# Applicability of Adults 2015 American Thyroid Association Differentiated Thyroid Cancer Guidelines for Postoperative Risk Stratification and Postradioiodine Treatment Dynamic Risk Stratification in Pediatric Population

Shashank Shekhar Singh[1]    Bhagwant Rai Mittal[1]    Ashwani Sood[1]    Anish Bhattacharya[1]
Ganesh Kumar[1]    Amit Singh Shekhawat[1]    Harpreet Singh[1]

[1] Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Address for correspondence  Ashwani Sood, DNB, Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh-160012, India (e-mail: sood99@yahoo.com).

## Abstract

**Purpose**   This retrospective study aimed to study the applicability of 2015 adult American Thyroid Association (ATA) differentiated thyroid cancer (DTC) postoperative risk stratification and guidelines in the pediatric population for evaluating the number of metastatic lymph nodes in the postoperative risk stratification and postradioactive iodine (RAI) treatment dynamic risk stratification (DRS) using response to treatment (RTT) reclassification. In addition, the effect of pubertal status and gender was assessed on disease presentation and prognosis.

**Methods**   Data of 63 DTC patients aged 20 years or less, stratified into prepubertal, pubertal, and postpubertal age groups, was divided into low, intermediate, and high-risk groups using pediatric ATA recurrence risk stratification. Forty-seven patients were classified as responders (excellent and indeterminate responses) and incomplete responders (biochemical and structurally incomplete responses) by assessing the RTT at 1.5 years follow-up similar to recommendation of 2015 adult DTC ATA guidelines.

**Results**   Female-to-male ratio showed a trend of gradual increase with increasing age. Significantly more responders were observed in low- and intermediate-risk groups than in high-risk group ($p = 0.0013$; $p = 0.017$, respectively), while prepubertal group had more extensive (N1b) disease. Using DRS at follow-up of 1.5 year, pubertal and postpubertal groups showed significantly better response to RAI. More female than male patients showed response and took significantly less time to respond to RAI ($p = 0.003$).

**Conclusion**   RAI response in pediatric DTC depends on pubertal status, gender, and number of malignant nodes. DRS using RTT classification may be applicable early at 1.5 years after initial therapy in different pubertal age and risk groups.

**Keywords**
► differentiated thyroid cancer
► puberty
► children
► radioactive iodine
► age
► dynamic risk stratification

## Introduction

Thyroid cancer in childhood is rare compared with adults, with higher risk of malignant nodules (22–26%), regional nodal (~80%), and pulmonary metastases (9–30%); however, it is associated with better sodium iodide symporter expression and response to radioactive iodine (RAI).[1–7] Acknowledging the importance of these differences on the disease course and patients' management, the American Thyroid Association (ATA) in 2015 published a dedicated guideline for the management of differentiated thyroid cancer (DTC) in children with recommendations to provide important insights about disease and different aspects of patients' management.[8] However, a few areas still remain contentious due to rarity of the disease and dearth of data and one such aspect is influence of pubertal status of the pediatric patients. Some studies have shown the behavior of thyroid cancer is diverse in different age groups and its clinical course may be influenced by various physiological milestones such as gender, puberty, and menopause.[9] Thus, the task force suggested segregation of further data according to pubertal status at the time of disease presentation in children.[8] The postoperative risk stratification used for persistent/recurrent disease evaluation in children is still categorical unlike a continuum in the revised 2015 adult DTC ATA guidelines. The pediatric ATA (2015) guidelines have divided pediatric patients into three risk categories for persistent/recurrent disease to devise further treatment strategy based on "minimal" or "extensive" metastatic cervical lymph nodal involvement.[8] However, data defining the number of metastatic lymph nodes involved for this classification is not clear. In addition, criteria for the assessment of response to treatment (RAI and levothyroxine) have not been well established in the pediatric age group.

This retrospective study aimed to determine whether ATA 2015 risk stratification system and response to treatment (RTT) reclassification for adults can be applied in the pediatric population. The study evaluated for any differential response to RAI treatment among different pubertal age groups in DTC patients aged 20 years or less, using RTT reclassification adopted from ATA adult DTC 2015 guidelines. We also evaluated whether the presence of more than five metastatic cervical lymph nodes may help in differentiating between extensive and minimal disease for risk stratification of patients according to ATA pediatric risk of persistent/recurrent disease classification.

## Patients and Methods

A total of 63 consecutive DTC patients (aged ≤ 20 years) after initial thyroid surgery were included in the study from 2009 to 2018. Treatment and follow-up of the whole cohort were guided by a multidisciplinary team consisting of surgeons, nuclear medicine physicians, and endocrinologists. Data was collected from the medical charts of the patients and consisted of details of initial diagnostic workup, surgery, treatment with RAI, and their outcome at every 6 monthly follow-ups. This retrospective study was duly approved by Institute

Ethics Committee vide letter no INT/IEC/2019/000534 with waiver for patients' consent.

Besides the presurgery workup, details of initial surgery (total/hemi-thyroidectomy followed by completion thyroidectomy, type of lymph node dissection), histopathology (type of DTC, number of lymph nodes positive for metastatic deposits), first I-131 diagnostic whole-body scan (DxWBS) findings, and RAI ablation/treatment were reviewed. The follow-up ultrasonography (USG) of neck and serial serum thyroglobulin (Tg) and antithyroglobulin (ATg) antibodies (stimulated and unstimulated values) wherever available were taken for analysis. The study patients were divided on the basis of age into three groups: prepubertal (≤ 10 years), pubertal (11–15 years), and postpubertal (16–20 years) based on the median age of puberty in Indian population.[10,11]

