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Restricting Ultrasound Thyroid Fine Needle Aspiration biopsy by nodule size: which tumors are we missing? A population-based study

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Abstract

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Context—Clinicians use nodule size to determine which thyroid nodules should receive cytological evaluation. The American Thyroid Association (ATA) has recommended against cytological evaluation for nodules < 1 cm. It is unknown, however, if nodule size can accurately discriminate lesions that will represent tumors with favorable vs. unfavorable prognosis. Also, the characteristics of thyroid cancers that would not be diagnosed if a strict 1 cm size cut off is used as the threshold for biopsy of intrathyroidal nodules are not well established.

Methods—Using the Rochester Epidemiology Project, a population based cohort, we identified all thyroid nodules in Olmsted County residents from 2003-2006. To assess the presence of favorable or unfavorable features for each nodule size cutoff, each patient found to have thyroid cancer was risk-stratified using the ATA risk score, which predicts risk of recurrence and persistent disease. Thyroid cancer cases in which a biopsy was done for factors other than thyroid nodule size or suspicious ultrasound features were excluded.

Results—We identified 485 thyroid nodules, 46 (9.5%) harbored thyroid cancer. Of the 46 thyroid cancers, 37 (7.6%) had ATA low risk; 8 (1.6%) had intermediate, and only 1 (0.2%) had an ATA high risk scores. The frequency of thyroid cancer and the distribution of ATA risk scores were similar across tumor sizes. In thyroid nodules of < 1 cm, 92 (87%) were benign, while 13 (13%) were malignant (11% ATA low risk, 2% ATA intermediate risk) without extrathyroid extension, aggressive histology, or distant metastasis. For all thyroid cancer patients, no cases of persistent disease were found after a median follow up of 7 years.

Conclusions—In highly selected patients, the ATA recommendation to avoid cytologic evaluation to thyroid nodule less than 1 cm would not miss any thyroid cancer with high risk features. However, thyroid nodule size at presentation did not accurately discriminate between tumors with favorable vs. unfavorable clinicopathologic features. A lack of high risk features was also observed with other size cutoffs. Thus, if further discrimination is desired, for example to avoid overdiagnosis, features other than size at presentation need to be evaluated.

Keywords

thyroid cancer; population based cohort; thyroid ultrasound; fine needle aspiration; biopsy; diagnosis

Introduction

There is a large reservoir of thyroid nodules in the general population. Random neck ultrasonography assessment of patients reveals that approximately 30 to 67% have undiagnosed thyroid nodules. [1] [2] Although most of these thyroid nodules are benign, 5-20% are malignant. [3] As a result, when a thyroid nodule is suspected, diagnostic work up begins with the assessment of thyroid function and ultrasonography of the neck, often followed by ultrasound-guided fine needle aspiration (USFNA). [4]

A recent study showed that the incidence of well differentiated thyroid cancer has increased in the United States from 4.9 per 100,000 to 14.3 per 100,000 between 1975 and 2009; [5] with a comparable increase seen worldwide. [6] Unsurprisingly, the increased incidence of thyroid cancer has been paralleled by a rise in thyroid surgeries; from 99,613 in 2006 to 130,216 in 2011, [7] corresponding to a 12 % annual percentage increase.

Although this unparalleled surge of thyroid cancer makes it one of the fastest growing diagnoses, thyroid cancer related mortality has not changed over the same period. [5] This paradox between a surge of new cases and a flat mortality has raised concerns that thyroid cancer is being overdiagnosed.[8] One approach to reduce the excessive diagnosis of potentially indolent thyroid cancers and subsequent thyroid surgeries is to decrease the number of USFNAs. USFNA is used in the diagnostic work-up of thyroid nodules to help determine their malignant potential and its use has paralleled the increase in the detection of thyroid nodules. Between 2006 and 2011 the rate of USFNA doubled in the United States (a 16% annual growth). [7] The American Thyroid Association (ATA) guidelines recommend against performing USFNA for thyroid nodules < 1 cm regardless of the ultrasonographic features of the nodule as long as it is confined to the thyroid. [4]

These recommendations are based on the assumption that size is a good predictor of clinicopathologic features; that is, subcentimeter thyroid nodules likely harbor low risk tumors and are unlikely to cause harm. However, it is unknown whether thyroid nodule size is actually an accurate predictor of tumors with favorable vs. unfavorable clinicopathologic features. Also, It is unclear, the characteristics of the thyroid cancers that would not be diagnosed if a strict 1 cm size cut off threshold for biopsy is used.

