Frequent Screening With Serial Neck Ultrasound Is More Likely to Identify False-Positive Abnormalities Than Clinically Significant Disease in the Surveillance of Intermediate Risk Papillary Thyroid Cancer Patients Without Suspicious Findings on Follow-Up Ultrasound Evaluation

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Context: American Thyroid Association (ATA) intermediate-risk thyroid cancer patients who achieve an excellent treatment response demonstrate a low risk of structural disease recurrence. Despite this fact, most patients undergo frequent surveillance neck ultrasound (US) during follow-up.

Objective: The objective of the study was to evaluate the clinical utility of routine screening neck US in ATA intermediate-risk patients documented to have a nonstimulated thyroglobulin less than 1.0 ng/mL and a neck US without suspicious findings after therapy.

Patients and Design: Retrospective review of 90 ATA intermediate-risk papillary thyroid carcinoma patients treated with total thyroidectomy and radioactive iodine ablation in a tertiary referral center.

Main Outcome Measures: A comparison between the frequency of finding false-positive US abnormalities and the frequency of identifying structural disease recurrence in the study cohort was measured.

Results: Over a median of 10 years, 90 patients had a median of six US (range 2–16). Structural disease recurrence was identified in 10% (9 of 90) at a median of 6.3 years. Recurrence was associated with other clinical indicators of disease in 5 of the 90 patients (5.6%, 5 of 90) and was detected without other signs of recurrence in four patients (4.8%, 4 of 84). False-positive US abnormalities were identified in 57% (51 of 90), leading to additional testing, which failed to identify clinically significant disease.

Conclusions: In ATA intermediate-risk patients who have a nonstimulated thyroglobulin less than 1.0 ng/mL and a neck US without suspicious findings after therapy, frequent US screening during follow-up is more likely to identify false-positive abnormalities than clinically significant structural disease recurrence. (J Clin Endocrinol Metab 100: 1561–1567, 2015)
For the determination of risk of recurrence, the American Thyroid Association (ATA) classifies patients as intermediate risk if they have microscopic tumor invasion into the perithyroidal tissue on initial histology, cervical lymph node metastases, $^{131}$I uptake outside the thyroid bed on posttherapy whole-body scan done after thyroid remnant ablation, or a tumor with aggressive histology or vascular invasion (1). In ATA intermediate-risk thyroid cancer patients, the initial risk of recurrent or persistent structural disease is as high as 21% (2). However, the risk of recurrence drops to 2% or less in intermediate-risk patients that demonstrate an excellent response to initial therapy (2). Furthermore, the few recurrences that develop in these patients are most often identified at least 3–5 years after the initial therapy (3). Nevertheless, many ATA intermediate-risk patients undergo intensive surveillance testing with frequent imaging studies and laboratory evaluations during the first few years of follow-up.

The ATA recommends that the neck ultrasound (US) should be performed 6–12 months after surgery to establish the patient response to therapy and then periodically, depending on the patient’s risk for recurrent disease and serum thyroglobulin (Tg) status (1). This lack of clarity in the ATA recommendations with regard to the timing of follow-up neck US coupled with the fear of recurrence on the part of both the clinician and the patient often leads to US examinations being done on a yearly basis (or more often) for at least the first 5 years of follow-up in ATA intermediate-risk patients, regardless of their response to therapy.

The goal of this study was to critically evaluate the sonographic findings obtained when serial US evaluations were used for routine screening in a cohort of ATA intermediate-risk patients who had a nonstimulated Tg less than 1.0 ng/mL and a neck US without clear evidence of persistent/recurrent disease after total thyroidectomy and radioactive iodine ablation. We hypothesized that routine serial neck US screening in this group of patients would be very unlikely to identify clinically significant disease in the early years of follow-up and would be more likely to identify nonspecific false-positive findings that would lead to additional testing, biopsies, and empirical treatments.

