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Frequent adverse events after treatment for childhood-onset differentiated thyroid carcinoma: a single institute experience

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Abstract

Since the mortality rate for childhood differentiated thyroid carcinoma is nearly zero, the focus must be to minimise morbidity following treatment. Our aim was to analyse early and late adverse events. Twenty-five of 26 children treated between 1962 and 2002 were evaluated. Median follow-up was 14.2 years (range 0.9–39.4 years). All underwent total thyroidectomy, 15 (60%) with lymph node dissection and 15 (60%) with adjuvant radio-iodide therapy. Mortality was zero. Seven developed recurrent disease, two developed a third recurrence. Twenty-one (84%) had $\geqslant 1$ adverse event. Eight had permanent hypoparathyroidism (PH), six permanent recurrent nerve paralysis (PRNP) and two Horner's syndrome. Risk factors for PH and PRNP were total thyroidectomy with lymph node dissection (RR: 6.45, $P = 0.015$) and recurrent nerve tumour encasement (RR: 8.00, $P = 0.001$), respectively. Other adverse events were fatigue ($n = 5$), scar problems ($n = 4$) and chronic myeloid leukaemia ($n = 1$). These results emphasise the need to improve treatment strategies.

Keywords: Differentiated thyroid cancer; Childhood; Adolescence; Complications; Late effects

1. Introduction

Thyroid carcinoma during childhood has an incidence of 0.2–3 per 100 000 [1] and comprises approximately 1.5% of all paediatric tumours [2,3]. In the Netherlands, 103 children (70 girls) were diagnosed with differentiated thyroid carcinoma under the age of 19 years in the period 1989–1997 (incidence 0.4 per 100 000 for boys and 1.0 per 100 000 for girls) [4].

Thyroid tumours in children are often diagnosed in a more advanced stage than in adults; in 71–90% of

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children metastases in the cervical lymph nodes are found at diagnosis, and distant metastases (mainly in the lungs) are described in 10–21% of the patients [5]. Nevertheless, childhood-onset differentiated thyroid cancer generally has an excellent survival rate [2]. Therefore, at present, the goal of treatment must be to achieve the highest therapeutic efficacy with the lowest morbidity. Hence, awareness of the occurrence of adverse events in this group of children followed up into adulthood is of substantial importance. Knowledge gained this way may lead to changes in treatment strategies aimed to improve the quality of life of these survivors by reducing the number of adverse events.

Risk factors to develop differentiated thyroid carcinoma are female gender and age between 7 and 12 years [6]. In addition, elevated plasma thyroid stimulating hormone (TSH) concentration, Hashimoto's disease, exposure to radiation, and mutations in the *RET*-oncogene [7–11] have been suggested. Of these, only exposure to radiation and mutations in the *RET*-oncogene have been proven to cause childhood thyroid carcinoma. Examples of radiation-induced thyroid cancer are patients who previously received mantle field irradiation [12]. In the Ukraine-region, following the Chernobyl nuclear disaster, an increased incidence of thyroid cancer, mainly of the papillary type, was found in children exposed to radio-iodide [13]. It has been shown that thyroid tissue in children is more sensitive to radiation than in adults [8].

The currently recommended diagnostic test when confronted with a thyroid nodule is ultrasonography combined with fine needle aspiration cytology (FNAC) to differentiate between benign or malignant [14]. As lymph node involvement is present in 71–90% of cases [5], lymph node biopsy is a diagnostic option. Histological classification of thyroid carcinoma can be difficult and inter-observer disagreement has been reported in the range of 7–27% [15]. For staging, radio-iodide is used to detect metastases.

The cornerstone of treatment for thyroid carcinoma at all ages is surgery, with or without adjuvant radio-iodide ablation. In cases of a unilateral tumour without lymph node involvement there is, worldwide, no consensus whether a hemi- or a total thyroidectomy should be preferred [16,17]. At all other tumour stages, total thyroidectomy is indicated. In case of total thyroidectomy, radio-iodide is considered for adjuvant therapy for several reasons [14]. First, to detect and destroy occult microscopic local remnants and distant metastases (if these accumulate radio-iodide). Second, to destroy all remaining normal thyroid remnants, in order to increase both specificity of measurements of plasma thyroglobulin (TG) and its sensitivity during follow-up. Third, to permit post-ablative radio-iodide total body scanning for persistent or recurrent carcinoma. Whether radio-iodide could also be effective in an earlier stage of the treatment, for example administered preceding the surgical intervention, has never been investigated. There is no place for chemotherapy. Thyroxine supplementation is given to correct the inevitable hypothyroidism and to diminish proliferation of remnant thyroid (cancer) cells by suppressing pituitary TSH secretion.

