Head and Neck

Clinicopathologic characteristics of familial versus sporadic papillary thyroid carcinoma

Caratteristiche clinicopatologiche del carcinoma tiroideo papillare familiare a confronto con il carcinoma tiroideo papillare sporadico

L. Jiwang1, L. Zhendong1, L. Shuchun1, H. Bo2, L. Yanguo1
1 Department of Head and Neck Surgery, Liaoning Cancer Hospital & Institute, Shenyang, People’s Republic of China; 2 Department of Pathology, Liaoning Cancer Hospital & Institute, Shenyang, People’s Republic of China

SUMMARY

It is unclear whether familial non-medullary thyroid carcinoma (FNMTMC) is more aggressive than sporadic carcinoma, and its prevalence is still under debate. In this study, we investigated the clinicopathologic features of familial papillary thyroid carcinoma (PTC) compared with its sporadic counterpart. We used data from our hospital between 2008 and 2014 to compare the features of 24 familial PTC with 80 sporadic PTC. The prevalence of familial PTC was 1.5%; 25% of familial PTC exhibited a parent-offspring relationship, and 75% exhibited a sibling relationship. There were significant differences in terms of Hashimoto’s thyroiditis, nodular goiter, multicentricity, bilaterality, histologic variant, T stage and N stage between the familial and sporadic PTC groups (all p < 0.05). When we compared sporadic PTC with parent-offspring or sibling familial PTC separately, parent-offspring familial PTC was more Hashimoto’s thyroiditis and central LNM, while sibling familial PTC was more prevalent in multifocality and bilaterality than sporadic PTC. The recurrence rate was not significantly higher than that of sporadic PTC in familial PTC. The second generation in parent-offspring familial PTC patients exhibited an earlier age at diagnosis, greater multifocality and a higher metastasis rate than the first generation. Based on our results, we conclude that familial PTC is a clinically distinct entity with an aggressive nature. Because of the frequent presence of benign nodules, multifocality, bilaterality and high rate of recurrence, total or near-total thyroidectomy with neck dissection in these patients might be recommended. To date, the optimal clinical treatment is yet to be established, but improved awareness and screening will permit earlier detection, more timely intervention and improved outcomes for patients and their families.

KEY WORDS: Thyroid carcinoma • Papillary carcinoma • Familial • Clinicopathologic characteristics

INTRODUCTION

Thyroid cancer is the most common form of neoplasia of the endocrine system, accounting for about 1-3% of all cancers, and in the USA the yearly incidence has increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 20021. The incidence of thyroid carcinoma is rapidly
increasing, with one of the fastest rates of increase among common human cancers. Currently, non-medullary thyroid carcinoma (NMTC) is the seventh most common tumour in women. Thus, it is important to identify patients at high risk for thyroid cancer. Differentiated thyroid carcinoma, which includes papillary cancer, comprises the majority of all thyroid cancers. Differentiated thyroid carcinoma is usually sporadic except for some rare inherited diseases such as familial adenomatous polyposis, Gardner syndrome and Cowden’s disease. However, in 1955, Robinson and Orr first reported NMTC in monozygotic twins, while increased risk of thyroid cancer in individuals with a first-degree relative with thyroid cancer has been reported by population studies. Because some susceptibility genes have not been clearly identified, the entity of familial non-medullary thyroid carcinoma (FNMTC) is established as a diagnosis in patients with one or more affected persons among their first-degree relatives. The estimated frequency of FNMTC ranges from 2.5 to 11.3% among all thyroid cancer patients, although the precise prevalence is unknown. Based on previous studies from various countries, the aggressiveness of FNMTC remains a topic of debate, and it remains controversial whether the biological characteristics including prognosis in patients with FNMTC differ from those with sporadic carcinoma. Thus, we undertook a retrospective study to investigate the difference in clinicopathological features and prognoses between FNMTC and sporadic NMTC.

