Well-differentiated Thyroid Carcinoma of Childhood and Adolescence- A Long Term Experience at a Single Institute

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ABSTRACT

Background: **Thyroid carcinoma is rare in childhood and adolescence. The presentation is more advanced in case of children as compared to adults. However, the prognosis for survival in children is reportedly excellent.**

The aim of the study was to see the outcome of patients with well differentiated thyroid carcinoma during childhood and adolescence treated at a single institute.

Patients and methods: **A retrospective study of 61 children and adolescent patients (age ≤18years) with well differentiated thyroid carcinoma (DTC) enrolled in the National Institute of Nuclear Medicine & Allied Sciences, Dhaka during the period of January1986 up to December 2007 was carried out. To allow for a theoretical follow up of at least 5 years the last inclusion year was 2007 and follow up was carried on up to June 2013. All patients were treated by thyroidectomy followed by radioiodine ablation therapy. Whole body scans, Tg, anti Tg Ab and neck ultrasound findings were recorded six months to one year after initial therapy to classify patients into remission, persistent or recurrent disease. Status on last follow up was noted to estimate the survival rate.**

Results: **A total of 40 patients had papillary carcinoma, 18 had follicular variant of papillary carcinoma (FVPCT) and three had follicular carcinoma. Age range at diagnosis was nine to 18 years with a mean of 15± 2 years. The number of patients ≤10 years were five and > 10 years were 56. There were 12 males and 49 females giving a M: F ratio of about 1:4. Among the 61 patients 30 patients had lymph node metastases and two had both nodal and lung metastases at initial presentation. After one year follow up from the initial radioiodine therapy, 30 patients were in remission and 31 patients had persistent disease. Eventually recurrence occurred in five patients. Three patients died during the whole observation period and all of them were cancer related giving a cancer specific mortality ratio of 0.049%, 95% CI 0 to 0.105%. Cancer specific survival by Kaplan-Meier curve was 98.2%, 98.2% and 66% at 5, 10 and 15 years respectively.**

Conclusion: **DTC in children and adolescent has a good prognosis in the presence of neck and distant metastases. Awareness of the patient and regular follow up with life long surveillance is essential to obtain a favorable outcome.**

Key Words: **Well-differentiated thyroid carcinoma, Childhood, Adolescent**

INTRODUCTION

Thyroid carcinoma is rare in childhood and adolescent (1). Thyroid carcinoma accounts for 1-2% of all pediatric malignancies (2). The incidence of childhood differentiated thyroid carcinoma (DTC) ranges from 1-10% as observed from different published series (3, 4). The majority of DTC in children is papillary thyroid carcinoma (PTC) whereas follicular carcinoma is less common (5). Thyroid carcinoma in children behaves differently from the adults regarding the presentation and prognosis. Thyroid nodule is uncommon in children but has five fold increased propensity to be malignant as compared with adults (6). There is also higher incidence of cervical lymph node (40-60%) and distant metastases (25%) at the time of diagnosis (7). However, despite having an extensive disease, childhood DTC has a better prognosis. Childhood DTC thus having an aggressive course with a favorable outcome poses some challenges in the management. There is no unanimity regarding the management of the disease. This quandary over the management prompted the authors to present a retrospective review of all childhood DTC patients referred to National Institute of Nuclear Medicine & Allied Sciences during the study period to find out the experiences and outcome of the study population.

PATIENTS AND METHODS

This was a retrospective cohort study where secondary data of 61 children and adolescent with DTC enrolled in the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Dhaka during the period of January 1986 up to December 2007 were analyzed. To allow for a theoretical follow up of at least five years the last inclusion year was 2007 and follow up was carried on up to 2013. Status on last follow up was noted to estimate survival rate. Patients included in the study (inclusion criteria) were at the age of ≤18 years with DTC treated by thyroidectomy, lymph node

dissection in cases of nodal metastases followed by radioactive iodine (RAI) therapy. The patients had their whole body scan, thyroglobulin (Tg) assessment (since 1998), anti Tg Antibodies (since 2008) and neck ultrasound one year after initial radioiodine therapy. During the follow up same protocol was maintained after each RAI therapy when multiple doses were required. If patients were in remission the aftercare program was based on the assessment of Tg, anti Tg Ab, ultrasonogram of neck and thyroid hormone level.