The goal of this study was to obtain insight in early and late adverse events due to paediatric differentiated thyroid cancer, in relation to the therapeutic strategies used, in a cohort of consecutive paediatric patients in one academic medical centre.

2. Patients and methods

All consecutive patients treated for (assumed) paediatric papillary or follicular thyroid carcinoma in the Emma Children's Hospital of the Academic Medical Center (EKZ-AMC), in the period 1962–2002, were evaluated for complications and late adverse events caused by the tumour and the treatment given.

Data were collected from office notes, surgical reports and pathology reports of the departments of paediatric oncology, paediatric endocrinology, and paediatric surgery and from patient charts and the database of the late effects outpatient clinic (PLEK [6]). Patients, who were in complete remission for at least 5 years after finishing treatment and were registered at the paediatric oncology department, were invited to the PLEK. They were either referred by their present physician, or were contacted and invited to visit the hospital for follow-up investigations. At the outpatient clinic, the history was taken and a complete physical examination was performed. Those, who were not able not visit the PLEK, were sent questionnaires. In case of non-responders, the last available follow-up data of the other outpatient clinics were used.

If, after reviewing pathology, the lesion was re-classified as a benign thyroid disorder, patients were not excluded from evaluation of late events when treatment had already been completed.

Data were analysed using Statistical Package for the Social Sciences (SPSS) 10.0.7 and MS Excel '97 software. Statistics were calculated using Pearson χ^2 tests. For occurrence of permanent hypoparathyroidism and injury to the recurrent nerve, relative risks of risk factors were calculated separately. P values of 0.05 or less were considered to indicate statistical significance.

[6] PLEK, Polikliniek Late Effekten Kindertumoren.

3. Results

3.1. Patients

Between 1962 and 2002, 26 patients (20 girls, 77%), with a mean age of 12.5 years (range 5–19 years) were treated for (assumed) differentiated thyroid carcinoma in the EKZ/AMC. Of them, 20 (77%) were initially diagnosed with papillary carcinoma (including one follicular variant), five (19%) with follicular carcinoma and one with a dyshormonogenetic goiter with multiple follicular adenoma.

Data inclusion closed in August 2002. The median follow-up time was 14.2 years (range 0.9–39.4 years). Twenty-one patients were examined at outpatient clinics. Two responded to a questionnaire and in two cases the general practitioner responded to the questionnaires. One girl with papillary carcinoma was lost to follow-up. At last follow-up, all patients were alive.

Of the 25 included patients, five females, at ages ranging from 12–19 years, developed a thyroid carcinoma following irradiation of the cervical region for various reasons (haemangioma, leukaemia and lung metastases of Wilms' tumour), with doses ranging from 7.5 to 32 Gray. The median time between exposure to irradiation and the diagnosis of thyroid carcinoma was 12 years (range 4–16 years). At diagnosis, one patient, who had also received cranial radiation, had thyroxine supplementation because of pituitary insufficiency. Four had a normal thyroid function.

The 20 patients who had been diagnosed with primary thyroid carcinoma (no prior irradiation) had a median age of 13.0 years (range 5–18 years) at diagnosis. Three patients had an impaired thyroid function at diagnosis, one of them was known to have congenital hypothyroidism due to a thyroperoxidase (TPO)-deficiency.

