases are generally treated by cyclic ^{131}I administrations, with the activity of ^{131}I being a matter of discussion (7). To decrease the risk of recurrent disease, TSH suppressive therapy with thyroid hormone has for decades been considered necessary during follow-up, but its use is currently tempered in patients showing no evidence of disease (4, 8–10).

Awareness regarding treatment-related morbidity is growing. However, long-term follow-up data, especially long-term data on morbidity, of children not exposed to the post-Chernobyl fallout are limited. Past studies in children ≤ 18 years at diagnosis have frequently been hampered by short follow-up, small patient series, series including patients with benign conditions, or treatment

regimens not representative of current practice (eg, including external beam radiotherapy) (11–15). Therefore, detailed insight into relevant clinical parameters of DTC in children is necessary to improve evidence-based treatment and follow-up strategies. The objective of this nationwide study was to evaluate the presentation, complications, and long-term outcome in patients with pediatric DTC in the Netherlands.

Patients and Methods

Study design and population

In this nationwide retrospective cohort study, children ≤ 18 years diagnosed with PTC or FTC between January 1970 and December 2013 and treated in the Netherlands were eligible for inclusion. The Dutch population is considered to be iodine-sufficient with virtually no exposure to the post-Chernobyl radioiodine fallout (16). To create a national cohort with coverage as high as reasonably feasible, patients were traced using data from the Netherlands Cancer Registry (1989–2013) and from hospital registries of the University Medical Centers (UMCs), in which patients were generally registered from 1970 onwards. Mortality data were obtained from electronic hospital patient information systems. For patients lost to follow-up, linkage with the database of the Central Bureau for Genealogy in the Netherlands was performed to identify deceased subjects. The Institutional Review Board of the University Medical Center Groningen approved the study. Informed consent was given by the patients and/or by their parents, for minors.

Data collection

Medical history, diagnosis, and treatment details were obtained from patients' medical records. Histopathological data were obtained from the original pathology reports. As the TNM Classification of Malignant Tumors was changed several times within the period covered by this study, tumor stage was (re-)classified according to the seventh edition of the TNM classification to facilitate comparison of the tumors (17). Data regarding ^{131}I administrations (number and activities of ^{131}I , and results of scans, both therapeutic and imaging) were collected from reports of the Departments of Nuclear Medicine. To calculate the cumulative administered ^{131}I activity, only ablative and therapeutic ^{131}I administrations were taken into account. TSH values were collected from the laboratory reports. In case of missing data, medical correspondence and the general practitioner were consulted.

Study definitions

Date of diagnosis was defined as the date of histological confirmation of thyroid carcinoma. Follow-up time was calculated from the date of diagnosis until the date of the patient's last known assessment or the date of the patient's death. Age at diagnosis was classified into 3 groups: age 0–10, 11–14 and 15–18 years. Transient and permanent hypoparathyroidism were defined by the use of calcium or vitamin D supplements for less than 6 months, and more than 6 months after thyroidectomy, respectively, or if these conditions were reported as such in the medical records. Recurrent laryngeal nerve (RLN) injury was defined as injury mentioned in Ear Nose and Throat report or, if this report was not available, in other medical records. Injury due to encasement by tumor was also defined as recurrent laryngeal nerve injury. Remission was defined as the absence of clinical, scintigraphical, or radiologic evidence of disease and undetectable serum Tg under TSH suppressive therapy for at least 1 year after the last ^{131}I therapy. Persistent disease was defined as the absence of remission. Recurrent disease was defined as histological, cytological, radiological, or biochemical evidence of disease after remission. Patients were classified according to risk of recurrence: low (T1–T2, N0, M0), intermediate (any T3 or N1 tumor), or high (any T4 or M1 tumor).

Statistical analysis

Groups were compared using χ^2 or Fisher's exact tests (if conditions for χ^2 test were not met) in the case of categorical variables. Mann-Whitney U and Kruskal-Wallis tests were performed for non-normally distributed continuous variables. Missing or unknown values were excluded from statistical testing. The TSH level for each year of follow-up was expressed as the geometric mean of the observed TSH values during that year. TSH values that were obtained before thyroidectomy until 12 weeks postoperatively were excluded, as well as TSH values obtained 6 weeks before until 12 weeks after thyroid hormone withdrawal or use of recombinant human (rh) TSH. The TSH level during the entire follow-up was defined as the geometric mean of the calculated TSH levels per year (18). Logistic regression analyses were performed to explore the associations between TSH level and recurrent disease, and between the occurrence of surgical complications and hospital volume, time of surgery, and age group. Regarding the association between TSH and recurrent disease, TSH was entered continuously in the crude model, followed by adjustment for risk classification. The associations between surgical complications and hospital volume, time of surgery, and age group were explored in a crude model, followed by adjustment for T-stage (T1–T2 vs T3–T4) and the performance of lymph node dissection. Patients surgically treated in > 1 hospital were excluded from the analysis, as it was retrospectively unclear in which hospital the complication occurred. All tests were two-sided. A P value of < 0.05 was considered significant. IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA) was used for statistical analyses.

Results

As shown in the study flowchart (Figure 1), 170 patients with pediatric DTC were identified. One patient with familial adenomatous polyposis died at the age of 20 years

due to complications of a colon carcinoma. He had been diagnosed 5 years earlier with PTC with lung metastases. Overall survival was 99.4% after a median follow-up of 13.5 (range 0.3–44.7) years. Of the 169 survivors, 105 (62.1%) gave informed consent and were included in this study. The patients from whom no informed consent was obtained were more often male (29.7% vs. 16.2%, $P = .038$), and more often had distant metastases ($P = .031$) and a longer follow-up time (median 18.1 (range 0.3–40.4) years vs. 11.7 (range 1.1–44.7) years, $P = .043$, Supplemental Table 1).