For each patient, decision for initial RAI ablation/treatment was taken based on initial postsurgical risk stratification (according to ATA guidelines) along with findings of first DxWBS. Dose of RAI administered was scaled down to body weight of the pediatric patient using the formula: Pediatric dose = adult dose × patient's body weight (kg)/70 (kg) based on the empirical adult doses: 1,110–1,850 MBq (30–50 mCi) for remnant, 3,700 MBq (100 mCi) for regional nodal metastases and/or intermediate risk patients, 5,550 MBq (150 mCi) for lung and 7,400 MBq (200 mCi) for bone metastases. In-between the follow-ups, appropriate suppressive doses of L-thyroxine were given and stopped 3 to 4 weeks before the date of next DxWBS. Stimulated tumor markers (Tg and ATg) were determined prior to the DxWBS done with 55.5 to 74 MBq (1.5–2 mCi) of diagnostic RAI dose. Further treatment with RAI was based on 6 monthly follow-up of DxWBS, neck USG, and stimulated serum tumor markers (Tg and ATg). After two consecutive negative DxWBS, patients were followed up with unstimulated Tg/ATg and neck USG only.

We retrospectively incorporated the cutoff of 5 for the number of metastatic lymph nodes used to define "minimal" and "extensive" disease. Patients with more than five histopathological proven metastatic lymph nodes were characterized as having "extensive" nodal disease (for both N1a and N1b nodal stations) and 5 or less metastatic lymph nodes as "minimal" disease. Fifty-six out of 63 patients had information about the number of resected metastatic lymph nodes and were stratified into high, intermediate, and low-risk groups according to ATA pediatric DTC guidelines with incorporation of above-mentioned criteria (►**Table 1**).

Data of three or more consecutive visits was available for 47 patients and used for assessing the response to treatment (RTT) at 1.5 years after initial RAI dose. For response assessment, we retrospectively applied the criteria akin to adult ATA guidelines 2015 dynamic risk stratification (DRS) using RTT where findings of DxWBS and stimulated/unstimulated serum Tg/ATg were used to classify patients into excellent, indeterminate, biochemically incomplete, and structurally incomplete response categories. In this study, we defined "responders" having RAI negative disease on DxWBS with stimulated serum Tg (< 10 ng/mL) or undetectable unstimulated Tg (< 1 ng/mL) levels similar to adult ATA categories of excellent and indeterminate responses. "Incomplete

**Table 1** Criteria for defining the postoperative risk category in pediatric patients of thyroid cancer (adapted from reference[8])

| Risk category | Definition |
|---|---|
| Low | Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease, that is, microscopic metastasis to a small number, that is, ≤5 central neck lymph nodes |
| Intermediate | Extensive (> 5) N1a or minimal (≤ 5) N1b disease |
| High | Regionally extensive disease (> 5 N1b lymph nodes) or locally invasive disease (T4 tumors), with or without distant metastasis |

responders" were defined as patients having RAI avid disease on DxWBS or those with negative DxWBS but elevated stimulated serum Tg values (> 10 ng/mL), unstimulated serum Tg (> 1 ng/mL) along with USG neck findings resulting into biochemically and structurally incomplete response categories of adult ATA response criteria. Values of serum Tg were interpreted along with serum ATg antibodies. Recurrence was defined as responders showing new structural or biochemical disease at 6-month follow-up. The response was assessed after 1.5 years of continual RAI treatment/follow-up.

### Statistics

Data analysis was performed using SPSS software, Version 22.0 (SPSS, Inc., Chicago, Illinois, United States). Differences between the three groups (prepubertal, pubertal, and postpubertal) were tested using one-way analysis of variance for variables with normal distribution, Kruskal–Wallis test for continuous variables with skewed distribution, Fisher exact, and $X^2$ tests were used for categorical variables. A $p$-value of less than 0.05 was considered significant. Kaplan–Meier curves were derived to look for the difference in response among the three age groups and between two genders.

### Results

**Patient characteristics:** A total of 63 patients (39 females; 62%) with median age of 16 years (range: 5.5–20) at presentation were taken. Female to male ratios in prepubertal, pubertal, and postpubertal age groups were 0.75, 0.90, and 2.7, respectively. The mean lag time between onset of symptoms and first RAI administration was 1.28 years (►**Table 2**).

Neck swelling was predominant presenting symptoms (98.4%) in patients' cohort, and seven patients had additional symptoms of fever, hoarseness of voice, dysphagia, cyanosis, dyspnea, and weight loss. Two patients of less than 10 years of age with fever, dyspnea, cough, weight loss, cyanosis (central and peripheral), and miliary picture on chest X-ray were initially diagnosed as military tuberculosis. Eventually, both of them had extensive pulmonary metastases of papillary thyroid carcinoma (PTC) along with concomitant pulmonary tuberculosis.

Fifty-three patients (84%) underwent total thyroidectomy, whereas completion thyroidectomy following hemithyroidectomy was performed in nine patients (14%). Surgery could not be performed in one patient, due to extensive soft tissue and vascular structure invasion by the tumor. Central neck dissection was performed in 45 patients (71.4%), while 38 patients (60%) underwent additional lateral neck dissection as well.

The most common histopathology subtype encountered was classical PTC ($n = 45$; 71.4%) followed by follicular ($n = 11$; 17.5%) and tall cell ($n = 2$; 3.2%) variants of PTC. Follicular carcinoma was diagnosed in two patients. PTC variants of mixed histology were found in three patients. According to American Joint Committee on Cancer tumor node metastasis staging (8th edition) for thyroid cancer, the study cohort showed T2 (39%) was the most frequent T stage, followed by T1 (31%), T3 (22%), and T4 (8%) tumor, respectively. Mean tumor diameter was $2.6 \pm 1.2$ cm. Lymph node histopathology was available only in 55 out of 62 patients, and majority of them had N1B nodal metastases (~65%) followed by N1A in 22% and N0 in 5.5% patients, respectively. Sixteen out of 63 patients (25%) presented with RAI-avid pulmonary metastases with 13 of them had diffuse lung uptake and 3 had few foci of tracer uptake on first DxWBS; micrometastases (< 2 mm) were present in 6, whereas 10 patients had lung nodules of greater than 2 mm size. Pulmonary metastases were present in prepubertal (71.4%), pubertal (36.8%), and postpubertal (10.8%) age groups, respectively ($p < 0.05$), and all patients with pulmonary lesions had extensive neck lymph nodal metastases also (N1b; > 5 metastatic lymph nodes in the surgical histopathology). Type of initial surgery, histopathological subtypes, and longest diameter of primary tumor did not differ significantly across all three age groups.

