ORIGINAL ARTICLE
HEAD AND NECK SURGERY & ONCOLOGY
DOI: 10.5152/B-ENT.2021.20010

Is familial papillary thyroid carcinoma different from sporadic form in terms of clinicopathological features and outcome?

Fatma Dilek Dellal[1], Didem Ozdemir[2], Cevdet Aydin[2], Berna Ogmen[2], Aydan Kilicarslan[3], Mehmet Kilic[4], Reyhan Ersoy[2], Bekir Cakir[2]

[1]Department of Endocrinology and Metabolism, Ankara City Hospital, Ankara, Turkey
[2]Department of Endocrinology and Metabolism, Yıldırım Beyazıt University Medical Faculty, Ankara, Turkey
[3]Department of Pathology, Yıldırım Beyazıt University Medical Faculty, Ankara, Turkey
[4]Department of General Surgery, Yıldırım Beyazıt University Medical Faculty, Ankara, Turkey

Cite this article as: Dellal FD, Ozdemir D, Aydin C, et al. Is familial papillary thyroid carcinoma different from sporadic form in terms of clinicopathological features and outcome? B-ENT 2020; 16(4): 222-8.

ABSTRACT

Objective: Familial papillary thyroid cancer (FPTC) is an uncommon and not well-defined clinical entity. Although some studies report more aggressive characteristics in FPTC, others do not favor these findings. This study aimed to analyze the ultrasonographic and cyto-histopathological features of patients with FPTC and sporadic papillary thyroid cancer (SPTC).

Methods: The data of 292 patients diagnosed with PTC histopathologically between 2007 and 2018 were retrospectively reviewed; and their thyroid function tests, ultrasonographic properties, and cyto-histopathological results were compared.

Results: We analyzed 132 tumor foci in 69 patients with FPTC and 322 foci in 223 patients with SPTC. Sex distribution, rate of thyroid autoantibody positivity, and median nodule number were similar in the 2 groups. In preoperative ultrasonographic (US) examination of malignant nodules, the mean nodule diameter was smaller, microcalcification was lower, and isoechogenity were higher in patients with FPTC than in those with SPTC (p=0.001, p=0.005, p=0.0.025, respectively). Cytological results were distributed similarly (p=0.100). Multifocality was higher in patients with FPTC (47.8% vs 30.9%, p=0.009). The median tumor diameters, rate of microcarcinoma, distribution of PTC variants, extracapsular extension, and vascular invasion were comparable. Capsular invasion and regional nodal metastasis were significantly increased in the SPTC group (17.4% vs 9.1%, p=0.024 and 13.0% vs 2.9%, p=0.018; respectively). Although stimulated thyroglobulin levels at the 6th month were higher in the sporadic group, the conventional and dynamic responses were similar in both groups.

Conclusion: Whether FPTC is more aggressive than SPTC is debatable. We found a higher rate of multifocality, but a lower rate of lymph node metastasis in FPTC. The prognosis was similar in patients with FPTC and SPTC. Early detection might lead to an early diagnosis in the familial form of the disease.

Keywords: Familial, histopathology, papillary thyroid cancer, prognosis, ultrasonography

Introduction

Thyroid cancer is a common clinical entity, and its prevalence is gradually increasing worldwide. Although familial predisposition remains medullary thyroid cancer (MTC), familial cases with nonmedullary thyroid cancer (NMTC) are reported to be growing. Robinson and Orr firstly reported cases of a familial form of papillary thyroid cancer (PTC) in monozygotic twins in 1955 (1).

NMTC which originates from the follicular epithelial cells accounts for 95% of all thyroid cancers. It includes PTC, follicular thyroid cancer, Hürthle cell cancer, and anaplastic thyroid cancer. Among these, PTC is the most frequently occurring, and the increased prevalence in the last decades is mostly ascribed to increased use of imaging techniques (2). The majority of PTC is sporadic; however, familial inheritance was reported ranging between 1.5% and 9.4% in different studies (3-6). Contrary to the MTC which has a familial predisposition in 25% of patients and which is associated with RET gene mutation, the genetic linkage is less well described in familial NMTC (FNMTC). Studies determine that familial PTC (FPTC) is a heterogeneous disorder related to multiple susceptibility genes and somatic mutations (5,7). Rarely, FNMTC may be a component

Corresponding Author: Fatma Dilek Dellal, drdellal@yahoo.com
Received: November 10, 2020 Accepted: March 11, 2021
Available online at www.b-ent.be

of a familial cancer syndrome such as Werner's syndrome, Carney's complex, Gardner's syndrome, Cowden disease, and familial adenomatous polyposis (8).