Baseline characteristics

Baseline characteristics are provided in Table 1. The female: male ratio was 5.2:1. Median age at diagnosis was 15.6 (range 5.8–18.9) years. PTC was diagnosed in 81.0% of the patients; the remaining 19.0% had FTC. At initial diagnosis, histologically confirmed cervical lymph node metastases were found in 46 (43.8%) patients and distant metastases in 14 (13.3%) patients. Of these, 11 patients had lung metastases, 1 patient with FTC had a metastasis in the seventh thoracic vertebra and 2 patients with PTC and FTC, respectively, had both lung and bone metastases.

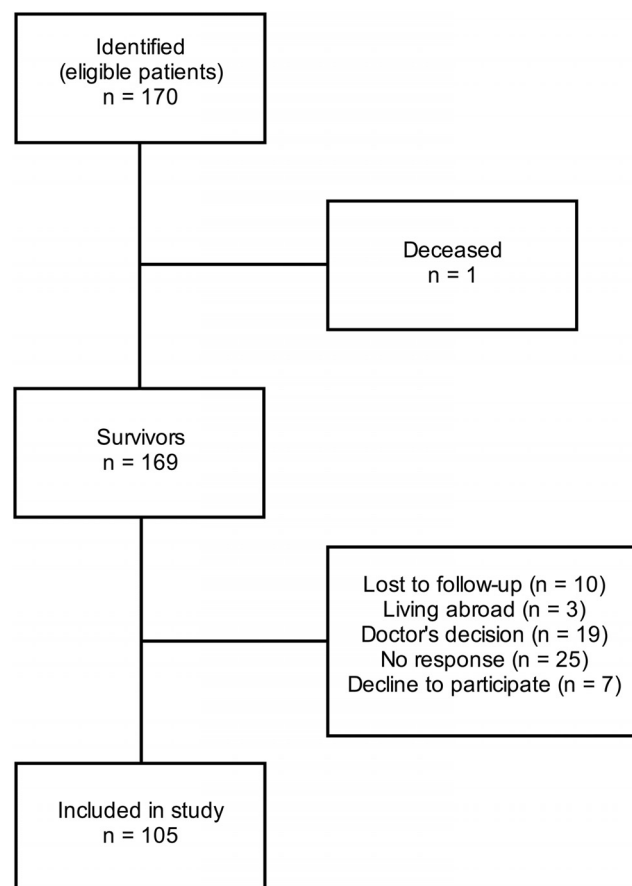


Figure 1. Study flowchart, showing final number of included patients and reasons for nonparticipation of eligible patients.

Table 1. Baseline characteristics

Variable		All patients (n = 105)		0–10 yr (n = 10)		11–14 yr (n = 34)		15–18 yr (n = 61)		P value ^a
Sex, no. (%)										
	Male	17	(16.2)	5	(50.0)	6	(17.6)	6	(9.8)	0.006
	Female	88	(83.8)	5	(50.0)	28	(82.4)	55	(90.2)	
Age at diagnosis, years										
	Median (range)	15.6	(5.8–18.9)	9.5	(5.8–10.8)	13.0	(11.1–14.8)	17.1	(15.3–18.9)	-
Histology, no. (%)										
	Papillary	85	(81.0)	9	(90.0)	25	(73.5)	51	(83.6)	0.363
	Follicular	20	(19.0)	1	(10.0)	9	(26.5)	10	(16.4)	
Primary tumor size, cm										
	Median (range)	2.5	(0.3–9.0)	1.4	(0.8–5.0)	2.9	(1.0–5.5)	2.5	(0.3–9.0)	0.193
Localization, no. (%)										
	Unilateral	67	(63.8)	5	(50.0)	23	(67.7)	39	(63.9)	0.493
	Bilateral	28	(26.7)	3	(30.0)	9	(26.5)	16	(26.2)	
	Other ^b									
	Isthmus	3	(2.9)	1	(10.0)	0	(0.0)	2	(3.3)	
	Thyroglossal duct	1	(1.0)	0	(0.0)	0	(0.0)	1	(1.6)	
	Unknown	6	(5.7)	1	(10.0)	2	(5.9)	3	(4.9)	
Multifocality, no. (%)										
	No	50	(47.6)	4	(40.0)	18	(52.9)	28	(45.9)	0.632
	Yes	29	(27.6)	3	(30.0)	7	(20.6)	19	(31.1)	
	Unknown	26	(24.8)	3	(30.0)	9	(26.5)	14	(23.0)	
TNM stage, no. (%)										
T										
	T1-T2	65	(61.9)	6	(60.0)	21	(61.8)	38	(62.3)	0.960
	T3-T4	26	(24.8)	2	(20.0)	9	(26.5)	15	(24.6)	
	Tx	14	(13.3)	2	(20.0)	4	(11.8)	8	(13.1)	
N										
	N0	53	(50.5)	4	(40.0)	15	(44.1)	34	(55.7)	0.339
	N1a-N1b	46	(43.8)	6	(60.0)	17	(50.0)	23	(37.7)	
	Nx	6	(5.7)	0	(0.0)	2	(5.9)	4	(6.6)	
M										
	M0	82	(78.1)	8	(80.0)	25	(73.5)	49	(80.3)	0.752
	M1 ^b	14	(13.3)	1	(10.0)	6	(17.6)	7	(11.5)	
	Lung	11		1		5		5		
	Bone	1		0		0		1		
	Lung and bone	2		0		1		1		
	Mx	9	(8.6)	1	(10.0)	3	(8.8)	5	(8.2)	
Surgery, no. (%)										
	Total thyroidectomy	105	(100)	10	(100)	34	(100)	61	(100)	-
Lymph node dissection										
	None	49	(46.7)	4	(40.0)	15	(44.1)	30	(49.2)	0.045
	Central LND	10	(9.5)	4	(40.0)	1	(2.9)	5	(8.2)	
	LND incl. lateral levels	36	(34.3)	2	(20.0)	15	(44.1)	19	(31.1)	
	Unknown	10	(9.5)	0	(0.0)	3	(8.8)	7	(11.5)	

Abbreviation: LND, lymph node dissection. ^a Differences tested between the 3 age groups. Missing or unknown values excluded from statistical testing. ^b Summarized as 1 variable for statistical testing.