3.2. Diagnostic strategy

Of the 25 patients that could be evaluated, the main presenting symptom was a mass in the thyroidal region and lymphadenopathy. In 20 patients (80%) radionuclide imaging, using $^{99m}TcO_4^-$ ($n = 1$) or $^{123}I^-$ ($n = 18$) or both ($n = 1$), was used in the diagnostic work-up (Table 1). Cold nodules were observed in 13 patients (65%). Ultrasonography was performed, since 1980, in 11 of 18 patients (61%), and showed one or more suspicious lesions in all investigations. FNAC was performed in six patients (24%), and led to the diagnosis of carcinoma in three. All three diagnostic procedures (scan, ultrasound and FNAC) were performed in five patients (20%). In four patients, none of these three procedures were performed, prior to surgical treatment, since in these cases the diagnosis was established after biopsy of an enlarged lymph node.

In 22 patients, the definite diagnosis was obtained with pathology, either by lymph node biopsy ($n = 7$), thyroid biopsy ($n = 2$), frozen section ($n = 2$), hemi/subtotal thyroidectomy ($n = 9$) or by total thyroidectomy ($n = 2$).

3.3. Pathology

The initial pathological examination showed papillary carcinoma in 19 (76%), follicular carcinoma in five (20%) and a benign lesion in one patient. This latter patient was known since birth to have congenital hypothyroidism due to a TPO-deficiency. A FNAC showed suspicious cytology for follicular carcinoma and he underwent total thyroidectomy after which he was diagnosed with a dyshormonogenetic goiter with multiple follicular adenoma. After reviewing the pathology, the diagnosis was changed in another three patients, in two cases to benign lesions (Table 1). Of our 25 patients, eventually 18 (72%) were diagnosed with papillary carcinoma, four (16%) with follicular carcinoma, and three (12%) with benign thyroid lesions.

3.4. Treatment

Initially, all patients were treated surgically, with either hemi-($n = 2$) or total thyroidectomy, with ($n = 13$) or without ($n = 10$) lymph node extirpation. No significant differences in the initial surgical approach were found between the first and second half of the study period. Twelve patients were initially given adjuvant treatment with radio-iodide (retrievable doses ranging from 2.0 to 7.9 Giga-Becquerels (Gbq)). Three other patients received radio-iodide at a later stage of the treatment.

3.5. Stage of disease and recurrence

Of the 22 patients with proven thyroid malignancy after final pathology, 13 (59%) presented with metastases at diagnosis (TNM-stages see Table 2). Seven patients (32%) had a first recurrence of their carcinoma after 0.5–7 years; two of them developed a second and a third relapse. The very first patient in this series, treated in 1962, had cervical and lung metastases after 11 and 39 years, respectively. Both times ablative doses of $^{131}I^-$ were given. However, the metastases after 39 years did not accumulate radio-iodide anymore. Both relapses in the other patient responded well to radio-iodide treatment. Two patients without metastases at diagnosis developed metastases in the lungs, after 2.5 and 3 years, respectively. One of them again developed recurrent lung metastases 7 years later.

In total, at last follow-up, 19 patients were in complete remission, two had persistent disease (elevated but not progressive levels of TG) and one had recurrent disease.

Table 1
Diagnostic tests and histology of assumed differentiated thyroid carcinoma during childhood

