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Thyroid Disease

Treating papillary and follicular thyroid cancer in children and young people: Single UK-center experience between 2003 and 2018☆,☆☆

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ABSTRACT

Aim: Differentiated thyroid cancer (DTC) in children and adolescents is rare and data about its presentation and management are not well known. The aim of this study was to provide evidence of the current practice in the United Kingdom before the launch of the Rare National Paediatric Endocrine Tumours Guidelines (to be published in 2020).
Methods: Seventy-two children and adolescents with DTC (<18 years) who were treated at our institution between 2003 and 2018 were identified and their presentation, treatment and outcomes were reviewed.
Results: Median age at presentation was 12.7 years [range: 1–18] and fifty-two (72%) were girls. Fifty (69.4%) children and adolescents presented with a thyroid nodule. Thirteen (18%) had cervical adenopathy and seven of them (54%) underwent an excision biopsy under GA. Eight patients (11%) had evidence of lung metastases at presentation. Twenty-four patients (33%) underwent a hemithyroidectomy and 22 of those had a completion thyroidectomy subsequently, ten (14%) a total thyroidectomy alone and 37 (51%) a total thyroidectomy with lymph nodes dissection. Seventy patients (97%) underwent adjuvant RAI at our institution. The median number of children and adolescents managed per year was five [range: 0–10]. After an overall median follow-up of 40 months, eight patients (11%) had developed recurrent disease. The 1- and 5-year recurrence-free-survival-rates were 93% and 87%, respectively. Overall survival was 100%, with eight children and adolescents (11%) being alive with disease.
Conclusion: This study confirms that DTC in children and adolescents is uncommon, is frequently advanced at presentation and has considerable recurrence rates. Despite this, overall survival is excellent. Although the work-up was generally appropriate (image-guided cytology), open biopsy for the diagnosis of lymph node involvement was still employed. The introduction of a specific UK guideline for this age-group will likely result in more tailored-made treatment-pathways and thereby hopefully improve quality and outcomes even further.
Type of study: Prognosis study.
Level of evidence: Level IV.

Papillary (PTC) and follicular (FTC) thyroid carcinomas are rare among children and adolescents and comprise about 0.7% of all childhood cancers [1–4]. In the United Kingdom, there are approximately 145 new cases of DTC in children and adolescents reported annually, but only about eight of them occur in patients less than the age of 16, as the incidence of DTC gradually rises with age [1–4].

Children and adolescents, compared to adults, present with more advanced stages of disease and have higher recurrence rates. At the

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same time, their overall survival rates are excellent. Consequently, DTC in children and adolescents does not seem to be the same disease as among adults [5,6]. A more favorable tumor biology is thought to be an important factor attributing to the reported 40-year survival rate of about 98% [5–7]. Moreover, adjuvant radioactive iodine (^{131}I, RAI) has been shown to improve disease-free survival in children and adolescents but not in adults [8,9]. A general consensus emerged that children and adolescents should not be treated by the pathway proposed by adult patients [10–13]. New American Thyroid Association (ATA) [14] pediatrics guidelines was published in 2016 [15–20] with an objective to steer away from the one-size fits all protocols and introduce a more tailor-made approach. By taking into account different features of children and adolescents with DTC, its recommendations aim to avoid under- or overtreatment [14].

There is a paucity of information on children and adolescents diagnosed and treated for DTC in the UK [21–23]. Therefore, the aim of our study was to present the data available on the full diagnostic and therapeutic process and to assess the current practice for children and adolescents with DTC (<18 years of age) who underwent treatment in a large tertiary referral center in the UK. Since the National Improving Outcomes Guidelines for children with cancer [24] require that the definitive investigations and treatment of children and adolescents with a suspected diagnosis of any type of cancer should only take place in principal treatment centers, we also aimed to assess if present data could contribute to the discussion about the proposed centralization of services for children and adolescents with DTC in the UK. Moreover, evidence presented in this paper will possibly allow us to assess the impact of the UK guidelines (i.e. “National Rare Paediatric Endocrine Tumour Guidelines: Differentiated Thyroid Carcinoma” [25]) on the management of children and adolescents with DTC in 5- and 10-years' time.

