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Do patients with familial nonmedullary thyroid cancer present with more aggressive disease? Implications for initial surgical treatment

Mustapha El Lakis, MD^a, Andreas Giannakou, MD^b, Pavel J. Nockel, DO^a, Douglas Wiseman, MD^a, Sudheer Kumar Gara, PhD^a, Dhaval Patel, MD^a, Zahraa Abdul Sater, MD^c, Yevgeniya Y. Kushchayeva, MD, PhD^c, Joanna Klubo-Gwiezdzinska, MD, PhD^d, Naris Nilubol, MD^a, Maria J. Merino, MD^e, Electron Kebebew, MD^{a,f,*}

^aEndocrine Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland ^bNational Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland ^cDiabetes, Endocrinology, and Obesity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland ^dMetabolic Disease Branch, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland ^eLaboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland ^fStanford University, School of Medicine, Stanford, California

Abstract

Background: There are conflicting reports on whether familial nonmedullary thyroid cancer is more aggressive than sporadic nonmedullary thyroid cancer. Our aim was to determine if the clinical and pathologic characteristics of familial nonmedullary thyroid cancer are different than nonmedullary thyroid cancer.

Methods: We compared patients with familial nonmedullary thyroid cancer to a cohort of 53,571 nonmedullary thyroid cancer patients from the Surveillance, Epidemiology, and End Results database.

Results: A total of 78 patients with familial nonmedullary thyroid cancer from 31 kindreds presented at a younger age ($P=.04$) and had a greater rate of T1 disease ($P=.019$), lymph node metastasis ($P=.002$), and the classic variant of papillary thyroid cancer on histology ($P<.001$) compared with the Surveillance, Epidemiology, and End Results cohort. Patients with 3 affected family members presented at a younger age ($P=.04$), had a lesser female-to-male ratio ($P=.04$), and had a greater rate of lymph node metastasis ($P=.009$). Compared with the Surveillance, Epidemiology, and End Results cohort, we found a higher prevalence of lymph node metastasis in familial nonmedullary thyroid cancer index cases ($P=.003$) but not in those diagnosed by screening ultrasonography ($P=.58$).

*Reprint requests: Stanford University, 300 Pasteur Drive, H3642 Stanford, California, 94305, kebebew@stanford.edu (E. Kebebew).

Conflicts of interest

There are no conflicts of interest for all of the authors.

Conclusion: Patients with familial nonmedullary thyroid cancer present at a younger age and have a greater rate of lymph node metastasis. The treatment for familial nonmedullary thyroid cancer should be more aggressive in patients who present clinically and in those who have 3 first-degree relatives affected.

Introduction

Thyroid cancer is the most common endocrine malignancy with more than 56,000 cases expected to occur in 2018. Thyroid cancers originating from follicular cells account for approximately 95% of all thyroid cancer cases, and the remaining cancers originate from parafollicular cells (medullary thyroid cancer).¹ Familial non-medullary thyroid cancer (FNMTC) accounts for 3–9% of all thyroid cancer cases.^{2,3} Most FNMTC cases are due to papillary thyroid cancer and its histologic variants, but follicular thyroid cancer, Hürthle cell carcinoma, and anaplastic thyroid cancer have also been reported, albeit rarely. FNMTC has an autosomal dominant pattern of inheritance with incomplete penetrance and may be syndromic or nonsyndromic. Nonsyndromic FNMTC accounts for most (>95%) cases of FNMTC.^{2,3}

