

The Natural History of the Benign Thyroid Nodule: What Is the Appropriate Follow-Up Strategy?



Saad Ajmal, MD, Sarah Rapoport, BS, Haiyan Ramirez Batlle, BS, MA, Peter J Mazzaglia, MD, FACS

- BACKGROUND:** Long-term monitoring of benign thyroid nodules is not addressed in the present American Thyroid Association guidelines. The objective of this study was to determine the appropriate nature and length of follow-up for patients with a benign thyroid nodule.
- STUDY DESIGN:** A retrospective review was performed of all patients referred to single endocrine surgeon for evaluation of thyroid nodules between 2006 and 2012. The review included 263 patients who had benign fine needle aspiration (FNA) cytology and either underwent thyroidectomy or had at least a 1-year follow-up ultrasound. Main outcomes measures were repeat FNA and pathology results.
- RESULTS:** There were 231 women and 32 men. Forty-eight patients underwent immediate thyroidectomy, with pathology showing 2 papillary thyroid cancers (PTC), and 215 patients were followed with annual ultrasounds. During follow-up, 89 (41.3%) nodules underwent repeat FNA after initial biopsy. The repeat FNA cytology showed 91% benign, 7% follicular neoplasm, and 2% PTC. During follow-up, 81 (37.6%) patients underwent thyroidectomy after 3.3 ± 2.8 years. Reasons for surgery included development of symptoms in 58 (71.6%), a non-benign repeat FNA in 8 (9.8%), or patient preference in 15 (18.5%). Surgical pathology identified 70 (86.4%) benign, 7 (8.6%) PTC, 3 (4%) follicular thyroid cancers, and 1 (1.2%) lymphoma. Median time from initial FNA to thyroidectomy in patients who had malignancy was 4.3 years. The maximum initial nodule size and average increase in nodule size did not differ between benign and malignant nodules ($p = 0.54$ and $p = 0.75$, respectively).
- CONCLUSIONS:** Significant numbers of benign thyroid nodules enlarge more than 5 mm over 3 years, triggering repeat FNA or thyroidectomy. Larger diameter nodules and more rapidly growing nodules were not predictive of malignancy. The practice of annually obtaining ultrasound for benign thyroid nodules should be discouraged. (J Am Coll Surg 2015;220:987–992. © 2015 by the American College of Surgeons)

The prevalence of palpable thyroid nodules is approximately 5%. However, the true prevalence of thyroid nodular disease is closer to 50% when one considers nodules that are detectable by ultrasound, or some other

radiologic study.^{1,2} Because such radiographic tests are being performed with ever-increasing frequency, more and more of these nodules are being identified and subsequently biopsied. In an effort to minimize unnecessary procedures, current guidelines of the American Thyroid Association do not recommend biopsy of any nodule under 1 cm unless there is a very strong suspicion of carcinoma.³

Well established is the fact that approximately 90% of nonfunctioning thyroid nodules are benign.⁴ Although certain ultrasound characteristics, such as hypoechogenicity, microcalcifications, irregular borders, and hypervascularity, all increase the probability of a thyroid nodule harboring malignancy, performance of a fine needle aspiration biopsy (FNAB), remains an essential component of the evaluation.⁵ Approximately 60% of thyroid FNABs that are performed are benign; the remainder show

CME questions for this article available at
<http://jacsme.facs.org>

Disclosure Information: Authors have nothing to disclose. Timothy J Eberlein, Editor-in-Chief, has nothing to disclose.

Presented at the 95th Annual Meeting of the New England Surgical Society, Stowe, VT, September 2014.

Received October 12, 2014; Revised December 4, 2014; Accepted December 8, 2014.

From the Department of Surgery, Warren Alpert School of Medicine, Brown University, Providence, RI.

