Pediatric Patients With Multifocal Papillary Thyroid Cancer Have Higher Recurrence Rates Than Adult Patients: A Retrospective Analysis of a Large Pediatric Thyroid Cancer Cohort Over 33 Years

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Context: Large-sample studies with long-term follow-up data are limited for pediatric patients with thyroid cancer.

Objective: Secular changes in clinicopathological characteristics and outcomes in pediatric patients with thyroid cancer were investigated and compared with those of adults.

Design and Patients: A retrospective review of 150 pediatric patients with thyroid cancer managed between 1980 and 2013 was conducted. The long-term outcomes of 124 patients followed up for 12 months or longer were evaluated. Predictors of recurrence-free survival (RFS) in pediatric patients with papillary thyroid cancer (ped-PTC group) were compared with those of 3071 adult patients.

Results: The proportion of small tumors ($<$1 cm) increased from 9.0% before 2010 to 36.8% after 2010 ($P < .001$); however, neither pathological presentations such as multifocality, extrathyroidal extension (ETE), lymph node (LN) metastasis, or lung metastasis nor the RFS rate changed over time. The 5- and 10-year recurrence rates were 14.5% and 34.4% in pediatric patients, respectively. In respective analyses of the ped-PTC group and patients of all ages with papillary thyroid cancer (all ages group), the rates of ETE, LN metastasis, and lung metastasis were higher with younger age (all P for trend $<.05$). RFS was lower in the pediatric than the adult patients aged 20–54 years ($P < .005$) and was comparable with that of older patients ($\geq$55 y). Only tumor multifocality and size predicted recurrence in the ped-PTC group ($P < .05$), whereas LN metastasis and ETE also predicted recurrence in the all-ages group ($P < .01$). Among patients in the all-ages group with multifocal tumors, pediatric patients had the lowest RFS ($P < .05$).

Conclusions: The pathological characteristics and recurrence rates of pediatric thyroid cancer have not changed over 33 years. Although younger patients present with more advanced disease, multifocality rather than age at diagnosis predicted recurrence. Recurrence was higher in pediatric than adult patients with multifocal papillary thyroid cancer. **(*J Clin Endocrinol Metab* 100: 1619–1629, 2015)**

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Abbreviations: CI, confidence interval; CT, computed tomography; ETE, extrathyroidal extension; FTC, follicular thyroid cancer; HR, hazard ratio; LN, lymph node; MTC, medullary thyroid cancer; NED, no evidence of disease; PDTC, poorly differentiated thyroid cancer; ped-PTC, pediatric patients with papillary thyroid cancer; PTC, papillary thyroid cancer; RAI, radioactive iodine; RFS, recurrence-free survival; RR, recurrence rate; Tg, thyroglobulin; TT, total thyroidectomy; USG, ultrasonography; WBS, whole-body scan; YRR, year recurrence rate.

Although thyroid cancer is far less common in pediatric than adult patients, the incidence of pediatric thyroid cancer has increased gradually both in Korea and throughout the world (1, 2). Thyroid cancer has become the fifth most common cancer in children aged 0–14 years (3) and the most common cancer in adolescents and young adults (2). Cancer screening tests for early detection have been implicated as the cause of the rise in adult thyroid cancer. However, because children and adolescents generally do not undergo such tests, genetic or environmental factors have been suggested as possible causes of the increased incidence of pediatric thyroid cancer (4–6).

Pediatric thyroid cancer tends to be more advanced at the time of diagnosis and has a higher frequency of recurrence than adulthood thyroid cancer (7–9). However, whether the pathology at diagnosis and long-term outcomes differ between children and adolescents remains unclear (10–13).

Furthermore, despite their pathological presentations at advanced stages (9, 14, 15), pediatric patients have a better prognosis and significantly lower mortality rates than adult patients (15–19). These findings suggest that, even in a similarly advanced stage at the time of diagnosis, long-term outcome and prognosis may differ between pediatric and adult patients. Because the prognostic implications of the pathology according to age at diagnosis are unknown, no age-optimized clinical practice guidelines for treatment and monitoring of thyroid cancer in pediatric patients are available (15, 20). The clinicopathological characteristics and outcomes of thyroid cancer in adults were recently published (21). The comparison between pediatric and adult patients with thyroid cancer in this study may help to develop age-optimized management and follow-up guidelines in the future.

We investigated secular changes in the clinicopathological presentation and long-term outcomes of pediatric thyroid cancer according to the age at diagnosis over a 33-year period. We compared the clinicopathological predictors of recurrence-free survival (RFS) between pediatric and adult patients with papillary thyroid cancer (PTC).

Materials and Methods

Subjects

The medical records of 165 pediatric patients (<20 y of age) with thyroid cancer diagnosed between June 1980 and December 2013 at Seoul National University Hospital were retrospectively reviewed. Twelve patients with missing data regarding operative and/or pathological findings and three patients who had undergone cranial irradiation to treat a previous malignancy were excluded from further analysis. Thus, a total of 150 pediatric patients with thyroid cancer (26 male patients) were included in the study. The pathological diagnoses were 131 PTCs, 12 follicular thyroid cancers (FTCs), six medullary thyroid cancers (MTCs), and one poorly differentiated thyroid cancer (PDTC). Clinicopathological characteristics including age, sex, primary tumor size, multifocality, extrathyroidal extension (ETE), and lymph node (LN) and/or distant metastasis at diagnosis were investigated. Next, we assessed the long-term outcomes of 124 pediatric patients (22 male patients; 107 PTCs, 10 FTCs, six MTCs, and one PDTC) who had been followed up for 12 months or longer after surgery. The pediatric patient data were compared with those of 3071 adult patients with PTC (adult PTC group; 484 men, 47.1 ± 12.0 y of age) who underwent thyroid surgery after 1980 and were included in a recently published study (21). Supplemental Figure 1 shows a flow diagram describing the inclusion criteria of pediatric patients according to the duration of follow-up and the disease outcome. This study was approved by the Institutional Review Board of Seoul National University Hospital (number 1306-061-497).