Several investigators have suggested that FNMTC is associated with earlier age of onset, a greater rate of multifocal tumors, extrathyroidal extension, lymph node metastases, disease recurrence, and a decreased, disease-specific survival.^{4–11} A recent meta-analysis, which included 12 studies with a total of 12,741 patients who were followed for 1.5–12.1 years, evaluated the aggressiveness of FNMTC in comparison to sporadic nonmedullary thyroid cancer (NMTC).¹² The analysis was based on retrospective studies, including 8 cohort studies and 4 case-control studies, of which 5 were conducted in Asia,^{4,6,13–15} 4 in North America,^{2,7,16,17} 2 in Europe,^{18,19} and 1 that was a combined US and Japanese cohort study.⁵ Based on data extracted from 6 eligible studies, FNMTC was found to have a greater rate of recurrence and a decreased disease-free survival compared with patients with sporadic NMTC.¹² They also found a younger age at diagnosis (2.4 years less on average for FNMTC patients as compared to sporadic NMTC) and a greater rate of multifocal tumors, bilateral disease, extrathyroidal extension, and lymph node metastases, but no difference in primary tumor size.¹² Taken together, these findings suggest that FNMTC is characterized by more aggressive behavior than sporadic disease, but none of these data were based on prospective studies, the study sample size was small in most studies, and in none of the kindred studied were disease status ascertained by screening to provide an accurate assessment of affected disease status.

In this study, we determined if the clinical and pathologic characteristics of patients with FNMTC were different than those with sporadic NMTC. We compared the clinical and pathologic characteristics of patients with FNMTC (papillary thyroid cancer and its subtypes) with at-risk kindred who underwent prospective screening to the cohort of 53,571 patients with papillary thyroid cancer and its subtypes from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods and patients

The Institutional Review Boards of the National Cancer Institute and the National Institutes of Health approved this study, and patients gave written informed consent before evaluation and testing ().

FNMTc cohort evaluation and screening

A total of 31 kindreds with FNMTc were enrolled in a prospective cohort study. All patients had at least 2 first-degree relatives affected with NMTC. Family members with a clinical presentation of thyroid cancer were diagnosed and treated at other centers before referral to the study protocol. Individuals younger than 7 years of age or with syndromic FNMTc were excluded from the study. A family history questionnaire was obtained from all kindred. Demographic, clinical, and pathologic data were collected from medical records, family history questionnaires, and patient interviews. Patient histories, family pedigrees and physical examinations, high-resolution neck ultrasonographic imaging, and laboratory tests were performed at enrollment and annually in all patients enrolled. All pathology slides were reviewed at our institution to confirm the thyroid cancer diagnoses and histologic subtype. Response to treatment in affected members was defined as an excellent response if follow-up studies revealed negative imaging or suppressed thyroglobulin (Tg) <0.2 ng/mL or stimulated Tg <1ng/mL with negative anti-Tg antibodies.

SEER cohort

Of 62,585 patients from the SEER Program of the National Cancer Institute between 1988 and 2007, 9,014 patients were excluded for unknown pathology and for pathology consistent with medullary thyroid cancer, anaplastic thyroid cancer, and poorly differentiated thyroid cancer. Information on 53,571 patients, including demographics, tumor characteristics, initial treatment, tumor histopathology, and stage at diagnosis, were compared to our cohort of FNMTc. The SEER data used in this study were derived from various geographic locations throughout the United States and did not report family history status for thyroid cancer.

Statistical analyses

For parametric and nonparametric data, 2 group comparisons were performed using Student's *t*-test, chi-squared test, and Mann-Whitney U test as appropriate. The log-rank test was used for Kaplan-Meier survival analysis. A 2-tailed *P* value of <.05 was considered statistically significant. The data were analyzed using SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL). Continuous data were expressed as means ± standard deviations.

Results

Extent of disease in FNMTc cohort

Enrolled in our prospective cohort study were 31 kindreds with FNMTc. A total of 78 patients underwent operative management and were diagnosed with thyroid cancer on histologic examination. Details on demographics, clinical presentation, and pathologic findings are summarized in Table 1. The FNMTc patients had an average age of 43 ± 15

years at diagnosis with a peak incidence between the ages of 30 and 44 years (51%); 56 patients (72%) were women. Seventy-four patients (95%) underwent total thyroidectomy, 36 (46%) underwent therapeutic central neck lymph node dissection, and 9 (12%) underwent therapeutic lateral neck dissection for papillary thyroid cancer (99%) and follicular thyroid cancer (1%). Most patients had tumor node metastasis (TNM) stage I cancers (92%), with a tumor greatest dimension on histopathology of 1.3 ± 1.1 cm. Papillary thyroid cancer was present in both thyroid lobes (bilateral) in 33% of the specimens and was multifocal in 53% of the specimens. Extrathyroidal extension was present in 7 patients (9.5%).

