

# Routine pre-operative ultrasonography for papillary thyroid cancer: Effects on cervical recurrence

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**Background.** Pre-operative ultrasonography (US) is now part of published treatment guidelines for papillary thyroid carcinoma (PTC), despite the lack of long-term data on its potential value in preventing neck recurrence. We report the follow-up of patients with PTC in whom pre-operative US was used to accurately stage the extent of neck disease.

**Methods.** Patients with PTC who underwent pre-operative US and surgery were evaluated by indication for surgery (primary surgery, surgery for persistent PTC, and surgery for recurrent PTC). Patients who underwent their primary surgery at our institution were further evaluated by time period in which their pre-operative US was performed. Primary outcome studied was cervical recurrence.

**Results.** A total of 275 patients underwent pre-operative US; median follow-up was 41 months. Neck recurrence occurred in 6% of primary surgery patients, 5% of persistent-disease patients, and 23% of recurrent-disease patients ( $P < .001$ ). By multivariate analysis, the era in which US was performed appeared to be an independent predictor of disease-free survival, with less cervical recurrences in the recent eras during which there was more US specialization.

**Conclusion.** Once a patient with PTC experiences neck recurrence, they are at an increased risk for subsequent neck recurrence. Pre-operative US followed by compartment-oriented surgery may decrease recurrence rates in patients if performed before their primary operation. (*Surgery* 2009;146:1063-72.)

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THE INCIDENCE OF PAPILLARY THYROID CANCER (PTC) has increased 2.9-fold over the last 2 decades, accounting for the majority of the overall increase in incidence of thyroid cancer from 3.6 per 100,000 to 8.7 per 100,000 individuals in 2002.<sup>1</sup> PTC is characterized by early spread to regional lymph nodes and occasional extrathyroid extension into the soft tissue, with a low incidence of distant metastases and infrequent death.<sup>2,3</sup> Cervical recurrence of PTC, which consists primarily of regional lymph node metastases, occurs in up to 20% of patients with low-risk disease and 59% of patients with high-risk disease.<sup>4-7</sup> Such high rates

of recurrence suggest that many patients may have lymph node metastases at the time of initial surgery. This observation underscores the need for a thorough pre-operative evaluation, so that the appropriate extent of neck dissection may be completed (in the form of compartment-oriented surgery [COS]) at the first operation whenever possible.

The utility of pre-operative ultrasonography (US) in patients with differentiated thyroid cancer has been reported by our institution previously.<sup>8</sup> In this study, pre-operative US found lymph node or soft-tissue metastases in neck compartments believed to be uninvolved by physical exam in 39% of patients, thus altering their operative procedure. Because of the findings of this study and others like it, US was incorporated in published treatment guidelines.<sup>9,10</sup> However, long-term data on the true impact of high-quality pre-operative US and standardized COS on rates of cervical recurrence in patients with PTC have not been reported. Therefore, we sought to determine the long-term cervical recurrence rates in a mature data set that included patients with PTC who

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received pre-operative US and a standardized operation by experienced endocrine surgeons.

## METHODS

**Patients.** From our prospective database of 877 patients who underwent thyroid/neck surgery from January 1991 to January 2008, we retrospectively analyzed the medical records of a subset of patients with the diagnosis of PTC without distant metastases. All patients included in this study underwent pre-operative cervical US followed by operation in the Department of Surgical Oncology at The University of Texas M. D. Anderson Cancer Center (MDACC) during this time period; all patients also had a minimum of 1-year postoperative follow-up. Details of our US and fine-needle aspiration (FNA) techniques have been published previously.<sup>8</sup>

Based on the indication for initial surgery at our institution, this subset of patients was divided into 3 groups: group 1, primary thyroid/neck surgery or completion thyroidectomy; group 2, reoperation for persistent disease, defined as disease recognized within 6 months of the initial pre-referral operation; and group 3, reoperation for recurrent PTC, defined as disease recognized greater than 6 months from the original pre-referral operation(s). The operation done after pre-operative US at our institution will be referred to herein as the "index" operation. The stage of disease, based on the TNM (tumor, node, metastasis) system defined by the American Joint Committee on Cancer,<sup>11</sup> was determined from the histopathologic report from all operations performed within 6 months of the initial operation.

If lymph node status was not mentioned on the histopathologic report, N status was considered N0. Patients initially assigned to stages I and II were designated as low risk, and those patients assigned to stages III and IV were designated as high risk. Patients were recorded as being alive without disease, alive with the presence of recurrence, dead due to thyroid cancer, or dead from other causes.