FPTC can be defined as 2 or more first-degree family members with PTC without another familial syndrome and radiation exposure history (9). It is controversial whether FPTC has more aggressive behavior than its sporadic counterpart. Although some studies have found more advanced features in FPTC (10,11), others do not support these findings (4,12). This study aimed to compare ultrasonographic and cyto-histopathologic features of patients with FPTC and sporadic PTC (SPTC).

Methods

Study population

Patients who underwent thyroidectomy and were diagnosed with thyroid cancer between January 2007 and March 2018 were retrospectively analyzed for the study. Patients having a history of thyroid surgery or radiation therapy to the head and neck region and patients with non-thyroidal malignancy were excluded. FNMTC was defined when the patient had at least 1 first-degree relative with NMTC (5). Because all cases with FNMTC had PTC, cancer types other than PTC were also excluded from the sporadic NMTC group.

Thyroid functions, ultrasonography (US) features, and cyto-histopathological findings were reviewed from the medical records. Ethical approval was received from our institutional ethics committee (13.07.2016-2637996/211). Our study was conducted in accordance with the Declaration of Helsinki.

Laboratory

Thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), antithyroid peroxidase (anti-TPO), and anti-thyroglobulin (anti-TG) antibodies were determinated in serum with chemiluminescent immunoassay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA, and the UniCel DxI 800, Beckman Coulter, CA, USA).The normal reference levels for TSH, fT3, fT4, anti-TPO, and anti-Tg were 0.4–4 mIU/mL, 1.57–4.71 pg/mL, 0.61–1.12 ng/dL, <10 IU/mL, and <30 IU/mL, respectively. Thyroid autoantibody levels above the upper limit of normal were considered positive. Patients on levothyroxine treatment and/or patients with a serum TSH >4 mIU/mL in the preoperative evaluation were defined to have hypothyroidism. Patients taking antithyroid medication and/or patients with a serum TSH <0.4 mIU/mL in the preoperative evaluation were grouped as hyperthyroidism. Patients with TSH levels in normal ranges were accepted as euthyroid.

Main Points:

- Familial papillary thyroid cancer (FPTC) is a rare clinical entity.
- We found a higher rate of multifocality, but a lower rate of lymph node metastasis in patients with FPTC.
- We found the prognosis was similar in patients with FPTC and sporadic papillary thyroid cancer (SPTC).
- To our knowledge, this is the first study to compare ultrasound features of patients with FPTC and SPTC, although clinical comparisons were made in other studies.

Imaging studies

Esaote color Doppler US (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) and a superficial probe (Model LA523 13–4, 5.5–12.5 MHz) was used for the ultrasound examination. The localization, diameters, ratio of the antero-posterior to the transverse diameter (AP/T), echogenicity, texture, border regularity, micro-macrocalcification, peripheral halo, and exophytic appearance of nodules were evaluated.

Fine needle aspiration biopsy and cytopathology

US-guided FNAB was carried out using a 23-gauge needle and 20-mL syringe (General Electric Logiq pro 200, model no.: 2270968; GE Healthcare Korea, Seongnam-si, Gyeonggi-do, Korea). Written consent was obtained from all the patients before FNAB. Materials were dried in air and stained with May-Grünwald-Giemsa. The cytological evaluation was made according to the Bethesda System (13).

Histopathology

Histopathologic diagnosis of PTC was made when there was a papillary growth pattern, nuclear grooves ground glass nuclei, and nuclear inclusions in a lesion. Tumor size, bilaterality, multifocality, extrathyroidal extension, capsular and vascular invasion, and lymph node metastasis (LNM) were noted. Variants of PTC were grouped as classical, follicular, oncocytic, tall cell, and others. The seventh edition of the American Joint Committee on Cancer TNM classification system for differentiated thyroid carcinoma was used for staging of patients (14).

Follow-up

Radioactive iodine (RAI) ablation treatment in doses of 50–200 mCi was administered along with TSH stimulation and a low-iodine diet for at least 2 weeks. After 6–9 months, patients who received RAI ablation treatment underwent diagnostic 131I whole-body scanning (DxWBS) using 185 MBq of 131I. Additional RAI ablation was administered for residual/recurrent disease. During follow-up, serum TG and anti-TG were measured and neck ultrasound was performed and every 3–12 months according to the clinical condition.