Materials and methods

Patients

Between January 2008 and July 2014, 2,402 patients underwent surgical treatment for thyroid cancer at the Department of Head and Neck Surgery in Liaoning Cancer Hospital & Institute. Exclusion criteria included prior exposure to radiation, non-curative surgery, anaplastic thyroid carcinoma, medullary carcinoma, malignant lymphoma, metastatic carcinoma from other organs and other inherited familial cancer syndromes; thus 815 patients were excluded from the study. Among the remaining 1,587 patients, 24 from 9 families were classified as having FNMTC as they had one or more first-degree relatives with thyroid cancer. First-degree relatives included parents, offspring and siblings. Because 24 FNMTC patients were all papillary thyroid carcinoma (PTC): 12 belonged to families having two affected members and the remaining 12 belonged to those having three or more affected members, we randomly selected 80 patients with sporadic PTC in the same study period as the control group. Clinicopathologic features were then analysed statistically in the two groups. Clinicopathologic parameters included age, gender, tumour diameter, multifocality, bilaterality, extrathyroidal invasion, method of surgery, preoperative thyroid stimulating hormone (TSH), combined chronic thyroiditis, presence of benign nodules, histologic subtype, lymph node metastasis (LNM), TNM stage and recurrence status. Patients were staged according to the seventh edition of the UICC/AJCC TNM staging system. All subjects gave their informed consent for the study, and the protocol was approved by our institutional review board.

Preoperative diagnostic protocol

Diagnosis and preoperative evaluation of each patient in our hospital were performed according to a strategy that was not changed during the study period. In our department, all patients underwent a careful history and thorough physical examination. Ultrasoundography, fine needle aspiration biopsy (FNAB) and ultrasonography-guided FNAB were used. In this study, all patients underwent ultrasonography examination and qualitative evaluation of the nodules was performed according to these criteria. Diagnosis of papillary cancer was confirmed by FNAB guided either by palpation or ultrasonography. Furthermore, when a small nodule was present in the contralateral lobe, we sometimes used additional FNAB for the nodule to decide the extent of thyroidectomy. Metastases to the lung and mediastinal lymph nodes were evaluated by preoperative imaging studies, such as CT.

Follow-up

Patient progress was followed by clinical examination, ultrasonography and laboratory tests (i.e., TSH, free thyroxine, and thyroglobulin) to examine for signs of local recurrence. Moreover, we also performed FNAB on suspected masses or lymph nodes, and cytopathologic diagnosis was obtained. All patients were closely followed after surgery until August 2014. The median follow-up duration of patients was 59.7 months (range, 0.3-79.9 months).

Statistical analyses

Continuous data are presented as mean ± standard deviation (SD). A chi-square test was used for comparison of categorical variables. Continuous variables were compared using Student’s t-test. All analyses were performed using SPSS 16.0 statistical packages (SPSS, Inc., Chicago, IL, USA). A value of p < 0.05 was considered statistically significant.

Results

Surgical designs and clinical outcomes of PTC patients

The extent of surgery was decided based on preoperative findings and intraoperative pathological results. In the familial PTC group, 14 (58.3%) patients underwent total or near-total thyroidectomy and 10 (41.7%) patients underwent lobectomy or isthmusectomy or partial lobectomy. In the sporadic PTC group, 34 (42.5%) patients under-
went total or near-total thyroidectomy, 8 (10.0%) patients underwent subtotal thyroidectomy and 38 (47.5%) patients underwent lobectomy or isthmusectomy or partial lobectomy. We carried out neck lymph node dissection (LND) in 73 patients (70.2%). Twenty (83.3%) in the familial PTC and 52 (65.0%) in the sporadic PTC underwent a central LND. In 44 of these patients, an additional therapeutic unilateral LND was performed, mostly due to enlarged and suspicious nodes detected with preoperative ultrasound. Fifty-three of these 73 patients (72.6%) with LND had histological evidence of lymph node involvement. During lymphadenectomy, one to 23 lymph nodes were removed. The number of involved lymph nodes varied between 0 and 18.

To date, 26 patients developed recurrence: 3 had thyroid recurrence, and 4 had lymph node recurrence in the familial PTC; 9 had thyroid recurrence, and 10 had lymph node recurrence in sporadic PTC. These patients underwent re-operation, and they remain alive with no symptoms of further recurrence after second surgery. One patient with familial PTC had lung metastasis, and died of the disease 24 months after initial surgery.

