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Prevalence and Prognosis of Familial Follicular Thyroid Carcinoma

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Abstract. Although the responsible gene has not yet been identified, patients with differentiated thyroid carcinoma, including papillary and follicular carcinomas, demonstrating a family history have been reported and patients having one or more family members with differentiated carcinoma among their first-degree relatives are designated as having familial nonmedullary thyroid carcinoma (FNMTC). In this study, we investigated the biological characteristics, including prognosis, of familial follicular carcinoma. Three hundred and nineteen patients who underwent initial surgery for follicular thyroid carcinoma between 1987 and 2004 who were enrolled in this study. Of these 319 patients, 6 patients (1.9%) in 6 families were classified as having familial follicular carcinoma based on the criteria described above. The incidence of aggressive characteristics such as male gender, age 45 years or older, poor differentiation, widely invasive carcinoma, tumor larger than 4 cm and distant metastasis at diagnosis did not differ between familial and sporadic follicular carcinomas. One patient with familial follicular carcinoma underwent re-operation because of newly detected papillary carcinoma in the remnant thyroid 160 months after the initial surgery, but none of the 6 patients with familial carcinoma showed recurrence or died of follicular carcinoma. We can therefore conclude that FMNTC of the follicular type is very rare and there is no evidence that familial follicular carcinoma is more aggressive or has a worse prognosis than sporadic follicular carcinoma. The therapeutic strategy for follicular carcinoma might depend on conventional prognostic factors such as poor differentiation and distant metastasis at diagnosis, but not on whether the carcinoma is familial or sporadic.

Key words: Follicular carcinoma, Thyroid, Familial, Prognosis

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DIFFERENTIATED thyroid carcinoma consists of papillary and follicular carcinomas. Although papillary carcinoma is easy to diagnose by imaging studies and fine needle aspiration biopsy (FNAB), follicular carcinoma is difficult to diagnose, because its cell morphology is similar to that of follicular adenoma. Papillary carcinoma frequently metastasizes to the lymph node, but its distant metastasis is only occasional. However, follicular carcinoma predominantly metastasizes to the distant organs and its prognosis is worse than that of papillary carcinoma. We previously demonstrated that the prognosis of follicular carcinoma in Japan is better than that reported from many Western countries, but poorly differentiated or widely invasive carcinomas showed a worse prognosis [1]. Therefore, postoperative pathological examination is important to predict patient prognosis.

Differentiated thyroid carcinoma is usually sporadic except for some rare inherited diseases such as familial adenomatous polyposis, Gardner syndrome, and Cowden disease [2, 3]. However, Robinson and Orr first reported nonmedullary thyroid carcinoma in monozygotic twins [4], while increased risk of thyroid carcinoma in individuals with a first-degree relative with thyroid carcinoma has been reported by population studies [5, 6]. The entity of familial nonmedullary

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thyroid carcinoma (FNMTC) was thus established as a diagnosis in patients with one or more affected persons among their first-degree relatives [7], although the responsible genes have yet to be identified. The biological aggressiveness of FNMTC remains controversial and previous studies have investigated the issue in a series of patients that included those with papillary and follicular carcinomas [8–11], even though these two carcinomas demonstrate different characteristics and prognoses. In this study, we investigated the difference in biological characteristics and prognoses of patients with sporadic and familial follicular carcinomas.

Patients and Methods

Patients

Between 1987 and 2004, 319 patients underwent initial surgical treatment for follicular carcinoma at Kuma Hospital. All patients were interviewed to determine whether they had family histories of thyroid carcinoma. Further strategy for histological confirmation was the same as that described by Uchino *et al.* [8]. Six of these patients (1.9%) in 6 families were recognized as having FNMTC because their family histories showed one or more first-degree relatives who underwent surgical treatment for differentiated carcinoma in our hospital or other hospitals. Patients with prior exposure to radiation, coexistence of anaplastic carcinoma, medullary carcinoma, malignant lymphoma, and metastatic carcinoma from other organs were excluded from this study.

Postoperative evaluation of recurrence

We followed patients by ultrasonography once per year to detect any signs of local recurrence. Either chest roentogenography or CT scan was also performed once per year. Median postoperative follow-up periods for familial and sporadic patients averaged 100.3 ± 65.9 and 68.4 ± 44.4 months (average $\pm$ SD), respectively. Median follow-up period of familial patients tended to be longer than that of sporadic patients, but there was no significant difference between the two ($p = 0.0765$).

