



Does microscopic positive tumor margin in papillary thyroid cancer really matter?



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ARTICLE INFO

Article history:

Accepted 11 July 2019

Available online 30 September 2019

ABSTRACT

Background: The clinical impact of microscopically positive tumor margin in papillary thyroid cancer is not well studied. The aim of this study is to evaluate the clinical importance of a microscopically positive margin for recurrence in papillary thyroid cancer patients and to examine whether recurrence and recurrence-free survival were affected by the location of the positive margin—anterior or posterior.

Methods: We conducted a retrospective cohort study at a single institution. From January 1997 to June 2015, 6,293 papillary thyroid cancer patients who underwent total thyroidectomy with or without neck dissection (central and/or lateral) at the Thyroid Cancer Center of Samsung Medical Center (Seoul, South Korea) were included in the analyses.

Results: Of the 6,293 papillary thyroid cancer patients, an operative margin was microscopically involved in 313 (5.0%) on final pathologic report. The mean follow-up time was 77.5 months, and locoregional recurrence was observed in 244 (3.9%) patients. The presence of a microscopically positive margin did not increase the risk of locoregional recurrence (adjusted hazard ratio = 1.079, $P = .140$) after adjustment for other statistically significant factors in the Cox proportional hazard model. In addition, posterior positive margin was not a risk factor for locoregional recurrence as well (adjusted hazard ratio = 1.24, $P = .672$). In a propensity score–matching analysis, a microscopically positive margin did not increase the risk of locoregional recurrence.

Conclusion: Microscopic involvement of the operative margin in papillary thyroid cancer patients, whether anteriorly or posteriorly, does not appear to be an independent prognostic factor in recurrence-free survival rates.

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Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, and an excellent overall survival rate. Because the 10-year disease-free survival rate is >95%,^{1,2} the practical issue for PTC patients focuses on prediction of disease recurrence. In most cases, morbidities in PTC patients are associated with recurrence or metastases.^{3,4} Therefore, an accurate risk stratification for recurrence is important in the management of PTC patients.

According to the guidelines of the American Thyroid Association (ATA) and European Thyroid Association, PTC patients with

macroscopic tumor invasion, incomplete tumor resection, distant metastasis, and thyroglobulinemia after total thyroidectomy (TT) are categorized into a high-risk group for recurrence.^{5,6} The metastasis, patient age, completeness of resection, local invasion, and tumor size staging system also suggests that complete resection, invasion, tumor size, metastasis, and age are significant risk factors for disease-specific survival.⁷ ATA management guidelines recommend adjuvant therapy, such as radioactive iodine (RAI) and external beam radiation therapy, for patients at high risk;⁵ however, controversies persist with the lack of clear guidelines on the clinical relevance of a microscopically positive margin as an independent, statistically significant risk factor for recurrence.

The purpose of the current study was to investigate whether the presence and location (anterior versus posterior) of a microscopically positive margin affects recurrence and recurrence-free survival in PTC patients.

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Patients and Methods

Patient selection

We conducted a retrospective cohort study at a single institution. From January 1997 to June 2015, 20,030 patients underwent thyroidectomy with or without neck dissection at the Thyroid Cancer Center of Samsung Medical Center, a tertiary referral center in Korea. The Institutional Review Board at Samsung Medical Center approved this study, and consent had been obtained from every patient. Of them, 13,042 patients with the following conditions were excluded: a history of thyroidectomy, age younger than 20 years, lobectomy, sub-/near-total thyroidectomy, non-PTC carcinoma (follicular/medullary/anaplastic), PTC variants whose behavior and prognosis have not been clearly verified (except conventional, follicular, diffuse sclerosing, and tall cell),^{8–11} gross residual disease, distant metastasis, and a follow-up duration less than 6 months (residual tumor or suspicious lymph node [LN] detected within 6 months after initial TT, reoperation within 6 months after initial TT, or loss to follow-up within 6 months). Particularly, we excluded PTC patients with multifocality or bilaterality to decrease the discordance between primary tumor and margin status. Finally, a total of 6,293 PTC patients who underwent TT with or without neck dissection (central and/or lateral) were included in the analyses.

