

Differentiated thyroid cancer is more aggressive in prepubertal children, but the short-term outcomes are similar in prepubertal and pubertal children

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* January 21, 2009. S0022-3476(08)01063-9 [pii];10.1016/j.jpeds.2008.11.059 [doi]

SUMMARY

BACKGROUND Differentiated thyroid cancer is uncommon in children and adolescents. As a result, very young patients tend to be grouped with adolescents and young adults in clinical thyroid cancer studies. Thus, few studies address the differences in presentation and outcome between prepubertal children and adolescents. The aim of this study was to compare the clinical characteristics, course, and outcome of these tumors in prepubertal children and adolescents.

METHODS This is a retrospective study of 10 prepubertal and 17 pubertal patients with differentiated thyroid cancer that was initially diagnosed and treated from 1990 through 2008 at Schneider Children’s Medical Center of Israel. All were treated with total thyroidectomy and postoperative ¹³¹I for remnant ablation or treatment of metastases. Postoperative ¹³¹I therapy was given empirically using doses suitable for adults of 30 to 100 mCi for remnant ablation, 150 mCi for neck or mediastinal lymph-node metastases, and 175 to 200 mCi for distant metastases—modified for children using the following formula: pediatric dose = adult dose × body weight (kg)/70—followed by thyroid-hormone thyrotropin (TSH) suppression to <0.05 μIU/ml. Patients with locoregional or distant metastases were retreated with ¹³¹I. In addition, patients had repeated measurements of body-mass index (BMI). Follow-up at 3 to 6 month intervals consisted of clinical examinations, serum thyroglobulin (Tg) and anti-Tg antibody (TgAb) determinations, neck ultrasonography, chest radiography, and 2 to 5 mCi diagnostic whole-body ¹³¹I scans and TSH-stimulated serum Tg measurements every 6 to 12 months within

the first 2 years after initial therapy. Patients were considered to be free of tumor if the following were present: 2 consecutive negative diagnostic whole-body ¹³¹I scans, undetectable or low serum (<2 μg/L) Tg levels during TSH suppression and stimulation (thyroid hormone withdrawal), and negative neck ultrasonography. Repeated evaluations were performed every 2 years for 4 years and every 5 years thereafter. Recurrent or persistent disease was identified by physical examination or neck ultrasonography and increasing serum Tg levels, with or without positive diagnostic whole-body scans.

RESULTS The study subjects comprised 27 patients less than 17 years of age, of whom 10 (37%) were prepubertal (Tanner stage 1) and 17 (63%) were pubertal (Tanner stage 4 to 5); 30% and 17.5% were males and 70% and 83% were females in the two age groups, respectively. The mean age (±SD) at diagnosis was 9.5±2.2 years (range, 6.1 to 11.5) in the prepubertal group and 14.7±1.7 (range, 12.5 to 17) in the pubertal group. The rate of familial thyroid cancer was higher in the prepubertal group (50%) as compared with the pubertal group (17.5%). Only the pubertal group had one patient with differentiated thyroid cancer associated with familial adenomatous polyposis and another with Cowden syndrome, and a third with exposure to external irradiation. At the time of initial diagnosis, more prepubertal than pubertal patients were symptomatic (60% vs. 41%), and a thyroid lump with enlarged cervical lymph nodes was found more often in prepubertal than pubertal patients (70.5% vs. 29.5%, P = 0.009).

Initial Patient and Tumor Characteristics in Prepubertal and Pubertal Patients

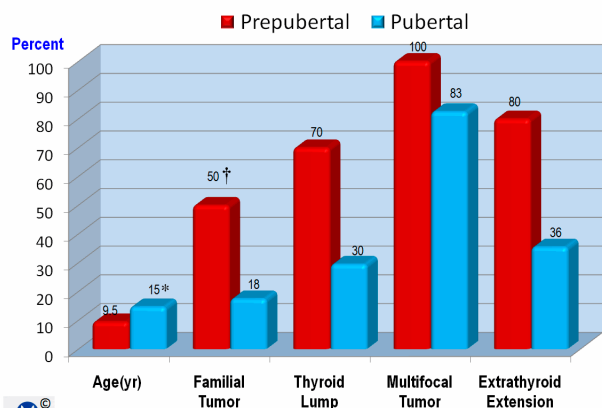


Fig. 1

Figure 1. Patient age and initial tumor characteristics (numbers rounded to integer). *P<0.01, †P = 0.009, comparing prepubertal and pubertal children. This figure and Figure 2 are adapted from data in Table 1 by Lazar et al.