A better understanding of the characteristics of thyroid tumors that might not be diagnosed if the need for cytology is based on size cutoffs is needed. This information would help guideline panelists assess the significance of size thresholds for performing USFNA. Additionally, it would help clinicians and patients better understand the risks and benefits of a diagnostic work up for thyroid nodules and thus, create a more informed decision making process.

Methods

We used the Rochester Epidemiology Project (REP) to identify Olmsted County, MN residents with thyroid cancer. The REP medical records linkage system was initiated to study disease epidemiology and patterns of health care among the residents of Olmsted County. [9] This database includes patients from all medical care facilities accessed by all residents of Rochester, Minnesota (an estimated population in 2012 of 164,129): the Mayo Clinic, the Olmsted Medical Center and several private practices. The REP gives investigators the ability to examine the health care of Olmsted County's residents regardless of age, sex, ethnicity, insurance and socioeconomic status and setting of care delivery. Therefore, it allowed us to estimate the prevalence and incidence of medical conditions of a community; and it allows us to avoid selection bias. [10] [11]

Our study was approved by the institutional review boards at the Mayo Foundation and Olmsted Medical Center. We used the REP to identify all cases of thyroid nodules that underwent neck ultrasound followed by USFNA with available cytology from pathology department records from 2003 to 2006. These thyroid nodules underwent USFNA due to their size and presence of suspicious ultrasonographic features (e.g., microcalcifications). Our rationale for this interval was to allow us enough follow up to capture the completeness of the diagnostic work up and follow up for each nodule.

Reviewers extracted from each chart: the size of the thyroid nodule that was evaluated by USFNA, the results of the cytology and demographic data. We also extracted the final pathology results of the nodules that underwent histological confirmation at any point during the follow-up period. Although all thyroid nodules with malignant cytology and cytology suspicious of papillary thyroid cancer underwent surgery, some nodules with benign or indeterminate cytology did as well. Therefore, histological confirmation of malignancy was sought in every nodule regardless of the cytology results. Thus, our gold standard for the diagnosis of cancer was histology. The reference standard for thyroid nodules that did not undergo histological (e.g. nodule with benign cytology) evaluation was clinical follow up (last assessment was December, 2012). When the histology confirmed thyroid malignancy, we extracted the presence or absence of the following: aggressive histology (e.g. tall cell), tumor vascular or capsular invasion, extrathyroid extension, cervical lymph node metastasis, gross extrathyroid extension, complete tumor resection, distal metastasis, surgical treatment, postsurgical treatment with I131, the uptake outside thyroid bed if I131 was given, and personal history of radiation exposure. To assess the presence of favorable or unfavorable clinicopathological features, each patient was risk-stratified using modified ATA risk score that predicts risk of recurrence and persistent disease. [4] (**Table 1**) This modified classification includes small lymph node metastasis as ATA low risk; however, when size and the number of lymph nodes were not specifically stated or clear, we classified them as ATA intermediate risk. For the final clinical endpoint, we extracted the clinical status at the time of the last follow up for each case with a histological diagnosis of thyroid cancer. Each case was classified as having no evidence of disease, persistent disease, recurrent disease or indeterminate. (**Table 2**). We excluded all the thyroid nodules with malignant histology in which the diagnostic work up was initiated for reasons other than the size and sonographic characteristics of the thyroid nodule. Therefore, those patients with suspicious adenopathy were excluded from the study because the reason of USFNA for these patients was not the size of the thyroid nodule.