Statistical analysis: Survival curves were estimated by the Kaplan-Meier product limit method. The Log rank test was used to assess difference between subgroups. Significance was defined at $p<0.05$ level. The SPSS (16.0) statistical package was used for analysis.

RESULTS

Total number of DTC patients referred to NINMAS during the period 1986-2007 was 1336 (Figure 1). Among the DTC patients 81 were at the age of ≤ 18 years which accounts for 6% of the total referral. However, the study population fulfilling the inclusion criteria was 61. A total of 40 patients (66%) had papillary carcinoma, 18 patients (29%) had follicular variant of papillary carcinoma (FVPTC) and three patients (5%) had follicular carcinoma.

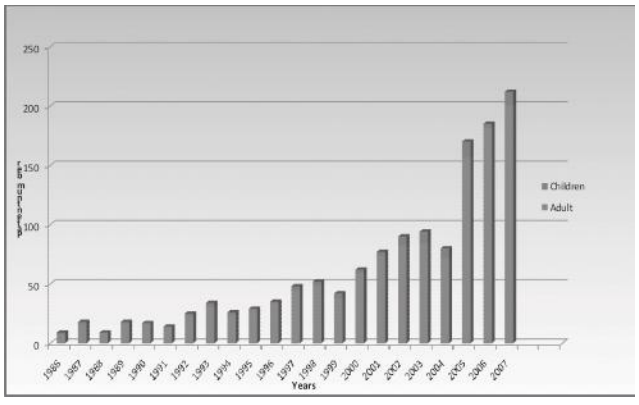

Figure 1: Graphical representation of DTC patients referred to NINMAS

The age range during diagnosis was nine to 18 years with a mean of 15 ± 2 years. The number of patients ≤ 10 years were five and >10 years were 56. The study population consisted of 12 males and 49 females giving a M:F ratio of about 1:4. Table 1 provides the characteristics of the 61 patients in our series. At initial presentation 28 patients had lymph node metastases and two had both nodal and lung metastases.

Table 1: Characteristics of the study group

	No	%
Total number of patients	61	
Sex		
Male	12	20
Female	49	80
Age (in years)		
≤ 10	5	8
11 – 18	56	92
Mean age	15 ± 2 Years	
Range	9-18 Years	
Tumour Histology		
Papillary	40	66
Follicular variant of papillary carcinoma (FVPTC)	18	29
Follicular	3	5

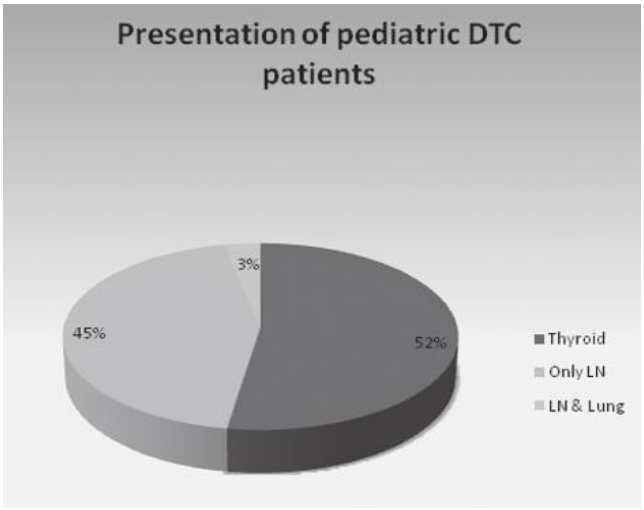

Figure 2: Pie- Chart showing the initial presentation of pediatric DTC patients

A total of 47 patients had total or near total thyroid surgery, one had subtotal thyroidectomy and 13 patients required completion surgery. Seven patients underwent modified radical neck dissection, 23 patients underwent

selective neck dissection and none of the patients had prophylactic neck dissection. Radioiodine dose varied from 30 mCi to 200 mCi in this study group. Among 61 patients, 25 patients received a single dose, 24 patients received two doses and 12 patients received more than two doses of RAI.

