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Differentiated Thyroid Cancer in Adolescents: Single Center Experience and Considerations for Surgical Management and Radioiodine Treatment

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What is already known on this topic?

Although most studies of pediatric differentiated thyroid cancer include all patients aged less than 18 years, the "adolescent" group, defined by World Health Organization as patients between 10 and 19 years of age, seem to present a less aggressive course than in children under 10 years old. Compared to patients older than 19 years, they also seem to have higher cure rates, despite higher rates of cervical lymph node and pulmonary metastasis.

What this study adds?

This study focused on adolescents aged between 10 and 19 years and treated at a single center. There was a higher rate of follicular variant papillary thyroid cancer than other previous pediatric studies but also a high cure rate at a median of 60.7 months after surgery and following first-line 2-3.7 GBq radioiodine treatment (RAIT) administered postoperatively. Adjuvant RAIT may thus obviate the postoperative morbidity of prophylactic lymphadenectomy for these young patients.

Abstract

Objective: Differentiated thyroid cancer (DTC) in adolescents rare but with a favorable outcome, despite higher rates of cervical lymph node and pulmonary metastasis compared to adults. The aim of this study was to critically evaluate treatment of adolescents with DTC at a single center.

Methods: Patients receiving postoperative radioiodine treatment (RAIT) for DTC between 2005 and 2020 at our institution were screened to identify adolescents according to the World Health Organization definition (10-19 years of age). Demographics, clinico-pathological characteristics, treatment and outcome were analyzed.

Results: Among 1,897 DTC patients, 23 (1.3%) were adolescents with a median (range) age of 16 (10-18) years. The female to male ratio was 3.6:1. Sixty percent had classic papillary thyroid cancer, with follicular variant in 40%, which was higher than previously reported (15-25%) for this age group. pT-status was pT1 in 9 (39.2%), pT2 in 8 (34.8%), pT3 in 3 (13%) and pT4 in 3 (13%) patients. In 19 (82.6%) patients, central lymphadenectomy was performed and metastasis was seen in 57%. All patients received RAIT with initial activities of 1.2 (n=1, 4.3%), 2 (n=12, 52.2%) or 3.7 GBq (n=10, 43.5%). Eighteen (78.2%) patients were free of biochemical and radiologic disease at a median follow-up of 60.7 months. Second-line surgery for lymph node relapse was necessary in 3 (13%) cases. There was one disease-associated death.

Conclusion: Despite high rates of metastasis, most patients were cured, and second-line surgery was rarely required. Further prospective studies are needed to determine whether less aggressive surgical management or omitting adjuvant RAIT are feasible in patients with limited stages at diagnosis.

Keywords: Differentiated thyroid cancer, adolescents, prophylactic lymphadenectomy

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Introduction

Differentiated thyroid cancer (DTC) is rare in the population younger than 19 years of age (1). The currently available published evidence about this topic is limited due to the paucity of cases but suggests some interesting differences in comparison to adult DTC. For example, reported rates of cervical lymph node involvement are higher (40-80% vs. 20-50% in adults) (2,3). Even pulmonary metastases are more common (9-30% vs. 2-9%) (2). Nevertheless, the long-term outcome has been found to be generally favorable, with low mortality rates for non-radiation induced DTC (2). In a retrospective Italian analysis of 250 patients with a mean age of 14.2 years (range 4-18 years), the overall survival was 100% (4). Data from the US on patients with a median age of 17.7 years at diagnosis reported overall survival at 20 and 30 years of 100% and 94.4%, respectively. The progression free survival rates at 10, 20, and 30 years were 71%, 62%, and 55%, respectively (5). Compared to both adults and patients younger than 10 years of age, the course of disease in the 10-19 years age group seems to be less aggressive (3), suggesting that pediatric and adolescent DTC should be considered as separate entities.