### Postoperative Risk Stratification

After incorporating more than 5 malignant positive lymph nodes as criteria for "extensive nodal disease" into the postoperative risk stratification for recurrence/persistent disease in existing ATA pediatric DTC guideline 2015, 30 out of 56 patients (54%) were classified into high-risk group, whereas 18 (32%) and 8 (14%) of them were categorized into intermediate and low-risk groups of having recurrent/persistent disease, respectively. Presence of extensive nodal metastases (N1b stage) was higher in prepubertal (~86%) and pubertal (74%) age groups compared with postpubertal age group (55%) ($p$-value = 0.027). Similarly, prepubertal and pubertal age group patients (71.4 and 73.6%, respectively) had significantly more high-risk recurrent/persistent disease compared with postpubertal group (36.7%; $p$-value 0.03), whereas all the postpubertal patients had low-risk of disease recurrence ($p < 0.05$).

**Table 2** Clinical, histopathological characteristics of 63 patients with AJCC TNM staging and ATA pediatric DTC risk stratification

| | Total, n = 63 (%) | Prepubertal, n = 7 (%) | Pubertal, n = 19 (%) | Postpubertal, n = 37 (%) | p-Value |
|---|---|---|---|---|---|
| Age (Mean ± SD) | 15.2 ± 3.5 | 7.9 ± 1.9 | 13.4 ± 1.5 | 17.6 ± 1.3 | 0.044 |
| Male | 24 (38.1) | 4 (57.2) | 10 (52.6) | 10 (27.1) | 0.099 |
| Female | 39 (61.9) | 3 (42.8) | 9 (47.3) | 27 (72.9) | 0.099 |
| Symptom to first hospital visit (years) | 1.28 | 0.92 | 1.47 | 1.24 | 0.017 |
| Symptoms | | | | | |
| Neck swelling | 62 (98.4) | 7 (100) | 18(94.7) | 37 (100) | 0.772 |
| Others | 7 | 3 | 1 | 3 | |
| Thyroid surgery | | | | | |
| Total | 53 (84.1) | 6 (85.7) | 16 (84.2) | 31 (83.8) | 0.992 |
| Hemi + completion | 9 (14.2) | 1 (14.3) | 2 (10.6) | 6 (16.2) | 0.849 |
| No surgery | 1 (0.01) | 0 | 1 (5.2) | 0 | 0.314 |
| Lymph node dissection | | | | | |
| Central neck | 45 (71.4) | 7 (100) | 15 (78.9) | 23 (62.1) | 0.090 |
| Lateral neck | 38 (60.3) | 6 (85.7) | 12 (63.2) | 20 (54) | 0.284 |
| Unilateral | 15 (39.4) | 1 (16.7) | 5 (41.7) | 9 (45.0) | 0.813 |
| Bilateral | 23 (60.6) | 5 (83.3) | 7 (58.3) | 11 (55.0) | 0.114 |
| Histopathology | | | | | |
| Classical PTC | 45 (71.4) | 4 (57.1) | 15 (79.0) | 26 (70.3) | 0.540 |
| Follicular variant | 11 (17.5) | 2 (28.6) | 4 (21.0) | 5 (13.6) | 0.562 |
| Tall cell | 2 (3.2) | 1 (14.3) | 0 | 1 (2.7) | 0.182 |
| Follicular | 2 (3.2) | 0 | 0 | 2 (5.4) | 0.490 |
| Others | 3 (4.7) | 0 | 0 | 3 (8.0) | 0.336 |
| T stage (n = 51) | | | | | |
| T1 | 16 (31.4) | 3 (42.8) | 6 (35.3) | 7 (26.0) | 0.318 |
| T2 | 20 (39.2) | 4 (51.2) | 4 (23.5) | 12 (44.4) | 0.218 |
| T3 | 11 (21.6) | 0 | 5 (29.5) | 6 (22.2) | 0.285 |
| T4 | 4 (7.8) | 0 | 2 (11.7) | 2 (7.4) | 0.586 |
| N stage (n = 55) | | | | | |
| NX | 4 (7.3) | 0 | 1 (5.3) | 3 (10.3) | 0.707 |
| N0 | 3 (5.5) | 0 | 0 | 3 (10.3) | 0.336 |
| N1A | 12 (21.8) | 1 (14.3) | 4 (21.0) | 7 (24.2) | 0.928 |
| N1B | 36 (65.4) | 6 (85.7) | 14 (73.7) | 16 (55.2) | 0.027 |
| M stage (n = 63) | | | | | |
| M0 | 47 (74.6) | 2 (28.6) | 12 (63.2) | 33 (89.2 | 0.034 |
| M1 | 16 (25.4) | 5 (71.4) | 7 (36.8) | 4 (10.8) | 0.034 |
| Lungs | 16 | 5 | 7 | 4 | 0.034 |
| Bones | 0 | 0 | 0 | 0 | |
| ATA recurrence risk (n = 56) | | | | | |
| Low | 8 (14.3) | 0 | 0 | 8 (26.6) | 0.042 |
| Intermediate | 18 (32.1) | 2 (28.6) | 5 (26.4) | 11 (36.7) | 0.965 |
| High | 30 (53.6) | 5 (71.4) | 14 (73.6) | 11 (36.7) | 0.003 |

Abbreviations: AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; SD, standard deviation; TNM, tumor node metastasis.