1. Methods

1.1. Inclusion criteria

All children and adolescents (<18 years) who underwent surgery and/or radioactive iodine (RAI) treatment between 2003 and 2018 at a single, recognized, principal treatment center for children and adolescents with cancer at the University College London and Great Ormond Street Hospitals (UCLH & GOSH) were identified from our institutional database and included in this analysis. This retrospective review study was approved by the Institutional Review Board of University College London Hospitals (18/0072).

1.2. Data collected

Standard demographic (age, sex), clinical presentation (thyroid nodule, lymphadenopathy), diagnostic work-up (imaging, cytology), operative data (type of operation and postoperative morbidity), pathology (type and stage of the tumor), details of RAI (doses, number of treatments, long-term treatment-related adverse events), recurrence rates and overall survival were collected for all patients [26].

1.3. Management decisions

All patients included in this study underwent surgery and/or RAI at our institution. Children and adolescents who had surgery at our center were assessed with thyroid function tests and a neck ultrasound (US) scan was performed by a dedicated radiologist. A decision to perform fine needle aspiration cytology (FNAC) was based on National Guidelines and graded according to the Thy-classification [13]. All cases were formally discussed in our weekly Multidisciplinary Thyroid Meeting. This meeting was attended by endocrine surgeons, oncologists, radiologist, pathologists, nuclear physicians and endocrinologists. All of these professionals had extensive experience in managing adults as well as children and adolescents. Specifically, our Thyroid Meetings were attended by at least one specialized pediatric medical oncologist, one pediatric endocrinologist and one endocrine surgeon with extensive pediatric training and experience. Preoperative management decisions included need for further imaging (CT, PET, MRI) and proposed surgical strategy. Postoperative review of children and adolescents operated in our or other centers consisted of assessment of pathology and need for further treatment. Decisions about ablative or therapeutic doses of RAI were based on the national guidelines [13].

1.4. Statistical analyses

Summary statistics were obtained and presented as percentages or median values. Upon comparing categorical data, the χ^2 test, or if deemed appropriate Fisher's exact test, was used, while the Mann–Whitney U-test was used to compare continuous data. Factors associated with recurrent disease were examined in univariate Cox analyses. Overall, a p-value of less than 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 23.0 (IBM Corp. IMB SPSS statistics, Armonk, NY).

2. Results

2.1. Presentation and risk factors

Details on patient and tumor characteristics are depicted in Table 1. A total of seventy-two children and adolescents with the median age at presentation of 12.7 [range: 1–18] were included in the current study. Specifically, 59 patients (81.9%) were younger than 16 (Fig. 1). Furthermore, of those patients who underwent surgery at our center, 26 patients (89.7%) were less than 16 years of age. Per year, the median number of patients less than the age of 16 was 4 [range: 0–7]. Overall, the majority of patients were girls ($n = 52$; 72%). There was no difference in the male-to-female ratio when stratifying for pubertal stage ($p = 0.31$). The median number of patients treated for DTC was five per year [range: 0–10]. Overall, more than two-thirds of patients presented with a thyroid nodule ($n = 50$; 69.4%), while in 13 patients (18.1%) the presenting symptom was cervical adenopathy.

Two patients had a history of radiation exposure. One was a 16-year-old girl who underwent surgery and radiation for a medulloblastoma at the age of eight. The other was an 11-year-old girl, who underwent chemotherapy and whole-body-radiation followed by a bone marrow transplant for myelodysplasia at the age of seven. Two other patients had a history of antecedent thyroid disease: a 9-year-old girl who was known with Hashimoto's disease and had developed a thyroid nodule and a 12-year-old girl who was under surveillance for autoimmune thyroiditis and was found to have bilateral nodules on a US-scan. None of the included children and adolescents were known to have a history of iodine deficiency.

