Pediatric Thyroid Cancers: An Indian Perspective

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Abstract Pediatric thyroid cancer is a rare entity accounting for less than 5% of all thyroid cancers. This intriguing disease is characterized by advanced presentation, coupled with frequent lymph nodal metastases and often pulmonary metastases. It perhaps exhibits a distinct biology and behaviour, because in spite of its aggressiveness, survival is extremely good. This mandates meticulous treatment decisions that are well executed, because the complications of therapy in patients with good survival may spell prolonged morbidity. Being an unusual disease, it is unlikely that level I evidence guiding the management will come forth. There have been controversies regarding management, and the current consensus comes from large prospective studies. There have been only a few studies from India detailing pediatric thyroid cancers. In the current discussion, we review the existing evidence about pediatric thyroid cancers, and try to have an Indian perspective at the problem.

Keywords Thyroid cancer · Childhood cancers · Differentiated thyroid cancers · Radioiodine

Background

Pediatric thyroid cancer is a rare entity that is treatable with an excellent prognosis [1]. In spite of the fact that as compared to its adult counterpart pediatric differentiated thyroid cancer (DTC) presents at an advanced stage and has higher recurrence rates, mortality due to the disease is rare [2].

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This paradox is because this disease probably represents a different subset of thyroid cancers with a unique biological behaviour [3]. It therefore becomes imperative to correctly identify and treat this condition. Though adult thyroid cancers are much more common, even their management has been a subject of debates [4, 5]. This debate assumes greater importance in children where treatment complications and sequelae coupled with long life span may spell prolonged morbidity to the patient. While there have been controversies regarding the optimal management of pediatric DTC, guidelines and consensus are now evolving [6, 7].

Due to the rare occurrence of these cancers, it is unlikely that high level evidence from large randomized controlled trials will come forth. Hence management considerations will have to be based on retrospective and cohort studies. There have been only a handful of studies detailing thyroid cancer in children and adolescents from India, but the findings have been in keeping with the global literature. In this discussion, we review the existing literature regarding pediatric thyroid cancers, and look at the Indian perspective of this condition.

Epidemiology and Problem Statement

As mentioned earlier, pediatric DTC is rare, accounting for about 1.8%–5% of all thyroid cancers [8]. Kumar and Bal in a study from All India Institute of Medical Sciences (AIIMS) found that pediatric thyroid cancer accounted for 7% of all thyroid cancers [9]. Samuels et al. from Radiation Medicine Center (RMC), Mumbai found that pediatric DTC comprised 3% of all DTCs at their center [10]. More contemporary knowledge about this rare entity has come from the recent analysis of the Surveillance, Epidemiology, and End Results (SEER) registry from 1973 to 2004, which found an age-adjusted annual incidence of 0.54 cases per

100,000 persons in USA [1]. There have been no population based studies on this disease from India.

Thyroid cancer is even rarer below 10 years of age, with an estimated incidence of about 1 per million [1]. Adolescents have a 10-fold greater incidence than younger children [1]. The gender ratio is same for pre-pubertal boys and girls, while after puberty, girls are four to five times more likely to have thyroid cancer than boys [1, 11]. Similar gender distribution was also found in the Indian studies [3, 9, 10]. We found that the gender ratio was almost equal (1:1.5) in the pre-pubertal age group, whereas girls were three times more commonly involved in the post-pubertal age group [3]. It has been postulated that in girls, the onset of puberty and related endocrine changes may activate and exaggerate DTC by hormonal influence [9, 12].

Risk Factors for Thyroid Cancer in Children

Specific risk factors for DTC in children cannot be found in most cases. However, in a small subset, certain factors may predispose to childhood thyroid cancer. Exposure to low-level head and neck irradiation has been identified as predisposing to DTC since long, when children treated with low-level radiation for acne were found to develop thyroid cancers [13]. Low-level radiation less than 30 Gy to the thyroid increases the risk for cancer, and this increases progressively for ages below 20 years [14].