To evaluate the potential effect of the evolution of pre-operative US that has occurred at our institution during the time period of this study, we also evaluated group 1 patients according to the span of years (era) in which the US was performed: US Era 1 (1991–1996): a time in which US was not a specialty in our radiology group (US was performed by general sonographers and US technologists); US Era 2 (1997–2001): cervical US began to formalize as a designated specialty; and US Era 3 (2002–2007): our group included 5

designated neuroradiologists and 8 technologists with a standardized protocol for performing US and reporting results.

Data on patient demographics, histopathology, TNM staging, high- and low-risk status, extent of dissection, radioactive iodine (RAI) therapy status, and extent of thyroid-stimulating hormone (TSH) suppression were evaluated. Extent of dissection during the primary operation was designated as 1 of the following: total thyroidectomy, total thyroidectomy plus paratracheal lymph node dissection, total thyroidectomy plus central neck dissection, or total thyroidectomy plus central neck dissection and lateral neck dissection (either ipsilateral or bilateral).

Designation was also made between a paratracheal dissection, which was defined as the removal of grossly normal ipsilateral paratracheal lymph nodes,<sup>8</sup> and a central neck dissection, which was an anatomically defined level VI lymph node dissection performed either for biopsy-proven central compartment disease or for abnormal lymphadenopathy seen either on pre-operative US or at the time of surgery. RAI therapy status was based on whether a patient received therapeutic RAI after his or her primary operation. Extent of TSH suppression was measured as described previously by Jonklaas et al,<sup>12</sup> with the TSH categories designated as undetectable, subnormal, normal, or elevated.

**Recurrence.** Recurrence of PTC after the index operation at our institution was recorded and was based on a standardized follow-up evaluation that included a physical examination, chest radiograph, neck US, thyroglobulin (Tg) levels, and the selective use of neck computed tomography (CT), total body RAI scanning, and FNA biopsy. Standardized follow-up evaluation occurred at 6 months after the index operation and every 6 months thereafter. The type of recurrence was defined as either distant metastasis or documented clinical recurrence in the neck. The designation of cervical (neck) recurrence served as the primary outcome in this study, because recurrence in this region was felt to be a result of the adequacy of the index operation performed. Status of cervical recurrence was recorded as 1 of the following: no evidence of neck disease, recurrence of neck disease, and indeterminate neck disease.

At the time of their last follow-up, patients who were recorded as having no evidence of neck disease met 1 of the following criteria: (1) neck US negative with undetectable serum Tg levels; (2) neck US negative with detectable Tg levels; and (3) written correspondence from the referring

physician reporting that the patient was free from cancer and had not received treatment for thyroid cancer. Of note, an abnormal serum Tg level often stimulated further evaluation. The characteristics of the absolute Tg value, the trend of serum Tg levels over time, and the setting in which Tg was measured (stimulated or TSH-suppressed) would usually prompt further studies such as neck US, RAI scanning, and CT. Neck US was the usual modality used to determine if the potential source of elevated Tg levels occurred in the cervical region.

Patients were considered to have PTC recurrence in the neck if they had any of the following: (1) detection of PTC on FNA biopsy; (2) PTC found at the time of reoperation; (3) interval increase in activity on serial RAI imaging that prompted treatment with RAI; or (4) correspondence from their referring physicians that reported PTC recurrence. A patient was considered indeterminate for recurrent neck disease if they met criteria consistent with recurrence or suspicion for recurrence on cervical US (that had not been biopsy-proven), or if they had discordant disease as outlined in Table I.

Disease-free survival (DFS) was calculated from the date of the index operation at MDACC (which included pre-operative US) to the date of tumor recurrence or the date of last follow-up evaluation.

**Statistical analysis.** The Kaplan-Meier method was used to determine DFS. Log-rank analysis was used to evaluate differences in DFS between subgroups. A value of  $P < .05$  was considered statistically significant. Categorical data were analyzed with the Chi-square test or the Fisher exact test, as indicated. Continuous data were analyzed by the Student  $t$  test. For group 1 patients, the US era during which surgery was performed and other potential prognostic factors (race, sex, age, extent of dissection, T stage, N stage, and extent of TSH suppression) were included in a multivariate model using Cox proportional hazards regression models. During model building, variables with a value of  $P > .25$  from univariate analysis were excluded from the multivariate model. Likelihood ratio tests were then used to compare the larger models and smaller models to identify the most parsimonious model that represented the data. All analyses were performed using a statistical software package (SAS, version 9.1; SAS Institute, Cary, NC).