Materials and Methods

Subjects

After obtaining approval from our institutional review board, we conducted a retrospective analysis of the medical records of 293 patients with thyroid cancer treated with total thyroidectomy and radioiodine ablation (RAI) who had serial neck US performed during their early follow-up at our center between 1999 and 2009. For inclusion into the study, patients had to have ATA intermediate-risk (1), papillary thyroid cancer treated with total thyroidectomy and RAI, with a nonstimulated Tg of less than 1.0 ng/mL in the absence of interfering anti-Tg antibodies (TgAbs), and no suspicious findings on postoperative neck US (2, 4). ATA intermediate-risk patients with initial incomplete treatment response who required additional neck dissection before attaining a nonstimulated Tg of less than 1.0 ng/mL and a neck US without suspicious findings were included. A total of 90 patients satisfied the inclusion criteria for data analysis. The remaining patients were excluded based on the following findings: other histological subtypes of thyroid cancer, ATA low or high risk of recurrence, nonstimulated Tg of greater than 1.0 ng/mL, interfering anti-TgAbs, persistent suspicious US findings on postoperative evaluation, lobectomy as the only surgery, or only 0–1 neck US during follow-up.

Neck US evaluation

US examinations were performed according to standard protocol that included gray-scale and color Doppler US assessment of the thyroid bed and cervical lymph nodes in all neck compartments. Examinations were performed by technologists and supervised by experienced attending radiologists, who reviewed images in real time. The US studies were performed with Siemens AcusonS2000 (Siemens Medical Solutions), Siemens Acuson SEQUOIA (Siemens Medical Solutions), or the GE Logiq 9 (GE Healthcare) units, using 8–15 MHz linear 15L8W transducers. All prior imaging and reports performed at our institutions were available on our Picture Archiving and Communication system at the time of the ultrasound examination. The technologist and attending radiologists reviewed prior imaging and reports before the patient left the department and issuing a final report as per our practice.

US reports included size, shape, echogenicity, internal vascularity, presence of cystic changes, and microcalcifications of thyroid bed nodules and cervical lymph nodes. Size was defined as the largest diameter among the three dimensions provided. Echogenicity was characterized relative to the strap muscles. Microcalcifications were defined as multiple punctate bright echoes without acoustic shadowing. Avascular nodules had absent Doppler flow. In the ultrasound report, a comment was made on the change from prior studies when applicable.

US findings were classified as suspicious, atypical, or negative. We defined sonographically suspicious findings as cervical lymph node with at least one of the following features: microcalcifications, cystic areas, or peripheral or diffuse vascularity and thyroid bed nodules with at least one of the following features: microcalcifications or increased vascularity, including those with either peripheral or intranodular vascular flow as well as structurally progressive lesions, regardless of size. We defined sonographically atypical findings as rounded cervical lymph nodes that lack a fatty hilum and are avascular or thyroid bed nodules that are avascular (5–10). We defined sonographically negative findings as two or more consecutive negative postoperative neck US evaluations.

Other imaging modalities used to investigate for recurrence

The use of other cross-sectional imaging (computed tomography scan or magnetic resonance imaging) as well as functional imaging (RAI whole body scan or 18-fluorodeoxyglucose-pos-
Clinical outcomes

A structural neck recurrence, defined as newly identified locoregional metastases with or without abnormal Tg, was included as a clinical end point. The structural neck recurrence is based on histology or sonographically suspicious findings along with the impression of the attending physician.

Response to therapy was classified as excellent, acceptable, or incomplete, based on reassessment at each follow-up visit after surgery and RAI therapy at 6–24 months after RAI. Patients were considered to have an excellent response during follow-up if they had a suppressed and stimulated (if available) serum Tg less than 1 ng/mL and no structural evidence of disease on neck US and/or cross-sectional or nuclear medicine imaging. Patients were considered to have an acceptable (indeterminate) response if they had a suppressed serum Tg of less than 1 ng/mL and stimulated serum Tg 1 ng/mL or greater but less than 10 ng/mL (if available) and nonspecific changes on neck US and/or cross-sectional or nuclear medicine imaging. Patients were considered to have an incomplete therapy response if they had a suppressed serum Tg of 1 ng/mL or greater or stimulated serum Tg of 10 ng/mL or greater, or rising Tg values, and persistent or newly identified disease on neck US, cross-sectional, or nuclear medicine imaging (2).

Patients dying of unrelated conditions had the final end point determined based on data available before their demise.

Atypical US abnormalities identified during serial follow-up evaluations that were stable and not subsequently determined to be structural disease recurrence (by cytology, histology or RAI imaging) were considered to be false-positive findings. Although we recognize that some of these stable atypical ultrasonographic findings could be small volume, stable, or very slowly progressive papillary thyroid cancer, we classified all of them as false positive for the purposes of this study because they did not develop into clinically significant structural disease during a median follow-up period of 10 years.

