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ORIGINAL SCIENTIFIC REPORT

Should Total Thyroidectomy Be Recommended for Patients with Familial Non-medullary Thyroid Cancer?

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Abstract

Background It is unknown whether familial non-medullary thyroid cancer (FNMTC) has more aggressive clinical features and a worse prognosis than sporadic non-medullary thyroid cancer (SNMTC).

Methods We retrospectively reviewed 2894 patients with differentiated thyroid cancer who underwent primary thyroidectomy, identified 391 FNMTC cases, and compared the prevalence, surgical extension, and clinicopathologic features of FNMTC and SNMTC.

Results A family history of thyroid cancer was noted in 391 patients (13.5%), with 85% having two affected relatives and 15% with ≥3 affected relatives. A sibling was affected in 52.9% of cases, and in 47.1%, both parent and child were affected. There were no significant between-group differences in sex, age, tumor size, extrathyroidal extension, or central lymph node metastases. Significantly more patients with FNMTC exhibited multifocal disease ($p = 0.020$) or benign nodules ($p = 0.015$). Lateral neck lymph node metastases were noted in 6.6% (SNMTC) and 9.7% (FNMTC, $p = 0.021$) of patients. Multifocality and combined benign masses were more frequently observed in patients with FNMTC in multivariate analysis. In the FNMTC group, seven experienced disease recurrence, with no mortality noted during follow-up.

Conclusions FNMTC is not more aggressive than SNMTC; however, FNMTC should be treated with total thyroidectomy because of the increased disease multifocality and the presence of benign nodules. Lateral neck lymph node metastases were more likely in patients with FNMTC, although we could not estimate prognosis. All patients with thyroid cancer should be checked for family disease history and undergo preoperative ultrasonography to determine the extent of node dissection and the need for total thyroidectomy.

Introduction

Thyroid cancer is the most common cancer in the USA [1] and South Korea [2], and its incidence is increasing. More than 40,000 cases of thyroid cancer are diagnosed every year in South Korea [2]. Most are non-medullary thyroid cancer (NMTC), originating from the follicular cells of the thyroid gland. NMTC accounts for >95% of all thyroid cancers in Korea. Most cases occur sporadically, and ~3–10% cases have a family history of NMTC [3, 4].

Familial NMTC (FNMTC) was first identified in twin sisters in 1955 [5]. FNMTC is a follicular cell thyroid cancer with a family history of two or more first-degree relatives, without another familial syndrome, and without

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exposure to environmental thyroid carcinogens [4, 6]. FNMTC frequency is 9.6–11.5% in Korea [7, 8]. There are many reports on the clinicopathologic features and prognosis of FNMTC. However, it is unknown whether patients with FNMTC experience more aggressive disease and more frequent recurrence than those with sporadic non-medullary thyroid cancer (SNMTC) [4, 6, 9–14].

We compared the clinicopathologic features of FNMTC and SNMTC at a single institution to determine whether FNMTC was associated with more aggressive disease and more invasive treatments than SNMTC.

Materials and methods

Patients

We retrospectively examined 2894 patients who underwent thyroidectomy for differentiated thyroid carcinoma (DTC) by a single surgeon at Ulsan University Hospital (IRB 2011-04-041). No patient had a history of thyroid surgery, and all underwent total or hemi-thyroidectomy and central lymph node dissection, with or without lateral lymph node dissection, according to lateral neck lymph node metastasis. Central cervical lymph node dissection was performed in all patients. All patients were questioned regarding family history and had no radiation history or other familial cancer syndromes. Since all patients were referred for surgery after PTC was diagnosed, it was unknown whether these patients were diagnosed by screening or surveillance.