Profiles of familial PTC patients and treatment

Of the 1,587 enrolled patients, 24 (1.5%) from 9 different families were diagnosed as having FNMTMC. Table I summarises the backgrounds and clinicopathological features of these patients. Histology of carcinoma of 24 patients was all PTC, and the rate of histological variants was 50.0%, 37.5%, 4.2%, and 8.3% in classic, follicular, mixed, and tall cell, respectively. There were 9 males and 15 females (1:1.7) with an average age of 44 years (18-61 years). The average tumour size was 2.5 cm (0.3-5.0 cm). Twenty patients were stage I, and 4 patients were stage IV.

Table I. Backgrounds and clinicopathological features of 24 patients with familial PTC.

| Patient No. | Family No. | Gender | Age (years) | Tumour size (cm) | Combined thyroid disease | Histological variants | Bilaterality | Multifocality | Extrathyroidal invasion | LN M | pTNM classification |
|-------------|------------|--------|-------------|------------------|-------------------------|-----------------------|-------------|--------------|-----------------------|------|--------------------|
| 1           | 1          | Male   | 61          | 5.0              | Absent                 | Follicular            | Present     | Positive, 4  | Positive              | Positive | T3N1bM0             |
| 2           | 1          | Female | 32          | 1.0              | Absent                 | Follicular            | Absent      | Negative    | Negative              | Positive | T1aN1bM0             |
| 3           | 2          | Male   | 34          | 2.5              | Absent                 | Classic               | Present     | Positive, 2  | Negative              | Positive | T2N1aM0             |
| 4           | 2          | Female | 32          | 0.5              | Hashimoto’s thyroiditis | Classic               | Present     | Positive, 3  | Negative              | Negative | T1aN0M0             |
| 5           | 2          | Female | 36          | 1.8              | Absent                 | Follicular            | Present     | Positive, 2  | Negative              | Positive | T1bN1aM0             |
| 6           | 2          | Female | 56          | 2.5              | Nodular Goiter         | Follicular            | Present     | Positive, 3  | Negative              | Positive | T2N1bM0             |
| 7           | 3          | Female | 36          | 2.0              | Absent                 | Classic               | Absent      | Positive, 2  | Negative              | Positive | T1bN1bM0             |
| 8           | 3          | Male   | 40          | 1.5              | Absent                 | Classic               | Present     | Positive, 2  | Negative              | Negative | T1aN0M0             |
| 9           | 3          | Male   | 37          | 0.3              | Nodular Goiter         | Classic               | Present     | Negative    | Negative              | Positive | T1aN1bM0             |
| 10          | 4          | Male   | 61          | 5.0              | Cystadenoma            | Classic               | Present     | Positive    | Negative              | Positive | T3N1bM0             |
| 11          | 4          | Male   | 40          | 3.0              | Absent                 | Classic               | Absent      | Positive, 3  | Positive              | Positive | T3N1aM0             |
| 12          | 5          | Male   | 40          | 3.0              | Absent                 | Classic               | Absent      | Negative    | Negative              | Positive | T3N1aM0             |
| 13          | 5          | Female | 18          | 3.0              | Nodular Goiter         | Tall cell             | Present     | Positive, 3  | Positive              | Negative | T2N0M0              |
| 14          | 6          | Female | 32          | 3.0              | Nodular Goiter         | Tall cell             | Present     | Positive    | Negative              | Negative | T3N1bM0             |
| 15          | 6          | Female | 37          | 1.5              | Hashimoto's thyroiditis | Follicular            | Present     | Positive, 3  | Negative              | Positive | T1bN1bM0             |
| 16          | 7          | Female | 40          | 2.5              | Absent                 | Follicular            | Present     | Positive, 2  | Negative              | Positive | T2N1bM0             |
| 17          | 7          | Female | 35          | 3.0              | Hashimoto’s thyroiditis | Follicular            | Absent      | Negative    | Negative              | Positive | T2N1bM0             |
| 18          | 7          | Female | 37          | 2.0              | Hashimoto’s thyroiditis | Mixed                 | Absent      | Positive, 3  | Positive              | Positive | T1bN1aM0             |
| 19          | 7          | Male   | 32          | 4.5              | Absent                 | Follicular            | Present     | Positive, 3  | Negative              | Positive | T3N1aM0             |
| 20          | 7          | Female | 42          | 1.5              | Hashimoto’s thyroiditis | Follicular            | Present     | Positive, 2  | Negative              | Negative | T1bN0M0              |
| 21          | 8          | Female | 43          | 3.0              | Absent                 | Follicular            | Present     | Negative    | Negative              | Positive | T2N1bM0             |
| 22          | 8          | Female | 58          | 0.3              | Nodular goiter, adenoma | Classic               | Present     | Negative    | Negative              | Negative | T1aN0M0             |
| 23          | 9          | Male   | 47          | 5                | Absent                 | Classic               | Absent      | Negative    | Negative              | Positive | T3N1bM0             |
| 24          | 9          | Female | 45          | 4                | Absent                 | Classic               | Present     | Positive, 2  | Negative              | Negative | T3N0M0              |

