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Original Article

Differentiated Thyroid Cancer in Children: A UK Multicentre Review and Review of the Literature

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Abstract

Aims: To obtain an overview of the management and outcomes of children aged 18 years or younger diagnosed with differentiated thyroid carcinoma of follicular cell origin across the UK, by collecting and analysing data from the limited number of centres treating these patients. This multicentre data might provide a more realistic perspective than single-institution series.
Materials and methods: Six centres submitted data extracted from historical records on patients aged 18 years or younger, diagnosed between 1964 and 2017. The univariate and multivariable Cox proportional hazard model was used to identify potential predictors of progression-free survival, using national data as a control.
Results: Data on 166 patients were available for analysis. Females (74%) were predominant, and the age ranged from 3 to 19 years at diagnosis, mean 14.1 years. Nodal metastases were present in 51%; 12% had distant metastases. After surgery, 95% received radioactive iodine (39% on more than one occasion) and 4% received external beam radiotherapy. With a median follow-up duration of 5 years, 69% are alive with no evidence of disease; 20% are alive with a raised thyroglobulin level as the only evidence of residual disease; 6% have residual structural disease detectable on imaging; 2% have died, from cerebral metastases.
Conclusion: Despite most patients having advanced disease at presentation, outcomes are very good. A national prospective registry should allow systematic collection of good-quality data and may facilitate research to further improve outcomes.

Key words: Childhood; differentiated thyroid cancer; paediatric; radioactive iodine

Introduction

Differentiated thyroid cancer (DTC) is rare but remains the most common endocrine malignancy in children (defined in this study as ≤18 years old). DTC is an umbrella term that includes both papillary and follicular thyroid carcinoma (PTC and FTC). The annual incidence of 0.5/million/year is equivalent to about 10 new paediatric cases annually in England and Wales [1–3]. The incidence of DTC is increasing worldwide, largely due to increased detection, but this does not account entirely for the rise in cases and a true increase cannot be excluded [4]. A recent nationwide review from Denmark noted an increase in incidence in DTC presenting in young adults but not in children or adolescents [5]. DTC occurs in the teenage years more commonly than in prepubertal children. Data from the US suggest that

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in 15–19 year olds DTC is the eighth most frequently diagnosed malignancy and the second most common cancer in females [6–8]. A female preponderance is seen in postpubertal children at 5:1, but this is not seen in prepubertal children [7,8].

Thyroid nodules in children require investigation as the rate of malignancy is reported to be between 10 and 50%, so significantly higher than in adults, where rates are between 5 and 15% [9–11]. Most cases of DTC in children and adolescents are PTC. FTC is uncommon in this age group. DTC in children seems to differ in its behaviour to that in adults. Children with DTC tend to present with more advanced disease [12–14], with lymph node involvement in as many as 90% at diagnosis [14] compared with between 20 and 50% in adults [15]. Distant metastases, most commonly pulmonary, are also more frequent; 20–30% in children, compared with less than 10% in adults [12,13].

Ionising radiation is a risk factor for thyroid cancer. Historically common childhood conditions, including hyperplasia of the thymus, tinea capitis, acne and hirsutism, were treated with ionising radiation and a peak in incidence of DTC was seen in these children after a latency of 10–20 years [16,17]. Such practices have now ceased, but therapeutic ionising radiation remains an effective treatment for many childhood cancers and patients who have undergone these treatments are at risk of developing DTC as a radiation-induced second primary malignancy (SPM) [18–20]. DTC is the most common SPM in survivors of childhood lymphoma and the third most common after treatment for leukaemia [21]. Environmental ionising radiation exposure has also been responsible for spikes in the incidence of childhood DTC and the Chernobyl disaster in 1986 resulted in a peak incidence in the 1990s. This highlighted the particular sensitivity of children to ionising radiation with respect to the development of DTC. The first cases were reported about 4–5 years after the accident. Those most at risk were children aged 5 years or under at the time of exposure [22–24].

There may be a difference in the natural history of DTC in prepubertal children compared with teenagers and young adults, although the data are conflicting [25–29]. Those children diagnosed before the age of 10 years have been reported to have more advanced disease, higher rates of recurrence and a poorer prognosis than if presenting after the tenth year [25,26,29]. However, although childhood DTC has relatively high rates of recurrence, overall the prognosis in terms of survival is reassuringly excellent. This is probably in part due to DTC in children being well differentiated and very responsive to treatment.