Pathological features and TNM stage did not differ between the 3 age groups.

Medical history

Four (3.8%) patients developed DTC as a second malignant neoplasm (SMN); 2 of them had been treated with cranial radiotherapy (Supplemental Table 2). One patient with a neuroblastoma had been treated with 131-I-meta-iodobenzylguanidine (previously reported (19)). The fourth patient had been treated for Langerhans cell histiocytosis. She did not receive radiotherapy. Two (1.9%) patients developed PTC after radiotherapy directed to the neck for benign conditions.

Surgical treatment

Total thyroidectomy was performed in all patients. In 65 (61.9%) patients the total thyroidectomy was performed as a single procedure. In the remaining 40 (38.1%) patients a diagnostic hemithyroidectomy was performed, followed by a completion thyroidectomy. The mean time

span between both procedures was 31.5 (range 2–210) days.

Lymph node dissection was performed as part of initial therapy in 46 (43.8%) patients, of whom 40 (87.0%) had histologically proven lymph node metastases. In 10 (9.5%) patients the central compartment (level VI) was dissected; in 36 (34.4%) patients a lateral lymph node dissection was performed, including other levels (II–V) on one or both sides of the neck (Table 1). In 6 patients not initially treated with a lymph node dissection, positive lymph nodes were found during histopathological examination. Central compartment dissection alone was performed more frequently in children aged 0–10 years, while in older children lateral levels were more often included in the lymph node dissection ($P = .045$, Table 1).

Throughout the entire study period, patients were surgically treated in 39 hospitals, including 9 UMCs and 30 general hospitals. During this period, in our cohort, the median number of surgical procedures (hemi- or total thy-

roidectomy, or lymph node dissection, when performed at different dates) per hospital was 2 (range 1–30). Over the past decade, 50 patients were treated in 16 different hospitals, including 9 UMCs and 7 general hospitals.

Surgical complications

As shown in Table 2, postoperative transient and permanent hypoparathyroidism were observed in 16 (15.2%) and 25 (23.8%) patients, respectively. Both transient and permanent hypoparathyroidism occurred more often in patients who underwent a lymph node dissection. Unilateral RLN injury occurred in 12 (11.4%) patients. Bilateral RLN injury occurred only in a 15-year-old patient with extended disease who was treated with a total thyroidectomy, a central compartment dissection and a bilateral modified lymph node dissection. The right RLN was encased by the tumor and was removed as part of the surgical procedure. RLN injury occurred more often in patients with tumors staged T3-T4 compared to stage T1-T2 ($P < .001$), and in patients with lymph node involvement ($P < .001$). The frequency of surgical complications did not differ between initial surgery performed before or during the last decade, either in a crude model or after adjustment for T-stage and performance of lymph node dissection (OR 0.96, 95% CI 0.42 to 2.17, $P = .912$ and OR 0.94, 95% CI 0.32 to 2.72, $P = .904$, respectively). Finally, age group was not related to the occurrence of surgical complications, either in a crude or adjusted model ($P = .550$ and $P = .189$, respectively).

131-I administrations and TSH suppressive therapy

Data regarding 131-I administrations are provided in Table 3. One hundred and two (97.1%) patients were treated with 131-I, with a median cumulative activity administered during initial treatment and follow-up of 5.66 (range 0.74–35.15) GBq. The median number of 131-I administrations was 1 (range 1–6). Ninety-four (89.5%) patients underwent 131-I ablation therapy within 6 months after initial surgical treatment. By doctor's choice, 3 patients did not receive 131-I ablation therapy. Higher tumor stage (T3-T4), lymph node involvement, and dis-

tant metastases were independently associated with a higher administered cumulative 131-I activity ($P < .001$) and with an increase in the number of 131-I administrations ($P < .001$). The cumulative 131-I activity and the number of 131-I administrations during initial treatment and follow-up did not differ between age groups at diagnosis ($P = .227$ and $P = .225$, respectively, data not shown). Pulmonary fibrosis was not encountered in the medical charts. No patients were treated with external beam radiotherapy, chemotherapy or tyrosine kinase inhibitors for DTC. TSH values of 104 (99.0%) patients were available for analysis. Median TSH level during follow-up was 0.17 (range 0.01–4.74) mU/L. TSH was suppressed below 0.10 mU/L during the entire follow-up in 36 (34.6%) patients. The TSH level was not associated with recurrent disease, either in a crude model (OR 1.98, 95% CI 0.80 to 4.86, $P = .140$), or after adjustment for risk classification (OR 2.00, 95% CI 0.78 to 5.17, $P = .152$).