## RESULTS

From January 1991 to January of 2008, of the 877 patients in our database, 392 had the diagnosis

of PTC, 123 had medullary carcinoma/C-cell hyperplasia, 47 had follicular carcinoma, 17 had Hurthle cell carcinoma, 3 had combined cancers, 4 had other neoplasms, and 291 had benign disease. Of the 392 patients with PTC, 275 met the criteria for this study, having undergone pre-operative US and COS before their index operation. Of the 275 patients, 202 (73%) were women and 73 (27%) were men; the median age at diagnosis was 44 years (range, 3–82). The median follow-up was 41 months from the time of the index operation; follow-up was complete through February of 2009.

Of the 275 total patients, 34 (12%) recurrences (including neck and elsewhere) occurred in 32 patients. Extracervical recurrences occurred in 6 patients, including 3 patients with lung metastases, 2 with bone metastases, and 1 patient with disease metastasizing to the salivary gland. Isolated lymph node recurrence or soft-tissue neck recurrence occurred in 26 (9.3%) of the 275 patients.

**Outcome of patients by group.** Evaluating patients by indication for index operation, group 1 patients were significantly older at age of diagnosis (median, 46 years; range, 13–82) than those patients in both group 2 (median, 36 years; range, 3–66) and group 3 (median, 36 years; range, 16–79;  $P = .0002$ ). Pathologic tumor stages by operative indication are shown in Table II. There was a significant relationship between the study group and initial T stage ( $P < .01$ ) as well as N stage ( $P < .0001$ ). No relationship was found between low- and high-risk status and the study group. Only 109 (40%) of 275 patients had node-negative disease on initial pathologic staging.

Cervical recurrence occurred in 13 (6%) of 203 group 1 patients, 1 (5%) of 20 group 2 patients, and 12 (23%) of 52 group 3 patients ( $P = .0009$ ; Table III). US studies interpreted as indeterminate for disease were found in 11 (4%) of 275 patients: 6 patients in group 1, 1 patient in group 2, and 4 patients in group 3. The median DFS had not yet been reached for groups 1 and 2 patients, and was 110 months for group 3 patients ( $P = .0007$ ; Fig 1). The 5-year DFS rate for patients in group 1 was 89% (95% confidence interval [CI], 81–94) compared with 76% (95% CI, 60–87) for group 3 patients.

The method of diagnosis of recurrence is outlined in Table III. Of the 26 patients who had recurrence in the neck, the recurrence was detected by US in 19 (73%). The median size of the disease on US was 1.35 cm (range, 0.8–3.0), and the disease was proven by biopsy in 17 of the 19 patients. The 2 patients without

**Table I.** Findings in follow-up ultrasonography (US) after surgery for papillary thyroid carcinoma (PTC)

	<i>Thyroid bed (between carotid and trachea)</i>	<i>Lymph node (central and lateral compartments)</i>	<i>Recommendations</i>
Consistent with recurrence	Nodule or mass with 1 or more of the following characteristics: <ul style="list-style-type: none"> <li>• Calcification</li> <li>• Cystic component</li> <li>• Disorganized vascular flow</li> <li>• Progression in size</li> </ul>	Lymph node that has 1 or more of the following characteristics: <ul style="list-style-type: none"> <li>• Calcification</li> <li>• Cystic component</li> <li>• Disorganized vascular flow*</li> <li>• Rounded or full appearance*</li> <li>• Disruption or absence of normal echogenic hilum</li> </ul>	FNA for both thyroid bed and lymph node, or consider close observation if no surgery planned regardless of biopsy results
Suspicious for recurrence	Nodule or mass in thyroid bed without features described for disease consistent with recurrence, often not seen on previous exam	Lymph node that has 1 of the following characteristics:* <ul style="list-style-type: none"> <li>• Disorganized vascular flow</li> <li>• Rounded or full in appearance</li> </ul>	Thyroid bed: 6 month follow-up US Lymph node: FNA to rule out benign reactive vs recurrent disease
Discordant disease	Suspicious disease with nondiagnostic FNA or 1 in which no malignant cells were aspirated; continued concern for recurrent disease based on sonographic appearance	Suspicious disease with nondiagnostic FNA or 1 in which no malignant cells were aspirated; continued concern for recurrent disease based on US features†	3- to 6-month follow-up US

\*Characteristics shared by both benign reactive disease and recurrent disease.

†Most frequently occurs in a lymph node that has a cystic component or is completely cystic.

FNA, Fine-needle aspiration.