Correspondence address: Peter J Mazzaglia, MD, FACS, Warren Alpert School of Medicine, Brown University, 2 Dudley St, Providence, RI 02906. email: peterjmazzaglia@gmail.com

Abbreviations and Acronyms

FNA	= fine needle aspiration
FNAB	= fine needle aspiration biopsy
FTC	= follicular thyroid cancer
FVPTC	= follicular variant papillary thyroid cancer
PTC	= papillary thyroid cancer
PTMC	= papillary thyroid microcarcinoma

papillary thyroid cancer (5% to 10%), follicular neoplasm (20% to 30%), or are nondiagnostic due to an inadequate cell sampling (10% to 15%). The risk of a false negative FNAB is <5%.^{6,7} Therefore, current recommendations are to perform follow-up ultrasounds in all these patients. Because ultrasound is much more accurate than palpation for assessing nodule size, it is the preferred mode for long-term surveillance.

Present American Thyroid Association guidelines for all benign thyroid nodules state that they should be followed with serial ultrasound examinations 6 to 18 months after the initial FNA. If there is evidence for nodule growth either by palpation or sonographically (more than a 50% change in volume or a 20% increase in at least 2 nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic-solid nodules), the FNA should be repeated, preferably with ultrasound guidance.⁸ The goal of this study was to examine the long-term outcomes for these patients with benign thyroid nodules, and to determine what percent of them went on to require thyroidectomy, as well as how well the final pathology correlated with the initial benign FNAB. These data should help in determining what the most appropriate follow-up is for these patients.

METHODS

After obtaining Institutional Review Board approval, analysis of a prospectively maintained database was performed to identify all patients referred to a single endocrine surgeon for evaluation of thyroid nodular disease, between September 2006 and December 2012. Inclusion criteria were the presence of ultrasound-proven thyroid nodular disease; a benign FNA biopsy, performed either by the referring provider or by the endocrine surgeon at the time of referral; and surgical pathology after thyroidectomy, or a follow-up ultrasound 12 months or longer after the original ultrasound. All of the final follow-up ultrasound examinations in the study were performed by the endocrine surgeon. Patients were excluded if there were other nodules present that had a biopsy result other than benign, or if there was evidence of hyperthyroidism.

Nodules whose size could not be accurately determined or followed due to a substernal location were not included.

Outpatient office charts and electronic medical records were reviewed. Records were reviewed for demographics, diagnosis, size of nodule at first ultrasound, number of ultrasounds performed, number of years followed, and size of nodule at last ultrasound. The analysis focused on identifying patients who underwent a repeat FNA and the reasons for it, as well as identifying patients who subsequently underwent thyroidectomy. Reason for thyroidectomy, type of operation, final pathology, and size of tumor or nodule were recorded. All FNA biopsies were ultrasound-guided, whether performed by endocrine surgeons or another physician. If the cytology was initially read at an outside institution, it was always reviewed by the cytology department at the tertiary care center where the study was performed. Student's *t*-test was used to compare continuous variables and chi-square analysis was performed for categorical variables.

RESULTS

There were 263 patients who had a benign thyroid nodule FNA, and had either an immediate thyroidectomy or at least a 1-year follow-up ultrasound. There were 231 women and 32 men. The mean age of the patients was 53.2 ± 15.76 years (range 17 to 90 years). Ninety-four patients had solitary nodules (35.7%) and 169 had multiple (64.3%) (2 or more) nodules on ultrasound. The mode of discovery for these nodules was variable. Seventy-one nodules (27%) were detected by physical exam, 75 (28.5%) were found on imaging, 20 (7.6%) were identified by patients themselves, and the mode of discovery was unknown in 97 (36.8%) patients.

There were 48 patients who underwent immediate thyroidectomy. The reasons for surgery were symptoms in 28 (58.3%) and patient preference in 14 (29.1%) patients. Reasons were not well documented in the rest. Pathology in these 48 patients showed 46 to have benign nodules (96%, including 3 with PTMC), and 2 to have papillary thyroid cancer within the index nodule (4%). Both patients with papillary thyroid cancer were symptomatic and had highly suspicious ultrasound findings. The false-negative biopsy rate in this group was 4.2%.