Treatment and follow-up strategy

The treatment and follow-up protocols were previously reported (21, 22). Briefly, all patients underwent total thyroidectomy (TT), subtotal thyroidectomy, or lobectomy. Regional LN dissection was performed in cases of LN metastasis detected by palpation and/or preoperative ultrasonography (USG) or computed tomography (CT) prior to 2003. The use of prophylactic central or anterior neck LN dissection began in 2003 and has been increasingly performed in most patients with PTC of 1 cm or greater in our hospital since 2007. The histological findings were obtained from the patients' clinical pathology reports. Tumor size was based on direct measurements of the surgical thyroid specimens. Each tumor was classified as solitary or multifocal according to whether the number of tumor foci was one or two or more. When multifocal tumors were present, only the maximal diameter of the largest tumor (centimeters) was considered. The presence of lung metastasis was determined using radiological examinations, including ^{131}I whole-body scan (WBS), chest CT, and/or chest X-ray. We recommended postoperative radioactive iodine (RAI) therapy for patients with a large tumor (>1 cm), ETE, LN metastasis, and/or lung metastasis. For physically mature children, activity in the range of 30–100 mCi was prescribed for remnant ablation, and activity of 100–200 mCi was administered for the treatment of cervical or mediastinal LNs and/or distant metastasis. For young children, nuclear physicians modified the activity to be administered on a body weight basis so that the pediatric activity equaled the adult activity given under the same clinical circumstances multiplied by the patient weight in kilograms and divided by 70 (23). The timing and number of doses were individualized according to the patient's clinical circumstances.

After the initial treatment, patients were monitored regularly by clinical examinations, serum thyroglobulin (Tg), and anti-Tg antibody levels, and neck USG. CT, ^{131}I WBS, or positron-emission tomography was performed if indicated. Regular monitoring of Tg levels was initiated in the mid-1990s, and neck USG has been conducted at our institution since 2000. Patients were treated with levothyroxine to suppress serum thyrotropin to an undetectable level for 5–10 years. The biochemical methodologies and commercial kits used changed during the study period, as described previously (21, 22).

Definition of disease outcome

All-cause mortality and thyroid cancer-specific mortality were investigated. The specific mortality from thyroid cancer was obtained from the Statistics Korea National Database for each patient until the year 2013. Median survival period (range) and median disease-free period (range) were calculated. Disease outcome was classified as no evidence of disease (NED) or persistent/recurrent disease. NED was defined as the absence of structural abnormalities on imaging and undetectable Tg levels (suppressed or stimulated) for 12 months or longer until the last follow-up. Among 78 patients with NED, the absence of structural abnormalities was confirmed by neck USG and WBS in 40 patients who underwent radioremnant ablation and by USG in 38 patients who did not undergo radioremnant ablation. Persistent disease was defined as the presence of persistent structural abnormalities from after the initial therapy to the last follow-up (for ≥2 y), and recurrent disease was characterized by the detection of new abnormalities in patients with NED for 12 months or longer after the initial therapy. Recurrence was pathologically confirmed by fine-needle aspiration or surgical excision. Although pathological confirmation was not attained, patients with highly suspicious lesions on imaging modalities such as ^{131}I WBS, CT, or positron-emission tomography were considered to have tumor recurrence. Isolated elevation of the serum Tg level after the initial therapy was not defined as persistent or recurrent disease because the serum Tg level was not routinely monitored in our institution prior to the mid-1990s.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 19.0 (IBM SPSS Statistics). Differences in continuous variables between two groups were analyzed using Student's *t* tests, and one-way ANOVA were performed for groups of three or more. The χ^2 or Fisher's exact test was used to compare categorical variables between two groups, and comparisons of three or more groups were performed using the χ^2 test for linear trend or a logistic regression analysis. Recurrence-free survival plots were constructed using the Kaplan-Meier method, and groups were compared using the log-rank test. The Cox proportional hazard model was used to assess the predictors of RFS. The hazard ratio (HR), 95% confidence interval (CI), and *P* value were reported. Values of $P < .05$ were deemed to indicate statistical significance.

Results

Secular changes in pediatric thyroid cancer clinicopathological characteristics over 33 years

The average age at diagnosis of thyroid cancer was 15.3 ± 3.5 years. Pediatric thyroid cancer was most often detected by symptoms, eg, neck swelling or discomfort and a palpable neck mass (93.3%). The pathological findings were PTC (n = 131, 87.3%), FTC (n = 12), MTC (n = 6), and PDTC (n = 1). The rates of multifocality, ETE, LN metastasis, and lung metastasis were 38.7%, 57.5%, 65.9%, and 14.0%, respectively (Table 1).

Neither the age at diagnosis nor the sex ratio changed significantly over the study period. Female predominance was noted in all time periods. The percentage of PTC cases decreased gradually prior to 2010 (1981–1989, 100%; 1990–1999, 88.8%; 2000–2009, 82.4%; $P = .017$). The proportion of small tumors (<1 cm) increased significantly from 9.0% before 2010 to 36.8% after 2010 ($P < .001$) (Table 1). However, the proportion of small tumors detected by screening USG did not differ between 2000 and 2009 (33.3%) and after 2010 (35.7%). The rates of multifocality, ETE, LN metastasis, and lung metastasis did not differ over time. The proportion of patients who underwent TT ($P < .001$) and LN dissection ($P = .016$) significantly increased over the study period. The proportion of patients who underwent RAI therapy increased marginally ($P = .051$) (Table 1).

No pediatric patients died of causes directly associated with thyroid cancer; however, six deaths occurred from nonthyroidal second primary malignancies (n = 4), brain trauma by accident (n = 1), and septic shock (n = 1). Of the 124 patients followed up for 12 months or longer, 46 (37.1%) were classified as having persistent or recurrent disease: 14 persistent tumors (all PTCs) and 32 recurrent tumors (31 PTCs and one MTC) (Supplemental Figure 1). The 5- and 10-year recurrence rates (YRRs; 5 YRRs and 10 YRRs) of pediatric thyroid cancer were 14.5% and 34.4%, respectively. Although the proportion of patients with recurrent tumors tended to decrease over time, there was no significant decrease in the RFS rate (Figure 1A), and the 5 YRR was 14.3% in 1980–1989, 13.3% in 1990–1999, and 15.6% in 2000–2009.