Pat ID	Year of diagnosis	$^{123}I^{-}/^{99m}TcO_4^{-}$	Ultra-sonography	FNAC	Definite diagnosis	First histology	Histology after revision
1	1962	–	–	–	Enucleation lump	pap. ca	pap. ca
2	1973	Normal	–	–	Frozen section	pap. ca	–
3	1975	Normal	–	–	Lymph node biopsy	pap. ca	pap. ca
4	1975	Normal	–	–	Lymph node biopsy	pap. ca	pap. ca
5	1976	Cold node	–	–	Thyroid biopsy	pap. ca	**dysh.goiter**
6	1977	Cold node	–	–	Hemi-thyroidectomy	pap. ca	pap.ca
7	1977	Cold node	–	–	Lump enucleation	foll. ca	**foll.ad.**
8	1980	Cold node	–	–	Lymph node biopsy	pap. ca	pap. ca
9	1980	Cold node	1 lesion	–	Subtotal thyroidectomy	pap.ca	**foll. variant pap.ca**
10	1980[a]	Cold node	1 lesion	–	Frozen section	pap.ca	pap. ca
11	1980	Normal	–	–	Hemi-thyroidectomy	foll. ca	–
12	1980	–	–	–	Subtotal thyroidectomy with l.n. extirpation	pap. ca	pap. ca
13	1981	mn goiter	>1 lesion	–	Hemi-thyroidectomy	foll.ca	foll. ca
14	1983	Cold node	–	–	Lymph node biopsy	pap. ca	pap. ca
15	1985	Cold node	–	–	Hemi-thyroidectomy	pap. ca	pap. ca
16	1986	No cold node	1 lesion	Yes	Total thyroidectomy	**dysh. goiter + foll ad.**	–
17	1986[a]	–	–	–	Lymph node biopsy	pap. ca	–
18	1988	Cold node	1 lesion	Yes	Lymph node biopsy	pap. ca	pap.ca
19	1992[a]	Cold node	1 lesion	Yes	FNAC	foll.variant pap.ca.	–
20	1993[a]	Cold node	1 lesion	–	Thyroid biopsy	pap. ca	–
21	1995	Cold node	1 lesion	Yes	FNAC	foll. ca	–
22	1997[a]	Less uptake	1 lesion	–	Total thyroidectomy	pap.ca	–
23	1997	–	1 lesion	Yes	FNAC	pap. Ca	–
24	2000	–	–	–	Lymph node biopsy	pap. Ca	–
25	2001	Cold node	1 lesion	Yes	Hemi-thyroidectomy	foll.ca.	–

In 12 patients (48%) diagnosis was obtained pre-operative by FNAC (12%), thyroid biopsy (8%) or lymph node biopsy (28%). In the other 13 patients, diagnosis was definite after surgery. In two patients (8%), a frozen section was made during surgery. –, Not performed; FNAC, fine needle aspiration cytology; mn goiter, multinodular goiter: dysh. goiter, dyshormonogenetic goiter; pap ca, papillary carcinoma; foll. ca, follicular carcinoma; ad, adenoma; Pat ID, patient ID; l.n., lymph node.

[a] (Peri)cervical irradiation in history.

Table 2
Stage of disease, treatment and recurrence of 22 patients with proven malignant disease

Pat ID	Age at D_x	Histology (after revision)	Metastases at diagnosis	Initial R_x	Adjuvant $^{131}I^-$	TNM-classification	First recurrence	Years to first recurrence	R_x first recurrence
6	16	pap. ca	None	Total with ln_x	+	T3N0M0	–	–	–
9	13	foll. variant pap.ca	None	Total T_x	+	T3N0M0	–	–	–
10	17	pap. ca.	None	Total T_x	–	T2N0M0	–	–	–
11	16	foll. ca	None	Total T_x	+	T3N0M0	–	–	–
13	13	foll. ca	None	Total T_x	–	T3N0M0	–	–	–
15	16	pap. ca	None	Total T_x	–	T2N0M0	–	–	–
25	7	foll. ca	None	Total T_x	+	T2N0M0	–	–	–
3	9	pap. ca	Cerv ln	Total T_x with ln_x	–	T3N1aM0	–	–	–
12	18	pap. ca	Cerv ln	Total T_x with ln_x	+	T3N1M0	–	–	–
14	13	pap. ca	Cerv ln	Total T_x with ln_x	–	T4N1bM0	–	–	–
17	19	pap. ca	Cerv ln	Total T_x with ln_x	+	T4N1M0	–	–	–
18	13	pap. ca	Cerv ln	Total T_x with ln_x	–	T3N1M0	–	–	–
19	16	foll. variant pap. ca.	Cerv ln	Total T_x with ln_x	+	T4N1aM0	–	–	–
20	12	pap. ca	Cerv ln	Total T_x with ln_x	+	T4N1aM0	–	–	–
24	13	pap. ca	Lungs + Cerv ln	Total T_x with ln_x	+	T4N1bM1	–	–	–
1	11	pap. ca	Cerv ln	Lump ext. + ln_x (uni)	–	T2N1aM0	Cerv ln	0.7	Total with ln_x + $^{131}I^{-a}$
2	8	pap. ca	Local lymph- and blood vessel-infiltration	Total T_x	–	T2N1aM0	Cerv ln	7	$^{131}I^{-b}$
4	10	pap. ca	None	Total with ln_x	–	T2N0M0	Lung	3	Metastectomy[c]
8	16	pap. ca	Lungs + Cerv ln	Total with ln_x	+	T3N1bM1	Lung	0.8	$^{131}I^-$
21	8	foll. ca	None	Hemi T_x + ln_x (uni)	–	T3N0M0	Lung	2.5	Total + $^{131}I^-$
22	16	pap. ca	Cerv ln	Total T_x	+	T4N1aM0	Cerv ln	1	mod. ln_x + $^{131}I^{-d}$
23	12	pap. ca	Lungs + Cerv ln	Total T_x with ln_x	+	T4N1bM1	Cerv ln	0.5	mod. ln_x + $^{131}I^{-d}$