In Germany, there are no specific guidelines for children and adolescents with DTC, so they are treated according to protocols for adult patients (6). The German Pediatric Oncology Hematology-Malignant Endocrine Tumor (GPOH-MET) protocol from 1995 recommended total thyroidectomy including routine central neck dissection for all children and adolescents with DTC, as well as postoperative treatment with ^{131}Iodine (^{131}I) radioiodine treatment (RAIT) (3). The American Thyroid Association (ATA) pediatric guidelines from 2015 recommend "future studies to assess if total thyroidectomy with prophylactic central node dissection will lead to reduced reliance on ^{131}I treatment, re-operative procedures, and improved diseases free survival" (7), but these studies are still pending.

Some retrospective analyses have reported recurrence rates as high as 35.7% in children and adolescents (5), generally occurring within the first five years after treatment in patients who underwent immediate postoperative RAIT (3,4,5); but there is also evidence of late events, more than 10 years after primary treatment, particularly in those patients who did not receive RAIT (5).

In order to optimize clinical management of adolescents with DTC, demographics, clinico-pathological characteristics, treatments and outcomes of adolescents treated at a single center were evaluated. Furthermore, a review of the current literature on this subject was undertaken.

Methods

Patients and Tumors

Patients who underwent postoperative RAIT for DTC between 01.01.2005 and 31.07.2020 at the University Hospital of Cologne, Germany were screened. From these patients, the adolescent group, defined as patients between 10 and 19 years of age according to the current World Health Organization (WHO) definition, was identified. Patients receiving surgical treatment at our institution as well as those only referred to our center for RAIT and oncologic care after external surgery were included in the present study.

Histologic classification was made according to the current International Agency for Research on Cancer WHO classification of tumors of endocrine organs at the time of diagnosis and staging was performed using the Union for International Cancer Control TNM classification of malignant tumors (8). The current American Joint Committee on Cancer 8th edition (9) classifies papillary thyroid cancer (PTC) as follows: pT1, tumor ≤2 cm in greatest dimension limited to the thyroid (pT1a, tumor ≤1 cm in greatest dimension limited to the thyroid; pT1b, tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid); pT2, tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid; pT3, tumor >4 cm limited to the thyroid or gross extrathyroidal extension invading only strap muscles (pT3a, tumor >4 cm limited to the thyroid; pT3b, gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid or omohyoid muscles) from a tumor of any size); pT4, gross extrathyroidal extension into major neck structures (pT4a, gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve from a tumor of any size; pT4b, gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size).

Primary Treatment

In Germany the primary surgical management of DTC in patients <19 years is the same as in adults, according to the current guidelines (6): for PTC >1 cm diagnosed preoperatively by fine needle biopsy or intraoperatively by frozen section, the guidelines recommend total thyroidectomy and, depending on the experience of the operating surgeon, prophylactic central lymphadenectomy. Therapeutic lymphadenectomy due to proven or suspicious lymph nodes is always recommended. In case of diagnosis of follicular thyroid cancer (FTC), which is generally postoperative, the need for thyroidectomy depends on the

presence of angio-invasion. Thus, hemithyroidectomy is followed by contralateral hemithyroidectomy and RAIT, if the final histopathology report diagnoses widely invasive FTC (WIFTC) (6).

RAIT is recommended in all patients with PTC > 1 cm, PTC < 1 cm with lymph node metastases or WIFTC.

Diagnostic whole-body scintigraphy scan (DWBS) is regularly performed three months after RAIT and represents the only staging routinely performed for DTC, beside comprehensive cervical sonography.

Evaluation of Response

Evaluation of response at our institution is routinely based on physical examination, thyroglobulin blood levels (Tg) and imaging studies, including cervical sonography, DWBS with 185-370 MBq of radioiodine (^{131}I) and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), if necessary. Complete response is defined as Tg ≤0.2 ng/mL, negative neck ultrasound and negative DWBS six to nine months after RAIT.