Thyroid cancer rates were observed to increase in children exposed to the atomic blasts in Japan [15]. The latency period between the time of radiation exposure and cancer onset in children is typically 10–20 years [14]. More than 5,000 children developed DTC after radiation exposure after the nuclear reactor explosion tragedy at Chernobyl in 1986 [16]. Cancers were seen as early as 5 years after the reactor explosion in the young children. An important risk group for thyroid cancer is childhood cancer survivors who received head and neck irradiation. Thyroid cancers are the most common second malignancy in children who have had lymphomas and the third most frequent malignancy in leukemia survivors [17].

Amongst the Indian studies, only one patient from the AIIMS study had a previous history of radiation exposure. Thus the reported increase in incidence seen in areas of nuclear radiation fallout is not evident in India.

An estimated 5% of patients with PTC have a family history of this disease, which may portend a worse prognosis and require more aggressive treatment [7, 18].

Pathology

Most thyroid cancers in children are papillary (PTC), followed by follicular (FTC) and, more rarely, medullary

carcinoma [19, 20]. Among Indian studies, Samuel et al. found pediatric DTC at a frequency of 30% PTC and 30% mixed papillary and follicular variants [10]; whereas Kumar and Bal reported PTC in 85% of the cases [9]. In our previous study, the histology was PTC in about 58% and follicular variant of PTC in an additional 25% cases [3].

PTC is usually multifocal and bilateral in children, and metastasizes to regional neck lymph nodes. In adult PTC, hematogenous metastases are much less common and generally occur only with bulky regional lymph node metastases. Whereas in children, hematogenous metastases, mainly to lungs are more frequent, and may occur in as much as 25% patients on presentation. This probably reflects distinct tumor biology and pathologic behaviour of PTC in childhood. PTC in children younger than 10 years may be pathologically more aggressive, being unencapsulated, widely invasive throughout the gland, and may have a follicular and solid architecture with unique nuclear features [21].

FTC is usually a unifocal tumor and tends to have initial hematogenous metastases to lungs and bones, while lymph node metastases are uncommon [7, 22]. Multifocal disease is more common in children than adults, being seen in about 40% of pediatric DTC cases [6].

Clinical Features and Behaviour

The most common presentation for pediatric DTC is that of a palpable thyroid nodule. However, PTC also frequently presents as neck nodes with or without a palpable thyroid lesion [7]. Occasionally, the only initial presentation may be of distant metastases [23].

Among the Indian studies, we found that a solitary thyroid nodule was the presenting feature in 43%, whereas 57% had neck nodes with or without a thyroid nodule [3]. Samuels reported solitary thyroid nodule in about 54% and neck nodes at presentation in about 50% patients [23].

There are several important clinical distinctions between pediatric and adult thyroid cancers:

To begin with, there should be an index of suspicion about malignancy in pediatric thyroid nodules, since thyroid nodules are 5-fold more likely to be malignant in children (26%) than in adults (5%) [24].

Secondly, pediatric DTC are more likely to have regional lymph node involvement and extrathyroidal extension [7]. As compared with adults, children with DTC present with more extensive disease [2, 25, 26]. Lymph node involvement at diagnosis is seen in 40–90% of children [2, 25, 26], compared with 20–50% of adults [27].

Thirdly, distant metastases, usually pulmonary, are commoner (20–30%) in children, whereas they are seen

in about 2% adults [2, 9, 22, 26, 28]. We found pulmonary metastases in about 20% of patients in our series; these were significantly higher in patients with lymph nodal involvement than in those with solitary thyroid nodule. We postulate nodal disease may be a harbinger of distant metastases in pediatric patients.

However, importantly, despite having more advanced disease, children are less likely to ultimately die of the disease than adults [29, 30]. Fortunately, even in the presence of metastatic disease, 30-yr survival rates are as high as 90–99% [25, 31]. Survival is favourable in children even in metastatic disease than adults, since pulmonary metastases can remain stable for extended periods [28, 32].

The favourable prognosis has been variously attributed to the fact that most young patients have well-differentiated tumor types, few have bone metastasis, and usually respond well to RAI therapy [3, 6].

