
Followup of Patients with Papillary Thyroid Cancer: In Search of the Optimal Algorithm

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- BACKGROUND:** Cervical recurrence occurs in up to 30% of patients after surgical treatment for papillary thyroid cancer. This study sought to determine an appropriate algorithm for followup evaluation.
- STUDY DESIGN:** Patients undergoing total thyroidectomy for papillary thyroid cancer were identified. Clinico-pathologic data were recorded, as were the results of all followup evaluations including radioiodine scan, cervical ultrasonography, and serum thyroglobulin levels. The disease recurrence-free survival probability was estimated, and risk factors for recurrence were determined.
- RESULTS:** Thyroidectomy with or without neck dissection was performed in 162 patients. We excluded 36 patients (followup less than 6 months in 26, extracervical disease at diagnosis in 4, unknown tumor size in 6) from the analysis. Of the remaining 126 patients, 109 (86.5%) had no evidence of disease, with serum thyroglobulin < 1 ng/mL at last followup; 4 (3.2%) had no evidence of disease (negative imaging), with serum thyroglobulin > 1 ng/mL, and 13 (10.3%) had recurrent disease. Cervical recurrence occurred in nine patients, all detected by routine ultrasonography. Pulmonary metastases occurred in four patients; three were diagnosed by chest CT and one by radioiodine scan. Thyroid stimulating hormone-suppressed thyroglobulin levels were available in 11 of the 13 patients and were elevated in 9. Patients with high T stage (extrathyroidal extension), or high N stage had an increased risk of recurrence.
- CONCLUSIONS:** A followup strategy emphasizing routine cervical ultrasonography and unstimulated thyroglobulin is effective in identifying patients with recurrent papillary thyroid cancer, and may minimize the indiscriminate use of therapeutic radioiodine for radiographically occult disease. Surgery remains the optimal treatment of cervical recurrence, which is the dominant pattern of treatment failure. (J Am Coll Surg 2007;205:239–247. © 2007 by the American College of Surgeons)
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Papillary thyroid cancer (PTC) is the most common endocrine malignancy, with an incidence of 8 cases per 100,000 people.¹ In general, patients with PTC do very well, with a 10-year cancer-specific mortality rate of < 10%.² Despite the low mortality rate, cervical recurrence after initial treatment, primarily in the form of regional lymph node metastases, is a major concern, oc-

curing in 9% to 30% of patients, depending on risk stratification.³⁻⁵ The appreciation that even low risk patients are at clinically significant risk for recurrence has generated an interest in more comprehensive preoperative evaluation and more frequent and detailed followup of the thyroid cancer patient than was previously thought necessary.⁶ This change in practice pattern has been reflected in many of the published thyroid cancer guidelines, such as those from the National Comprehensive Cancer Network (NCCN) and the American Thyroid Association (ATA), and represents a recent shift in patient care from a focus on overall survival to a focus on recurrence-free survival. This emphasis has been made possible by continued advances in transcutaneous ultrasonography (US), an improvement in the sensitivity of the thyroglobulin (Tg) assay,⁷ and greater patient awareness and concern. To put this rapid change in practice pattern into perspective, we first described the benefit of routine comprehensive US evaluation of the neck before

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Abbreviations and Acronyms

ATA	= American Thyroid Association
NCCN	= National Comprehensive Cancer Network
PTC	= papillary thyroid cancer
RAI	= radioiodine
RFS	= recurrence-free survival
rhTSH	= recombinant human TSH
Tg	= serum thyroglobulin
Tg-Ab	= thyroglobulin antibodies
TSH	= thyroid stimulating hormone
US	= ultrasonography

thyroidectomy 3 years ago.^{8,9} At that time, there was no uniform consensus by even experienced endocrine surgeons as to the value of finding subclinical lymph node metastases preoperatively. Now, preoperative cervical US is part of all treatment guidelines, and US findings are commonly used to guide the extent of lymph node dissection at the time of thyroidectomy.