2.2. Preoperative investigations

All children and adolescents for whom details on imaging were known, underwent at least a US-scan ($n = 60$; 83.3%). Moreover, in 22 of them (30.6%), one or more cross-sectional imaging techniques were also used (computed tomography (CT) scan in 13 (18.1%) and magnetic resonance imaging (MRI) in 11 (15.3%)). Exact imaging work-up was unknown for 12 patients (16.7%).

Preoperative imaging showed that the median maximum diameter of the tumor was 2.5 cm [range: 1–10]; majority of patients had a unilateral ($n = 43$; 59.7%) and unifocal disease ($n = 45$; 62.5%). Three patients (4.2%) had a diffuse spread of tumor.

Of the 46 children and adolescents in whom data on FNA-cytology were available, the most common result was Thy-5 ($n = 23$; 50.0%) followed by Thy-3f ($n = 10$; 21.7%). A specific ultrasonographic assessment of the cervical lymph nodes was described in 57 patients (79.2%). Moreover, in 14 patients (24.5%) there was suspicion of lymph node

Table 1
Patient and tumor characteristics.

Variable; *n* (%)	Number (%); *n* = 72
Patient and disease characteristics	
Sex (male)	20 (27.8)
Age (median [range]), years	12.7 [1–18]
Pubertal status	
Prepubertal	43 (59.7)
Postpubertal	29 (40.3)
Presenting symptom, more options possible	
Palpable thyroid nodule	50 (69.4)
Cervical adenopathy	13 (18.1)
Incidental/other	6 (8.3)
Distant metastasis at presentation present	9 (12.5)
History of radiation exposure	2 (2.8)
History of iodine deficiency	0
History of thyroid disease	2 (2.8)
Specifics of diagnostics	
Type of imaging performed, more options possible	
Ultrasound (US) scan	60 (83.3)
Computed tomography (CT) scan	13 (18.1)
Magnetic resonance imaging (MRI)	11 (15.3)
Unknown	12 (16.7)
Maximum diameter on imaging (median [range]), cm	2.5 [1–10]
Diffuse thyroid disease	3 (4.2)
Location of tumor	
Right	28 (38.9)
Left	15 (20.8)
Bilateral	8 (11.1)
Unknown	21 (29.2)
Focality on imaging	
Unifocal	45 (62.5)
Multifocal	11 (15.3)
Unknown	16 (22.2)
Neck US scan performed	
Yes	57 (79.2)
Unknown	15 (20.8)
Fine needle aspiration (FNA)	
None	6 (8.3)
Thy-3a	1 (1.4)
Thy-3f	10 (13.9)
Thy-4	6 (8.3)
Thy-5	23 (31.9)
Unknown	35 (48.6)
Node positive disease diagnosed prior to thyroid surgery	
None	26 (36.1)
Suspicion on US-scan	14 (19.4)
Cytologically proven	10 (13.9)
Excision biopsy of lymph node performed	7 (9.7)
Unknown	15 (20.8)

disease on US-scan, while this was cytologically proven in an additional ten patients (17.5%). This brings the total of (probable) node positive disease on 31 patients (43.1%).

Seven out of thirteen patients (54%) who presented with lymphadenopathy had the diagnosis of thyroid carcinoma made after an excision biopsy of their cervical lymph nodes. None of these procedures was done at our treatment center; three of these patients (42.9%) were subsequently referred to us for further surgical management.

A total of eight patients (11.1%) had evidence of distant metastatic disease on their preoperative work-up; all had pulmonary nodules.

2.3. Surgical management

During the 15 years covered by this study, twenty-nine children and adolescents (40.3%) had surgery at our institution and forty-three (59.7%) at 30 other hospitals, of which 24 centers referred one (33.3%), three (2.8%) two, two (5.6%) four and one (6.9%) five patients. Median number of patients referred to us after surgery at another hospital was one per center [range: 1–5]. Comparison of children and adolescents who underwent surgery at our center and those who were referred for RAI from other hospitals showed no difference regarding sex, pubertal stage or extent of initial surgery (all $p > 0.05$).

