Results of screening in familial nonmedullary thyroid cancer

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Abstract

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Reference

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Results of screening in familial nonmedullary thyroid cancer

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Abstract

Background: Although a family history of thyroid cancer is one of the main risk factors for thyroid cancer, the benefit of screening individuals with a family history of thyroid cancer is not known.

Methods: We performed a prospective cohort study with yearly screening using neck ultrasound and fine needle aspiration biopsy (FNAB) of the thyroid nodule(s) >0.5 cm in at risk individuals whose relatives were diagnosed with familial nonmedullary thyroid cancer (FNMTC). The eligibility criteria were the presence of thyroid cancer in ≥2 first-degree relatives, and an age of >7 years. Twenty-five kindred were enrolled in the study (13 families with 2 members affected, and 15 with ≥3 members affected at enrollment).

Results: Thyroid cancer was detected by screening in 4.6% (2/43) of at risk individuals from families with 2 members affected, and in 22.7% (15/66) of at risk members from families with ≥3 patients affected (p=0.01). FNMTC detected by screening was characterized by a smaller tumor size (0.7 cm+/–0.5 vs. 1.5+/–1.1, p=0.006), a lower rate of central neck lymph node metastases (17.6% vs. 51.1%, p=0.02), a less extensive surgery [hemi-thyroidectomy 23.5% vs. 0%, p=0.002] and a lower rate of radioactive iodine therapy (23.5% vs. 79%, p<0.001) as compared to those affected at enrollment.

Conclusions: Screening of at risk family members resulted in earlier detection of low-risk FNMTC and was associated with a less aggressive initial treatment. Screening with thyroid ultrasound should be considered in kindred with ≥3 family members affected by FNMTC. Since active screening might be associated with the risk of overtreatment, it should be implemented with caution specifically in elderly individuals.

Introduction

There has been an increasing incidence of thyroid cancer diagnoses worldwide, and it is currently the fastest growing cancer diagnosis in the United States. In 2016, it is estimated that more than 65,000 new cases of thyroid cancer will occur in the United States. The two main risk factors of thyroid cancer are a family history of thyroid cancer, and previous radiation exposure (therapeutic radiation to the head and neck and
radioactive isotope).(2) Familial nonmedullary thyroid cancer (FNMTc) accounts for 3%–9% of all nonmedullary thyroid cancer (NMTC) cases. FNMTc may occur as a minor component of syndromic familial cancer syndromes (Gardner and Cowden syndrome, Carney complex type 1, Werner and DICER1 syndromes) or as a nonsyndromic familial disease.(3)

The majority of FNMTc cases is nonsyndromic with unknown susceptibility gene(s), and defined as two or more first-degree relatives affected with NMTC. Most, but not all studies suggest more aggressive clinical behavior of FNMTc with higher rates of locoregional lymph-node metastases, extrathyroidal invasion, multifocal tumors, and higher recurrence rates as compared to sporadic NMTC.(4),(5–14) A recent meta-analysis that included 12 studies involving 12,741 patients who were followed for 1.5–12.1 years attempted to clarify these controversies.(4) The analysis was based on retrospective studies, including eight cohort studies and four case-control studies, of which five were conducted in Asia (7, 9, 15-17), four in North America (10, 18-20), two in Europe (21, 22), and one in a combined U.S. and Japanese cohort. (8) The study revealed increased rate of recurrence (OR 1.72, 95% CI: 1.34 to 2.20) and decreased disease-free survival (HR 1.83, 95% CI: 1.34 to 2.52) in FNMTc cases as compared with sporadic disease.(4) In this meta-analysis, younger age at diagnosis (2.4 years lower on average for FNMTc patients compared with the sporadic cases), higher risk of multifocal tumor growth (OR 1.50, 95% CI: 1.32 to 1.71), bilateral disease (OR 1.29, 95% CI: 1.00 to 1.66), extrathyroidal invasion (OR 1.20, 95% CI: 1.02 to 1.41), and lymph node metastases (OR 1.18, 95% CI: 1.01 to 1.38) was observed in FNMTc, but no difference in tumor diameter was appreciated (4).

