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Journal Articles:

Ebina A et al. 2014. Risk-Adapted Management of Papillary Thyroid Carcinoma according to our own Risk Group Classification System: Is Thyroid Lobectomy the Treatment of Choice for Low-Risk Patients? Surgery. 156:6. 1579-1589.

Wang LY et al. 2015. Thyrotropin Suppression Increases the Risk of Osteoporosis Without Decreasing Recurrent in ATA Low- and Intermediate-Risk Patients with Differentiated Thyroid Carcinoma. Thyroid. 25:3. 300-307.

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Risk-adapted management of papillary thyroid carcinoma according to our own risk group classification system: Is thyroid lobectomy the treatment of choice for low-risk patients?

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Background. *Our original system for risk group classification for predicting cause-specific death from papillary thyroid carcinoma (PTC) defined patients with distant metastasis and older patients (≥50 years) with either massive extrathyroidal extension or large (≥3 cm) lymph node metastasis as high risk; all others are low risk. For unilateral, low-risk PTC, the extent of thyroidectomy (less-than-total thyroidectomy vs total or near-total thyroidectomy) has been determined based on the choice of the patient since 2005.*

Patients. *Of 1,187 patients who underwent initial thyroidectomy for PTC (tumor size [T] >1 cm) between 1993 and 2010, 967 (82%) were classified as low risk. Among low-risk patients, 791 (82%) underwent less than total thyroidectomy.*

Results. *The 10-year cause-specific survival and disease-free survival rates did not differ between patients who underwent total thyroidectomy versus less than total thyroidectomy (cause-specific survival, 99% vs 99% [P = .61]; disease-free survival, 91% vs 87% [P = .90]). Age ≥60 years, T ≥3 cm, and lymph node metastases >3 cm represented significant risk factors for distant recurrence.*

Conclusion. *The favorable overall survival of low-risk patients, regardless of the extent of thyroidectomy, supports patient autonomy in treatment-related decision making. Low-risk patients possessing risk factors for distant recurrence would be likely to benefit from total thyroidectomy followed by radioactive iodine. (Surgery 2014;156:1579-89.)*

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Papillary thyroid carcinoma (PTC) is usually an indolent disease associated with a favorable prognosis for most patients. Some patients, however, exhibit local invasion or extensive metastasis, and a small proportion of patients die of the disease. According to retrospective, uncontrolled studies examining the cancer-specific mortality of PTC, several systems of risk group classification have been advocated to predict mortality based on the initial presentation.[1-3] These systems classify the majority of patients (nearly 90%) as low risk, with a 1–2% cause-specific mortality rate. The minority of residual patients belonging to the high-risk group display a poor prognosis, with 50–75% mortality by 10 years after thyroidectomy.

Total or near-total thyroidectomy (TT) followed by radioactive iodine (RAI) ablation therapy and lifelong thyroid-stimulating hormone (TSH) suppression therapy has been the mainstay of treatment for patients with PTC in Western countries.[4] High value has been set recently on the concept of risk-adapted management and omission of central compartment neck dissection and RAI ablation or moderation of the degree of TSH suppression have been approved in select cases of low-risk PTC.[4,5] In contrast, less-than-total thyroidectomy

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(LTT; lobectomy or subtotal thyroidectomy) has been the preferred operative approach for the majority of patients with PTC in Japan.[6,7] Japanese clinical guidelines for the treatment of thyroid tumor stated that there is insufficient evidence for TT improving disease-free and cause-specific survivals (CSS) of patients compared with lobectomy, but the committee consensus is that TT is recommended for patients considered to be at high risk.[8] At a Japanese tertiary oncology referral center, we performed TT only for patients with bilateral disease or distant metastases. From a retrospective study using a cohort treated between 1976 and 1998, we designed our system of risk group classification for predicting cause-specific death from PTC in 2004.[9] From 2005 onward, we adopted our own risk-adapted approach to patients with PTC based on the risk group stratification system. Patients classified into the high-risk group are patients who underwent TT, postoperative RAI, and TSH suppression therapy; in those patients with low-risk PTC diagnosed as unilateral by preoperative ultrasonography, the extent of thyroidectomy has been determined based on the choices of the patient. The objectives of this study were to verify the validity of our risk group definitions and to evaluate treatment outcomes for low-risk patients according to the extent of thyroidectomy.

PATIENTS AND METHODS

Patients and the risk group classification system. After approval by the institutional review board, we reviewed the medical records of 1,187 consecutive patients with PTC who underwent primary thyroid surgery at the Cancer Institute Hospital, Tokyo, Japan, between 1993 and 2010. Patients with papillary microcarcinoma ≤1.0 cm in maximum diameter were excluded. The series included 288 males (24%) and 899 females (76%). Mean age at initial treatment was 54 ± 14 years (range, 15–89).

All patients were examined routinely by preoperative neck ultrasonography by the same radiologist (K.Y.) to estimate the size and intrathyroidal spread of primary lesion and existence and size of cervical lymph node metastases (LNM). Chest computed tomography was used routinely to assess lung and mediastinal metastases. Neck enhanced computed tomography was carried out to evaluate extrathyroidal invasion and LNM, if needed. Patients were classified preoperatively into low- and high-risk groups according to our risk group classification system.[9] That is, patients with distant metastasis and older patients (≥50 years) with "massive" extrathyroidal invasion or large LNM (≥3 cm) were defined as high-risk patients; all other patients were defined as low risk. As we have reported previously,[9,10] patients with extrathyroidal invasion of PTC were defined as follows: (1) Patients without any extrathyroidal invasion were classified as Ex0; (2) patients with extrathyroidal invasion to the sternothyroid muscle or perithyroid soft tissues or patients who showed superficial invasion of the recurrent laryngeal nerve, trachea, larynx, esophagus, or pharynx, but completed curative resection without resection of these organs were classified as Ex1; (3) patients with further invasion to the surrounding organs were classified as Ex2. When we "shaved off" tumors from the laryngotracheal structures, resected the muscular layer of esophagus, or resected recurrent laryngeal nerve for patients without recurrent laryngeal nerve palsy before surgery, those patients were also classified as Ex2; and (4) We defined only patients who had preoperative recurrent laryngeal nerve palsy or patients in whom the tumor had invaded to the mucosa of the tracheal and/or esophagus as Ex3, corresponding with "massive" extrathyroidal invasion, as discussed.

Treatment methods and the risk-adapted approach. Of the 1,187 operations, 710 (60%) were performed by a single surgeon (I.S.) and all others were assisted by the same surgeon. Until 2004, when a tumor was limited to 1 lobe and no distant metastases were present, we performed LTT on the affected side, even for patients with high-risk features. During this period, TT was performed when a tumor extended to the upper part of the contralateral lobe, when LNMs were evident bilaterally in the neck, and/or when a patient showed distant metastasis. LTT represented resection of the affected lobe and the lower third of the contralateral lobe for the purpose of preserving thyroid function. TT leaving behind approximately 1 g of thyroid tissue in the vicinity of the Berry's ligament to preserve the blood supply to the superior parathyroid gland was referred to as TT. Postoperative RAI therapy was not conducted routinely, except for patients with distant metastasis.

Since 2005, we have adopted a risk-adapted treatment strategy based on our risk group classification system. For patients classified to the high-risk group, routine TT followed by RAI ablation and TSH suppression therapy are indicated. In contrast, when low-risk PTC is diagnosed as unilateral by preoperative ultrasonography, the extent of thyroidectomy has been determined based on the choices of the patient after explaining 2 policies for treatment: TT followed by RAI ablation with

TSH suppression, or thyroid-conserving resection without any adjuvant therapies. The explanation format includes (1) our risk group classification system for cause-specific mortality from PTC and previous outcomes, (2) the potential benefits and disadvantages of the 2 policies, and (3) postoperative adjuvant therapies and methods of surveillance. Afterward, we request an informed decision from the patient regarding which policy they choose.

During the whole study period, we conducted lymph node dissection based on the findings of preoperative ultrasonography, as follows[11]: (1) Dissection of the central-compartment (level VI) alone for patients with LNM only in the central zone or with no LNM, and (2) modified-radical lateral neck dissection (basically, levels II, III, IV, and VI) when the patient was diagnosed with lateral neck LNM. Bilateral neck dissection was performed only when preoperative ultrasonography showed bilateral neck LNM. When adjacent structures were invaded by cancer (in cases of Ex3 or sometimes Ex2), we performed radical resection of the organs and reconstruction if needed. Curative operations for locally advanced disease was unable to be performed in only 3 cases.

Follow-up and evaluation. Patients were evaluated for structural tumor recurrence at lymph nodes, thyroid bed, remnant thyroid tissue, and distant sites every 6 months by physical examination, chest x-ray, or lung computed tomography, in addition to neck ultrasonography. Confirmation of recurrence required cytologic or pathologic evaluation for cervical lesions. For hematogenous metastasis, imaging studies were considered sufficient. As of 2013, the mean duration of follow-up after thyroidectomy was 8.3 years (range, 3–20). No patient was lost to follow-up. Patients with distant metastasis at the time of initial thyroidectomy or who underwent noncurative surgery were excluded from analyses of tumor recurrence.