Clinicopathological characteristics of pediatric thyroid cancer according to age at diagnosis

There were no significant differences in sex or tumor size among the age groups (Figure 1B). Furthermore, the younger the patient at diagnosis, the higher the percentage of PTC ($P = .034$), multifocality ($P = .034$), ETE ($P < .001$), LN metastasis ($P = .049$), and lung metastasis ($P < .001$) (Figure 1, C and D). The proportion of patients who underwent TT, LN dissection, and RAI remnant ablation did not differ by age (data not shown). Although patients younger than 10 years old had the highest percentage of poor outcomes (57.2%), the differences among age groups were not significant (10.0–14.9 years, 36.8%; 15.0–17.9 years, 34.9%; and 18.0–19.9 years, 28.9%) (Figure 2A). The 5 YRRs and 10 YRRs were not significantly different among the pediatric age groups (Figure 2B).

Risk factors associated with persistent or recurrent disease in pediatric patients with differentiated thyroid cancer

Analysis of the 117 patients with differentiated thyroid carcinoma (107 PTCs and 10 FTCs) followed up for 12

Table 1. Clinicopathological Characteristics of PTC According to Time Period

	Total	1981–1989	1990–1999	2000–2009	Post-2010
Patients, n	150	25	36	51	38
Male:female, n (male %)	26:124 (17.3)	3:22 (12.0)	5:31 (13.9)	8: 43 (15.7)	10: 28 (26.3)
Mean age at diagnosis, y (SD)	15.3 (3.5)	15.1 (3.6)	15.4 (4.0)	15.8 (3.2)	14.9 (3.3)
Age group at diagnosis (10, 10–14.9: 15–17.9: 18–19.9 y), n, %	10: 46: 51: 43 (6.7: 30.7: 34.0: 38.7)	2: 8: 9:6 (8: 32: 36: 24)	3: 9: 10: 14 (8.3: 25: 27.8: 38.9)	2: 16: 17: 16 (3.9: 31.4: 33.3: 31.4)	3: 13: 15:7 (7.9: 34.2: 39.5: 18.4)
Pathology type (PTC: FTC: MTC: poorly differentiated), n (%)	131: 12: 6: 1[b] (87.3: 8.0: 4.0: 0.7)	25: 0: 0:0 (100[c]: 0: 0: 0)	32: 2: 2:0 (88.8[c]: 5.6: 5.6: 0)	42: 7: 2:0 (82.4[c]: 13.7: 3.9: 0)	32: 3: 2:1 (84.2: 7.9: 5.3: 2.6)
Mean tumor size, cm (SD)[a]	2.2 (1.2)	2.3 (0.99)	2.5 (1.08)	2.5 (1.3)	1.7 (1.1)
Tumor size (<1: 1.0–1.9: 2.0–3.9: ≥4 cm), n, %[a]	23: 37: 64: 14 (16.7: 26.8: 46.4: 10.1)	2: 7: 11:2 (9.1[d]: 31.8: 50.0: 9.1)	1: 6: 21:1 (3.4[d]: 20.7: 72.5: 3.4)	6: 14: 19: 10 (12.2[d]: 28.6: 38.8: 20.4)	14: 10: 13:1 (36.8[d]: 26.3: 34.2: 2.6)
Multifocality, n, %[a]	53 (38.7)	7 (35.0)	13 (44.8)	20 (40.0)	13 (34.2)
ETE, n, %[a]	65 (57.5)	8 (80.0)	10 (52.6)	25 (54.3	24 (57.9)
LN metastasis, n, %[a]	85 (65.9)	12 (75.0)	23 (71.9)	30 (66.7)	20 (55.6)
Lung metastasis, n, %[a]	21 (14.0)	1 (4.5)	6 (17.6)	9 (18.8)	4 (10.5)
Type of surgery (TT: ST: lobectomy: others), n, %[a]	102: 15: 22:8 (69.4: 10.2: 15.0: 5.4)	7: 10: 7:1 (28.1[d]: 40.0: 28.0: 4.0)	16: 3: 10:6 (45.7[d]: 8.6: 28.6: 17.1)	46: 2: 1:1 (92.0[d]: 4.0: 2.0: 2.0)	33: 0: 4:0 (89.2[d]: 0: 10.3: 0)
LN dissection, n, %[a]	96 (67.1)	12 (50.0)[c]	20 (64.5)[c]	34 (68.0)[c]	30 (78.9)[c]
RAI ablation, n, %[a]	82 (59.0)	9 (40.9)	19 (57.6)	30 (63.8)	24 (64.9)
Outcome[e]					
Median survival period (range)	10.5 (1–32.2)	24.8 (10.5–32.2)	17.7 (10.6–24.0)	7.6 (3.9–13.3)	1.6 (1–3.9)
All-cause mortality[a]	6 (4.9)	5 (20.8)[d]	1 (3.3)[d]	0 (0)[d]	0 (0)[d]
Median disease-free period (range)	10.1 (1–31.)	9.5 (1–31.0)	11.7 (1–24.0)	5.2 (1–13.0)	2.3 (1–4.0)
NED: persistent/recurrent disease, n, %	78: 46 (62.9: 37.1)	9: 13 (40.9: 59.1)[d]	19: 14 (57.6: 42.4)[d]	31: 16 (66.0: 34.0)[d]	19:3 (86.4: 13.6)[d]

Abbreviation: ST, subtotal thyroidectomy.

[a] Missing values; tumor size (n = 12), multifocality (n = 13), ETE (n = 37), LN metastasis (n = 21), distant metastasis (n = 8), type of surgery (n = 3), LN dissection (n = 7), RAI ablation (n = 11), death (n = 28), and outcome (n = 26).

[b] All components of poorly differentiated thyroid cancer (100%) was noted in two patients without concomitant presence of well-differentiated or anaplastic thyroid cancer.

[c] $P < .05$ using χ^2 for trend analysis

[d] $P < .01$ using χ^2 for trend analysis.

[e] Outcome was analyzed in 124 patients who had been followed up for 12 months or longer after surgery.

months or longer revealed that all patients with FTC showed NED, whereas 45 of 107 pediatric patients with PTC (ped-PTC) had persistent (n = 14) or recurrent disease (n = 31). Prognostic factors were evaluated by comparing the NED and persistent/recurrent groups. There were no significant differences in age or sex between the groups. Additionally, no difference in the median disease-free period was found between the NED and persistent/recurrent groups among patients with differentiated thyroid carcinoma or PTC (median 7.2 vs. 5.9 y, respectively). Patients in the persistent/recurrent group had larger tumors (2.6 vs 2.1 cm, respectively; $P = .041$) and significantly higher frequencies of multifocality (68.6% vs 27.5%, respectively; $P < .001$), ETE (80.8% vs 50.9%, respectively; $P = .008$), LN metastasis (88.2% vs 62.1%, respectively; $P = .005$), and lung metastasis (30.8% vs 5.6%, respectively; $P = .001$) than patients in the NED group (Table 2).