D_x, diagnosis; R_x, treatment; (Cerv) ln, (cervical) lymph nodes; total T_x, total thyroidectomy; Mod ln_x, modified lymph node dissection; ext, extirpation.
[a] Second and third recurrence 11 and 39 years after first diagnosis. At last follow-up, still recurrent disease.
[b] Second and third recurrence 8 and 9 years after first diagnosis.
[c] Second lung recurrence 10 years after first diagnosis.
[d] At last follow-up, persistent disease (elevated levels of thyroglobulin (TG)).

There was no significant correlation between recurrence of the disease and T-stage, N-stage, M-stage, or type of tumour (*P* values 0.6, 0.2, 0.5 and 0.6, respectively).

3.6. Complications and late effects

The observed early complications and late effects are shown in Table 3.

Twenty-one patients (84%) had one or more other late complications of treatment, other than the inevitable hypothyroidism.

Six (24%) patients developed permanent recurrent nerve injury. Information about pre-operative vocal cord examination by an oto-rhino-laryngologist could not be retrieved for all of the patients. However, in the surgical reports of five of these patients it was reported that the nerve was encased by tumour that had been removed. In all of these cases, the nerve anatomically seemed to have remained intact. In one patient, hoarseness had already been present at diagnosis, but the contralateral nerve apparently had also been partially injured during surgery due to removal of the encasing tumour.

Eight (32%) patients had developed permanent hypoparathyroidism. In one patient, the parathyroid glands could not be identified in the tumour mass. In five patients, it was reported by the surgeon that at least two parathyroid glands had been saved. However, one developed transient and the other four permanent hypoparathyroidism. For two patients, no information of the parathyroid glands was given.

Three patients had both permanent hypoparathyroidism and permanent recurrent nerve injury. Table 4

Table 3
Adverse events occurring after treatment for (assumed) thyroid carcinoma during childhood

Adverse event	Transient N (%)	Permanent N (%)	Total N (%) 25 (100)	Due to T/T_x[a]
Athyrosis	0	25 (100)[b]	25 (100)[b]	Yes
Lymph leakage	3 (12)	0 (0)	3 (12)	Yes
Tracheostoma	1 (4)	1 (4)	2 (8)	Yes
Horner's syndrome	0 (0)	2 (8)	2 (8)	Yes
Recurrent nerve lesion	2 (8)	6 (24)	8 (32)	Yes
Hypoparathyroidism	5 (20)	8 (32)	13 (52)	Yes
Scar/cosmetic	–	4 (16)	4 (16)	Yes
Depression/fatigue	–	5 (20)	5 (20)	Possible
CML	–	1 (4)	1 (4)	Possible
MS	–	1 (4)	1 (4)	Unlikely
Total of patients with unintended events			21 (84)	

CML: chronic myeloid leukaemia, MS: multiple sclerosis. Mean follow-up time was 14.2 years (0.9–39.4 years). In the fourth column, the probability of a causal relationship, based on data from literature, between the event and the treatment for thyroid carcinoma is given. Lymph leakage occurred in three patients; one patient had long-lasting lymph leakage, one developed lymph oedema in the neck and one patient temporarily suffered from a hydrothorax.

[a] T, tumour; T_x, treatment.

[b] Intended adverse effect.