Statistical analyses

Fisher's exact test was used to compare variables. Kaplan-Meier method and log rank test were adopted to analyze time-dependent variables. Cox-regression model was adopted for multivariate analysis. These analyses were performed using StatView-J 5.0. A p value less than 0.05 was regarded as significant.

Results

Surgical designs and clinical outcomes of 319 follicular carcinoma patients

Table 1 summarizes the surgical designs of follicular carcinoma patients in our series. Subtotal or more limited thyroidectomy was performed in 83.4% of familial and 73.4% of sporadic follicular carcinoma patients, respectively. Furthermore, 83.5% of familial and 87.2% of sporadic carcinoma patients did not undergo lymph node dissection. To date, 33 patients with sporadic follicular carcinoma developed recurrence in various organs as shown in Table 2 and 14 of these patients died of carcinoma. However, none of 6 patients with familial follicular carcinoma showed recurrence or died of follicular carcinoma despite the fact that one patient underwent re-operation because papillary carcinoma was newly detected in the remnant thyroid 160 months after initial surgery. This patient remains alive with no symptoms of further recurrence for 60 months after second surgery.

Table 1. Surgical designs of 319 patients with follicular carcinoma

	Familial (6 patients)	Sporadic (313 patients)
Thyroidectomy		
Total	1 (16.7%)	79 (25.2%)
Near total	0	4 (1.2%)
Subtotal	1 (16.7%)	7 (2.2%)
Lobectomy or partial lobectomy	4 (66.7%)	223 (71.2%)
Lymph node dissection		
Bilateral *MND	0	1 (0.3%)
Unilateral MND	0	18 (5.8%)
Central only	1 (16.7%)	21 (6.7%)
Not done	5 (83.5%)	273 (87.2%)

*Modified radical neck dissection

Table 2. Recurrence in 33 patients (10.3%) with follicular carcinoma

	Familial (0 patient)	Sporadic (*33 patients)
Thyroid	0	1 (2.7%)
Lymph nodes	0	9 (24.3%)
Lung	0	21 (56.8%)
Bone	0	15 (40.5%)
Brain	0	1 (2.7%)
Liver	0	1 (2.7%)
Other organs	0	4 (10.8%)

*10 showed recurrence in two or more organs

Profiles of familial follicular carcinoma patients

Of 319 patients with follicular carcinoma, 6 (1.9%) were diagnosed as having FNMTC. Table 3 summarizes the backgrounds and clinicopathological features of these patients. They consisted of 1 male and 5 females with an average age of 49.0 years (22–79 years). All patients showed well differentiated carcinomas, although one was diagnosed as having widely invasive carcinoma. Patient 2 underwent lymph node dissection in the central compartment because the surgeon intraoperatively considered the possibility of papillary carcinoma. Five patients belonged to families having 2 affected members and the remaining one belonged to a family having 4 affected members. Histology of carcinoma of other affected members for 6 patients was papillary carcinoma (patients No. 1, 2, 3, and 6) or suspected of papillary carcinoma (patients No. 4 and 5). Patient No. 1 underwent re-operation (completion total thyroidectomy and lymph node dissection) because of newly detected papillary carcinoma in the remnant thyroid. However, as indicated above, none of these patients showed recurrence or died of follicular carcinoma.

Difference in clinicopathological features and prognosis between patients with familial and sporadic follicular carcinomas

We then compared clinicopathological features between patients with familial and sporadic follicular carcinomas. Table 4 summarizes the clinicopathological features of familial and sporadic follicular carcinomas. There were no significant differences in gender, age, carcinoma differentiation, minimally or widely invasive, tumor size, distant metastasis at surgery, massive extrathyroid extension accounting for pT4a in the UICC TNM classification [13], and lymph node metastasis between FNMTC and sporadic follicular carcinoma. Although there was no significant difference, none of FNMTC patients were classified as having poorly differentiated carcinoma and none had distant metastasis at surgery, massive extrathyroid

Table 3. Backgrounds and clinicopathological features of 6 patients with familial follicular carcinoma

Patient No.	1	2	3	4	5	6
Gender	Female	Male	Female	Female	Female	Female
Age (years)	39	60	44	50	22	79
Tumor size (cm)	2.8	1.9	6.0	2.5	4.0	4.1
Range of thyroidectomy	Lobectomy	Total	Subtotal	Lobectomy	Lobectomy	Lobectomy
Lymph node dissection	*ND	Central	ND	ND	ND	ND
Carcinoma differentiation	Well	Well	Well	Well	Well	Well
Minimally (M) or widely (W) invasive	M	M	M	M	W	M
Number of affected members	4	2	2	2	2	2
Relationships of other affected members	Sisters	Sister	Father	Mother	Mother	Daughter
pTNM classsification (UICC staging system [13])	T2N0M0	T1N0M0	T3N0M0	T2N0M0	T2N0M0	T3N0M0