Despite the increasing incidence of DTC worldwide, the diagnosis in children remains relatively rare. Therefore, treatment concepts for this patient cohort are derived from experience in the adult population. Data to provide a solid evidence base for the management of DTC specifically in children are lacking and controversy exists in many aspects of the treatment of childhood DTC. The rarity of the disease, excellent prognosis, the management by several different specialties (endocrinology, nuclear medicine, oncology, thyroid surgery) and the challenges inherent in performing prospective trials in children, are all factors likely to have contributed to this. There is also an increasing understanding and subsequent caution around the treatment-related morbidity in a disease that has, on the whole, a good prognosis [30,31]. The National Cancer Intelligence Network examined the incidence of second malignancy after treatment for a primary cancer in UK teenagers and young adults (age 15–24 years) and in those diagnosed with thyroid cancer between 1985 and 2003; 2% developed a second cancer over a median follow-up period of 9.6 years (range: 1 day to 20 years) [32].

Therefore, there is a clear need to better understand this disease in the paediatric population in order to achieve cure while minimising treatment-induced morbidity. We are moving from an era of intensive therapy in which children with DTC have generally been treated along adult guidelines to one of personalised therapy in which treatment is individualised based on staging and adapted according to continuous risk stratification, thereby reducing risks associated with unnecessary treatment.

The national associations involved in thyroid cancer management are trying to address this need. The American Thyroid Association published guidelines in 2015 to specifically discuss the evolving treatment of children with DTC [33]. A Multi-Disciplinary Consensus Statement of Best Practice from a working group convened under the auspices of the British Society for Paediatric Endocrinology and Diabetes (BSPED) and United Kingdom Children's Cancer Study Group (UKCCSG) published a report and recommendations in 2005 [34]. These guidelines are currently being updated. The European Thyroid Association Cancer Research Network is also working towards data collection across European countries [35].

We present the first retrospective review of children with DTC treated in the UK in an attempt to gain better insight into the incidence, management and outcomes of this disease.

The objective of this study was to retrospectively collect historical and current data from UK centres treating paediatric DTC with the aim of setting up a prospective database in the future. The data in this study should inform the management of this patient population and provide more information for clinicians about outcomes. It will also highlight gaps in current data, which will guide the development of ongoing prospective data collection.

Materials and Methods

We carried out a retrospective observational study of patients diagnosed with DTC aged 18 years or younger. The study was open to all UK centres; data were received from six. This number reflects the small number of centres with age-appropriate facilities and experience in treating children. It has been an aim within the UK to reduce the number of centres managing children and young adults with thyroid cancer in order to centralise the expertise and support. A case report form was used to collect the data set. Data from these centres were sent to The Royal

Marsden Thyroid Unit, where it was entered on to a secure database.

In order to complete the case report form we asked collaborators to examine the available records, including death certificates where appropriate, of all patients aged 18 years or under at initial diagnosis of DTC. Inclusion criteria for this study were: patients with a diagnosis of DTC aged ≤18 years and available medical records. Exclusion criteria included medullary thyroid cancer, thyroid lymphoma, metastases to the thyroid and patients whose pathology reports were not available.

The univariate and multivariable Cox proportional hazard model was used to identify potential predictors of progression-free survival [36]. Age, gender, histology, cumulative radioactive iodine (RAI) dose, type of surgery, presence of metastases and nodal involvement at presentation and type of surgery were analysed. Monte-Carlo simulations were used to generate a background (control) population using age, gender and year-matched probabilities of survival taken from the Office of National Statistics.

Results

Data on 166 patients treated between 1964 and 2017 were collected across six UK centres. The mean age at diagnosis was 14.1 years (3–18 years). Table 1 shows the demographic data collected from this cohort.

All patients were treated surgically with thyroid lobectomy ± completion thyroidectomy. In total, 157 (95%) underwent iodine-131 ablation with 62 (39%) receiving more than one treatment.

The mean follow-up was 8.2 years; the median follow-up was 5.5 years. Three patients died as a result of brain metastases at 12.5, 5.5 and 7.5 years after diagnosis. All three deaths occurred among the 140 patients with PTC histology and all were female. Figure 1 depicts outcome data collected at the most recent follow-up of 166 known outcomes (of which six have been lost to follow-up). No evidence of disease was defined as thyroglobulin <1; biochemical residual disease refers to patients with thyroglobulin >1 with no structural disease; structural disease refers to patients with radiologically evident disease.

Compared with N0, N1 disease at presentation was associated with a significantly higher risk of progression, with hazard ratio of 2.06 ($P = 0.01$). Similarly, compared with M0, M1 disease was associated with significantly higher risk of progression, with hazard ratio of 4.05 ($P < 0.001$).