The details of surgery and postoperative outcomes for all patients are described in Table 2. Twenty-four patients underwent hemithyroidectomy as their first procedure; for 15 of them (62.5%), the FNA-results were available. In 12 (80.0%), the FNA-cytology reported either Thy-3a or Thy-3f, in two (13.3%) Thy-4, while in one (6.7%) the result was Thy-5. Three patients who had a hemithyroidectomy and Thy-4 or Thy-5 cytology, had tumors thought to be unilateral, unifocal, subcentimeter lesions. Twenty-two patients (91.7%) went on to get a completion thyroidectomy, with or without additional neck-dissection. The two patients who did not undergo additional surgery both had a tumor measuring less than 10 mm without risk factors [13].

Forty-seven patients (65.3%) underwent a total thyroidectomy (TT) as their first procedure, ten had TT alone, four had TT and central neck dissection (CND) and thirty-three TT plus CND plus lateral neck dissection (LND).

One other child (1.4%) had such extensive disease that only a debulking could be undertaken at time of initial surgery.

2.4. Complications

Twenty-eight children and adolescents (38.9%) developed complications after the surgery, ten (34.5%) operated in our center and 18 (41.9%) in other institutions ($p = 0.7$). The commonest ($n = 27$; 37.5%), postoperative complication was immediate hypoparathyroidism necessitating prescription of calcium supplements and alfacalcidol. Long-term hypoparathyroidism (i.e. dependency on supplements for a period extending six months after surgery) persisted in 18 patients (25.0%). Impairment of the recurrent laryngeal nerve was described in two patients (2.8%); one had a unilateral injury to the recurrent nerve during a completion thyroidectomy and bilateral central lymph node dissection, and the other had deliberate excision of the nerve owing to tumor infiltration. No bleeding and return to theater or wound infections were reported.

2.5. Histology

On final histopathology, 57 patients (79.2%) had PTC and 15 (20.8%) had FTC. More than half of patients had lymph node metastases ($n = 41$; 56.9%). Further details on histopathology are described in Table 2.

Upon comparing children and adolescents who had PTC to those who had FTC, the male-to-female ratio was similar (girls: $n = 40$ (70.2%) versus $n = 11$ (73.2%); $p = 0.88$). Both groups also had a similar median age at presentation (12.3 years [range: 1.1–18.0] versus 14.8 [range: 6.5–18.0]; $p = 0.062$). However, patients with FTC presented more often with a palpable thyroid nodule ($n = 14$; 93.3%) than patients with PTC ($n = 37$; 64.9%); $p = 0.028$. While the rates of distant metastatic disease were statistically similar for both subtypes of thyroid cancer (PTC: $n = 9$ (15.8%) versus FTC: $n = 0$ (0%); $p = 0.19$), patients with PTC more often had node positive disease ($n = 40$; 70.2%) than patients with FTC ($n = 1$; 6.7%) ($p < 0.001$).

2.6. Postoperative treatment with RAI

All children and adolescents ($n = 70$; 97.2%), apart from the two who only underwent a hemithyroidectomy, went on to have adjuvant RAI treatment. Thirty patients (42.9%) underwent only a single ablation, while the other forty (57.1%) had an ablative dose followed by one or more therapeutic doses of RAI.