**Table 3** Summary of radioactive iodine treatment in different pubertal age groups

| Follow-up data | Total, $n = 47$ (%) | Prepubertal, $n = 7$ (%) | Pubertal $n = 12$ (%) | Postpubertal, $n = 28$ (%) |
|---|---|---|---|---|
| Follow-up duration (mo) | | | | |
| Mean (range) | 46.3 (18–102) | 35.2 (18–74) | 48.5 (21–102) | 48.3 (18–96) |
| Radioactive iodine treatment | | | | |
| Received | 46 | 7 | 12 | 27 |
| Not received | 1 | – | – | 1 |
| Number of I-131 doses: | | | | |
| Single dose | 21 | 1 (14) | 4 (33) | 16 (59) |
| Two doses | 5 | 1 (14) | 1 (8) | 3 (11) |
| ≥ 3 doses | 20 | 5 (71) | 7 (58) | 8 (30) |
| Average cumulative dose (MBq) | 9,879 | 12,606 | 12,595 | 7,992 |
| Risk category | | | | |
| High | 27 (57) | 6 (86) | 8 (67) | 13 (46) |
| Intermediate | 14 (30) | 1 (14) | 4 (33) | 9 (32) |
| Low | 6 (13) | 0 | 0 | 6 (22) |
| Responders | 24 (51) | 0 | 7 (58) | 17 (61) |
| Nonresponders | 23 (49) | 7 (100) | 5 (42) | 11 (39) |

Time lag between symptom presentation and first DxWBS was shorter in the prepubertal age group than pubertal and postpubertal age ($p < 0.05$).

## Dynamic Risk Stratification (DRS) and Response to Treatment Reclassification (RTT)

Sufficient follow-up data was available for 47 patients with median follow-up duration of 3.6 years (range: 1.5–8.5). In these 47 patients, 44, 36, and 13 patients had thyroid bed, lymph nodal, and lung uptake, respectively, on the first DxWBS. Forty-six (one of them with a tall cell variant of PTC, elevated Tg levels and negative first DxWBS) out of 47 patients were treated with RAI ablation/treatment. One patient was not given RAI ablation due to low recurrence risk and negative DxWBS and did not show any evidence of recurrence on 6 monthly follow-ups, till the last follow-up. Twenty-one patients received a single dose of RAI, 5 and 20 patients received 2 and greater than or equal to 3 doses of RAI, respectively. The average cumulative dose was 9,879 MBq (267 mCi). Second neck dissection in view of enlarged lymph nodes was performed in five patients to obviate the need for RAI (►**Table 3**).

Out of 47 patients, 24 patients (~51%) were classified as responders, whereas 23 (~49%) remained as incomplete responders after 1.5 year of first DxWBS.

*RTT among different pubertal age groups:* About 58% pubertal and 61% postpubertal patients, respectively, were classified as responders and showed similar responses to RAI. None of the patients from the prepubertal cohort were classified as responders and was statistically significant different from the other two groups ($p = 0.01$). Also, reduction in lymph nodal disease by RAI was significantly higher in postpubertal and pubertal groups than prepubertal patients ($p = 0.0024$ and $p = 0.0094$, respectively) who had persistent lymph nodal metastases at 1.5 years of follow-up.

In follow-up cohort of 47 patients, 46 patients received RAI and 13 of them had lung metastases in prepubertal (83%; 5/7), pubertal (33%; 4/12), and postpubertal (~15%; 4/27) group, respectively. Pulmonary metastases across all three age groups in follow-up of 1.5 years did not show significant response to RAI, with only three patients showing resolution of RAI avid disease. One prepubertal patient having high-risk histology (tall cell of PTC) with baseline negative DxWBS and stimulated Tg value of 70 ng/mL developed bone metastases (►**Fig. 1**).

*RTT among different risk categories:* Overall, there was a significant difference in response to RAI among different risk categories ($p < 0.05$). Response rates were 100, 64, and 33% for low-, intermediate-, and high-risk groups, respectively. All the low-risk group patients (6/6) belonging to postpubertal age group were classified as responders at 1.5 years of follow-up. There was no significant difference in response between intermediate- and high-risk groups in the postpubertal age group. In the pubertal age group, the number of responders in the intermediate-risk category was significantly higher than the high-risk group (►**Table 4**).

