# Prospective Screening Protocol for FNMTC Family Members: Ultrasound Versus Physical Examination

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**Abstract**

Non-medullary thyroid cancer (NMTC) of follicular cell origin make up 95% of thyroid cancers, of which 85% are papillary thyroid cancer (PTC). Generally, these tumors have an excellent prognosis. Since the first description of identical twins with papillary thyroid cancer in 1955, epidemiological data have shown that up to 8% of these tumors are familial in etiology, despite not being related to other known cancer syndromes.

**Keywords**

Thyroid nodule · Well-differentiated thyroid cancer · Familial non-medullary thyroid cancer · Cancer genetics · Thyroid ultrasound

## Overview of Familial Non-medullary Thyroid Cancer (FNMTC)

Non-medullary thyroid cancer (NMTC) of follicular cell origin make up 95% of thyroid cancers, of which 85% are papillary thyroid cancer (PTC). Generally, these tumors have an excellent prognosis [1]. This chapter deals with the question of

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P. Angelos, R. H. Grogan (eds.), *Difficult Decisions in Endocrine Surgery*, Difficult Decisions in Surgery: An Evidence-Based Approach,
https://doi.org/10.1007/978-3-319-92860-9_6

ultrasound versus physical examination as the best screening protocol for FNMTC family members (Table 6.1).

Since the first description of identical twins with papillary thyroid cancer in 1955, epidemiological data have shown that up to 8% of these tumors are familial in etiology, despite not being related to other known cancer syndromes [2] (Table 6.2). First degree family members of patients with thyroid cancer have up to ninefold increase in also developing the disease [3, 4]. The classic definition of FMNTC describes the presence of NMTC in a family in which two or more first degree relatives are affected [5, 6]; however, there is no consensus agreement on this number of affected relatives, with other authors using different cutoffs for the number of affected relatives [5, 7]. Most of these tumors are PTC (>90%); in addition, other benign thyroid conditions such as goiter and thyroiditis are found in over 50% of cases [3, 6]. Swedish epidemiological data have found an over threefold and sixfold increased risk of NMTC in a PTC patient's parent and sibling, respectively [8].

There is much still to be understood regarding the inheritance of FNMTC; however, autosomal dominance with incomplete penetrance and variable expressivity continues to be generally accepted as the most likely pattern [9–13]. Families with two first degree relatives have between a 33% and 50% probability of belonging to an FNMTC kindred, and those with three or more first degree relatives have a 95% chance [14]. The dramatic increase in probability of FNMTC between a cutoff of 2 versus ≥3 affected family members is simply due to the difference in statistical possibility of these relatives sharing a diagnosis of NMTC but actually having separate incidences of sporadic disease.

## Genetics of FNMTC

In contrast to other hereditary syndromes well described in the literature, FNMTC has less understood genome differences. Of the four other named cancer syndromes of which NMTC is a component, three are autosomal dominant (Gardner's

**Table 6.1** PICO table

| | |
|---|---|
| **P**opulation | Relatives of FNMTC patients |
| **I**ntervention | Ultrasound screening |
| **C**omparator | Physical exam |
| **O**utcomes | Survival, recurrence, age at operation, size of tumor |

**Table 6.2** Author recommendations in the screening of FNMTC

| Number of family members with WDTC | Recommendation |
|---|---|
| None | No screening |
| One | Physical exam yearly |
| Two | Ultrasound yearly |
| Three or more | Ultrasound yearly |

syndrome, Cowden disease and Carney Complex) and one is autosomal recessive (Werner Syndrome). Each of these syndromes has a specific gene mutation [15–19]. It is important to note, however, that the risk of thyroid cancer within these entities is highly variable and even within each syndrome the range of reported risk of well differentiated thyroid cancer is very broad. FNMTC which as of yet has not been associated with a single mutation has not been as well described; one reason may be that other epigenetic mechanisms play a more significant role in the heredity of FNMTC. Nevertheless, several implicated genes and loci have been described, although it remains unclear whether these genetic alterations specifically cause thyroid cancer to develop, or rather that they are associated with increased thyroid follicular cell growth/function in general, since families with FNMTC also have higher rates of benign adenomas, Hashimoto's thyroiditis and multinodular goiters.

An overview of the genetic regions implicated in FNMTC is shown in Table 6.3 [20]. MNG1 was one of the first genetic loci to be associated with FNMTC; however, follow-up analysis showed that it was more closely related with familial multinodular goiters. The TCO, fPTC/PRN, and FTEN regions have had mixed results showing an association with FNMTC, with limited confirmatory datasets. NMTC1 has had multiple large studies showing its association with FNMTC, but particularly with follicular variant of PTC. A SNP array-based linkage analysis of 38 FNMTC kindreds revealed 2 loci on chromosomes 1q21 and 6q22, but these results have not been broadly validated [21]. Recently, there has been increased evidence for FOXE1 on chromosome 9q22.33 in several large FNMTC kindreds in both Europe and the U.S. Further, there has also been recent evidence that telomere telomerase complex may play a larger role in the genetics of familial thyroid cancer. The evidence however, is still limited and far from conclusive. Overall, the genetic underpinnings of FNMTC has yet to be fully characterized.