*ND; not done

Table 4. Clinicopathological features of familial and sporadic follicular carcinomas

		Familial	Sporadic	Total	p values
Gender	Male	1	55	56	
	Female	5	258	263	>0.9999
Age (yrs)		49.0 ± 17.6	51.3 ± 18.7		0.7224
Differentiation	Poor	0	41	41	
	Well	6	272	278	>0.9999
Minimally or widely invasive					
	Widely	1	56	57	
	Minimally	5	216	221	>0.9999
Tumor size (cm)	>4.0	2	184	186	
	≤4.0	4	129	133	0.2392
Distant metastasis at surgery					
	Yes	0	16	16	
	No	6	297	303	>0.9999
Massive extrathyroid extension					
	Yes	0	6	6	
	No	6	307	313	>0.9999
Lymph node metastasis					
	Yes	0	9	9	
	No	6	304	310	>0.9999

extension or lymph node metastasis.

We then compared the prognoses of patients with FNMTC and sporadic follicular carcinoma. Fig. 1-a compares the Kaplan-Meier curves of disease-free survival (DFS) of patients in these two groups. Five-year and 10-year DFS rates of FNMTC patients were 100%, while those of sporadic carcinoma patients were 88.3% and 73.3%, respectively. Fig. 1-b shows the cause specific survival (CSS) of patients with FNMTC and sporadic follicular carcinoma. Fourteen patients with sporadic carcinoma died of carcinoma and their 5-year and 10-year CSS rates were 96.6% and 90.5%, respectively. Since none of the patients with familial carcinoma showed recurrence or died of follicular carcinoma, p value and risk ratio for the analyses of DFS and CSS were not calculable.

Prognostic significance of conventional clinicopathological features

On univariate analysis, poor differentiation ($p<0.0001$), massive extrathyroid extension ($p = 0.0021$), tumor larger than 4 cm ($p = 0.0268$), and lymph node metastasis ($p = 0.0164$) predicted a worse DFS for patients. Table 5 indicates univariate and multivariate analyses for DFS of patients in our series. On multivariate analysis, only poor differentiation was recognized as an independent prognostic factor for DFS ($p<0.0001$). For CSS, poor differentiation ($p< 0.0001$), distant metastasis at surgery ($p<0.0001$), massive extrathyroid extension ($p = 0.0002$), age 45 years or older ($p = 0.0153$), and tumor larger than 4 cm ($p = 0.0463$) significantly affected patient prognosis on univariate analysis (Table 6). On multivariate analysis, poor differentiation ($p = 0.0030$) and distant metastasis at surgery ($p<0.0001$) independently predicted worse CSS of patients (Table 6).

Discussion

In this study, we demonstrated that 1) the incidence of familial follicular carcinoma was 1.9% and 2) none of these patients with familial follicular carcinoma showed recurrence or died of follicular carcinoma, although one patient underwent completion total thyroidectomy with lymph node dissection due to newly detected papillary carcinoma in the remnant thyroid 160 months after initial surgery. The incidence of familial follicular carcinoma was not discrepant with the findings of another study from Japan [8], indicating that familial follicular carcinoma is more rare than familial papillary carcinoma.

In our series, conventional prognostic factors such as poor differentiation, distant metastasis at diagnosis, patient age and large tumor size [1, 13–20] were