Extent of disease in FNMTTC versus SEER cohort

Patients from the FNMTTC group compared to the SEER database had a similar sex distribution with female predominance (female-to-male: 2.5 vs 3.6; $P = .106$) and were diagnosed at a younger age (age ≥ 45 years: 62% vs 49.5%; $P = .041$). Most patients in the FNMTTC group underwent a total thyroidectomy (95% vs 84.6%; $P = .04$) and had more cases of the classic variant of papillary thyroid cancer on histology compared with patients in the SEER database (84% vs 63.3%; $P < .001$). FNMTTC patients had a greater rate of lymph node metastasis to the central and lateral neck compartments ($P = .002$) despite presenting with a greater rate of T1 stage (75% vs 57.8%; $P = .01$; Table 2).

An analysis of the patients who presented clinically ($n = 58$) and those diagnosed by screening ($n = 20$) in comparison to the SEER cohort is summarized in Table 3. In patients who presented clinically with FNMTTC, we found a younger age at diagnosis ($P = .038$) as well as a greater rate of histologic subtype of papillary thyroid cancer ($P = .02$), lymph node metastases ($P = .003$), and rate of total thyroidectomy (98%; $P = .019$) as compared to the SEER cohort (Table 3). In contrast, in our patients diagnosed with FNMTTC by screening, we found no difference in tumor stages, extent of operation, or the rate of lymph node metastasis compared with the SEER cohort. We did, however, observe a greater rate of classic variant of papillary thyroid cancer ($P = .017$) compared to the SEER cohort (Table 3). When comparing patients who presented clinically ($n = 58$) to those diagnosed by screening ($n = 20$), we found smaller tumor size and a lesser rate of central and lateral lymph node metastases in the screened group and greater rate of hemithyroidectomies, but no difference in the rate of extrathyroidal extension, bilateral tumor, or multifocality (Table 4).

A total of 14 kindreds had 2 first-degree relatives affected and 17 kindreds had 3 or more first-degree relatives affected. Patients from kindred with 2 affected members had a similar age at diagnosis ($P = .19$), sex distribution ($P = .42$), extent of thyroidectomy ($P = .12$), histologic diagnosis ($P = .2$), rate of extrathyroidal extension ($P = .29$), and TNM stage ($P = .73$) compared to the SEER cohort (Table 5). In contrast, patients from kindred with 3 or more affected members presented at a younger age ($P = .04$) and had a more classic variant of papillary thyroid cancer ($P = .001$), greater rate of T1 tumors ($P = .04$), and a greater rate of lymph node metastasis ($P = .009$) compared to patients in the SEER database (Table 5). There was no difference in clinical and pathologic characteristics nor type of treatment between kindred with 2 affected members in comparison to those with 3 or more affected members (Table 6). Analysis of 55 patients from kindred with 3 or more affected members who presented clinically (37 patients) compared to those diagnosed by screening (18

patients) showed a greater rate of lateral neck nodal metastasis ($P = .05$) but no difference in TNM stage ($P = .32$) or central neck nodal metastasis rate ($P = .129$).

At a median follow-up of 54 months, there was no difference in disease-specific survival between the FNMTC (3/78, 96%) and the SEER cohort (98.4%; $P = .145$). The recurrence rate in patients with FNMTC was 13% (10/78) with recurrence data not available in the SEER database for comparison.

Discussion

In this study, we evaluated the clinical characteristics, operative approach, and pathology results of our FNMTC cohort compared to patients with NMTC in the SEER database, excluding cases of medullary thyroid cancer, anaplastic thyroid cancer, and poorly differentiated thyroid cancer. We found that patients from kindred with 3 or more affected members were younger at the presentation and had a greater rate of lymph node metastasis despite presenting with a lesser tumor stage.