DTC having onset before 10 years tend to be even more aggressive, and may be more widespread, with increased recurrences and mortality [22, 33]. Kumar and Bal reported similar aggressive disease in children below 10 years of age [9]. The mortality of 3.2% in their cases was entirely contributed by patients developing cancer below age of 10 years.

A summary of the clinical findings of the Indian studies is given in Table 1.

Initial Evaluation

The initial evaluation is similar as in adults and includes a detailed clinical examination, ultrasonography (USG) of the neck, serum TSH levels and fine needle aspiration cytology (FNAC).

Table 1 Indian studies detailing pediatric thyroid cancers

Authors	Setting and duration	Number	Nodal metastases (%)	Pulmonary metastases (%)	Survival/Mortality/Recurrence	Comments and conclusions
Chaukar et al. [3]	TMH 1964–2000	83 (57 for survival analysis)	57.8%	19.2%	100% 5 year OAS 82% 5 year DFS	- Nodal metastasis is a harbinger of distant metastasis - Advocated total thyroidectomy and radioactive iodine as the best management option
Kumar & Bal [9]	AIIMS 1967–2002	122	64%	23%	97.5% 7 year OAS 87% 7 year DFS	- Younger the age, more aggressive is the disease - Post-operative radioiodine therapy is an important and effective adjuvant
Samuel & Sharma [10]	RMC 1963–1989	59	50%	15%	100% 10 year OAS 8.5% recurrence or relapse	- Radioiodine is safe and effective for adjuvant treatment of advanced thyroid cancers and metastases - In patients with only minimal residual tissue and also those with nodal metastases the prognosis is good even without radioiodine therapy
Bal et al. [12]	AIIMS 1967–2000	80	67%	29%	3.8% disease specific mortality	- Studied pediatric thyroid cancers in sub-Himalayan iodine deficient region - Except for the relatively higher incidence of follicular thyroid cancer and higher mortality in <10 year age group, the course is no different from that in children in iodine-sufficient areas
Samuel et al. [28]	RMC 1963–1996	121	Not studied	22%	1/26 patients (3.8%) with metastatic disease died of disease	- Studied pulmonary metastases in pediatric thyroid cancer - Complete response of pulmonary metastases after radioiodine therapy is difficult to achieve - Partial response with reduction of metastatic disease is possible and the patients had a good quality of life with a low mortality rate.

TMH Tata Memorial hospital

AIIMS All India Institute of Medical Sciences

RMC Radiation Medical Centre

OAS Overall Survival. DFS Disease Free Survival

Clinical examination includes both a general examination and a thyroid-focused evaluation. A detailed local examination should include assessment of thyroid size, nodularity, airway status, neck nodes and vocal cord status.

USG should be done in all patients with thyroid nodules to find out about the size, number and nature of the lesions. It will furnish additional information regarding involvement of contralateral lobe, central and lateral neck nodes and extra-thyroidal extension; as well as guide FNAC.

As in adults, thyroid nodules in children are best assessed by FNAC. FNAC in children has similar sensitivity and specificity as for adults [34]. It has been suggested that FNAC may be done even for nodules less than 1 cm in children because of the greater risk of malignancy in pediatric nodules [6].

Pre-operative staging should always include an X-ray examination of the chest to interrogate pulmonary metastases. Kumar et al. suggested that in developing countries like India where tuberculosis is endemic, pulmonary metastases may sometimes be misinterpreted as miliary tuberculosis, and neck nodes may be misdiagnosed as nodal tuberculosis, causing a delay in diagnosis of pediatric DTC [9]. Hence, there should be an index of suspicion in children presenting with neck nodes and chest X-ray changes.

In children with bulky neck nodes, a CT scan may be done to aid surgical planning. CT scan of the chest is done only in select cases to investigate abnormalities on X-ray.

Nuclear scintigraphy is not recommended for the initial evaluation of DTC in children with an intact thyroid and a normal TSH level [7].