In our study group, 2 out of total of 63 patients succumbed to the disease. One patient in pubertal age died within 6 months of hospital visit due to extensive pulmonary metastases complicated with pulmonary tuberculosis that led to respiratory failure. Another patient with uncontrolled hypocalcemia postthyroidectomy in the postpubertal age
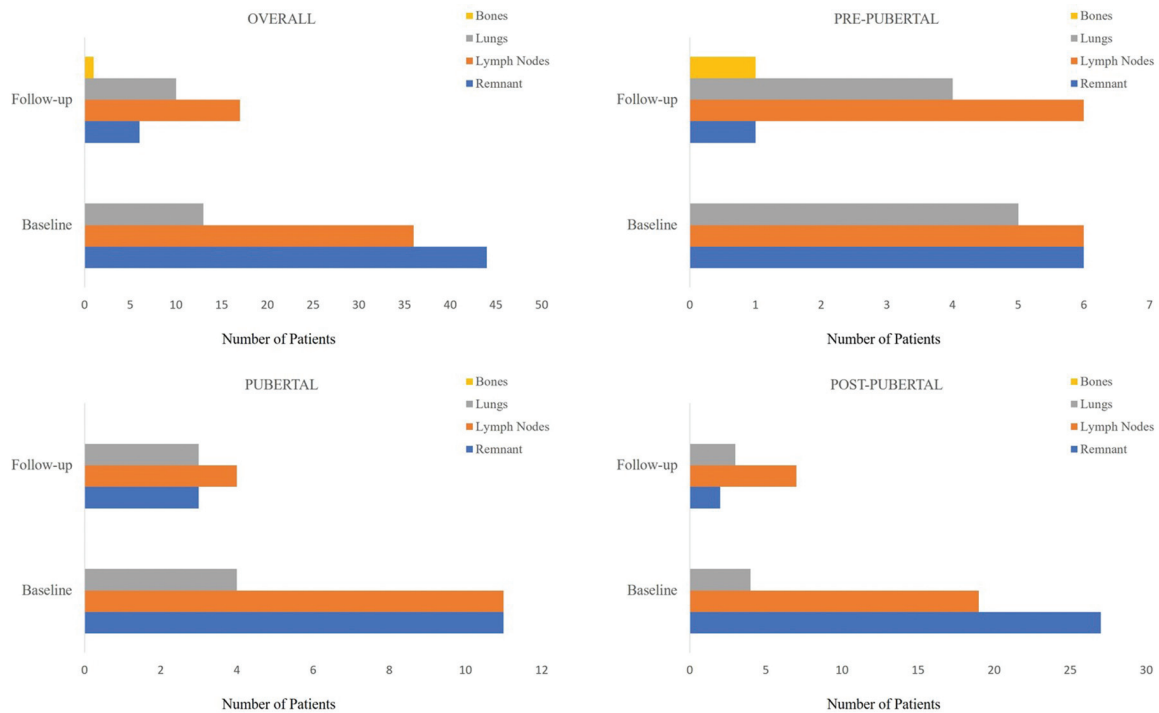
**Fig. 1** Response to radioactive iodine treatment for different metastatic sites assessed at 1.5-year in post-treatment follow-up diagnostic whole-body scan in overall and different pediatric age groups.

group died, probably due to the complications of hypocalcemia.

*Kaplan-Meier analysis of probability of having incomplete response*: None of the prepubertal patients achieved the desired response at 1.5 years of follow-up. The probability of incomplete response was significantly less in the post-pubertal group compared with other two groups ($p = 0.04$) in the follow-up. Pubertal group took significantly longer mean time to achieve the status of responder compared with the postpubertal group ($p = 0.039$) (►**Fig. 2**).

Response to RAI was also significantly different between males and females with 48.3% of female patients becoming responders compared with only 16.6% of males. Mean time to response in the female population was also significantly shorter than males ($p = 0.003$) (►**Fig. 3**).

## Discussion

Due to the rarity of DTC in the pediatric age group, there is paucity of prospective as well as retrospective data to draw definite conclusions to guide the management of DTC in

children. In this retrospective study, we divided our study cohort of 63 DTC pediatric patients (aged < 20 years) in three age groups according to pubertal status at the time of disease presentation as recommended by ATA 2015 guidelines for pediatric age group. We also evaluated the effect of defining the number of metastatic lymph nodes for risk stratification and application of DRS during follow-up for evaluating the response to treatment by RAI as recommended by ATA 2015 adult DTC guidelines.

Most common histology encountered in our cohort was classical papillary thyroid cancer ($\sim$71%) followed by follicular variant of PTC, though the histology was not influenced by pubertal status.

In our study, the number of patients were lowest in the prepubertal group (11%) followed by pubertal (30%) and postpubertal (59%) groups. However, the disease was most aggressive in the prepubertal age group at the presentation with the highest incidence of extensive regional cervical lymph nodal (86%) and distant pulmonary metastases (71%). Various studies have also observed similar findings with extensive regional lymph nodal and pulmonary

**Table 4** Responders in different pubertal status according to risk categories at follow-up of 1.5 years ($n = 24$)

|  | Prepubertal (0) | Pubertal (7) | Postpubertal (17) |
|---|---|---|---|
| Low-risk category ($n = 6$) | – | – | 6 |
| Intermediate-risk category ($n = 9$) | 0 | 3 | 6 |
| High-risk category ($n = 9$) | 0 | 4 | 5 |

(–) since there were no prepubertal and pubertal patients in low-risk category.
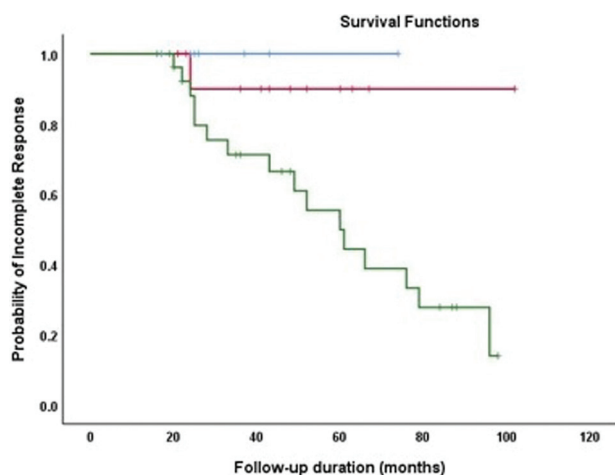
**Fig. 2** Probability of incomplete responders to radioactive iodine at subsequent follow-ups in different pubertal age groups. Prepubertal and pubertal groups showed significantly higher rate of incomplete responders compared with postpubertal group. *Blue line*: prepubertal age group, *pink line*: pubertal age group, *green line*: postpubertal age group.
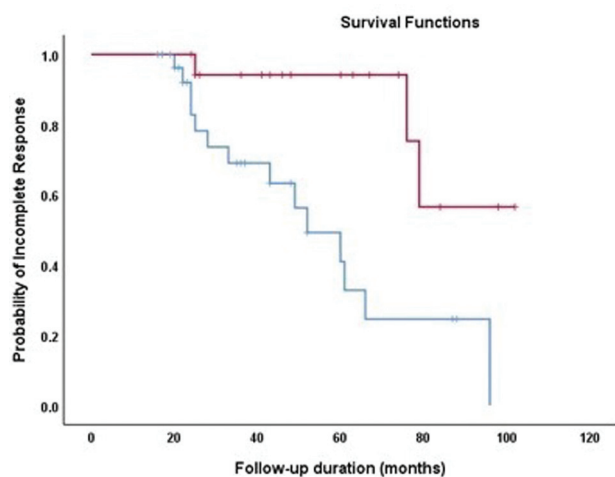