There were 215 patients followed with annual ultrasounds. Follow-up in these patients varied from 1 to 15 years, with a mean of 3.04 ± 3.25 years. Ninety-five patients (44.1%) were followed for less than 3 years, and 120 patients (55.9%) had 3 or more years of follow-up. The mean number of ultrasounds was 2.9 ± 1.62 per patient during follow-up, indicating that most patients had an ultrasound performed annually.

Table 1. Observed Patients Who Underwent Repeat Fine Needle Aspiration

Fine needle aspiration variable	n	%
Repeat fine needle aspiration	89/215	41.4
Reasons for repeat fine needle aspiration		
Nodule growth	78	87
Concerning ultrasound features	11	13
Fine needle aspiration results		
Benign	81	91
Follicular neoplasm	6	7
Papillary thyroid cancer	2	2

At the time of the first ultrasound, the mean largest diameter of the nodule was 2.74 ± 1.52 cm (range 0.4 to 11 cm). By the time of the last ultrasound, the mean largest diameter was 3.07 ± 1.67 cm (range 0.5 to 11.8 cm). When comparing patients who underwent immediate thyroidectomy with patients who were observed, the mean largest diameter of the nodule on initial ultrasound for immediate thyroidectomy was 3.84 cm as compared with 2.51 cm for observed patients (p value = 1.73).

During follow-up, 89 (41.3%) nodules underwent repeat FNA from 1 to 13 years (median 3 years) after initial biopsy (Table 1). Reasons for repeat FNA were growth of nodule in 78 (87%) patients and development of concerning ultrasonographic features in 11 (13%) patients. The mean increase in nodule diameter that triggered a repeat biopsy was 0.71 cm. The repeat FNA cytology showed 81 (91%) benign nodules, 6 (7%) follicular neoplasms, and 2 (2%) papillary thyroid cancers. In the 6 cases in which the repeat FNA revealed a follicular neoplasm, final surgical pathology of the index nodules showed 1 PTC, 1 FTC, and 4 benign lesions.

In the group of 215 patients who were followed, 81 (37.6%) patients underwent thyroidectomy after a mean of 3.3 ± 2.8 years (Table 2). Fifty-four patients had total thyroidectomy and 27 underwent lobectomy. Reasons for surgery included development of symptoms in 58

(71.6%), a nonbenign (either papillary or follicular) repeat FNA in 8 (9.8%), or patient preference in 15 (18.5%). Surgical pathology in these 81 patients was reviewed, and the results are reported specifically for the nodules that had been originally biopsied. There were 70 (86.4%) benign nodules (which includes 5 PTMC), 7 (8.6%) papillary thyroid cancers, 3 (4%) follicular thyroid cancers, and 1 (1.2%) thyroid lymphoma. Thus, well-differentiated thyroid cancer was discovered in 11 of 215 (5.1%) patients who were followed at a median follow-up time of 3.3 years. The false negative rate for FNA in patients observed was 5.1%.

When looking at the entire group of 263 original patients, 128 underwent thyroidectomy, and the final pathology was benign (including micro carcinomas) in 115 and malignant in 13 patients. The overall false negative biopsy rate was 4.9%. The time between initial FNA and thyroidectomy was not significantly different between malignant and benign lesions: 4.3 vs 3.0 years ($p = 0.33$). Maximum size of the nodule preoperatively did not differ between benign and malignant lesions: 3.83 cm for benign vs 4.14 cm for malignant ($p = 0.54$). Similarly, the average increase in size of the nodule during follow-up also did not differ between benign and malignant lesions: 0.48 cm for benign vs 0.57 cm for malignant ($p = 0.75$).

Six of the 13 (46.1%) patients in the malignancy group had had a repeat FNA before thyroidectomy, compared with 36 of 115 patients (31.3%) in the benign group (Table 3). Three of those 6 FNA results were actually benign, despite a final diagnosis of either PTC or FTC. One of the 2 repeat FNA biopsies that were positive for PTC turned out to be benign, and two-thirds of the repeat FNA biopsies showing follicular neoplasms were benign. There were 3 patients who had a false negative repeat FNA. Details are shown in Table 4. The decision for thyroidectomy was based on compressive symptoms in all of them. Two had follicular variant PTC, and 1 had FTC. Disease was stage I in all of them.