## Prognostic Differences in FNMTC Patients

It is generally accepted that NMTC found in two family members may be more aggressive and portend a worse prognosis than those without a positive family history [22]. Several studies have supported this assertion. A retrospective analysis of 1262 patients of whom 113 (9%) were diagnosed with FNMTC found that those

**Table 6.3** Genetic regions associated with familial nonmedullary thyroid cancer

| Gene | Location |
|---|---|
| MNG1 | 14q31 |
| TCO | 19q13.2 |
| fPTC/PRN | 1q21 |
| NMTC1 | 2q21 |
| FTEN | 8p23.1-p22 |
| | 1q21, 6q22 |
| FOXE1 | 9q22.33 |
| Telomere telomerase complex | |

associated with FNMTC were associated with worse outcomes, particularly with respect to disease free survival [23]. McDonald et al. [24] echoed these findings, showing that FNMTC patients had higher rates of reoperation, additional treatment with radioactive iodine, distant metastasis, and death [24]. In addition, a multicenter matched case control series showed 48 patients with FNMTC compared with non-familial disease had shorter disease free survival [10]. Furthermore, Uchino et al. reviewed 6458 Japanese patients with NMTC and found 258 patients implicated in familial disease. In this study, disease free survival was worse overall in FNMTC patients, although the mechanism was unclear as rates of invasive tumors and lymph node metastasis were similar [7].

## Screening for FNMTC

### Detection of the Abnormal Thyroid

Before the introduction of ultrasound into clinical practice, the physical exam of the thyroid remained the mainstay of detection of suspicious goiters requiring intervention. Multiple studies done to assess the utility of clinical exam have been extremely variable. Studies looking at sensitivity of detecting presence of goiter by physical exam have be estimated to be as low as 64% [25, 26], and sensitivity for nodules as low as 31% [27]. On the other hand, assessment of specificity in detecting abnormal thyroid goiter has approached 100% in many studies [25, 28, 29]. Nevertheless the variability in physical examination's sensitivity led to widespread adoption of the use of ultrasound in detecting thyroid abnormalities. Since one of the first descriptions of use of ultrasound to view the thyroid gland in 1967, [30] the ultrasound rapidly became a central clinical tool in detecting pathology. Currently, ultrasound technology has integrated into the clinicians practice so much so that it has become an extension of the physical exam. Surgeon performed ultrasound has become accepted as an integral part of the assessment of thyroid nodules within national guidelines [31].

### Defining the Population Most Likely to Benefit from Screening

There has been a growing concern regarding the overdiagnosis of thyroid cancer in the general population. The initiation of whole-population screening with thyroid ultrasound in South Korea has led to a striking increase in the diagnosis of thyroid cancer since the beginning of this millennium, but no change in cancer-related mortality. Although not nearly as dramatic, this phenomenon has been demonstrated to a lesser degree in the United States. This discrepancy between the rate of diagnosis versus rate of mortality has raised the concern that this detection strategy is leading to the workup and treatment of many smaller thyroid cancers which may otherwise never become clinically significant [32]. The implications on treatment-related complications/morbidity as well as costs and resources are evident.

On the other hand, FNMTC tumors do exhibit more aggressive behavior and confer a worse prognosis, as described above. In addition, it appears that early diagnosis and appropriate treatment in FNMTC patients increases their disease free and overall survival [5], which certainly suggests a benefit to screening at-risk family members. Therefore, any proposal for a screening strategy for FNMTC kindreds would do best to implement an adequately sensitive screening strategy for those families most at risk, while minimizing the pitfalls related to overdiagnosis and cost.

Identifying the FNMTC population most likely to benefit from screening depends critically upon whether FNMTC is defined as a family with ≥2 or 3 affected first-degree relatives. This is because the probability of a true genetic component in any given family with differentiated thyroid cancer increases (and that of a random sporadic cancer inversely decreases) as the number of known affected relatives increase [14] and (Table 6.3). Table 6.4 summarizes screening recommendations by breaking down the probability estimates of detecting a true FNMTC-related differentiated thyroid cancer using ultrasound versus physical exam, depending on the family history of a hypothetical screening subject. The key dependent variables in this model that were derived from the literature are (1) the prevalence of a thyroid nodule, (2) probability of a differentiated thyroid cancer in that nodule, (3) sensitivity of ultrasound versus physical exam in detecting this nodule/cancer, and (4) the likelihood that this cancer has a true heritable component (as opposed to a sporadic cancer). One limitation of this model is that the increased prevalence of a thyroid nodule and cancer in a subject with a positive family history remains static (52% and 20%, respectively) regardless of the number of affected family members. One would assume that there would be a more proportional relationship, but in the absence of robust evidence, the static prevalence numbers were left in place, and thought to represent a more conservative strategy from a cost-effectiveness standpoint.

Based on this model, it appears clear that any screening strategy for thyroid cancer (either ultrasound or physical exam) in the absence of any related family history would be ineffective, with an overall detection rate of 0.01%–0.02%. Conversely, ultrasound appears justified as an effective screening strategy for families with ≥2 affected members, with its ability to detect a true FNMTC-related cancer in 10% of this population. In comparison, screening strategies for colorectal cancer in the US addresses an approximately 1% cancer prevalence in people over the age of 50, and for breast cancer addresses a 3% prevalence in women over the age of 40.