**Fig. 3** Probability of incomplete responders to radioactive iodine at subsequent follow-ups in males and females. Follow-up showed more females were responders and shorter time taken to response compared with males. *Blue line*: females, *pink line*: males.

involvement at the time of presentation serving the important prognostic marker.[3,12–14] The aggressive presentation could be one of the reasons for the shorter time lag between the clinical manifestation and first hospital visit in the prepubertal group. Owing to rarity of DTC in less than 10 years of age and higher prevalence of mycobacterium tuberculosis infection in the Indian subcontinent, two children of prepubertal age group in our cohort were initially misdiagnosed with tuberculosis (miliary appearance) resulting in delayed diagnosis.

Lungs are the most common site for distant metastases in papillary DTC with approximately 70% of prepubertal children having extensive pulmonary metastases at initial presentation in different studies.[3] In our cohort, overall (25%; 16/63) patients had lung metastases with prepubertal chil-

dren had highest rate of pulmonary metastases (∼71%) followed by pubertal (∼37%) and postpubertal (∼11%) age groups ($p < 0.05$), though all of them had extensive N1b regional nodal metastases. The prepubertal and pubertal group had significantly higher number of patients with high-risk disease (71.4 and 73.6%, respectively, ►**Table 1**) than the postpubertal group (36.7%) ($p$-value 0.03), whereas all the patients of postpubertal group had low-risk of disease recurrence ($p < 0.05$).

Differential behavior of thyroid cancer according to the gender has been well established. There is a gradual decline in female-to-male ratio with advancing age, falling from more than 5 at age of 20 to 24 years to 3.4 at the age of 35 to 44 years and this ratio approaches 1 after 80 years.[8,14–21] In our pediatric cohort, female-to-male ratio remained approximately 1 with slight male preponderance in prepubertal and pubertal groups, but showed female preponderance with female-to-male ratio changing to approximately 2.7:1 in the postpubertal group. Majority of the studies of pediatric DTC with similar age group divisions showed the identical findings, and demonstrated a continually increasing incidence in female patients from puberty to adulthood with female-to-male ratio in the postpubertal age approaching to the average adult values of approximately 3:1.[1,3,22–24]

**Postoperative Risk Stratification**
It has been well established that initial postoperative risk stratification (of having recurrent/persistent disease) has an important role in determining the RAI ablation/treatment and prognosis in both adult and pediatric populations. One of the major changes from 2009 to 2015 adult ATA guidelines is the shift from a three-tier classification to a continuum risk system by incorporation of interplay among tumor size and extent, number of metastatic lymph nodes and mutation status. The status of initial lymph nodal metastases is useful in predicting the disease-free survival in young patients with PTC and it can be used to determine the further treatment strategy.[25,26] However, due to dearth of data in the pediatric population, postoperative risk stratification in ATA 2015 pediatric DTC guidelines is limited to classifying the patients on the basis of minimal or extensive N1a and N1b nodal metastases. There is still no consensus regarding the number of metastatic lymph nodes to be considered in differentiating the minimal and extensive nodal disease. Jeon et al in a study of 203 DTC patients under 20 years showed extrathyroidal extension, lateral cervical, or more than 5 metastatic lymph nodes were independent predictors for structural persistent/recurrent disease. They also found that intermediate- and high-risk groups had significantly greater risk of persistent/recurrent disease compared with low-risk groups.[27] In the present study, we tried to assess whether patients could be categorized into low, intermediate, and high-risk group, similar to adult ATA guidelines on the basis of a cutoff of more than five metastatic lymph nodes. Retrospectively incorporating this criterion into the ATA pediatric DTC 2015 risk stratification classification, most of the patients (∼54%) from the present study were classified into high-risk groups and only 14% were categorized into

low-risk categories for recurrent/persistent disease. Using this criterion, all the patients with lung metastases were automatically classified under high-risk group. Also, there was a significant difference in response to RAI among different risk categories ($p < 0.05$) with 100, 64, and 33% response rates in low, intermediate, and high-risk groups, respectively. This shows that criteria of using more than five metastatic lymph nodes for postoperative risk stratification is reliable and it may help in determining the prognosis of the patients for response to RAI therapy.

## Dynamic Risk Stratification by Response to Treatment Reclassification

The standard management of DTC in children as well in adults consists of surgery (total/near total thyroidectomy) followed by postoperative risk stratification and subsequent RAI ablation/treatment.[8] Most of the pediatric patients usually receive one or more doses of RAI owing to the extensive disease at presentation. In our study, 45% of patients were treated with a single dose of RAI and most of them (∼76%) belonged to the postpubertal group since the majority of them had less extensive disease. Conversely, all the patients in the prepubertal group required more than one cycle of RAI due to their high-risk category.