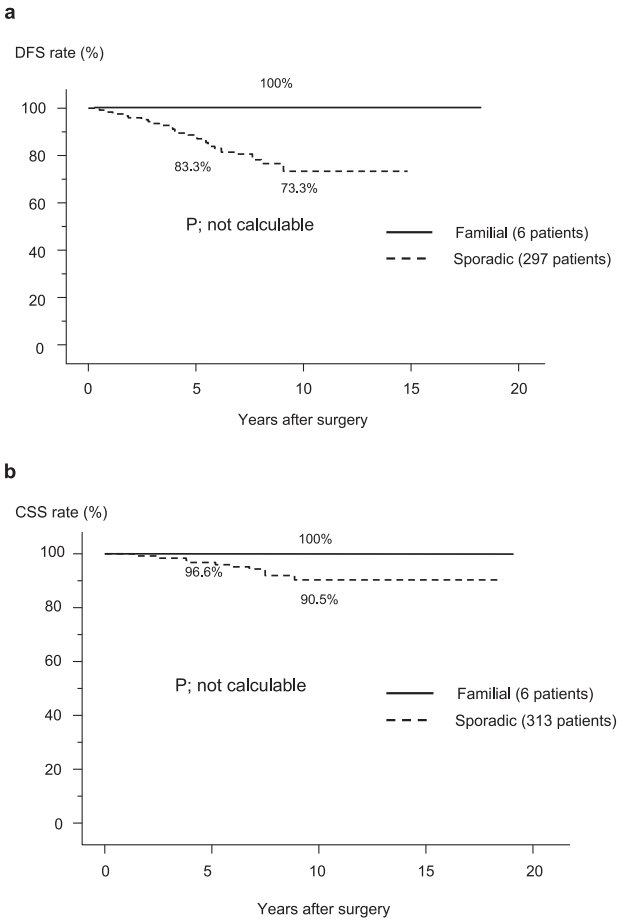

Fig. 1. (a) Kaplan-Meier curves for DFS of familial and sporadic folllicular carcinoma patients. (b) Kaplan-Meier curves for CSS of familial and sporadic papillary carcinoma patients.

recognized as having prognostic impact on univariate and/or multivariate analyses, indicating that our series of follicular carcinoma is suitable for statistical analysis. In this study, familial follicular carcinoma showed even better prognosis than sporadic follicular carcinoma, because none of these patients showed recurrence or died of follicular carcinoma. These six patients did not include any patients with poorly differentiated carcinoma or showing distant metastasis at diagnosis, which independently affected the prognosis of these patients [1]. Furthermore, the incidence of other prognostic factors such as patient age and tumor size did not differ between familial and sporadic carcinomas. Therefore, we can hypothesize that the lack of clinicopathological features significantly affecting patient prognosis is the reason for even better prognosis of familial carcinoma patients in our series.

Table 5. Univariate and multivariate analyses of DFS for clinicopathological features

	Univariate	Multivariate	Risk ratio
Carcinoma differentiation	<0.0001	<0.0001	4.98
pT4a	0.0021	0.6055	1.90
Tumor size (>4 cm)	0.0268	0.0282	2.40
pN	0.0164	0.7140	1.46

Table 6. Univariate and multivariate analyses of CSS for clinicopathological features

	Univariate	Multivariate	Risk ratio
Carcinoma differentiation	<0.0001	0.0030	6.17
Distant metastasis at surgery	<0.0001	<0.0001	13.2
pT4a	0.0002	0.2738	2.64
Age (≥45 years)	0.0153	0.2360	3.60
Tumor size (>4 cm)	0.0463	0.5270	1.59

However, it is not known whether lack of aggressive characteristics of familial carcinoma is merely aleatoric because of the small number of cases or whether these findings indicate the typical character of this type of carcinoma. This issue remains to be elucidated by analyzing larger number of cases in the future.

In contrast to papillary carcinoma, it is difficult to preoperatively diagnose follicular carcinoma by imaging studies and FNAB cytology. Most follicular carcinomas are surgically resected as benign nodules and diagnosed as carcinoma by postoperative pathological examination. Therefore, the initial surgical design is normally hemithyroidectomy, unless there are multiple nodules in both lobes of the thyroid. We previously demonstrated that there were no additional surgical procedures such as completion total thyroidectomy and lymph node dissection for follicular carcinoma unless it shows aggressive characteristics such as poorly differentiated carcinoma and widely invasive carcinoma, because the prognosis of follicular carcinoma without such characteristics is generally good [1]. It remains debatable whether additional surgery after hemithyroidectomy should be performed after pathological diagnosis of follicular carcinoma if the patient has a family history of differentiated carcinoma in first-degree relatives. After postoperative pathological diagnosis of FNMTC, completion

total thyroidectomy may be a strategy, since one patient showed the novel appearance of papillary carcinoma in the remnant thyroid. However, since this patient remains alive after the second surgery with no symptoms of recurrence, it might be appropriate to just follow patients with family history after hemithyroidectomy, unless the carcinoma shows any of the aggressive characteristics indicated above. If carcinoma has aggressive characteristics, completion total thyroidectomy is recommended regardless of whether the disease is familial or sporadic.

In this study, we failed to find any evidence that familial follicular carcinoma is more aggressive or shows a worse prognosis than sporadic follicular carcinoma. Therapeutic strategy for follicular carcinoma might depend on conventional prognostic factors such as carcinoma differentiation, range of invasiveness and distant metastasis at surgery, but not whether there is a family history of differentiated carcinoma.

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