LNM: lymph node metastasis; Sibling relationship: family 2, 3, 6, 7, 8, 9; Parent-offspring relationship: 1, 4, 5.
The incidence of bilaterality and multifocality was 54.2% and 62.5%, respectively. Extrathyroidal invasion and LNM were found in 4 and 18 patients, respectively. There were 6 patients with a parent-child relationship and 18 with a sibling relationship. Thyroid disease other than microcarcinomas occurred in 11 patients: Hashimoto’s thyroiditis in 5, nodular goiter in 4, cystadenoma in 1 and nodular goiter with adenoma in 1 patient.

Comparison of clinicopathological differences between sibling and parent-offspring familial PTC

We evaluated whether there were any differences in the clinicopathological characteristics of patients with sibling and parent-offspring familial PTC (Table II). Preoperative TSH was higher in sibling group than in parent-offspring group (2.78 ± 2.04 vs 1.28 ± 1.18, p = 0.34). Hashimoto’s thyroiditis (100% vs 27.8%, p < 0.01) and extrathyroidal invasion (50% vs 5.6%, p = 0.04) were more frequent in the parent-offspring group than in the sibling group. Women more commonly exhibited sibling PTC (72.2% vs 33.3%), and the rate of patients who were < 55 years was higher in the sibling PTC group (88.9% vs 66.7%); however, these differences were not significant (all p > 0.05). No significant differences between the two groups were seen considering other parameters.

Comparison of clinicopathological characteristics of familial and sporadic PTC

We next compared clinicopathological features between patients with familial and sporadic PTC (Table III). Hashimoto’s thyroiditis (45.8% vs 16.2%, p < 0.01), multifocality (62.5% vs 25.0%, p < 0.01) and bilaterality (54.2% vs 15.0%, p < 0.01) were more frequent in the familial PTC group than the sporadic PTC group. The incidence of central LNM was higher in the familial PTC group (70.8% vs 53.8%, p = 0.16). There was a significant difference in terms of histological subtype between the two groups (p < 0.01). There were no significant differences between the two groups considering other parameters, except for T stage, N stage and nodular goiter. Comparing the clinicopathologic parameters between sporadic PTC and parent-offspring or sibling PTC separately, we found that sibling PTC was associated with more multifocality (66.7% vs 25.0%, p < 0.01) and bilaterality (55.6% vs 15.0%, p < 0.01) than sporadic PTC. There were significant differences between the two groups in terms of T stage (p < 0.01) and N stage (p = 0.04). We also found that parent-offspring PTC was more prevalent in T3-4 stage patients (66.7% vs 13.7%, p < 0.01) and presented a higher rate of Hashimoto’s thyroiditis (p < 0.01) and central LNM (p = 0.04).

Discussion

The reported prevalence of FNMTCS is ~5% of cases, varying from 2.5% to 11.3%. Due to the high prevalence of thyroid cancer, clustering of sporadic thyroid cancer in familial vs sporadic papillary thyroid carcinoma
A vast majority of patients with FNMT present PTC, although benign thyroid lesions, such as multinodular goiter, are commonly found in members of these families. Our results revealed 9 families including 24 individuals affected with PTC, and thus the incidence was 1.5% in our series of 1,587 consecutive patients. Currently, the frequency of familial PTC is difficult to establish and only a few isolated case reports exist in the literature. Ozaki et al. reported 23 cases among 11 families, but did not give the frequency in comparison with sporadic PTC. Stoffer et al. in their study reported a 6.2% familial PTC rate among 226 consecutive patients. Thus, further study including a large number of patients with familial PTC is necessary to elucidate this issue.

