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

Abstract
Background: Differentiated thyroid cancer (DTC) in adolescents is a rare disease with favorable outcome, despite higher rates of cervical lymph node and pulmonary metastasis compared to adults. Aim of this study was to critically evaluate its treatment.

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

Results: Among 1897 DTC patients 23 (1.3%) were adolescents (median age 16 years, range 10-18). The female to male ratio was 3.6:1. Classic papillary thyroid cancer was seen in 60%, follicular variant in 40% of cases, which is higher than reported in the literature (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 status in 3 (13%) patients. In 19 (82.6%) patients, central lymphadenectomy was performed revealing metastasis in 57%. All patients received RAIT with an initial activity of 1.2 (n=1, 4.3%), 2 (n=12, 52.2%) or 3.7 GBq (n=10, 43.5%) of radioiodine. Eighteen (78.2%) patients are free of biochemical and radiologic disease in a median follow-up of 60.7 months. Second-line surgery or lymph nodal 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 limited stages.

Keywords: differentiated thyroid cancer, adolescents, prophylactic lymphadenectomy

Introduction
Differentiated thyroid cancer (DTC) is rare in the population younger than 19 years of age (1). The currently available evidence on 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 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). Not only compared to adults but also compared to patients younger than 10 years of age, the course of disease seems to be less aggressive between 10 and 19 years (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 131Iodine (RAIT) (3). The ATA pediatric guidelines of 2015 recommend “future studies to assess if total thyroidectomy with prophylactic central node dissection will lead to reduced reliance on 131I treatment, re-operative procedures, and improved diseases free survival” (7), however 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 5 years after treatment in patients who underwent immediate postoperative RAIT (3,4,5); but also late events, more than 10 years after primary treatment, particularly in those patients who did not receive RAIT (5).

In order to optimize our management of adolescents with DTC, we analyzed demographics, clinico-pathologic characteristics, treatment and outcome of adolescents treated at our institution and reviewed the current literature on this subject.

Methods

Patients and tumors

Patients, who underwent postoperative RAIT between 01.01.2005 and 31.07.2020 at the University Hospital of Cologne, Germany for differentiated thyroid cancer were screened. The group of adolescents, defined as patients between 10 and 19 years of age according to the current WHO definition, was identified. Patients receiving surgical treatment at our institution as well as those only referred to our center to radioiodine treatment and oncologic care after external surgery were included in the present study. Histologic classification was made according to the at the time current IACR WHO classification of tumors of endocrine organs and staging was performed using the UICC TNM classification of malignant tumors (8). The current AJCC 8th edition (9) classifies 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

Primary surgical management of DTC in patients <19 years is the same as in adults in Germany according to the current Guidelines (6): for PTC >1cm 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 FTC diagnosis, which is generally postoperative, the need for thyroidectomy depends on the presence of angioinvasions. Thus, hemithyroidectomy is followed by contralateral hemithyroidectomy and radioiodine treatment, if final histopathologic report diagnoses widely invasive follicular thyroid carcinomas (WIFTC) (6).

Radioiodine therapy is recommended in all patients with PTC > 1 cm, PTC < 1 cm with lymph node metastases and widely invasive follicular thyroid carcinomas (WIFTC).

Diagnostic whole-body scintigraphy scan (DWBS) is regularly performed 3 months after radioiodine treatment 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, diagnostic whole-body scintigraphy scan (DWBS) with 185-370 MBq of radioiodine (I-131) and 18F-FDG 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 radioiodine treatment.

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) led to a diagnostic whole-body scintigraphy scan (DWBS) with 185-370 MBq of radioiodine (I-131)-followed by 18F-FDG PET-CT if radioiodine uptake was low or absent. If DWBS was positive, patients received a therapeutic activity of 3.7 GBq of radioactive iodine (I-131). If DWBS was negative, but 18F-FDG PET-CT confirmed structural recurrence, surgery was considered. If the imaging studies did not display recurrence, serum Tg levels were monitored, as described above (10).

In case of Tg antibodies, which are also a routine component of the follow up labs, Tg cannot be used to diagnose biochemical recurrence and follow up is mainly based on radiologic studies, including complete neck ultrasound, DWBS and/or 18F-FDG PET-CT, in case of suspicion.