Operative methods

TT was performed according to published guidelines.^{5,12} Therapeutic central neck dissection was typically performed after any central LN metastasis was detected during preoperative ultrasonography. Patients who were node negative at the time of preoperative ultrasonography or who had advanced primary tumors (T3/T4) underwent prophylactic central neck dissection at the surgeon's discretion. At our institution, we only performed therapeutic lateral neck dissection when lateral LN metastases were demonstrated on fine-needle aspiration biopsy. Lateral neck dissection, which included modified radical neck dissection and selective neck dissection, was performed as described in the literature.¹³ Open (conventional low collar approach) or oncoplastic (remote access thyroidectomy; endoscopic, or robotic) thyroidectomy was chosen based on patient preference after a thorough discussion of the pros and cons of each approach.

Histopathologic examination of surgical specimens

Surgical specimens were microscopically examined by two or more experienced pathologists, and the following histopathologic factors were assessed: main tumor size (greatest diameter of the largest lesion), cell type of the tumors, multifocality, bilaterality) extrathyroidal extension ([ETE] microscopic or gross), regional LN metastasis (central or lateral), and underlying conditions of the thyroid such as chronic lymphocytic thyroiditis. The staging of thyroid cancer was determined in accordance with the 7th edition of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual and the Future of TNM*,¹⁴ and key parameters were described in the [Tables 1 and V](#) to compare the 7th¹⁴ and 8th¹⁵ edition of AJCC staging system. Careful inking of the outer surface of the TT specimen was performed in the pathology department before macroscopic dissection. A microscopically positive margin was defined as the

presence of tumor at the inked margin edge on histopathologic examination. In particular, a recently published article from Lang et al¹⁶ suggested that a small resection margin could be achieved on the posterior side of the thyroid because of the proximity of vital structures, including the esophagus, recurrent laryngeal nerve, and trachea. Therefore, we stratified margin status as either anterior and posterior. A positive anterior margin was defined as an involved margin that lay on the anterior surface between the two lateral edges of the thyroid regardless of anatomic position. A positive posterior margin was defined as an involved margin that lay on the posterior surface between the two lateral edges of the thyroid regardless of anatomic position. Microscopic ETE was defined as a tumor in an attached tissue on an adjacent structure outside of the thyroid capsule attributable to extrathyroidal extension. If there were a microscopic ETE and a tumor remaining on the final inked surface, the pathologists reported both microscopic ETE and positive margin simultaneously.

Postoperative follow-up and management

After the initial TT, all patients underwent regular follow-up at 6- to 12-month intervals. The follow-up visits included clinical evaluations with physical examination, ultrasonography, computed tomography, iodine-131 scans, and serum thyroglobulin measurement. After TT, thyroid-stimulating hormone (TSH) suppression therapy (serum TSH level < 0.5 mU/l), using levothyroxine, with or without RAI, was considered as the initial postoperative therapy. RAI was administered after thyroid hormone withdrawal or after stimulation with recombinant TSH. Although RAI was generally proposed for aggressive features as recommended by established guidelines,^{5,12} the final decision was at the discretion of the physician or patient. When RAI was no longer required, patients resumed regular follow-up. The last date of follow-up was defined as loss to follow-up, withdrawal, recurrence, or death. Suspicious lesions were confirmed by ultrasonography-guided fine-needle aspiration biopsy with or without measurement of washout thyroglobulin level and/or computed tomography or positron emission tomography. Recurrence was defined as the presence of tumor or metastatic LN on cytology from fine-needle aspiration biopsy or on histopathology from reoperation after 6 months of the initial TT. Because the prevalence of mortality is extremely low in PTC patients,¹⁷ we adopted locoregional recurrence as our primary end point.

Statistical analysis

Statistical analyses were performed using SPSS v 22.0 software (IBM Corp, Armonk, NY, USA), and statistically significant differences were defined as those with *P* values less than .05. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as number and percentage of cases. The χ^2 test and linear-by-linear association were used for categorical variables and the Student's *t* test for continuous variables. Kaplan-Meier methods and the log-rank test were adopted to analyze time-dependent variables. The adjusted hazard ratio (HR) and 95% confidence interval (CI) for locoregional recurrence were calculated using Cox regression models.