For the prospective screening subject with only one affected first-degree family member with NMTC, however, it remains unclear whether the more modest improvement in sensitivity of ultrasound compared to physical exam (3.6% vs 1%) justifies the extra cost and resources. One could argue that these percentages are still within the range of those for general-population screening for colon and breast cancer; however, the consequences of delayed diagnosis are admittedly more severe in these cancers compared to either sporadic NMTC or FNMTC. Based on the current evidence, a firm recommendation cannot be made about the preferred screening modality for people with only one first-degree family member with NMTC.

**Table 6.4** Understanding risks with numbers—hypothetical scenario of patient without known thyroid disease

| Family members with WDTC, *N* | Overall chance of detected thyroid nodule, % | Chance of the nodule being a cancer, % | Chance ultrasound would detect cancer, % | Chance physical exam would detect cancer, % | Likelihood that identified cancer is associated with FNMTC, % (%) | Overall FNMTC-related cancer detection with ultrasound, % | Overall FNMTC-related cancer detection with physical exam, % | Difference, % |
|---|---|---|---|---|---|---|---|---|
| None | 10 | 5 | 100 | 31[b] | 4[c] | ***0.021*** | ***0.007*** | ***0.14*** |
| One | 52[a] | 20[a] | 100 | 31[b] | 35[c] | ***3.6*** | ***1.1*** | ***2.5*** |
| Two | 52[a] | 20[a] | 100 | 31[b] | 94[c] | ***9.8*** | ***3.0*** | ***6.8*** |
| Three | 52[a] | 20[a] | 100 | 31[b] | 100[c] | ***10.4*** | ***3.2*** | ***7.2*** |

[a]Charkes 1998 and 2006 Thyroid [14]
[b]Eden et al. 2001 Med Pediatr Oncol [27]
[c]Uchino 2004 World J Surg [7]

Lastly, a key question also remains as to the proper timing of screening, both with respect to initiation and frequency. Limited evidence currently exists to support any frequency longer than yearly screening, and more studies are needed in order to address this.

## Understanding Risks with Numbers: Hypothetical Scenario of Patient Without Known Thyroid Disease

As can be seen from Table 6.4, the hypothetical calculation above shows that comparing physical exam to ultrasound screening of patients with only one first degree relative having thyroid cancer shows a 3.6% vs 1.1% detection rate of thyroid cancer. This illustrates a potential miss rate of 2.5%. What is not calculated in this model is the cost of regular ultrasounds for many family members of thyroid cancer patients, as well as the rate of detection, workup and follow-up of benign or inconsequential thyroid nodules. Depending on the practice setting, the absolute risk reduction may or may not justify the extra costs associated with ultrasound screening in this cohort. Our tentative recommendation would be to.

On the other hand, it would be prudent to use ultrasound in families with two or more affected members with NMTC, due to the higher risks associated with a true FNMTC tumor. These are the patients who would most benefit from treatment and are least likely to belong to the category of patients with overdiagnosed thyroid cancer. According to this model, ultrasound would be effective in capturing the significantly higher proportion (~10%) of family members with FNMTC.

## Fine Needle Aspiration of Thyroid Nodules

The American Thyroid Association recommends considering fine needle aspiration biopsy (FNAB) for all thyroid nodules >5 mm in patients with a first degree family member with NMTC (recommendation I—neither for nor against). Micropapillary thyroid cancer in the general population is an extremely indolent disease; however, little is known about these tumors in the context of FNMTC, and it is reasonable to assume that the more aggressive characteristics associated with FNMTC apply even to tumors <1 cm in size (Ito). We therefore suggest using the ATA recommendations specifically performing fine needle aspirations in thyroid nodules >5 mm with suspicious features or < 1 cm without (ATA recommendation A- strongly recommend and B—recommend respectively).

**Conclusion**

Although its genetics have yet to be elucidated, FNMTC is a clinically distinct entity with a worse prognosis compared to sporadic NMTC. For this reason, we recommend screening family members of FNMTC patients who are at risk for this disease; however it is important to stratify the modality of screening based

on the overall probability of having FNMTC. There is a high variability in the sensitivity and specificity of physical exam, and an overall superior detection of suspicious thyroid nodules with ultrasonography. With no cost considerations, it is therefore clear that ultrasound is superior to physical exam. Further, as many studies have shown (Rosario etc), it is important to recognize these malignancies earlier as familial cancers portend a worse prognosis than sporadic ones. Without formal cost effective studies taking into consideration the prevalence of FNMTC, current recommendations suggest screening all those with a single first degree family member with NMTC. Considering that the prevalence of true FNMTC is relatively low, as well as the high cost of regular ultrasounds, biopsies and health professional follow-up, the authors recommend yearly ultrasound screening for those with ≥2 family members with NMTC, and physical exam with aggressive management of any detected thyroid nodules in those families with only one affected member with NMTC.

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