To evaluate postoperative hypothyroidism, we adopted the values of serum free thyroxine, free tri-iodothyronine, and TSH at 1 year after the initial thyroidectomy. We have already reported the result from a randomized, controlled study investigating the effect of TSH suppression therapy since 1996.[12] Patients assigned to the group with TSH suppression therapy were, therefore, excluded from the evaluation. As for parathyroid function, we used the value of serum intact parathyroid hormone at postoperative day 1 for transient and at 1 year postoperatively for permanent hypoparathyroidism. Recurrent laryngeal nerve palsy was assessed by laryngeal fiberscopy on postoperative day 1 for transient and at 1 year postoperatively for permanent findings. Patients with preoperative recurrent laryngeal nerve palsy (Ex3) or who underwent resection of the nerve owing to tumor invasion (Ex2) were excluded.

Statistical analysis. The comparison of clinical characteristics between groups was performed using the Chi-square test for categorical variables and Student t test for continuous variables. Survival curves as determined using the Kaplan–Meier method were compared for statistical significance by the log-rank test. Multivariate analysis of prognostic variables was performed using Cox proportional hazard modeling. When we set up the cutoff value for the continuous variables and performed bimodal classification, we drew the receiver operator characteristics curve and defined the Youden index (the point of maximum value for sensitivity + specificity − 1) as the cutoff point. All analyses were performed using JMP for Windows version 10.0.2 software (2012 SAS Institute, Cary, NC).

RESULTS

Risk group classification and outcomes. There were 967 patients (82%) classified into the low-risk group, and 220 patients (18%) categorized to the high-risk group. Patient characteristics for each group are shown in Table I. Patients in the low-risk group were significantly younger, had a greater female/male ratio, and lesser TNM stage according to the sixth edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system compared with patients in the high-risk group. As a whole, 400 patients (34%) were classified as AJCC/UICC stage IV and 197 of 967 low-risk patients (20%) were stage IV.

CSS curves for patients in each risk group are compared in Fig 1, *A*. Cause-specific deaths were found in 11 patients (1%) in the low-risk group and 44 patients (20%) in the high-risk group. CSS rates were 100% at 5 years and 99% at 10 years for the low-risk group, compared with 88% at 5 years and 74% at 10 years for the high risk group, respectively. Patients in the high-risk group had a poorer CSS rate than those in the low risk group ($P < .0001$). Recurrences were identified in 79 patients (8%) from the low-risk group and 62 (44%) from the high-risk group. Patients in the low-risk group exhibited disease-free survival (DFS) rates of 94% at 5 years and 88% at 10 years. In contrast, high-risk patients showed a 5-year DFS rate of 64% and a 10-year DFS rate of 43% (Fig 1, *B*; $P < .0001$).

Table I. Characteristics of 1,187 patients with papillary thyroid carcinoma for each risk group

Characteristics	*Total* (n = *1,187*)	*Low-risk group* (n = *967*)	*High-risk group* (n = *220*)	P *value* *(low risk vs high risk)*
Mean age, y (range)	54 ± 14 (15–89)	52 ± 14 (15–86)	62 ± 12 (23–89)	<.0001
Sex, *n* (%)				
Female	899 (76)	766 (79)	133 (60)	<.0001
Male	288 (24)	201 (21)	87 (40)	
T, *n* (%)				
1	358 (30)	345 (36)	13 (6)	<.0001
2	150 (13)	145 (15)	5 (2)	
3	407 (34)	363 (38)	44 (20)	
4a	268 (23)	113 (12)	155 (70)	
4b	4 (0)	1 (0)	3 (1)	
N, *n* (%)				
0	638 (54)	601 (62)	37 (17)	<.0001
1a	124 (10)	104 (11)	20 (9)	
1b	425 (36)	262 (27)	163 (74)	
M, *n* (%)				
0	1,110 (94)	967 (100)	143 (65)	<.0001
1	77 (6)	0 (0)	77 (35)	
UICC/AJCC stage, *n* (%)				
I	466 (39)	466 (48)	0 (0)	<.0001
II	74 (6)	60 (6)	14 (6)	
III	247 (21)	244 (25)	3 (1)	
IVA	334 (28)	196 (20)	138 (63)	
IVB	3 (0)	1 (0)	2 (1)	
IVC	63 (5)	0 (0)	63 (29)	
Maximum diameter of largest nodal metastasis (cm), *n* (%)				
<3	1,026 (86)	917 (95)	109 (50)	<.0001
≥3	161 (14)	50 (5)	111 (50)	
Degree of extrathyroidal invasion, *n* (%)				
Ex0	531 (45)	516 (53)	15 (7)	<.0001
Ex1	366 (31)	329 (34)	37 (17)	
Ex2	167 (14)	113 (12)	54 (25)	
Ex3	123 (10)	9 (1)	114 (52)	
Extent of thyroidectomy, *n* (%)				
Isthmusectomy	22 (2)	22 (2)	0 (0)	<.0001
Lobectomy	728 (61)	674 (70)	54 (25)	
Subtotal thyroidectomy	117 (10)	95 (10)	22 (10)	
Near-total thyroidectomy	82 (7)	62 (6)	20 (9)	
Total thyroidectomy	238 (20)	114 (12)	124 (56)	
Extent of neck dissection, *n* (%)				
Not performed	31 (3)	31 (3)	0 (0)	<.0001
Central compartment only	722 (61)	668 (69)	54 (25)	
Central and unilateral compartment	342 (29)	231 (24)	111 (50)	
Central and bilateral compartment and/or mediastinal	92 (8)	37 (4)	55 (25)	

UICC/AJCC, International Union Against Cancer/American Joint Committee on Cancer.

Extent of thyroidectomy and outcomes for low-risk patients. Between 1993 and 2004, among the 471 low-risk patients, 12 (3%) underwent isthmusectomy, 322 (68%) had lobectomy, 81 (17%) had LTT, and 56 (12%) underwent TT. Since 2005, we have adopted patient autonomy into the decision-making process for the treatment of unilateral low-risk PTC, as discussed. Among the 496 low-risk patients treated from 2005 to 2010, 122 (25%) required a TT (or LTT) owing to bilateral disease or coexisting Graves disease. Among the other 374 patients, 11 (3%) opted to receive TT and 308 (82%) chose lobectomy. The remaining 55 patients (15%) could not reach a decision by themselves and left the matter to discretion of the doctor. Consequently, after 2005, 10 patients

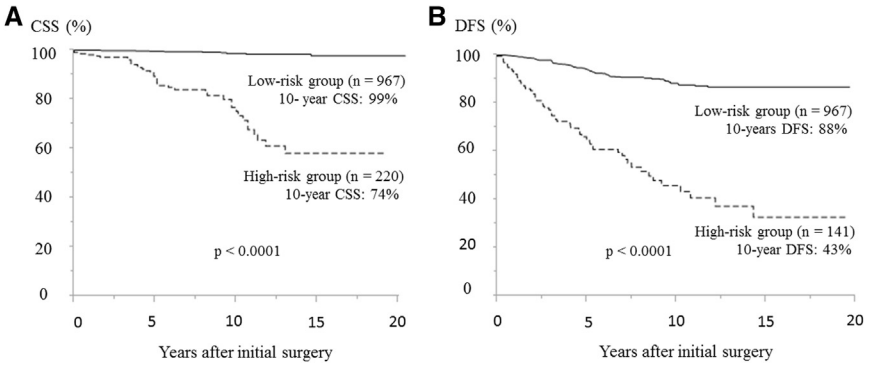

Fig 1. (*A*) Cause-specific survival (CSS) curves for low- and high-risk groups. (*B*) Disease-free survival (DFS) curves for low- and high-risk group. Patients with distant metastasis at the time of initial operation or who underwent noncurative operation were excluded.

(2%) underwent isthmusectomy, 352 (71%) had lobectomy, 14 (3%) had LTT, and 120 (24%) underwent TT.

Disease characteristics and treatment outcomes for patients who underwent LTT and TT are shown in Table II. Patients with multiple intrathyroidal lesions, lateral LNM (N1b) and large LNM were more often treated with TT. Ten-year CSS and DFS rates did not differ between patients who underwent TT and LTT (CSS, 99% vs 99% [$P = .61$]; DFS, 91% vs 87% [$P = .90$], respectively; Fig 2). Among patients treated by LTT, 4 (0.5%) developed recurrence in the remnant thyroid, whereas 87% of patients who underwent lobectomy could avoid overt hypothyroidism. They also had a significantly lesser risk of hypoparathyroidism compared with patients who underwent TT (Table III).

Risk factors for recurrence in low-risk patients. Univariate analysis for clinicopathologic characteristics associated with overall recurrence, lymph node, and distant metastasis in the low-risk group was carried out (Table IV). Age ≥60 years, male sex, primary tumor ≥3 cm, extrathyroidal invasion of Ex2 or Ex3, clinically evident lateral LNM (N1b), LNM ≥2 cm, ≥5 pathologic LNMs, and tumor with poorly differentiated component all were associated with worse outcomes than their counterparts, both overall and in terms of lymph node and distant recurrence.