During follow-up, significant elevation of basal and stimulated serum Tg compared to the nadir value, as well as all values > 1 ng/mL measured with an ultrasensitive assay (incomplete biochemical response) again led to DWBS with 185-370 MBq of radioiodine followed by ^{18}F-FDG PET/CT if radioiodine uptake was low or absent. If DWBS was positive, patients received a therapeutic activity of 3.7 GBq of radioiodine ^{131}I. If DWBS was negative, but ^{18}F-FDG PET/CT confirmed structural recurrence, surgery was considered. If the imaging studies did not indicate recurrence, serum Tg levels were monitored, as described above (10).

In case of Tg antibodies, which are also routinely tested during follow-up, Tg cannot be used to diagnose biochemical recurrence and follow-up is mainly based on radiologic studies, including complete neck ultrasound, DWBS and/or ^{18}F-FDG PET/CT, in case of suspicion.

Surgery in Cases of Recurrence

Indication for surgery is always initiated by the multidisciplinary tumor board (MTB) at our institution. The MTB includes experts in surgery, nuclear medicine, endocrinology, histopathology and radiation therapy. Surgery for recurrence consists in resection of isolated soft tissue tumors in the perithyroidal/paratracheal space or systematic lymphadenectomy, in case structural recurrence does not appear iodine-avid on DWBS or is deemed too large for repeated ^{131}I therapy. Surgery in these cases was always performed by specialized endocrine surgeons with intraoperative frozen section and neuromonitoring.

Follow-up

Follow-up examinations took place every six months for five years after initial diagnosis and thereafter once every year in the nuclear medicine department and included physical examinations, Tg level, Tg antibodies test, and cervical ultrasound. DWBS and/or magnetic resonance imaging (MRI) and ^{18}F-FDG PET/CT were performed only if clinically indicated. Median follow-up was 60.7 months (range 12-177) after thyroidectomy. All follow-up examinations performed up to December 2021 were included in this study. Response was regularly re-evaluated according to Dietlein et al. (11).

The study was performed according to the rules and regulations for retrospective analysis of the Ethical Committee of the University Hospital Cologne (decision no: 22-1100, date: 02.03.2022).

Statistical Analysis

Data from electronic and paper records of patients identified as eligible for this study were retrospectively collected and analyzed. Data were analyzed using IBM Statistical Package for the Social Sciences statistics for Windows, version 25.0. (IBM Inc., Armonk, NY, USA).

Results

Patient Characteristics

During the review period, 1,897 patients with a median (range) age of 49 (7-87) years received RAIT for DTC. Of these 1,897, 25 (1.3%) met the study definition of adolescent at the time of diagnosis and so were included in this study. In two cases, documentation was incomplete, and these cases were, therefore, excluded. The median (range) age of adolescents with DTC undergoing RAIT was 16 (10-18) years (Figure 1).

There was a female predominance (3.6:1), with no significant (p = 0.22) age difference between male and female patients with median (range) ages of 16 (11-17) and 16.5 (10-18) years, respectively. Only one 17-year-old girl had FTC while all other cases were diagnosed with PTC, thirteen (59.1%) with classic and 9 (40.9%) with follicular variants.

Tumor Stages and Metastatic Disease at the Time of Diagnosis

One patient (4.3%) had pT1a, eight (34.7%) patients had pT1b tumors, eight (34.7%) had pT2 while there were three (13%) of each of pT3 and pT4 tumors.

Central lymphadenectomy was performed in 19 (82.6%) patients. In 11 (57.9%) cases lymph node metastases were found with a median rate of positive versus collected lymph nodes of 0.48 (range: 0.12-1). Extracapsular extension (ECE)

of metastasis was not documented regularly in pathology reports.

Distant metastases were present in 2 (8.7%) patients, both with pT4a tumors.

Radioiodine Treatment

Patients initially received RAIT with an activity of 1.2 (n = 1, 4.3%), 2.0 (n = 12, 52.2%) or 3.7 GBq (n = 10, 43.5%). One 16-year-old female patient with a pT4a pN1 (29/39) cM1 classic variant PTC (patient 23, Table 1) received a mean cumulative activity of 16.4 GBq for lymph node and lung metastases at the time of diagnosis.

