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Follicular thyroid cancer in children and adolescents: clinicopathologic features, long-term survival, and risk factors for recurrence

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Abstract. Children and adolescents represent 1–1.5% of all patients with thyroid cancer (TC). The vast majority of TC in children and adolescents is papillary TC; follicular TC (FTC) is exceedingly rare. In this study, we evaluate the clinical and pathological features of FTC in children and adolescents. We also report the risk factors for post-operative tumor recurrence and the associated outcomes. Twenty children and adolescents (under 21 years old) with FTC have been treated and followed at Noguchi Thyroid Clinic and Hospital Foundation since 1946. All patients underwent surgery (lobectomy, 11; subtotal thyroidectomy, 8; and total thyroidectomy, 1), and 8 patients received postoperative external beam radiation therapy. The incidence of FTC in children and adolescents was 1.9% among all FTC patients treated in our hospital. Histopathology revealed vascular and capsular invasion in 9 and 20 patients, respectively. The tumor recurrence rate in FTC with vascular invasion is significantly higher than in those without it ($p = 0.038$). No other factors were significant. Patients with recurrences were treated with completion thyroidectomy and ^{131}I radioactive iodine therapy. There were no significant differences in the rates of disease-free survival or cause-specific survival when pediatric/adolescent FTC patients were compared to adults with FTC. FTC is very rare among children and adolescents, but the outcomes are similar to those observed among adults. Vascular invasion is poor prognostic indicator in pediatric/adolescent FTC patients.

Key words: Follicular thyroid cancer, Children, Adolescents, Risk factors, Prognosis

THYROID CANCER is rarely found in pediatric or adolescent patients, and the incidence is reported to be 2.6–12.9% of all thyroid cancer patients [1-9]. The most common subtype is papillary thyroid cancer (PTC), followed by follicular thyroid cancer (FTC), which is exceedingly rare in children and adolescents. The diagnosis of FTC requires the involvement of blood vessel, capsular invasion in resected specimens and/or the existence of distant metastasis [10, 11]. Previous reports have identified the prognostic factors for FTC as age, gender, and the degree of invasion. Infiltration beyond the tumor capsule and/or tumor vessel can be used to predict outcomes among patients with FTC [12-19].

Many reports concerning the clinical features and prognosis of thyroid cancer in children and adolescents have focused on patients with PTC. Radiation-induced thyroid cancer has been investigated extensively among children who survived the Chernobyl radiation crisis, most of whom suffered from PTC. However, there are only a few reports of FTC occurring in children and adolescents [20, 21]. Zou *et al*. [20] reported on 2 children with minimally invasive FTC who were treated by lobectomy and subtotal thyroidectomy, respectively. Kim *et al*. [21] reported a pediatric case of solitary lytic skull metastasis from an FTC. After excision of the metastasis, the patient underwent total thyroidectomy and radioiodine ablation therapy. To the best of our knowledge, this is the first study to present the clinical and pathological features, as well as the long-term outcome and risk factors for post-operative tumor recurrence among children and adolescents with FTC.

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Materials and Methods

During the period from January 1946 to December 2005, a total of 1070 FTC patients were treated at

Noguchi Thyroid Clinic and Hospital Foundation, and patients of children and adolescents (<21 years old) were extracted from the database of the hospital. An expert pathologist histologically confirmed the diagnosis of FTC in all children and adolescents. Follicular thyroid tumors with capsular invasion, vascular invasion and/or remote metastasis were diagnosed as follicular carcinomas exclusive of papillary carcinomas and nodular goiters. Capsular invasion and vascular invasion were defined according to the widely accepted histologic criteria [22]. In the WHO blue book, capsular invasion is defined by tumor penetration through the tumor capsule unassociated with the site of a previous fine needle aspiration biopsy and vascular invasion is defined by the presence of intravascular tumors cells either covered by endothelium or associated with thrombus in the vessels within or beyond the tumor capsule [23]. Follicular carcinomas with and without macroscopically discernable capsular invasion were subdivided into widely and minimally invasive, respectively. The medical records were reviewed with respect to age; gender; serum thyroglobulin levels (ng/dL); initial surgical procedure (lobectomy, subtotal thyroidectomy, or total thyroidectomy); postoperative external radiation therapy; postoperative TNM staging (UICC) [24]; maximum diameter of the tumor (mm); the existence of vascular invasion and/or capsular invasion; tumor multifocality; pathological lymph node metastasis; familial history of thyroid cancer; history of neck irradiation; and prognosis.