Multivariate analysis was performed using confirmed preoperative or intraoperative predictors shown to be significant on univariate analysis (Table V). Age ≥60 years, primary tumor ≥3 cm, presence of Ex2 or Ex3, and LNM ≥2 cm were identified as significant and independent factors predicting both overall and lymph node recurrence in low-risk patients. As for distant recurrence, age ≥60 years, primary tumor ≥3 cm, and LNM ≥2 cm were significant predictors. Low-risk patients were stratified according to the number of these significant risk factors present (Fig 3). Twenty-nine of 147 patients (20%) who possessed ≥2 risk-factors for distant metastasis showed distant recurrence within 10 years after the initial operation.

DISCUSSION

Experts agree that 2 biologically different categories of PTC exist and cancers in low-risk group usually do not progress to high-risk cancer throughout the patient's life, and sometimes regress spontaneously or remain dormant.[13,14] Various systems have been proposed to differentiate between these 2 groups.[1-3,15,16] In addition to predicting the risk of mortality and recurrence accurately on an individual level, risk group stratification is useful not only to tailor selective operative intervention and postoperative adjunctive therapy on an individual patient basis, but also to determine the intensity of surveillance for tumor recurrence. Inconsistency among various risk group definitions continue, however, regarding the relative importance of prognostic factors. This inconsistency may result from the bias of unique characteristics of patient populations, heterogeneous distribution of histologic types affected by iodine intake, and differences in the therapeutic philosophies of individual institutions. Our department belongs to a tertiary oncology referral center in an iodine-intake sufficient country and specializes in the treatment of highly advanced head and neck cancer. We have performed >3,000 head and neck operations with free-flap reconstruction using microvascular technique since the early 1980s; in addition, we have been conducting a prospective trial of

Table II. Characteristics and treatment outcomes of 967 patients with low-risk PTC according to extent of thyroidectomy

Characteristics	*Total* (n = *967*)	*LTT* (n = *791*)	*TT* (n = *176*)	P *value (LTT vs TT)*
Mean age, y (range)	52 ± 14 (15–86)	52 ± 14 (15–86)	53 ± 14 (16–83)	.63
Sex, *n* (%)				
Female	766 (79)	630 (80)	136 (77)	.48
Male	201 (21)	161 (20)	40 (23)	
T, *n* (%)				
1	345 (36)	285 (36)	60 (34)	.044
2	145 (15)	126 (16)	19 (11)	
3	363 (38)	294 (37)	69 (39)	
4a	113 (12)	86 (11)	27 (15)	
4b	1 (0)	0 (0)	1 (1)	
N, *n* (%)				
0	601 (62)	517 (65)	84 (48)	<.0001
1a	104 (11)	83 (10)	21 (12)	
1b	262 (27)	191 (24)	71 (40)	
UICC/AJCC stage, *n* (%)				
I	466 (48)	394 (50)	72 (41)	.0002
II	60 (6)	53 (7)	7 (4)	
III	244 (25)	203 (25)	41 (23)	
IVA	196 (20)	141 (18)	55 (31)	
IVB	1 (0)	0 (0)	1 (1)	
Maximum diameter of largest nodal metastasis (cm), *n* (%)				
<3	917 (95)	759 (96)	158 (90)	.0008
≥3	50 (5)	32 (4)	18 (10)	
Degree of extrathyroidal invasion, *n* (%)				
Ex0	516 (53)	433 (55)	83 (47)	.074
Ex1	329 (34)	264 (33)	65 (37)	
Ex2	113 (12)	89 (11)	24 (14)	
Ex3	9 (1)	5 (1)	4 (2)	
Anti-thyroglobulin or thyroid peroxidase antibody, *n* (%)				
Negative	662 (68)	551 (70)	111 (63)	.089
Positive	305 (32)	240 (30)	65 (37)	
Anti-TSH receptor antibody, *n* (%)				
Negative	948 (98)	778 (98)	170 (97)	.13
Positive	19 (2)	13 (2)	6 (3)	
Family history of PTC, *n* (%)				
Absent	929 (96)	761 (96)	168 (95)	.64
Present	38 (4)	30 (4)	8 (5)	
Intrathyroidal multifocality, *n* (%)				
Single lesion	540 (56)	499 (63)	41 (23)	<.0001
Multiple lesions	427 (44)	292 (37)	135 (77)	
Treatment outcomes, *n* (%)				
Cause-specific death	11 (1)	9 (1)	2 (1)	1.0
Recurrence	79 (8)	67 (8)	12 (7)	.47
Site of recurrence, *n* (%)				
Cervical lymph node(s)	63 (7)	52 (7)	11 (6)	.87
Remnant thyroid	4 (0.4)	4 (0.5)	0 (0)	.34
Thyroid bed or other neck	7 (1)	6 (0.8)	1 (0.6)	.79
Distant site	37 (4)	32 (4)	5 (3)	.45

LTT, Less-than-total thyroidectomy; *PTC*, papillary thyroid carcinoma; *TSH*, thyroid-stimulating hormone; *TT*, total or near-total thyroidectomy; *UICC/AJCC*, International Union Against Cancer/American Joint Committee on Cancer.

nonoperative observation for patients with asymptomatic papillary microcarcinoma.[17] As with many other Japanese institutions, our facility for high-dose RAI therapy was closed in 1996 owing to socioeconomic reasons. Our basic standard of primary operation for patients with PTC has

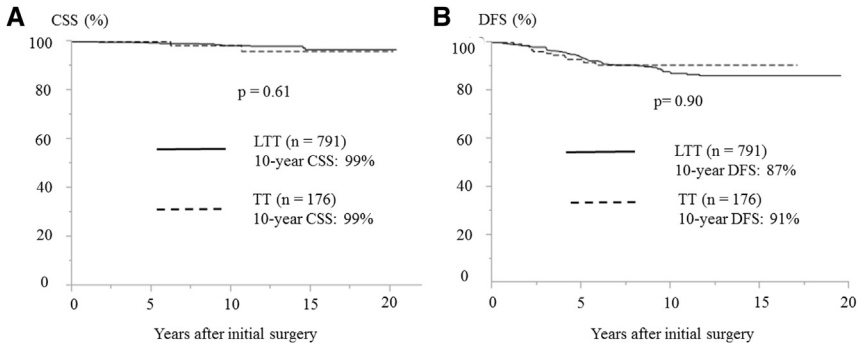

Fig 2. (*A*) Cause-specific survival (CSS) curves for low-risk group patients who underwent less-than-total thyroidectomy (LTT) or total or near-total thyroidectomy (TT). (*B*) Disease-free survival (DFS) curves for low-risk group patients who underwent less-than-total thyroidectomy (LTT) or total or near-total thyroidectomy (TT).

Table III. Postoperative complications in patients with low-risk papillary thyroid carcinoma according to the extent of thyroidectomy

		LTT, n/N *(%)*			*TT*, n/N *(%)*		
Complication	*Total* (n = *967*)	*Isthmusectomy* (n = *22*)	*Lobectomy* (n = *674*)	*Subtotal thyroidectomy* (n = *95*)	*Near-total thyroidectomy* (n = *62*)	*Total thyroidectomy* (n = *114*)	P *value (LTT vs TT)*
Overt hypothyroidism (excluding patients assigned to undergo TSH-suppression therapy)							
	234/775 (30)	2/16 (13)	72/558 (13)	25/66 (38)	39/39 (100)	96/96 (100)	<.0001
Hypoparathyroidism							
Transient	83/967 (9)	0/22 (0)	3/674 (0.4)	7/95 (7)	11/62 (18)	62/114 (54)	<.0001
Permanent	16/967 (2)	0/22 (0)	0/674 (0)	3/95 (3)	3/62 (5)	10/114 (9)	<.0001
Recurrent laryngeal nerve palsy per nerve at risk (excluding patients with Ex2 or Ex3 to the recurrent nerve)							
Transient	98/1,832 (5)	1/44 (2)	66/1,288 (5)	8/172 (5)	7/118 (6)	16/210 (8)	.14
Permanent	33/1,832 (2)	0/44 (0)	20/1,288 (2)	3/172 (2)	3/118 (3)	7/210 (3)	.061

LTT, Less-than-total thyroidectomy; *TT*, total or near-total thyroidectomy.

involved a macroscopically complete resection of the cancer by thyroidectomy and lymph node dissection, and we had favored thyroid-conserving surgery, even in advanced cases. Under these circumstances, we devised the novel system of risk group classification described.[9] The present study reevaluated and confirmed the validity of our system of risk group classification. The AJCC/UICC TNM staging system has seen wide acceptance recently owing to its universal utility; however, according to TNM staging, 34% of all patients and 20% of low-risk patients were classified as stage IV in our series. The TNM staging system might thus cause patient anxiety and overtreatment of a disease with an overall 10-year CSS rate of 94%.

Several investigators have emphasized the importance recently of risk-adapted management for patients with PTC and have explored the possibilities of selective (reduced) approaches to initial treatment and follow-up management, maintaining quality of life in patients with low-risk PTC and minimizing potential complications and medical costs.[4,5,18,19] As for the extent of thyroidectomy, Western guidelines have recommended TT for the majority of PTCs. The revised guidelines of the American Thyroid Association[4] permit lobectomy only for patients with small (<1 cm), unifocal, intrathyroidal PTC. Using the National Cancer Data Base, Bilimoria et al[20] demonstrated that TT for PTC ≥1 cm results in lesser recurrence rates and even improved survival compared with lobectomy. In contrast, Mendelsohn et al[21] analyzed outcomes for patients with PTC using the Surveillance, Epidemiology, and End Results Program (SEER) database and found no survival difference between patients who had undergone TT and those who had undergone lobectomy. Nixon et al[22] also demonstrated excellent outcomes of thyroid lobectomy in patients with pT1T2N0 well-differentiated thyroid carcinoma.