We performed an additional analysis of the 107 patients in the ped-PTC group to exclude any confounding effect of FTC. The differences in pathological characteristics were similar; patients in the persistent/recurrent group had larger tumors ($P = .009$) and higher rates of multifocality ($P < 0.001$), LN metastasis ($P = .036$), and lung metastasis ($P = .002$) than patients in the NED group. However, the percentage of ETEs was not significantly different (Table 2). Multivariate logistic regression analysis among patients in the ped-PTC group revealed that only multifocality ($P = .036$) was a significant predictor for persistent/recurrent disease after adjusting for sex, age at diagnosis, primary tumor size, ETE, LN metastasis, and lung metastasis (Supplemental Table 1). Most of the multifocal tumors were macroscopic in the ped-PTC group (93.8%).

Predictors of RFS among pediatric patients with PTC

Because no patient with FTC displayed evidence of disease during follow-up (Table 2), the predictors of RFS were evaluated in the ped-PTC group using Cox proportional hazards models. The 14 patients with persistent disease were excluded from this analysis. After adjusting for sex, age at diagnosis, primary tumor size, LN metastasis, and ETE, only multifocality was marginally related to poor RFS ($P = .061$) (Table 3). After adjusting for sex, age at diagnosis, primary tumor size, and LN metastasis, (ETE was excluded because of several missing values), multifocality (HR 5.4; $P = .005$) and a primary tumor size of 4 cm

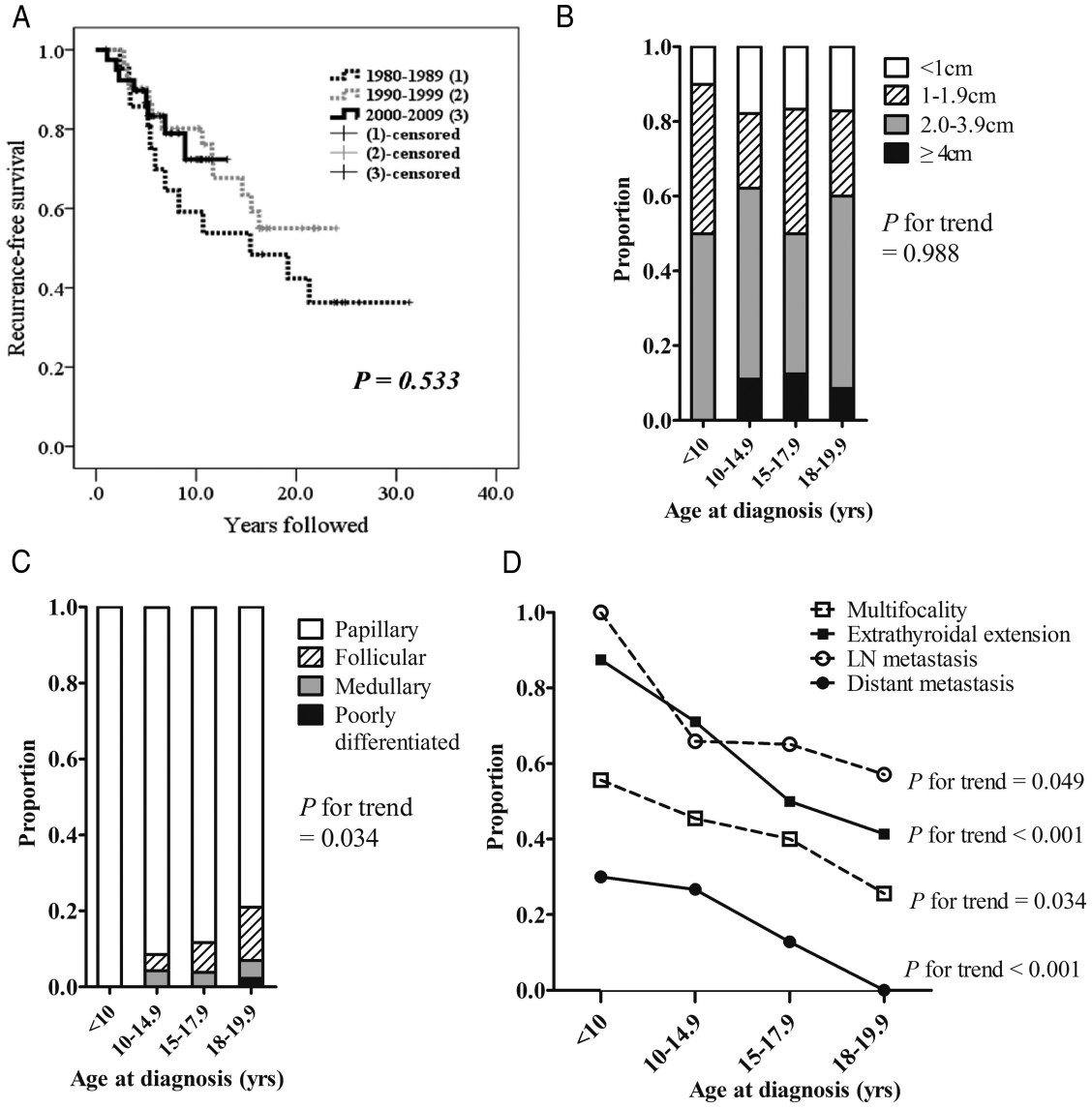

Figure 1. A, Comparison of RFS among pediatric patients with thyroid cancer according to time period. B–D, Clinicopathological characteristics of thyroid cancer according to age at diagnosis (<10.0, 10.0–14.9, 15.0–17.9, and 18.0–19.9 y). B, Primary tumor size (<1.0 cm, white columns; 1.0–1.9 cm, hatched columns; 2.0–3.9 cm, gray columns; and ≥ 4.0 cm, black columns). C, Pathological type of thyroid cancer (papillary, white columns; follicular, hatched columns; medullary, gray columns; and poorly differentiated, black columns). D, Percentage of multifocal tumors (dashed line, open square), ETE (solid line, closed square), LN metastasis (dashed line, open circle), and lung metastasis (solid line, closed circle) according to age at diagnosis.

or greater (HR 11.2; $P = .015$ vs 1.0–1.9 cm) were independently associated with poor RFS (Table 3). The primary tumor size was based on 1.0–1.9 cm because few PTCs of less than 1 cm were detected and reports of recurrent cases prior to 2010 are rare (Table 1).

