Familial Nonmedullary Thyroid Carcinoma: A Retrospective Analysis of 117 Families

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Abstract

Background: The first and most important step in characterizing familial nonmedullary thyroid carcinoma (NMTC) is to distinguish the true familial patients, which is the prerequisite for all accurate analyses. This study aimed to investigate whether patients from families with ≥3 first-degree relatives affected with NMTC have different characteristics than patients from families with only two affected members, and to compare these patients with those with sporadic disease.

Methods: We analyzed the clinicopathological features and prognosis of 209 familial and 1120 sporadic cases of NMTC. Familial patients were further divided into two subgroups: families with two affected members and families with ≥3 affected members.

Results: The familial group had a significantly higher risk of bilateral growth, multifocality, extrathyroidal extension, and lateral lymph node metastasis than the sporadic group (P < 0.05). These main features were also different between the group with ≥3 affected members and the sporadic group. The only difference between the two affected members’ group and the sporadic group was incidence of multifocality (P < 0.05). The probability of disease recurrence in patients from families with ≥3 affected members was significantly higher than that in sporadic cases (14.46% vs. 5.27%; P = 0.001), while the probability in patients from families with two affected members was similar to that in sporadic patients (6.35% vs. 5.27%; P = 0.610). The Kaplan–Meier survival analysis showed a statistically significant difference in disease-free survival between the two subgroups (85.54% vs. 93.65%; P = 0.045).

Conclusions: Patients from families with ≥3 members affected by NMTC have more aggressive features and a worse prognosis than those from families with only two affected members. Patients from families with ≥3 affected first-degree relatives may be considered to have true familial NMTC.

Key words: Carcinoma; Nonmedullary; Thyroid; True Familial

INTRODUCTION

Nonmedullary thyroid carcinoma (NMTC) is a type of thyroid malignancy that arises from thyroid follicular epithelial cells and has relatively mild biological behavior and an excellent prognosis. Exposure to ionizing radiation is a definite risk factor for the development of thyroid cancer, particularly in children; however, a family history of thyroid cancer is also considered a possible risk factor for NMTC. Although many cases of NMTC are sporadic, familial nonmedullary thyroid carcinoma (FNMTc) comprises approximately 5% of differentiated thyroid carcinoma cases.¹-³ Despite accounting for a relatively small number of cases of NMTC, FNMTc is believed to be a distinct clinical entity and has unique clinicopathological and prognostic features that differentiate it from sporadic NMTC (SNMTC). FNMTc is diagnosed when two or more first-degree relatives have NMTC, without other known associated familial syndromes or history of radiation exposure.

Several case-control studies have revealed the clinicopathological characteristics and prognosis of FNMTc, but controversy remains regarding whether FNMTc is more aggressive than the sporadic forms of NMTC. Some
studies support the finding that the biological behavior of FNMTC tends to be more aggressive than that of SNMTC and is associated with an increased risk of multicentric tumors, bilateral growth, capsular and vascular invasion, and lymph node metastasis, with relatively short disease-free survival (DFS).\(^{[1,8]}\) However, conflicting evidence has been reported. A family history alone is not sufficient to predict a poor prognosis for patients with NMTC.\(^{[6,7]}\)

Many researchers have suggested that a patient with suspected FNMTC with only two affected first-degree relatives may not have a truly familial tumor and rather may be a sporadic case with unrelated family clustering.\(^{[1,8]}\) This hypothesis has been postulated not only because the incidence of NMTC is rapidly growing, leading to an increasing number of patients being diagnosed with the disease but also because a hereditary basis of FNMTC has not been identified. Another hypothesis is that a patient with NMTC and one affected first-degree relatives may have true familial NMTC, with some undetected genetic changes. However, the clinicopathological features and overall prognosis of FNMTC are similar to those of SNMTC, and the treatment of familial cases is similar to that for the sporadic forms. This suggests that the number of affected relatives in a family may be related to the aggressiveness and prognosis of NMTC.

In this study, we retrospectively analyzed 209 patients with FNMTC and 1120 sporadic patients who underwent primary surgery performed by the same surgical team and investigated the differences in clinical characteristics, pathological features, and outcomes between the two groups. We placed great emphasis on the analysis of the differences between patients from families with two affected first-degree relatives and those from families with \(\geq 3\) affected first-degree relatives and investigated whether patients from families with \(\geq 3\) affected first-degree relatives had tumors with more aggressive biological behavior.