Recently published thyroid cancer guidelines from the NCCN and ATA also emphasize a more comprehensive followup program to detect recurrent disease in patients with PTC. Previous guidelines advocated annual radioiodine (RAI) scans as the preferred imaging modality. These more recent guidelines advocate the use of routine cervical US.^{6,10} Cervical US is highly sensitive in the identification of cervical metastases, including local-regional metastatic disease as small as 2 to 3 mm.¹¹⁻¹³ Local-regional metastases occasionally are detected by cervical US even when thyroid stimulating hormone (TSH)-stimulated serum Tg levels remain undetectable.¹⁴

Importantly, the treatment for cervical lymph node recurrence is reoperation, not additional therapeutic RAI. To what degree the discovery of US occult, very small volume disease in low risk patients is leading to the indiscriminate use of diagnostic and therapeutic RAI is unknown, but is worthy of concern. This concern, prompted by our anecdotal experience with a number of patients receiving additional doses of therapeutic RAI in the setting of minimal elevation in stimulated Tg with a negative cervical US, caused us to review the outcomes of patients treated for PTC in our department. Our followup algorithm emphasizes cervical US and unstimulated Tg.

METHODS

Using the prospective database of the Department of Surgical Oncology at the University of Texas MD

Anderson Cancer Center, we identified all patients with PTC who underwent total thyroidectomy as their definitive surgical procedure at our institution, from 1991 to 2005. Demographic data including gender and age were recorded. Initial treatment to include the extent of operation, completeness of resection, and the use of post-operative RAI ablation were also determined.

Our surgical approach to patients with PTC emphasized complete resection of clinically and radiographically evident disease within the neck. Preoperative evaluation routinely included high quality US of the thyroid and the soft tissues of the neck to identify suspicious lymph nodes in the central or lateral compartments.⁹ US characteristics of a suspicious lymph node were based on the presence of intranodal calcifications, a full or rounded shape, disorganized extrahilar vascularity on color Doppler imaging, or the presence of a cystic component and the absence of a central hilum or alteration in its appearance or position. For patients with suspicious or clearly abnormal clinical or US findings in the central or lateral neck, we performed compartment-oriented surgery to include a central or lateral compartment dissection. A central compartment dissection involved removal of all lymph nodes and soft tissues in level VI, with preservation of the recurrent laryngeal nerves and parathyroid preservation in situ (usually the superior glands) or by autografting (common with the inferior glands), or both. Lateral compartment dissection (modified radical neck dissection) was performed only if disease was seen on US or was palpable on physical examination, and involved removal of all lymph nodes and soft tissues in levels IIA, III, IV, and V, with preservation of the jugular vein, carotid artery, vagus nerve, phrenic nerve, and spinal accessory nerve when possible. Patients without a cytologic diagnosis of PTC before operation (for example, indeterminate thyroid nodule on fine-needle aspiration) and no evidence of adenopathy did not undergo any form of lymphadenectomy. In addition, our approach to the ipsilateral central neck in patients with known PTC and no adenopathy evolved over the course of this experience.

In the past 6 to 8 years, thyroidectomy was combined with elective ipsilateral paratracheal lymph node dissection, even if the preoperative US showed no abnormal adenopathy. Paratracheal lymph node dissection involved removal of all lymph nodes anterior and medial to the recurrent laryngeal nerve. On the right side, where the recurrent nerve does not hug the tracheoesophageal

groove, this dissection also included removal of lymph nodes posterior to the recurrent nerve. We routinely removed the pyramidal lobe and adjacent lymph nodes on the thyroid cartilage. So operations included total thyroidectomy, total thyroidectomy with elective ipsilateral level VI dissection, total thyroidectomy with therapeutic level VI (central compartment) dissection, total thyroidectomy with central and ipsilateral modified radical neck dissection, and total thyroidectomy with central and bilateral modified radical neck dissection. The completeness of resection (R status) was recorded, with R0 indicating no residual disease, R1 indicating residual microscopic disease, and R2 indicating residual macroscopic disease. During the study period from 1991–2005, we routinely performed postoperative RAI total body scanning with 5 mCi of iodine 131 before therapeutic RAI treatment (at present 1-mCi of I123 is used for diagnostic scans). Patients with a negative total body scan did not receive a therapeutic dose of RAI. Adjuvant RAI was administered at the discretion of the attending physician, but in general, it was routinely given to all patients except those under 45 years of age with T1N0 disease.