These patients were classified into two groups. Patients without a family history of DTC were assigned to the SNMTC group, whereas those with two or more first-degree affected relatives with DTC comprised the FNMTC group. We retrospectively investigated the clinicopathologic features including age at diagnosis, sex, follow-up period, tumor size, extent of operation, disease multifocality, combined benign mass, extrathyroidal extension, tumor stage (T-stage), number of central and lateral lymph nodes metastases, recurrence, and overall survival. TNM classification was determined using the 8th edition of AJCC Cancer Staging Manual. Preoperative ultrasonography was performed in all patients to identify metastases in the central and lateral neck lymph nodes and to evaluate disease recurrence after surgery. Multifocality was defined as multiple tumors, regardless of whether they were located on one or both sides after histological workup. The definition of disease recurrence was limited to structural relapse. In patients with family histories of DTC, we investigated the number of family members and their relationships to the patients.

Statistical analyses

Statistical analyses were performed using the IBM SPSS ver. 21.0 (IBM Co., Armonk, NY, USA). Chi-square test, *t* test, Fisher's exact test, Student's *t* test, and logistic regression analyses were used to determine variables related to family history. A p value <0.05 was regarded as statistically significant.

Results

Among those with family histories of DTC, 207 (52.94%) were affected by a sibling and 184 (47.06%) by parents. Paternal transmission was noted in 22 (5.63%) and maternal transmission in 162 (41.43%). Most patients in the FNMTC group had two first-degree relatives with thyroid cancer (n = 332; 84.9%), 35 (9.0%) had three first-degree relatives, 12 (3.1%) had four first-degree relatives, and 12 (3.1%) had five first-degree relatives with DTC (Table 1). There were no significant differences in age, sex, tumor size, tumor number, extrathyroidal extension, tumor stage, central and lateral neck lymph node metastases, and recurrence rate between patients with two and three or more first-degree relatives with DTC. Multifocality was more frequently observed in those with three or more first-degree relatives (52.5%) than in those with two first-degree relatives (36.1%; p = 0.017). We compared the SNMTC patient group (2503 cases) with the patients having three or more members with family histories of DTC (59 cases). Multifocality was frequently observed in those with three or more first-degree relatives (52.5%) than in those with SNMTC (32.6%; p 0.001). Except for multifocality, no differences were observed between the two groups (data not shown). Therefore, subsequent analyses compared patients with SNMTC and those with FNMTC with two or

Table 1 Familial non-medullary thyroid cancer relationships

	FNMTC (n = 391)
Relationship	
Siblings	207 (52.94%)
Parent–child	184 (47.06%)
Paternal	22 (5.63%)
Maternal	162 (41.43%)
Number of affected members	
2	332 (84.9%)
3	35 (9.0%)
4	12 (3.1%)
5	12 (3.1%)

FNMTC familial non-medullary thyroid cancer

Table 2 Univariate analysis of clinicopathologic characteristics

Variable	SNMTC (n = 2503) (86.5%)	FNMTC (n = 391) (13.5%)	P value
Gender ratio (M/F)	326:2177 (13.0%:87.0%)	64:327 (16.4%:83.6%)	0.072
Age (years)	47.54 ± 11.01	47.55 ± 11.73	0.996
Tumor type			0.448
Papillary thyroid cancer (n)	2434 (97.2%)	384 (98.2%)	
Follicular thyroid cancer (n)	66 (2.6%)	7 (1.8%)	
Hürthle cell thyroid cancer (n)	3 (0.1%)	0 (0.0%)	
Follow-up period (month)	61.34 ± 36.55	58.71 ± 35.22	0.186
Extent of thyroidectomy			0.007
Lobectomy	408 (16.3%)	43 (11.0%)	
Total thyroidectomy	2095 (83.7%)	348 (89.0%)	
Tumor size (cm)	1.01 ± 0.86	1.01 ± 0.86	0.961
Multifocality			0.020
Solitary tumor	1686 (67.4%)	240 (61.4%)	
Multiple tumors	817 (32.6%)	151 (38.6%)	
Combined benign mass			0.013
No	1567 (62.6%)	219 (56.0%)	
Yes	936 (37.4%)	172 (44.0%)	
Extrathyroidal extension			0.930
No	1197 (47.8%)	188 (48.1%)	
Yes	1305 (52.2%)	203 (51.9%)	
T-stage			0.278
Less than T2	2047 (81.8%)	310 (79.5%)	
More than T3	456 (18.2%)	80 (20.5%)	
Central neck LN metastasis (%)			0.132
No	1412 (56.9%)	206 (52.8%)	
Yes	1070 (43.1%)	184 (47.2%)	
Lateral neck LN metastasis (%)			0.022
No	2339 (93.4%)	353 (90.3%)	
Yes	164 (6.6%)	38 (9.7%)	
Recurrence rate			0.193
No	2477 (99.0%)	384 (98.2%)	
Yes	26 (1.0%)	7 (1.8%)	
Radioactive iodine ablation			0.136
No	744 (31.3%)	103 (27.5%)	
Yes	1634 (68.7%)	272 (72.5%)	
Complication			0.144
No	2272 (90.8%)	344 (88.4%)	
Yes	231 (9.2%)	45 (11.6%)	