Whether FNMT is more aggressive than sporadic disease remains controversial. This aggressiveness in many studies is characterised by multicentricity, bilaterality, LNM, larger tumour, extrathyroid invasion, increased incidence of benign thyroid nodules and recurrent disease. One study found that FNMT patients with tumour size < 1 cm had significantly higher frequencies of multicentricity, bilaterality and LNM than sporadic NMTC. Uchino et al. did not find a significant increase in local invasion or LNM, but reported a significantly higher rate of recurrence and multicentricity in FNMT. Moreover, some authors have indicated that FNMT often presents with more advanced UICC stages. On the other hand, many investigations also have claimed that there are no differences between the two entities. These studies have proposed that the therapeutic strategy for FNMT might depend on the same conventional prognostic factors as those for sporadic NMTC, and not on whether the cancer was familial or sporadic. With regards to aggressiveness, we found that the familial PTC group had a significantly higher rate of multicentricity, bilaterality and T3-4 stage. Although there were no significant differences between the two groups, the rates of central and lateral LNM, and recurrence in the familial group were higher than in the sporadic group. In addition, our result also showed that the rate of classic variant type in the sporadic group is significantly higher than the familial group, but the follicular type rate was less frequent than the familial group. On the basis of these results, we conclude that familial PTC might have more aggressive behaviour than sporadic PTC.

| Table III. Clinicopathological features of familial and sporadic PTC. |
|-----------------------------------------------|
| **Gender** | Familial PTC (n = 24) | Sporadic PTC (n = 80) | P value |
| Male | 9 (37.5%) | 15 (18.8%) | 0.09 |
| Female | 15 (62.5%) | 65 (81.2%) | |
| **Age (years)** | | | 0.74 |
| < 55 | 20 (83.3%) | 69 (86.3%) | |
| ≥ 55 | 4 (16.7%) | 11 (13.7%) | |
| **Tumour size (cm)** | 2.52 ± 1.49 | 2.31 ± 1.48 | 0.65 |
| **Preoperative TSH** | 2.41 ± 1.95 | 2.18 ± 1.61 | 0.82 |
| **Hashimoto’s thyroiditis** | | | < 0.01 |
| Present | 11 (45.8%) | 13 (16.2%) | |
| Absent | 13 (54.2%) | 67 (83.8%) | |
| **Nodular goiter** | | | 0.02 |
| Present | 5 (20.8%) | 39 (48.8%) | |
| Absent | 19 (79.2%) | 41 (51.2%) | |
| **Multicentricity** | | | < 0.01 |
| Positive | 15 (62.5%) | 20 (25.0%) | |
| Negative | 9 (37.5%) | 60 (75.0%) | |
| **Bilaterality** | | | < 0.01 |
| Positive | 13 (54.2%) | 12 (15.0%) | |
| Negative | 11 (45.8%) | 68 (85.0%) | |
| **Extrathyroidal invasion** | | | 1.00 |
| Positive | 4 (16.7%) | 16 (20.0%) | |
| Negative | 20 (83.3%) | 64 (80.0%) | |
| **Histological variants** | | | < 0.01 |
| Classic | 12 (50.0%) | 72 (90.0%) | |
| Follicular | 9 (37.5%) | 8 (10.0%) | |
| Mixed | 1 (4.2%) | 0 | |
| Tall cell | 2 (8.3%) | 0 | |
| **T stage** | | | 0.04 |
| T1 | 10 (41.7%) | 46 (57.5%) | |
| T2 | 6 (25.0%) | 23 (28.8%) | |
| T3 | 8 (33.3%) | 8 (10.0%) | |
| T4 | 0 | 3 (3.7%) | |
| **N stage** | | | 0.03 |
| N0 | 6 (25.0%) | 14 (17.5%) | |
| N1a | 6 (25.0%) | 44 (55.0%) | |
| N1b | 12 (50.0%) | 22 (27.5%) | |
| **pTNM classification** | | | 0.17 |
| I | 20 (83.3%) | 57 (71.3%) | |
| II | 0 | 9 (11.3%) | |
| III | 0 | 5 (6.3%) | |
| IV | 4 (16.7%) | 9 (11.1%) | |
| **Central LNM** | | | 0.16 |
| Positive | 17 (70.8%) | 43 (53.8%) | |
| Negative | 7 (29.2%) | 37 (46.2%) | |
| **Lateral LNM** | | | 0.10 |
| Positive | 13 (54.2%) | 28 (35.0%) | |
| Negative | 11 (45.8%) | 52 (65.0%) | |
| **Recurrence** | | | 0.56 |
| Positive | 5 (20.8%) | 13 (16.3%) | |
| Negative | 19 (79.2%) | 67 (83.7%) | |