**Methods**

**Ethical approval**

All procedures in this study were approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Science, and informed consent for this retrospective study was exempted.

**Patients**

This study included 209 patients with FNMTC who underwent primary surgery performed by the same surgical team in the Department of Head and Neck Surgery, Cancer Hospital, Chinese Academy of Medical Science, from January 2005 to December 2016. Two hundred and nine FNMT patients represented 117 families. We divided the FNMT group into two subgroups: (1) 126 patients belonged to 81 families with two affected first-degree relatives, referred to as the two affected members’ group, (2) and the remaining 83 patients belonged to 36 families with \(\geq 3\) affected first-degree relatives, referred to as the three or more affected members’ group. The age of disease onset ranged from 17 to 67 years old. The median age was 42.0 years old, and 145 female patients (69.4%) and 64 male patients (30.6%) were included. Only patients with complete medical records were enrolled in our study. The family history of all enrolled patients was obtained from the medical records and confirmed with the patients by telephone. The control group contained 1120 patients with SNMTC who underwent initial surgery performed by the same surgical team and met the inclusion criteria. The median age was 43.0 years old (range: 17–70 years old), and 833 female patients (74.4%) and 287 male patients (25.6%) were included in the study. All patients were treated during the corresponding period. The two groups were matched by the approximate duration of follow-up.

The inclusion criteria for the study were as follows: (1) The patient underwent primary surgery in our hospital and had complete medical records and follow-up. (2) The diagnosis of NMTC was confirmed by postoperative histopathological results. (3) The patient had no other known familial syndromes or history of radiation exposure.

**Study protocol**

The clinicopathological characteristics of all patients were collected, including the age of onset, sex, whether the disease was accompanied by benign thyroid lesions, surgical methods, extrathyroidal extension, lymph node metastasis, capsular invasion, persistent or recurrent disease, distant metastasis, and DFS at the end of follow-up. Multifocality was defined as having more than one focus in the tissue according to the postoperative pathological results. Disease persistence or relapse was defined as serum thyroglobulin elevated to detectable levels in patients who underwent total thyroidectomy; cervical lymph node metastasis was detected by ultrasound and confirmed by fine-needle aspiration (FNA) cytology or surgery, or abnormal iodine uptake. Ultrasound, computed tomography, magnetic resonance imaging, FNA cytology, nuclear scintigraphy, and other corresponding diagnostic tests were performed in patients with persistent or recurrent disease. Extrathyroidal extension referred to tumor penetration of the thyroid capsule, leading to invasion of the perithyroidal tissue and the result must be confirmed by postoperative pathology. Distant metastasis was diagnosed when NMTC was discovered in other body parts distant from the neck through surgical resection or tissue biopsy or by persistent iodine uptake in abnormal sites.

In our study, all patients were treated by the same team of surgeons, and the surgical recommendations were based on the guidelines of the Chinese Thyroid Association, irrespective of the family history of thyroid cancer. Sixty-seven patients with FNMTC underwent lobectomy, and the remaining 142 patients with FNMTC (67.9%) underwent total thyroidectomy. All familial patients underwent central neck dissection, and 113 familial patients received lateral neck dissection. In addition, postoperative radioactive iodine
therapy was performed in 53 cases, and all patients received postoperative thyroid hormone suppressive therapy.

The postoperative pathological diagnosis was determined by the final pathological results reported by a professional pathologist. The FNMT group consisted entirely of papillary thyroid carcinomas including 203 cases (97.1%) of classic papillary carcinoma and 6 cases (2.9%) of follicular papillary carcinoma. Ninety-nine patients (43.4%) with FNMT had concurrent nodular goiters and 29 patients (13.9%) had concurrent Hashimoto’s thyroiditis.

The median follow-up times were 45.0 months (2–132 months) and 44.6 months (2–132 months) in the FNMT group and the SNMT group, respectively.

### Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). Categorical parameters were compared between the two groups using the Chi-square test and Fisher’s exact test. Survival curves were determined using the Kaplan–Meier method, and the log-rank test was used to analyze time-dependent variables. A multivariate Cox model was used to evaluate the independent significance of prognostic factors that were determined to be significant in the univariate analysis. A value of $P < 0.05$ was defined as statistically significant.