The most common reason for thyroidectomy in the benign group was development of compressive symptoms, in 90 of 115 (78.2%) patients. This was similar to the malignant group in which symptoms prompted surgery in 8 of 13 patients (61.5%) (Table 5).

DISCUSSION

Identification of thyroid nodular disease has rapidly grown in the last 2 decades, as more and more neck imaging studies are being performed. These studies performed as part of the evaluation of neck pain, neurologic symptoms, vascular imaging, etc, are revealing

Table 2. Observed Patients Who Underwent Thyroidectomy

Variable	n	%
Thyroidectomy	81/215	37.6
Reasons for thyroidectomy		
Development of compressive symptoms	58	71.6
Patient preference	15	18.5
Nonbenign repeat fine needle aspiration	8	9.8
Final pathology		
Benign	70	86.4
Papillary thyroid cancer	7	8.6
Follicular thyroid cancer	3	4
Lymphoma	1	1.2

Table 3. Surgical Outcomes in Patients Who Had a Repeat Fine Needle Aspiration

Fine needle aspiration result (n = 89)	Surgical pathology, n		
	Benign	Follicular thyroid cancer	Papillary thyroid cancer
Follicular neoplasm (n = 6)	4	1	1
Papillary thyroid cancer (n = 2)	1		1
Benign (n = 34)*	31 [†]	1	2

*Only 34 out of 81 patients with repeat benign fine needle aspiration biopsy underwent thyroidectomy.

[†]Includes 6 micropapillary thyroid cancer.

thyroid incidentalomas that would otherwise have gone undetected. Subsequently many more thyroid biopsies are being performed, the majority of which are benign. However, because up to 5% of benign thyroid FNA biopsies can be false negatives, follow-up ultrasonographic examinations for these patients have been recommended.⁸ Determining what is the most appropriate frequency and duration of follow-up ultrasound examinations was the focus of this study.

The study looked at 263 patients with benign thyroid nodules based on FNA, who were referred to endocrine surgery. In 48 patients who underwent thyroidectomy at the time of the initial referral, there were 2 papillary thyroid carcinomas identified, giving a false negative biopsy rate of 4.2% for our institution. This is in keeping with traditionally published rates of false negative thyroid biopsies.⁹ In both of these cases, the ultrasound findings were noted to be suspicious. The first patient was an 18-year-old college student who noticed a growing thyroid nodule. On ultrasound, the nodule measured 2.5 cm, and it was noted to be hypoechoic, very heterogeneous, with irregular borders, calcifications, and increased vascularity. The patient was also symptomatic, and a lobectomy was performed, which was positive for the follicular variant of PTC. In the second false negative case, the patient was a 33-year-old woman, whose nodule was detected on routine physical exam. The patient not only had a strong family history of thyroid cancer, but the ultrasound findings were considered highly suspicious, with hypoechogenicity and very irregular borders. Lobectomy was performed revealing a 1.5-cm PTC.

Each of these cases illustrates one of the critical roles played by ultrasound in the initial evaluation of thyroid

nodules, and their long-term follow-up.^{10,11} Findings associated with thyroid malignancy, which include hypoechogenicity, irregular borders, microcalcifications, hypervascularity, and nodule dimension that is taller than wide must be documented, and should enter into the equation when determining the best management of a thyroid nodule with a benign FNA biopsy.⁵ In this regard, it is beneficial for the consulting surgeon to have ultrasound available for real-time evaluation of such a nodule when the physical exam is being performed.¹²

Suspicious ultrasound findings cannot be ignored when the biopsy is benign. In these cases, the consulting surgeon must formulate a treatment recommendation not based solely on the FNA biopsy result. In addition, if a patient has significant risk factors for thyroid cancer, such as positive family history or radiation exposure, or there are worrisome physical exam findings, the option of thyroidectomy should be presented.