Table 4
Relative risks calculated for permanent hypoparathyroidism and permanent recurrent nerve injury after treatment for (assumed) thyroid carcinoma in 25 patients

Risk factor (% of total patients)	RR	(95% CI)	χ^2 statistic	*P* value
Permanent hypoparathyroidism (32%)				
Total thyroidectomy with lymph node dissection (ln_x) as first treatment (52)	6.45	(0.93–45.092)	5.940	0.015[b]
T-stage > 3 (36)	1.07	(0.329–3.456)	0.11	0.915
N-stage = 1 (52)	1.54	(0.456–5.093)	0.520	0.471
ln_x at any moment (60)	1.86	(1.053–3.282)	3.707	0.054[a]
Permanent recurrent nerve injury (24)	1.90	(0.634–5.698)	1.176	0.278
Permanent recurrent nerve injury (24%)				
Total thyroidectomy with ln_x as first treatment (52)	1.85	(0.410–8.317)	0.680	0.409
T-stage > 3 (36)	3.56	(0.803–15.745)	3.222	0.073[a]
N-stage = 1 (52)	4.61	(0.626–34.053)	3.105	0.078[a]
ln_x at any moment (60)	1.58	(0.907–2.763)	1.791	0.181
Nerve encasement in surgical report (20)	8.00	(2.001–31.988)	10.746	0.001[b]

RR, relative risk; CI, confidence interval given for the relative risk; ln, lymph nodes.

[a] Indicates near significance found at $P < 0.05$ level.

[b] Indicates strong significance found at $P < 0.05$ level.

shows the relative risks to develop permanent hypoparathyroidism and/or permanent recurrent nerve injury. The relative risk to develop hypoparathyroidism for patients with a total thyroidectomy and lymph node dissection as first treatment was 1.99 ($P = 0.015$). Tumour encasement of the recurrent nerve as mentioned in the surgical report was a significant risk factor to develop permanent recurrent nerve injury (RR: 8.00). Occurrence of permanent recurrent nerve injury and hypoparathyroidism were not significantly related to each other.

One survivor, treated with thyroidectomy and ablative radio-iodide for cervical lymph node metastases at diagnosis was diagnosed with (Philadelphia chromosome-positive) chronic myeloid leukaemia (CML) 22 years later.

Five patients (20%), of which four had thyroid carcinoma as their first malignancy, showed signs of depression and/or fatigue, which could not be related to hypothyroidism or hypocalcaemia. For patients who developed a relapse ($n = 7$), there was no increased risk to develop permanent hypoparathyroidism and/or permanent recurrent nerve injury. However, for this group of patients, a significant increased risk was found to develop signs of fatigue or depression (RR: 12.8, 95% CI: 1.034–157.14).

4. Discussion

A perfect treatment for malignant thyroid disease would be the complete removal of all malignant tissue, without any adverse events. As the mortality of patients, diagnosed with childhood-onset differentiated thyroid carcinoma, has become very low [18], increasing efforts should be directed to minimise or even prevent morbidity due to the disease and its treatment.

Our study substantiates the observation that thyroid tumours in the younger age group are found in a more advanced stage at diagnosis [19]. In these cases, the proper treatment consists of total thyroidectomy and adjuvant radio-iodide therapy. However, for unilateral non-metastasised well-differentiated thyroid carcinoma the question of whether or not to treat with a hemithyroidectomy or a total thyroidectomy remains an open one [16]. There are several arguments to initiate treatment with removal of all thyroid tissue. First, total thyroidectomy results in significantly higher disease-free survival than non-radical surgery [19]. Second, removal of almost all thyroid tissue (by surgery and adjuvant radio-iodide ablation) facilitates the use of radio-iodide imaging in order to detect recurrent disease. Third, plasma TG can, in the absence of TG-antibodies which occur in approximately 25% of patients [20], be used as a tumour-marker. In developed countries, where thyroxine is easily obtained, all these advantages outweigh the disadvantage of hypothyroidism. In the two patients in our cohort, who initially underwent a hemithyroidectomy, tumour recurrence necessitated total thyroidectomy.