Table 1
Clinicopathologic characteristics of 6,293 PTC patients according to the microscopic margin status

	Microscopic margin (–)	Microscopic margin (+)	P value
Total	5,980 (95.0)	313 (5.0)	NA
Sex			<.001
Female	4,783 (80.0)	275 (87.9)	
Male	1,197 (20.0)	38 (12.1)	
Age (y)			<.001
Mean ± SD	46.6 ± 11.7	44.0 ± 11.8	
<45	2,538 (42.4)	156 (49.8)	
≥45	3,442 (57.6)	157 (50.2)	.010
<55	4,525 (75.7)	257 (82.1)	
≥55	1,455 (24.3)	56 (17.9)	.009
BRAF mutation*			NA
Negative	323 (5.4)	8 (2.6)	
Positive	1,414 (23.6)	34 (10.9)	
Surgical approach			.053
Open	5,610 (93.8)	302 (96.5)	
Oncoplastic (endoscopic or robotic)	370 (6.2)	11 (3.5)	
Neck dissection			<.001
No	1,088 (18.2)	102 (32.6)	
Central	4,056 (67.8)	166 (53.0)	
Lateral	836 (14.0)	45 (14.4)	
TSH (mIU/l)			.008
Mean ± SD†	1.9 ± 1.6	1.6 ± 1.5	
Tumor size (cm)			<.001
Mean ± SD	1.1 ± 0.9	1.6 ± 1.0	
≤0.5	1,459 (24.4)	23 (7.3)	
0.5–1.0	2,130 (35.6)	102 (32.6)	
1.0–2.0	1,812 (30.3)	113 (36.1)	
2.0–4.0	506 (8.5)	71 (22.7)	
> 4.0	73 (1.2)	4 (1.3)	
Extrathyroidal extension			<.001
Absent	2,656 (44.4)	17 (5.4)	
Microscopic	3,324 (55.6)	296 (94.6)	
Chronic lymphocytic thyroiditis			<.001
Absent	4,441 (74.3)	268 (85.6)	
Present	1,539 (25.7)	45 (14.4)	
T stage (AJCC 7th)			<.001
T1	2,485 (41.6)	16 (5.1)	
T2	156 (2.6)	1 (0.3)	
T3	3,339 (55.8)	296 (94.6)	
T4	NA	NA	
T stage (AJCC 8th)			.615
T1	5,410 (90.5)	238 (76.0)	
T2	506 (8.5)	71 (22.7)	
T3a	73 (1.2)	4 (1.3)	
T3b–T4	NA	NA	
Nodal stage			.067
N0	3,229 (54.0)	148 (47.3)	
N1a	2,074 (34.7)	124 (39.6)	
N1b	677 (11.3)	41 (13.1)	
Adjuvant radioactive iodine (mCi)			<.001
Mean ± SD (mCi)†	72.2 ± 83.0	139.0 ± 116.9	
Absent	1,398 (23.4)	9 (2.9)	
≤30	1,118 (18.7)	25 (8.0)	
30–100	2,354 (39.4)	149 (47.6)	
>100	1,110 (18.6)	130 (41.5)	
Location of the involved margin			<.001
Anterior positive margin	NA	85 (27.2)	
Posterior positive margin	NA	228 (72.8)	
Recurrence			NA
Total	217 (3.6)	27 (8.6)	
Operation bed (thyroidectomy site)	21 (9.7)	1 (3.7)	
Central neck	38 (17.5)	8 (29.6)	
Lateral neck	158 (72.8)	18 (66.7)	
Remnant thyroid	0 (0.0)	0 (0.0)	

PTC, papillary thyroid carcinoma; SD, standard deviation; NA, not available.

* BRAF mutation analysis was started in 2008 and was performed in 1,779 patients.

† Counted only in administered patients.