**Table II.** Pathologic tumor staging\* in 275 patients with papillary thyroid carcinoma, grouped by operative intervention

	<i>Group 1 (n = 203)</i>	<i>Group 2 (n = 20)</i>	<i>Group 3 (n = 52)</i>	<i>Total (n = 275)</i>	<i>P value</i>
Age at diagnosis, y, median (range)	46 (13–82)	36 (3–66)	36 (16–79)	44 (3–82)	.0002
Sex (F:M)	2.6:1	5.7:1	3:1	3:1	.43
Stage					
T stage, n (%)					
1	113 (56)	6 (30)	14 (27)	133 (48)	
2	28 (14)	5 (25)	14 (27)	47 (17)	
3	60 (29)	67 (35)	15 (29)	82 (30)	
4	2 (1)	1 (5)	4 (8)	7 (3)	
X	0 (0)	1 (5)	5 (10)	6 (2)	<.01
N					
0	101 (50)	4 (20)	4 (8)	109 (40)	
1a	64 (31)	7 (35)	12 (23)	83 (30)	
1b	38 (19)	9 (45)	36 (69)	83 (30)	<.0001
M					
0	203 (100)	20 (100)	52 (100)	275 (100)	
High-risk patients, n (%)	61 (30)	4 (20)	14 (27)	79 (29)	.26

\*Based on the TNM (tumor, node, metastasis) staging system defined by the American Joint Committee on Cancer.<sup>11</sup>

F, Female; M, male.

biopsy-proven disease were considered to have recurrence because pathology at the time of reoperative surgery was consistent with PTC. Of the 7

patients with neck recurrence not diagnosed by US, 1 patient was diagnosed with neck recurrence by CT, which was performed to evaluate the extent

**Table III.** Recurrence and outcome in patients with papillary thyroid carcinoma

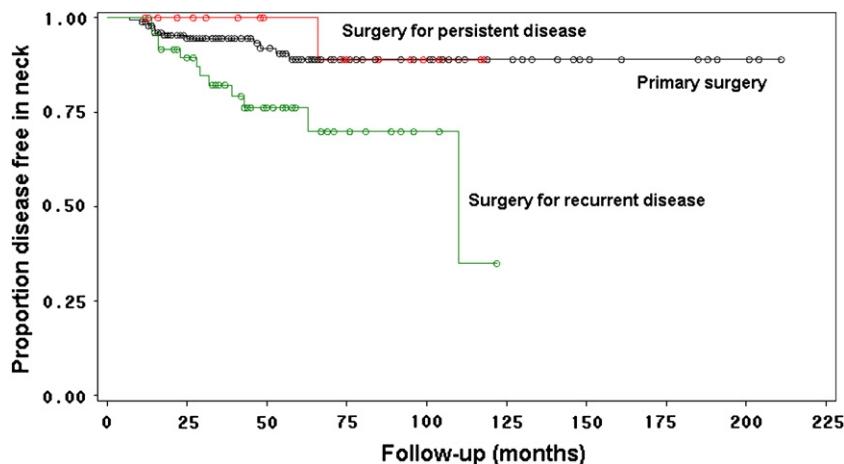
	Group 1 (n = 203)	Group 2 (n = 20)	Group 3 (n = 52)	Total (n = 275)	P value
Median follow-up, n (range)*	31 (12–210)	48 (12–119)	46 (17–194)	41 (12–210)	.39
Recurrence					
Patients with cervical					
Recurrence, n (%)	13 (6)	1 (5)	12 (23)	26 (9)	.0009
Diagnosis method, n (%)					
US	7	0	12	19 (73)	
Nuclear scan	5	1	0	5 (23)	
CT	1	0	0	1 (4)	
Recurrence in previously dissected compartment, ratio (%)†	5/13 (38)	1/1 (100)	11/12 (92)	17/26 (65)	.01
Further treatment, n (%)					
Patients operated on for recurrence	7/13 (54)‡	0/1 (0)	12/12 (100)	19/26 (73)	
Patients receiving RAI for recurrence	5/13 (38)	1/1 (100)	0/12 (0)	6/26 (23)	
Outcome					
Patients alive, NED	192	17	40	249	
Patients alive, AWD	12	1	11	24	
Patients deceased, DOD	1	0	1	2	
Patients deceased, DND	5	1	0	6	

\*Time 0 = date of first operation at M. D. Anderson Cancer Center. All patients had at least 12 months of follow-up.

†Recurrence diagnosed by tissue diagnosis, total body scan, or CT.

‡Of the 13 patients in group 1, 1 patient was offered surgery but refused further treatment.

US, Ultrasonography; CT, computed tomography; RAI, radioactive iodine; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; DND, dead with no evidence of disease.



**Fig 1.** Disease-free survival (DFS) of patients who underwent surgery for primary disease, persistent disease, and recurrent disease. Median follow-up was 41 months; the 5-year recurrence rates were 11%, 12%, and 30%, respectively ( $P = .0007$ ).

of his pulmonary metastasis; no US was performed in this case, and the cervical pathology at surgery was consistent with PTC. The remaining 6 patients had neck recurrence diagnosed by serial RAI scans that documented a change we considered consistent with recurrent disease in the neck. Of these 6 patients, 5 had negative US, and 1 patient had a 0.7-cm single lesion seen on US that was not amenable to biopsy. Recurrent PTC in the neck was not pathologically confirmed in any of these 6 patients.