Endocrine surgeons in Japan have preferred thyroid-conserving surgery with curative lymph node dissection for the majority of patients with PTC.[6,7] They have determined the extent of

Table IV. Univariate analysis of risk factors for recurrence in patients with low-risk PTC

		Overall recurrence			*Lymph node recurrence*			*Distant recurrence*		
Variables	*No. of patients*	*Recurrences,* n *(%)*	*10-y DFS (%)*	P *value*	*Lymph node recurrences,* n *(%)*	*10-y N-DFS (%)*	P *value*	*Distant recurrences,* n *(%)*	*10-y D-DFS (%)*	P *value*
Age (y)										
≥60	327	43 (13)	78	<.0001	35 (11)	81	<.0001	23 (7)	90	<.0001
<60	640	36 (6)	92		28 (4)	94		14 (2)	96	
Sex										
Male	201	25 (12)	79	.0019	20 (10)	84	.0057	13 (6)	89	.0084
Female	766	54 (7)	90		43 (6)	92		24 (3)	96	
Family history of PTC										
Absent	929	77 (8)	88	.56	61 (7)	90	.80	36 (4)	94	.73
Present	38	2 (5)	91		2 (5)	91		1 (3)	95	
Anti-thyroglobulin or thyroid peroxidase antibody										
Absent	662	60 (9)	86	.16	48 (7)	89	.14	26 (4)	94	.83
Present	305	19 (6)	91		14 (5)	93		11 (4)	95	
Anti-TSH receptor antibody										
Absent	948	78 (8)	87	.61	62 (7)	90	.24	36 (4)	94	.76
Present	19	1 (5)	94		0 (0)	100		1 (5)	95	
Maximum diameter of primary tumor (cm)										
≥3	240	42 (18)	73	<.0001	35 (15)	78	<.0001	25 (10)	84	<.0001
<3	727	37 (5)	92		28 (4)	94		12 (2)	97	
Degree of extrathyroidal invasion										
Ex0 or Ex1	845	51 (6)	91	<.0001	40 (5)	92	<.0001	21 (2)	96	<.0001
Ex2 or Ex3	122	28 (23)	69		23 (19)	76		16 (13)	79	
N										
N0 or N1a	705	40 (6)	91	<.0001	32 (5)	93	<.0001	16 (2)	96	<.0001
N1b	262	39 (15)	78		31 (12)	82		21 (8)	89	
Maximum diameter of largest nodal metastasis (cm)										
≥2	153	30 (20)	71	<.0001	22 (14)	79	<.0001	18 (12)	82	<.0001
<2	814	49 (6)	91		41 (5)	92		19 (2)	97	
Number of pathologic node metastases										
≥5	267	39 (15)	80	<.0001	32 (12)	83	<.0001	11 (4)	89	<.0001
<5	700	40 (6)	91		31 (4)	93		26 (4)	97	
Poorly differentiated component										
Absent	907	60 (7)	90	<.0001	49 (5)	92	<.0001	25 (3)	96	<.0001
Present	60	19 (32)	57		14 (23)	66		12 (20)	73	
Intrathyroidal multifocality										
Absent	540	43 (8)	87	.69	33 (6)	91	.48	19 (4)	93	.53
Present	427	36 (8)	89		30 (7)	89		18 (4)	95	

DFS, Disease-free survival; *N-DFS*, lymph node recurrence-free survival; *D-RFS*, distant recurrence-free survival; *PTC*, papillary thyroid carcinoma; *TSH*, thyroid-stimulating hormone.

thyroidectomy and lymph node dissection using preoperative ultrasonography and followed patients without postoperative adjuvant therapies. Matsuzu et al[23] reported recently their long-term outcomes (median, 18 years) of 1,088 PTC patients who underwent thyroid lobectomy with curative intent at a Japanese hospital specializing in thyroid diseases, showing a 95% CSS rate at 25 years. Distant recurrence-free survival and CSS rates were both significantly less in patients ≥45 years old, with tumors >4 cm, or with extrathyroidal invasion. They concluded that lobectomy (without RAI therapy) represents a valid alternative to TT for selected patients. The present study also showed that LTT for low-risk patients offered excellent outcomes that were not inferior to those for TT, although a selection bias was present and the follow-up period was rather short. In addition, rates of complications were significantly greater in the TT group than in the LTT group.

Because most evidence regarding the extent of thyroidectomy comes from retrospective studies in which therapy has not been assigned randomly, the level of evidence is not generally high, and

Table V. Multivariate analysis of risk factors for recurrence in patients with low-risk papillary thyroid carcinoma

Risk factors	*Overall recurrence*			*Lymph node recurrence*			*Distant recurrence*		
	Risk ratio	*95% CI*	P *value*	*Risk ratio*	*95% CI*	P *value*	*Risk ratio*	*95% CI*	P *value*
Age ≥60 y	3.23	1.67–4.50	<.0001	3.27	1.96–5.55	<.0001	4.55	2.29–9.36	<.0001
Male sex	1.30	0.79–2.09	.29	1.30	0.74–2.20	.35	1.33	0.65–2.58	.43
Maximum diameter of primary tumor ≥3 cm	2.75	1.68–4.50	<.0001	2.97	1.70–5.17	.0001	4.79	2.27–10.47	<.0001
Ex2 or Ex3	1.83	1.06–3.10	.029	1.86	1.02–3.33	.044	1.73	0.79–3.73	.17
N1b	0.91	0.43–1.81	.80	1.10	0.49–2.24	.81	0.71	0.20–2.04	.54
Maximum diameter of largest nodal metastasis ≥2 cm	3.83	2.04–5.16	<.0001	2.89	1.37–6.47	.0049	7.22	2.59–24.14	<.0001

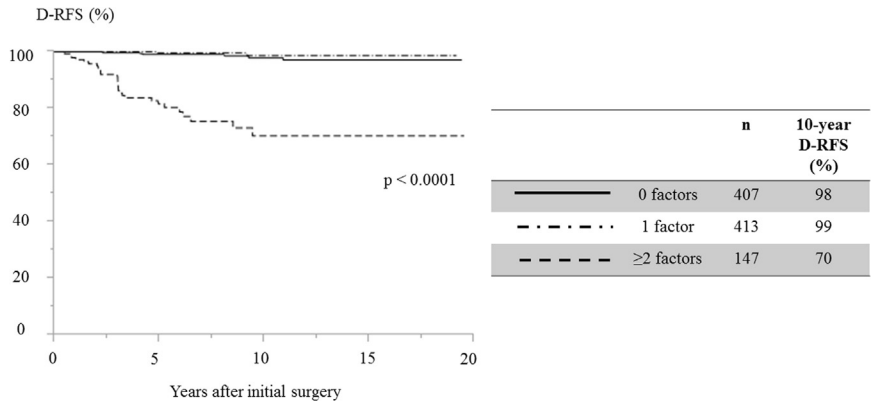

Fig 3. Distant recurrence-free survival (D-RFS) curves according to the number of risk factors for distant recurrence; namely, age ≥60 years, maximum diameter of primary tumor ≥3 cm, and maximum diameter of largest nodal metastasis ≥2 cm.

controversy about the management of PTC remain. Hence, when we established our risk-adapted management based on our risk group definitions, we followed the idea that the patient's decisions about their care must be paramount.[24] We prepared a preoperative information format explaining the advantages and disadvantages of both LTT and TT in as equitable a manner as possible for patients with unilateral low-risk PTC to empower patients to make informed decisions about their treatment. As a result, a surprisingly high percentage of low-risk patients chose LTT, although we have the limitation that our information format was nonvalidated. Patient-oriented communication and shared decision making should be considered key concepts in improving the modern relationship between doctors and patients, particularly in fields lacking high-level clinical evidence.[25]

Our system of risk group classification focused on disease-specific mortality and not on DFS. The definition of the low-risk group might thus be wider than in other systems of risk group classification, and some thyroxine, N1b, or TNM stage IV tumors were included among low-risk patients. The mortality rate for low-risk patients was still only 1%, although the recurrence rate among these patients was a relatively high 8%. Statistical analysis revealed that age ≥60 years, tumor size ≥3 cm, and LNM ≥2 cm represented significant risk factors for distant recurrence-free survival in the low-risk group. Patients possessing these factors for distant recurrence would be candidates for a prospective study investigating the advantages of TT followed by RAI.

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DISCUSSION

Dr Sareh Parangi (Boston, MA): What about thyroid hormone suppression? Are you keeping the patients that have their lobe left in on thyroid hormone suppression?