Outcome

At last known follow-up, 9 (8.6%) patients had persistent disease, 6 of whom were classified as such based on a detectable Tg level. Eight (7.6%) patients experienced a recurrence (Table 4). Recurrence free survival (RFS) from initial treatment to first recurrence ranged from 3.9 to 22.7 years. Three out of 8 patients relapsed within 5 years after initial treatment. Of the 11 (10.5%) patients who had not been treated with 131-I within 6 months after total thyroidectomy, 2 developed a recurrence ($P = .197$, data not shown). As shown in Table 5, T3-T4 stage, lymph node involvement, and distant metastases stage were associated with persistent disease ($P = .040$, $P = .010$ and $P = .020$, respectively). No associations were found between initial TNM stage and recurrences. The 3 patients who initially presented with bone metastases became free of disease after administration of 13.7, 11.8 and 14.8 GBq 131-I, and remained in remission after a follow-up of 2.9, 5.1 and 13.2 years, respectively. Outcome did not differ between patients with PTC and FTC, or between the 3 age groups ($P = .411$ and $P = .789$, respectively, data not shown).

Table 2. Surgical complications

Group	Hypoparathyroidism, no. (%)							Recurrent laryngeal nerve injury, no. (%)						
	None	Transient	Permanent	Unknown	None	Left	Right	Bilateral	Unknown	None	Left	Right	Bilateral	Unknown
All patients (n = 105)	51 (48.6)	16 (15.2)	25 (23.8)	13 (12.4)	69 (65.7)	5 (4.8)	7 (6.7)	1 (1.0)	23 (21.9)	52 (80.0)	1 (1.5)	0 (0.0)	0 (0.0)	12 (18.5)
T1-T2 (n = 65)	36 (55.4)	8 (12.3)	14 (21.5)	7 (10.8)	52 (80.0)	1 (1.5)	0 (0.0)	0 (0.0)	12 (18.5)	14 (53.8)	2 (7.7)	4 (15.4)	1 (3.8)	5 (19.2)
T3-T4 (n = 26)	10 (38.5)	7 (26.9)	8 (30.8)	1 (3.8)	3 (21.4)	2 (14.3)	3 (21.4)	0 (0.0)	6 (42.9)	3 (21.4)	2 (14.3)	0 (0.0)	0 (0.0)	6 (42.9)
Tx (n = 14)	5 (35.7)	1 (7.1)	3 (21.4)	5 (35.7)	39 (79.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (20.4)	39 (79.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (20.4)
No LND (n = 49)	32 (65.3)	6 (12.2)	5 (10.2)	6 (12.2)	28 (60.9)	4 (8.7)	6 (13.0)	1 (2.2)	7 (15.2)	2 (20.0)	1 (10.0)	1 (10.0)	0 (0.0)	6 (60.0)
LND (n = 46)	15 (32.6)	10 (21.7)	16 (34.8)	5 (10.9)	2 (20.0)	1 (10.0)	1 (10.0)	0 (0.0)	6 (60.0)	2 (20.0)	1 (10.0)	1 (10.0)	0 (0.0)	6 (60.0)
LND unknown (n = 10)	4 (40.0)	0 (0.0)	4 (40.0)	2 (20.0)	2 (20.0)	1 (10.0)	1 (10.0)	0 (0.0)	6 (60.0)	2 (20.0)	1 (10.0)	1 (10.0)	0 (0.0)	6 (60.0)

Abbreviation: LND, lymph node dissection. Differences tested between T1-T2 and T3-T4 and no LND and LND (see shaded numbers). Missing or unknown values excluded from statistical testing. * $P = 0.143$, ** $P = 0.001$, *** $P < 0.001$.

Table 3. 131-I administrations

Group	Cumulative 131-I activity (GBq)		P value ^b	I-131 administrations, no.		P value ^b
All patients (n = 100)^a	5.66	(0.74–35.15)		1	(1–6)	
T1-T2 (n = 62)	5.55	(0.74–31.49)	<0.001	1	(1–6)	<0.001
T3-T4 (n = 26)	12.36	(1.78–35.15)		3	(1–6)	
Tx (n = 12)	4.63	(1.22–27.85)	<0.001	1	(1–5)	<0.001
N0 (n = 49)	3.70	(1.00–21.46)		1	(1–6)	
N1a-N1b (n = 45)	11.10	(0.74–35.15)		2	(1–6)	
Nx (n = 6)	6.75	(1.85–8.33)	<0.001	1	(1–2)	<0.001
M0 (n = 77)	5.55	(0.74–35.15)		1	(1–6)	
M1 (n = 14)	14.43	(6.11–29.79)		3	(1–5)	
Mx (n = 9)	5.55	(1.85–27.85)		1	(1–5)	

All data expressed as median (range). ^a Administered 131-I activity unknown in 2 patients; 3 patients did not receive 131-I treatment. Therefore *n* = 100 instead of *n* = 105. ^b Differences tested between T1-T2 and T3-T4, N0 and N1a-N1b, M0 and M1. Tx, Nx, Mx excluded from statistical testing.