### Results

We compared the clinicopathological features of the FNMT group and the SNMT group. According to the univariate analysis, the FNMT group had a significantly higher risk of bilateral growth, multifocality, extrathyroidal extension, and lateral lymph node metastasis than the SNMT group ($P < 0.05$), as shown in Table 1. No significant difference in the incidence of other clinicopathological factors was observed between the two groups ($P > 0.05$; Table 1). The clinicopathological features of the different FNMT subgroups were also compared. The results showed that the incidence of bilateral growth, multifocality, extrathyroidal extension, thyroid nodular goiter, and lateral lymph node metastasis in the group with ≥3 affected members was significantly higher than in the group with only two affected members ($P < 0.05$; Table 1). Other factors were not significantly different between the two groups ($P > 0.05$; Table 1).

Forty-nine (38.9%) patients of the group with two affected members had extrathyroidal extension, and these patients all had infiltration of the perithyroidal soft tissues. In addition to infiltration into the fibrous adipose tissue outside the thyroid, eight patients also exhibited infiltration of the striated muscle, two patients showed infiltration of the parathyroid gland, and one patient exhibited infiltration of the tracheal wall and recurrent laryngeal nerve. Fifty-eight (69.9%) patients in the group with ≥3 affected members had infiltration of fibrous adipose tissue outside the thyroid. In addition, ten of these patients also had striated muscle invasion, five patients had parathyroid gland invasion, five patients had invasion of the recurrent laryngeal nerve, and one patient had invasion of the tracheal wall. One patient had not only extracapsular fibrous adipose tissue and striated muscle invasion but also invasion of the subcutaneous tissue, ipsilateral pyriform sinus, prevertebral muscle, and esophageal muscle. One patient had invasion of the striated muscle and recurrent laryngeal nerve in addition to invasion of the ipsilateral prevertebral muscle and arterial sheath.

The SNMT group was compared with the two affected members’ group and the ≥3 affected members’ group [Table 2]. The incidence of multifocality and Hashimoto’s thyroiditis in families with two affected members was significantly higher than that of the SNMT group ($P < 0.05$), but the other clinicopathological factors were not significantly different between the two groups. The group with ≥3 affected members had a significantly higher risk of bilateral growth, multifocality, extrathyroidal extension, thyroid nodular goiter, and lateral lymph node metastasis than the SNMT group ($P < 0.05$).

In terms of the prognosis, the incidence of persistence or recurrence of disease in patients with FNMT was significantly higher than that of SNMT patients (9.57% vs. 5.27%; $P = 0.016$). No statistically significant difference was observed in the probability of disease recurrence or persistence in the ≥3 members group compared to the two-members group (14.46% vs. 6.35%; $P = 0.051$), but the incidence in the former was obviously higher than in the latter [Table 1]. Further analysis revealed that the probability of recurrence or persistence of disease in patients from families with three or more affected members was significantly higher than in the SNMT group (14.46% vs. 5.27%; $P = 0.001$; Table 2), while the probability in patients from families with two affected members was similar to that in patients with SNMT [6.35% vs. 5.27%; $P = 0.610$; Table 2]. In addition, the Kaplan–Meier survival analysis showed a statistically significant difference in DFS between the familial group and the sporadic group [90.43% vs. 94.73%; $P = 0.008$; Figure 1] and between the two subgroups in familial group [85.54% vs. 93.65%; $P = 0.045$; Figure 2]. Multivariate analysis revealed that lateral lymph node metastasis was an independent risk factor for the recurrence or persistence of disease in the three-or-more-members group ($P = 0.027$).

### Discussion

FNMT has been regarded as an independent clinical entity that accounts for 3.3–8.9% of all thyroid cancer cases.\[1,2,9,10\] No consensus has been established on the typical clinical behavior and outcomes of FNMT. Some studies have found that familial cases display a more aggressive behavior and worse prognosis than their sporadic counterparts, while other studies did not obtain similar results.\[6,7,9\] We cannot distinguish familial and sporadic lesions based on histology,\[11\] but some differences were found in the clinicopathological characteristics.
The number of multifocal tumors and bilateral lesions in FNMTC patients were significantly higher than in the controls, and these features have been confirmed in many other studies. Cao et al. conducted a matched study and found that multifocality and bilateral foci were observed in 54.84% and 44.09% of familial cases, respectively, while in sporadic patients, the incidence rates were only 39.52% and 28.23%.[1] According to Tavarelli et al.,[11] patients with FNMTC were more likely to have multifocal and bilateral tumors than sporadic patients (45.7% vs. 33.2%; 31.7% vs. 24.5%). Uchino also obtained similar results and found that familial patients were multifocal in 42% of cases.[12] Other research also confirms these findings.[5,6,13-16]