Outcome of thyroid bed nodules and cervical lymph nodes

Each sonographically identified lesion was classified as either showing an increase in size or no increase in size. Growth was defined as an increase of at least 3 mm in the largest dimension when compared with the size of the nodule at initial detection. A 3-mm increase was selected because this is the minimal size change that can be reproducibly determined by high-resolution US while minimizing operator-dependent differences in size assessment (12). US images of the cases showing structural progression were submitted for a review by S.A.F., who is a recognized specialist in thyroid US.

Statistical methods

Continuous data were presented as means and SDs or median and ranges, as appropriate for each variable. A Fisher’s exact $\chi^2$ test was used to compare proportions. Analysis was performed using SPSS software (version 18.0.1; SPSS, Inc). A value of $P \leq .05$ was considered statistically significant.

Results

Initial clinicopathological characteristics

Patients were predominantly female (73%), with a median age of 45.9 years at the study entry, and a median follow-up duration of 10 years (range 1–15 y) (Table 1). Initial therapy included total thyroidectomy without neck dissection in 59%, central neck dissection in 14%, and central and lateral neck dissection in 27% of the patients. Most patients (47%) had classic papillary thyroid carcinoma; 29% had follicular variant papillary thyroid carcinoma, and 24% had tall-cell papillary thyroid carcinoma. Seventy percent of patients presented with lymph node metastasis; however, most the metastatic lymph nodes were small, with a median size of 0.8 cm (range 0.2–4.0 cm). Because patients with distant metastases had been excluded from the study, all the patients in the study cohort with an age younger than 45 years were classified as having American Joint Committee on Cancer (AJCC) stage I disease, and all patients with an age of 45 years and older were classified as having AJCC stage III or IV disease. At the initiation of the study, 54% of the patients (49 of 90) had an excellent response to therapy, whereas 46% of the patients (41 of 90) had an acceptable response to therapy (2). Prior to entering the study, a small number of patients (11%) who had an incomplete response to initial therapy underwent additional neck dissection, which rendered them free of disease.
**Table 1. Characteristics of the Patients at Baseline**

| Characteristics                                                                 | Value                                      |
|--------------------------------------------------------------------------------|--------------------------------------------|
| Patients, n                                                                     | 90                                         |
| Age at study entry, y [median (range)]                                         | 45.9 (22.5–86.1)                           |
| Gender                                                                         |                                            |
| Females                                                                        | 66 (73%)                                   |
| Males                                                                          | 24 (27%)                                   |
| Papillary thyroid carcinoma histological variantsa                             |                                            |
| Classic                                                                        | 42 (47%)                                   |
| Follicular variant                                                             | 26 (29%)                                   |
| Tall-cell variant/features                                                      | 22 (24%)                                   |
| Diffuse sclerosing variant                                                     | 2 (2%)                                     |
| Solid/trabecular pattern                                                       | 1 (1%)                                     |
| AJCC TNM stage                                                                 |                                            |
| I                                                                              | 46 (52%)                                   |
| II                                                                             | 0 (0%)                                     |
| III                                                                            | 31 (34%)                                   |
| IV                                                                             | 13 (14%)                                   |
| Lymph node metastases on initial history                                       | 63 (70%)                                   |
| Size of metastatic lymph node                                                  |                                            |
| Not reported                                                                   | 15 (24%)                                   |
| Reported, cm                                                                   | 48 (76%)                                   |
| Mean ± SD                                                                      | 1.4 ± 1.2                                  |
| Median (range)                                                                 | 0.8 (0.2–4.0)                              |
| Primary tumor with extrathyroidal extension                                    | 52 (58%)                                   |
| Primary tumor with vascular invasion                                           | 5 (6%)                                     |
| Basal nonstimulated serum Tg at study entry, ng/mL                             |                                            |
| Undetectable                                                                   | 41 (46%)                                   |
| Detectable                                                                     | 49 (54%)                                   |
| Mean ± SD                                                                      | 0.7 ± 0.1                                  |
| Median (range)                                                                 | 0.6 (0.6–0.8)                              |
| Extent of neck dissection at thyroidectomy                                      |                                            |
| No neck dissection                                                             | 53 (59%)                                   |
| Central neck dissection                                                        | 13 (14%)                                   |
| Central and lateral neck dissection                                             | 24 (27%)                                   |
| Response to initial therapy                                                    |                                            |
| Excellent                                                                       | 63 (70%)                                   |
| Acceptable                                                                     | 16 (18%)                                   |
| Incomplete                                                                     | 11 (12%)                                   |
| Additional neck dissection before study entry                                   | 10 (11%)                                   |
| Follow-up duration, y [median (range)]                                         | 10 (1–15)                                  |

Abbreviation: TNM, tumor node metastasis.