Cumulative radiation activity administered as radioiodine, age at diagnosis, histology and type of surgery did not predict progression-free survival according to both the univariate (with P values of 0.181, 0.809, 0.158 and 0.093, respectively) and multivariable Cox regression model.

As data were collected over such a wide timeframe and across multiple centres, we cannot state with certainty that patients were included consecutively.

Table 1
Patient demographics

Gender	
Male	43 (26%)
Female	123 (74%)
Age band at diagnosis	
<10 years	19 (11%)
10–14 years	54 (33%)
>14 years	93 (56%)
Histology	
Papillary thyroid carcinoma	141 (84%)
Follicular thyroid carcinoma	25 (15%)
Surgery at presentation	
Completion thyroidectomy (either lobectomy followed by completion surgery or initial completion thyroidectomy)	152 (91%)
Lobectomy alone	15 (9%)
Surgery after completion thyroidectomy, i.e. nodal dissection	
Yes	56 (34%)
No	108 (65%)
N/A	2 (1%)
Radioactive iodine	
Yes	157 (95%)
No	9 (5%)
Radiotherapy	
No	160 (96%)
Yes	6 (4%)

Discussion

As the incidence of DTC rises around the world in all age groups, evidence-based national guidelines assist clinicians to provide standardised and appropriate management with increasing emphasis on personalisation of treatment

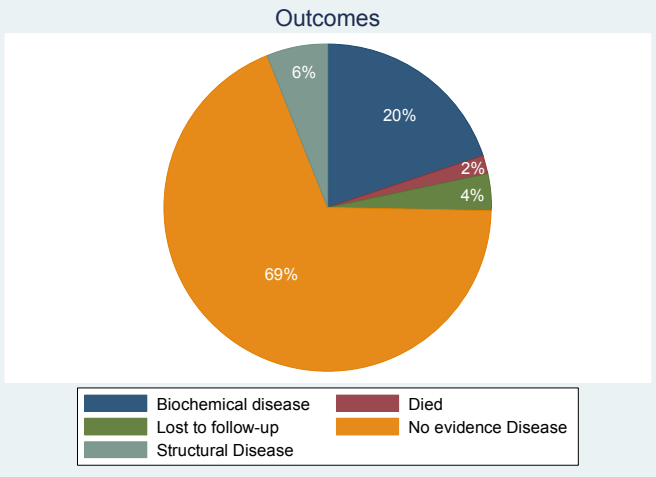

Fig 1. Outcome.

according to both patient and disease factors. Unfortunately, a comprehensive good-quality evidence base does not exist for DTC arising in the paediatric (18 years and under) population. The American Thyroid Association and British Society for Paediatric Endocrinology and Diabetes (BSPED) have published guidelines ([33,34] (currently under revision)) based on available data, which is mainly retrospective single-centre series and expert opinion. DTC in children does seem to behave differently in some aspects to that arising in adults; it tends to present at a more advanced stage but responds extremely well to treatment, resulting in an excellent prognosis. Concerns regarding unnecessary treatment and subsequent treatment-induced morbidity have been drivers to collect data on these children and to develop age-appropriate management strategies.

The available published data consist mainly of single-institution series, which have inherent bias and may not reflect populations outside that institution. The following are the larger of the published series. Welch Dinauer *et al.* [12] published a review of 137 cases of PTC and 33 cases of FTC diagnosed between 1953 and 1996 aged 21 or younger. Among those with PTC (median follow-up 6.6 years), one died, 21 developed local recurrence and six developed distant recurrence. By univariate analysis, they found recurrence to be more common in those with multifocal (odds ratio 7.5) or large tumours (odds ratio 3.0), palpable cervical lymph node metastases (odds ratio 3.0) or those who had distant metastases at diagnosis (odds ratio 2.8). In the FTC group, there were no deaths as a result of disease, but five patients developed recurrent disease. Handkiewicz-Junak *et al.* [37] investigated the efficacy of extensive surgery, postoperative RAI or a combination of both in reducing the risk of locoregional recurrence in 235 patients with DTC aged 18 years or younger. During a median follow-up of 7 years, there were no disease-specific deaths [37]. In total, 203 (86%) remained recurrence free; 32 patients (14%) had local recurrence. The median time from the initial surgery to local recurrence was 37 months [37]. Factors predictive of local relapse included classical papillary subtype, less than total thyroidectomy, either no lymph node assessment or excision of involved nodes only ('berry picking') without full compartmental dissection and no ablation RAI. No ablation RAI was the greatest predictor of recurrent disease after the presence of distant metastasis at presentation [37]. In 2006, Demidchik *et al.* [38] reported outcomes of 740 Belarussian children treated for DTC. The mean follow-up was 9.65 years. In total, 204 cases (27.6%) developed recurrent disease, including 73 (9.9%) with local relapse, 90 (12.2%) with distant metastatic disease and 41 (5.5%) relapsed with both local disease and distant metastases. Recurrent nodal disease was associated with young age at diagnosis, multifocality of disease, nodal involvement at presentation and no cervical lymph node dissection. Despite the rate of recurrence, 5- and 10-year survival rates remained excellent at 99.5 and 98.8%, respectively. The report concluded that total thyroidectomy followed by RAI was the optimal treatment strategy for this cohort of patients [38].