Dr Aya Ebina (Tokyo, Japan): Actually, we have conducted a randomized, controlled trial (RCT) for the effect of thyroid-stimulating hormone (TSH) suppression therapy on recurrence of papillary thyroid carcinoma. So, patients treated between 1995 and 2004 were randomly assigned to TSH suppression group or nonsuppression group regardless of the extent of thyroidectomy. Excluding this study period, we have basically not prescribed thyroid hormone for patients who had a normal TSH concentration postoperatively. As a result of the RCT, we have shown that disease-free survival of the non-TSH suppression group was not inferior to that of TSH suppression group (J Clin Endocrinol Metab 2010;95:4576-83). Moreover, older patients who underwent TSH suppression therapy showed significant decrease in bone mineral density (Surgery 2011;150:1250-7). We are now adjusting TSH level taking both the cancer mortality risk and the comorbidity risk, including heart failure and osteoporosis into consideration.

Dr Sareh Parangi: So the low-risk group that underwent lobectomy was not maintained on thyroid suppression?

Dr Aya Ebina: No, they did not usually receive TSH suppression therapy. But, patients who showed hypothyroidism despite lobectomy sometimes underwent TSH suppression.

Dr Sareh Parangi: Were you considering the nodal burden lateral and central nodes, or only lateral nodes when you mentioned nodal status >2 cm?

Dr Aya Ebina: We did not discriminate central nodes from lateral nodes, when we defined risk group. Large nodes—2 or 3 cm in diameter—can easily detected on preoperative ultrasonography.

Dr Sareh Parangi: So the procedure for a low-risk patient with a 3-cm tumor, do the lobectomy along with ipsilateral lymph node dissection, and leave the other side completely alone?

Dr Aya Ebina: According to our original risk group definition, patients ≥50 years with ≥3 cm lymph node were all classified into the high-risk group. Then, only younger patients with large node were stratified into low-risk group and would have a chance to undergo lobectomy with therapeutic lymph node dissection in our strategy. As a matter of course, patients with bilateral clinical nodes were treated by total thyroidectomy even when they were classified into the low-risk group.

Dr Blake Cady (Boston, MA): I would like to make a comment that papillary thyroid carcinoma in a low risk patient, as here, is the only human cancer where, in a 98 or 99%, 20-year survival, we continue to do total excision of the primary organ and systemic adjuvant therapy. So it is nice to see your study, which reaffirms some other work in the past.

I would like to make a comment about the fact that in the low-risk patients, the principal recurrence were lymph nodes, and yet the 99% long-term survival, which emphasizes that lymph nodes have no bearing on outcome.

How can we get the community to stop doing something that has been established as sort of a conventional therapy? American surgeons and Americans generally like to do more and more, but it is very hard to get people to back off and do less, although there are evidence-based data. For instance, in the Z11 trial that demonstrated the lack of effective axillary dissection in breast cancer, it did not change practice very much.

So my question is, how do we start on a program of convincing people they do not need to do total thyroidectomies in a cancer that carries such an outstanding long-term survival?

Dr Bhuvanesh Singh (New York, NY): I think the question was more of a philosophical question of how do we get people to do what you are doing?

Dr Ashok R. Shaha (New York, NY): I think I came to answer Blake Cady's question. The only disclosure I have is, for the past 24 years, we have been bringing this information to this organization again and again. The only thing we have been correlating, our experience at Memorial is risk group stratification. We have been dividing into low-, intermediate-, and high-risk groups. I think we have shown time again and again that the extent of surgery does not have any impact in the low-risk group in the long-term survival. It does have impact, I am convinced, as a quality of life of the patient. A patient who undergoes total thyroidectomy at the age of 25 is going to live on medication for 75 years. You leave half the thyroid behind, one half of them will not need thyroid medication, and the other quarter will live with thyroid medication, but happily ever after.

I think it is very important to realize this risk stratification is important. You have analyzed it, we have analyzed it, and I must say the ATA, in their 2009 guidelines, used the same risk stratification. The only difference was we were looking at mortality; they are looking at recurrence. We are looking at our recurrence, and there is no survival or recurrence difference in the low-risk group.

What I admire in your presentation is you have subclassified certain low-risk groups that are truly at high risk. I think that analysis is important, which we can do clinically on day 1 when we are operating on the patient. Yes, BRAF is important, but the clinical evaluation at the time of surgery will tell you who is a bad actor in the low risk and be more aggressive in that group. I think the message needs to go: Be more aggressive in aggressive cancers, you do not need to be aggressive in the low-risk group.

To answer Blake's question, this needs to go to the endocrinologist. I must say, even though Mike Tuttle is not here, the new guidelines, which will be coming next year, will reflect the role of lobectomy much more than what we all have done as a community.

Dr Quan-Yang Duh (San Francisco, CA): I am not going to defend total thyroidectomy, but I think one needs to be careful in interpreting the data. I am not quite sure it is clear to the audience that the operation here is a lobectomy with routine central neck lymph node dissection. It is not a lobectomy. It is a lobectomy plus routine central neck lymph node dissection.

Dr Aya Ebina: Yes, we have undertaken lobectomy with routine central neck dissection even for clinically N0 patients. However, the dissection of contralateral central zone has often been omitted.

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Thyrotropin Suppression Increases the Risk of Osteoporosis Without Decreasing Recurrence in ATA Low- and Intermediate-Risk Patients with Differentiated Thyroid Carcinoma

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Background: Levothyroxine suppression of thyrotropin (TSH) is broadly applied to patients with thyroid cancer despite lack of consensus on the optimal TSH concentration necessary to reduce cancer recurrence while minimizing toxicity from subclinical hyperthyroidism. The objectives of this study were to examine the beneficial effects and the cardiac and skeletal toxicity of TSH suppression in well-differentiated thyroid carcinoma (DTC).

Methods: A total of 771 patients (569 women) at ATA low or intermediate risk of recurrence, with a mean age of 48 ± 14 years, and undergoing total thyroidectomy at a tertiary care center between 2000 and 2006 were followed for a median of six and a half years. They were divided into a suppressed TSH group (median TSH ≤ 0.4 mIU/L) and a nonsuppressed group (median TSH > 0.4 mIU/L). Structural recurrence of thyroid cancer, postoperative atrial fibrillation (AF), and osteoporosis were examined in the two groups. Osteoporosis was only examined in women.

Results: A total of 43/771 (5.6%) patients recurred, 29/739 (3.9%) patients were diagnosed with postoperative osteoporosis, and 17/756 (2.3 %) were diagnosed with postoperative AF. Despite similar rates of recurrence (HR 1.02, $p = 0.956$ [CI 0.54–1.91]), patients treated to a median TSH ≤ 0.4 mIU/L were at increased postoperative risk of a composite outcome of AF and osteoporosis (HR 2.1, $p = 0.05$ [CI 1.001–4.3]) compared to those not suppressed. A differential risk of AF alone (HR 0.78, $p = 0.63$ [CI 0.3–2.1]) was not detected, but postoperative osteoporosis was increased among women with a suppressed TSH compared to those not suppressed (HR 3.5, $p = 0.023$ [CI 1.2–10.2]). The increased risk of postoperative osteoporosis disappeared when the patient's median TSH was maintained around 1 mIU/L.

Conclusion: TSH suppression significantly increases the risk of postoperative osteoporosis without changing tumor recurrence in ATA low- and intermediate-risk patients with DTC. Future interventions should focus on avoiding harm in indolent disease.

Introduction

Total thyroidectomy with or without ^{131}I ablation followed by long-term levothyroxine suppression of thyrotropin (TSH) is the traditional treatment for well-differentiated thyroid carcinoma (DTC) (1–4). Currently, most patients with thyroid cancer are given a dose of levothyroxine that suppresses TSH levels below the normal range, inducing a state of subclinical hyperthyroidism. The rationale for this approach stems from experimental and clinical data showing that TSH stimulates thyroid cell proliferation, radioiodine uptake, and thyroglobulin (Tg) production (5–8). Removing this stimulus, at least theoretically, will inhibit growth of residual neoplastic tissue (5,6,9).

In patients affected by DTC, TSH suppression with levothyroxine is associated with a decreased risk of tumor recurrence (5,10–14), and endogenous or exogenous increases in TSH may occasionally induce clinical progression of thyroid cancer (15,16). Doses of levothyroxine that reduce circulating TSH to 0.4 mIU/L reportedly induce maximum

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suppression of serum Tg (17), suggesting that increasing the degree of TSH suppression beyond this threshold may not further decrease tumor function (18). Others have found that serum Tg continues to decrease in thyroid cancer patients when TSH is further suppressed to undetectable levels (< 0.1 mIU/L) (19).

Despite clinical practice guidelines addressing the need for TSH suppression in patients with DTC (1–4), there is currently no evidence-based consensus on the optimal TSH concentration that would reduce tumor recurrence while ensuring minimal adverse effects from subclinical hyperthyroidism. Also, no recommendations currently take into account the patient's age, underlying comorbidities, tumor stage, or response to therapy to balance the benefits of levothyroxine suppressive treatment with the cardiovascular and skeletal risks of iatrogenic thyrotoxicosis. So, prolonged TSH suppression in relatively low-risk patients could easily lead to more harm than good.