**Ultrasonographic and clinical outcome during follow-up**

Overall, 10% of the patients (9 of 90) developed suspicious US findings that led to identification of structural neck disease during surveillance. The disease was identified at a median of 6.3 years after the last surgery (range 3.0–14.5 y). These nine patients underwent a median of 10 neck US (range 4–16 US), over a median follow-up of 10 years (range 3.0–14.0 y). Three (3 of 9) patients had initial incomplete treatment response and required additional neck dissection before attaining a nonstimulated Tg of less than 1.0 ng/mL and a neck US without suspicious findings for initial study inclusion.

Five of the nine patients with structural disease recurrence had clinical indications for additional surveillance testing including a rising Tg level or a palpable neck mass (Table 2). In the absence of clinical indications for US examination, routine screening US identified structural disease recurrence in only four patients (4 of 84, 4.8%) at a median of 4.9 years after the last surgery (range 4.3–11.5 y) (Table 2).

Among the nine patients who developed suspicious ultrasound findings during follow-up, five patients underwent further surgery, and one of these patients received 131I therapy after surgery. The remaining four patients had stable low-volume disease based on clinical assessment without cytological evaluation and were observed. Of the five patients who underwent further intervention, the histology revealed low-volume nodal disease. Two patients had an excellent response to treatment, whereas three patients had an acceptable or incomplete response.

The only clinical predictor for structural disease recurrence in this cohort of ATA intermediate-risk thyroid cancer patients was an initial acceptable or incomplete response to therapy [78% (7 of 9) vs 25% (20 of 81), respectively, \(P < .05\)]. As expected, those patients with a less complete response to treatment had an increased risk of developing structural recurrence. A larger proportion of patients with structural recurrence had metastatic lymph nodes on initial histology [89% (8 of 9)] compared with the patients without structural recurrence [68% (55 of 81)], but this was not a significant difference (\(P > .05\)).

Conversely, a total of 51 patients (51 of 90, 57%) had atypical US findings during the early follow-up period either on initial postoperative neck US or subsequent surveillance US. These findings resulted in a median of six neck US during follow-up (range 2–14 US). Furthermore, these atypical US findings led to three biopsies under US guidance with benign cytological results, six RAI whole-body scans (none leading to further 131I therapy), 11 computed tomography/magnetic resonance imaging scans, nine positron emission tomography scans, and 238 additional neck US in total. None of these additional investigations revealed structural disease (Figure 1).

Overall, of the 90 patients, 49 had a negative postoperative neck US and 41 had atypical findings on US after treatment (none had suspicious US findings on posttreatment evaluation because these patients were excluded from the study) (Figure 1). Four of the 49 patients (8%) with negative postoperative US developed structural neck recurrence during surveillance and 15 patients (15 of 49,
31%) developed atypical US findings, with none having evidence of structural disease. Thirty patients (30 of 49, 61%) continued to have normal neck US over a median follow-up period of 9.0 years (range 3.0–14.0 y) and had a median of four neck US (range 2–11 US). None of the patients who had two or more negative ultrasounds developed recurrence during surveillance.

Of the 41 patients (41 of 90) who had atypical findings on postoperative neck US, 5 (5 of 41, 12%) developed structural neck recurrence during surveillance. The re-
mainly 36 patients (36 of 41, 88%) had persistent atypical findings, which led to an ongoing evaluation with no evidence of structural disease (Figure 1).

**Discussion**

We reviewed the records of a cohort of 90 patients with ATA intermediate-risk thyroid cancer treated with total thyroidectomy and RAI ablation who had a nonstimulated serum Tg less than 1 ng/mL without suspicious US findings. Consistent with our previous studies, the overall rate of recurrence was 10% during a median follow-up of 10 years. Importantly, in the absence of other clinical indicators of disease recurrence, routine screening US identified structural disease in only 4.8% of patients (4 of 84) at a median of 4.9 years after treatment (range 4.3–11.5 y). In the other five patients with structural disease recurrence, the disease would have been detected due to clinical indicators without the use of regular surveillance US. Conversely, routine surveillance neck US identified many false-positive results. Fifty-seven percent of the neck US showed atypical findings, which led to a wide variety of procedures and tests without identifying clinically significant disease. Only 30% of the patients (30 of 90) had a persistently negative high-resolution neck US during the course of follow-up. None of these patients developed recurrent disease. Thus, in this group of patients at low risk for recurrent disease, frequent US monitoring in the first 5 years of follow-up was far more likely to identify nonspecific false-positive findings than to identify clinically significant structural disease recurrence. Because all the patients in the study received RAI, the clinical utility of surveillance neck US in patients who have not undergone RAI ablation still needs to be evaluated.