The conventional and dynamic responses were evaluated at the last visit. The conventional response was classified as remission, persistence, and recurrence. Remission was defined as an absence of clinical or imaging finding of tumor, serum TG levels under 2 ng/mL at the time of TSH suppression/stimulation, and negative anti-TG antibodies. The patient was considered to have persistence if these remission criteria were not achieved during clinical monitoring. Patients who met remission criteria previously but had current evidence of tumor were defined to have a recurrence (15). Dynamic response was classified as excellent, biochemical incomplete, structural incomplete, and indeterminate (16).

Statistical analysis

The statistical analysis of data was performed with The Statistical Package for Social Sciences version 20.0 software (IBM Corp.; Armonk, NY, USA). The distribution of variables was evaluated by the Shapiro-Wilk test. Variables with normal distribution were presented as mean±standard deviation and those that were not normally distributed were presented as median (minimum-maximum). The number and percent (%) of categorical variables were given. Student's t-test and

Mann-Whitney U test were used to evaluate the differences in groups for parametric and non-parametric variables, respectively. The categorical variables were compared by Chi-squared test. A p value of less than 0.05 was considered to indicate statistical significance.

Results

There were 69 patients with FPTC and 223 with SPTC; of whom, 60 (87.0%) patients had 1, 8 (11.3%) had 2, and 1 (1.7%) had 4 family members with PTC. Parent-child, sibling, and both parent-child and sibling relationships were present in 29 (42.0%), 36 (52.2%), and 4 (5.8%) patients with FPTC, respectively. The median age and sex distribution were comparable in the 2 groups (Table 1). Median TSH and anti-TG positivity were higher in patients with FPTC than in those with SPTC (p=0.031 and p=0.032, respectively). Hypothyroidism was more prevalent among patients with FPTC. There was not any significant difference in anti-TPO positivity and the nodule number in the ultrasound between the 2 groups. The rate of patients operated for cytological indications was 85.5% in FPTC and 66.7% in SPTC (p=0.004).

Lymphocytic thyroiditis in histopathology was found with similar rates in the 2 groups. Rates of multifocality and bilaterality were higher in patients with FPTC (p=0.009 and p=0.011, respectively). LNM was observed in 2 (2.9%) patients with FPTC and 29 (13.0%) patients with SPTC (p=0.018). There were 3 patients with distant metastasis in the SPTC group, whereas no patient with FPTC had distant metastasis. TNM staging was not different, and stage I was the most frequent stage in the 2 groups (88.4% and 80.9%) (Table 1).

Preoperative ultrasound data were available in 58 and 144 malignant nodules in FPTC and SPTC groups, respectively (Table 2). All 3 dimensions of the malignant nodule were significantly smaller in the FPTC group (<0.05). Localization, rate of nodules with anteroposterior/transverse diameter >1, texture, presence of hypoechoic halo, presence of macrocalcification and irregular margins were similar in both the groups (p=0.194, p=0.208, p=0.321, p=0.144, p=0.070, and p=0.822, respectively). The rate of isoechoic nodules was significantly higher in the FPTC group compared with those in the SPTC group. Microcalcification was more prevalent in malignant nodules of patients with SPTC (47.9% vs 25.9%, p=0.005). The distribution of cytological results of malignant nodules in FPTC and SPTC groups were similar.

The total number of tumor foci was 132 in patients with FPTC and 322 in patients with SPTC. Histopathologic features of malignant foci in the 2 groups are compared in Table 3. Median tumor diameter, rate of microcarcinoma, distribution of variants, extrathyroidal extension, and vascular invasion did not differ in the 2 groups. The only histopathological difference was a significantly higher capsular invasion in the SPTC group (17.4% vs 9.1%, p=0.024) (Table 3).

The rate of patients who received RAI treatment was similar; however, the rate of patients who received RAI doses >100 mCi was higher in patients with SPTC. Uptake in a (Dx-WBS performed between the 6th and 9th month of RAI treatment was similar in the 2 groups. Median stimulated TG levels at the time of Dx-WBS was higher in patients with SPTC (2.25 [0.01–505.00] ng/mL vs 0.92 (0.02–57.65) ng/mL, p=0.036]. Additional RAI treatment was required in 1 and 4 patients with FPTC and SPTC, respectively (1.7% vs 2.3%). At the last visit, conventional response rates (remission, recurrence, and persistence) and dynamic response rates (excellent, biochemical incomplete, structural incomplete, and indeterminate) were similar in the 2 groups (Table 4).