The aims of this study are thus twofold; first, to examine the impact of TSH suppression on recurrence in a well-characterized cohort of patients with DTC at low and intermediate risk of recurrence as defined by the American Thyroid Association (ATA) (20); and second, to examine the harmful effects of TSH suppression as measured by the diagnosis of postoperative osteoporosis and atrial fibrillation (AF) in the same cohort.

Materials and Methods

Following Institutional Review Board approval, the charts of 1100 consecutive patients who had undergone total thyroidectomy at our institution for DTC between January 1, 2000, and December 31, 2006, were reviewed. Patients were excluded if they were at high risk of tumor recurrence as defined by the ATA (macroscopic tumor invasion, gross residual disease, distant metastases) (20), as it is believed that there is evidence to support the beneficial effect of TSH suppression in a significant subset of these patients (21,22). Patients with a preexisting diagnosis of hyperparathyroidism were also excluded, as this is an independent risk factor for the development of osteoporosis; men, since they are not routinely screened for osteoporosis; and patients who had fewer than three postoperative TSH laboratory measurements, to ensure adequate follow-up to evaluate this variable. No patients had a diagnosis of permanent hypoparathyroidism. A total of 771 patients were considered for analysis. Patients with known preoperative AF and osteoporosis were excluded from the respective event-specific analyses (Fig. 1).

The cohort was divided into TSH-suppressed and TSH-nonsuppressed groups based on a median TSH level of 0.4 mIU/L. Postoperative TSH values were analyzed up to the date of the event or the last follow-up. TSH values within seven days of radioactive iodine (RAI) scan or therapy were excluded from the analysis, as our institution commonly administers recombinant human TSH, and blood determinations of TSH are often confounded by exogenously administered TSH. The TSH-suppressed group had a mean $\pm$ standard deviation (*SD*) of 12 ± 6 TSH determinations, and the TSH-nonsuppressed group had a mean $\pm$ *SD* of 9.7 ± 6 TSH determinations. Patient demographic and clinicopathological characteristics were collected as outlined in Table 1. Preoperative risk categories for osteoporosis and AF were adapted from Biondi and Cooper (23) and are described in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/thy). Low-, intermediate-, and high-risk categories were given values of one, two, and three,

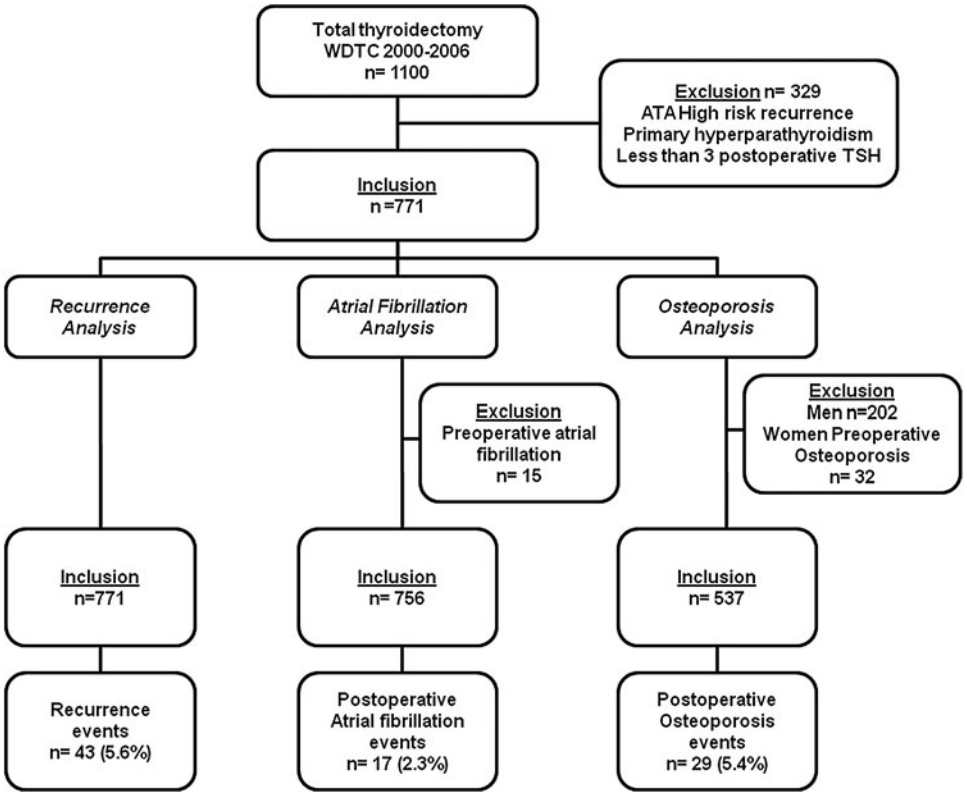

FIG. 1. Inclusion criteria.

Table 1. Comparison of Suppressed and Nonsuppressed Groups

Characteristics	*Suppressed TSH ≤0.4 mIU/L* (n = *465*)	*Nonsuppressed TSH >0.4 mIU/L* (n = *306*)	p-*Value*
Age, years (mean ± *SD*)	46.6 ± 13.9	49.8 ± 14.9	<0.01
Sex, females, *n* (%)	353 (76%)	215 (70%)	0.08
Histology			0.245
Classical type	153 (33%)	83 (27%)	
Follicular variant	135 (29%)	79 (26%)	
Tall cell variant	73 (16%)	43 (14%)	
Other	51 (11%)	45 (15%)	
Microcarcinomas	53 (11%)	56 (18%)	<0.01
Extrathyroidal extension	165 (36%)	89 (29%)	0.16
Vascular invasion	11 (2.4%)	15 (4.9%)	0.30
N stage			0.05
N0	179 (38%)	124 (41%)	
N1a	102 (22%)	53 (17%)	
N1b	78 (17%)	38 (12%)	
Nx	106 (23%)	91 (30%)	
RAI therapy	348 (75%)	184 (60%)	<0.01
ATA risk			<0.01
Low	187 (40%)	154 (50%)	
Intermediate	278 (60%)	152 (50%)	

TSH, thyrotropin; *SD*, standard deviation; RAI, radioactive iodine; ATA, American Thyroid Association.

respectively, and all calculations of postoperative AF and osteoporosis events were adjusted by this preoperative risk. Locoregional recurrence required tissue confirmation; distant recurrence was diagnosed by appropriate imaging criteria with or without tissue confirmation. Patients with biochemical recurrences defined by elevated Tg levels without a structural correlate on imaging were purposefully excluded, as it is believed that structural recurrences are a more robust endpoint to measure this outcome. Postoperative AF was defined by EKG evidence of persistent arrhythmia or new documentation of disease in the notes of a physician; transient episodes of AF attributed to acute illness or operative procedures were excluded. Postoperative osteoporosis was defined by a bone mineral density (BMD) T-score <-2.5 standard deviations below that of a young white adult at the anteroposterior lumbar spine, femoral neck, or total hip. New osteoporosis was also considered if the patient had been started on bisphosphonate therapy in the absence of a known indication such as metastases or Paget's disease, or if specified in the notes of the treating physician. Postoperative AF and osteoporosis were adjudicated as events whether they had been diagnosed within or outside the institution, and whether they had been detected by the treating endocrinologist or by the general practitioner. Two reviewers scrutinized the medical records of patients to adjudicate the events of recurrence, AF, and osteoporosis, and two additional reviewers reexamined these medical records in instances of disagreement.

Statistical analysis was carried out using Stata Statistical Software v12 (StataCorp., College Station, TX). Student's *t*-test was used to compare continuous variables in the TSH treatment arms and Pearson's chi-square test to examine categorical variables. Recurrence and harm were analyzed using survival analysis. Kaplan–Meier curves were built and the log-rank test was used to assess for significance of the surviving function. Cox proportional hazards models were built to allow for multivariate adjustment by variables that proved to be statistically different in the TSH treatment arms. Additionally, to account for indication biases of levothyroxine administration and balance differences in prescription practices in this retrospective study, propensity score analysis was used. A *p*-value of <0.05 was considered statistically significant.

Results

The clinicopathological characteristics of patients with median TSH levels ≤ 0.4 mIU/L and >0.4 mIU/L are outlined in Table 1. No significant differences were found in terms of sex, histological subtype of thyroid cancer, vascular invasion, extrathyroidal extension, or nodal stage between the suppressed and nonsuppressed groups. However, clinicians were more likely to suppress younger patients ($p<0.01$), patients at higher risk of tumor recurrence evidenced by a tumor size >1 cm ($p<0.01$), and ATA intermediate risk group ($p<0.01$; Table 1). Suppressed patients were also more likely to have received ^{131}I therapy ($p<0.01$).