Pathology reports were reviewed and the following were recorded: tumor size; presence or absence of extrathyroidal extension; T stage as determined by the American Joint Committee on Cancer (AJCC) staging system, 6th edition; and N stage as determined by the AJCC staging system.¹⁵ Patients were classified using this data and age as being at low, intermediate, or high risk for recurrent disease. Patients were considered to be at low risk if they were less than 45 years old, with T1-2,N0-1a disease. Patients were considered to be at intermediate risk if they were less than 45 years of age, with T3,N0-1a disease or if they were older than 45 years of age with T1-2,N0-1a disease. Patients were considered to be at high risk for recurrence if they were older than 45 years of age, with T3 disease or of any age with T4 or N1b disease.

Clinical course was determined and patients with recurrent disease were identified. Cervical recurrence was defined as metastatic involvement of any cervical lymph node or soft tissue in the neck. All other recurrences were considered extracervical. For patients with recurrent disease, the time to recurrence, serum TSH and Tg levels, and anti-Tg antibody status at the time of the diagnosis of recurrence were recorded. The method of detection of the recurrent disease was also identified. For patients whose recurrence was not identified specifically on rou-

tine RAI scanning, records were reviewed to determine if an RAI scan had been performed on an annual basis in accordance with previous NCCN guidelines. If a routine RAI scan had been performed, the results of the study were recorded. For patients without recurrence, the date of their most recent followup and results of their most recent laboratory evaluation to include serum TSH, Tg, and anti-Tg antibody levels were recorded. In the majority of patients, the serum Tg was unstimulated. Results of any additional radiographic studies performed were also noted.

This study was approved by the MD Anderson Cancer Center Institutional Review Board. The end point for our analysis was time to disease recurrence. Statistical analysis was performed to determine if specific risk factors, including age, gender, extent of operation, R status, T stage, N stage, and administration of adjuvant RAI ablation, could predict the development of recurrent disease. Patient characteristics were summarized using median (range) for continuous variables and frequency (percentage) for categorical variables. The disease recurrence-free survival (RFS) probability was estimated using the method of Kaplan and Meier. The log-rank test was used to assess the difference in RFS between subgroups of patients. Univariate Cox proportional hazards models were fit for each risk factor, including age, gender, N stage, T stage, extent of operation, pathologic evidence of extrathyroidal extension, and use of adjuvant RAI therapy. The association between a patient's risk factors was evaluated using Fisher's exact test. Because of the small number of disease recurrences and the strong association between key risk factors, no multivariable Cox model was able to be fit for the data set. All analyses were carried out in S-Plus (Insightful Corp); a *p* value < 0.05 was considered statistically significant.

RESULTS

We identified 162 patients who underwent total thyroidectomy with or without central or lateral compartment dissection as their definitive surgical procedure for PTC. We excluded 36 patients from analysis: followup was < 6 months in 26, size of the primary tumor was unknown in 6, and there was extracervical disease at the time of diagnosis in 4, leaving a study population of 126 patients. Patient characteristics are summarized in Table 1. There were 94 women (75%) and 32 men (25%), with a median age at initial PTC diagnosis of 44 years (range 13 to 79 years). The extent of operation included

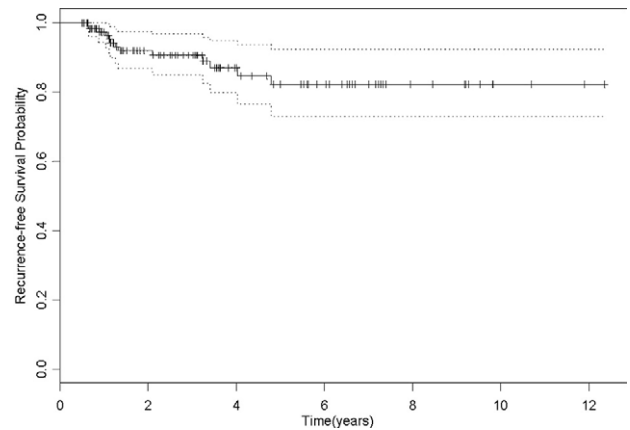
Table 1. Patient Characteristics (n = 126)

Variable	Median (range)	n	%
Age, y	44 (13-79)		
Gender			
Female		94	75
Male		32	25
R status			
0		121	96
1		5	4
Extent of operation			
TT		45	36
TT+C		46	36
TT+C/B		11	9
TT+C/I		24	19
T stage			
1		65	52
2		27	21
3		32	25
4		2	2
N stage			
N0		63	50
N1a		36	29
N1b		27	21
Radioiodine			
No		19	15
Yes		107	85
Extrathyroidal extension			
No		98	78
Yes		28	22