Statistical Analysis

Each patient was stratified by the size of the primary tumor in centimeters. Continuous data are presented as means and standard deviations (SD) or median and range values, as appropriate for each variable. Categorical variables were summarized as percentages. Comparison between groups was based on a two-sample t-test for continuous variables and Pearson's chi-squared test for categorical variables.

Results

From 2003 to 2006, 458 patients with 521 thyroid nodules underwent USFNA in Olmsted County, MN. We excluded 36 thyroid nodules that did not have documentation of the size of the nodule on neck ultrasound; none of these tumors were proven to have thyroid cancer. Of the 439 patients with 485 thyroid nodules the mean age at diagnosis was 51.8 years SD 16; 77% were female, and the mean thyroid nodule size evaluated by US was 2.1 cm, SD 1.3. One hundred one (21%) thyroid nodules were ≤ 1 cm in size and 201 (42%) were between 1 and 2cm in size. (**Table 3**)

The work up of these thyroid nodules revealed that 46 (9.5%) harbored thyroid cancer in the index nodule. None of these patients had prior exposure to radiation. The mean age of the thyroid cancer group at diagnosis was 44.7 SD 14.9; 66% were female, 72% were papillary thyroid cancers, 17% follicular variant papillary thyroid cancer. The mean tumor size assessed by US was 1.8 cm SD 1.2 cm and the tumor size by histology 1.96 cm, SD 1.4 cm

ATA Risk and final clinical outcome by thyroid nodule size

In total, 37 (7.6%) thyroid nodules harbored thyroid cancers that were ATA low risk; 8(1.6%) were intermediate risk and only 1(0.2%) was high risk. This high risk patient was a 61 year old patient with a large, 7 cm, primary tumor with incomplete surgical resection. The distribution of ATA risk categories was not affected by the tumor size, $p=0.15$. **Table 4 and Figure 1**

The clinical outcome at final follow-up was available for all but one patient with thyroid cancer. The median follow-up was 7 years (range 1-11 years). Three patients died from non-thyroid cancer related reasons and they were found to have no evidence of disease (NED) at the time of death; 3 patients had no evidence of structural disease but persistent low levels of thyroglobulin antibodies and were classified as intermediate; and the remainder, 39 (8%), were classified as NED. The frequency of NED did not differ by the size of the primary tumor, $p=0.37$.

Thyroid nodules equal or less than 1 cm

A total of 101 thyroid nodules with a size equal or less than 1 cm were assessed. Of the 13 thyroid cancers found in this group, no thyroid cancers were found to have extrathyroid extension, aggressive histology or distant metastasis. As a result, 12 (11%) were ATA low risk; 1 (2%) was ATA intermediate risk and no ATA high risk thyroid cancers were found. The only case of ATA intermediate risk had minimal vascular invasion and positive lymphadenopathy; the patient received radioactive iodine without any uptake outside the thyroid bed.

Discussion

This population based study shows that thyroid nodule size is not an accurate discriminator of tumors with favorable or unfavorable clinicopathological features. The lack of discriminatory accuracy of different thyroid nodule size cutoffs to predict clinicopathologic features does not, however, suggest that we need to conduct USFNA on all thyroid nodules. On the contrary, despite the negative finding regarding nodule size, our findings strengthen the argument that thyroid nodules without ultrasound evidence of extrathyroidal extension or cervical lymphadenopathy have a favorable prognosis - of 485 thyroid nodules only 1 was found to have high risk features. The outcome of these tumors, when treated surgically, is excellent and after a median follow up of 7 years the vast majority of patients have no evidence of disease.

Our findings also help to inform patients and clinicians on the type of tumors that might be not diagnosed depending on the cutoff used for deciding to proceed with an USFNA. In particular, we found that no thyroid cancer with high risk features would have missed if

clinicians and patients follow the ATA recommendation to limit cytologic evaluation for thyroid nodules greater than 1 cm.