Surgery of recurrence

Indication to surgery is always initiated by the MTB (multidisciplinary tumor board) at our institution. The MTB includes surgery, nuclear medicine, endocrinology, pathology 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 in DWBS or is deemed too large for repeated 131I therapy. It was always performed by specialized endocrine surgeons with intraoperative frozen section and neuronavigation.

Follow-up examinations take place every half a year for 5 years after initial diagnosis and thereafter once every year in the department for Nuclear Medicine and include physical examinations, thyroglobulin (Tg) level, Tg antibodies, and cervical ultrasound. DWBS and/or MRI and 18F-FDG PET-CT are done only if clinically indicated. Median follow up was 60.7 months (range 12-177) after thyroidectomy. Follow up examinations until December 2021 were included in this study. Response was regularly reevaluated according to (11).

Data Collection and Analysis

Electronic and paper data of the University Hospital of Cologne were retrospectively collected and analyzed. The study was performed according to the rules and regulations for retrospective analysis of the ethical committee of the University Hospital Cologne. Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY.

Results

Patient characteristics

1897 patients received radioiodine treatment (RAIT) for DTC. Their median age was 49 years (range 7-87), 25 (1.3%) of them were defined as “adolescents” and included in this study. In two cases, documentation was incomplete and these cases were, therefore, excluded. The median age of adolescents with DTC undergoing RAIT was 16 years (range 10-18) (figure 1).

There was a female predominance (3.6:1), with no significant (p=0.22) age difference between male (median age 16 years, range 11-17) and female patients (median age 16.5, range 10-18). Only one 17-year-old girl had follicular thyroid cancer (FTC). In all other cases, papillary thyroid cancer (PTC) was diagnosed: thirteen (59.1%) classic and 9 (40.9%) 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, 8 (34.7%) had pT2. pT3 tumors and pT4 were seen each in three (13%) subjects respectively.

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

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Patients received initially radioiodine therapy 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 cM1 classic variant PTC (Pt 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 recurrence after thyroidectomy was performed in 3 (13%) of these patients: pt 19, 22 and 16 (table 1). One 15-year-old female patient with a pT2m pN1b (4/31) cM0 tumor developed an 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 (Pt 19). It was surgically removed since it was too large for 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, 18F-FDG-PET positive lymph nodes in the lateral compartment and underwent lateral lymphadenectomy, delivering four lymph node metastases (maximal size 1.8 cm) without extracapsular extension in 12 harvested nodes. Patient 16, initially diagnosed with a pT4a (4.2 cm), L0, V0, pN1b (12/25), M0, R0 classic PTC developed 52 months after primary treatment non-radioiodine-avid, 18F-FDG-PET positive lymph nodes in the ipsilateral central lymph node compartment and 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 female with metastatic classic PTC pT4 (lung, liver and bone metastases). The patient died despite chemotherapy and TKI treatment with Sunthinimit approximately 2 years after thyroidectomy and RAIT (pt. 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 including a 16-year-old female patient with a pT4a pN1 cM1 PTC (pt. 23, last follow up 01/2022, 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. Pt 19 and 22 have currently no sign of radiologic disease but slightly elevated Tg levels (incomplete biochemical response 107 and 12 months after surgery respectively). Pt 16 underwent surgery for paratracheal metastatic lymph nodes diagnosed 52 months after first treatment and also a further radioiodine treatment only few weeks before completion of this manuscript. Therefore, early follow-up is not available yet.

Finally, a 15-year-old female patient with a pT2 pN1 (3/13) cM0 classic PTC, without evidence of radiologic disease has a slightly elevated Tg level (0.79ng/L) without evidence of structural disease. None of the patients experiencing recurrence/persistence had a complete response after initial surgery and radioiodine treatment. Tg antibodies were present in one patient only (patient 6, table 1).

Discussion

Thyroid cancer is rare in patients younger than 19 years. The recent publication of the “German Pediatric Oncology Hematology-Malignant Endocrine Tumor registry” (GPOH-MET) for the years 1995-2019 included 354 patients (3), but approximately 14 patients/year in Germany. In the Netherlands, in 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, on which we decided to focus in the present study. pT1 and pT2 status were frequent and comparable to the literature on adolescent DTC (7.9% versus 69.6% (5) and 58.4% (4)). Rates of lymph nodal involvement were also comparable to those reported in similar groups (37.1% versus 60% (4) and 65.2% (5)). The rate of PTC follicular variant, however, was higher in our patients than in other collectives (90% versus 24.8% in an Italian (4) and 20.6% (5) and 15% (13) in US American collectives). The reasons underlying these differences might be of demographic, ethnic or environmental nature, but addressing this point would go beyond the scope of our study.