TT+C, total thyroidectomy with central compartment dissection; TT+C/I, total thyroidectomy with central compartment dissection and ipsilateral lateral compartment dissection; TT+C/B, total thyroidectomy with central compartment dissection and bilateral lateral compartment dissection.

total thyroidectomy in 45 (36%), total thyroidectomy with ipsilateral or bilateral central compartment dissection in 46 (36%), total thyroidectomy with central and ipsilateral modified radical neck dissection in 24 (19%), and total thyroidectomy with central and bilateral modified radical neck dissection in 11 (9%). Complete extirpation of macroscopic disease was achieved in all patients: 121 (96%) had an R0 resection, and 5 (4%) had an R1 resection. No patient had macroscopic disease (R2) left at the time of operation. After the initial operation, 36 (29%) patients were considered low risk, 53 (42%) were intermediate risk, and 37 (29%) were high risk, according to our classification system. So adjuvant RAI was administered to 107 (85%) of the 126 patients.

After a median followup of 34 months (range 6 to 148 months), 13 (10.3%) patients were identified with recurrent disease. The median time to disease recurrence

**Figure 1.** Kaplan-Meier estimates for recurrence-free survival (n = 126; recurrence n = 13). The median time to disease recurrence has not been reached for the study population.

has not been reached for the study population (Fig. 1). The site of recurrence was cervical in nine patients and extracervical in four. All four patients with extracervical disease had pulmonary metastases. Additional clinicopathologic data for the 13 patients with recurrent disease are shown in Table 2. At a minimum, all patients who experienced recurrent disease underwent total thyroidectomy with central compartment dissection as their initial surgical procedure; an R0 resection was achieved in all 13. Adjuvant RAI was delivered to 12 of the 13 patients; 1 did not receive RAI because she was pregnant at the time of diagnosis and treatment. This patient was scheduled to receive adjuvant RAI in the postpartum period, but during evaluation for this therapy, pulmonary metastases were identified.

Only 1 of the 13 patients with recurrent disease had their recurrence diagnosed by RAI scanning. In the remaining 12 patients, recurrence was identified either by cervical US or chest CT. Of these 12 patients, 8 had RAI scanning performed within 1 month after the diagnosis of recurrent disease had been established. RAI scanning confirmed the diagnosis of recurrence in two (25%) of these eight patients. In all nine patients with cervical recurrence, the disease was identified on US of the neck.

There was no evidence of disease at the time of last followup evaluation in 113 (90%) of the 126 patients. Of these 113 patients, 109 (96%) had Tg \leq 1 ng/mL, 98 of whom had negative thyroglobulin antibodies (Tg-Ab), 6 had positive Tg-Ab, and in 5, the Tg-Ab status was not known. Serum Tg was $>$ 1 ng/mL in four patients who were without evidence of disease by imaging and physical examination; Tg levels in these patients were

Table 2. Clinicopathologic Data for Papillary Thyroid Cancer Patients with Recurrent Disease

Pt. no.	Stage	Extent of operation	R status	Adjuvant RAI	Time to recurrence, mo	Site of recurrence	Tg	TSH	Tg-Ab	How recurrence identified	Seen on RAI?
1	T2N1a	TT+C	0	Yes	25	Cervical	18	29	Neg	Cervical US	ND
2	T3N1a	TT+C	0	Yes	15	Cervical	8	0.24	Neg	Cervical US	ND
3	T2N1a	TT+C	0	Yes	11	Cervical	2	0	Neg	Cervical US	ND
4	T3N1b	TT+C/B	0	Yes	39	Cervical	90	7	Neg	Cervical US	No
5	T3N1b	TT+C/B	0	Yes	13	Cervical	27	<0.1	Neg	Cervical US	No
6	T2N1a	TT+C	0	Yes	14	Cervical	Unk	Unk	Neg	Cervical US	No
7	T3N1b	TT+C/B	0	Yes	58	Cervical	84	0	Neg	Cervical US	ND
8	T3N1b	TT+C/I	0	Yes	16	Cervical	9	21.6	Neg	Cervical US	No
9	T3N1b	TT+C/B	0	Yes	48	Cervical	0.1	1.6	Neg	Cervical US	Yes
10	T2N1b	TT+C/B	0	Yes	8	Lung	29	28	Neg	RAI scan	Yes
11	T3N1b	TT+C/B	0	Yes	12	Lung	0.9	36	Neg	CT	No
12	T1N1b	TT+C/I	0	Yes	41	Lung	24	Unk	Neg	CT	No
13	T3N1b	TT+C/I	0	No	8	Lung	37	0	Neg	CT	ND