Table 4. Patients with recurrent and persistent disease

Sex and age at diagnosis, years		Follow-up, years	Histology, TNM ^a		Initial treatment ^b	Evidence of disease	Localization of recurrence	RFS c, years	Remission after recurrence	2nd recurrence	Remission after 2nd recurrence
Recurrent disease (n = 8)											
F,	18.9	33.3	PTC,	T2N0M0	TT + 131-I	Scintigraphical	Thyroid bed	3.92	yes	no	n.a.
F,	18.3	10.7	PTC,	T1bN0M0	TT + 131-I	Scintigraphical	Cervical LN	4.16	yes	no	n.a.
F,	17.1	17.5	PTC,	T3N1bM0	TT + 131-I	Cytological	Cervical LN	4.81	yes	yes	yes
F,	13.3	41.5	FTC,	T4aN1bM0	TT + 131-I ^d	Scintigraphical	Cervical LN	6.15	yes	yes	no
F,	16.3	12.0	PTC,	T2N0M0	TT + 131-I	Scintigraphical	Cervical LN	8.96	yes	no	n.a.
F,	13.1	32.4	PTC,	T1bN1bM0	TT + LND + 131-I	Biochemical ^e	Not specified	11.04	yes	no	n.a.
F,	13.1	25.2	PTC,	T1bN1bM0	TT + LND	Histological	Cervical LN	16.62	yes	no	n.a.
F,	18.8	24.3	PTC,	T1bN0Mx	TT	Histological + radiological ^f	Cervical LN, lung	22.65	no	n.a.	n.a.
Persistent disease (n = 9)											
F,	12.5	23.3	PTC,	T2N1M0	TT + LND + 131-I	Radiological	Lung				
M,	10.5	8.4	PTC,	T4aN1bM1	TT + LND + 131-I	Radiological	Lung				
F,	18.5	1.7	PTC,	T4bN1bM1	TT + LND + 131-I	Scintigraphical + radiological ^g	Cervical LN, lung				
F,	12.1	4.9	PTC,	T2N1bM0	TT + LND + 131-I	Biochemical	Not specified				
F,	16.1	5.5	PTC,	T1N1bM0	TT + LND + 131-I	Biochemical	Not specified				
M,	12.7	14.8	PTC,	T3N1bM0	TT + LND + 131-I	Biochemical	Not specified				
M,	14.7	4.4	PTC,	T3N0M1	TT + 131-I	Biochemical	Not specified				
F,	15.9	2.0	PTC,	T4aN1bM1	TT + LND + 131-I	Biochemical	Not specified				
F,	16.7	36.1	PTC,	TxN1bMx	TT + LND + 131-I	Biochemical	Not specified				

Abbreviations: F, female; M, male; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; TT, total thyroidectomy; LND, lymph node dissection; 131-I, radioiodine administration; LN, lymph node; RFS, recurrence-free survival; n.a., not applicable. ^a Initial TNM classification, ^b 131-I is mentioned as part of initial therapy if performed <6 months after surgical treatment, ^c RFS calculated from date of diagnosis until first recurrence, ^d Unknown if LND was performed; ^e Patient treated with 131-I because of increasing thyroglobulin level. Unknown if post therapy scan was performed; ^f Cervical lymph nodes proved histologically. Lung metastases visible on CT; ^g Cervical lymph nodes detected scintigraphically. Lung metastases visible on CT.

Outcome could not be assessed for 2 patients because of follow-up < 1 year. For another patient, information to evaluate outcome was not available.

Median follow-up in patients with recurrent disease was 24.7 (10.7–41.5) years, significantly longer than in patients who remained in remission (11.4 (1.3–44.7) years) and in patients with persistent disease (5.5 (1.7–36.1) years) (*P* = .030, data not shown).

Data regarding SMNs after pediatric DTC are provided in Supplemental Table 3.

Discussion

This nationwide study of pediatric patients with well-differentiated thyroid cancer in the Netherlands confirms an

excellent overall survival. All patients underwent total thyroidectomy with nodal dissection in 43.8%, followed in most patients by high-dose 131-I ablation therapy. Over a 43-year period, 105 patients were surgically treated in 39 hospitals. In 32.4% of them lifelong postoperative complications (permanent hypoparathyroidism and/or RLN injury) were present. A significant number of patients had persistent disease or experienced a recurrence. Despite small patient numbers, our cohort is one of the largest to be described for this rare disease in children. It gives insight into relevant clinical parameters that can be used to improve evidence-based treatment and follow-up strategies.

In our opinion, the incidence of hypoparathyroidism, using strict definitions in our cohort, seems to be relatively high compared to comparable cohorts of pediatric pa-

Table 5. Outcome

Group	Remission, no. (%)		Recurrence, no. (%)		P value ^{a,b}	Persistent disease, no. (%)		P value ^{a,c}	Unknown, no. (%) ^d	
All patients (n = 105)	85	(81.0)	8	(7.6)		9	(8.6)		3	(2.9)
T1-T2 (n = 65)	54	(83.1)	6	(9.2)	1.000	3	(4.6)	0.040	2	(3.1)
T3-T4 (n = 26)	18	(69.2)	2	(7.7)		5	(19.2)		1	(3.8)
Tx (n = 14)	13	(92.9)	0	(0.0)		1	(7.1)		0	(0.0)
N0 (n = 53)	47	(88.7)	4	(7.5)	0.713	1	(1.9)	0.010	1	(1.9)
N1a-N1b (n = 46)	32	(69.6)	4	(8.7)		8	(17.4)		2	(4.3)
Nx (n = 6)	6	(100.0)	0	(0.0)		0	(0.0)		0	(0.0)
M0 (n = 82)	70	(85.4)	7	(8.5)	1.000	4	(4.9)	0.020	1	(1.2)
M1 (n = 14)	10	(71.4)	0	(0.0)		4	(28.6)		0	(0.0)
Mx (n = 9)	5	(55.6)	1	(11.1)		1	(11.1)		2	(22.2)

^a Differences tested between T1-T2 and T3-T4, N0 and N1a-N1b, M0 and M1. Tx, Nx, Mx and unknown outcome excluded from statistical testing.