Interestingly, FNMTc might be more aggressive, with higher thyroid cancer-specific mortality, in families with 3 or more members affected by FNMTc as compared with families with 2 members affected.(23) To our knowledge, there has been no prospective screening study in patients with FNMTc to determine who should have screening based on the number of affected members, what is the impact of screening on detection of thyroid cancer, treatment utilization, and/or treatment-associated morbidity and mortality.

In this study, we report the screening results of kindred with FNMTc. We found a high rate of thyroid cancer in families with three or more first-degree relatives affected by
Furthermore, screening resulted in the detection of the disease in a less advanced stage and utilization of less aggressive initial treatment.
Methods

We analyzed the screening results in kindred with FNMT who enrolled in a prospective cohort study at the National Institutes of Health (NIH) Clinical Center between April 2010 and December 2015 (Clinicaltrials.gov: NCT-01109420). All participants provided written informed consent. The main inclusion criteria were the presence of at least two first-degree relatives affected with NMTC and an age of >7 years. Individuals with syndromic FNMT were excluded from the study and a family history questionnaire was obtained from all kindred. The study was approved by the Office of Human Subjects Research Protections at the NIH.

Demographic, clinical, and pathologic data were collected from medical records, family history questionnaires, and patient interviews. Patient histories, family pedigrees and physical examinations, imaging studies, and laboratory tests were obtained from all patients enrolled in the protocol. All pathology slides were reviewed at our institution to confirm the thyroid cancer diagnoses and histologic subtype.

All at-risk family members, who agreed to participate in the study, were screened yearly by physical examination and thyroid ultrasound (US) using a linear 7.5 MHz transducer. According to practice guidelines at the time of study initiation, 2009 American Thyroid Association Guidelines, thyroid nodules larger than 5 mm in size were biopsied under US-guidance. The Bethesda classification system was used to categorize the cytology diagnosis: I—nondiagnostic, II—benign, III—atypia of undetermined significance/ follicular lesion of undetermined significance (AUS/FLUS), IV—follicular neoplasm, V—suspicious for cancer, and VI—thyroid cancer. Treatment of patients with NMTC was consistent with established clinical practices and all patients were followed annually. Response to treatment was defined as excellent response if follow up studies revealed negative imaging and/or suppressed Tg <0.2 ng/mL or stimulated Tg < 1 ng/mL with negative anti-Tg antibodies.

We compared the age of diagnosis of FNMT in the study group with the age of onset of thyroid cancer in the general population as reported in the Surveillance, Epidemiology and End Result (SEER) data on thyroid cancer, representing 28% of the US
population. Only non-medullary thyroid cancer cases (N=61,523) were included from the SEER data for the comparison.

Statistical analyses

For parametric and nonparametric data, a two-sided two-sample t test and Mann-Whitney test were used, respectively. A Chi square test of independence and a Fisher exact test were used for categorical data. A p value of <0.05 was considered statistically significant. The data were analyzed using RStudio software (Boston, MA).
Results

Twenty-five kindred with FNMTNC were enrolled in the prospective cohort study. Twelve families had 2 first-degree relatives affected, and 13 families had 3 or more first-degree relatives affected at the time of enrollment as documented in 25 pedigrees in Supplemental Figure 1. The study cohort consisted of 252 individuals; 69 patients with an established diagnosis of thyroid cancer before enrollment, of whom 56 were included in the study (13 patients were excluded as 10 died before enrollment and 3 did not provide tissue samples for review) and 183 unaffected at risk relatives among whom 109 (59.6%) underwent screening (Figure 1). Among patients with FNMTNC diagnosed before enrollment, there was no difference in baseline clinic-pathological characteristics between the kindred with 2- and ≥3-affected members (tumor size 1.8 vs 1.5 cm, p=0.49, gross extrathyroid extension 9% vs 8%, p=0.6, central neck LN metastases 51% vs 50%, p=0.99, lateral neck LN metastases 25% vs 16.7%, p=0.68, respectively).