ND, not done; Neg, negative; RAI, radioiodine scan; Tg, thyroglobulin; Tg-Ab, thyroglobulin antibodies; TSH, thyroid stimulating hormone; TT+C, total thyroidectomy with central compartment dissection; TT+C/B, total thyroidectomy with central compartment dissection and bilateral lateral compartment dissection; TT+C/I, total thyroidectomy with central compartment dissection and ipsilateral lateral compartment dissection; Unk, unknown; US, ultrasonography.

2.0 ng/mL (in 2 patients), 2.7 ng/mL, and 5.0 ng/mL. These patients were all evaluated with RAI scans, neck US, and chest radiography at a minimum; no recurrent disease was identified by any imaging modality.

Comparison was made between the 113 patients without evidence of disease and the 13 with recurrence to determine if any clinicopathologic data could predict the development of recurrent disease. Because only two patients had T4 disease, these two were excluded from this analysis for RFS. Figure 2 shows the Kaplan-Meier estimates for RFS probabilities by T stage, the presence of extrathyroidal extension, and N stage. Univariate Cox proportional hazards models were then fit for RFS (Table 3). The models suggest that patients with high T stage (T3 versus T1), namely, the presence of extrathyroidal extension, or high N stage (N1b versus N0 or N1a) had an

increased risk of disease recurrence. In addition, the risk of disease recurrence increased for patients who underwent more extensive operations, including total thyroidectomy with ipsilateral or bilateral modified radical neck dissection, which suggests that the extent of disease was recognized at the time of initial operation. There was no marked predictive effect because of age, gender, or the administration of adjuvant RAI. With respect to risk stratification, recurrent PTC was detected in 10 (27%) of 37 high risk patients, 0 of 52 intermediate risk patients, and 3 (8%) of 37 low risk patients.

DISCUSSION

After initial treatment, patients with PTC are monitored in an effort to identify recurrent disease when it is relatively small volume and amenable to treatment. Recur-

Table 3. Univariate Cox Proportional Hazards Model for Recurrence-Free Survival

Variable	Coefficient	Standard error	Relative risk	p Value
Age	-0.02	0.02	0.98	0.27
Gender = male (versus female)	0.62	0.57	1.86	0.28
N stage = N1b (versus N0 or N1a)	2.26	0.60	9.55	< 0.001
Extent of operation = TT+C/B or TT+C/I (versus T or TT+C)	2.09	0.60	8.11	0.001
Extrathyroidal extension = yes (versus no)	1.69	0.56	5.42	0.003
T stage = T2 (versus T1)	2.02	1.12	7.56	0.07
T stage = T3 (versus T1)	2.72	1.06	15.13	0.01
RAI = yes (versus no)	0.57	1.04	1.78	0.58

T stage and N stage determined by the American Joint Committee on Cancer TNM staging system, 6th edition.

RAI, radioiodine; T, thyroidectomy; TT+C, total thyroidectomy with central compartment dissection; TT+C/B, total thyroidectomy with central compartment dissection and bilateral lateral compartment dissection; TT+C/I, total thyroidectomy with central compartment dissection and ipsilateral lateral compartment dissection.