Tumor recurrence

A total of 43/771 (5.6%) patients developed a structural tumor recurrence during a median follow-up of 6.5 years (Fig. 2). Fifteen patients out of 306 (4.9%) treated to a TSH level >0.4 mIU/L developed tumor recurrence compared with 28/465 (6.0%) in the suppressed group. There was no statistically significant difference in the disease-free survival (DFS) rate of TSH-suppressed compared to TSH-nonsuppressed patients (HR 1.02 [CI 0.54–1.91], $p=0.956$). Given the retrospective and nonrandomized nature of this study, it was found that physicians tended to suppress younger patients and patients at higher risk of recurrence (Table 1). To account for these differences in therapeutic

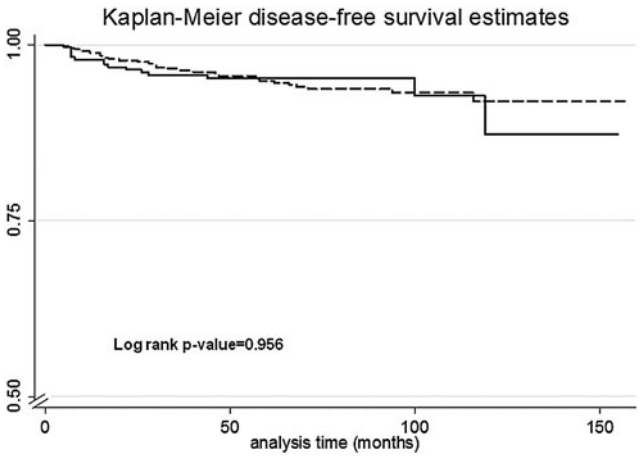

FIG. 2. Recurrence-free survival in patients treated to a median thyrotropin (TSH) of ≤0.4 mIU/L (dashed) or >0.4 mIU/L (solid).

Table 2. Multivariate Analysis for Tumor Recurrence

Multivariate analysis	*HR*	*CI*	p-*Value*
TSH suppression	0.88	[0.46–1.66]	0.692
Age	0.99	[0.97–1.02]	0.862
Sex	0.53	[0.29–0.96]	0.038
RAI therapy	1.5	[0.55–3.94]	0.437
ATA risk	6.5	[2.2–19.3]	0.001

HR, hazard ratio; CI, confidence interval.

practices, multivariate analyses were conducted as well as adjustment by propensity scores. TSH suppression did not significantly decrease the risk of recurrence in low- and intermediate-risk patients when adjusting for age, sex, RAI administration, and ATA risk category (HR 0.88 [CI 0.46–1.66], $p = 0.692$; Table 2). Male sex and ATA ''intermediate risk'' were independent predictors of tumor recurrence ($p = 0.038$ and $p = 0.001$, respectively). Interestingly, when RAI was incorporated into the multivariate model, it did not independently predict for increased risk of recurrence ($p = 0.437$). In addition to conducting multivariate analyses, propensity scores analyses were performed to account for indication biases at the time of prescribing levothyroxine suppressive therapy. TSH suppression ≤ 0.4 mIU/L was not associated with a decreased risk of recurrence when stratified on propensity score (HR 1.08 [CI 0.45–2.63], $p = 0.856$).

Composite event of skeletal and cardiovascular toxicity

Despite similar rates of recurrence between the suppressed and nonsuppressed groups, subjects treated to a median TSH ≤ 0.4 mIU/L developed an adverse effect to levothyroxine suppression, defined as the first event of AF or osteoporosis, at 2.1 times the rate of their nonsuppressed counterparts (HR 2.1 [CI 1.001–4.3], $p = 0.05$; Fig. 3A).

AF risk

Fifteen patients had a preoperative diagnosis of AF in this study and were thus excluded from the postoperative AF analysis. Of the remaining 756 patients, 17 (2.3%) developed AF during the course of their follow-up (Fig. 3B). Given the small number of events, no differential risk of postoperative AF was detected among patients suppressed versus those not suppressed (HR 0.78 [CI 0.3–2.1], $p = 0.63$). No difference in the development of AF was detected, even after adjusting for preoperative risk of AF (Supplementary Table S1).

Osteoporosis risk

The osteoporosis analysis was limited to female patients without a preoperative diagnosis of osteoporosis. Men were excluded from the analysis, as they are not routinely screened for osteoporosis. All calculations were adjusted by preoperative risk of developing osteoporosis (Supplementary Table S1). Among 537 women, 29 (5.4%) were diagnosed with postoperative osteoporosis. The risk of postoperative osteoporosis among women was 3.5 times greater (HR 3.5 [CI 1.2–10.2], $p = 0.023$) when they were suppressed (TSH ≤ 0.4 mIU/L) compared to those who were not suppressed (Fig. 3C). Given that age is a known risk factor for the development of osteoporosis, multivariate analyses were conducted adjusting for this variable. Women had a 4.3 times higher risk of developing osteoporosis when they were suppressed compared to the nonsuppressed group when age was taken into account (HR 4.3 [CI 1.45–12.85], $p = 0.009$). The higher HR of 4.3 in the multivariate model demonstrates a synergistic effect between increasing age and TSH suppression, suggesting that TSH

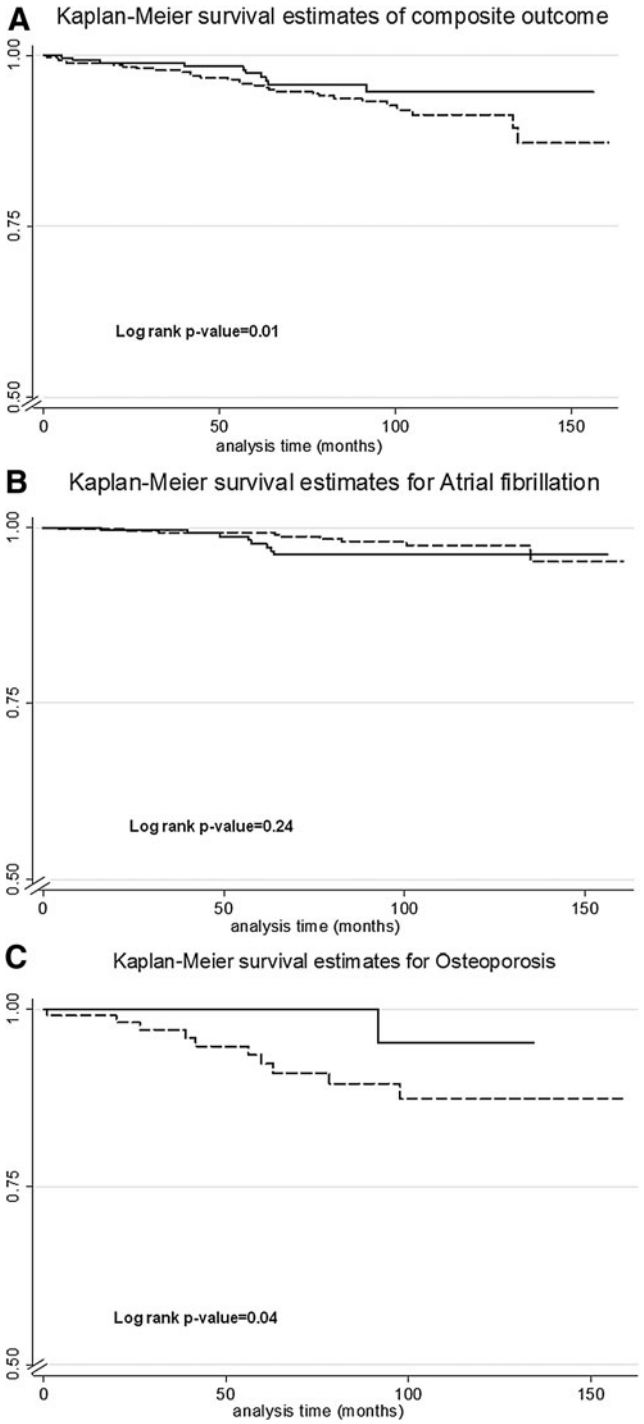

FIG. 3. (**A**) Composite of harm (first event of atrial fibrillation or osteoporosis), (**B**) atrial fibrillation, and (**C**) osteoporosis in patients treated to a median TSH of ≤ 0.4 mIU/L (dashed) or > 0.4 mIU/L (solid).

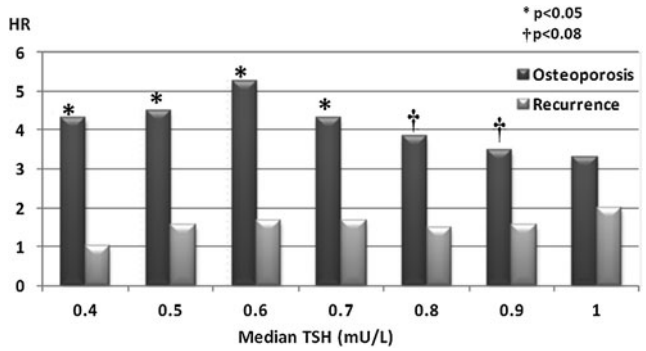

FIG. 4. Risk of osteoporosis and tumor recurrence as a function of median TSH level.

suppression in elderly women may cause even greater bone toxicity.

Optimal TSH level

The ideal TSH level for patients with low and intermediate DTC would be one that does not increase the risk of adverse cardiovascular and skeletal events while maintaining beneficial effects on tumor recurrence. Figure 4 demonstrates the risk of osteoporosis and tumor recurrence at incremental TSH levels between 0.4 and 1.0 mIU/L. Each bar represents a comparison of patients below a certain TSH median value and the rest of the cohort. As median TSH levels approach 1.0 mI/L, the hazard ratio of post-operative osteoporosis becomes nonsignificant while the risk of recurrence remains unchanged. Interestingly, the data suggest that at the lower limit of normal TSH (between 0.5 and 0.7 mIU/L), there is also increased risk of osteoporosis. It would appear that a TSH level around 0.9 or 1 mIU/L is optimal for maintenance treatment of ATA low- to intermediate-risk patients, as the risk of osteoporosis disappears yet the risk of recurrence remains unchanged.