^b Patients in remission and with recurrent disease compared. ^c Patients in remission and with persistent disease compared. ^d Outcome unknown in 1 patient and could not be assessed in 2 patients due to follow-up <1 yr (all summarized as unknown outcome).

tients treated for DTC (transient and permanent hypoparathyroidism in 15.2% and 23.8%, respectively, previously described in 7.4–32.7% and 0%–32%, respectively) (12, 20–23). In adults, these complications were less frequently encountered (6.2–14.2% and 0–4.0%, respectively) (24, 25). The occurrence of RLN injury in our cohort (12.4%) was comparable with other pediatric cohorts (0%–40%), as well as with reported adult data (0–38.4%) (14, 21, 26, 27). However, it should be considered that definitions of surgical complications are heterogeneous. Complication rates therefore vary widely in the literature. Total thyroidectomy, which is recommended for the vast majority of pediatric patients with DTC, is associated with a higher complication risk than partial thyroidectomy, particularly when combined with lymph node dissection (4–6, 13). Another major factor that could have contributed to our complication rates might be the high number of centers where surgery was performed on this low volume high-risk patient group. Due to the low numbers of surgical treatments per hospital in our cohort we were not able to analyze differences in the occurrence of surgical complications between high- and low-volume centers. However, it has been shown that complications of thyroid surgery in pediatric patients are reduced when surgery is performed by high-volume surgeons (6). High-volume surgery may also be associated with fewer incomplete resections. Therefore the need for further centralization of care for pediatric patients with DTC is essential, as has been recommended by the ATA (4).

The cumulative therapeutic 131-I activity during initial treatment and follow-up in our cohort was relatively high. Given the good survival rate, it can be questioned whether children could just as well be treated with lower therapeutic activities, as suggested by recent guidelines (4, 5).

The dosage of 131-I is of importance, given that pulmonary fibrosis was observed as a side effect in 7.2% of patients with lung metastases in a high-risk Chernobyl-related pediatric cohort (28). In our cohort we did not observe pulmonary fibrosis after a similar follow-up period. As the presence of pulmonary fibrosis was assessed from medical records in our study, we may have missed subclinical cases. Nevertheless, it is our opinion that the administration of 131-I should be considered very carefully in pediatric patients to prevent possible early and late adverse effects (29, 30). This is especially the case in children with low-risk DTC as no benefit of 131-I ablation therapy has been shown in adults with low-risk disease (31). High 131-I activities should be reserved for children with metastatic disease, as advocated earlier by Verburg et al (7).

In about one-third of the patients in our cohort TSH was suppressed during the entire follow-up. To the best of our knowledge, our study is the first to report that TSH level is not associated with recurrent disease in children with DTC. This finding upholds the first ATA guidelines for pediatric patients with DTC, which recommend tempering TSH suppression in children showing no evidence of disease (4). However, this should be interpreted carefully as our study probably has a lack of power.

The prevalence of cervical lymph node metastases at initial diagnosis in our cohort (43.8%) is in the lower range of prevalences as reported in other pediatric series (39%–90%) (15, 21, 22, 32–34). The prevalence of distant metastases in our study is comparable to that from other pediatric cohorts (32, 33).

Persistent disease was more often found in patients with higher T stage, cervical lymph node involvement and distant metastases at diagnosis. One-third of the patients with persistent disease had lung metastases at last known

follow-up. The other two-thirds were classified as having persistent disease based on a detectable Tg level. It must be considered that Tg levels are not always analyzed in the literature, and that patients with detectable Tg levels are not always classified as having persistent disease in other studies.

We report a recurrence rate of 7.6%, which is low compared with a study involving comparable treatment and follow-up (18.8%) (33). Our study definitions of recurrent disease may have contributed to the low recurrence rate, as we did not interpret disease activity within 1 year after initial treatment as recurrent disease. In contrast to some other studies, in our cohort recurrences were not associated with initial TNM stage and did not differ between age groups (14, 33, 35). RFS ranged from 3.9–22.7 years. This favors lifelong follow-up of children. Patients with recurrent disease were significantly longer in follow-up compared to patients in remission and with persistent disease. This prolonged follow-up might be explained by the wish of physicians to follow patients with recurrent disease for a longer time than patients who remain in remission.

Possible differences in presentation of sporadic DTC compared to radiation-induced DTC could not be detected, as the number of patients with SMN in our cohort was low and the median follow-up was relatively short to develop a SMN.

Limitations of this study are related to its retrospective design. As patients were treated in many hospitals over more than 40 years, complete information from medical records could not always be retrieved. Furthermore, preoperative staging and patient management were not similar in all hospitals and have evolved over time. In addition, the association between lymph node dissection and occurrence of surgical complications should be interpreted carefully as the number of procedures per hospital was small and information on the selection criteria for the extent of surgery was often lacking. However, over the last decades the general consensus on treatment for pediatric DTC has in the Netherlands remained roughly unchanged. Finally, various TSH assays have been used. However, we expect limited influence of the assay differences on the results, as the lower limits of the reference ranges remained more or less stable.

In conclusion, the life expectancy for children with DTC is excellent. However, many patients experience adverse effects from thyroid surgery, resulting in lifelong complications in 32.4%. Centralization of care for pediatric patients with DTC is crucial to reduce treatment-related damage in this young patient group. In the near future, treatment for pediatric patients with DTC will be further centralized in one or two hospitals in The Netherlands.

Furthermore, the administration of ¹³¹I should be weighed very carefully to prevent early and late adverse events. Further studies are needed to evaluate long-term sequels. International collaboration using homogeneous definitions can accelerate evaluation and improvement of treatment for children with DTC.