LNM: lymph node metastasis; TSH: thyroid stimulating hormone.
| Table IV. Clinicopathological features of sibling and parent-offspring familial PTC and sporadic PTC. |
|-------------------------------------------------|-------------------------------------------------|----------------|----------------|
| **Gender**                                      | **Sporadic PTC (n = 80)**                       | **Sibling (n = 18)** | **Parent-offspring (n = 6)** | **P value** |
|                                                |                                                |                  |                              |             |
| Male                                           | 15 (18.8%)                                     | 5 (27.8%)        | 4 (66.7%)                    | 0.52        |
| Female                                         | 65 (81.2%)                                     | 13 (72.2%)       | 2 (33.3%)                    | 0.02        |
| **Age (years)**                                | **Sporadic PTC (n = 80)**                      | **Sibling (n = 18)** | **Parent-offspring (n = 6)** | **P value** |
| < 55                                           | 69 (86.3%)                                     | 16 (88.9%)       | 4 (66.7%)                    | 1.00        |
| ≥ 55                                          | 11 (13.7%)                                     | 2 (11.1%)        | 2 (33.3%)                    | 0.22        |
| **Tumour size (cm)**                           | **Sporadic PTC (n = 80)**                      | **Sibling (n = 18)** | **Parent-offspring (n = 6)** | **P value** |
|                                               | 2.31 ± 1.48                                    | 3.08 ± 1.38      | 3.17 ± 1.60                  | 0.75        |
| **Hashimoto's thyroiditis**                    | **Sporadic PTC (n = 80)**                      | **Sibling (n = 18)** | **Parent-offspring (n = 6)** | **P value** |
| Present                                       | 13 (16.2%)                                     | 5 (27.8%)        | 6 (100.0%)                   | 0.31        |
| Absent                                        | 67 (83.8%)                                     | 13 (72.2%)       | 0                            | < 0.01      |
| **Nodular goiter**                             | **Sporadic PTC (n = 80)**                      | **Sibling (n = 18)** | **Parent-offspring (n = 6)** | **P value** |
| Present                                       | 39 (48.8%)                                     | 4 (22.2%)        | 1 (16.7%)                    | 0.06        |
| Absent                                        | 41 (51.2%)                                     | 14 (77.8%)       | 5 (83.3%)                    | 0.21        |
| **Multifocality**                              |                                               |                  |                              | < 0.01      |
| Positive                                      | 20 (25.0%)                                     | 12 (66.7%)       | 3 (50.0%)                    | 0.34        |
| Negative                                      | 60 (75.0%)                                     | 6 (33.3%)        | 3 (50.0%)                    |             |
| **Bilaterality**                               |                                               |                  |                              | < 0.01      |
| Positive                                      | 12 (15.0%)                                     | 10 (55.6%)       | 1 (16.7%)                    | 1.00        |
| Negative                                      | 68 (85.0%)                                     | 8 (44.4%)        | 5 (83.3%)                    |             |
| **Extrathyroidal invasion**                    |                                               |                  |                              | 0.19        |
| Positive                                      | 16 (20.0%)                                     | 1 (5.6%)         | 3 (50.0%)                    | 0.12        |
| Negative                                      | 64 (80.0%)                                     | 17 (94.4%)       | 3 (50.0%)                    |             |