Criteria for response evaluation to RAI are not well-defined in recent 2015 ATA pediatric guidelines as done for adults. In the management of adult DTC, focus has been shifted from a permanent risk categorization of patients at the time of initial DxWBS to DRS strategy based on response to treatment reclassification using DxWBS and serum Tg values in the subsequent follow-ups in the adults. Adult DRS criteria may not be applicable in the pediatric population due to several factors. Serum Tg levels may be higher in the pediatric population compared with adults for the similar extent of disease,[28,29] making the adult Tg cutoff values unreliable in pediatric age. In addition, studies have demonstrated that even after cessation of RAI treatment, the serum Tg levels may continue to decline in all age groups, particularly in patients with negative DxWBS and low level of stimulated serum Tg values ($< 10$ ng/dL) and these patients may remain disease-free for many years after RAI treatment.[28,30–34] Kim et al applied the adults DRS system in their pediatric DTC population and concluded that DRS from 1 to 2 years after diagnosis can provide useful prognostic information along with ATA risk stratification in pediatric patients with DTC.[35] Considering these observations, we assessed the response after 1.5 years of diagnosis by taking a cutoff value of 10 ng/dL (stimulated) and 1 ng/dL (unstimulated) for classifying "responders" and "incomplete responders."

In the present study, dismal response to RAI was noted in the prepubertal group as none of seven patients became free of RAI avid disease (median follow-up of 26 months). Postpubertal and pubertal groups showed a significantly better response to RAI than the prepubertal cohort. These findings are in agreement with prior studies assessing the response to RAI in pediatric age groups according to pubertal status.[3,7,17,22–24,28,29] In the study of 54 patients of DTC by Lazar et al with similar age group divisions based on pubertal status, children in the prepubertal age group had the highest incidence of bilateral cervical lymph nodal and pulmonary metastases. Assessing the response to RAI at 2 years (using criteria similar to 2015 ATA adult criteria for response to treatment), the authors found that prepubertal children frequently showed incomplete response to RAI therapy, whereas postpubertal children responded well to RAI treatment, similar to our observations.[19]

Data on long-term survival in prepubertal patients with the majority of them presenting with extensive pulmonary metastases has been promising. Studies with long-term follow-up have shown that disease-specific mortality and morbidity remained low even with extensive pulmonary metastases and incomplete remission at the cessation of RAI therapy. The patients may remain symptom free with adequate thyroid-stimulating hormone suppression without further need of RAI.[6,7,28] Owing to the low disease-specific mortality and excellent survival in children with DTC, further research should be emphasized to ascertain for maximum cumulative dose of RAI for optimal response without increasing the life-time risks of second malignancy associated with the treatment.[36,37] In our cohort, patients in the postpubertal group demonstrated highest reduction in RAI avid remnant, regional nodal, and pulmonary metastases among all three defined groups. There is a need to ascertain whether certain biological factors associated with puberty and age itself or reduced aggressiveness of disease at first presentation are the reasons for the favorable response to RAI after puberty. However, we are of the opinion that DRS could be robustly applied in the pediatric population and future research in this cohort by applying DRS could help in guiding the follow-up and prognosis.

In conclusion, the present study reflects the characteristic differences in behavior of the pediatric DTC according to the pubertal status and gender. Pediatric DTC, although rare, has more aggressive presentation in both genders before the onset of puberty with more female predilection at the onset of puberty gradually. A cutoff of more than five metastatic lymph nodes may be employed reliably to classify patients into different postoperative risk categories that can also assist in predicting the RAI response. Additionally, DRS using serum Tg values and DxWBS may be robustly used in the pediatric age group as early as 1.5 year, where pubertal and postpubertal groups show better response to RAI treatment compared with the prepubertal group.

The present study has limitations inherent to the retrospective nature of any study, shorter duration of follow-up, and lack of histopathological parameters known to influence the disease outcome.

## Conclusion

Clinical course and outcome of pediatric DTC are influenced by the gender and pubertal status at disease presentation. Prepubertal children usually present with more extensive disease and less likely favorable response to RAI treatment.

A cutoff of more than five metastatic lymph nodes may be reliably employed to categorize children with DTC into various risk subsets. The "response-to-treatment" classification based on established criteria for the adult population may be applied as early as 1.5 years after initial therapy that may be more appropriate for guiding the surveillance.

### Ethical Approval

This single institution retrospective study was approved by the Institutional Ethical Committee. Informed consent was waived due to the retrospective nature of the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Conflicts of Interest

None declared.

## References

1   Alessandri AJ, Goddard KJ, Blair GK, Fryer CJ, Schultz KR. Age is the major determinant of recurrence in pediatric differentiated thyroid carcinoma. Med Pediatr Oncol 2000;35(01):41–46

2   Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26(01):1–133

3   Lazar L, Lebenthal Y, Steinmetz A, Yackobovitch-Gavan M, Phillip M. Differentiated thyroid carcinoma in pediatric patients: comparison of presentation and course between pre-pubertal children and adolescents. J Pediatr 2009;154(05):708–714

4   Demidchik YE, Saenko VA, Yamashita S. Childhood thyroid cancer in Belarus, Russia, and Ukraine after Chernobyl and at present. Arq Bras Endocrinol Metabol 2007;51(05):748–762

5   Gupta A, Ly S, Castroneves LA, et al. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab 2013;98(08):3238–3245

6   Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg 2010;34(06):1192–1202

7   Pawelczak M, David R, Franklin B, Kessler M, Lam L, Shah B. Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following ^{131}I treatment: a systematic review. Thyroid 2010;20(10):1095–1101

8   Francis GL, Waguespack SG, Bauer AJ, et al. Management guidelines for children with thyroid cancer. Thyroid 2015;25:716–759

9   Kilfoy BA, Devesa SS, Ward MH, et al. Gender is an age-specific effect modifier for papillary cancers of the thyroid gland. Cancer Epidemiol Biomarkers Prev 2009;18(04):1092–1100

10  Surana V, Dabas A, Khadgawat R, et al. Pubertal onset in apparently healthy Indian boys and impact of obesity. Indian J Endocrinol Metab 2017;21(03):434–438