Initial Patient and Tumor Characteristics in Prepubertal and Pubertal Patients

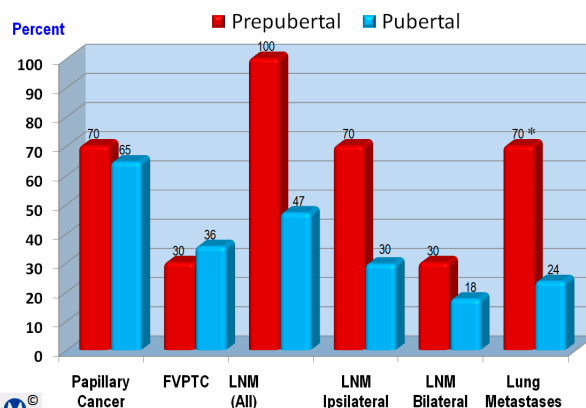
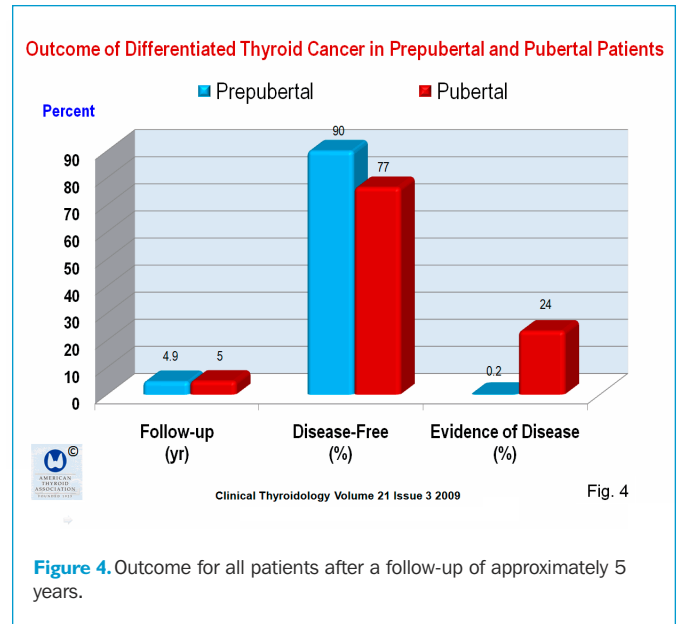
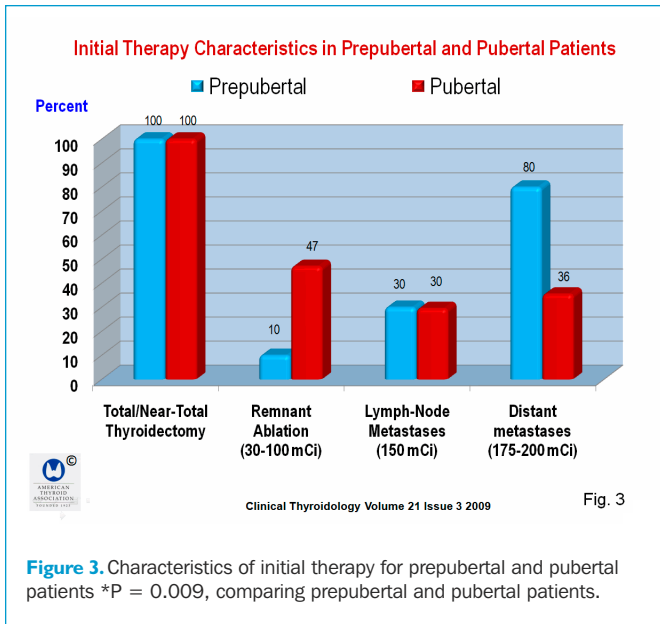


Fig. 2

Figure 2. Initial patient and tumor characteristics. *P = 0.009, comparing prepubertal and pubertal children. PTCFC denotes Follicular variant papillary thyroid cancer, LNM denotes Lymph-node metastases, and All denotes ipsilateral and bilateral lymph-node metastases.