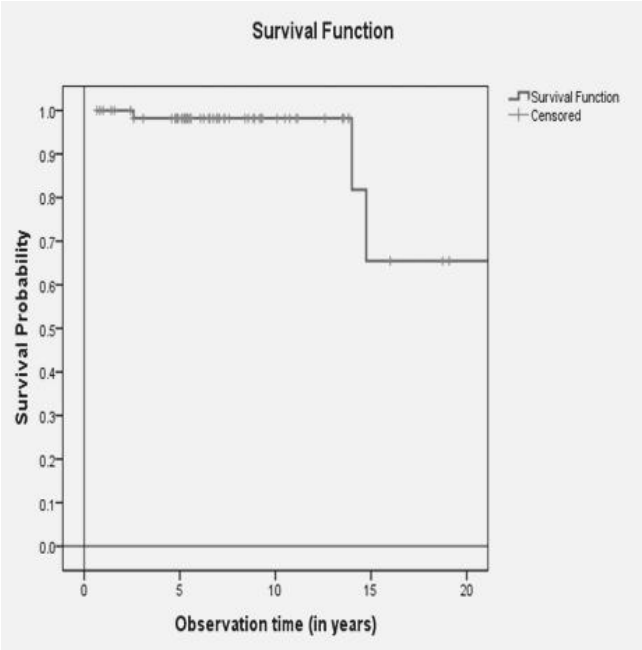

Figure 3: Kaplan Meier survival curve

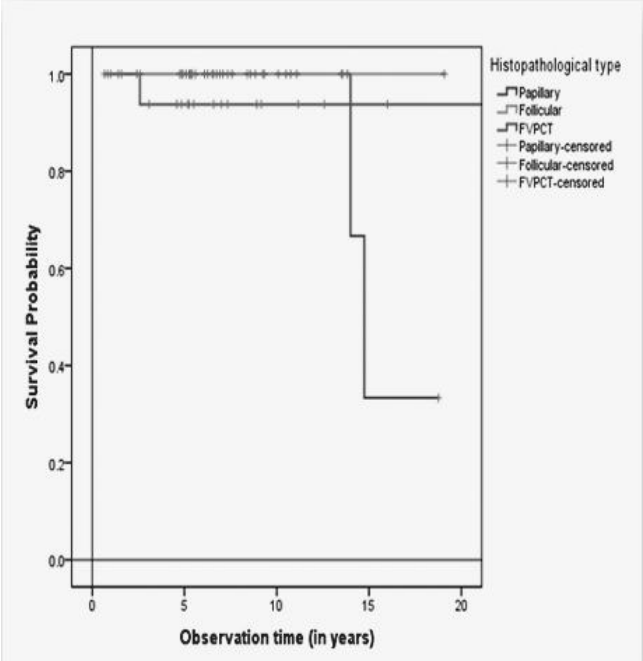

Figure 4: Kaplan Meier Survival curve regarding histopathology

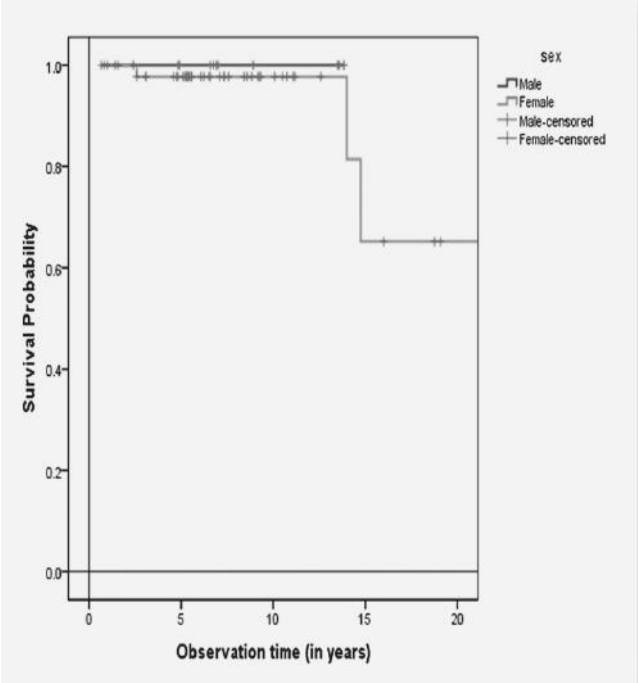

Figure 5: Kaplan Meier Survival curve regarding Sex

Maximum eight doses of RAI was received by one patient. The average observation period was 8 years (range 1 year to 22 years). The median time for follow up was 78 months. Seventeen patients were lost during follow up at different times including three deaths. Only four patients were lost just after 1 year. Forty four patients (72%) had follow up till the end of the study period. Three patients died in the whole observation period and all of them were cancer related giving a cancer specific mortality ratio of 0.049%, 95% CI 0 to 0.105%. Cancer specific survival by Kaplan-Meier curve was 98.2%, 98.2% and 66% at 5, 10 and15 years respectively.

DISCUSSION

Thyroid carcinoma is an adult disease. However, it also occurs in pediatric population having a clinical course different from those of adults. Thyroid malignancy (up to 93%) in pediatric group tends to fall in the well differentiated thyroid carcinoma group and presents with advanced disease (8). Despite the presentation this age group has a favorable survival outcome.

In our institute 6% of all referred DTC patients were at the age of ≤18 years. The annual adult to paediatric

ratio did not vary significantly during the study period. Due to lack of national oncological data base and as this institute is not the only hospital to attend thyroid carcinoma the incidence of pediatric thyroid carcinoma could not be estimated.

There were five (8%) patients aged ≤10 years and 56 (92%) patients ranging from 11 to 18 years. The youngest patient in this study was nine years old. There were no cases of DTC below five years which is reported as an extreme rarity (9). The female to male ratio in this series was 4:1, which is consistent with published data (10). When categorized by age female to male ratio was 2:1 at the age of ≤12 and 5:1 at the age >12 years. This observed preponderance of female justifies the fact that onset of puberty may activate and enhance thyroid carcinoma in female (11). However, it is also established that the gender difference is reduced with the increase of age.