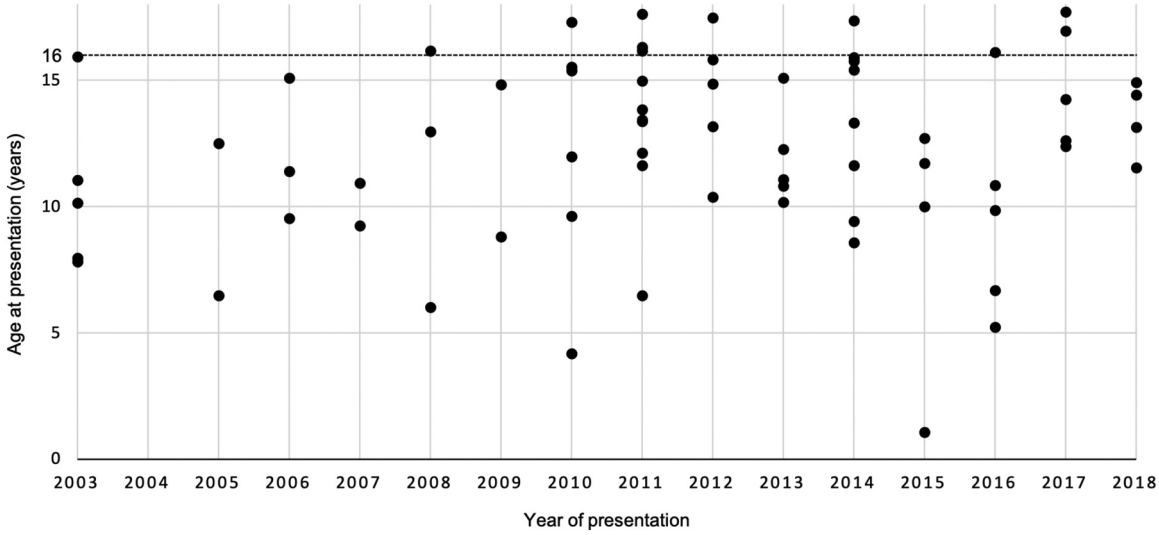

Fig. 1. Plot showing the age of included patients stratified by year of referral.

2.7. Long-term outcomes

After a median follow-up of 39.7 months, three patients (4.2%) had stable persistent distant disease from time of initial diagnosis onward. Eight patients (11.1%) developed recurrent disease of which four (5.6%) had local recurrence in the neck or cervical lymph node metastasis, three (4.2%) pulmonary metastases and one recurrent disease at both of these locations (1.4%). Half of these ($n = 4$; 50.0%) underwent curative intent surgery for their neck disease, while the other four patients (50.0%) were treated with RAI. Overall median recurrence-free survival (RFS) was 36.7 months, with a 1-year-RFS of 93% and a 5-year-RFS of 87%.

Among our cohort, no factors associated with recurrence could be identified. Specifically, male sex (HR = 0.32 [95% CI: 0.03–2.57]; $p = 0.28$), age at presentation (HR = 0.89 [95% CI: 0.75–1.07]; $p = 0.23$), prepubertal stage at presentation (HR = 1.76 [95% CI: 0.35–8.72]; $p = 0.49$) and more advanced disease at presentation (node-positive: HR = 1.72 [95% CI: 0.33–8.83]; $p = 0.52$ or distant metastasis: HR = 3.84 [95% CI: 0.77–19.08]; $p = 0.10$) were not found to be associated with recurrence of disease.

No second malignancies were reported. In one patient (1.4%) who received multiple courses of RAI after diagnosis at age 10, a late onset menses was reported as well as a small stature. Two others (2.8%), who also received multiple cycles of RAI, required long-term intensive follow-up by psychologists, as they suffered from low mood and depression.

At time of last follow-up, all patients were alive ($n = 72$; 100%), of whom eight were alive with disease (11.1%).

Table 2
Operative and direct-postoperative outcomes.

Variable; *n* (%)	Number (%); $n = 72$
Surgery variables	
Type of initial operation	
Hemithyroidectomy	24 (33.3)
Total thyroidectomy alone	10 (13.9)
Total thyroidectomy + central neck dissection	4 (5.6)
Total thyroidectomy + central & lateral neck dissection	33 (45.8)
Debulking	1 (1.4)
Type of second operation	
Completion thyroidectomy only	18 (25.0)
Completion thyroidectomy + central neck dissection	2 (2.8)
Additional central & lateral neck dissection	2 (2.8)
Major postoperative morbidity after all surgery	
None reported	45 (62.5)
Hypocalcemia/hypoparathyroidism	27 (37.5)
Long-term (i.e. >6 months)	18 (25.0)
Injury to recurrent laryngeal nerve	1 (1.4)
Histopathology	
T-stage, 7th edition	
T1	11 (15.3)
T2	18 (25.0)
T3	22 (30.6)
T4	7 (9.7)
Unknown	14 (19.4)
*p*Nodal stage	
Positive	41 (56.9)
Negative	25 (34.7)
Unknown	6 (8.4)
Focality	
Unifocal	45 (62.5)
Multifocal	22 30.6
Unknown	5 (6.9)
Resection margin	
R0	55 (76.4)
R1	9 (12.5)
R2	3 (4.2)
Unknown	5 (6.9)