Staging and Risk Grouping

While several prognostic staging systems for thyroid cancer have been described, the American Joint Committee on Cancer (AJCC) TNM staging may be preferred [7]. However some believe that even this system is not without its shortcomings when used for pediatric thyroid cancer [6]. All pediatric DTCs by virtue of age will be stage I or II (age <45 years); this in spite of their aggressiveness. This may seem incongruous especially in children diagnosed before 10 years of age who have a higher risk for recurrence and ultimately death [12, 33].

Thyroid cancers are considered high risk in various prognostication systems if they have distant metastases, regional metastases and extrathyroidal extension; thus most pediatric DTCs will be high risk thyroid cancers.

Indeed there is a need for developing a new prognostication system for pediatric thyroid cancers.

Treatment - Surgery

Thyroid Surgery A standardised approach to surgery in pediatric thyroid cancer is lacking. Some surgeons cite the excellent survival in these patients counterbalancing the morbidity of aggressive surgery, and hence recommend conservative surgery [35, 36].

Most surgeons prefer to perform a total thyroidectomy for pediatric DTCs [6, 7, 22, 25, 29, 37–40], and the arguments in favour of this are multifold: (a) Multifocal disease occurs in 40% of pediatric PTC, and has a greater risk for recurrence; (b) Pediatric DTC commonly has regional lymph node disease and a greater risk for distant metastasis; (c) Total thyroidectomy will facilitate the future use of radioactive iodine (RAI) where indicated; (d) Post-operative RAI scans and thyroglobulin assays can be best used after total thyroidectomy, these are especially useful in picking pulmonary metastases that may be undetected on initial X-ray. We found that an initial X-ray of chest picked only about 31% of pulmonary metastases [3]. Pulmonary metastasis may be present in one-third to half of the patients with a normal X-ray chest. These can only be detected on a post-operative RAI scan, after a total thyroidectomy.

Further support for total thyroidectomy in pediatric thyroid cancers comes from four large cohort studies, which have found that relapse rates are more with lobectomy than with total thyroidectomy [2, 29, 39, 40].

To keep the controversy alive, there is a school of thought from Waguespack and Francis, who consider lobectomy for *'low-risk patients with incidental micro-PTC or small (< 1 cm) unifocal tumors as long as pre- and postoperative staging fail to identify multifocal disease in the thyroid or cervical lymph node involvement'* [7].

Neck Node Dissection It has been shown that lymph node dissection in children with PTC reduces recurrence risk and improves progression-free survival [39–41]. 'Berry picking' should be avoided since it leads to greater recurrence rates [42]. Hence lymph node dissections should be comprehensive and compartment-focused.

It is recommended that central compartment neck dissection be done for children with overt PTC. A thorough central compartment dissection need not be done in children with small PTC (<1 cm) who have no evidence of nodes on ultrasound. Waguespack and Francis recommend that lateral neck dissection should be done only when there is USG or FNAC documented nodal disease in the lateral compartment [7].

Our policy is to perform total thyroidectomy for all pediatric cancers except for small PTC (<1 cm). We also perform routine central compartment clearance in pediatric thyroid cancers; at least a central compartment examination in cases where an experienced sonologist has reported no nodes in the central compartment. On account of high nodal

spread in pediatric DTCs, it is also our policy to perform at least a lateral compartment sampling (levels II to IV) even when there is no USG evidence of lateral nodes.

Complications At the cornerstone of the controversy regarding surgery for pediatric DTCs are the complications of surgery, and the morbidity thereof. There is increased risk of complications in complete resection of the thyroid as well as addition of central and lateral nodal dissections. In the largest study of pediatric DTCs, Demidchik found a complication rate of 22%, including permanent recurrent nerve damage in 6.2% and permanent hypoparathyroidism in 12.3% [39]. Children have higher endocrine-specific complication rates than adults after thyroidectomy (9.1 vs. 6.3%) [43].

Hence it is recommended that these surgeries be performed by high-volume thyroid surgeons (defined as performing more than 30 thyroid surgeries per year) to minimise complications [6, 7, 43], which may still occur in about 6% of cases [43].