Discussion

Although the prevalence of FPTC was reported between 1.5% and 9.4% in different studies (3-6), the true incidence is unclear as the diagnosis largely depends on the history rather than genetic studies in clinical practice. An autosomal dominant inheritance is the most commonly observed mode of inheritance (17); however, polygenic inheritance can also be seen particularly in families with only 2 family members with PTC or in those that are associated with carcinogenic events like radiation exposure (18).

FNMTC occurs 2–3 times more frequently in women than SPTC (19); however, the male ratio is higher than expected in some studies (20). Compatible with the literature, the women/men ratio was higher in FPTC than in SPTC (6.7 vs 4.0); however, the difference was not significant in our study (19, 21).

Whether the behavior of FPTC is more aggressive or not is unclear. Some authors suggest that the biological behavior is more aggressive, and the recurrence rate is higher than SPTC and recommend more aggressive treatment in these patients (10, 11, 21, 22, 23), although others accept that both FPTC and SPTC have a similar clinical course and can be treated similarly (4, 12, 24, 25). Owing to the high prevalence of benign thyroid diseases (26) and detection of thyroid cancer in the second generation at a younger age among the relatives of patients with FPTC (3, 5), annual follow-up of family members was recommended. The content of the term "aggressiveness" varies in different articles. It could include 2 or more of the features such as earlier diagnosis, multifocality, bilaterality, LNM, extrathyroidal extension, as well as more frequent relapses, distant metastasis, and shorter disease-free survival. The ideal screening and treatment strategy are still controversial in patients with FPTC and their family members.

Studies have shown that FNMTC was diagnosed earlier than SPTC (4, 10, 19, 27, 28). Because FNMTC diagnosis was made almost a decade earlier than SPTC, the family members of patients with FPTC should be scanned 5–10 years before the age of diagnosis of the index patient or beginning from 18 years of age (8, 19). In contrast, however, there are also studies with comparable results for the age of diagnosis for patients with FPTC and SPTC (5, 19, 21, 22). Similar to these studies, the mean age at diagnosis did not differ in the 2 groups in our study.

Higher nodule numbers were detected ultrasonographically in patients with FNMTC in some studies (3, 10, 11, 19, 24). However, we found similar mean nodule numbers in patients with FPTC and SPTC. The diameter of the malignant nodules on the preoperative ultrasound was significantly lower in patients with FPTC. To the best of our knowledge, ultrasound characteristics

Table 1. Demographic, clinical, and histopathological features of patients with familial and sporadic differentiated thyroid cancer

	Familial (n=69)	Sporadic (n=223)	p
Age (years)	46.6±11.7	47.7±13.0	0.609
Sex			
Female	60 (87.0%)	178 (79.8%)	0.182
Male	9 (13.0%)	45 (20.2%)	
TSH (μIU/mL)	1.790 (0.004–65.800)	1.455 (0.005–21.000)	0.031
fT3 (pg/mL)	3.09 (0.55–4.58)	3.2 (1.03–13.47)	0.303
fT4 (ng/dL)	1.15 (0.11–2.72)	1.16 (0.36–3.61)	0.320
Functional status			
Euthyroid	50 (72.9%)	182 (81.6%)	0.113
Hypothyroid	15 (21.4%)	23 (10.3%)	0.016
Hyperthyroid	4 (5.7%)	18 (8.1%)	0.514
Anti-TPO positivity (n=237)	17 (28.3%)	34 (19.2%)	0.137
Anti-TG positivity (n=233)	19 (29.2%)	28 (16.7%)	0.032
Nodule number on US	4 (1-10)	3 (0-14%)	0.667
Surgical indications (n=281)	n=62	n=219	
Giant nodule	5 (8.1%)	39 (17.8%)	0.062
Hyperthyroidism	3 (4.8%)	14 (6.4%)	0.650
Cytology	53 (85.5%)	146 (66.7%)	0.004
Other/unknown	1 (1.6%)	20 (9.1%)	0.047
Histopathologically lymphocytic thyroiditis (n=280)	35 (61.4%)	138 (61.9%)	0.947
Multifocality	33 (47.8%)	69 (30.9%)	0.009
Bilaterality	26 (37.7%)	50 (22.4%)	0.011
Lymph node metastasis	2 (2.9%)	29 (13.0%)	0.018
Distant metastases	0 (0.0%)	3 (1.4%)	NA
T			0.313
T1a	40 (58.8%)	122 (56.0%)	
T1b	20 (29.4%)	50 (22.9%)	
T2	2 (2.9%)	16 (7.3%)	
T3	6 (8.8%)	30 (13.8%)	
N			0.051
N0	66 (97.1%)	191 (87.2%)	
N1a	2 (2.9%)	15 (6.8%)	
N1b	0 (0.0%)	13 (5.9%)	
Stage			0.296
I	61 (88.4%)	177 (80.5%)	
II	2 (2.9%)	8 (3.6%)	
III	6 (8.7%)	21 (9.5%)	
IVa	0 (0.0%)	11 (5.0%)	
IVc	0 (0.0%)	3 (1.4%)	