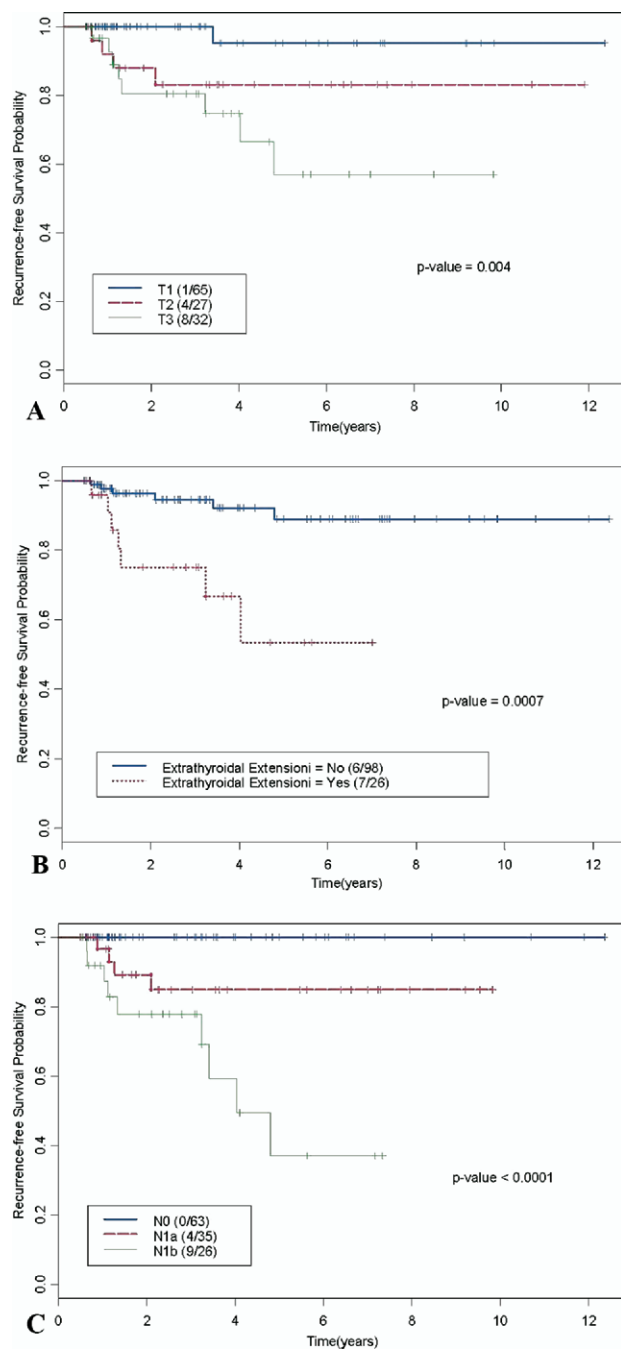


Figure 2. Kaplan-Meier estimates for recurrence-free survival by (A) T stage, (B) extrathyroidal extension, and (C) N stage ($n = 124$).

rent disease is treated with curative intent whenever possible, in the hope of delaying future morbidity or mortality. The preferred treatment for local-regional recurrence is surgical excision (reoperation). Additional therapeutic RAI should be reserved largely for patients with extracervical (distant) disease.⁶ Local-regional dis-

ease identified only on RAI scanning and not seen on anatomic imaging such as US should be the subject of observation and close followup, especially in low to intermediate risk patients. In our series of patients with PTC who underwent total thyroidectomy with or without central or lateral compartment dissection, the majority of patients with recurrent disease had their recurrence identified on routine followup neck US if the recurrence was cervical, or by CT scanning prompted by an elevated unstimulated Tg if the recurrence was extracervical.

Importantly, the NCCN has recently published revised guidelines for postoperative surveillance of patients with PTC. These revised guidelines include more restrictive recommendations for RAI scanning and a greater emphasis on the utility of neck US. Specifically, the recommendations include periodic neck ultrasonography; measurement of recombinant human TSH (rhTSH)-stimulated Tg in low risk patients with recent negative neck US and negative TSH-suppressed Tg without distant metastases or soft tissue invasion on initial staging; RAI scan every 12 months until absence of treatable disease if detectable Tg, distant metastases, or soft tissue invasion on initial staging; and consideration of additional nonradioiodine imaging if the RAI scan is negative and the stimulated Tg is > 2 to 5 ng/mL.¹⁰ The guidelines go on to support the use of therapeutic RAI if the stimulated Tg is > 10 ng/mL and imaging studies are negative. Recent management guidelines from the ATA are similar and suggest consideration of empiric therapeutic RAI if the stimulated Tg level is > 10 ng/mL after withdrawal, or 5 ng/mL after rhTSH, and all imaging studies, including noncontrast chest CT, are negative. For patients with stimulated Tg levels < 5 (rhTSH) or 10 ng/mL (withdrawal), 6 to 12 months' followup is recommended. The ATA guidelines also limit the use of RAI scanning to the followup of patients with high or intermediate risk disease.⁶ A 6- to 12-month post-treatment Tg that fails to rise with rhTSH or T4 withdrawal may effectively define a population of low to intermediate risk patients who are at very low risk for recurrence.