Consistent with most studies, the current study identified aspects of FNMTC that suggest a more aggressive disease than sporadic NMTC with a greater rate of lymph node metastasis and an earlier age of onset compared with patients in the SEER database. It has been estimated that 2.6% of all NMTC cases are FNMTC when using the definition of at least 2 first-degree, consanguineous family members.²⁰ But statistical analysis of all reported FNMTC cases up to the year 2006 showed that 62–69% of families with only 2 affected members may have sporadic NMTC and not FNMTC. Consistent with this probability estimation, in a prospective screening study of at-risk family members with FNMTC, we found a greater rate of diagnosis of thyroid cancer by screening when 3 or more first-degree relatives were affected than when only 2 first-degree relatives were affected.²¹ Indeed, in the current study, patients from kindred with only 2 affected members had similar age at presentation, similar sex distribution, and similar T and N stages compared to the SEER database. In contrast, compared to the SEER database, patients from kindred with 3 or more affected members presented at a younger age, presented with a lesser T stage, had a greater rate of lymph node metastasis, and a lesser proportion were female. The rate of extrathyroidal extension was similar between the FNMTC group and the SEER cohort. The lesser T stage observed in kindred with 3 or more affected members is likely a result of at-risk members being diagnosed by screening because we did not observe the same findings in patients who clinically presented with FNMTC.

In the current study, we found that patients with FNMTC presented at a younger age, which is consistent with previous studies; 20 patients in the FNMTC group diagnosed by screening had a median age at diagnosis of 42 years old. Although screening for cancer may result in earlier diagnosis and younger age at diagnosis, all first-degree relatives in the kindred were screened (including the parental generation), thus the younger age observed in our study is unlikely to be due to screening. Moreover, when comparing patients who clinically presented with FNMTC, we still observed a younger age at diagnosis as compared to the SEER cohort.

Our FNMTC cohort comprises patients diagnosed clinically (clinical presentation) and by screening. This means of diagnosis may pose concerns for selection bias because FNMTC diagnosed by screening may have been diagnosed before manifesting more aggressive features. Indeed, a subanalysis of the screened patients diagnosed with FNMTC showed less aggressive disease compared to the SEER database, whereas FNMTC diagnosed clinically was more advanced compared to the SEER database (Table 3). This subanalysis highlights that despite skewing the results by contaminating the whole cohort by screened FNMTC “less aggressive group,” the FNMTC cohort still had more aggressive disease at presentation. Furthermore, another potential selection bias could be that patients with a known family history of FNMTC may be treated with more extensive preoperative workup and with aggressive therapeutic procedures than sporadic NMTC cases. To further evaluate this potential bias, a comparison of the clinically diagnosed FNMTC (index cases and before referral to our center) versus screened FNMTC patients (Table 4) showed that the latter group had less advanced disease and a less extensive initial operation, which reflects no bias in the initial performed procedure.

Most patients with differentiated NMTC have an excellent survival rate, which makes detecting survival differences between different groups of patients difficult because of the lack of a large enough sample size and the long-term follow-up required. The disease-specific survival was similar between patients with FNMTC and the SEER cohort with a median follow-up of 54 months. In addition to the short follow-up duration, our FNMTC group had more of the classic papillary thyroid cancer subtype, which is less aggressive than the other subtypes.

The following findings in our cohort suggest that the surgical treatment should be more aggressive in FNMTC with 3 or more affected members: (1) patients who presented clinically with FNMTC had greater rates of lymph node metastasis than the SEER NMTC cohort, (2) patients diagnosed with FNMTC by screening had a lesser rate of extrathyroidal extension and lymph node metastasis, and (3) FNMTC patients from kindred with 3 or more affected members had more aggressive features.

The strength of the present study includes a relatively large number of FNMTC patients from 1 institution who underwent prospective comprehensive evaluations to ascertain disease status annually. Our cohort includes a substantial number of patients who were screened, which provided accurate information on the number of family members affected. Nevertheless, there are several limitations to the current study, including a short duration of follow-up that may not allow us to detect a difference in disease-free survival, and missing information on tumor bilaterally, multifocality, and exact tumor dimension in the SEER database that did not allow us to compare these variables to the FNMTC cohort. Lastly, it is possible that some cases in the SEER database may be cases of FNMTC and not sporadic, but given the large sample size in this database, we do not think this would significantly affect the results we observed.