TSH: thyrotropin, fT3: free triiodothyronine, fT4: free thyroxine, anti-TPO: antithyroid peroxidase antibodies, anti-TG: anti-thyroglobulin antibodies, US: ultrasonography, BTT/NT: bilateral total thyroidectomy/near-total thyroidectomy, T: tumor, N: node

of malignant nodules in patients with FPTC and SPTC were not compared in previous studies. We found that the microcalcification rate was lower in nodules of the FPTC group. In addition, isoechoic appearance was higher in these nodules. These suggest that ultrasound features that are known to be classically associated with a malignancy might be less prominent in patients with FPTC. However, it should be noted that the tendency to screen and recommend surgery with less clear indications in patients with a family member with PTC might cause detection of tumors without significant suspicious ultrasound features.

In the majority of studies, the rate of multifocality was higher in patients with FPTC (3, 5, 8, 10, 11, 19, 22, 29, 30), whereas a few studies showed a similar rate in the 2 groups of patients (12, 21). Similarly, there are controversial results in terms of the rate of bilateral disease. Some studies reported a higher rate of bilaterality in SPTC (10, 11, 19, 24, 25); however, others suggested no difference (21, 22). In our study, both multifocality and bilaterality were significantly higher in patients with FPTC than in those with SPTC. Tumor diameter was reported to be higher or lower in patients with FPTC compared with SPTC in different studies (10, 11, 19, 24, 28). Similar to our results, some studies did not find a trend or larger or smaller tumor size in patients with FPTC (3, 21, 22).

Table 2. Ultrasonography features and cytology results of malignant thyroid nodules in patients with familial and sporadic differentiated thyroid cancer

	Familial (n=58)	Sporadic (n=144)	p
Diameters (mm)			
Antero-posterior	7.8 (2.4–20.8)	9.7 (4.0–54.0)	0.003
Transverse	8.3 (4.8–26.1)	11.5 (4.3–67.9)	0.000
Longitudinal	10.3 (6.0–25.3)	12.8 (4.0–78.8)	0.001
AP/T>1	18 (31.0%)	32 (22.2%)	0.208
Solid texture	56 (96.6%)	142 (98.6%)	0.321
Echogenicity			
Isoechoic	22 (37.9%)	29 (20.1%)	0.025
Hypoechoic	11 (19.0%)	28 (19.4%)	0.880
Iso-hypoechoic	25 (43.1%)	87 (60.4%)	0.841
Microcalcification	15 (25.9%)	69 (47.9%)	0.005
Macrocalcification	16 (27.6%)	60 (41.7%)	0.070
Hypoechoic halo	7 (12.1%)	29 (20.1%)	0.144
Irregular margins	39 (67.2%)	97 (67.4%)	0.822
Cytological diagnosis	n=54	n=143	0.100
Nondiagnostic	3 (5.2%)	12 (8.3%)	
Benign	8 (13.8%)	16 (11.1%)	
AUS/FLUS	21 (36.2%)	26 (18.1%)	
FN/SFN	1 (1.7%)	4 (2.8%)	
Suspicious for malignancy	11 (19.0%)	32 (22.2%)	
Malignant	14 (24.1%)	54 (37.5%)	

AP/T: Ratio of anterior-posterior to transverse diameter
FN/FNS: follicular neoplasm/suspicious for follicular neoplasm, AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance

Table 3. Histopathological features of malignant foci in patients with familial and sporadic differentiated thyroid cancer

Histopathological features	Familial (n=132)	Sporadic (n=322)	p
Tumor diameter	6.0 (1.0–40.0)	7.0 (0.5–60)	0.086
Microcarcinoma	97 (73.5%)	212 (65.8%)	0.108
PTC variants			0.161
Classical	85 (69.1%)	243 (75.9%)	
Follicular	24 (19.5%)	53 (16.6%)	
Oncocytic	3 (2.4%)	10 (3.1%)	
Tall cell	6 (4.9%)	4 (1.2%)	
Other	5 (4.1%)	10 (3.1%)	
Capsular invasion	12 (9.1%)	56 (17.4%)	0.024
Vascular invasion	2 (1.5%)	10 (3.1%)	0.337
Extrathyroidal extension	6 (4.5%)	28 (8.7%)	0.127

PTC: papillary thyroid cancer,
a n=123 and n=320 for familial and sporadic foci, respectively

Table 4. Follow-up data of patients with familial and sporadic differentiated thyroid cancer

	Familial (n=69)	Sporadic (n=223)	p
Follow-up period (months)	32 (1–97)	46 (1–123)	0.055
RAI treatment	58 (84.1%)	175 (78.5%)	0.999
RAI dose, mCi			
≤100	50 (86.2%)	107 (61.1%)	0.001
>100	8 (13.8%)	68 (38.9%)	
Thyroid bed uptake in DxWBS	6 (17.1%)	9 (6.7%)	0.052
Stimulated TG levels at 6th month, ng/mL	0.92 (0.02–57.65)	2.25 (0.01–505.00)	0.036
Conventional response			0.814
Remission	55 (85.9%)	166 (86.9%)	
Persistence	8 (12.5%)	20 (10.5%)	
Recurrence	1 (1.6%)	5 (2.6%)	
Dynamic response			0.997
Excellent response	55 (85.9%)	165 (86.4%)	
Biochemical incomplete response	1 (1.6%)	3 (1.6%)	
Structural incomplete response	2 (3.1%)	5 (2.6%)	
Indeterminate response	6 (9.4%)	18 (9.4%)	

RAI: radioactive iodine; DxWBS: diagnostic whole body scan, TG: thyroglobulin (0–78 ng/mL)

The histological variant of PTC was assessed in a limited number of studies**.** In a study involving 24 patients with FPTC and 80 patients with SPCT, the incidence of a classical variant was lower, and the follicular variant was higher in patients with FPTC patients than in those with SPTC (3). The distribution of variants was comparable in patients with FPTC and SPTC in our study.

There are variations between studies in terms of features related to the aggressive behavior of PTC in familial cases. Although there is a preponderance of studies that reported higher rates of LNM, vascular invasion, and extrathyroidal extension (10, 11, 19, 24, 29-31), there are also studies that deny a higher risk of these features (12, 21, 22). The rates of vascular invasion and extrathyroidal extension were similar in both groups, and capsular invasion were increased significantly in SPTC group. Contrary to literature, the rate of LNM was higher in patients with SPTC. However, the distribution of stages was still similar in the 2 groups. Central lymph node dissection is not routinely performed on all patients with PTC in our center. This might partly explain the difference in rates of LNM. In addition, detection of thyroid cancer in the index case might lead to earlier and active screening of family members which subsequently cause earlier diagnosis before the development of LNM in the patients with FPTC.

The frequency of patients who received RAI treatment was similar in patients with FPTC and SPTC. However, a significantly higher rate of patients in the SPTC group was given an RAI dose of >100 mCi. In the literature, although some studies showed higher rates of recurrence, persistence, relapse, distant metastasis and mortality, and lower disease-free survival in patients with FPTC (5, 8, 10, 11, 19, 21, 22, 24, 30, 32), others reported no change in these parameters (3, 19, 25, 33). Pitoia et al. (29) have suggested that despite higher rates of multifocality and LNM in FPTC, these did not affect the outcome adversely. In our study, remission, recurrence**,** and persistence were similar in the 2 groups. There was an excellent response in more than 80% of patients with both FPTC and SPTC, and biochemical and structural incomplete response and indeterminate response did not change.