The obvious concern with these guidelines is the identification and subsequent management of patients with low-level elevations in stimulated Tg and negative neck US. First, the size of this group of patients will be proportional to the quality of the US. If the US is of poor quality and does not identify macroscopic disease, espe-

cially in the range of 1 to 2 cm in size, then this group of patients will be larger than the group for which high quality US is used. Such patients may then receive therapeutic RAI for cervical disease that would best be treated with operation (or continued observation until it reaches a size amenable to reoperation). With high quality US, one is less likely to miss small volume cervical recurrence as the cause for a minimal elevation in stimulated Tg. Second, we question if it is realistic to assume that physicians (and patients) have the discipline to simply follow patients with stimulated Tg levels < 10 ng/mL after T₄ withdrawal or in the range of 2 to 5 ng/mL after rhTSH. To the extent that treatment is more effective for small volume disease, treating early will be more beneficial—a philosophy that may prompt physicians to administer RAI in the setting of low-level elevations in stimulated Tg and negative anatomic imaging. The obvious problem with RAI treatment of these patients with low-level elevations in stimulated Tg is that most of the recurrences will be cervical, especially in low to intermediate risk patients, and cervical recurrences are most effectively treated with operation. Such patients may be better managed with serial neck US evaluation and measurement of suppressed Tg. When lymph node or soft tissue disease is found that is ≥ 1 cm and amenable to fine-needle aspiration biopsy, reoperation can be considered. We would always repeat CT imaging of the neck and mediastinum before reoperation as a guide to surgical planning and to ensure that all disease, especially at the thoracic inlet, is resected to limit the number of times a patient has to undergo reoperation.

Our algorithm for routine followup of patients with PTC emphasizes routine cervical US (Fig. 3). Cervical US as the primary imaging modality is in accordance with recent guidelines by the NCCN and the ATA, which recommend that US be performed 6 to 12 months after initial treatment for patients who have undergone total or near-total thyroidectomy and RAI ablation.^{6,10} In major referral centers, cervical US has been shown to be highly sensitive in detecting cervical metastases. This is particularly relevant in patients with low or intermediate risk PTC, in which the majority of recurrences occur in the neck. Three recent large studies documented the efficacy of cervical US.¹⁶⁻¹⁸ One study involved almost 500 patients with differentiated thyroid cancer, including both follicular and PTC, followed for more than 5 years. Approximately 10% of patients ex-

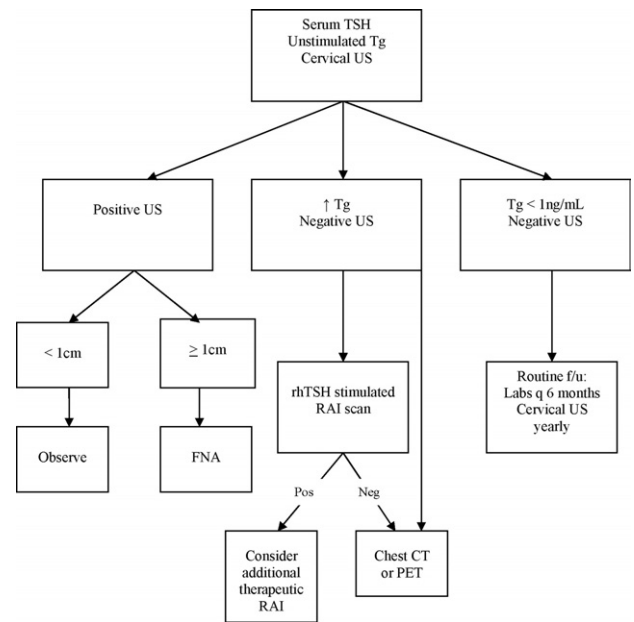


Figure 3. Algorithm for the followup of PTC patients successfully treated with total thyroidectomy and adjuvant RAI. The workup of a patient with a negative cervical US and elevated Tg is based on risk stratification and results of prior RAI scans. For example, a patient with a recent diagnostic or therapeutic RAI scan showing no evidence of extracervical uptake would be evaluated with a chest CT or PET scan, or both.

perienced recurrences in either the lateral or central neck. Cervical US had a 94% sensitivity in detecting the recurrences versus 57% and 45% sensitivities for withdrawal-aided Tg testing and RAI scanning, respectively.¹⁶ In our series, all patients with cervical recurrence were identified by routine cervical US. In the hands of an experienced ultrasonographer, lymph node metastases of < 1 cm can be found and successfully biopsied using fine-needle aspiration. At present, an additional challenge has emerged with regard to the surgical management of such small foci of recurrence, namely, how to find subcentimeter lymph node recurrences in the neck at the time of operation. US can now find disease that the surgeon may miss, so at present, the decision to proceed with surgery is becoming more complicated, even in patients with biopsy-proved recurrent disease. Subcentimeter foci of presumed recurrent disease should be biopsied only if a therapeutic strategy will be influenced by the biopsy result.