The most common histological type of thyroid carcinoma in the pediatric population is PTC whereas FTC is more uncommon (12, 13). In this series, PTC and FVPTC were found in 58 (95%) and FTC was found in 3 (5%) patients. Among 61 patients 31(52%) patients presented with thyroid nodule, 28 (45%) presented with nodal metastases and 2 (3%) patients had lung metastases along with nodal metastases (Figure 2). Fifty nine patients (97%) were TNM stage I and 2 (3%) patients were TNM stage II. Extensive regional nodal involvement occurs in 60%-80% of pediatric thyroid cancer (14). In this study lymph node metastases was present in a total of 30 (49%) patients. In a series of literature, it was found that up to 10-20% of children may have pulmonary metastasis at diagnosis (15,16) which indicates the aggressive nature of childhood thyroid carcinoma. Chest X ray yields a low positive finding as very few children have macronodular disease. However, unlike adults, almost all pulmonary lesions show ^{131}I uptake in children evaluated with ^{131}I whole body scan (WBS) which is beneficial for subsequent therapy and monitoring (11). In this study, 10 (16%) patients had lung metastasis. Among these patients two were diagnosed on initial presentation and eight were diagnosed on follow up. Eight patients with lung metastasis had associated lymph node metastasis. Bone metastasis is rare in pediatric population accounting for less than 5% (16) as compared to adult population. According to published literature the probable explanation to this is that growing bone does not provide a suitable environment for deposition of thyroid cancer cells and also in contrast to adults where the metastatic spread is mainly via hematogenous route the children have a lymphatic spread (11). In this study one patient developed bone metastasis during follow up period and died 15 years after initial therapy.