| **Histological variants**                      |                                               |                  |                              | < 0.01      |
| Classic                                       | 72 (90.0%)                                     | 9 (50.0%)        | 3 (50.0%)                    | < 0.01      |
| Follicular                                     | 8 (10.0%)                                      | 7 (38.9%)        | 2 (33.3%)                    |             |
| Mixed                                         | 0                                              | 1 (5.6%)         | 1 (16.7%)                    |             |
| Tall cell                                      | 0                                              | 1 (5.6%)         | 0                            |             |
| **T stage**                                    |                                               |                  |                              | < 0.01      |
| T1                                            | 46 (57.5%)                                     | 9 (50.0%)        | 1 (16.7%)                    | < 0.01      |
| T2                                            | 23 (28.8%)                                     | 5 (27.8%)        | 1 (16.7%)                    |             |
| T3                                            | 8 (10.0%)                                      | 4 (22.2%)        | 4 (66.7%)                    |             |
| T4                                            | 3 (3.7%)                                       | 0                | 0                            |             |
| **N stage**                                    |                                               |                  |                              | 0.04        |
| N0                                            | 14 (17.5%)                                     | 5 (27.8%)        | 1 (16.7%)                    | 0.48        |
| N1a                                           | 44 (55.0%)                                     | 4 (22.2%)        | 2 (33.3%)                    |             |
| N1b                                           | 22 (27.5%)                                     | 9 (50.0%)        | 3 (50.0%)                    |             |
| **pTNM classification**                       |                                               |                  |                              | 0.73        |
| I + II                                        | 66 (82.6%)                                     | 16 (88.9%)       | 4 (66.7%)                    | 1.00        |
| III + IV                                      | 14 (17.4%)                                     | 2 (11.1%)        | 2 (33.3%)                    |             |
| **Central LNM**                               |                                               |                  |                              | 0.61        |
| Positive                                      | 43 (53.8%)                                     | 11 (61.1%)       | 6 (100.0%)                   | 0.04        |
| Negative                                      | 37 (46.2%)                                     | 7 (38.9%)        | 0                            |             |
| **Lateral LNM**                               |                                               |                  |                              | 0.12        |
| Positive                                      | 28 (35.0%)                                     | 10 (55.6%)       | 3 (50.0%)                    | 0.66        |
| Negative                                      | 52 (65.0%)                                     | 8 (44.4%)        | 3 (50.0%)                    |             |
| **Recurrence**                                |                                               |                  |                              | 0.31        |
| Positive                                      | 13 (16.3%)                                     | 5 (27.8%)        | 0                            | 0.59        |
| Negative                                      | 67 (83.7%)                                     | 13 (72.2%)       | 6 (100.0%)                   |             |