However, the lack of discriminatory accuracy of different thyroid nodule size cutoffs to predict clinicopathologic features suggests that the decision to restrict cytological evaluation for thyroid nodules, for example to avoid overdiagnosis, needs to consider features other than size at presentation; particularly, because the lack of high risk features was seen in all the thyroid nodules with a size less than 4 cm. One of these factors is the tradeoff between the risks and benefits of conducting USFNA. The most important downside of USFNA, the initial step for the work up of these nodules, is the possibility of inconclusive results (non-diagnostic or indeterminate cytology) that can lead to other diagnostic procedures that carry additional cost and risk (e.g., diagnostic surgery). On the other hand, the risk of not pursuing the diagnostic work up for thyroid nodules is to miss thyroid cancers that will lead to more harm (local tumor progression, local and distal metastasis) if not diagnosed. Our results help inform the latter, and suggest that in highly selected thyroid nodules the likelihood of finding thyroid cancer with unfavorable features is very low. Another important factor to consider when evaluating a thyroid nodule is that the majority of micropapillary thyroid cancers do not show disease progression on active surveillance [12] [13]; and when disease progression occurs, delayed thyroid surgery does not carry additional risks. [12] [13] This piece of information could also help clinicians and patients discuss the need for cytologic evaluation, particularly for sub-centimeter nodules. Moreover, the need to perform USFNA for thyroid nodules needs to consider the patient's context. Particularly, it needs to reflect a careful assessment of comorbidities that affect patient's life-span and how the work up of a thyroid nodule will benefit or harm the patient.

Advancements in molecular biology may eventually help us identify, with the use of USFNA, those nodules that have a more malignant potential (growth and metastasis) than others. Molecular testing may also help us accurately identify currently indeterminate and non-diagnostic cytologies; and thus avoiding additional risk and expensive diagnostic procedures. Thus, the use of USFNA besides carrying a diagnostic advantage may also carry prognostic relevance when these technologies are proven to be predictive of tumor behavior

Limitations

The REP is a reliable source of information for population-based incidence rates. However, our data has some limitations. The population studied primarily consists of Caucasians, [10] and while this may affect the applicability of our results to other populations, there is no evidence that the natural history of thyroid nodules is affected by race. Additionally, this retrospective cohort has several limitations that weaken the inferences from this study. First, thyroid nodules underwent USFNA due to their size and the presence of ultrasound features. The latter, however, has shown not to be predictive of thyroid cancer. [14] Thus, it is possible that many thyroid cancers were missed due to the lack of suspicious sonographic features. Second, not all the thyroid nodules underwent gold standard histology. Ideally, all patients with thyroid nodules regardless of the cytology should have undergone histological confirmation. As this is not feasible in the current standard of practice, we used clinical follow up as a surrogate of the reference standard. As some thyroid cancers behave

indolently and never grow, [12] clinical follow-up could have missed thyroid cancers classified erroneously benign by cytology. Finally, the number of cancers per nodule size is small and different than other similar studies. The main reason for this incongruency is that this study includes patients who live in Olmsted County in Minnesota, United States, and received treatment for thyroid nodules; our study, however, does not include the overall population who sought attention at Mayo Clinic. This assessment of the community, as opposed to the analysis of a medical center, allows us to estimate the truth frequency of cancer in thyroid nodules in the population.

Conclusion

In highly selected patients, the ATA recommendation to avoid cytologic evaluation in thyroid nodules less than 1 cm would not miss any thyroid cancer with high risk features. However, thyroid nodule size at presentation did not accurately discriminate between tumors with favorable vs. unfavorable clinicopathologic features. A lack of high risk features was also observed with other size cutoffs. Thus, if further discrimination is desired, for example to avoid overdiagnosis, features other than size at presentation need to be evaluated.

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Figure 1.
Distribution of ATA risk tumors by different thyroid nodule size cutoffs.