Although we recognize that some of the atypical US findings could develop into a structural disease recurrence during long-term follow-up, our findings have relevance to the first 5 years of follow-up because none of the atypical findings were found to be clinically significant structural disease recurrence in that time frame. Furthermore, the structural disease recurrences were not detected during the first 3 years of follow-up indicating that nearly all atypical ultrasonographic findings obtained during this early follow-up period represent false-positive results rather than true structural disease recurrence. When coupled with our earlier observations that sonographically suspicious and atypical lymph nodes and thyroid bed nodules usually remain stable for many years or grow slowly over 2–3 years (13, 14), there appears to be little clinical justification for the routine use of US examination in the first 3 years of follow-up after ATA intermediate-risk patients attain a nonstimulated Tg less than 1.0 ng/mL and a neck US without suspicious findings. These observations would not be applicable to either ATA high-risk patients or ATA intermediate-risk patients with incomplete structural or biochemical response to therapy because the risk of structural disease recurrence in those patients is significantly higher and could present at earlier time points.

Historically, recurrence from thyroid cancer was observed many years after the initial treatment. In a long-term study of patients with well-differentiated thyroid cancer by Mazzaferri and Jhiang (15), 57% of recurrences were diagnosed in the first 5 years of follow-up, whereas 43% of the recurrences were detected 5–35 years after initial treatment. In another long-term study by Hay et al (16), thyroid cancer recurrence was detected up to 60 years after the initial treatment. These older studies were conducted when preoperative neck US was not the standard of care and when sensitive surveillance tools such as serum Tg and high-resolution neck US were not available. Because the time to detection of persistent/recurrent thyroid cancer has changed due to improving technology, the surveillance plan for thyroid cancer patients should adopt a more risk-stratified approach for better patient care and cost-effectiveness.

In a recent study by Durante et al (3), the authors evaluated the time to recurrence in 948 papillary thyroid carcinoma patients who had negative postoperative imaging over a median follow-up of 10.4 years (range 5.1–20.4 y). In this cohort, 61% of the patients had ATA low-risk disease and the overall recurrence rate was 1.4%. With the current technology, all of the recurrences were diagnosed less than 8 years (range 1.2–7.7 y) after the initial therapy. We had similar results in our study, with the diagnosis of recurrence at a median of 6.3 years after last surgery (range 3.0–14.5 y) over a median follow-up of 10 years (range 2–15 y). We postulate that after 10–15 years of follow-up in ATA intermediate-risk patients who have achieved a nonstimulated serum Tg less than 1 ng/mL with no suspicious findings on the surveillance neck US, further neck US is not required. However, long-term studies would be required to confirm this.

The European Thyroid Association does not recommend routine surveillance US for very low-risk and low-risk patients if the initial surveillance neck US is normal and the serum Tg is undetectable. They recommend more frequent surveillance US in patients at higher risk for recurrence (17, 18). Data from our study and the study by Durante et al (3) support the European Thyroid Association recommendation for less frequent US surveillance in thyroid cancer patients who have a low risk of recurrence.

In conclusion, serial neck US in the early years of follow-up in ATA intermediate-risk thyroid cancer patients
who achieve a nonstimulated serum Tg less than 1 ng/mL is more likely to identify false-positive results than true structural disease. Furthermore, routine US surveillance in the absence of clinical indications for recurrent disease rarely identifies clinically significant disease during the early follow-up. Routine surveillance US identified structural disease recurrence in only 4 patients (4 of 84, 4.8%) at a median of 4.9 years after the last surgery. Therefore, in the absence of suspicious clinical findings, we recommend surveillance neck US no more frequently than every 3–5 years in ATA intermediate-risk patients who have achieved a nonstimulated serum Tg less than 1 ng/mL with no suspicious findings on postoperative neck US. If these patients have two or more negative neck US, no further neck US is necessary in the absence of clinical indications of recurrence. The frequency and timing of surveillance neck US should be individualized according to the risk of recurrence and the response to therapy.

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