In our practice, we also obtain an unstimulated serum Tg level as part of routine followup in PTC patients successfully treated with total thyroidectomy and adjuvant RAI. We rarely obtain rhTSH-stimulated Tg levels.

The recommendation for obtaining TSH-stimulated Tg levels is based on the observation that approximately 20% of patients who are clinically free of disease with TSH-suppressed Tg < 1 ng/mL will have a serum Tg level > 2 ng/mL after rhTSH stimulation or thyroid hormone withdrawal.¹⁹ Patients with cervical disease, as discussed previously, will account for the majority of low-level elevations in stimulated Tg levels, and in these patients, cervical US is highly sensitive in the detection of recurrence. In fact, cervical disease may be detected by US even when TSH-stimulated Tg levels remain undetectable.¹⁴ So it is likely that the majority of macroscopic cervical recurrences will be detected early using a combination of cervical US and unstimulated serum Tg. For patients with extracervical disease in whom the concern may be that disease would go undetected without the routine use of RAI imaging and stimulated Tg, the unstimulated Tg level will be elevated in the vast majority of patients, prompting additional radiographic evaluation. Robbins and colleagues²⁰ analyzed serum Tg levels both unstimulated and stimulated with respect to sites of metastases. Patients with bone metastases had a median TSH-suppressed Tg of 687 ng/mL, which rose to 2,030 ng/mL after rhTSH treatment. Patients with lung metastases had a median suppressed Tg of 15 ng/mL, with a rise to 160 ng/mL after rhTSH treatment. Finally, patients with mediastinal disease had a median suppressed Tg of 5 ng/mL, with a rise to 18 ng/mL after rhTSH treatment. These data support our recommendation for a followup algorithm that emphasizes cervical US and unstimulated Tg (Fig. 3).

For patients with a negative cervical US but an unstimulated Tg > 1 ng/mL, we recommend additional radiographic evaluation to look for disease recurrence and to serve as a baseline for more imaging studies. An rhTSH-stimulated RAI scan is performed selectively based on the clinical situation to include the patient age and TNM stage, Tg level, and results from earlier RAI scans. If positive, consideration is given to additional RAI therapy. Like with any other solid malignancy, the potential benefit of the identification and treatment of small volume regional or extraregional recurrence must be assessed with an understanding of the efficacy of the potential therapies available and the toxicities associated with these therapies. In addition, consideration must be given to the fact that, in contrast to most other solid tumors, patients with thyroid cancer may have microscopic, radiographically occult disease that may never

become clinically significant. In the case of low to intermediate risk patients with low volume PTC recurrence in the neck, identified only by a stimulated Tg and RAI scanning, there are no data to support the therapeutic benefit of repeat RAI treatment, and side effects of this therapy can be severe and cumulative.

In conclusion, our data do not support routine use of RAI scanning in the followup of patients with PTC treated by total thyroidectomy and compartment oriented lymph node dissection. To what degree the results reported here were affected by a more aggressive initial surgical approach to the removal of the primary tumor and involved regional lymph nodes is hard to estimate. A less aggressive approach to the neck would be expected to result in an increased incidence of cervical recurrence. Regardless, routine RAI scanning was helpful in identifying recurrent disease in only 1 of the 13 patients with recurrence in this study group. Even in high risk patients, as identified by higher T stage, extrathyroidal extension, and higher N stage, a strategy emphasizing routine cervical US and unstimulated Tg was effective in identifying 12 of 13 patients with recurrent or metastatic disease.

Author Contributions

Study conception and design: Evans, Mittendorf
Acquisition of data: Mittendorf, Francis, Shapiro
Analysis and interpretation of data: Mittendorf, Wang, Lee, Evans
Drafting of manuscript: Mittendorf
Critical revision: Perrier, Edeiken, Lee, Evans

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