In patients with tumor recurrence, we calculated the time from the date of the initial operation to the date when the recurrence was first identified. All statistical analyses were performed using JMP 5.1.1 statistical software (SAS Institute, Cary, NC). Kaplan–Meier curves of disease-free survival (DFS) and cause-specific survival (CSS) were drawn in 19 FTC patients excluding 1 patient with concomitant occurrence of PTC from the date of initial operation to the date of cause-specific death or last contact. The rates of DFS and CSS for children and adolescents with FTC were compared to those of the 315 consecutive younger adult patients (aged between 21 and 44) and 505 older adults patients (aged 45 and over) with FTC excluding 32 and 178 patients with concomitant occurrence of PTC treated at our hospital during the same period.

The candidate risk factors for tumor recurrence were compared between patients with and without tumor recurrence using the χ^2-test or Student's *t*-test. A value of $p < 0.05$ was considered statistically significant for all analyses.

Results

The incidence of FTC in children and adolescents was 1.9 % (20 children and adolescents) among all 1070 FTC patients included in the study. Table 1 shows the characteristics and initial treatment of all children and adolescents with FTC. The average age was 17.3 ± 2.7 years (median, 18 years; range, 11–20 years). Two patients were male; 18 were female (male/female ratio, 1:9). The mean follow-up period was 23.7 ± 13.3 years (median, 23.5 years; range, 7–52 years). The serum thyroglobulin value before surgery was measured in only 10 patients because this assay was not available for the 10 patients operated upon prior to 1980. Thyroglobulin (Tg) levels ranged from 16 ng/dL to 11 × 10^6 ng/dL. All patients were initially treated surgically (lobectomy, 11; subtotal thyroidectomy, 8; and total thyroidectomy, 1), and 8 patients underwent postoperative external radiation therapy. Completion thyroidectomy with ^{131}I ablative therapy and TSH suppression therapy were not performed in any of patients. The pathological examination revealed lymph-node metastasis in 1 patient. The average tumor diameter was 27.9 ± 21.9 mm (range, 2–85 mm). Comparisons of above clinicopathological parameters in adults were seen in Table 2. The follow-up periods in older adults were significantly shorter than that in children and adolescent (<0.001). Other factors were not statistically significant. Histopathological analysis revealed vascular invasion and capsular invasion in 9 and 20 patients, respectively. Minimally invasive FTC was found in 16 patients, and widely invasive FTC was found in 4 patients. Tumor recurrence was not found in 5 patients with widely invasive FTC.

Tumor recurrence was observed in 3 patients (Table 3). The recurrences were found in lung (n = 1), bone (n = 1), thyroid remnants (n = 2), neck lymph nodes (n = 1) and an unknown area of the neck (n = 1). Patients with recurrences were treated with completion thyroidectomy with/without lymph node dissection and ^{131}I radioactive iodine therapy. The details of the treatment for 1 patient with a recurrence were not clear because the treatment was performed at another hospital. Presently, all patients from the study are alive. The DFS and CSS in children and adolescents with FTC excluding 1 patient with concomitant occurrence of PTC were

94.7% and 100% at 10 years, 75.4% and 100% at 20 years, and 62.8% and 100% at 30 years, respectively. There were no significant differences in DFS or CSS between pediatric/adolescent and younger adult FTC patients (Fig. 1A, $p = 0.166$, $p = 0.379$, respectively), and pediatric/adolescent and older adult FTC patients (Fig. 1B, $p = 0.371$, $p = 0.162$, respectively).

The clinical features and treatment of children and adolescents with FTC are summarized in Table 4. The patients with and without recurrence were similar in terms of age (15.0 ± 3.0 years *vs*. 17.6 ± 2.5 years, $p = 0.116$). The male/female ratio and the history of neck irradiation were also similar in both groups ($p = 0.144$, $p = 0.144$). One patient without recurrence

Table 1 Characteristics and initial treatment of the 20 pediatric patients with FTC