In patients who underwent thyroidectomy at the time of the original ultrasound and surgical referral, the mean longest diameter of the nodule was 3.8 cm, compared with 2.5 cm in patients who were assigned to observation ($p = 1.73$). It makes sense that larger nodules would cause more compressive symptoms and therefore lead to thyroidectomy. Although some centers have advocated resecting nodules ≥ 4 cm due to higher rates of false negative biopsies,¹³ other institutions have not found FNA to be less sensitive in larger nodules.¹⁴ In general, the endocrine surgery department at Rhode Island Hospital relies on the FNA to make decisions regarding thyroid resection, even for larger nodules. However, if additional ultrasound characteristics associated with thyroid malignancy are present, strong consideration for resection is given.¹⁵

Most of the patients with benign FNA results were minimally symptomatic or asymptomatic, and did not undergo thyroidectomy initially. These patients were scheduled to have a repeat ultrasound 1 year later, and this was performed by either the radiology department or the endocrine surgeon.

Of the 215 patients followed with benign thyroid nodule FNA biopsies, 41.3% subsequently had a repeat biopsy of the original benign nodule, over a median follow-up time of 3 years. The typical reason for repeating the biopsies was nodule growth (87%). Many benign

Table 4. Findings in Patients with a False Negative Second Fine Needle Aspiration

Age, y	Sex	Time interval between first and second FNA	Growth	Reason for surgery	Final pathology
44	Female	10 y	3.5 to 5.9 cm	Compressive symptoms	2.2 cm FVPTC
24	Female	1 y	11 to 11.8 cm	Compressive symptoms	1.5 cm FVPTC
36	Female	1 y	3.1 to 4.8 cm	Compressive symptoms	4 cm FTC

FNA, fine needle aspiration; FTC, follicular thyroid cancer; FVPTC, follicular variant papillary thyroid cancer.

Table 5. Surgical Indications for Benign vs Malignant Nodules

Reason for surgery	Benign (n = 115)		Malignant (n = 13)	
	n	%	n	%
Compressive symptoms	90	78.2	8	61.5
Change in fine needle aspiration	5	4.3	3	23.1
Patient preference	20	18.2	2	15.3

thyroid nodules can slowly increase in size, and this has historically been an indication for repeat biopsy.³ In the study by Alexander and colleagues,¹⁶ 268 patients with 330 benign thyroid nodules were followed for a mean of 20 months. Nodule growth occurred in 26%, using an increase in diameter of ≥ 3 mm, and in 39% using an increase in volume $\geq 15\%$.

There is no consensus as to what degree of nodule growth should prompt a repeat biopsy. Some groups recommend rebiopsy when there is a 15% increase in nodule volume; others recommend using an increase in diameter as the trigger for repeat biopsy. In the current American Thyroid Association guidelines, the authors suggest using a 20% increase in nodule diameter, with a minimum increase in 2 or more dimensions of at least 2 mm.³ If a repeat biopsy is indicated, ultrasound guidance should be used if the nodule is not easily palpable because it has been shown to decrease the false negative biopsy rate.¹⁷⁻¹⁹

In this study, we determined nodule growth based on the maximum measured diameter by ultrasound. The mean increase that prompted a repeat FNA biopsy was 7 mm. At the time of the initial ultrasound, benign and malignant nodules did not significantly differ in their mean longest diameters. Somewhat surprisingly, there was no significant difference in the growth that occurred in malignant vs benign nodules over time. Certainly this seems counter-intuitive because one would have expected thyroid cancers nodules to have grown more rapidly than benign nodules. However, because thyroid cancer is known to be a slow growing malignancy, this study may not have allowed for enough observation time to document a significant difference. The other possibility is certainly that there is actually not a significant difference between the rates of growth of benign and malignant thyroid nodules.

For patients eventually diagnosed with thyroid cancer, the time from initial ultrasound to thyroidectomy was actually longer than for those whose final pathology was benign: 4.3 years vs 3 years. One of the patients was diagnosed 9 years after initial biopsy. This finding again speaks to the fact that in most patients, thyroid cancer is a very slow growing process that may not progress substantially over many years. Therefore, the length of

ultrasound surveillance may need to be longer, but at less frequent intervals.