Screening thyroid US in 109 at-risk family members detected at least one thyroid nodule in 50.5% (55 of 109) of individuals. The mean age of individuals with thyroid nodules detected was 36 years (range 7-81) (Figure 2). The highest prevalence of thyroid nodules was in the parental generation of the index case (72.7%), but it was also high in the first (57.1%), second (48.9%), and third generation (27.8%) (Table 1). Thyroid nodules were detected at the initial screening thyroid US in 53 of 55 (96.4%) patients, at the third screening thyroid US in 1 of 55 (1.8%) patients (in one of the patients the nodule was not detected initially, in two
other patients initially detected nodule grew in size), after the fourth screening thyroid US in 5 of 41 (12.2%) patients (in all patients nodules were detected after first screening, but initially did not reach the threshold size for biopsy), and the fifth screening thyroid US in 3 of 41 (7.3%) patients (in all 3 patients the nodules were detected at initial screening, but reached the size threshold for FNAB after the 5th US) (Figure 3). The FNAB showed a cytological diagnosis of papillary thyroid cancer or features suspicious for papillary thyroid cancer in 12 patients, follicular neoplasm in 2 patients, AUS/FLUS in 4 patients, 4 patients had nondiagnostic FNAB, and the remainder of the patients had benign cytologic diagnosis.

During follow-up (42 +/- 15 months), 23 patients were treated surgically. Pathology showed follicular adenoma in 6 (26%) patients and papillary thyroid cancer in 17 (74%) patients. Among patients found to have thyroid cancer, the final diagnosis was established after initial screening in 8 of 17 (47.2%) patients, at the second screening in 1 of 17 (5.8%), at the third thyroid screening US in 3 of 17 (17.6%), at the fourth thyroid screening US in 2 of 17 (11.8%), and at the fifth thyroid screening US in 3 of 17 (17.6%) patients (Figure 4). The growth velocity of the nodules ranged between 0.1 cm to 0.5 cm per year. There were no abnormal lymph nodes detected during this follow up period.

The peak incidence of thyroid cancer in the cohort of FNMTC, which occurred between 30-39 years of age, was a decade earlier than the peak incidence of thyroid cancer observed in the general population (Figure 5). Among families with 2 first-degree relatives affected at enrollment 43 out of 62 at risk members were screened (71.9%) while among the families with 3 first-degree relatives affected, 66 out of 121 members were screened (55%) (p=0.06). Taking into consideration all at risk family members, thyroid cancer was detected in significantly higher proportion of kindred with ≥3 first-degree relatives affected 12.4% (15/121) compared with the ones with 2 members affected 3.2% (2/62) (p=0.04). Among the screened patients, papillary thyroid cancer was detected at a significantly higher rate in kindred with ≥3 first-degree relatives affected at enrollment, as compared to kindred who had 2 first-degree relatives affected [22.7% (15/66) vs 4.6% (2/43), p=0.01, respectively]. There was no difference in the screening strategy between patients with 2 and ≥3 first-degree relatives affected (Supplemental Table 1). There was no
difference in the age and gender in the screened subgroups of patients with 2 and ≥3 first-degree relatives affected by FNMT (34+/−19.7 years vs 36+/−18.9 years, p=0.45 and female 55.8% vs 60.6%, p=0.69, respectively)

Compared with index cases, FNMT that was detected by thyroid US screening was characterized by a smaller primary tumor size (0.7+/−0.5 vs. 1.5+/−1.1 cm, p=0.006) and a lower rate of central neck lymph node metastases (17.6% vs 51.1%, p=0.02) (Table 2). Patients diagnosed by screening had less extensive surgery [hemi-thyroidectomy 23.5% (4/17) vs. 0% (0/56), p=0.002] and a lower rate of radioactive iodine therapy (23.5% vs. 79%, p<0.001) than patients with an established diagnosis at enrollment (Table 2). There was no statistically significant difference in complications associated with treatment between those patients diagnosed by screening and those patients with an established thyroid cancer diagnosis at the time of enrollment. However, there were no permanent hypoparathyroidism or permanent vocal cord paralysis in the patients diagnosed by screening, while in one of the patients with an established diagnosis of thyroid cancer at enrollment, the recurrent laryngeal nerve was sacrificed due to invasion of the nerve (Table 3). Excellent response to initial treatment was more frequently achieved in patients with papillary thyroid cancer detected by screening compared with the index cases [93.3% (16/17) vs. 68.3% (28/41), p=0.045].