Case	Age/Sex	Tg (ng/mL)	Initial surgery	Supplemental treatment	pTNM (UICC)	Size (mm)	Capsular invasion	Vascular invasion	Degree of invasion
1	11 / F	20	Subtotal thyroidectomy	-	T1N0M0	3	Yes	No	MI
2	12 / F	-	Lobectomy	-	T2N0M0	36	Yes	Yes	MI
3	14 / F	-	Subtotal thyroidectomy	-	T1N0M0	2	Yes	No	MI
4	15 / F	120	Lobectomy	-	T2N0M0	48	Yes	No	MI
5	15 / F	-	Subtotal thyroidectomy	ERT	T2N0M0	25	Yes	Yes	MI
6	16 / F	235	Lobectomy	ERT	T3N0M0	85	Yes	No	MI
7	16 / F	-	Subtotal thyroidectomy+CND	ERT	T1N1aM0	20	Yes	No	MI
8	18 / F	248	Lobectomy	-	T3N0M0	49	Yes	Yes	MI
9	18 / F	37	Subtotal thyroidectomy	-	T3N0M0	34	Yes	Yes	WI
10	18 / F	2250	Lobectomy	ERT	T2N0M0	23	Yes	Yes	WI
11	18 / F	68	Lobectomy	-	T2N0M0	25	Yes	No	MI
12	18 / M	-	Lobectomy	ERT	T1N0M0	19	Yes	Yes	MI
13	19 / F	216	Subtotal thyroidectomy	-	T1N0M0	17	Yes	No	MI
14	19 / F	16	Lobectomy	-	T1N0M0	2	Yes	No	MI
15	19 / F	-	Lobectomy	-	T3N0M0	75	Yes	Yes	WI
16	19 / F	$11x10^6$	Total thyroidectomy	ERT	T1N0M0	15	Yes	No	MI
17	20 / F	-	Lobectomy	ERT	T1N0M0	20	Yes	No	MI
18	20 / F	192	Subtotal thyroidectomy	-	T2N0M0	33	Yes	Yes	WI
19	20 / F	231	Subtotal thyroidectomy	-	T1N0M0	12	Yes	No	MI
20	20 / M	5250	Lobectomy	ERT	T3N0M0	44	Yes	Yes	MI

ERT; external radiation therapy, MI; minimally invasion, WI; widely invasion, CND; central node dissection

Table 2 Comparison of clinicopatholocical characteristics of FTC patients according to age

Factors	Children and Adolescents (<21 years)	Younger Adults (21-44 years)	*p* value	Older Adults (45 ≤ years)	*p* value
No. of patients	20	367		683	
Age	17.3±2.7	35.1±6.5	<0.001	58.5±9.1	<0.001
Follow-up periods (years)	23.7±13.3	21.0±11.9	0.669	12.9±7.8	<0.001
Male gender (%)	2 (10.0)	36 (9.8)	0.978	91 (13.3)	0.831
Tumor diameter (mm)	29.4±22.3	23.0±17.1	0.111	22.4±18.0	0.092

Table 3 Recurrent cases

Case	Foci of recurrence	Treatment	Time to recurrence after initial surgery
2	Thyroid remnant, Bone	CT+RAI	14y4m
5	Neck	NA	6y6m
12	Thyroid remnant, Neck LNs, lung	CT+RAI+MND	24y

CT; completion thyroidectomy, RAI; radioactive iodine therapy, NA; data not available (treated in another hospital), LNs; lymph nodes, MND; modified radical neck dissection