In conclusion, FNMTC patients from families with at least 3 affected members presented with more aggressive features and a younger age, which suggests a more aggressive surgical management may be warranted.

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Table 1

FNMTC study cohort

Number of affected patients	78
Number of kindred	31
Kindred with 2 affected members	14
Kindred with 3 or more affected members	17
Number of patients in kindred with 2 affected members	23, (40)
Number of patients in kindred with 3 affected members	55, (60)
Number of patients diagnosed	
Clinically with thyroid cancer <i>n</i> , (%)	58, (74)
By screening <i>n</i> , (%)	20, (26)
Age (mean ± SD), (y)	43 ± 14.7
Female <i>n</i>, (%)	56, (72)
Fine need aspirate biopsy cytopathology *	
AUS/FLUS <i>n</i> , (%)	6, (10)
Follicular neoplasm <i>n</i> , (%)	4, (6.5)
Suspicious for malignancy <i>n</i> , (%)	4, (6.5)
Malignant <i>n</i> , (%)	46, (77)
Extent of surgery	
Total thyroidectomy <i>n</i> , (%)	74, (95)
Hemithyroidectomy <i>n</i> , (%)	4,(5)
Therapeutic central neck dissection <i>n</i> , (%)	36, (46)
Therapeutic lateral neck dissection <i>n</i> , (%)	8, (10)
Pathology	
Classic papillary thyroid cancer <i>n</i> , (%)	65, (83)
Follicular thyroid cancer <i>n</i> , (%)	1, (1–4)
Follicular variant of papillary thyroid cancer <i>n</i> , (%)	10, (13)
Tall-cell variant of papillary thyroid cancer <i>n</i> , (%)	2, (2.6)
Tumor size (mean ± SD); range (cm)	1.3 ± 1.1; 0.3–5
Multifocal <i>n</i>, (%)[†]	36, (53)
Bilateral <i>n</i>, (%)[‡]	23,(33)
Extrathyroidal extension <i>n</i>, (%)[§]	7, (9.5)
TNM stage <i>n</i>, (%)	
I	65,(83)
II	0,(0)
III	10, (13)
IV	3,(4)
Recurrence rate at 220 months mean follow-up <i>n</i>, (%)	10, (12.8)

* Data on the FNAB cytopathology were available for 58 of 78 patients

[†]Data on multifocality were available for 68 of 78 patients,

[‡]Data on unilateral versus bilateral disease were available for 69 of 78 patients

[§]Data on the exact extent of the surgery were available for 74 of 78 patients. *SD*, standard deviation; *AUS/FLUS*, Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance;

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Table 2

Comparison of patients with FNMTTC to patients from the SEER database

Groups (number)	FNMTTC (78)	SEER (53571)	P value
Age			.041
<45 y (%)	61.6	49.5	
45 y (%)	38.5	50.5	
Female:male	2.54	3.6	.106
Surgery (%)			
Less than lobectomy	0	0.9	.048
HT	5.3	14.5	
TT	94.7	84.6	
Histopathology (%)			
Classic	84.4	63.2	<.001
PTCFV	11.7	30.2	
PTCTCV/FTC	3.9	6.6	
ETE(%)	9.5	15.4	.101
TNM stage (%)			
T			.019
T0	0	0.1	
T1	75.3	57.8	
T2	8.2	19.1	
T3	11	18.6	
T4a	5.5	2.9	
T4b	0	1.4	
N	62.2	78.6	.002
N0			
N1NOS	8.1	4.2	
N1a	21.6	10.1	
N1b	8.1	7.1	
M			.417
M0	100	98.9	
M1	0	1.1	
Median follow-up (months)	54	56	.918
Mean follow-up (months) ± SD	220 ± 416	70 ± 58	<.001

PTC, papillary thyroid cancer; *HT*, hemithyroidectomy; *TT*, total thyroidectomy; *PTCFV*, follicular variant of PTC; *PTCTCV*, tall-cell variant of PTC; *FTC*, follicular thyroid cancer; *ETE*, extrathyroidal extension;