Conversely Hay *et al.* [30] argued that RAI is not an essential part of the management of DTC in children. In a series of 215 patients under the age of 21 years, no disease-related deaths occurred in the first 20 years and none of the 12 patients presenting with metastatic PTC died from their disease. Sixty-nine per cent of patients did not receive RAI ablation and had not died from their disease at the point of publication of the study. Additionally, the recurrence rates at both local and distant sites were not statistically significantly different in the 53 patients who had surgery and RAI ablation, compared with 116 who underwent surgery alone [30]. Of note, however, details of which patients received RAI are not available in this report, which makes it difficult to come to strong conclusions about the efficacy of RAI. To further bolster the authors' argument against the need for RAI, this study reported an unexpectedly high rate of SPM. Using a Minnesotan control population, 11 deaths would have been expected in this period of time, but twice this number were recorded, which was statistically significant ($P = 0.00045$). The SPM occurred with a latency of 30–50 years after the initial PTC diagnosis. Of the 15 patients who died from SPM, RAI had been delivered in 11 (73%). Although the authors are clear that one cannot implicate RAI as clearly causative, they raised the concern that treatment with RAI may cause SPM in patients with an otherwise excellent prognosis from their thyroid cancer [30].

A comprehensive review by Rivkees *et al.* [39] concluded that the risk of recurrence of DTC in children can be minimised with total thyroidectomy (and not lobectomy), compartmental lymph node dissection (rather than selective or no lymph node dissection) and ablative RAI. However, there is a move towards more centralised management of childhood DTC, with the aim to optimise outcomes for this specific population of patients while reducing treatment-related morbidity. With improved diagnostic techniques and therefore more accurate disease staging at presentation it is hoped that personalisation of treatment plans can avoid overtreatment of the majority while maintaining excellent outcomes and identifying the minority of cases that do require more intense management. In order to achieve this, good-quality, prospectively collected data are needed.

With this in mind we initiated a nationwide data collection in patients presenting with DTC aged 18 years or under. We have been able to conclude that prognosis is excellent, with only three deaths reported in the 166 patients reviewed. All three deaths were female. As such, female children with DTC had statistically significantly worse overall survival than their background population ($P = 0.000015$). By contrast, no statistically significant difference was observed between survivor functions of male patients and of their background population ($P = 0.85$). A similar finding has not previously been described in the literature and the relatively small numbers may skew this finding. We also conclude, as previously reported, that those presenting with node-positive disease and distant

metastases are more likely to progress than those presenting with N0 and M0 disease.

The study was limited, with data lacking on some aspects of care due to the inherent difficulty of retrospectively gathering data from multiple centres across the UK and the long period of time over which patients received treatment, during which management has changed. We did not collect data on treatment-related morbidity or secondary primary tumours and this will be very important in prospective data collection.

This is the first time the data for thyroid cancer in children has been collected in the UK. It provides the platform to collect data prospectively, which will be key to continuing to try to improve outcomes and reduce treatment-related morbidity in this population, ensuring the very best care is available to all. Risk stratification in the paediatric population is not yet described in the literature. However, we hope to move towards personalised treatment, whereby early risk stratification may enable tailored management of this patient cohort. Children diagnosed with thyroid cancer are often bounced between many teams before they reach a specialist unit and this causes anxiety, frustration and confusion. With an increased understanding of the pathways, outcomes and needs of this population of patients we hope to be able to inform the development of more streamlined and focused management.

Conclusion

Despite the presence of nodal and metastatic disease at presentation, the UK data confirm an excellent long-term prognosis for children diagnosed with DTC. Prospective data should be collected to understand the long-term impact of diagnosis and treatment.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.02.005.

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