There may be different causes of variations in the rates of aggressive features and clinical follow-up in different studies. There are differences in the number and relationship of patients in the same family among the studies. Choosing patients with more affected individuals in the family might increase aggressivity. There were some studies showing lower disease-free survival rates in patients with 3 compared with those with 2 affected family members (9, 23). In another study, survival was shorter in patients with ≥4 family members than in patients with 2 family members (23). Furthermore, the difference in possible genetic defects related to FPTC in different populations (34) might cause controversial findings in studies. Finally, because a majority of patients have stage 1 carcinomas, more aggressive behavior of FNMTC could not be confirmed (19).

The major limitation of our study was its retrospective nature. We also did not evaluate patients according to parent-child or sibling relationships. In addition, we did not have any genetic mutation data, particularly in familial cases.

To our best knowledge, this is the first study to compare ultrasound features of patients with FPTC and SPTC. Malignant nodules were smaller in the preoperative ultrasound examination in patients with FPTC than in those with SPTC. Although multifocality and bilateral disease were higher in FPTC, LNM was lower**,** and dynamic and conventional responses were similar. Screening of subjects with a family member with PTC might provide earlier detection of patients with FPTC.

Ethics Committee Approval: This study was approved by Ethics committee of Yildirim Beyazit University Faculty of Medicine, (Approval No: 26379996/211).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Supervision – R.E., B.C.; Design – F.D.D.; Resources – F.D.D., D.O., C.A.; Materials – F.D.D., D.O., C.A., B.O.; Data Collection and/or Processing – F.D.D., D.O., C.A., B.O., M.K., A.K..; Analysis and/or Interpretation – F.D.D., D.O., C.A.; Literature Search – F.D.D., D.O.; Writing Manuscript – F.D.D.; Critical Review – D.O.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Robinson DW, Orr TG. Carcinoma of the thyroid and other diseases of the thyroid in identical twins. Arch Surg 1955; 70: 923-8. [CrossRef]
2. Leenhardt L, Bernier MO, Boin-Pineau MH, et al. Advances in diagnostic practices affect thyroid cancer incidence in France. Eur J Endocrinol 2004; 150: 133-9. [CrossRef]
3. Jiwang L, Zhendong L, Shuchun L, Bo H, Yanguo L. Clinicopathologic characteristics of familial versus sporadic papillary thyroid carcinoma. Acta Otorhinolaryngol Ital 2015; 35: 234-42.
4. Moses W, Weng J, Kebebew E. Prevalence, clinicopathologic features, and somatic genetic mutation profile in familial versus sporadic nonmedullary thyroid cancer. Thyroid 2011; 21: 367-71. [CrossRef]
5. Lee YM, Yoon JH, Yi O, et al. Familial history of non-medullary thyroid cancer is an independent prognostic factor for tumor recurrence in younger patients with conventional papillary thyroid carcinoma. J Surg Oncol 2014; 109: 168-73. [CrossRef]
6. Farid NR, Shi Y, Zou M. Molecular basis of thyroid cancer. Endocr Rev 1994; 15: 202-32. [CrossRef]
7. Malchoff CD, Malchoff DM. Familial Papillary Thyroid Carcinoma. Farid NR, editor. Molecular Basis of Thyroid Cancer. Cancer Treatment and Research, vol 122. Boston, MD: Springer; 2005.p.381-7. [CrossRef]
8. Sippel RS, Caron NR, Clark OH. An evidence-based approach to familial nonmedullary thyroid cancer: screening, clinical management, and follow-up. World J Surg 2007; 31: 924-33. [CrossRef]
9. Sturgeon C, Clark OH. Familial nonmedullary thyroid cancer. Thyroid 2005; 15: 588-93. [CrossRef]
10. Alsanea O, Wada N, Ain K, et al. Is familial non-medullary thyroid carcinoma more aggressive than sporadic thyroid cancer? A multicenter series. Surgery 2000; 128: 1043-51. [CrossRef]
11. Mazeh H, Benavidez Al, Poehls J, Youngwirth L, Chen H, Sippel RS. In patients with thyroid cancer of follicular cell origin, a family his-