In our study, the FNMTC group exhibited a higher incidence of lateral cervical lymph node metastasis and extrathyroidal extension than to the control group. As early as 1955, Grossman reported that lymph node metastasis occurred in 57% of FNMTC cases, which is significantly higher than in SNMTC forms.[17] In a study by Zhang et al.,[4] patients with

| Variables                      | SNMTC (n = 1120) | FNMC (n = 209) | P     | Two affected members (n = 126) | Three or more affected members (n = 83) | P     |
|--------------------------------|------------------|----------------|-------|-------------------------------|-----------------------------------------|-------|
| Age                            |                  |                |       |                               |                                         |       |
| ≥45 years                      | 516 (46.07)      | 87 (41.63)     | 0.236 | 47 (37.30)                    | 40 (48.19)                              | 0.118 |
| <45 years                      | 604 (53.93)      | 122 (58.37)    |       | 79 (62.70)                    | 43 (51.81)                              |       |
| Gender                         |                  |                |       |                               |                                         |       |
| Male                           | 288 (25.71)      | 64 (30.62)     | 0.140 | 39 (30.95)                    | 25 (30.12)                              | 0.898 |
| Female                         | 832 (74.29)      | 145 (69.38)    |       | 87 (69.05)                    | 58 (69.88)                              |       |
| Bilaterality                   |                  |                |       |                               |                                         |       |
| Bilateral                      | 317 (28.30)      | 93 (44.50)     | <0.001| 45 (35.71)                    | 48 (57.83)                              | 0.002 |
| Unilateral                     | 803 (71.70)      | 116 (55.50)    |       | 81 (64.29)                    | 35 (42.17)                              |       |
| Focus                          |                  |                |       |                               |                                         |       |
| Multifocal                     | 453 (40.45)      | 125 (59.81)    | <0.001| 66 (52.38)                    | 59 (71.08)                              | 0.007 |
| Unifocal                       | 667 (59.55)      | 84 (40.19)     |       | 60 (47.62)                    | 24 (28.92)                              |       |
| Capsule invasion               |                  |                |       |                               |                                         |       |
| Present                        | 805 (71.88)      | 157 (75.12)    | 0.335 | 95 (75.40)                    | 62 (74.70)                              | 0.909 |
| Absent                         | 315 (28.12)      | 52 (24.88)     |       | 31 (24.60)                    | 21 (25.30)                              |       |
| Extrathyroidal extension       |                  |                |       |                               |                                         |       |
| Present                        | 346 (30.89)      | 107 (51.20)    | <0.001| 49 (38.89)                    | 58 (69.88)                              | <0.001|
| Absent                         | 774 (69.11)      | 102 (48.80)    |       | 77 (61.11)                    | 25 (30.12)                              |       |
| Tumor diameter                 |                  |                |       |                               |                                         |       |
| >1 cm                          | 394 (35.18)      | 75 (35.89)     | 0.844 | 46 (36.51)                    | 29 (34.94)                              | 0.817 |
| ≤1 cm                          | 726 (64.82)      | 134 (64.11)    |       | 80 (63.49)                    | 54 (65.06)                              |       |
| With Hashimoto Thyroiditis     |                  |                |       |                               |                                         |       |
| Yes                            | 203 (18.13)      | 29 (13.88)     | 0.137 | 14 (11.11)                    | 15 (18.07)                              | 0.154 |
| None                           | 917 (81.87)      | 180 (86.12)    |       | 112 (88.89)                   | 68 (81.93)                              |       |
| Thyroid nodular goiter         |                  |                |       |                               |                                         |       |
| Yes                            | 472 (42.14)      | 99 (47.37)     | 0.161 | 49 (38.89)                    | 50 (60.24)                              | 0.002 |
| None                           | 648 (57.86)      | 110 (52.63)    |       | 77 (61.11)                    | 33 (39.76)                              |       |
| Central lymph node metastasis  |                  |                |       |                               |                                         |       |
| Yes                            | 617 (55.09)      | 118 (56.46)    | 0.715 | 69 (54.76)                    | 46 (55.42)                              | 0.925 |
| None                           | 503 (44.91)      | 91 (43.54)     |       | 57 (45.24)                    | 37 (44.58)                              |       |
| Lateral lymph node metastasis  |                  |                |       |                               |                                         |       |
| Yes                            | 232 (20.71)      | 64 (30.62)     | 0.002 | 31 (24.60)                    | 33 (39.76)                              | 0.020 |
| None                           | 888 (79.29)      | 145 (69.38)    |       | 95 (75.40)                    | 50 (60.24)                              |       |
| Persistence or recurrence of disease |            |                |       |                               |                                         |       |
| Yes                            | 59 (5.27)        | 20 (9.57)      | 0.016 | 8 (6.35)                      | 12 (14.46)                              | 0.051 |
| None                           | 1061 (94.73)     | 189 (90.43)    |       | 118 (93.65)                   | 71 (85.54)                              |       |
| Distant metastasis             |                  |                |       |                               |                                         |       |
| Yes                            | 21 (1.88)        | 6 (2.87)       | 0.418 | 3 (2.38)                      | 3 (3.61)                                | 0.684 |
| None                           | 1099 (98.12)     | 203 (97.13)    |       | 123 (97.62)                   | 80 (96.39)                              |       |
| Death from disease             |                  |                |       |                               |                                         |       |
| Yes                            | 0                | 1 (0.48)       | 0.157 | 0                            | 1 (1.20)                                | 0.397 |
| None                           | 1120 (100.00)    | 208 (99.52)    |       | 126 (100.00)                  | 82 (98.80)                              |       |