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References

1. Vergamini LB, Frazier AL, Abrantes FL, Ribeiro KB, Rodriguez-Galindo C. Increase in the incidence of differentiated thyroid carcinoma in children, adolescents, and young adults: a population-based study. *J Pediatr*. 2014;164:1481–1485.
2. Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J. Cancer incidence rates and trends among children and adolescents in the United States, 2001–2009. *Pediatrics*. 2014;134:e945–e955.
3. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. *J Surg Res*. 2009;156:167–172.
4. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenega S, Cerutti JM, Dinanuer CA, Hamilton J, Hay ID, Luster M, Parisi MT, Rachmiel M, Thompson GB, Yamashita S. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2015;25:716–759.
5. Perros P, Colley S, Boelaert K, Evans C, Evans RM, Gerrard GE, Gilbert JA, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold KL, Taylor J, Thakker RV, Watkinson J, Williams GR. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)*. 2014;81:1–122.
6. Sosa JA, Tuggle CT, Wang TS, Thomas DC, Boudourakis L, Rivkees S, Roman SA. Clinical and economic outcomes of thyroid and parathyroid surgery in children. *J Clin Endocrinol Metab*. 2008;93:3058–3065.
7. Verburg FA, Reiners C, Hänscheid H. Approach to the patient: role of dosimetric RAI rx in children with DTC. *J Clin Endocrinol Metab*. 2013;98:3912–3919.
8. Pujol P, Daures JP, Nsakala N, Baldet L, Bringer J, Jaffiol C. Degree of thyrotropin suppression as a prognostic determinant in differen-

- tiated thyroid cancer. *J Clin Endocrinol Metab.* 1996;81:4318–4323.
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2016;26:1–133.
 10. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol.* 2006;154:787–803.
 11. Vassilopoulou-Sellin R, Goepfert H, Raney B, Schultz PN. Differentiated thyroid cancer in children and adolescents: clinical outcome and mortality after long-term follow-up. *Head Neck.* 1998;20:549–555.
 12. van Santen HM, Aronson DC, Vulsma T, Tummers RF, Geenen MM, de Vijlder JJ, van den Bos C. Frequent adverse events after treatment for childhood-onset differentiated thyroid carcinoma: a single institute experience. *Eur J Cancer.* 2004;40:1743–1751.
 13. Scholz S, Smith JR, Chaignaud B, Shamberger RC, Huang SA. Thyroid surgery at Children's Hospital Boston: a 35-year single-institution experience. *J Pediatr Surg.* 2011;46:437–442.
 14. Enomoto Y, Enomoto K, Uchino S, Shibuya H, Watanabe S, Noguchi S. Clinical features, treatment, and long-term outcome of papillary thyroid cancer in children and adolescents without radiation exposure. *World J Surg.* 2012;36:1241–1246.
 15. Fridman MV, Savva NN, Krasko OV, Zborovskaya AA, Mankovskaya SV, Schmid KW, Demidchik YE. Clinical and pathologic features of “sporadic” papillary thyroid carcinoma registered in the years 2005 to 2008 in children and adolescents of Belarus. *Thyroid.* 2012;22:1016–1024.
 16. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. UNSCEAR 2008 report to the general assembly with scientific annexes, Volume II: Annex D: Health effects due to radiation from the Chernobyl accident. New York: United Nations; 2011.
 17. Sobin LH, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*. 7th ed. Oxford, UK: Wiley-Blackwell; 2009.
 18. Klein Hesselink EN, Klein Hesselink MS, de Bock GH, Gansevoort RT, Bakker SJ, Vredevelt EJ, van der Horst-Schrivers AN, van der Horst IC, Kamphuisen PW, Plukker JT, Links TP, Lefrandt JD. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. *J Clin Oncol.* 2013;31:4046–4053.
 19. van Santen HM, Tytgat GA, van de Wetering MD, van Eck-Smit BL, Hopman SM, van der Steeg AF, Nieveen van Dijkum EJ, van Trotsenburg AS. Differentiated thyroid carcinoma after 131I-MIBG treatment for neuroblastoma during childhood: description of the first two cases. *Thyroid.* 2012;22:643–646.
 20. Haveman JW, van Tol KM, Rouwé CW, Piers DA, Plukker JT. Surgical experience in children with differentiated thyroid carcinoma. *Ann Surg Oncol.* 2003;10:15–20.
 21. Thompson GB, Hay ID. Current strategies for surgical management and adjuvant treatment of childhood papillary thyroid carcinoma. *World J Surg.* 2004;28:1187–1198.
 22. O’Gorman CS, Hamilton J, Rachmiel M, Gupta A, Ngan BY, Dane-man D. Thyroid cancer in childhood: a retrospective review of childhood course. *Thyroid.* 2010;20:375–380.
 23. Kundel A, Thompson GB, Richards ML, Qiu LX, Cai Y, Schwenk FW, Lteif AN, Pittock ST, Kumar S, Tebben PJ, Hay ID, Grant CS. Pediatric endocrine surgery: a 20-year experience at the Mayo Clinic. *J Clin Endocrinol Metab.* 2014;99:399–406.
 24. Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee RF, Rosai J, Shah JP, Fremgen AM, Stewart AK, Hölzer S. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation Study. *Cancer.* 2000;89:202–217.
 25. Kim SM, Kim HK, Kim KJ, Chang HJ, Kim BW, Lee YS, Chang YS, Park CS. Recovery from permanent hypoparathyroidism after total thyroidectomy. *Thyroid.* 2015;25:830–833.
 26. Jeannon JP, Orabi AA, Bruch GA, Abdalsalam HA, Simo R. Diagnosis of recurrent laryngeal nerve palsy after thyroidectomy: a systematic review. *Int J Clin Pract.* 2009;63:624–629.
 27. Bergenfelz A, Jansson S, Kristoffersson A, Mårtensson H, Reihner E, Wallin G, Lausen I. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbecks Arch Surg.* 2008;393:667–673.
 28. Reiners C, Biko J, Haenscheid H, Hebestreit H, Kirinjuk S, Baranowski O, Marlowe RJ, Demidchik E, Drozd V, Demidchik Y. Twenty-five years after Chernobyl: outcome of radioiodine treatment in children and adolescents with very high-risk radiation-induced differentiated thyroid carcinoma. *J Clin Endocrinol Metab.* 2013;98:3039–3048.
 29. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. *World J Surg.* 2010;34:1192–1202.
 30. Marti JL, Jain KS, Morris LG. Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer. *Thyroid.* 2015;25:681–687.
 31. Jonklaas J, Cooper DS, Ain KB, Bigos T, Brierley JD, Haugen BR, Ladenson PW, Magner J, Ross DS, Skarulis MC, Steward DL, Maxon HR, Sherman SI. Radioiodine therapy in patients with stage I differentiated thyroid cancer. *Thyroid.* 2010;20:1423–1424.
 32. Rivkees SA, Mazzaferri EL, Verbarg FA, Reiners C, Luster M, Breuer CK, Dinauer CA, Udelsman R. The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. *Endocr Rev.* 2011;32:798–826.
 33. Welch Dinauer CA, Tuttle RM, Robie DK, McClellan DR, Svec RL, Adair C, Francis GL. Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults. *Clin Endocrinol (Oxf).* 1998;49:619–628.
 34. La Quaglia MP, Black T, Holcomb GW 3rd, Sklar C, Azizkhan RG, Haase GM, Newman KD. Differentiated thyroid cancer: clinical characteristics, treatment, and outcome in patients under 21 years of age who present with distant metastases. A report from the surgical discipline committee of the children’s cancer group. *J Pediatr Surg.* 2000;35:955–959.
 35. Fridman M, Sawa N, Krasko O, Mankovskaya S, Branovan DI, Schmid KW, Demidchik Y. Initial presentation and late results of treatment of post-Chernobyl papillary thyroid carcinoma in children and adolescents of Belarus. *J Clin Endocrinol Metab.* 2014;99:2932–2941.