FNMT recurrence rate was 14.3% (8/56) and thyroid cancer-specific mortality was 3.6% (2/56) in patients with an established diagnosis and mean follow up time of 83+/−72 months, and no recurrences and deaths occurred in patients with FNMT detected by screening but the follow up time was shorter 18+/−11 months (range, 1−36 months).
Discussion

We performed a prospective study focused on screening for thyroid cancer in at-risk individuals in kindred with FNMT involving multiple generations. Our results demonstrate that screening of at-risk family members identifies thyroid cancer in a greater number of individuals with 3 or more first-degree relatives. As expected, thyroid cancers diagnosed by screening were less advanced and patients had less extensive initial treatment.

Screening programs in patients at risk of cancer are usually recommended when 1) the patient is indeed at risk of cancer and when the familial disease is more aggressive than sporadic disease; and 2) when screening results in the detection of the disease at an earlier stage and when early diagnosis has an impact on subsequent treatment and outcome with respect to all-cause mortality, cancer-specific mortality, and or quality of life. Additionally, it is also important to determine whether screening for cancer is cost-effective.

Our study addresses two key components when determining whether screening for thyroid cancer is appropriate in family members at risk for FNMT, and in whom a screening strategy should be utilized. We found that the prevalence of thyroid cancer in at-risk individuals from families with 2 first-degree relatives is like the general population (4.6% vs 4.5%, respectively) and is significantly lower than the rate of thyroid cancer in kindred with 3 or more first-degree relatives affected (22.7%).(20) Another prospective study by Rios and colleagues involving 9 families with 2 members affected and 1 family with three members affected reported that 5% of screened at risk individuals had thyroid cancer, similar to our study cohort in kindreds with 2 affected members and to the incidence in the general population.(26) These results are in agreement with Charkes’ probability estimates that in kindred with 2 first-degree family members affected, the probability that the disease is sporadic or a chance occurrence is as high as 62%, but that it decreases to less than 6% when 3 or more members are affected.(27) Taken together, these data suggest that active screening should be considered only in families with 3 or more first-degree members affected by NMTC, especially in light of the increasing incidence of thyroid cancer worldwide, which is in part due to universal screening.
implemented by some countries such as South Korea and increased detection of subclinical thyroid cancer. (28)

Another important observation from our study is the significantly higher prevalence of thyroid nodules in FNMT (50.5%) than the general population (19-35%) that was found when performing screening thyroid US, which is consistent with previous studies by our group (44.4%) and other investigators (52%). (29, 30) Furthermore, a high prevalence of thyroid nodules and thyroid cancer was documented not only in the first and second generations, but also in the parental generation (relative to index case). In our study, the prevalence of thyroid nodules in the parental generation was as high as 72.7%, consistent with previous reports documenting thyroid nodules in up to 90% of the parental generation. (29) This data suggests that screening, if recommended, should involve all generations. Furthermore, because not all thyroid nodules and thyroid cancers were detected after the initial screening thyroid US or grew after the initial screening thyroid US warranting a FNAB, screening thyroid US should be repeated during follow up. Our study also documents that physical examination is not a sufficient screening tool since only 12.7% of nodules were palpable and none of them were malignant.