In the prepubertal and pubertal patients, the rates of papillary thyroid cancer (70% vs. 64.5%), follicular variant papillary thyroid cancer (30% vs. 35.5%), average tumor size (1.87 ± 0.77 vs. 1.99 ± 0.94 cm), and the rates of tumor multifocality (100% vs. 82.5%) were not significantly different. However, the prepubertal group had more tumors with extrathyroidal extension (80% vs. 35.5%, $P = 0.012$), more lymph-node metastases (100% vs. 47%, $P = 0.009$) and more lung metastases (70% vs. 23.5%, $P = 0.009$) as compared with the pubertal group (Figures 1 and 2).

All patients had total or near-total thyroidectomy with excision of suspicious lymph nodes. Neck lymph-node dissection was performed in 15 patients (56%) with clinically positive lymph-node metastases. There was no substantial difference in the initial surgery or in the surgical complications in the two groups (transient hypocalcemia in two patients and vocal-cord dysfunction in two patients with very extensive disease at the time of presentation). Prepubertal and pubertal patients were all treated with the adjusted adult equivalents of ^{131}I as follows: 30 to 100 mCi for remnant ablation (10% vs. 47%, $P = 0.025$), 150 mCi for lymph-node metastases (30% vs. 29.5%, $P =$ not significant), and 175 to 200 mCi for lung metastases (60% vs. 23.5%, $P = 0.29$), in prepubertal and pubertal patients, respectively. The actual amount of ^{131}I administered ranged from 10 to 180 mCi on the basis of an adult-equivalent dose. The prepubertal

children, who had more invasive disease, were given an average of 140.9 ± 41.6 mCi of ^{131}I as compared with adolescents who were treated with an average of 80 ± 51.9 mCi ($P = 0.004$). Transient short-term adverse effects of ^{131}I were more common in the prepubertal children; however, mild myelosuppression was documented only in pubertal patients.

After a median follow-up of 5 years, the course and outcome were comparable in the two groups. One year after the initial ^{131}I therapy, 18 patients—7 prepubertal and 11 pubertal (67%)—had a complete remission of tumor, 4 patients (15%) had a partial response with residual locoregional tumor but achieved full remission after a second treatment with ^{131}I , and 4 pubertal patients (40% of the pubertal group) had persistent disease lasting longer than 4.5 to 5 years, 3 of whom developed iodine-non-avid tumors with elevated serum Tg levels in the range of 10 to 90 $\mu\text{g/L}$; 1 patient had locoregional disease in the thyroid bed and 3 had lung metastases. Five patients, 1 prepubertal and 4 pubertal, had a recurrence ranging from 2 to 10 years (median, 3.5) after therapy. The 20-year survival rate was 100% in both groups. During follow-up, the patients had normal growth and their BMI was within the reference range.

CONCLUSION Although differentiated thyroid cancer is more aggressive in prepubertal children, the clinical course and outcomes are similar in prepubertal and pubertal children.

COMMENTARY

Differentiated thyroid cancer in children and adolescents is uncommon, comprising only 1% of all cancers in prepubertal children and 7% in adolescents aged 15 to 19 years (1). However, 20% of thyroid nodules in children are malignant (2), as compared with only about 5% in adults (3). Moreover, children typically have more extensive disease than adults at the time of diagnosis, with approximately 40 to 90%, of children having lymph-node metastases (4) and about 20 to 25% having distant metastases (5,6), whereas the rates of lymph-node metastases in both low- and high-risk papillary thyroid cancers in adults range from 25 to 60%, (7,8) and only about 2% of adults have distant metastases at the time of diagnosis. In addition, tumors are multifocal more often in children than in adults. Yet despite more advanced disease, survival rates for children and young adults with papillary thyroid cancer are generally much more favorable than those in adults. Nevertheless, some children die from progressive disease decades after their initial therapy, some of whom were prepubertal at the time of initial diagnosis (9). The natural history of papillary thyroid cancer is such that many adults reach normal life expectancy after total thyroidectomy and radioiodine therapy (10); however, there are no studies comparing life expectancy of children with papillary thyroid cancer treated with surgery and radioiodine with that of the general population.