Of the 10 patients who had indeterminate disease on US, 4 had findings that were consistent with recurrence, 4 had findings suspicious for recurrence, and 2 had discordant disease. The median size of the consistent and suspicious lesions was 0.6 cm (range, 0.4–0.8). The patients with US suspicious for recurrence had newly identified subcentimeter disease that we elected to follow with serial US. All 4 of the patients with findings on US consistent with recurrence had a

**Table IV.** Demographics, stage, and treatment details of patients who underwent ultrasound during 3 different eras before their primary surgery at the M. D. Anderson Cancer Center

	Total	US era 1 1991–1996	US era 2 1997–2001	US era 3 2002–2007	P value
Sex					
Female:Male	3.1:1	1.9:1	3.2:1	2.6:1	.683
Race, n (%)					
White	157 (77)	22 (84)	31 (74)	104 (77)	.87
Black	11 (5)	2 (8)	3 (6)	6 (4)	
Hispanic	20 (10)	2 (8)	4 (10)	14 (11)	
Asian	15 (8)	0 (0)	4 (10)	11 (8)	
Extent of dissection, n (%)					
TT	64 (33)	10 (38)	19 (46)	35 (27)	.22
TT + PND	51 (26)	4 (16)	8 (20)	39 (30)	
TT + CLND	37 (19)	7 (27)	7 (17)	23 (18)	
TT/CCLN + LLND	43 (22)	5 (19)	7 (17)	31 (24)	
Histopathology, n (%)					
FVPTC	29 (14)	4 (15)	6 (14)	19 (14)	.98
CPTC	174 (86)	22 (85)	36 (86)	116 (86)	
Stage, n (%)					
Low risk	142 (70)	21 (81)	34 (81)	87 (64)	.05
High risk	61 (30)	5 (19)	8 (19)	48 (35)	
Age, y, n (%)					
<45	88 (43)	16 (62)	22 (52)	50 (37)	.03
≥45	115 (57)	10 (38)	20 (48)	85 (63)	
T stage, n (%)*					
T1	113 (56)	12 (46)	24 (57)	77 (57)	.53
T2	28 (14)	4 (15)	8 (19)	16 (12)	
T3	60 (30)	9 (35)	10 (24)	41 (30)	
T4	2 (1)	4 (4)	0 (0)	1 (1)	
N stage, n (%)*					
N0	101 (50)	13 (50)	23 (55)	65 (48)	.75
N1a	64 (31)	10 (38)	11 (26)	43 (32)	
N1b	38 (19)	3 (12)	8 (19)	27 (20)	
RAI therapy performed (%)	75	92	83	70	.02
TSH suppression, n (%)					.24
Undetectable	5 (3)	1 (5)	0 (0)	4 (3)	
Subnormal	94 (51)	7 (33)	14 (40)	73 (56)	
Normal	77 (41)	12 (57)	19 (54)	46 (36)	
Elevated	9 (5)	1 (5)	2 (6)	6 (5)	
Cervical recurrence, n (%)	13 (6.4)	6 (23)	4 (10)	3 (2)	<.001

\*Based on the TNM (tumor, node, metastasis) staging system defined by the American Joint Committee on Cancer.<sup>11</sup>

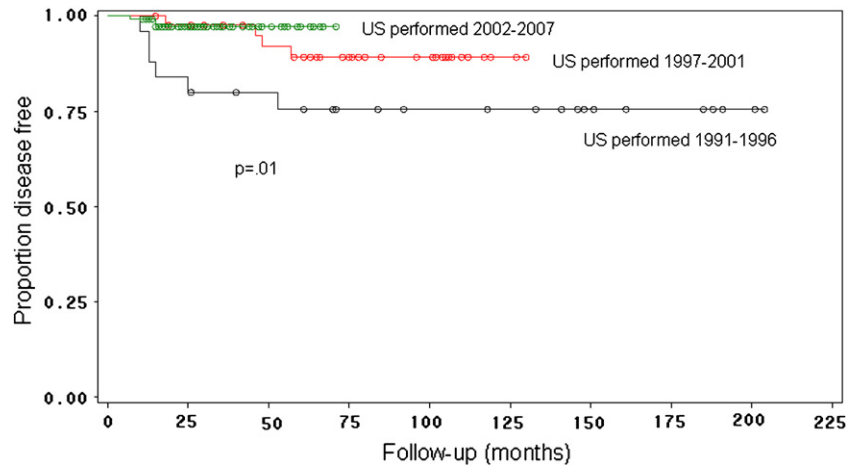
TT, Total thyroidectomy; PND, paratracheal neck dissection; CLND, central lymph node dissection; LLND, lateral lymph node dissection; FVPTC, follicular variant of papillary thyroid carcinoma; CPTC, conventional papillary thyroid carcinoma; RAI, radioactive iodine; TSH, thyroid-stimulating hormone.

single focus of possible recurrence that was subcentimeter in size; rather than biopsy these lesions, a decision was made to follow these patients.