SNMTC: Sporadic nonmedullary thyroid carcinoma; FNMTC: Familial nonmedullary thyroid carcinoma.
FNMTC more frequently had lymph node metastasis than sporadic patients (52.6% vs. 33.3%). A growing number of studies have found that FNMTC has a more invasive tendency, particularly with respect to invasion of the thyroid capsule and perithyroidal tissues. Our study also found that lateral lymph node metastasis was an independent risk factor for the recurrence or persistence of disease in the three-or-more-members group. Patients with a family history are more likely to have lateral lymph node metastasis. A family history has become an important risk factor for local invasion and lymph node metastasis, and aggressive characteristics are more common in families with three or more affected members.

In terms of the prognosis, Alsanea et al. discovered a higher recurrence rate (44%) in patients with FNMTC than in patients with SNMTC (17%), as well as a lower rate of DFS in familial forms than in sporadic forms. These results are consistent with the findings of Uchino et al. Although familial patients had a similar risk of local invasion and

| Table 2: Clinicopathological characteristics and prognostic factors of SNMTC vs. two affected members group and three or more affected members group |
| Variables | SNMTC (n = 1120) | Two affected members (n = 126) | P | Three or more affected members (n = 83) | P |
|-----------|-----------------|------------------|---|--------------------------|---|
| Age       |                 |                  |   |                          |   |
| ≥45 years | 516 (46.07)     | 47 (37.30)       | 0.061 | 40 (48.19) | 0.708 |
| <45 years | 604 (53.93)     | 79 (62.70)       |        | 43 (51.81)  |          |
| Gender    |                 |                  |   |                          |   |
| Male      | 288 (25.71)     | 39 (30.95)       | 0.205 | 25 (30.12) | 0.377 |
| Female    | 832 (74.29)     | 87 (69.05)       |        | 58 (69.88)  |          |
| Bilaterality |           |                  |   |                          |   |
| Bilateral | 317 (28.30)     | 45 (35.71)       | 0.082 | 48 (57.83) | <0.001 |
| Unilateral| 803 (71.70)     | 81 (64.29)       |        | 35 (42.17)  |          |
| Focus     |                 |                  |   |                          |   |
| Multifocal| 453 (40.45)     | 66 (52.38)       | 0.010 | 59 (71.08) | <0.001 |
| Unifocal  | 667 (59.55)     | 60 (47.62)       |        | 24 (28.92)  |          |
| Capsule invasion |        |                  |   |                          |   |
| Present   | 805 (71.88)     | 95 (75.40)       | 0.403 | 62 (74.70) | 0.580 |
| Absent    | 315 (28.12)     | 31 (24.60)       |        | 21 (25.30)  |          |
| Extrathyroidal extension |       |                  |   |                          |   |
| Present   | 346 (30.89)     | 49 (38.89)       | 0.067 | 58 (69.88) | <0.001 |
| Absent    | 774 (69.11)     | 77 (61.11)       |        | 25 (30.12)  |          |
| Tumor diameter |            |                  |   |                          |   |
| >1 cm     | 394 (35.18)     | 46 (36.51)       | 0.767 | 29 (34.94) | 0.965 |
| ≤1 cm     | 726 (64.82)     | 80 (63.49)       |        | 54 (65.06)  |          |
| With Hashimoto Thyroiditis |        |                  |   |                          |   |
| Yes       | 203 (18.13)     | 14 (11.11)       | 0.049 | 15 (18.07) | 0.990 |
| None      | 917 (81.87)     | 112 (88.89)      |        | 68 (81.93)  |          |
| Thyroid nodular goiter |        |                  |   |                          |   |