Supplemental Table 1. Participants versus non-participants

Variable	Participants (n = 105)		Non-participants (n = 64)		P value ^a
Sex, no. (%)					
Male	17	(16.2)	19	(29.7)	0.038
Female	88	(83.8)	45	(70.3)	
Age at diagnosis, years ^b					
Median (range)	15.6	(5.8-18.9)	15.5	(4.9-18.8)	0.498
Histology, no. (%)					
Papillary	85	(81.0)	50	(78.1)	0.394
Follicular	20	(19.0)	8	(12.5)	
Unknown	0	(0.0)	6	(9.4)	
TNM stage, no. (%)					
T					
T1-T2	65	(61.9)	21	(32.8)	0.217
T3-T4	26	(24.8)	14	(21.9)	
Tx	14	(13.3)	29	(45.3)	
N					
N0	53	(50.5)	17	(26.6)	0.194
N1a-N1b	46	(43.8)	24	(37.5)	
Nx	6	(5.7)	23	(35.9)	
M					
M0	82	(78.1)	27	(42.2)	0.031
M1	14	(13.3)	12	(18.8)	
Mx	9	(8.6)	25	(39.1)	
Follow-up, years					
Median (range)	11.7	(1.1-44.7)	18.1	(0.3-40.4) ^b	0.043

^a Missing or unknown values and Tx, Nx, Mx excluded from statistical testing. ^b If date of diagnosis was available (n = 61).

Supplemental Table 2. History of radiotherapy and malignant neoplasms during childhood

Variable	Patients (n = 105)	Age at diagnosis primary malignancy other than DTC	Age at diagnosis DTC	Histology and TNM DTC
DTC as primary malignancy, no. (%)				
No history of radiation	99 (94.3)	-	-	-
History of cervical radiation for benign conditions ^a	2 (1.9)	-	17 y; 16 y	PTC, TxN1bM0; PTC, T1bN0M0
DTC as Second Malignant Neoplasm, no. (%)				
Langerhans cell histiocytosis Chemo ^b	1 (0.95)	8 y	18 y	FTC, T2N0M0
Acute Lymphoblastic Leukemia Chemo + RT ^c	1 (0.95)	5 y	10 y	PTC T1bN0M0
Medulloblastoma Chemo + RT ^d	1 (0.95)	9 y	18 y	PTC, T3N1bM1
Neuroblastoma 131-I-MIBG + chemo ^e	1 (0.95)	4 m	6 y	PTC, T1N1M0

Abbreviations: DTC, differentiated thyroid carcinoma; Chemo, chemotherapy; RT, radiotherapy; 131-I-MIBG, 131-I-metaiodobenzylguanidine; y, years; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

^a One patient received cervical RT for eczema (total dose 7.2 Gy) between ages 4-17 years. The second patient received cervical RT (total dose breast and cervical region 32 Gy between ages 1-12 months for a nevus flammeus. Patients received RT between 1958 and 1970. ^b Vinblastine, prednisolone, cyclophosphamide. ^c Rubidomycin, adriamycin, cyclophosphamide + cranial RT dose 18 Gy. ^d Vincristine, cisplatin + craniospinal RT dose 23.4 Gy. ^e 4x 131-I-MIBG + carboplatin, vincristine, etoposide, carboplatin, ifosfamide (VECI).

Supplemental Table 3. Second malignant neoplasms after pediatric differentiated thyroid carcinoma

Sex	Histology and TNM	Age at diagnosis DTC, years	Cumulative 131-I activity (GBq) before SMN	SMN	Age at diagnosis SMN, years
F	PTC, TxNxMx	11	8.33	Breast cancer	39
F	FTC, T4aN1bM0	13	35.15 ^a	Breast cancer	53
F	PTC, T1bN1bM0	13	0	High-grade cervical intraepithelial neoplasia	26

Abbreviations: DTC, differentiated thyroid carcinoma; SMN, second malignant neoplasm; F, female; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma. ^a During follow-up, this patient developed 2 recurrences, for which she was treated with 131-I.