In most, but not all studies, the mean age of diagnosis for patients with FNMT is younger than those with sporadic thyroid cancer, with a peak age of onset in the fourth decade of life. (4, 5, 7, 16, 17, 19, 22, 31, 32) Similarly, in our study the peak incidence of FNMT was between 30 and 39 years of age as compared to the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program data in which the peak incidence in the general population is 10-15 years later. This phenomenon might be due to the ascertainment bias associated with the active screening strategy performed in our cohort, which involved all generations or might be due to the different biological behavior of FNMT. The youngest patient in our cohort found to have a thyroid nodule was 7 years old, and the youngest patients with papillary thyroid cancer were 18 years old (5 patients from 3 families). Thus, our data indicates that initiating screening before 18 years of age might be justified in some families.
Our study demonstrates that FNMTC detected by screening was characterized by less advanced disease at diagnosis and less extensive initial treatment. In fact, all FNMTC diagnosed by screening were microcarcinomas. Uchino and colleagues, in a retrospective study of a subgroup of FNMTC patients, reported that screening was associated with a small primary tumor size (9.1 ± 5.4 mm vs. 0.8 ± 0.6 mm) and a lower rate of multifocal tumors (47% vs. 53.3%). Thus, screening at-risk individuals in kindred with 3 or more first-degree relatives affected with FNMTC is likely to result in the detection of a less advanced disease that would allow less invasive treatment. In fact, none of the patient from the screened cohort had extrathyroidal tumor extension, thus in contrast to the patients with established diagnosis, none of the patient required sacrificing of vital structures such as the recurrent laryngeal nerve in order to achieve complete surgical resection. In our screened cohort, the patients underwent less aggressive initial treatment – less extensive surgery and radioiodine treatment (RAI). Since this observation might be due to the shift in thyroid cancer management guidelines towards less use of RAI therapy, we analyzed indications for RAI based on the current American Thyroid Association guidelines: (a) no RAI for low-risk patients, (b) individualized approach to RAI treatment in intermediate-risk patients, (c) uniform therapy with RAI for high-risk patients. Based on the current guidelines, only 51.1% instead of 79% of patients with a thyroid cancer diagnosis established before enrollment and presenting with lymph node metastases would have been treated with RAI. More importantly, a higher proportion of the probands would still require RAI therapy as compared with the at-risk individuals diagnosed by screening (51.1% vs 23.5%, p=0.05).

In our cohort of patients with FNMTC detected by screening, four patients with unilateral microcarcinomas were offered and elected to have a hemithyroidectomy as their surgical procedure of choice. Given the predisposition to development of thyroid cancer, these patients will need to be followed closely because of the risk of thyroid cancer in the remnant thyroid.

Our cohort was screened at a tertiary referral center; thus, the surgery was performed by high volume surgeons. The low complication rate in our study might not be generalizable to care at other medical centers, in which the majority of thyroidectomies are performed...
by low volume surgeons and as such may be associated with a higher risk of complications. Therefore, it might be justified to offer a watchful waiting strategy to the subset of patients with papillary microcarcinoma diagnosed by screening, especially when detected in older patients. Our study was initiated at the time of the 2009 American Thyroid Association guidelines. Therefore, the study design was consistent with the recommendation of performing FNAB in patients with a history of thyroid cancer in at least one relative, when thyroid nodule was larger than 5 mm in size. In view of the risk of complications associated with over-treatment, current 2015 American Thyroid Association guidelines recommend a nodule size threshold for FNAB of >1 cm in high risk patients.\(^{(33)}\)\(^{(34)}\) Changing the biopsy threshold from >0.5 cm to >1 cm most likely would not affect the ability of identifying thyroid cancer at an early stage and as such current guidelines should be followed. The growth velocity of the nodules harboring thyroid cancer ranged between 0.1 to 0.5 cm per year. There were no abnormal lymph nodes detected during this follow up period. Consequently, screening at longer intervals than in our study, every 2-3 years instead of yearly most likely would not affect the ability to detect the disease at an early stage.

The major limitation of our study is lack of long-term follow-up to determine the impact of screening on all-cause or cancer-specific mortality, or progression-free survival, and the effect on the long-term quality of life. Another limitation is that the classification of a family member as unaffected may require alteration if that family member was to later develop thyroid cancer, so the rate of thyroid cancer detected by screening may be even higher with long-term follow-up and screening. This is a shortcoming of any prospective screening study in familial cancer syndromes, especially when the susceptibility gene(s) are not known.