The frequency of adverse events, after treatment for (suspected) thyroid carcinoma, found in our study turned out to be rather high. Late adverse events, other than the intended hypothyroidism, were found in 84% of patients. The occurrence of permanent recurrent nerve paralysis (24%) and hypoparathyroidism (32%) was high, when compared with similar cohorts treated for childhood-onset thyroid carcinoma; 0–24% and 0–27%, respectively [18,19,21,22], and when compared with cohorts treated for adult thyroid carcinoma; 1.3–12.9% and 0–27.4%, respectively [23–27]. It must be considered that permanent paralysis of a recurrent nerve that has been taken out of encasing tumour is perhaps not defined as a surgical complication by all authors. These latter circumstances, although the recurrent nerves seemed to be anatomically intact, were found to be a significant risk factor to develop permanent injury. Unfortunately, we could not retrieve all pre-operative recurrent nerve ear-nose and throat (ENT) examinations to distinguish whether the paralysis had to be attributed to the tumour or to the surgical intervention. We expected tumour size and the presence of lymph node metastases to be risk factors for the development of recurrent nerve injury. Unexpectedly, this was not found to be the case, which can possibly be explained by the low patient number.

The percentage of surgical complications is partly related to the number of thyroidectomies performed per year and subsequently to the surgeon's expertise. For this reason, thyroid surgery should only be performed by experienced thyroid surgeons [16]. However, with the low incidence of thyroid malignancies during childhood the experience per paediatric surgeon will remain limited. In our centre, we try to solve this problem by the dedication of one paediatric surgeon of our group to thyroid surgery together with an endocrine surgeon, in order to combine expertise.

Patients, who underwent total thyroidectomy and a lymph node dissection as their primary treatment, were significantly at risk of developing permanent hypoparathyroidism. Most likely, this is due to the more extensive vascular injury induced by the lymph node dissection.

A preventive strategy for the occurrence of hypoparathyroidism, in case of performing a total thyroidectomy with modified radical neck dissection, could be the autotransplantation of parathyroid tissue [28]. Such an approach firstly needs evaluation in a well-performed clinical trial.

For removal of large lobar remnants after incomplete thyroidectomy, radio-iodide ablation has been reported to be safe and effective in adults [29]. With this in mind, a hypothetical strategy to save the recurrent nerve could be to leave some tumour around it and treat the remains

with adjuvant radio-iodide ablation, rather than surgically removing the smallest rests. This has never been done in humans and the feasibility should firstly be studied in an animal model.

Depression and fatigue as late adverse events, not related to hypocalcaemia or hypothyroidism were found in five patients. These have not previously been described after treatment for thyroid cancer. We found a strong significant risk for patients with recurrent disease. This should be a point of attention during treatment and follow-up. One patient has recently been diagnosed with multiple sclerosis (MS). However, a relationship between MS and thyroid carcinoma could not be found in the literature.

Special attention should be focused on the possible complications due to the use of radio-iodide. In general, $^{131}I^-$ treatment is accepted as a safe treatment, also in young patients [30]. Transient side-effects can be sialoadenitis, transient loss of taste and smell, xerostomia, nausea, vomiting, diarrhoea, gastralgia and leucocyte and platelet abnormalities [31,32]. The finding of one patient with CML might have been a coincidence. However, several cases of AML and CML have been observed after radio-iodide treatment for both thyroid carcinoma and hyperthyroidism [33–37]. Although, an increased risk for leukaemia has, to date, never been demonstrated in epidemiological analyses [38,39], we feel that these findings merit further follow-up of $^{131}I^-$ treated patients, to exclude a causative relationship.

In conclusion, life expectancy for a patient with childhood-onset differentiated thyroid carcinoma is very good, although the risk of developing adverse events in young adulthood appears to be quite high. Once the tumour has recurred, further recurrence of metastases can be expected even after several decades. We advocate that all thyroid tissue should be ablated in the treatment for differentiated thyroid carcinoma, as it facilitates adequate monitoring of recurrent disease and its treatment by plasma TG-measurement as a tumour marker. Considering the good prognosis of paediatric thyroid cancer, steps must be taken to reduce the long-term morbidity of the tumour and its treatment. Improvements in the quality of surgery should be aimed for. However, there are limits to the surgical possibilities, considering the delicacy and precision of the surgical technique needed for paediatric thyroid surgery. Therefore, it is our opinion that new treatment modalities as well as new applications of existing treatment modalities should be investigated.

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