We observed a recurrence/persistence rate of 17.3% in a median follow up of 60.7 months. In contrast, Markovina et al. (5) reported recurrence in 35.7% of patients. 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). On the other hand, the median follow up of 60.7 months in our study might not cover long-term recurrences.

The rate of patients receiving central lymphadenectomy in the collective of Markovina et al. (5) was similar to ours (70%), but having received central lymphadenectomy did not correlate with recurrence in their study (5). Both our data and the currently available evidence do not permit to formulate 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 with a negative comprehensive ultrasound exam of all neck regions performed by an experienced head and neck or (16,17). 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 (18).

Another possible reason for the higher recurrence rate reported in the study of Markovina et al. (5) might be that 18% patients did not initially receive 131I therapy. Routine postoperative RAIT is currently recommended in children and adolescents with tumors >1cm in Germany and in the Netherlands (12,19). The pediatric ATA guidelines recommend 131I only for nodal or other loco regional disease that is not amenable to surgery as well as distant metastases that are known or presumed to be iodine-avid (7). In addition, some experts also advocate routine 131I therapy in all T1 or T2 tumors or extensive regional nodal involvement (N1a or N1b) (7). In fact, some recent evidence for an increased risk of leukemia and other solid cancers more than 20 years after RAIT in the childhood has been reported and must be taken into consideration (20).

The recent data published by Redlich et al. indicate age <10 years, 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 tailoring a risk-adapted individualized therapy, restricting the need for prophylactic lymphadenectomy and adjuvant RAIT for poor responders to initial treatment. Molecular pathology (21,22) and new additional diagnostic tools like circulating tumor cells in patients’ blood might also play a role for guiding treatment in the future (23).

Study Limitations

The collective included in this study is not large enough for formulating general recommendations, especially concerning prophylactic lymphadenectomy, which was omitted in only four cases. In addition, it includes a high percentage of pT1 and pT2 tumors, which in general have a favorable outcome, also 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, due to the fact that RAIT is standard in all patients with tumors larger than 1 cm in Germany (19). Finally, it needs to be considered that age at presentation or thyroidectomy does not always represent the age at occurrence, due to the indolent biological behavior of DTC (24).

Conclusion

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 nodal involvement but behaving more favorably than in adults in terms of survival deserves more attention in the future and individualized treatment, as Redlich et al. recently recommended (3). Further prospective studies are needed to determine whether less aggressive surgical management or omitting adjuvant RAIT are feasible in limited stages.
“Law on the Protection of Personal Data in Healthcare (Health Data Protection Act - GDGS NRW)” the university staff is allowed to use clinical information to which they have access for scientific activity without patients consent, as long as personal rights are preserved.

Availability of data and materials
Data can be required on reasonable request to the author any time.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors’ contributions
Conceptionalization, C.C., H.A., and M.S.; methodology and software C.C.; formal analysis, H.A., M.F., M.S., M.J. M.H., B.D., T.S., C.J.B. and A.M.S.; investigation, C.C. and M.J.M.H.; resources, M.J.M.H., M.S.; data curation, C.C.; writing—original draft preparation C.C., H.A. and M.J.M.H.; writing—and reviewing editorial, M.S., F.M., A.M.S., B.D., T.S. and C.J.B. All authors have read and agreed to the published version of the manuscript.

References


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<td>16.4</td>
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Table 1: Three (13%) patients underwent repetitive surgery consisting of lateral node dissection (LND) in one case and resection of paratracheal recurrences in the others. Patient 21 was diagnosed in metastatic stadium and deceased, despite systemic treatment, as opposed to Pt 23, who was free of biochemical and radiologic disease at last follow-up.

LND = lymph nodal, class. PTC = classic variant papillary thyroid cancer, foll. PTC = follicular variant papillary thyroid cancer, FTC = follicular thyroid cancer, RAI = radioiodine, CR = complete response, IBR = incomplete biochemical response.
Figure 1: pT2 papillary thyroid carcinoma in a young patient included in the present study (pt 1). This MRI was performed after a fall, in order to rule out spine injury. The thyroid nodule was diagnosed incidentally.