In conclusion, screening with thyroid ultrasound should be considered in kindred with \(\geq 3\) first-degree relatives affected by FNMT. Fifteen percent of the study population was diagnosed with FNMT at the age <25 years old, while peak incidence occurred between the age of 30-39 years old. Therefore, we believe that it might be justified to start screening 10 years before the peak incidence - between the age 20-29 years old or 10 years before the earliest age of the diagnosis in the family, whichever occurs first. Our data indicate that screening should be performed in all generations of kindred affected by
FMTC in regular intervals (every 2-3 years) as only 47% of thyroid cancer cases were detected at the initial screening.
Acknowledgments: We would like to thank the patients and their family for participating in our study, and the health care providers who cared for them at our institution and who referred them to our institution for evaluation through our clinical protocol. This research was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health.

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References


<table>
<thead>
<tr>
<th>FAMILY MEMBERS AT RISK (N=109)</th>
<th>PARENTAL GENERATION</th>
<th>FIRST GENERATION</th>
<th>SECOND GENERATION</th>
<th>THIRD GENERATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of family members at risk</td>
<td>11</td>
<td>35</td>
<td>45</td>
<td>18</td>
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<tr>
<td>Mean age of thyroid cancer diagnosis [+/−SD, years]</td>
<td>75+/−2</td>
<td>43+/−16</td>
<td>40+/−9</td>
<td>NA</td>
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<tr>
<td>Malignant thyroid nodules (%)</td>
<td>26.3%</td>
<td>37.1%</td>
<td>22.7%</td>
<td>0%</td>
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<td>Mean age of thyroid nodule detection [+/−SD, years]</td>
<td>64+/−12</td>
<td>51+/−17</td>
<td>31+/−12</td>
<td>16+/−36</td>
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<tr>
<td>Patients with thyroid nodules (%)</td>
<td>72.7%</td>
<td>57.1%</td>
<td>48.9%</td>
<td>27.8%</td>
</tr>
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</table>

NA: not applicable.

*Parental generation was defined relative to the index case in the kindred.
Table 2 Comparison of baseline characteristic and treatment modalities between patients diagnosed with non-medullary thyroid cancer by screening and those with established diagnosis at enrollment.

<table>
<thead>
<tr>
<th>CLINICAL AND PATHOLOGIC FEATURES</th>
<th>PATIENTS WITH ESTABLISHED DIAGNOSIS (N=56)</th>
<th>PATIENTS DIAGNOSED BY SCREENING (N=17)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (+/- SD, years)</td>
<td>42 (+/- 14.4)</td>
<td>47 (+/- 15)</td>
<td>0.22</td>
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<tr>
<td>Female (%), number/total number</td>
<td>71.4% (40/56)</td>
<td>64.7% (11/17)</td>
<td>0.76</td>
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<tr>
<td>Classic papillary thyroid cancer (%), number/total number</td>
<td>91.1% (51/56)</td>
<td>94.1% (16/17)</td>
<td>0.84</td>
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<tr>
<td>Follicular variant of papillary thyroid cancer (%), number/total number</td>
<td>7.1% (4/56)</td>
<td>5.9% (1/17)</td>
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<tr>
<td>Tall cell variant of papillary thyroid cancer (%)</td>
<td>1.8% (1/56)</td>
<td>0% (0/15)</td>
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<tr>
<td>Trait</td>
<td>Familial Medullary Thyroid Cancer</td>
<td>Familial Non-medullary Thyroid Cancer</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------------------------</td>
<td>--------------------------------------</td>
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<tr>
<td>Mean tumor size (± SD, cm)</td>
<td>1.5 (± 1.1)</td>
<td>0.7 (± 0.5)</td>
<td>*0.006</td>
</tr>
<tr>
<td>Central neck lymph node metastases (%)</td>
<td>51.1% (22/43)</td>
<td>17.6% (3/17)</td>
<td>*0.02</td>
</tr>
<tr>
<td>Lateral neck lymph node metastases (%)</td>
<td>16.3% (7/43)</td>
<td>0% (0/17)</td>
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<tr>
<td>Extrathyroidal invasion (%)</td>
<td>11.6% (5/43)</td>
<td>0% (0/17)</td>
<td>0.3</td>
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<tr>
<td>Multifocal tumor (%)</td>
<td>34.9% (15/43)</td>
<td>47% (8/17)</td>
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<tr>
<td>Bilateral tumor foci (%)</td>
<td>75% (6/8)</td>
<td>87.5% (7/8)</td>
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<td>TNM STAGE#</td>
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<tr>
<td>I</td>
<td>39/49 (79.6%)</td>
<td>15/17 (88.2%)</td>
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</tr>
<tr>
<td>II</td>
<td>0/49 (0%)</td>
<td>0/15 (0%)</td>
<td>0.54</td>
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<tr>
<td>III</td>
<td>7/49 (14.3%)</td>
<td>2/17 (11.8%)</td>
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<tr>
<td>Stage</td>
<td>Hemithyroidectomy</td>
<td>Therapeutic central neck lymph node dissection</td>
<td>Therapeutic lateral neck lymph node dissection</td>
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<tr>
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<tr>
<td>IVa</td>
<td>0% (0/56)</td>
<td>51.2% (22/43)*</td>
<td>16.3% (7/43)*</td>
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<td></td>
<td>23.5% (4/17)</td>
<td>41.2% (7/17)</td>
<td>0% (0/17)</td>
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</table>