11  Khadgawat R, Marwaha RK, Mehan N, et al. Age of onset of puberty in apparently healthy school girls from Northern India. Indian Pediatr 2016;53(05):383–387

12  Faggiano A, Coulot J, Bellon N, et al. Age-dependent variation of follicular size and expression of iodine transporters in human thyroid tissue. J Nucl Med 2004;45(02):232–237

13  Marwaha RK, Tandon N, Desai AK, et al. The evolution of thyroid function with puberty. Clin Endocrinol (Oxf) 2012;76(06):899–904

14  Derwahl M, Nicula D. Estrogen and its role in thyroid cancer. Endocr Relat Cancer 2014;21(05):T273–T283

15  Dong W, Zhang H, Li J, et al. Estrogen induces metastatic potential of papillary thyroid cancer cells through estrogen receptor α and β. Int J Endocrinol 2013;2013:941568

16  Rajoria S, Suriano R, Shanmugam A, et al. Metastatic phenotype is regulated by estrogen in thyroid cells. Thyroid 2010;20(01):33–41

17  Kumar A, Klinge CM, Goldstein RE. Estradiol-induced proliferation of papillary and follicular thyroid cancer cells is mediated by estrogen receptors α and β. Int J Oncol 2010;36(05):1067–1080

18  Zeng Q, Chen GG, Vlantis AC, van Hasselt CA. Oestrogen mediates the growth of human thyroid carcinoma cells via an oestrogen receptor-ERK pathway. Cell Prolif 2007;40(06):921–935

19  Lazar L, Lebenthal Y, Segal K, et al. Pediatric thyroid cancer: postoperative classifications and response to initial therapy as prognostic factors. J Clin Endocrinol Metab 2016;101(05):1970–1979

20  Kumar A, Bal CS. Differentiated thyroid cancer. Indian J Pediatr 2003;70:707–713.21

21  Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. Future Oncol 2010;6:1771–1779

22  Chaukar DA, Rangarajan V, Nair N, et al. Pediatric thyroid cancer. J Surg Oncol 2005;92(02):130–133

23  Ye B, Shi J, Shen C, et al. Comparison of differentiated thyroid carcinoma recurrence and its clinical features in children of different ages. Oncotarget 2017;8(29):48051–48059

24  Poyrazoğlu Ş, Bundak R, Baş F, Yeğen G, Şanlı Y, Darendeliler F. Clinicopathological characteristics of papillary thyroid cancer in children with emphasis on pubertal status and association with BRAFV600E mutation. J Clin Res Pediatr Endocrinol 2017;9(03):185–193

25  Wada N, Sugino K, Mimura T, et al. Treatment strategy of papillary thyroid carcinoma in children and adolescents: clinical significance of the initial nodal manifestation. Ann Surg Oncol 2009;16(12):3442–3449

26  Wang C, Chen X, Wei X, Chen F, Wang Y, Shen Z. Recurrence factors and prevention of complications of pediatric differentiated thyroid cancer. Asian J Surg 2017;40(01):55–60

27  Jeon MJ, Kim YN, Sung TY, et al. Practical initial risk stratification based on lymph node metastases in pediatric and adolescent differentiated thyroid cancer. Thyroid 2018;28(02):193–200

28  Biko J, Reiners C, Kreissl MC, Verburg FA, Demidchik Y, Drozd V. Favourable course of disease after incomplete remission on (131)I therapy in children with pulmonary metastases of papillary thyroid carcinoma: 10 years follow-up. Eur J Nucl Med Mol Imaging 2011;38(04):651–655

29  Hänscheid H, Verburg FA, Biko J, et al. Success of the postoperative 131I therapy in young Belarusian patients with differentiated thyroid cancer after Chernobyl depends on the radiation absorbed dose to the blood and the thyroglobulin level. Eur J Nucl Med Mol Imaging 2011;38(07):1296–1302

30  Padovani RP, Robenshtok E, Brokhin M, Tuttle RM. Even without additional therapy, serum thyroglobulin concentrations often decline for years after total thyroidectomy and radioactive remnant ablation in patients with differentiated thyroid cancer. Thyroid 2012;22(08):778–783

31  Alzahrani AS, Mohamed G, Al Shammary A, Aldasouqi S, Abdal Salam S, Shoukri M. Long-term course and predictive factors of elevated serum thyroglobulin and negative diagnostic radioiodine whole body scan in differentiated thyroid cancer. J Endocrinol Invest 2005;28(06):540–546

32  Gutiérrez Cardo AL, Rodríguez Rodríguez JR, Borrego Dorado I, Navarro González E, Tirado Hospital JL, Vázquez Albertino R. [Patients treated for differentiated thyroid cancer with negative 131I whole-body scans and elevated thyroglobulin levels: a

possible course]. Rev Esp Med Nucl 2007;26(03):138–145(English Edition)

33 Pacini F, Agate L, Elisei R, et al. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic (131)I whole body scan: comparison of patients treated with high (131)I activities versus untreated patients. J Clin Endocrinol Metab 2001;86(09):4092–4097

34 Black EG, Sheppard MC, Hoffenberg R. Serial serum thyroglobulin measurements in the management of differentiated thyroid carcinoma. Clin Endocrinol (Oxf) 1987;27(01):115–120

35 Kim K, Kim WW, Choi JB, et al. Usefulness of dynamic risk stratification in pediatric patients with differentiated thyroid carcinoma. Ann Surg Treat Res 2018;95(04):222–229

36 Rubino C, de Vathaire F, Dottorini ME, et al. Second primary malignancies in thyroid cancer patients. Br J Cancer 2003;89(09): 1638–1644

37 Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. J Clin Endocrinol Metab 2008;93(02):504–515