*LNM: lymph node metastasis.*
MTC with sporadic NMTC. In the study by Park et al., it was reported that parent-offspring FNMT was more multifocal, while sibling FNMT was more prevalent in female patients and presented with smaller tumours than sporadic disease. Gao et al. reported that compared with sporadic NMTC and sibling FNMT presented a higher rate of central LN, while parent-offspring FNMT showed frequent tumour bilaterality and a higher rate of recurrence. When we compared the sibling group with the parent-offspring group, there were significant differences in extrathyroidal invasion and Hashimoto's thyroiditis. These findings suggested that the clinical characteristics of sibling and parent-offspring might be different in familial PTC. In recent investigations, the second generation in parent-offspring FNMT was associated with an earlier age at diagnosis, greater multifocality and a higher metastasis rate. In accordance with previous results, we found that the second generation was diagnosed at a younger age (26.7 years), supporting the presence of "genetic anticipation", a phenomenon defined as the occurrence of a genetic disease at progressively earlier ages and with increased severity in successive generations in FNMT. Simultaneously, the second generation also had more extrathyroidal invasion and multifocality than the first generation, which suggested that FNMT diagnosed in the second generation might need more aggressive treatment than sporadic NMTC.

In some studies, FNMT patients had several characteristics associated with poor prognosis. One study reported that patient's survival of FNMT was significantly shorter than that of sporadic disease, and prognosis was poorer among FNMT patients with 3 or more affected members. However, Maxwell et al. in their case-control study found no significant difference in prognosis between familial and sporadic PTC groups. In our study, there were no deaths in the sporadic PTC group during follow-up, in contrast to familial PTC which showed a higher, although not significant, incidence of disease mortality (5.0%). These relatively surprising findings might be explained by the fact that all patients in this study are PTC.

There are no clinical trials to demonstrate the best management strategy for FNMT at present. Due to a higher rate of LN even with small tumours, several studies have recommended that individuals with familial disease should be treated more aggressively. Such approach includes near-total or total thyroidectomy and regional lymphadenectomy as the initial surgery in view of the high incidence of multifocal and bilateral disease, and postoperative radioiodine ablation in surgically-cured patients to reduce the rate of recurrence and to facilitate follow-up monitoring with serum thyroglobulin levels. Because of the high incidence of LN in FNMT patients, some authors recommend performing prophylactic central LNND. If there are any clinically positive lateral nodes, a modified LND should also be performed.

Patients with morphologically suspicious lesions demonstrated by ultrasonography or with cold nodules shown by scintigraphy might immediately performed FNAB; if the cytology is benign, reexamination after six months is recommended. FNMT relatives with benign, stationary thyroid nodules may be examined once a year. Simultaneously, all patients with thyroid carcinoma should also have a comprehensive history to identify potential familial forms of papillary or follicular thyroid carcinomas. Since benign thyroid disorders such as Hashimoto's thyroiditis and multinodular goiter are often observed in patients with FNMT, families with affection of a first-degree relative with thyroid carcinoma and an accumulation of benign thyroid disease should be screened yearly with ultrasound. Because FNMT patients are frequently younger in the second generation compared to first generation, screening might start at the age of 18 years.

Genetic analyses of large FNMT patients not only support the hypothesis that there exists an inherited genetic predisposition to FNMT, but that it also represents the first steps in identification of the putative susceptibility genes by positional cloning methods. Several linkage studies have identified loci within specific families, but none appear to account for a significant number of cases. The loci that have been identified to date include: MNG1, TCO1, IPTC/PRN and NMCT1. The following loci, some of which have been implicated in sporadic carcinoma, have been excluded as the susceptibility gene in FNMT: RET/PTC, PTEN, TSHR and TRKA. As the genetic causes of FNMT remain unknown, widespread genetic testing is not available.

Large studies among kinds are still required to identify the genes that may play a role in the development of FNMT.

We acknowledge that there are several limitations in this study. First, all the FNMT patients included were PTC. Although the majority of FNMT is papillary carcinoma, this might be a bias for clearly evaluating the recurrence and metastasis. Secondly, we were not able to perform more detailed assess for prognostic outcome, because the follow-up period in this study was relatively short and the number of patients with familial PTC was small. In addition, it is very difficult for us to perform survival analysis, because the patients who died from thyroid carcinoma were very rare.

In summary, the prevalence of familial PTC in our study was 1.5%, which is lower than that reported in other studies. Familial PTC might be considered as a separate clinical entity with a higher frequency of multicentricity, bilaterality and T3-4 stage, as well as a higher rate of Hashimoto's thyroiditis than its sporadic counterpart. Familial PTC with a parent-offspring relationship exhibited a higher rate of Hashimoto's thyroiditis and central LN than sporadic PTC, while a sibling relationship exhibited a higher rate of multicentricity and bilaterality. The second generation in parent-offspring familial PTC...
was diagnosed at an earlier age and had a higher rate of extrathyroidal invasion and multifocality. Familial PTC might be treated aggressively, and patients need to be followed closely. Simultaneously, it should take into account careful familial histories of thyroid cancer patients and make decisions about diagnostic and treatment modalities after considering family incidence in NMTC patients with thyroid cancer or nodules. The rarity of FNMT and the retrospective method of our study implies that our findings need to be confirmed through larger, and possibly, multicentre series.

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Address for correspondence: Zhen-Dong Li, Department of Head and Neck Surgery, Liaoning Cancer Hospital & Institute, 44 Xiaoheyan Road, Dadong District, Shenyang, 110042, People’s Republic of China. Tel. 86 24 31916252. Fax 86 24 24315679. Email: 1349946150@qq.com

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