Clinicopathological characteristics and prognostic factors for RFS in pediatric and adult patients with PTC

Among patients of all ages with PTC, the younger the patient at diagnosis, the higher were the rates of large primary tumors, ETE, LN metastasis (all $P < .001$), and distant metastasis ($P < .01$). Furthermore, the ped-PTC group had a higher incidence of multifocality than the adult-PTC group ($P < .05$). No significant difference in the median survival period was found between the ped-PTC and adult-PTC groups (median 10.6 vs 9.0 years, respectively). Disease-specific mortality increased significantly with the age at diagnosis ($P < .001$) and was not observed in the ped-PTC group (Supplemental Table 2). No significant difference in the median disease-free period was observed between the ped-PTC and adult-PTC groups (median 5.0 vs 4.9 years, respectively). We used the Kaplan-Meier method to construct RFS curves for patients of all ages. Age at diagnosis was significantly predictive of RFS ($P < .001$ using the log-rank test) (Figure 3A), and the

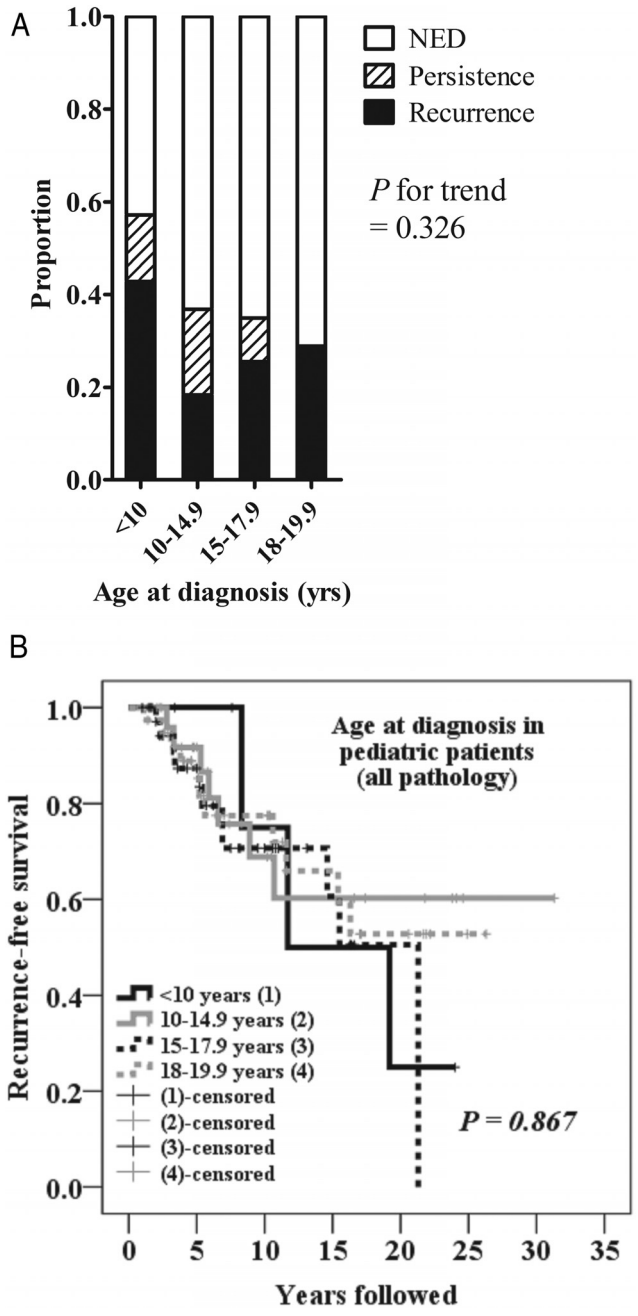

Figure 2. A, Long-term outcomes (NED, white columns; persistent, hatched columns; and recurrent, black columns) according to age at diagnosis. B, Comparison of RFS among pediatric patients with thyroid cancer according to age at diagnosis (<10.0, 10.0–14.9, 15.0–17.9, and 18.0–19.9 y).

RFS of pediatric patients was lower than that of adults aged 20–44 and 45–54 years (all $P < .005$) and comparable with that of adults aged 55 years or older ($P = .077$) (Figure 3A). However, the Cox proportional hazards model showed that a young age at diagnosis was not itself a predictor of recurrence after adjusting for sex, multifocality, primary tumor size, LN metastasis, and ETE (Table 3). Rather, male sex (HR 1.81; $P < .001$), multifocal tumors (HR 1.39; $P = .009$), a primary tumor of 4 cm or greater (HR 1.99; $P < .001$ vs 1.0–1.9 cm), LN metastasis (HR 2.61; $P < .001$), and ETE (HR 1.51; $P = .003$) were significant independent predictors for poor RFS among patients of all ages with PTC (Table 3).

Prognostic implications of pathological characteristics according to age at diagnosis among patients of all ages with PTC

The RFS in pediatric patients with PTC was lower than that in adult patients aged 20–44 and 45–54 years (Supplemental Table 2 and Figure 3A); however, the RFS in these pediatric patients was not worse than expected based on their pathological presentations at advanced stages. This finding suggests that the prognostic implications of pathological presentations at diagnosis differ between pediatric and adult patients. This hypothesis is also supported by the fact that the predictors of RFS in pediatric patients differed from those of patients of all ages (Table 3). Thus, we used the Kaplan-Meier method to construct RFS curves for each pathological presentation according to age at diagnosis. Interestingly, only multifocal tumors were associated with significantly lower RFS in the ped-PTC group compared with patients of all ages (all $P < .05$ compared with each adult group) (Figure 3B). Further analysis of patients with multifocal tumors revealed that the ped-PTC group had a significantly higher incidence of LN metastasis (97.8% vs 47.8%, respectively; $P < .001$), ETE (86.6% vs 61.8%, respectively; $P = .002$), and lung metastasis (25.5% vs 6.1%, respectively; $P < .001$) than did the adult-PTC group. Furthermore, the incidence of macroscopic multifocality was significantly higher in the ped-PTC group than in the adult-PTC group (93.8% vs 65.5%, respectively; $P < .001$). In separate analyses of larger tumors (≥2 cm) (Figure 3C), LN metastasis (Figure 3D), and ETE (Figure 3E), which were the most frequent in pediatric patients, the RFS of the pediatric group was comparable with that of the oldest adult group (≥55 y) and better than or similar to that of adults aged 20–44 and 45–54 years, although not significantly so.