3. Discussion

This paper describes the current status of the joint surgical and oncological management of children and adolescents with DTC in our tertiary referral and principal treatment center in the United Kingdom, which specializes in surgical and oncological treatment of children and adolescents with DTC. It is a central point for referring children and adolescents with DTC for surgery and RAI treatment for the whole country.

Published evidence suggests that children and adolescents with DTC present with more advanced disease and indeed more than half (56.9%) of patients had lymph node metastases and almost 1/5 had lung metastases at time of presentation. While this number could be artificial owing to our inclusion criteria (i.e. almost all received RAI), it is known that even when controlling for histology and tumor size, children and adolescents with thyroid cancer are more likely to have lymph node disease and distant metastases than adult patients [6,27,28]. Unfortunately, almost one-fifth of patients had their diagnosis of metastatic lymph nodes established by open biopsy which required general anesthesia. As stated in current guidelines [10–14], there is no place for an open biopsy of cervical lymph nodes in the work-up for children and adolescents with (potential) thyroid cancer; therefore, when lymphadenopathy in the neck is present, a thyroid US-scan should be performed with FNA to

facilitate accurate diagnosis/staging [29,30]. In case of preoperative evidence of locoregional (neck) lymph node metastases, guidelines suggest that a therapeutic central neck dissection (CND) should be performed, while prophylactic CND should be considered owing of the high incidence of positive lymph nodes at time of presentation [14,25]. A total of 40 patients (55.6%) underwent a lymph node dissection at time of initial surgery. Six patients underwent a CND only; of this group, the lymph node dissection was described as prophylactic in one patient (16.7%). While several studies have shown a somewhat controversial role for prophylactic CND without statistically significant differences in terms of regional recurrence [31,32], the decision to perform more extended surgery – especially for children and adolescents – should be carefully evaluated, also in light of a possible higher risk of complications such as hypoparathyroidism [33].

Recommended extend of surgical procedure in children and adolescents with DTC should be guided by the preoperative work-up. Current guidelines propose a total thyroidectomy for those with Thy-5 nodules only, as the likelihood of a malignancy in this category is 98%–100% [34] and several studies show an increased incidence of bilateral and multifocal disease [35–37]. Twenty-four patients (33.3%) in our series underwent a hemithyroidectomy as their initial operation and twenty-two of them (91.7%) went on to have a completion thyroidectomy. The decision to perform a completion thyroidectomy was based on factors increasing the risk of distant metastasis. This proportion is relatively high when compared to data from adult cohorts, where about a quarter of patients need a completion thyroidectomy [38,39]. Moreover, recent studies showed that, although the majority of indeterminate pediatric thyroid lesions are benign, the number of malignancies among indeterminate lesions is greater in children and adolescents than in adults [40–42]. These findings are important and should generate further discussion about indications for hemithyroidectomy.

Unfortunately, underreporting of surgical complications owing to poor recording and selective publishing exists. Moreover, it is important that several studies on complications for children and adolescents undergoing thyroid surgery have found that the complication rates are higher than for adult patients [43–45]. The rate of accidental injury to the recurrent laryngeal nerve was 1.4% in our cohort. This statistic is in concordance with the overall reported rates of this complication in literature (incidences ranging from 0% to 25%) [46–48]; however, this might be an underestimation of the actual incidence.