Most studies of papillary thyroid cancer in children include adolescents and young adults, making it difficult to know the differences in tumor presentation, diagnosis, treatment, and outcome in patients who are prepubertal at the time of diagnosis, as compared with older children. The study by Lazar et al. is one

of only a few showing that papillary thyroid cancer in prepubertal children has higher rates of extrathyroidal extension, lymph-node metastases and lung metastases at the time of diagnosis as compared with older children. This group of children received aggressive therapy. After 5 years of follow-up, 90% of the prepubertal children and 77% of the pubertal children were free of disease. Still, 24% of the pubertal patients had evidence of persistent disease.

A larger study by Handkiewicz-Junak et al. (11) of 235 children younger than 18 years of age with differentiated thyroid cancer, more than half of whom were younger than 15 years (10% <10 and 41% <15) found after a median follow-up of 6.8 years that total thyroidectomy and adjuvant radioiodine therapy independently decreased the risk for locoregional recurrence in childhood and adolescence. In all, 86% of the children remained free of recurrence and 14% had locoregional recurrence, including tumor in the thyroid bed, and none died of thyroid cancer. Multivariate analysis found that the significant risk factors for thyroid-bed recurrence were less than total thyroidectomy (relative risk, 9.5; $P = 0.04$) and lack of postsurgical radioiodine therapy (relative risk, 11, $P = 0.03$); and the significant factors for lymph-node recurrence were incomplete lymph-node surgery (relative risk, 1.9; $P = 0.02$) and lack of postsurgical radioiodine therapy (relative risk, 3.3; $P = 0.02$). An age of 18 years or less and sex did not correlate with locoregional recurrence. This robust study thus supports total thyroidectomy and postoperative radioiodine therapy for children.

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References

1. Howe HL, Wu X, Ries LA, et al. Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S. Hispanic/Latino populations. *Cancer* 2006;107:1711-42.
2. Hung W. Solitary thyroid nodules in 93 children and adolescents: a 35-years experience. *Horm Res* 1999;52:15-8.
3. Hegedus L. The thyroid nodule. *N Engl J Med* 2004;351:1764-71.
4. La Quaglia MP, Black T, Holcomb GW III, et al. Differentiated thyroid cancer: clinical characteristics, treatment, and outcome in patients under 21 years of age who present with distant metastases: a report from the Surgical Discipline Committee of the Children's Cancer Group. *J Pediatr Surg* 2000;35:955-60.
5. Okada T, Sasaki F, Takahashi H, et al. Management of childhood and adolescent thyroid carcinoma: long-term follow-up and clinical characteristics. *Eur J Pediatr Surg* 2006;16:8-13.
6. Samuel AM, Rajashekhara B, Shah DH. Pulmonary metastases in children and adolescents with well-differentiated thyroid cancer. *J Nucl Med* 1998;39:1531-6.
7. Chow SM, Law SC, Chan JK, et al. Papillary microcarcinoma of the thyroid—prognostic significance of lymph node metastasis and multifocality. *Cancer* 2003;98:31-40.
8. Pereira JA, Jimeno J, Miquel J, et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. *Surgery* 2005;138:1095-1001.
9. Vassilopoulou-Sellin R, Goepfert H, Raney B, et al. Differentiated thyroid cancer in children and adolescents: clinical outcome and mortality after long-term follow-up. *Head Neck* 1998;20:549-55.
10. Links TP, Van Tol KM, Jager PL, et al. Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis. *Endocr Relat Cancer* 2005;12:273-80.
11. Handkiewicz-Junak D, Wloch J, Roskosz J, et al. Total thyroidectomy and adjuvant radioiodine treatment independently decrease locoregional recurrence risk in childhood and adolescent differentiated thyroid cancer. *J Nucl Med* 2007;48:879-88.