The 2 patients with discordant disease had 1.1-cm and 1.3-cm single nodule disease, respectively, that were negative on biopsy; the findings on US, however, were significant enough to justify this classification. Of note, of the 19 patients who had biopsy- or surgery-proven recurrent disease originally diagnosed by US, 17 were read as consistent with disease on their prebiopsy or surgery US, and 2 were read as suspicious for disease.

#### Patients in group 1 during different US eras.

Data for group 1 patients during the 3 US eras are summarized in Table IV. Surgery was performed for more high-risk patients in the most recent era ( $P = .05$ ); however, when the TNM stage was broken down by its components, the T and N stages were not different among the 3 eras. Instead, more patients 45 years of age or older were operated on during the most recent era ( $P = .03$ ). RAI therapy was also performed significantly less often in the more recent eras ( $P = .02$ ). Otherwise, the patients in the 3 eras were well matched in terms of the extent of



**Fig 2.** Disease-free survival (DFS) of patients who underwent pre-operative ultrasonography and primary surgery in US Era 1: 1991–1996, US Era 2: 1997–2001, and US Era 3: 2001–2007. Median follow-up was 34 months; the 3-year recurrence rates were 3%, 3%, and 19%, respectively ( $P = .01$ ).

dissection and level of TSH suppression, as well as sex, race, and histopathology type. Treatment in the most recent US era was associated with an improved DFS, with a 3-year recurrence rate of 3% compared to 19% in the first era ( $P = .01$ ; Fig 2).

**Univariate and multivariate predictors of outcome in group 1 patients.** Potential and actual predictors of DFS in patients who underwent primary surgery for PTC are summarized in Table V. Variables investigated on univariate analysis included sex, age, race, histopathology, T staging, N staging, extent of dissection, RAI status, and extent of TSH suppression. These same variables were included in the multivariate model with the exception of sex, histopathology, and RAI therapy status. The factors significantly associated with an increased risk of disease recurrence after surgery on univariate analysis were race, T stage, N stage, and US time period. The final multivariate models demonstrated that race ( $P = .02$ ), T stage ( $P = .004$ ), TSH suppression ( $P = .02$ ), and US time period ( $P = .03$ ) were the independent prognostic factors predicting an increased risk of disease recurrence after surgery.

## DISCUSSION

Factors that influence PTC recurrence can be grouped into those that decrease recurrence rates and those that increase recurrence rates. Factors that may decrease recurrence rates include more comprehensive surgery, very sensitive pre-operative staging with routine cervical US, and the use of routine central neck dissection to remove lymph nodes that could cause recurrence. Factors that may increase recurrence include any methods that

improve the sensitivity for detection of neck recurrence, such as high-quality cervical US and stimulated Tg. Analyses of contemporary series can help determine the impact of these potentially powerful recent changes in how we care for patients.

In this study, we expanded on our original work,<sup>8</sup> in which pre-operative US findings resulted in a more comprehensive COS in 43% of cases, to determine the true impact of high-quality preoperative US and standardized COS on rates of cervical recurrence. For purposes of the current analysis, we used a clinically practical definition of cervical recurrence in this era of high-quality US and sensitive Tg assays. We defined a cervical recurrence as pathologically proven PTC (either at FNA or at the time of reoperation) or an interval increase in activity on serial nuclear imaging that prompted treatment with RAI.

As US has become more sensitive, we have developed a vocabulary and algorithm (Table I) with which to interpret its findings. For example, we included the indeterminate designation (indeterminate for recurrence) as a possible outcome for patients in this study because of the observation that some patients without biopsy-proven neck recurrence have follow-up radiographic findings that cannot be classified as normal. This additional categorization reflects the situation that we currently encounter due to the increased sensitivity of high-quality cervical US and Tg assays, as well as the increased rigor with which patients are being followed. Also for the purposes of this study, patients with elevated Tg levels in the setting of normal imaging studies were considered negative for cervical disease. An abnormal Tg would

**Table V.** Univariate and multivariate analysis of disease-free survival of patients who underwent primary operation for papillary thyroid carcinoma (PTC) at the M. D. Anderson Cancer Center