Repeated Cervical Surgery

Second-line surgery for relapse after thyroidectomy was performed in 3 (13%) of these patients: patients 19, 22 and 16 (Table 1). One 15-year-old female patient (patient 19) with a pT2m pN1b (4/31) cM0 tumor developed an

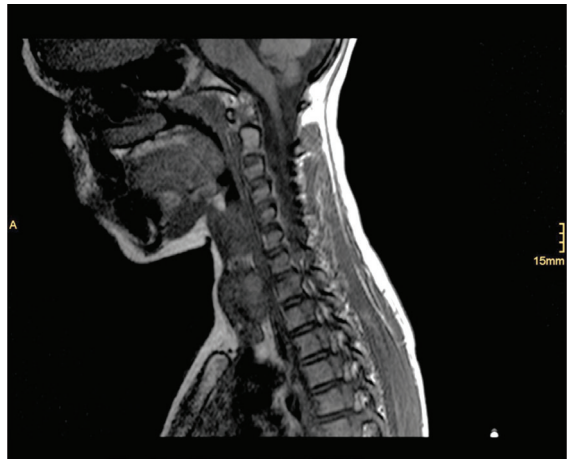

Figure 1. pT2 papillary thyroid carcinoma in a young patient included in the present study (patient 1). This MRI was performed after a fall, in order to rule out spine injury. The thyroid nodule was diagnosed incidentally

MRI: magnetic resonance imaging

Table 1. Three (13%) patients underwent repeat surgery consisting of lateral node dissection in one case and resection of paratracheal recurrences in the others. Patient 21 was diagnosed when metastatic disease was already present and subsequently deceased, despite systemic treatment. In contrast, patient 23 was free of biochemical and radiologic disease at last follow-up

Pt number	Gender, age (years)	pT	Variant	pN	cM	Cumulative RAIT activity (GBq)	Repeat surgery	Last recorded response
1.	**M, 11**	pT2	Foll. PTC	0	0	1.2	-	CR
2.	**F, 10**	pT1b	Class. PTC	1	0	2.0	-	CR
3.	**F, 17**	pT1b	Foll. PTC	0	0	2.0	-	CR
4.	**F, 14**	pT2	Foll. PTC	cN0	0	2.0	-	CR
5.	**F, 17**	pT2	Class. PTC	0	0	2.0	-	CR
6.	**F, 14**	pT3	Foll. PTC	0	0	2.0	-	CR
7.	**F, 16**	pT2	Class. PTC	0	0	2.0	-	CR
8.	**F, 17**	pT1b	Class. PTC	0	0	2.0	-	CR
9.	**F, 17**	pT1b	Class. PTC	cN0	0	2.0	-	CR
10.	**F, 17**	pT2	Class. PTC	1	0	2.0	-	CR
11.	**M, 14**	pT3	Class. PTC	1	0	2.0	-	CR
12.	**M, 17**	pT1b	Foll. PTC	cN0	0	2.0	-	CR
13.	**M, 16**	pT2	Foll. PTC	cN0	0	2.0	-	CR
14.	**F, 15**	pT3b	Class. PTC	1	0	3.0	-	CR
15.	**F, 17**	pT1b	FTC	0	0	3.5	-	CR
16.	**F, 18**	pT4a	Class. PTC	1	0	3.7	Paratracheal LN recurrence	Not available yet
17.	**F, 17**	pT2m	Class. PTC	1	0	3.7	-	CR
18.	**F, 14**	pT1m	Class. PTC	0	0	3.7	-	CR
19.	**F, 15**	pT2	Class. PTC	1	0	3.7	Paratracheal LN recurrence	IBR
20.	**F, 16**	pT1m	Foll. PTC	1	0	3.7	-	CR
21.	**F, 17**	pT4a	Class. PTC	1	1	3.7	-	Deceased
22.	**M, 17**	pT1a	Foll. PTC	1	0	3.7	Lateral LN recurrence	IBR
23.	**F, 16**	pT4a	Class. PTC	1	1	16.4	-	CR