Lee and colleagues²⁰ studied the question of how long benign thyroid nodules should be followed with ultrasound. They reviewed their experience by dividing patients into short-term (<3 years) and long-term (>3 years) observation groups. The false negative FNA rate in their study was only 1.5%. Although they documented an increased number of ultrasounds and repeat FNAs in the long-term group, no difference in interval thyroidectomies or malignant final pathology was observed. They recommended against long-term follow-up of benign thyroid nodules beyond 3 years, stating that any meaningful management decisions based on follow-up ultrasound occurred in the first 3 years. In their experience, indications for surgery after 3 years were due to development of compressive symptoms or patient preference.

In the present study, well over one-third of patients with benign thyroid nodules on FNA biopsy subsequently underwent thyroidectomy. The rate of false negative FNA biopsy was $<5\%$ in patients who underwent immediate thyroidectomy and 5% for those who were initially observed. There were no clear predictors of which nodules would subsequently be found to be malignant. Repeat FNA biopsy of nodules that grew was also not found to be an accurate predictor of malignancy.

Six of the 13 observed patients who were found to have cancer, had a repeat FNA before thyroidectomy. Three of those repeat FNA biopsies were benign, 1 was follicular neoplasm, and 2 were PTC. Therefore only in a minority of patients did the repeat FNA play a role in the decision to operate. Table 3 compares the reasons for thyroidectomy between benign and malignant nodules in patients who were initially observed. Most frequently, that determination was made because of the development of compressive symptoms, and this held true for both benign and malignant nodules.

Most of the patients in this study were being followed with ultrasounds on an annual basis. This is a common practice among many health care providers. Although the American Thyroid Association guidelines suggest an initial follow-up ultrasound 6 to 18 months after the initial, they do not specify any time frame for subsequent ultrasound evaluation.³ The average time to thyroidectomy for patients who were eventually diagnosed with thyroid cancer was more than 4 years, and less than half were identified by a repeat FNA. Rather, the usual indication for thyroidectomy was development of compressive symptoms. Fortunately, during this period of observation, none of these patients developed advanced thyroid cancer. They all had T1 or T2 tumors without lymph node or distant metastases.

So, there is no evidence to support the current practice of annual ultrasounds followed by many. Based on the findings of this study, if the initial follow-up ultrasound does not demonstrate significant growth ≥ 3 mm in any dimension, and there are no highly concerning ultrasound features, subsequent annual ultrasounds cannot be recommended. The initial follow-up of these nodules is likely best performed by a surgeon familiar with thyroid disease or an endocrinologist. However, once stability of the nodule has been established, it is reasonable to turn the follow-up over to the patient's primary care physician. The consulting surgeon or endocrinologist should provide well-documented guidance regarding the nodule's malignant potential, and an appropriate schedule of ultrasound and physical exam surveillance.

CONCLUSIONS

The average time to diagnosis of cancer in patients with false negative FNA biopsies was more than 4 years, despite the use of annual ultrasonography. Therefore, a reasonable follow-up strategy would be to obtain an ultrasound 1 year after biopsy, and if there has been no substantial growth or change, to obtain subsequent ultrasounds every 2 or 3 years for a period of 5–10 years. Because the development of compressive symptoms was identified as the most common indication for surgery in the observed patients, and because repeat FNA lacked sensitivity, an annual focused history and physical are likely the most important means of following these patients.

Author Contributions

Study conception and design: Mazzaglia

Acquisition of data: Ajmal, Rapaport, Ramirez Batlle

Analysis and interpretation of data: Ajmal, Rapaport, Mazzaglia

Drafting of manuscript: Ajmal, Mazzaglia

Critical revision: Mazzaglia

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Invited Commentary



Dougald C MacGillivray, MD, FACS
Portland, ME

When a thyroid nodule is found on physical examination or detected incidentally on an imaging study, the question the patient wants answered is, “Is this a cancer?” When a