SNMTC sporadic non-medullary thyroid cancer, *FNMTC* familial non-medullary thyroid cancer, *LN* lymph node

more first-degree relatives. Eighty-four (21.5%) index cases were observed.

Table 2 presents characteristics of patients with SNMTC and FNMTC. Of those with FNMTC, 327 were female (83.6%), and 64 were male (16.4%). In the SNMTC group, there were 2177 females (87.0%) and 326 males (13.0%). The mean ages were 47.54 ± 11.01 (SNMTC) and 47.55 ± 11.73 (FNMTC). The mean follow-up period was 61.34 ± 36.55 (SNMTC) and 58.71 ± 35.22 months (FNMTC). We did not observe significant between-group differences in age, sex, follow-up period, tumor size, T-stage, or central lymph node metastases ($p > 0.05$). Of the 2894 patients, we found patients with papillary thyroid cancer (n = 2818), follicular thyroid cancer (n = 73), and Hürthle cell thyroid cancer (n = 3; Table 2). The incidence of cancer was 2503 (86.5%) in the SNMTC group and 391 (13.5%) in the FNMTC group. Total thyroidectomies were

Table 3 Multivariate analysis of clinicopathologic characteristics

	Coefficient	SE	Wald χ^2	*P*	Odds ratio	95% confidence interval
Sex (M/F)	− 0.261	0.152	2.956	0.086	0.771	0.573–1.037
Age, years	− 0.003	0.005	0.323	0.570	0.997	0.987–1.007
Multifocality	0.239	0.113	4.447	0.035	1.270	1.017–1.586
Combined benign mass	0.311	0.113	7.551	0.006	1.365	1.093–1.704
Lateral neck LN metastasis	0.364	0.192	3.585	0.058	1.440	0.987–2.099

performed in 348 FNMTC (89.0%) and 2095 (83.7%) SNMTC cases (Table 2).

In the FNMTC group, 151 cases (38.6%) had multiple tumors (multifocality) and 240 (61.4%) had a single tumor, whereas in the SNMTC group, 817 (32.6%) had multiple tumors and 1686 (67.4%) had a single tumor, indicating a significant between-group difference ($p < 0.05$). Combination benign masses were noted in 172 cases (44.0%) in the FNMTC group and in 936 (37.4%) in the SNMTC group, indicating that the FNMTC group had a significantly higher prevalence of combined benign masses ($p < 0.05$).

In the FNMTC group, there were 203 cases (51.9%) of extrathyroidal extension, compared to 1305 (52.2%) in the SNMTC group, indicating no significant between-group difference ($p > 0.05$). This suggests that tumors in the FNMTC were not more invasive than those in the SNMTC group. The overall frequencies of lateral neck lymph node metastases were 6.6% (SNMTC) and 9.7% (FNMTC) ($p = 0.021$). In the SNMTC group, there were 26 cases (1.0%) of recurrence, compared with seven (1.8%) in the FNMTC group, indicating no significant between-group difference ($p = 0.191$). Notably, no patients in either group died from the disease during the follow-up period.