Discussion

In this study, the beneficial effects of TSH suppression on thyroid cancer recurrence and the cardiovascular and skeletal toxicity that results from long-term iatrogenic thyrotoxicosis in patients at ATA low and intermediate risk of recurrence were examined. It was found that TSH suppression increased the postoperative likelihood of being diagnosed with osteoporosis, and it did not improve recurrence rates in this population. This finding was not altered after a multivariate analysis or a propensity score analysis, suggesting that TSH suppression is an independent predictor of skeletal toxicity that may not improve recurrence rates of patients with low- and intermediate-risk DTC.

The lack of a beneficial effect of TSH suppression on recurrence of low- and intermediate-risk patients with DTC in this study is supported by other groups. Cooper *et al*. found that TSH suppression to very low levels reduced recurrence in Stage 3 and 4 patients, but not in low-risk patients. When RAI was included in the model, the effect of TSH suppression in high-risk patients disappeared (24). Similarly, Jonklaas *et al*. were not able to show a beneficial impact of TSH suppression in Stage 1 patients (25). A comprehensive review of the literature by Biondi and Cooper concluded that aggressive TSH suppression is likely to be important in high-risk patients and less critical in low-risk patients (23). The only prospective randomized controlled trial published to date in all risk thyroid cancer patients showed that DFS, especially in low-risk patients without TSH suppression, was not inferior to that of patients with TSH suppression (26). The findings in this study support this conclusion and suggest that TSH suppression may not improve DFS in low- and intermediate-risk patients.

The cardiovascular morbidity and mortality associated with subclinical hyperthyroidism has been confirmed in multiple studies (27,28), and there is increasing awareness of this toxicity, as more severe effects have been documented with advanced age (29,30). Due to the small number of events in this study, there was not enough power to detect the effect of TSH suppression on the risk of postoperative AF. Also, the hazard ratio of <1 in the AF results suggests that clinicians were averse to suppressing patients with preexisting cardiac conditions.

In terms of the skeletal events, a significantly increased risk of osteoporosis was detected in the women who had a TSH suppressed ≤ 0.4 mIU/L compared to those not suppressed. Menopausal status was not specifically collected, but older women were at a higher risk of osteoporosis than younger women were. Two recent reviews on the effects of TSH suppression in DTC concluded that postmenopausal women were at increased risk of bone loss when TSH was suppressed, but the effect of hyperthyroidism on premenopausal women and men was conflicting (31,32). Furthermore, TSH levels <0.1 mIU/L and even 0.1–0.5 mIU/L were associated with increased risk of hip and vertebral fractures (27,33). In 2011, Sugitani *et al*. published the results of a randomized controlled trial of TSH suppression and its impact on bone mineral density. TSH suppression to <0.1 mIU/L conferred a significant reduction in BMD in older patients within one year of suppression comparable to the reduction in BMD seen after five years in nonsuppressed patients (34). The reduction in BMD in the nonsuppressed group was attributed to the natural bone density decline in postmenopausal women. It was found that the effect of TSH and age was synergistic in terms of bone loss; the combined effect of TSH suppression and older age was more toxic to the bone than each of these were individually.

A biological explanation for the observed skeletal toxicity may be related to the well-documented effects of triiodothyronine on osteoblasts to stimulate osteoclasts and in turn bone resorption (35), or to the reported direct effects of TSH on bone. TSH has been shown to bypass the thyroid to exert direct protective effects on the skeleton. Through a fast-forward short loop involving Wnt5a production, TSH may enhance osteoblast differentiation and stimulates osteoprotegerin to attenuate bone resorption by osteoclasts (36,37). Lowering TSH levels in DTC may result in bone loss from a direct effect of thyroid hormones or from failure to maintain this TSH protective effect.

Total thyroidectomy with or without remnant ablation with ^{131}I followed by long-term levothyroxine suppression of TSH is the traditional treatment for DTC (38). TSH suppression is generally recommended in well-meaning efforts to prevent or decrease the likelihood of tumor recurrence (5,10–14), and increases in TSH are thought to lead to clinical progression of thyroid cancer (15,16). Thus, TSH suppression has been

associated with increased survival or delayed progression to recurrence, especially in high-risk patients (21,22). This viewpoint is reflected in current ATA and ETA guidelines where TSH suppression <0.1 mIU/L is recommended for high-risk thyroid cancer patients, and suppression between 0.1 and 1–2 mIU/L is suggested for low-risk patients (1,2). In addition to this, there is clear indication that driver mutations in thyroid cancer have distinct effects on thyroid-differentiated properties, including TSH responsiveness. For instance, RAS mutant tumors, such as follicular variant papillary thyroid cancers, retain expression of the TSH receptor and may remain dependent on TSH signaling (39). Other cancers lose expression of the TSH receptor (40,41), particularly those with BRAF mutations, which represent approximately 50% of the low- and intermediate-risk ATA categories. Hence, some tumors progress independent of the effects of TSH (42), others are cured by the initial intervention (43), and yet TSH suppression as a goal of therapy is applied indiscriminately to most patients with the disease, in many cases as a life-long treatment.

While the evidence for the recommendations of the major thyroid societies is clearer for patients at high risk of recurrence, the optimal TSH maintenance level for patients at low and intermediate risk of recurrence or patients with tumors that may not respond to TSH suppression remains elusive. These results suggest that a TSH cutoff of 0.9–1.0 mIU/L is optimal for low- and intermediate-risk patients to balance the risk of osteoporosis development whilst not increasing the risk of tumor recurrence. Furthermore, no further benefit from TSH suppression may be obtained after formal documentation of absent residual or recurrent disease (44). A large, prospective, randomized, controlled study is required, however, to clarify definitively the optimal TSH level that would minimize the adverse effects of iatrogenic hyperthyroidism and maximize the beneficial effects of TSH suppression on recurrence in this growing population of ATA low- and intermediate-risk patients.

Due to its retrospective nature, this study has several limitations. The TSH treatment groups were not randomized and therefore suffered from inherent indication biases; ATA intermediate-risk patients were treated more aggressively than low-risk patients in that they were more likely to be suppressed and also more likely to have received RAI therapy. This may have prevented a beneficial effect of TSH suppression on recurrence from being detected. An attempt was made, however, to account for this limitation by performing multivariate analyses as well as propensity score analyses, but even after these adjustments, a statically significant effect of TSH suppression on tumor recurrence in ATA low- or intermediate-risk patients could not be detected. Not every patient had a pre and postoperative bone density test. Hence, it is possible that treating clinicians may have been more likely to investigate and thus diagnose osteoporosis and AF in patients on TSH suppression. However, the majority of these adverse events were found by nonendocrinologists within or outside the institution so the real impact of the above limitation is likely to be minimal. Information was not collected on estrogen replacement therapy, calcium and vitamin D supplementation, but the majority of patients were prescribed calcium and vitamin D after thyroidectomy. Clinicians may have been less likely to suppress patients at greater risk of AF or osteoporosis. This would have resulted in an underestimation of harm. Even so, more than a fourfold increase in the rate of age-adjusted osteoporosis was detected in patients with a median TSH ≤ 0.4 mIU/L compared to those with a nonsuppressed TSH. Initiation of bisphosphonate therapy was considered for indications other than bone metastasis or Paget's disease as one of the criteria to adjudicate osteoporosis. It is possible that some physicians may have begun bisphosphonate therapy for osteopenia or for prevention of osteoporosis. Given that information was not collected on menopausal status, a T-score of <-2.5 was used as a diagnosis of osteoporosis, although a Z-score is often used in premenopausal women. In addition, a low T-score may not always reflect osteoporosis, and may sometimes reflect osteomalacia or other conditions associated with a low BMD. Finally, the osteoporosis analysis was only performed in women, as men are generally not screened for osteoporosis at our institution. It is therefore not possible to comment directly on the skeletal effects of TSH suppression in men.

Conclusion

TSH suppression ≤ 0.4 mIU/L increases the risk of osteoporosis without changing tumor recurrence in thyroid cancer patients at ATA low and intermediate risk of recurrence. The findings of this study suggest that further research is required to delineate the role of TSH suppression in low- and intermediate-risk patients with thyroid carcinoma to avoid causing more harm than good. In particular, strategies currently employed to prevent recurrence need to be redefined to avoid long-term cardiovascular and skeletal toxicity in this population. The observations in this study extend to a median follow-up of 6.5 years where most recurrences would have been found. Longer TSH suppression may result in an even worse risk–benefit ratio. Definitive prospective, randomized, controlled studies that take into account individual patients' risks of osteoporosis and AF would ultimately be required to confirm these results. In the meantime, counseling on calcium and vitamin D supplementation, exercise, and screening of vitamin D levels may be considered where applicable. The paradigm outlined in this study could be extended to examine other types of thyroid cancer where the biology of the disease may drive the progression of the tumor independent of the effects of TSH suppression.

Author Disclosure Statement

The authors have no conflicts of interest to declare.

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