RAIT: radioiodine therapy; M: male; F: female; Class. PTC: classic variant papillary thyroid cancer; Foll. PTC: follicular variant papillary thyroid cancer; LN: lymph node; CR: complete response; IBR: incomplete biochemical response; FTC: follicular thyroid cancer

enlarged retroclavicular and paratracheal located lymph node measuring 1.9x1.2x2.6 cm one year after initial surgery, diagnosed by sonography, MRI and positive DWBS. This was surgically removed, since it was too large for successful treatment with RAIT. Another 17-year-old male patient with a pT1a pN1 (2/2) cM0 follicular variant PTC was diagnosed 6 months after initial surgery with non-radioiodine-avid, ^{18}F-FDG-PET positive lymph nodes in the lateral compartment and underwent lateral lymphadenectomy, delivering four lymph node metastases (maximal size 1.8 cm) without ECE in 12 harvested nodes. Patient 16, initially diagnosed with a pT4a (4.2 cm), L0, V0, pN1b (12/25), M0, R0 classic PTC developed non-radioiodine-avid, ^{18}F-FDG-PET positive lymph nodes in the ipsilateral central lymph node compartment 52 months after primary treatment with small pulmonary metastases and underwent cervical surgery shortly before completion of the present study.

Overall Outcome

There was one disease-associated death in a 17-year-old girl with metastatic, classic PTC pT4 (lung, liver and bone metastasis). The patient died despite chemotherapy and tyrosine kinase inhibitors treatment with sunitinib approximately two years after thyroidectomy and RAIT (patient 21, Table 1).

Eighteen patients (78%) were cured and are free of biochemical and radiologic disease after a median follow-up of 60.7 months. These eighteen included a 16-year-old girl with a pT4a pN1 cM1 PTC (patient 23) who was last followed-up in January 2022, 120 months after first diagnosis of pulmonary involvement and 54 months after last RAIT.

Three (13%) patients required additional surgery for relapse and are currently in early follow-up. Patients 19 and 22 currently have no sign of radiologic disease but do have slightly elevated Tg levels indicating incomplete biochemical response at 107 and 12 months after surgery, respectively. Patient 16 underwent surgery for paratracheal metastatic lymph nodes diagnosed 52 months after first treatment and a further RAIT only a few weeks before completion of this manuscript. Therefore, early follow-up is not yet available.

Finally, a 15-year-old female girl with a pT2 pN1 (3/13) cM0 classic PTC, without evidence of radiologic disease had a slightly elevated Tg level (0.79 ng/L) without evidence of structural disease. None of the patients experiencing recurrence/persistence had a complete response after initial surgery and RAIT. Tg antibodies were found in only one patient (patient 16, Table 1).

Discussion

Thyroid cancer is rare in patients younger than 19 years. The recent publication of the "GPOH-MET" for the years 1995-2019 included 354 patients (3), thus there was approximately 14 patients/year in Germany. In the Netherlands, over a 43-year period, 170 patients were identified (12). Although most studies include all patients aged less than 19 years, DTC seems to be more aggressive in patients younger than 10 years of age than in adolescents (3,13,14). Thus, adolescent DTC seems to present a specific entity, which we believed warranted special focus, hence the present study.

In the present study, pT1 and pT2 status were frequent and comparable to the literature on adolescent DTC, identified in 73.9% of the cohort compared to rates of 69.6% and 58.4% previously reported by Markovina et al. (5) and Spinelli et al. (4). Similarly, rates of lymph node involvement were also comparable to those reported in similar groups, at 57.1% in the present study versus 60% reported by Spinelli et al. (4) and 65.2% reported by Markovina et al. (5). The rate of PTC follicular variant (40.9%), however, was higher in our cohort compared to these earlier studies, that reported rates of 24.8% (4) and 20.6% (5) and also when compared to a report from the USA of 15% (13). The reasons underlying these differences might be due to demographic, ethnic and/or environmental differences, but addressing this point would go beyond the scope of this study.