^ Total number of patients with established diagnosis before enrollment n=69, 10 patients died before enrollment and 3 did not have pathology slides for review, leaving n=56 study participants.

^^ Data on unilateral versus bilateral multifocal tumors not ascertained for 7 of 15 patients

*Data on the exact extent of the surgery was available for 43 of 56 patients with established thyroid cancer diagnosis at enrollment

# TNM: Tumor node metastasis staging according to the American Joint Committee on Cancer 7th Edition

+Data on the stage was available for 49/56 patients with established thyroid cancer diagnosis at enrollment
<table>
<thead>
<tr>
<th>COMPLICATIONS</th>
<th>PATIENTS WITH ESTABLISHED DIAGNOSIS (N=41)</th>
<th>PATIENTS DIAGNOSED BY SCREENING (N=17)</th>
<th>P VALUE</th>
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<tr>
<td>Transient hypocalcemia</td>
<td>21.9% (9/41)</td>
<td>11.8% (2/17)</td>
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<td>Permanent hypoparathyroidism</td>
<td>2.4% (1/41)</td>
<td>0% (0/17)</td>
<td>0.51</td>
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<tr>
<td>Vocal cord paresis/paralysis</td>
<td>4.9% (2/41)^</td>
<td>0% (0/17)</td>
<td>0.89</td>
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<tr>
<td>Sialadenitis/xerostomia</td>
<td>7.3% (3/41)</td>
<td>0% (0/17)</td>
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</tbody>
</table>

^ One patient had resection of the recurrent laryngeal nerve because of tumor invasion which was done at another institution. The other patient had a transient vocal cord paresis which resolved approximately 6 months after the initial operation done at another institution.
Thyroid

Results of screening in familial nonmedullary thyroid cancer (DOI: 10.1089/thy.2016.0668)

This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.
Figure 2: Rate of thyroid nodule detected at screening and patient age.
Figure 3

![Diagram showing the process of fine needle aspiration biopsy (FNAB) in patients with thyroid nodules.](image)

**Figure 3** Summary of indications for fine needle aspiration biopsy (FNAB) in patients with thyroid nodules.
Figure 4: Screening strategy in 17 patients for whom the final diagnosis of thyroid cancer was established.
Figure 5. Age at diagnosis of familial non-medullary thyroid cancer (FNMT) in study group versus general population. The age of diagnosis was earlier compared to the general population as reported in the Surveillance, Epidemiology, and End Results (SEER) data on thyroid cancer. The data used in the current study were derived from 17 registries at various geographic locations throughout the United States, representing 28% of the US population. Only non-medullary thyroid cancer cases (N=61,523) were included from the SEER data for the comparison.