Comparison of patients clinically diagnosed with FNMTC and screened FNTMC to patients from the SEER database

Table 3

Groups (number)	Clinically diagnosed FNMTC (58)	Screened FNMTC (20)	SEER (53571)	P value *	P value †
Age				.038	.310
<45 y	62.1	57.9	49.5		
45 y	37.9	42.1	50.5		
Female:male	2.8	2.1	3.6	.268	.217
Surgery (%)					
Less than lobectomy	0	0	0.9	.019	.905
HT	1.8	15.8	14.5		
TT	98.2	84.2	84.6		
Histopathology (%)					
Classic	80.7	94.7	63.2	.02	.017
PTCFV	14	5.3	30.2		
PTCTCV/FTC	5.3	0	6.6		
ETE (%)	12.5	0	15.4	.355	.05
TNM stage (%)					
T				.112	.05
T0	0	0	0.1		
T1	68.5	94.7	57.8		
T2	9.3	5.3	19.1		
T3	14.8	0	18.6		
T4a	7.4	0	2.9		
T4b	0	0	1.4		
N				.003	.575
N0	56.4	78.9	78.6		
N1N0S	9.1	5.3	4.2		
N1a	23.6	15.8	10.1		
N1b	10.9	0	7.1	.521	.808
M					
M0	100	100	98.9		

Groups (number)	Clinically diagnosed FNMTC (58)	Screened FNMTC (20)	SEER (53571)	P value *	P value †
MI	0	0	1.1		

* comparison of clinically diagnosed FNMTC to SEER

† comparison of FNMTC diagnosed by screening to SEER PTC, papillary thyroid cancer; PTCFV, follicular variant of PTC; PTCCTCV, tall-cell variant of PTC; FTC, follicular thyroid cancer; HT, hemithyroidectomy; TT, total thyroidectomy; ETE, extrathyroidal extension;

Comparison of clinical and pathologic characteristics and treatment modalities between those who clinically presented and those who were diagnosed by screening in FNMTTC cohort

Table 4

Groups (number)	Patients diagnosed by screening (20)	Patients who presented clinically (58)	P value
Age at diagnosis (\pm SD, y)	46.8 \pm 16.7	41.0 \pm 14.7	.15
Female n (%)	14, (70)	41, (70.7)	1.000
Histologic subtype of thyroid cancer n, (%)			
Classic	19, (95)	45, (77.6)	.367
PTCFV	1, (5)	0, (0)	
PTCTCV	0,(0)	2, (3.4)	
FTC	0, (0)	1, (1.7)	
Mean tumor size (\pm SD, cm)	0.74 \pm 0.53	1.56 \pm 1.18	.008
Central neck lymph node metastasis n/N, (%)	4/19, (21)	22/48, (45.8)	.05
Lateral neck lymph node metastasis n/N, (%)	0, (0)	11/48, (23)	.018
Extrathyroidal invasion n/N, (%)	0, (0)	7/54, (13)	.179
Multifocal tumor n/N, (%)	10/19, (52.6)	26/49, (53)	1.000
Bilateral tumor foci n/N, (%)	8/11, (73)	17/32, (53)	.22
TNM stage n/N, (%)			
I	17/20, (85)	48/58, (83)	.565
II	0, (0)	0, (0)	
III	3/20, (15)	7/58, (12)	
IV	0, (0)	3/58, (5)	
Extent of surgery n/N, (%)			
HT	3/20, (15)	1/56, (1.8)	.05
TT	17/20, (85)	55/56, (98.2)	
Therapeutic CND	8/19, (42.1)	27/51, (53)	.296
Therapeutic LND	0, (0)	8/51, (16)	.067

PTC, papillary thyroid cancer; PTCFV, follicular variant of PTC; PTCTCV, tall-cell variant of PTC; FTC, follicular thyroid cancer; n, number; N, number of patients with available information; HT, hemithyroidectomy; TT, total thyroidectomy; CND, central nodal dissection; LND, lateral nodal dissection;