Using the variation inflation factor, we found no multicollinearity (1.012–1.048). Therefore, the data were appropriate for logistic regression analysis. Multivariate analyses were performed to determine whether there was a relationship between family history and independent variables, with $p < 0.1$. The results indicated that multifocality and combined benign masses were more frequently observed in patients with FNMTC. The Hosmer–Lemeshow goodness-of-fit test produced significant results, with a probability of 0.597. Therefore, the estimated statistical model seems appropriate (Table 3).

Transient hypocalcemia was the most frequent postoperative complication, and there was no difference between the two groups. Postoperative complications, including hoarseness and bleeding, did not differ between the two groups (Table 3).

Discussion

Our results indicated that FNMTC was not more aggressive than SNMTC. Increasing the number of affected family members significantly increased the incidence of multifocality. All patients who visited the study center were asked about family history of thyroid cancer. FNMTC prevalence was 13.5%, which was significantly higher than results reported by other studies [3, 7]. The high prevalence of family history is due to the fact that, in this small city, our hospital is the only one that can perform thyroid surgery, and in this area, many relatives live together. In our study, the FNMTC group included patients with only two family members, likely a heterogeneous group [15]; therefore, the actual percentage of patients with FNMTC could be higher. Many studies have reported that patients with more affected family members tended to have poorer outcomes. McDonald et al. [16] reported that patients with FNMTC and more than three family members with DTC had higher rates of reoperation, distant metastases, and death. Triponez et al. [17] reported that survival was significantly shorter in patients with three or more first-degree relatives and recommended more aggressive surgery for these patients. We found no difference in tumor size, recurrence rate, or metastases (except multifocality) between patients with two and three or more first-degree relatives with DTC. Ito et al. [10] reported that the prognosis of patients with two affected family members did not differ from that of patients with three or more affected family members. Although patients with only two family members with DTC may develop sporadically [18], we compared patients with SNMTC and those with two or more first-degree relatives. The most frequent mode of cancer transmission was sibling–sibling (52.9%) and parent–child, and maternal transmission was more frequent than paternal transmission, as previously reported [19].

The most frequent pathological thyroid cancer type in our study was papillary thyroid carcinoma, similar to that in another study [19].

Most authors have accepted that FNMTC tends to behave more aggressively than SNMTC; however, the clinical characteristics of FNMTC are still controversial,

with different opinions about aggressiveness, recurrence, and outcomes [3, 10–14, 16, 20, 21].

There were no significant between-group differences in age at diagnosis, as reported in other studies [10, 11, 13, 16, 21]. However, patients with FNMTC tend to be younger than those with SNMTC [4, 6, 12, 19, 20, 22].

Our analysis shows that FNMTC was not more aggressive than SNMTC, in contrast to other studies [10–12, 21, 22]. Additionally, tumor size and extrathyroidal extension did not differ between the groups, as reported in another study [20]. FNMTC is associated with higher capsular invasion [14, 16, 23]. Our research showed extrathyroidal extension was not higher in the FNMTC group; both groups demonstrated equivalent invasiveness.

In our study, FNMTC cases exhibited multifocality, appeared in combination with benign masses and lateral neck lymph node metastases. Multifocality is a prominent feature of FNMTC [10, 14, 20, 24]. Uchino et al. [13] showed that tumor size at diagnosis did not differ between patients with FNMTC and SNMTC; however, those with FNMTC were more likely to have intraglandular dissemination (40.7% vs 28.5%). Capezzone et al. [25] also showed more multifocality in patients with FNMTC. Ito et al. showed that multicentricity was the only clinicopathologic feature that differed between FNMTC and SNMTC [10]. Grossman et al. reported that FNMTC was multifocal in 93% cases. However, this study featured a relatively small (n = 14) study cohort, suggesting that the multifocality ratio was too high [26]. In contrast, SNMTC was reportedly multifocal in 20–32% [4, 27, 28]. As with other studies, we found more multifocality in the FNMTC (38.6%) than in SNMTC group (32.6%).