tory of nonmedullary thyroid cancer in one first degree relatives is associated with more aggressive disease. Thyroid 2012; 22: 3-8. [CrossRef]
12. Robenshtok E, Tzvetov G, Grozinsky-Glasberg S, et al. Clinical characteristics and outcome of familial nonmedullary thyroid cancer: a retrospective controlled study. Thyroid 2011; 21: 43-8. [CrossRef]
13. Jo VY, Stelow EB, Dustin SM, Hanley KZ. Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol 2010; 134: 450-6. [CrossRef]
14. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. Thyroid cancer staging. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A,editors. AJCC Cancer Staging Manual. 7th edition. Newyork, MD: Springer-Verlag; 2010.p.59-64.
15. Kim HJ, Sohn SY, Jang HW, Kim SW, Chung JH. Multifocality, but not bilaterality, is a predictor of disease recurrence/persistence of papillary thyroid carcinoma. World J Surg 2013; 37: 376-84. [CrossRef]
16. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26: 1-133. [CrossRef]
17. Lote K, Andersen K, Nordal E, Brennhovd IO. Familial occurrence of papillary thyroid carcinoma. Cancer 1980; 46: 1291-7. [CrossRef]
18. Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl. Nature 1992; 359: 21. [CrossRef]
19. Hillenbrand A, Varhaug JE, Brauckhoff M, et al. Familial nonmedullary thyroid carcinoma-clinical relevance and prognosis. A European multicenter study. ESES Vienna presentation. Langenbecks Arch Surg 2010; 395: 851-8. [CrossRef]
20. Lupoli G, Vitale G, Caraglia M, et al. Familial papillary thyroid microcarcinoma: a new clinical entity. Lancet 1999; 353: 637-9. [CrossRef]
21. McDonald TJ, Driedger AA, Garcia BM, et al. Familial papillary thyroid carcinoma: a retrospective analysis. J Oncol 2011; 2011: 948786. [CrossRef]
22. Capezzone M, Marchisotta S, Cantara S, et al. Familial non-medullary thyroid carcinoma displays the features of clinical anticipation suggestive of a distinct biological entity. Endocr Relat Cancer 2008; 15: 1075-81. [CrossRef]
23. Triponez F, Wong M, Sturgeon C, et al. Does familial nonmedullary thyroid cancer adversely affect survival? World J Surg 2006; 30: 787-93. [CrossRef]
24. Ito Y, Fukushima M, Yabuta T, et al. Prevalence and prognosis of familial follicular thyroid carcinoma. Endocr J 2008; 55: 847-52. [CrossRef]
25. Maxwell EL, Hall FT, Freeman JL. Familial nonmedullary thyroid cancer: a matched-case control study. Laryngoscope 2004; 114: 2182-6. [CrossRef]
26. Pal T, Vogl FD, Chappuis PO, et al. Increased risk for nonmedullary thyroid cancer in the first degree relatives of prevalent cases of nonmedullary thyroid cancer: a hospital-based study. J Clin Endocrinol Metab 2001; 86: 5307-12. [CrossRef]
27. Lote K, Andersen K, Nordal E, Brennhovd IO. Familial occurrence of papillary thyroid carcinoma. Cancer 1980; 46: 1291-7. [CrossRef]
28. Ozaki O, Ito K, Kobayashi K, Suzuki A, Manabe Y, Hosoda Y. Familial occurrence of differentiated, nonmedullary thyroid carcinoma. World J Surg 1988; 12: 565-71. [CrossRef]
29. Pitoia F, Cross G, Salvai ME, Abelleira E, Niepomniszcze H. Patients with familial non-medullary thyroid cancer have an outcome similar to that of patients with sporadic papillary thyroid tumors. Arq Bras Endocrinol Metabol 2011; 55: 219-23. [CrossRef]
30. Uchino S, Noguchi S, Kawamoto H, et al. Familial nonmedullary thyroid carcinoma characterized by multifocality and a high recurrence rate in a large study population. World J Surg 2002; 26: 897-902. [CrossRef]
31. Park YJ, Ahn HY, Choi HS, Kim KW, Park DJ, Cho BY. The long-term outcomes of the second generation of familial nonmedullary thyroid carcinoma are more aggressive than sporadic cases. Thyroid 2012; 22: 356-62. [CrossRef]
32. Takami H, Ozaki O, Ito K. Familial nonmedullary thyroid cancer: an emerging entity that warrants aggressive treatment. Arch Surg 1996; 131: 676. [CrossRef]
33. Loh KC. Familial nonmedullary thyroid carcinoma: a meta-review of case series. Thyroid 1997; 7: 107-13. [CrossRef]
34. Peiling Yang S, Ngeow J. Familial non-medullary thyroid cancer: unraveling the genetic maze. Endocr Relat Cancer 2016; 23: 577-95. [CrossRef]