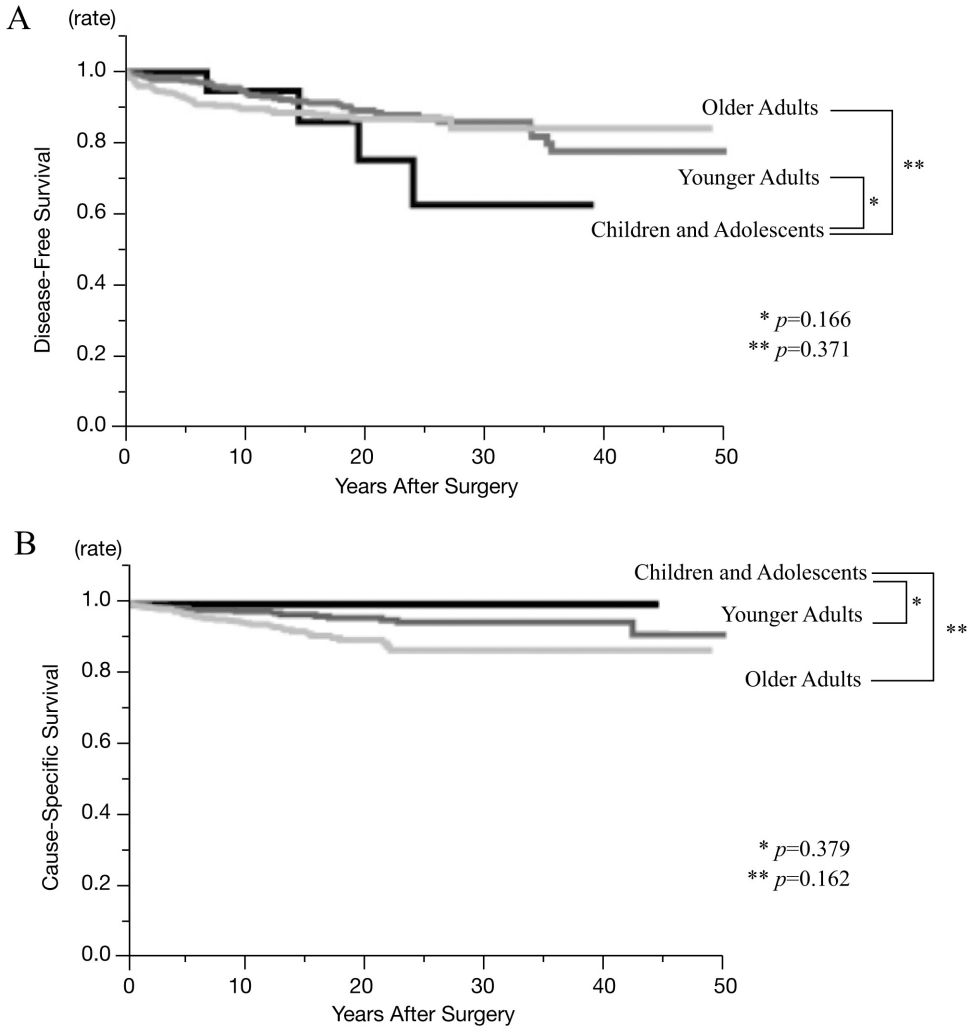

Fig. 1 Overall disease-free survival (DFS) and cause-specific survival (CSS) among patients with follicular thyroid cancer (FTC). FTC children and adolescents were similar to FTC younger adults and older adults in terms of DFS (A, $p = 0.166$ and $p = 0.371$, respectively) and CSS (B, $p = 0.379$ and $p = 0.166$, respectively).

Table 4 Risk factors for tumor recurrence

	Recurrence (n=3)	Non-recurrence (n=17)	*p* value
Age	15.0±3.0	17.6±2.5	0.116
Male Gender	1	1	0.144
History of neck irradiation	1	1	0.144
Family history of thyroid cancer	0	1	0.666
Tumor diameter (mm)	26.7±8.6	28.1±23.6	0.922
Lymph node metastasis (pathologically)	0	1	0.666
Pathology, vascular invasion (+)	3	6	0.038
Degree of invasion, Widely invasion	0	4	0.348
Post-operative ERT	2	6	0.306

ERT; external radiation therapy

had a familial history of thyroid cancer, but none of the patients with tumor recurrence had any family history of the disease ($p = 0.666$). The maximum tumor diameter was 26.7 ± 8.6 mm and 28.1 ± 23.6 mm in patients with and without recurrences, respectively ($p = 0.922$). In the recurrence-free group, multiple cancer was not seen ($p = 0.484$). Lymph-node metastasis was found in 1 patient without recurrence, but not in any of the patients with recurrence ($p = 0.666$). The vascular invasion was significantly higher in patients with recurrence (3 of 3) than in patients without recurrence (6 of 17, $p = 0.038$). Widely invasive carcinoma was found in 4 patients without recurrence but not found in patients with recurrence ($p = 0.348$). Postoperative ERT was performed in 2 patients in the group with tumor recurrence and in 6 patients in the group without recurrence. The postoperative ERT revealed no significant difference between the 2 groups ($p = 0.306$).

Discussion

The vast majority of previous reports of childhood thyroid cancer were case series of PTC patients, with only a small minority of reports documenting childhood FTC [20, 21]. To clarify the clinical features of childhood FTC, it is important to collect a series of pediatric and adolescent FTC patients. Therefore, this study examined the clinical features and outcomes in 20 pediatric and adolescent FTC patients.