The FNMTC cases were frequently combined with a benign mass in our study, as with other studies [22, 29]. Alsanea et al. [20] reported that patients with FNMTC had more benign thyroid disease, although the difference did not rise to the level of statistical significance. FNMTC might, therefore, develop as a gradual multi-step progression from a benign mass [20].

Compared with SNMTC, FNMTC is associated with a higher incidence of lymph node metastases [4, 14, 20, 24, 25]. Our report showed that there was no difference in central neck lymph node metastases; however, the incidence of lateral neck lymph node metastasis was higher in the FNMTC group (9.7%) than in the SNMTC group (6.6%). Therefore, preoperative ultrasonography is strongly recommended for patients with FNMTC.

The recurrence rates were not significantly different between the two groups, and no deaths occurred during the follow-up period. Therefore, we could not compare mortality between the groups. Those with FNMTC and 2–3 or more first-degree relatives had no difference in mortality. Therefore, our study did not show a worse prognosis, in comparison with other studies [11]. The mean follow-up period was 60.99 ± 36.38 (0–139) months, which was considerably shorter, so fewer recurrences occurred, and no patients died. However, many studies have reported that FNMTC was associated with more aggressive disease and poorer outcomes [14, 19, 20]. Some studies found more recurrence in the FNMTC group and significantly shorter median disease-free survival [4, 14, 20]. Mcdonald et al. reported that incidences of reoperation, distant metastases, and death were higher among those with FNMTC. Uchino et al. [13] reported higher recurrence and poorer disease-free survival in patients with FNMTC than in those with SNMTC; there was no significant between-group difference in overall survival. The follow-up period was mostly short, and there was limited information about patient survival in that study.

FNMTC behaves more aggressively than SNMTC [14], and the patients with three or more family members tend to exhibit more aggressive tumors [17, 20]. Therefore, patients with FNMTC require more aggressive treatments such as total thyroidectomy and central neck lymph node dissection. In our study, patients with FNMTC did not show aggressive disease; however, it may be preferable to consider total thyroidectomy. Uchino et al. [13] recommended total thyroidectomy with modified radical neck dissection for patients with FNMTC. Ito et al. [10] recommended total thyroidectomy in cases of recurrence within the remnant thyroid. Furthermore, Tavarelli et al. [19] recommended total thyroidectomy to avoid the proliferation of residual tumor tissue and central node dissection due to the high incidence of central lymph node metastases at the time of diagnosis [4, 6, 9]. In our study, total thyroidectomy was frequently performed in the FNMTC group, similar to other studies. Although the tumors were not more aggressive, the multifocality and combinations with benign masses were more common in the FNMTC cases. There was a tendency to undergo total thyroidectomy, suggesting that total thyroidectomy might be the reason for no significant differences in postoperative recurrence or prognosis. High rates of central lymph node metastases were not observed; however, FNMTC was associated with a higher incidence of lateral neck lymph node metastases than SNMTC. Preoperative cervical ultrasound should be performed to confirm metastases of cervical lymphadenectomy. Because recurrence risk was not high in the FNMTC group, postoperative follow-up should resemble that of the SNMTC group. Further genetic studies are needed to predict the prognosis of each patient and to perform optimal surgical treatments.

There were some limitations to the study. The results might be less accurate due the retrospective nature of the study. The follow-up period was also too short to identify the true rates of survival or recurrence.

Thus, 13.5% patients exhibited FNMTC, which was significantly higher than that reported in other studies, and there were no significant clinical differences between patients in the FNMTC and SNMTC groups. Multifocality and combined benign masses were more likely to be found in the FNMTC group. We found no between-group differences in disease aggressiveness or prognosis; however, the FNMTC group had significantly more instances of lateral neck lymph node metastases during univariate analysis. These results suggest that all patients with DTC should undergo comprehensive history-taking to identify the presence or absence of familial disease. Moreover, preoperative ultrasonography should be performed to determine the extent of node dissection in patients who require surgery; total thyroidectomy is recommended for patients with FNMTC.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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