Staging system of pediatric DTC patients can be defined as TNM stage I or stage II according to the presence or absence of synchronous distant metastasis, regardless of the degree of extrathyroidal extension or lymph node metastasis. In general, stage II patients receive total thyroidectomy followed by RAIT whereas a more conservative approach is advocated for stage I disease. However there are still controversies regarding the treatment of pediatric thyroid carcinoma. There is general agreement for total thyroidectomy for FTC but disagreement about the surgical management of PTC (17). The benefits after total thyroidectomy is a) Radioactive iodine (^{131}I) can be used to detect and treat remnant thyroid, local and distant metastasis b) Serum thyroglobulin measurement will be more sensitive in case of persistent and recurrent disease. In this study 47 patients had total or near total thyroidectomy, one patient had subtotal thyroidectomy and 13 patients required completion surgery. In the cases of nodal metastases, seven patients had modified radical neck dissection, 23 patients had selective neck dissection. None of the patients had prophylactic neck dissection. The major complications of surgery were permanent hypocalcemia which occurred in two (3%) patients, recurrent laryngeal nerve injury occurred in four (7%) patients and tracheostomy was required for one patient.

The role of radioactive iodine therapy in children and adolescents is still controversial. In our study all patients received radioiodine. However the clinical data dated back as far as 21 years, a time when treatment standard and protocol was different than present. The lack of consensus on ^{131}I treatment was evidenced by wide dosage range of ^{131}I. Chow et al in a study showed that adjuvant therapy with ^{131}I decreased the recurrence rate from 42% to 6.3% (18), however other studies showed no major impact on recurrence and overall survival (19). In the context of the socioeconomic condition of our country, the lack of awareness in patients hinders regular follow up. So RAI was given to all of the patients instead of conservative therapy to avoid untoward events in the future.

In this series, follow up ranged from one year to 22 years. Thirty patients became disease free (DF), 31 patients were not disease free (NDF) after one year follow up. Five (8%) patients developed recurrence from the DF group but became DF on last follow up. The level of serum thyroglobulin (Tg) was measured since 1998 and the presence of Tg Antibody was evaluated since 2008. The serum Tg was a valuable tool to diagnose disease recurrence or progression only in a selected group of patient in this study. Therefore the level of serum Tg was not evaluated statistically in this study. Seventeen patients were lost during follow up at different times including three deaths. Only four patients were lost after one year. Forty four patients (72%) had follow up till the end of the study period. The prognosis of pediatric patients with DTC is favorable with less than 5% deaths caused by cancer according to various studies (16). This study has similar findings (3 deaths out of 61 patients) giving a cancer specific mortality ratio of 0.049%, 95% CI 0 to 0.105%. Cancer specific survival by Kaplan-Meier curve was 98.2%, 98.2% and 66% at 5, 10 and 15 years respectively (Figure 3). There was no significant difference of survival over time regarding histopathological variant (p=.758 by Log Rank Test) (Figure 4) and sex (p=.617 by Log Rank Test) (Figure 5). There was also no significant difference of survival over time regarding presence or absence of metastasis at initial presentation (p=.867 by Log Rank Test) encompassing the fact that distant metastasis does not necessarily portend a poor prognosis in pediatric population.

Larger cumulative lifetime RAI doses are associated with the long term complication like second malignancy. No such long term effect was noted in this study. One patient received eight doses of radioiodine with a cumulative dose of 1500 mCi and died 14 years after initial therapy.

The important observations of the study are

- Increased referral of overall DTC patients from 2005 onwards
- 50% of the pediatric DTC became DF after a single RAI therapy
- 80% of lung metastasis cases had concomitant lymph node metastases
- Female patients were more irregular in follow up than male patients which may be the reason of that all three cancer specific death occured in females
- Those patients who became DF after first therapy had a good prognosis even if they had recurrence

This study is limited by the inherent bias of retrospective review and lack of details particularly in old cases. Clinical data dated back as far as 21 years a time when treatment standard and care was different from present. The range of follow up varied greatly and patient outcomes often could not be correlated to follow up time.

CONCLUSION

DTC in children and adolescent has a good prognosis even in the presence of neck and distant metastasis. Awareness of the patient and regular followup with life long surveillance is essential to obtain a favorable outcome.

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