Gross or microscopic metastasis to the lymph nodes is more frequent in pediatric than adult PTC patients [7-9]. Childhood PTC is also characterized by a high recurrence rate and a low mortality rate. We recently reported the clinical features and prognostic indicators of PTC in children who had not been exposed to radiation [25]. Younger age, a familial history of thyroid cancer, the existence of lymph-node metastasis at the time of diagnosis, larger tumor diameter, and the presence of capsular invasion were associated with a higher rate of recurrence. The results also showed that the existence of lymph-node metastasis and distant metastasis at the time of diagnosis could predict the survival rate. Unlike PTC, FTC is characterized by infrequent metastasis to the lymph nodes but frequent metastasis through the blood. In the present study population of 20 pediatric FTC patients, 3 exhibited tumor recurrences and no died of the disease. The recurrence rate and the survival rate in children and adolescents were not different from those in adults, even when children and adolescents were compared to subgroup of adults according to age.

The established risk factors for FTC were the degree of invasion, age, gender, tumor diameter, and distant metastasis at the time of diagnosis [12-19]. It is well known that widely invasive FTC has a worse prognosis than minimally invasive FTC [12-16]. In our series, widely invasive FTC and minimally invasive FTC were seen in 4 and 16 patients, respectively. None of 4 patients with widely invasive FTC experienced a recurrence, but tumors recurred in 3 of the 16 FTC patients with minimal invasion. For a valid conclusion, screening of a larger number of pediatric and adolescent FTC patients will be necessary.

A higher rate of distant FTC metastasis to the lung and bone is associated with vascular invasion as opposed to capsular invasion [18, 19]. Our data in children and adolescent similarly showed that the recurrence rate was higher in FTC with vascular invasion than in FTC without it. Furlan *et al*. [26] reported that vascular invasion did not affect short-term outcomes or long-term prognoses in 17 patients with angioinvasive and 33 patients with non-angioinvasive FTC (mean follow-up period, 72.3 months). But, their follow-up period may be too short to conclude the importance of vascular invasion. Indeed, the recurrence in our series of children and adolescents was found during 6 to 24 years after initial surgery. Other factors such as male gender and tumor diameter were not associated with tumor recurrence. In this series, only 1 patient (5.0%) had a familial history of thyroid cancer. We previously reported that compared to familial PTC, familial FTC is very rare, [27] and Ito *et al*. [28] reported that there is no evidence that familial FTC is more aggressive or has a worse prognosis than sporadic FTC. Notably, exposure of the neck to radiation is one factor that promotes the risk of thyroid cancer [29-31]. In this series, a history of neck irradiation was present in 2 patients (10.0%) but was not associated with tumor recurrence.

Completion thyroidectomy and subsequent ^{131}I ablative therapy may decrease recurrence and mortality rates by eradicating microscopic residual postoperative tumor foci and facilitates the early detection of recurrence based on serum thyroglobulin measurement and ^{131}I total body scans. Mazzafferi *et al*. reduced recurrence and mortality rates by adapting the total thyroidectomy to incorporate postoperative ^{131}I ablative therapy in the treatment of DTC patients with-

out distant metastasis at the time of surgery [32, 33]. Sampson *et al*. advocated that patients presenting with metastatic disease should be managed aggressively with total thyroidectomy followed by radioactive iodine treatment [34]. However, completion thyroidectomy following ^{131}I ablative therapy requires the patient to commit to levothyroxine supplementation for the rest of the patient's life. This approach also carries the risk of surgical complications such as recurrent laryngeal nerve palsy and postoperative hypoparathyroidism. The impairment of growth and development is of primary concern when evaluating the likelihood that young patients will comply with levothyroxine treatment. Poor compliance will also negatively influence gastroenteric function. Importantly, longstanding hypothyroidism in childhood may induce mental retardation [35-37]. Therefore, completion thyroidectomy and ^{131}I ablative therapy with levothyroxine supplementation should be limited to high-risk group children such as vascular invasion-positive children or children with postoperative high thyroglobulin levels.

Conclusions

FTC in children and adolescents is very rare. The outcome of FTC in children and adolescents is not different from that in adults. In FTC in children and adolescents with vascular invasion, the tumor recurrence rate is significantly higher than in those without vascular invasion.

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