Variable	Univariate analysis			Multivariate analysis*		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Sex	1.55	0.51–4.7	.44			NA
Male vs female						
Race			.0015			.02
Black vs white†	9.47	2.77–32.39		12.7	1.83–78.03	
Hispanic vs white	2.85	0.59–13.73		2.90	0.44–19.67	
Extent of dissection			.08			.81
TT + PND vs TT	3.40	0.31–38.54		6.44	0.25–169.48	
TT + CLND vs TT	5.66	0.59–54.44		11.39	0.21–620	
TT/CLND + LLND vs TT	14.35	1.78–117.11		8.35	132–527	
Histopathology						NA
FVPTC vs CPTC	1.04	2.31–4.71	.95			
Stage						NA
High risk vs low risk	1.34	0.41–4.38	.63			
Age, y	.570	0.185–1.75	.33	1.35	0.32–5.58	.68
≥45 vs <45						
T stage‡			.002			.004
T2 vs T1	3.60	0.23–57.50		9.52	0.36–255.31	
T3, T4 vs T1	25.3	3.3–196.2		45.79	3.88–540.27	
N stage‡			.03			.20
N1a vs N0	2.34	0.52–10.40		1.10	0.18–6.52	
N1b vs N0	6.18	1.54–24.75		5.03	0.82–31.08	
RAI therapy			1.0			NA
No vs yes						
TSH suppression			.137			.02
Subnormal vs undetectable	.11	0.001–1.05		0.7	0.003–1.39	
Normal vs undetectable	.25	0.029–2.09		0.44	0.04–5.30	
Elevated vs undetectable	.80	0.071–9.0		6.17	0.22–170.44	
Unknown vs undetectable	.14	0.009–2.3		0.43	0.02–12.17	
US time period			.035			.03
1991–1996 vs 2002–2007	6.17	1.48–25.7		9.75	1.64–58.07	
1997–2001 vs 2002–2007	2.36	0.51–11.0		1.54	0.28–8.45	

\*Includes Asian patients.

†The model for the multivariate analysis included race, age, T stage, N stage, TSH suppression status, and US time period.

‡Based on the TNM (tumor, node, metastasis) staging system defined by the American Joint Committee on Cancer.<sup>11</sup>

CI, Confidence interval; NA, not analyzed; TT, total thyroidectomy; PND, paratracheal neck dissection; CLND, central lymph node dissection; LLND, lateral lymph node dissection; FVPTC, follicular variant of papillary thyroid carcinoma; CPTC, conventional papillary thyroid carcinoma; RAI, radioactive iodine; TSH, thyroid-stimulating hormone; US, ultrasonography.

lead to further evaluation with radiographic studies in attempts to locate the cause of the biochemical abnormality; if these studies found no disease in the neck, however, such patients were classified as without cervical recurrence.

When analyzing the 275 patients by indication for index surgery, the recurrence rate in the reoperative group (group 3) was significantly greater than in the other 2 groups. When these reoperative group 3 patients experienced recurrences, they were most often located in previously dissected compartments (Table III). This suggests that our ability to adequately dissect a neck

compartment is impaired by previous surgery in that compartment. In interpreting these findings, however, it is important to recognize that differences exist in the T and N stages between the primary and reoperative surgery groups (Table II). For example, reoperative patients were less likely to have T1 tumors and more likely to have N1b disease than primary surgery patients. Therefore, factors that could contribute to the difference in DFS between the primary and reoperative surgery groups include tumor biology. This is reflected by the increased T and N stages in the reoperative patient group versus completeness of surgery

related to the difficulty of reoperation in a previously dissected compartment due to adhesions and fibrosis.

We chose to further examine the effects of tumor biology and the completeness of surgery by examining the outcome of patients who received their primary surgery at our institution (Group1) over the time course of 3 US eras. Evaluating our patients in such a manner allowed us to determine whether recurrence rates were influenced by the quality of US as it improved over time. As seen in Table IV, the 3 groups were well matched for extent of disease, extent of dissection, and level of TSH suppression, as well as sex, race, and histopathology type.

We performed RAI less often in the latest era, which may be explained in part by the fact that we administer RAI based largely on whether disease is found on the diagnostic scan. Because we are doing more disease-directed surgery, less detectable disease is left in place and, as a result, less RAI is being administered. We performed surgery for more high-risk patients in the most recent era. Even though operations were increasingly performed in high-risk patients, the rate of cervical recurrence was actually the lowest in the most recent era of US evaluation.