| Yes       | 472 (42.14)     | 49 (38.89)       | 0.483 | 50 (60.24) | 0.001 |
| None      | 648 (57.86)     | 77 (61.11)       |        | 33 (39.76)  |          |
| Central lymph node metastasis |       |                  |   |                          |   |
| Yes       | 617 (55.09)     | 69 (54.76)       | 0.944 | 46 (55.42) | 0.953 |
| None      | 503 (44.91)     | 57 (45.24)       |        | 37 (44.58)  |          |
| Lateral lymph node metastasis |        |                  |   |                          |   |
| Yes       | 232 (20.71)     | 31 (24.60)       | 0.310 | 33 (39.76) | <0.001 |
| None      | 888 (79.29)     | 95 (75.40)       |        | 50 (60.24)  |          |
| Persistence or recurrence of disease |        |                  |   |                          |   |
| Yes       | 59 (5.27)       | 8 (6.35)         | 0.610 | 12 (14.46) | 0.001 |
| None      | 1061 (94.73)    | 118 (93.65)      |        | 71 (85.54)  |          |
| Distant metastasis |       |                  |   |                          |   |
| Yes       | 21 (1.88)       | 3 (2.38)         | 0.728 | 3 (3.61)   | 0.227 |
| None      | 1099 (98.12)    | 123 (97.62)      |        | 80 (96.39)  |          |
| Death from disease |        |                  |   |                          |   |
| Yes       | 0               | 0                | NS    | 1 (1.20)   | 0.069 |
| None      | 1120 (100.00)   | 126 (100.00)     |        | 82 (98.80)  |          |

NS: Not significant; SNMTC: Sporadic nonmedullary thyroid carcinoma.
lymph node metastasis to sporadic patients, the recurrence rate was significantly higher (16.3% vs. 9.6%; \( P = 0.0005 \)), and the DFS was significantly shorter (\( P = 0.004 \)). In our study, the incidence of persistence or recurrence of disease in patients with FNMTC was 9.57%, which was much higher than in the SNMTC group (\( P = 0.016 \)), and the survival curve showed that patients with FNMTC had shorter DFS than the patients with SNMTC. In particular, the families with three or more affected members showed a higher recurrence rate than families with two affected members, and the DFS of the former was lower than that of the latter. This indicates that familial patients are more likely to have a worse prognosis, especially if they belong to a family with three or more affected members.

Whether the number of affected members in a family is associated with tumor aggressiveness remains unknown. Some scholars believe that FNMTC patients from families with three or more affected members have more aggressive disease than those from families with two affected members. \[^{8,18}\] In this study, we found that compared to the two affected members’ group, patients in the three or more affected members’ group were more likely to have multifocality, bilateral lesions, extrathyroidal extension, and lateral lymph node metastasis, which are features related to a poor prognosis. These findings suggest that the number of affected family members should be taken into account when determining the prognosis. Further analysis showed that only the incidence of multifocality in the two affected members’ group was higher than that in the sporadic group. However, patients in the three or more affected members’ group had more clinicopathological characteristics that differed from the sporadic group, and these differences were similar to the overall differences between the FNMTC group and the SNMTC group. This illustrates that the families with three or more affected members have similar characteristics with the overall FNMTC group.