The most common complication in our series was related to calcium homeostasis, with 27 patients (37.5%) needing prescription of calcium supplements and alfacalcidol. Hypoparathyroidism dependent on supplements for a period extending six months after surgery persisted in 18 children and adolescents (25.0%). These results are comparable to several other series, with ranges from one-in-four to more than half of children and adolescents suffering from calcium related morbidity [45,49–54]. Conversely, in more recent series, the incidence of long-term hypoparathyroidism is markedly lower than in our current cohort. In these series, rates of persistent hypoparathyroidism at six months of 0.6%–12% were reported, with risk factors for development of long-term hypoparathyroidism being surgery for DTC and undergoing a neck dissection [55–57]. Moreover, two of these series specifically describe the incidence and risk of complications in high-volume centers [56,57] . Specifically, Baumgarten et al. [57] report that thyroid surgery performed at a high-volume center is associated with a very low-risk of surgical complications such as long-term hypoparathyroidism. While within our data we could not find a difference in the occurrence of complications in higher- versus lower-volume centers, this could be the result of the small numbers of cases analyzed. This is especially the case since the aforementioned studies on complications in high-volume pediatric hospitals do seem to offer evidence to support centralization of thyroid surgery for children and adolescents, with a higher yield for younger children [56,57]. Moreover, there is strong evidence for other types of surgery that treatment in a higher-volume center reduces the postoperative morbidity and mortality [58]. This is of specific importance, as complications following surgery in childhood could have long-term effects and even impact the quality of life of patients.

In line with this, a strong recommendation in the upcoming UK guidelines is that surgery in children and adolescents with DTC should be performed by high volume thyroid surgeons, defined as those who perform more than 30 cervical endocrine procedures per year in adults and children and adolescents, ideally with collaborative care between endocrine and pediatric surgeons. Centralization of oncological services, which are responsible for managing children and adolescents with DTC and administration of RAI, has already taken place in the UK and currently there are only 3–4 centers that provide such treatment. This, unfortunately, has not happened for the surgical part of treatment although previously published literature strongly suggests that consideration of this is necessary [24,43,44,56,57,59–61]. Based on these reports, we feel that centralization of surgery, especially for younger children, is therefore desirable and should be formally implemented along the lines of centralization of oncology services, i.e. with 3–4 regional specialized centers as primary referral and treatment hospitals. This is particularly important as the total number of children and adolescents diagnosed and treated for DTC is so small, as only 72 pediatric patients were treated here during a 15-year period. Most of the children and adolescents treated surgically outside our center came from 30 different hospitals which treated only 1–2 children and adolescents during this period. Moreover, as only about eight new cases of DTC in children and adolescents less than the age of 16 are expected annually in the whole UK, it could be a first step to centralize the care for this subgroup in 3–4 surgical centers which should be aligned with oncology services.

The current study has several limitations. Although it has one of the largest numbers of children and adolescents treated for thyroid cancer within the UK, the included number of patients is still low. While this does stress the highly selected nature of the cohort of children and adolescents who undergo treatment for this disease, it has statistical disadvantages. Owing to the small sample size, our study has limited statistical power and statistical inferences were therefore also restricted, while the performance of subanalyses was not possible. Moreover, as data from children and adolescents and adolescents from centers all over the country were included, some of the data were relatively low-quality with missing variables predominantly in the fields of imaging/preoperative work-up as well as short-term outcomes. Furthermore, like all retrospective studies, selection bias may also have influenced certain variables measured; in this cohort specifically that most patients were included after their referral to our center for RAI, thus leading to a skewed distribution of probably both disease burden as well as adjuvant therapy compared to the overall cohort of children and adolescents receiving surgery for thyroid cancer.

In conclusion, this study shows that DTC among children and adolescents (<18 years of age) is an uncommon disease which can present as a thyroid nodule or isolated neck lymphadenopathy and affects mostly girls, while its incidence increases with age. Although the work-up was generally appropriate (image-guided cytology), open biopsy for the diagnosis of lymph node involvement was still employed. This study once more shows that while most of these patients present with more advance disease and experience considerable rates of recurrence, overall survival rates are excellent. The introduction of a specific UK guideline for this age-group will result in more tailored-made treatment-pathways and thereby hopefully improve quality and outcomes as well as quality of available data even further.

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