We observed a recurrence/persistence rate of 17.3% at a median follow-up of slightly more than five years. In contrast, Markovina et al. (5) reported recurrence in 35.7% of patients with a median follow-up duration of 18.1 years. Most recurrences observed in their study occurred within the first 10 years. One reason for the discrepancy might be because they also included some patients younger than 10 years, in whom DTC seems to be more aggressive (3,13,14). Moreover, the median follow-up of 60.7 months in our study may have missed some longer term recurrences.

The proportion of patients undergoing central lymphadenectomy in the cohort of Markovina et al. (5) was similar to ours (70%), but undergoing central lymphadenectomy did not correlate with recurrence in their study. Both our data and the currently available evidence do not allow the development of clear recommendations concerning prophylactic central lymphadenectomy for adolescent DTC. In the recent Dutch guidelines for pediatric DTC, prophylactic lymphadenectomy is not recommended in patients <18 years with a negative comprehensive ultrasound exam of all neck regions performed by a radiologist experienced in head and neck imaging (15,16).

However supporters of prophylactic central lymph node dissection underline the problems associated with decades of long-term follow-up, pleading for treatments that minimize the risk of persistence and recurrence (17).

Another possible reason for the higher recurrence rate reported by Markovina et al. (5) might be that 18% patients did not initially receive ^{131}I therapy. Routine postoperative RAIT is currently recommended in children and adolescents with tumors >1 cm in Germany and in the Netherlands (12,18). The pediatric ATA guidelines recommend ^{131}I only for nodal or other loco-regional disease that is not amenable to surgery, as well as for distant metastases that are known or presumed to be iodine-avid (7). In addition, some experts also advocate routine ^{131}I therapy for children with T3 tumors or extensive regional nodal involvement (N1a or N1b) (7). Another factor to consider is that some recent evidence has been presented suggesting that there is an increased risk of leukemia or solid cancers more than 20 years after childhood RAIT (19).

The recent data published by Redlich et al. (3) indicate age <10 years at diagnosis, ATA high-risk level, and poor response to initial therapy as significant negative prognostic factors for event free survival in pediatric DTC (5). This might help to tailor a risk-adapted individualized therapy, restricting the need for prophylactic lymphadenectomy and adjuvant RAIT for poor responders to initial treatment. Molecular pathology (20,21) and new additional diagnostic tools, such as detection of circulating tumor cells in patients' blood might also play a role for guiding treatment in the future (22).

Study Limitations

The present study cohort was not large enough to permit the formulation of robust general recommendations, especially concerning prophylactic lymphadenectomy, which was omitted in only four cases. In addition, the cohort included a high percentage of pT1 and pT2 tumors, which in general have a favorable outcome, as in adults. However, these survival rates are similar to rates reported in other studies and seem to be common in adolescents. In addition, we do not have a control group of adolescents undergoing thyroidectomy without RAIT, as RAIT is standard treatment for all patients with tumors larger than 1 cm in Germany (18). Finally, it should be remembered that age at presentation or thyroidectomy does not always represent the age at occurrence, due to the indolent biological behavior of DTC (23).

Conclusion

The need for prophylactic lymphadenectomy and adjuvant RAIT remain a matter of debate, due to the rarity of DTC in adolescents. The unique nature of these tumors presenting as more aggressive, in terms of lymph node involvement but behaving more favorably than in adults in terms of survival, deserves more attention in the future and the development of individualized treatments, as Redlich et al. (3) recently recommended. Further prospective studies are needed to determine whether less aggressive surgical management or omitting adjuvant RAIT are feasible in some patients with less severe staging at diagnosis.

Ethics

Ethics Committee Approval: The study was performed according to the rules and regulations for retrospective analysis of the Ethical Committee of the University Hospital Cologne (decision no: 22-1100, date: 02.03.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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