The comparison between the two subgroups of familial patients showed that the persistence or recurrence rate of the three or more affected members’ group was much higher than that of the two affected members’ group, although the difference was not statistically significant. Survival analysis showed a meaningful reduction in DFS in the three or more affected members’ group compared to the two affected members’ group. This finding is consistent with the findings of Uchino \textit{et al.}\[^{12}\] In addition, the recurrence rate of the two affected members’ group was similar to that of the sporadic group (\( P = 0.610 \)), while in the three or more affected members’ group, the recurrence rate was significantly higher than in the sporadic cases (\( P = 0.001 \)). These indicate that the families with three or more NMTC patients have truly familial cases, and patients with only two affected family members may be an occasional cluster of sporadic cases. Thus, if the proportion of families with two affected members in the study is high, the difference between the familial and sporadic patients may be reduced and perhaps even concealed. According to Charkes, if only two patients have NMTC in the same family, the probability that these patients are not sporadic cases is 38%, and this probability increases to greater than 95% when three or more family members are affected.\[^{19,20}\] Therefore, families with more affected members have a greater probability of nonsporadic lesions. If all the families with only two members affected by NMTC are regarded as FNMTC, it
will appear as a large bias in the number of familial cases and reduce the degree of malignancy for FNMT. This can result in overtreatment of sporadic cases, while some of the true familial patients may have inadequate treatment as well as increased postoperative complications, a greatly reduced quality of life, and increased recurrence rates. In summary, a clinical definition that can help to identify true FNMT should require two or more first-degree relatives diagnosed with the same type of thyroid carcinoma, in addition to the proband.

True FNMT patients should undergo more aggressive procedures as part of their initial treatment. Due to the high incidence of multifocality and bilateral lesions, all familial patients should undergo total thyroidectomy instead of lobectomy to avoid incomplete removal of occult lesions. Due to the high rate of lymph node metastasis in FNMT cases, central lymph node dissection should be routinely performed for patients with FNMT.\[10,16\] Despite the high rate of lateral lymph node metastasis, no evidence has shown that prophylactic lateral neck dissection can improve the prognosis. Therefore, while the lateral lymph nodes do not require routine dissection, they should be evaluated carefully. If a suspicious lymph node is discovered, a comprehensive examination should be performed to rule out metastasis. For most patients who do not have true FNMT, especially the patients from the families with two affected members, a family history can be recorded, but it should not affect the initial therapeutic schedule. In contrast, patients with evidence of a true hereditary background should be considered high-risk cases and should undergo more aggressive treatment regimens. Because patients with FNMT have a high risk of recurrence, which is the leading cause of a shorter DFS, it is recommended that all patients with familial disease undergo postoperative iodine treatment and L-T4 suppressive therapy. In particularly, if the FNMT patients are from families with three or more affected members and concomitant with lateral lymph node metastasis, we should strengthen the monitoring of the patient’s condition.

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**Conflicts of interest**

There are no conflicts of interest.

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目的：分析家族性甲状腺非髓样癌（NMTC）中具有3名或3名以上患者的家庭与只有2名患者的家系在临床病理学及预后方面是否存在差异，并将这两种家系分别与散发性患者进行对比，探讨两者之间在临床特征方面的不同。

方法：回顾性分析2005年1月至2016年12月于我院头颈外科同一手术组行初次手术治疗的209例家族性NMTC患者及1120例散发性NMTC患者，将家族性患者进一步分为两个亚组：只有2名患者的家系（简称2名患者组）及≥3名患者的家系（简称≥3名患者组），分析这些患者在临床病理学及预后方面的差异。

结果：家族性患者的双侧叶病变、多灶、甲状腺外侵犯及侧颈淋巴结转移的发生率明显高于散发性患者（P<0.05），这些特征也是≥3名患者组与散发性患者间的主要差异（P<0.05），而2名患者组与散发性患者间的唯一不同特征就是多灶的发生率（P<0.05）。≥3名患者组的疾病复发率明显高于散发性患者（14.46% vs. 5.27%；P=0.001），而2名患者组的疾病复发率与散发性患者相似（6.35% vs. 5.27%；P=0.610）。生存分析显示≥3名患者组的无病生存率明显低于2名患者组，差异有统计学意义（85.54% vs. 93.65%；P=0.045）。

结论：家族性甲状腺非髓样癌中≥3名患者的家系与只有2名患者的家系相比，肿瘤恶性程度更高，预后更差。具有3名或3名以上甲状腺非髓样癌患者的家系或许才是真正的家族性肿瘤。