Table 1

American Thyroid Association Risk of recurrence

Low Risk	Classic PTC Confined to the thyroid Absence of vascular invasion No uptake outside the thyroid bed when RAI is given Follicular variant with minimal vascular invasion
Intermediate Risk	Aggressive histology Extrathyroid extension Vascular invasion Cervical lymph node Metastasis
High Risk	Gross extrathyroidal Extension Incomplete tumor Resection Distant metastases

PTC; Papillary thyroid cancer, RAI; radioactive iodine

Table 2

Classification for final clinical endpoint

	Total Thyroidectomy	Lobectomy
NED	Suppressed Tg < 1 ng/mL No detectable TgAb and No structural or functional evidence of disease	Stable, nonstimulated Tg level <30 ng/ml and Undetectable TgAb and Negative imaging
Persistent disease	Suppressed Tg values > 1 ng/mL Stimulated Tg values > 2 ng/mL Evidence of persistent disease in structural or function imaging or Biopsy-proven disease	Nonstimulated Tg level >30 ng/ml and Increasing Tg level values over time with similar TSH values or Evidence of persistent disease in structural or function imaging or Biopsy-proven disease
Indeterminate	Nonspecific findings on imaging studies or TgAb levels stable or declining in the absence of structural or functional disease	

NED; no evidence of disease Tg; thyroglobulin, TgAb; thyroglobulin antibodies; TSH thyroid stimulating hormone

Table 3

Features of the thyroid cancer by size

	1.0 cm	1.1-2.0 cm	2.1-3.0	3.1-4.0	4.1	Total
Benign thyroid nodules (n)	88(87)	184(92)	94(91)	36(90)	36(92)	438(90)
Thyroid cancer (n)	13(13)	17(8)	9(9)	4(10)	3(8)	46(10)
Type of thyroid cancer						
Papillary	11(11)	13(6)	6(6)	2(5)	1(3)	33(7)
Papillary follicular variant	1(1)	4(2)	1(1)	0(0)	2(5)	8(2)
Follicular	1(1)	0(0)	1(1)	1(2)	0(0)	3(1)
Hürthle	0(0)	0(0)	1(1)	0(0)	0(0)	1(0)
Medullary	0(0)	0(0)	0(0)	1(2)	0(0)	1(0)
Extra thyroid Extension						
None	13(13)	17(8)	7(7)	4(10)	3(8)	44 (10)
Present	0(0)	0(0)	2(2)	0(0)	0(0)	2 (0)
Aggressive histology						
None	13(13)	17(8)	9(9)	4(10)	3(8)	46(10)
Present	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Uptake outside thyroid bed						
Did not receive	12(12)	14(6)	6(6)	1(2)	1(1)	34 (7)
None	1(1)	1(0)	3(3)	3(8)	2(7)	10 (3)
Present	0(0)	2(1)	0(0)	0(0)	0(0)	2 (0)
Incomplete tumor resection						
No	13(13)	17(17)	9(9)	4(10)	2(7)	45 (10)
Present	0(0)	0(0)	0(0)	0(0)	1(1)	1 (0)
Distant Metastasis						
None	13(13)	17(17)	9(9)	4(10)	3(8)	46 (100)
Present	0(0)	0(0)	0(0)	0(0)	0(0)	0 (0)
Vascular invasion *						
None	12(12)	16(8)	9(9)	3(8)	2(7)	42 (9)
Present	1(1)	1(0)	0(0)	1(2)	1(1)	4 (1)
Neck lymphadenopathy						
NO	11(11)	14(7)	5(5)	4(10)	1(1)	35 (8)
N1a	1(1)	3(1)	3(3)	0(0)	2(7)	9 (2)
N1b	1(1)	0(0)	1(1)	0(0)	0	2 (0)
ATA risk						
Low	12(12)	14(7)	6(6)	3(8)	2(5)	37(7)
Intermediate	1(1)	3(1)	3(3)	1(2)	0(0)	8(2)
High	0(0)	0(0)	0(0)	0(0)	1(3)	1(1)
Final Outcome						

	1.0 cm	1.1-2.0 cm	2.1-3.0	3.1-4.0	4.1	Total
NED	12(12)	16(7)	7(7)	3(8)	2(5)	40(8)
Indeterminate	0(0)	1(1)	1(1)	1(2)	0(0)	3(1)
Death/Not thyroid related	1(1)	0(0)	1(1)	0(0)	1(0)	3(1)

None of the comparisons were statistically significant ($p < 0.05$)

* Minimally invasive