Treatment - Radioactive Iodine (RAI) Therapy

Similar to surgical management, the controversy in management also extends to post-operative radioiodine therapy.

In adults, it has been established that RAI therapy leads to a reduced risk of recurrence and mortality in DTC with postsurgical residual disease [44, 45]. In a meta-analysis, RAI benefit was demonstrated in adults with stage III and IV disease but not in stage I [46]. However this issue has not been well addressed in children. While in patients with iodine-avid distant metastases, the role of RAI therapy is established, routine RAI treatment for children with DTC has been debated.

The controversy regarding the routine use of RAI centres around the risks associated with excessive RAI use in children. These include risk of second primary malignancies, salivary gland effects, pulmonary fibrosis and reproductive issues. Hence it is vital to weigh the possible benefits against the potential risks of RAI on an individual basis.

Some authors do not favour routine remnant ablation in lower-risk children with optimum primary surgery [7]. On the other hand, some authors do not feel that these recommendations for adults should be applied to children due to aggressive disease with high recurrence rates [6]. They suggest that for low-risk pediatric patient with microcarcinoma (tumor <1 cm) and no lymph node involvement, remnant ablation may be done with 30 mCi of I131.

All Indian studies have recommended routine post-operative RAI scanning and therapy in view of increased local recurrences and the incidence of pulmonary metastases not detected on routine imaging [3, 9, 10, 12, 28].

In the context of metastatic disease, Bal et al. from AIIMS demonstrated RAI efficacy in children and adults, with the pulmonary lesions responding in 70% [47]. Samuel et al. from RMC showed that ablation was achieved in 86% of all patients, and 57% of those with lung involvement [10].

Before RAI scan, a thyroid withdrawal (with TSH > 30 μ IU/ml) is necessary by withholding thyroxine for 2–4 weeks. This is followed by a stimulated serum Tg and a diagnostic 123I or 131I whole-body scan.

For therapy, usually an empiric dosing is used according to the uptake on diagnostic scan and the site of disease or metastases: 50–100 mCi for remnant and neck residual, 150 mCi for pulmonary metastases, and 200 mCi for bony and other metastases [22]. We practise a similar strategy.

TSH Suppression

TSH suppression is vital in DTC treatment, but the optimal level of suppression is debated. The recent ATA guidelines recommend that TSH should be 0.1–0.5 μ IU/mL in low-risk patients and less than 0.1 μ IU/mL in high-risk patients [48]. However, children were not defined as low- or high-risk patients. Some experts have recommended thyroid hormone suppression in most children with a goal of maintaining a serum TSH level of 0.1 to 0.5 μ IU/mL in the absence of symptoms of hyperthyroidism [7].

Follow-up and Disease Surveillance

Recurrences after childhood thyroid cancer may take place over a long period of time. Therefore, a life-long follow-up is mandatory.

Waguespack recommends a policy of determining suppressed serum Tg and Tg antibodies every 3 to 6 months after initial therapies and neck ultrasound every 6 to 12 months during the first 1–2 years of follow-up, and then decrease the frequency. A stimulated Tg test with a whole-body scan are obtained in patients previously treated with 131I, usually a year after RAI therapy, and yearly thereafter [7].

Conclusions

Pediatric and juvenile DTC is a rare disease which represents a unique behaviour pattern. Though being aggressive and frequently metastatic, it has excellent long-term survival. In the Indian context, radiation exposure is a rare cause of pediatric DTCs. There is no level I evidence to guide management in these rare cancers, but guidelines have evolved from cohort studies. Treatment should be based on their increased risk for recurrence but overall low mortality, and

lifelong follow-up is required because recurrence and death may not occur for decades after diagnosis. Hence the need for utmost care while choosing therapy, and executing it. Evidence suggests that more extensive surgery is associated with lower rates of recurrence. Surgery is also associated complications rates that can be minimized when surgery is performed by high-volume thyroid surgeons. Evidence shows that, in well selected cases, RAI is associated with lower recurrence rates. However the risks of toxicity and second primary malignancy associated with RAI needs to be counterweighed against the potential benefit of repetitive therapy.

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