In a multivariate analysis of DFS that included race, extent of dissection, age, T stage, N stage, TSH suppression, and US time period, the independent predictors of an improved DFS were race, T stage, TSH suppression therapy, and US time period. In terms of race, previous studies have shown an association with survival in thyroid cancer,<sup>13,14</sup> whereas others have shown no relationship.<sup>15</sup> The suggestion of delay in diagnosis of thyroid cancer in black patients because of its relative rarity and consequent advanced stage of diagnosis in this group is a potential contributor to our findings of increased recurrence and warrants further investigation.<sup>15</sup>

Interestingly, T stage remained an independent predictor of recurrence on multivariate analysis, whereas N stage did not. A possible explanation for this observation is that a comprehensive surgery renders N1a and N1b patients node-negative in the neck, in essence making them comparable to N0 patients when taking other contributing factors into account. TSH suppression therapy appeared to make a difference in DFS only when comparing elevated TSH to undetectable TSH. No benefit for THS therapy at undetectable levels of TSH compared to subnormal or normal levels can be determined from the data.

In the later 2 US eras, cervical US has evolved at our institution into its current format of scrupulous evaluation of lymph nodes in the lateral compartment and of the thyroid and associated soft tissue of the central neck compartment. Because US specialization occurred over time, there was a trend toward fewer cervical recurrences when all other factors were equal. These results suggest that a well-planned operation performed in a comprehensive manner with the aid of pre-operative US may decrease the risk of recurrence. It should be noted that, because our event of interest (cervical recurrence) is relatively rare and our current cohort is small, we need to continue to gather long-term follow-up data and increase the study population. Such measures will allow us to better elucidate the impact of pre-operative US in the treatment and outcome of these patients.

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## DISCUSSION

**Dr Allan Siperstein** (Cleveland, OH): Can you give a little more detail in terms of whether the presence of recurrent disease was diagnosed sonographically as opposed to being diagnosed by thyroglobulin measurements or imaging scan?

Additionally, the location of the recurrence, how often was ultrasound the defining tool in terms of where the recurrence was as opposed to physical examination or radioiodine scan?

My third question is, when were these scans performed in relationship to the operation? That is, how far preoperatively were they performed?

Also, did you perform on-table ultrasound at the time of the surgery? We've found surgeon-performed ultrasound when the patient is on the operating room table particularly useful in terms of being able to pick up disease that was not previously appreciated often due to the ability to use greater compression.

**Dr Elizabeth G. Grubbs** (Houston, TX): Nineteen patients were diagnosed with recurrent disease by ultrasound, 5 by nuclear scan, and 1 by computed tomography. For purposes of this analysis, we used a clinically practical definition of cervical recurrence in this era of high-quality ultrasound (US) and sensitive thyroglobulin assays.

We defined a cervical recurrence as pathologically proven papillary thyroid cancer (either at fine-needle aspiration or at the time of reoperation) or an interval increase in activity on serial nuclear imaging that

prompted treatment with radioiodine. As US has become more sensitive, we have developed a vocabulary and algorithm with which to interpret its findings. At our institution, US is performed by the neuroradiology section of dedicated ultrasonographers. We are very fortunate that we work extremely closely with these people.

And you're right, they come with us to the operating room and perform on-table US just prior to operation. So, we do use this modality to help us plan our surgery, which is especially helpful in our reoperative cases.

**Dr Henning Dralle** (Halle, Germany): I think the ultrasound methodology is really very important first to identify those patients who may have a local recurrence as thyroglobulin level-increased situations.

However, regarding the accuracy, did you correlate the number of involved nodes to the ultrasound findings? That means, how many nodes did you identify with ultrasound that really have been involved by histopathology?

And the second question is, did you correlate the size of the nodes you can identify by ultrasound that have been involved with histopathology by PTC, so the correlation of the true number of positive nodes on ultrasound was histopathology and the size?

What was the cutoff you can identify by ultrasound?

**Dr Elizabeth G. Grubbs** (Houston, TX): In the 2003 paper that Dr Kouvaraki presented for us at this meeting, we evaluated the relationship between pre-operative ultrasound findings and histopathologic findings and found good correlation, especially in the lateral compartments.

This work did not address number of nodes found, nor did we evaluate this in the setting of recurrence in our current work.

As far as your size question, yes, you will see that all of our proven recurrences (biopsy-proven or at the time of surgery) are 1 cm or greater.

**Dr Henning Dralle** (Halle, Germany): So the cutoff was 1 cm, no less?

**Dr Elizabeth G. Grubbs** (Houston, TX): Since we do not routinely operate on patients unless they have greater than 1-cm recurrent disease, we do not prove recurrence until they are of this size. We usually follow subcentimeter-suspicious recurrences by ultrasound. We chose the 1-cm cutoff because we have found that, at operation, subcentimeter disease, especially in a reoperative setting, is often extremely difficult to find at the time of surgery.