Discussion

The pathological characteristics of pediatric thyroid cancer and long-term outcomes have remained stable over the past 33 years in Korea, although detection of smaller tumors increased after 2010. In contrast to adults (21), recurrence rates (RRs) did not decline over time in pediatric patients with thyroid cancer. A younger age at diagnosis was associated with a more advanced pathological stage at diagnosis, and the RFS was lower in pediatric than adult patients with thyroid cancer. However, among patients

Table 2. Comparison of Clinicopathological Characteristics Associated With Good and Poor Outcomes in Pediatric Patients With Papillary Thyroid Tumors

		NED			Persistent/ Recurrent Disease
	Total	All (PTC + FTC)	PTC	FTC	All PTC
Patients, n	117	72	62	10	45 (14 persistent, 31 recurrent)
Median disease-free period (range)	6.7 (1.0–31.0)	7.2 (1.0–31.0)	7.2 (1.0–31.0)	7.50 (3.0–22.2)	5.9 (1.0–21.0)
Males, n, %	18 (15.4)	11 (15.1)	10 (16.1)	1 (10.0)	7 (15.6)
Mean age at diagnosis, y (SD)	15.4 (3.5)	15.9 (3.2)	15.9 (3.2)	16.2 (3.4)	14.5 (3.9)
Age group at diagnosis (10, 10–14.9: 15–17.9: 18–19.9 y), n, %	7: 35: 40: 35 (4.2: 27.8: 34.7: 33.3)	3: 21: 25: 24 (4.1: 28.8: 34.2: 32.9)	3: 18: 21: 20 (4.8: 29.0: 33.9: 32.3)	0: 2: 4:4 (0: 20.0: 40.0: 40.0)	4: 15: 15: 11 (8.9: 33.3: 33.3: 24.4)
Mean tumor size, cm (SD)	2.3 (1.2)	2.1 (1.0)[a]	2.0 (1.0)[b]	3.0 (1.5)	2.6 (1.2)
Tumor size (<1: 1.0 −1.9: 2.0 −3.9: ≥4 cm), n, %[c]	12: 29: 53: 11 (11.4: 27.6: 50.5: 10.5)	11: 19: 34:6 (15.7: 27.1: 48.6: 8.6)	10: 17: 31:2 (16.7: 28.3: 51.7: 3.3)[a]	1: 2: 3:4 (10.0: 20.0: 30.0: 40.0)	1: 10: 19:5 (2.9: 28.6: 54.3: 14.3)
Multifocality, n, %[c]	43 (41.3)	19 (27.5)[b]	17 (28.8)[b]	2 (20.0)	24 (68.6)
ETE, n, %[c]	50 (60.2)	29 (50.9)[a]	29 (38.7)	0 (0)	21 (80.8)
LN metastasis, n, %[c]	71 (71.0)	41 (62.1)[b]	40 (69.0)[a]	1 (12.5)	30 (88.2)
Distant metastasis, n, %[c]	16 (14.4)	4 (5.6)[b]	4 (5.6)[b]	0 (0)	12 (30.8)
Type of surgery (TT: ST: lobectomy: others), n, %[c]	77: 15: 18:6 (66.4: 12.9: 15.5: 5.2)	49: 9: 11:3 (68.1: 12.5: 15.3: 4.2)	42: 8: 9:3 (67.7: 12.9: 14.5: 4.8)	7: 1: 2:0 (70.0: 10.0: 20.0: 0)	28: 6: 7:3 (63.6: 13.6: 15.9: 6.8)
LN dissection, n, %[c]	77 (70.0)	46 (65.7)	42 (68.9)	4 (44.4)	31 (77.5)
RAI remnant ablation, n, %[c]	70 (60.3)	37 (52.1)[a]	31 (50.8)[a]	6 (60.0)	33 (73.3)

Abbreviation: ST, subtotal thyroidectomy.

[a] $P < .05$ vs persistent/recurrent disease (all PTC).

[b] $P < .01$ vs persistent/recurrent disease (all PTC).

[c] Missing values; tumor size (n = 12), multifocality (n = 13), ETE (n = 34), LN metastasis (n = 17), distant metastasis (n = 6), type of surgery (n = 1), and LN dissection (n = 7).

with PTC in this study, age at diagnosis was not a predictor of RFS in either pediatric patients or patients of all ages after adjusting for pathology. This finding suggests that young age in pediatric patients, unlike older age in adults (24, 25), is not an independent predictor of poor RFS. Interestingly, the prognostic implications of the clinicopathological characteristics differed between pediatric and adult patients; only multifocality and size were predictors of RFS in pediatric patients with PTC, whereas LN metastasis and ETE were also predictors in patients of all ages with PTC. Among patients of all ages with multifocal tumors, pediatric patients had the lowest RFS rate.