Table 5
 Comparison of patients from kindred with 2 affected members to patients from the SEER database

Groups (number)	FNMTIC 2 affected members / fam (23)	FNMTIC 3 affected members / fam (55)	SEER (53571)	P value *	P value †
Age				.190	.046
<45 y	60.9	61.8	49.5		
45 y	39.1	38.2	50.5		
Female:male	4.75	2.0	3.6	.419	.04
Surgery (%)					
Less than lobectomy	0	0	0.9	.123	.268
HT	0	7.5	14.5		
TT	100	92.5	84.6		
Histopathology (%)					
Classic	78.3	87	63.2	.202	.001
PTCFV	13	11.1	30.2		
PTCTCV/FTC	8.7	1.9	6.6		
ETE (%)	8.7	9.8	15.4	.291	.184
TNM stage (%)				.728	.044
T					
T0	0	0	0.1		
T1	72.7	76.5	57.8		
T2	13.6	5.9	19.1		
T3	9.1	11.8	18.6		
T4a	4.5	5.9	2.9		
T4b	0	0	1.4		
N				.169	.009
N0	59.1	63.5	78.6		
N1NOS	9.1	7.7	4.2		
N1a	18.2	23.1	10.1		
N1b	13.6	5.8	7.1	.772	.539
M					

Groups (number)	FNMTC 2 affected members / fam (23)	FNMTC 3 affected members / fam (55)	SEER (53571)	P value *	P value †
M0	100	100	98.9		
M1	0	0	1.1		

* comparison of FNMTC from families with 2 affected members to SEER

† comparison of FNMTC from families of 3 or more affected members to SEER PTC, papillary thyroid cancer; PTCFV, follicular variant of PTC; PTCCTV, tall-cell variant of PTC; FTC, follicular thyroid cancer; HT, hemithyroidectomy; TT, total thyroidectomy; ETE, extrathyroidal extension;

Table 6

Comparison of clinical and pathologic characteristics and treatment modalities between patients diagnosed with FNMTC from kindreds with 2 affected members to those with 3 or more affected members

Groups (number)	FNMTC with 2 affected members (14 kindreds)	FNMTC with 3 affected members (17 kindreds)	P value
Age at diagnosis (± SD, y)	38.7 ± 16	44.0 ± 15	.185
Female n (%)	18, (78)	37, (67)	.246
Histologic subtype of thyroid cancer n/N, (%)			
Classic	17/23, (74)	47/55, (85.5)	.126
PTCFV	4/23, (17.4)	7/55, (12.7)	
PTCTCV	2/23, (8.7)	0, (0)	
FTC	0, (0)	1/55, (1.8)	
Mean tumor size (± SD, cm)	1.5 ± 1.1	1.23 ± 1.1	.364
Central neck lymph node metastasis n/N, (%)	9/21, (43)	17/46, (37)	.422
Lateral neck lymph node metastasis n/N, (%)	5/20, (25)	6/46, (13)	.188
Extrathyroidal invasion n/N, (%)	2/22, (9)	5/50, (10)	.647
Multifocal tumor n/N, (%)	12/23, (52)	24/45, (53)	.565
Bilateral tumor foci n/N, (%)	8/14, (57)	17/29, (59)	.591
TNM stage n/N, (%)			
I	21/20, (90)	44/55, (80)	.380
II	0, (0)	0, (0)	
III	2/23 (10)	8/55, (14.5)	
IV	0, (0)	3/55, (5.5)	
Extent of surgery n/N, (%)			
HT	0, (0)	4/53, (7.5)	.228
TT	23/23, (100)	49/53, (92.5)	
Therapeutic CND	13/22, (59)	22/48, (46)	.22
Therapeutic LND	4/22, (18)	4/48, (8)	.209

PTC, papillary thyroid cancer; PTCFV, follicular variant of PTC; PTCTCV, tall-cell variant of PTC; FTC, follicular thyroid cancer; n, number; N, number of patients with available information; HT, hemithyroidectomy; TT, total thyroidectomy; CND, central nodal dissection; LND, lateral nodal dissection