A younger age at diagnosis was associated with higher proportions of multifocality, ETE, and LN and/or lung

Table 3. Cox Model Predictors of Recurrence Among Patients With Papillary Thyroid Cancer

	Pediatric Patients With PTC (<20 y old)					Patients With PTC of All Ages	
	Model 1		Model 2			Model 1	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value		HR (95% CI)	*P* Value
Sex (vs females)	1.60 (0.22–11.7)	.646	2.57 (0.54–12.2)	.234	Sex (vs females)	1.81 (1.37–2.38)	<.001
Age group at diagnosis					Age group at diagnosis		
<10 y old	Reference		Reference		<20 y old	Reference	
10.0–14.9 y old	0.65 (0.05–7.93)	.740	0.17 (0.03–1.13)	.066	20–44 y old	0.75 (0.43–1.31)	.304
15.0–17.9 y old	0.76 (0.11–5.36)	.783	0.71 (0.14–3.49)	.673	45–55 y old	0.69 (0.39–1.25)	.223
18.0–19.9 y old	0.83 (0.11–6.23)	.851	0.59 (0.12–2.97)	.523	≥55 y old	1.10 (0.62–1.93)	.765
Primary tumor size					Primary tumor size		
<1 cm	2.23 (0.20–24.4)	.512	1.25 (0.14–11.6)	.844	<1 cm	0.68 (0.44–1.07)	.096
1.0–1.9 cm	Reference		Reference		1.0–1.9 cm	Reference	
2.0–3.9 cm	0.79 (0.20–3.07)	.732	0.94 (0.31–2.85)	.907	2.0–3.9 cm	1.34 (1.01–1.76)	.040
≥4.0 cm	5.51 (0.39–77.7)	.206	11.2 (1.59–78.7)	.015	≥4.0 cm	1.99 (1.36–2.91)	<.001
Multifocal (vs solitary)	3.80 (0.94–15.4)	.061	5.40 (1.67–17.5)	.005	Multifocal (vs solitary)	1.39 (1.09–1.77)	.009
LN metastasis (vs no)	0.83 (0.13–5.21)	.844	0.53 (0.13–2.25)	.387	LN metastasis (vs no)	2.61 (2.01–3.41)	<.001
ETE (vs no)	1.70 (0.33–8.88)	.530	—	—	ETE (vs no)	1.51 (1.15–1.98)	.003

Model 1 included all potential confounders (sex, age group at diagnosis, multifocality, primary tumor size, LN metastasis, and ETE). Model 2 included potential confounders such as sex, age group at diagnosis, multifocality, primary tumor size, and LN metastasis, excluding ETE, which had many missing values among patients diagnosed at younger than 20 years of age.

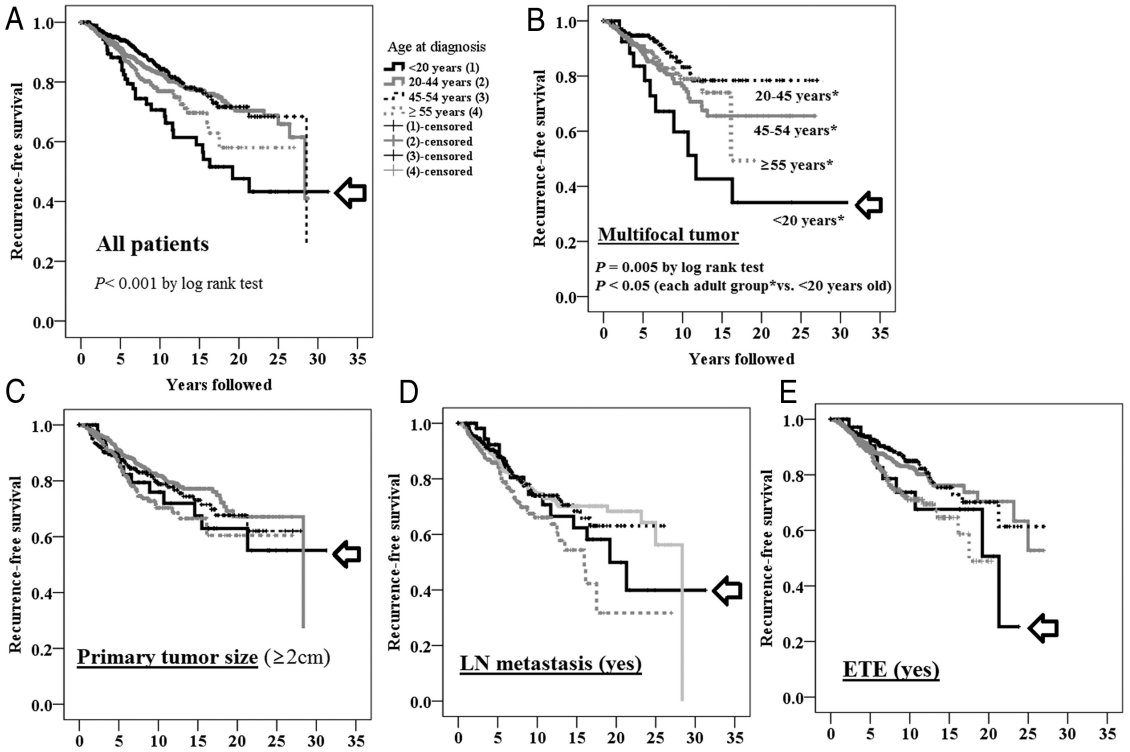

Figure 3. A, Comparison of RFS among patients with PTC of all ages at diagnosis (<20, 20–44, 45–54, and ≥55 y). B–F, Kaplan-Meier RFS curves for each pathological characteristic [B, multifocal tumor; C, primary tumor size of ≥ 2 cm; D, LN metastasis (yes); and E, ETE (yes) according to age at diagnosis (<20, 20–44, 45–54, and ≥55 y)]. The arrow in each panel indicates the RFS curves in the pediatric patients (<20 y).

metastasis among pediatric patients (Figure 1D). The reason for this is unclear; however, our findings are consistent with those of previous studies (10, 13, 19, 26). One reason may be that because the thyroid volume is smaller in young children than in older children and adolescents, a similarly sized small tumor could extend beyond the thyroid capsule and invade adjacent tissues and neck LNs. Genetic factors may also contribute to advanced disease at diagnosis, although distinct gene expression profiles have not been identified for various age groups (9).

An important aspect of having an advanced stage at diagnosis in pediatric patients with PTC is its association with the risk of recurrence; however, whether age at diagnosis is an independent predictor of prognosis is unclear. Although higher RRs have been reported in patients diagnosed at younger ages (9, 17, 27, 28), recent studies reported no difference in RRs between prepubertal children and adolescents when rigorous surgery and RAI therapy were conducted (12, 13, 19, 26). In the present study, RRs did not differ according to age at diagnosis in pediatric patients with PTC. After adjusting for clinicopathological characteristics, age at diagnosis was not an independent risk factor for recurrence in pediatric patients or patients of all ages with PTC (Table 3). Accordingly, pathological presentation at an advanced stage, rather than young age, at diagnosis was a predictor of poor RFS. Furthermore, no thyroid cancer-specific mortality was found among pediatric patients who initially presented with advanced disease. These findings differ from reports stating that older age itself is independently predictive of recurrence and associated with a higher risk of death due to tumor recurrence in adult patients with thyroid cancer (24, 25). The relatively good prognosis of pediatric patients despite pathologic presentation at an advanced stage may be explained by the high expression of proteins such as the sodium/iodine symporter, which is involved in iodine metabolism in pediatric cells. These proteins may facilitate the response to RAI therapy and enhance the survival rate (11).

RFS in pediatric patients was not worse than expected based on the advanced disease at diagnosis. Moreover, the multivariate analysis confirmed that tumor multifocality and size were the only significant predictors of recurrence in pediatric patients with PTC; thus, LN metastasis and ETE were not independent predictors of RFS (Table 3). These results differ from those of our all-age-group analysis (Table 3) and previous studies in adults (20, 29). Thus, the prognostic implications of the various pathological characteristics differ between pediatric and adult patients. Interestingly, pediatric patients with multifocal tumors had the lowest RFS among patients of all ages with PTC, whereas the RFS of pediatric patients with a tumor of greater than 2 cm, LN metastasis, or ETE was not significantly lower than that of adults of any age. Although

multifocality has been identified as an important risk factor for recurrence or poor outcomes in several adult studies (30–32), the American Thyroid Association does not routinely recommend RAI therapy for patients with multifocal tumors, in contrast to their recommendations for patients with LN metastasis or ETE (20).

Multifocal PTC appears to develop from discrete tumor foci bearing independent clonal origins rather than intrathyroidal spread of foci with identical clonal origins (31, 33). Additionally, discordant heterogeneous BRAF mutation patterns were found in approximately 40% of the multifocal PTCs in adults of one study (34). Although pediatric patients who have metastatic multifocal tumors at diagnosis are at the greatest risk of recurrence (17, 35), the prognostic implications of multifocal tumors in pediatric patients remain unclear. Multifocal tumors initially presented with LN metastasis (97.8%), ETE (87.2%), and lung metastasis (25.5%) in our pediatric patients with PTC, suggesting occult lymphatic spread.

An interesting and important point in our study is that most multifocal tumors were macroscopic in the ped-PTC group (93.8%), in contrast to those in the adult-PTC group (65.5%). This may explain why pediatric patients with multifocal PTC showed higher recurrence rates than adult patients. In a recent study, a primary tumor size of 1 cm or greater was significantly associated with disease persistence/recurrence in patients with multifocal PTC (30). In another study, multifocality was an independent predictor of disease persistence/recurrence in patients with macroscopic PTC but not in patients with papillary thyroid microcarcinoma (36). Therefore, a careful treatment and follow-up approach should be considered for pediatric patients with multifocal PTC.

Unlike previous reports of an increasing rate of small tumors (<1 cm) among adults during a 30-year period (21), pediatric patients did not show a definite decrease in tumor size prior to 2010, and the proportion of small tumors (<1 cm) only recently increased to 36.8% after 2010. The more frequent diagnosis of small tumors since 2010 does not appear to be related to an increase in early cancer screening because the proportion of small tumors (<1 cm) detected using USG screening did not change after 2010 compared with the years 2000–2009. Thus, health screening had little, if any, effect on the increased incidence of pediatric thyroid cancer in Korea (2). Rather, the decrease in tumor size since 2010 may have resulted from detection by more careful palpation performed due to increased concerns of thyroid nodules and cancer. With the exception of a slight nonsignificant decrease in the rate of LN and/or lung metastasis after 2010, the pathological stage at diagnosis of pediatric thyroid cancer has been consistently advancing. This situation differs from the decreasing severity in the state at diagnosis reported for adult thyroid cancer in Korea and other countries (21).

Despite the consistently advanced pathological stage at diagnosis and increasing rates of TT, LN dissection, and/or RAI ablation therapy, the long-term prognosis of pediatric thyroid cancer did not improve until 2010. The 5 YRR was calculated and its secular trend was compared between pediatric and adult patients. Whereas the 5 YRR of adult patients steadily decreased (10.6% in 1980–1989, 7.1% in 1990–1999, and 5.9% in 2000–2009) (21), the 5 YRR of pediatric patients did not improve (14.3% in 1980–1989, 13.3% in 1990–1999, and 15.6% in 2000–2009). Because the number of patients followed up for 10 years or longer was relatively low over the 33-year period of our study, it is difficult to ascertain long-term outcomes. The number of pediatric patients who underwent long-term follow-up was too small to prove a significant improvement in RFS according to the time period. Additionally, the higher rate of large tumors (≥4 cm) detected from 2000 to 2009 may have affected the absence of a decline in the RRs over time. Moreover, diagnostic advances leading to the early detection of recurrence likely offset the improvements in treatment modalities. Although the rates of multifocality and LN metastasis were consistently high over time, as mentioned above, these rates slightly decreased after 2010 in pediatric patients. Therefore, further analysis is warranted regarding whether the 5 YRR of pediatric patients diagnosed with PTC after 2010 will decrease.

Our retrospective study has certain limitations. Several patients with missing pathology, treatment, and outcome data were excluded from some analyses. Referral bias is another possible limitation because the mix of patients at a tertiary medical center differs from that of the general population. Patients who developed recurrence after initial management may be preferentially referred to tertiary medical centers. Nonetheless, because previous data on patients with pediatric thyroid cancer are relatively limited (11, 17, 28, 37), the large sample size of this cohort and its long-term follow-up are noteworthy. Furthermore, this study was strengthened by its suggestions of predictors of long-term outcomes in pediatric patients with PTC compared with adult patients with PTC; such information provides the clinician with practical implications such that pediatric patients with multifocal PTC should be carefully managed and followed up. This study will contribute to and facilitate the construction of a pediatric-specific staging system in the future.

In conclusion, neither pathological presentations nor long-term outcomes of pediatric PTC have changed significantly over the past 33 years in Korea. Although younger patients present with more advanced disease at

diagnosis, multifocality rather than young age at diagnosis is predictive of recurrence. Moreover, recurrence is higher in pediatric than in adult patients with multifocal tumors, suggesting the necessity of careful treatment and follow-up for pediatric patients with multifocal PTC.

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