Table II
Logistic regression analysis for locoregional recurrence in PTC patients

	Locoregional recurrence	
	Adjusted OR (95% CI)	P value
Male sex	1.222 (0.864–1.728)	.258
Age (y)	0.994 (0.982–1.005)	.293
<45 (reference)	NA	
≥45	0.875 (0.647–1.184)	.387
<55 (reference)	NA	
≥55	1.338 (0.865–2.070)	.190
Surgical approach		
Open (reference)	NA	NA
Oncoplastic (endoscopic or robotic)	0.738 (0.293–1.860)	.520
Neck dissection		
Absent (reference)	NA	NA
Central	0.428 (0.271–0.676)	<.001
Lateral	0.371 (0.112–1.227)	.104
TSH	0.684 (0.600–0.781)	<.001
Tumor size	1.643 (1.459–1.851)	<.001
Extrathyroidal extension		
Absent (reference)	NA	NA
Microscopic	1.875 (1.302–2.699)	.001
Chronic lymphocytic thyroiditis	0.916 (0.626–1.341)	.851
Microscopic positive margin	1.442 (0.887–2.344)	.140
Nodal stage		
N0 (reference)	NA	NA
N1a	4.036 (2.637–6.178)	<.001
N1b	8.994 (2.701–29.948)	<.001
Adjuvant radioactive iodine	1.481 (0.787–2.788)	.224

PTC, papillary thyroid carcinoma; OR, odds ratio; CI, confidence interval; NA, not available.

Results

Clinicopathologic characteristics of the 6,293 PTC patients according to microscopic margin status

Of the 6,293 PTC patients, microscopic involvement of the operative margin was present in 313 (5.0%) patients (Table I). Female ($P < .001$), younger age ($P < .001$), larger tumor size ($P < .001$), microscopic ETE ($P < .001$), and adjuvant RAI ($P < .001$) were more frequent in the group with a microscopically positive margin. Of note, chronic lymphocytic thyroiditis was less frequent in the microscopically positive margin group ($P < .001$). TSH suppression levels were 1.9 and 1.6 in the microscopically negative margin and in the positive margin groups, respectively.

Prognostic impact of microscopically positive margin on locoregional recurrence in PTC patients

The mean follow-up was 77.5 months (range, 6.2–228.6). Locoregional recurrence was observed in 244 (3.9%) patients. The recurrence sites were in the lateral neck in 176 (78.6%) patients, central neck in 46 (18.3%) patients, and operation bed (thyroidectomy site) in 22 (8.8%) patients. Recurrence-free survival rates in the microscopically negative/positive margin group were 99.7% vs 94.0% at 5 years, 99.5% vs 92.7% at 10 years, and 99.4% vs 90.4% at 15 years ($P = .002$). In risk factor analysis, tumor size (adjusted odds ratio [OR] 1.643, $P < .001$), higher TSH level (adjusted OR 0.684, $P < .001$), microscopic ETE (adjusted OR 1.875, $P < .001$), higher nodal stage (adjusted OR 4.036, 8.994, $P < .001$) were significant predictors for locoregional recurrence (Table II). However, positive microscopic margin were not related to high risk of locoregional recurrence (Table II). After adjustment for clinicopathologic characteristics in the Cox proportional hazard model (Table III), however, a microscopically positive margin did not increase the risk of

Table III
Cox proportional hazards model for loco-regional recurrence in PTC patients

	Locoregional recurrence	
	Adjusted HR (95% CI)	P value
Male sex	1.357 (0.983–1.872)	.064
Age (y)	0.979 (0.964–0.995)	.012
<45 (reference)	NA	
≥45	0.983 (0.593–1.627)	.945
<55 (reference)	NA	
≥55	1.955 (1.185–3.224)	.009
Surgical approach		
Open (reference)	NA	NA
Oncoplastic (endoscopic or robotic)	1.042 (0.418–2.599)	.929
Neck dissection		
Absent (reference)	NA	NA
Central	0.647 (0.418–1.001)	.054
Lateral	0.626 (0.202–1.937)	.416
TSH	0.700 (0.617–0.795)	<.001
Tumor size (cm)		
≤ 0.5 (reference)	NA	NA
0.5–1.0	2.019 (1.059–3.849)	.033
1.0–2.0	3.032 (1.611–5.705)	.001
2.0–4.0	5.640 (2.922–10.887)	<.001
>4.0	10.802 (1.946–23.590)	<.001
Extrathyroidal extension		
Absent (reference)	NA	NA
Microscopic	1.705 (1.194–2.435)	.003
Chronic lymphocytic thyroiditis	0.961 (0.674–1.370)	.738
Microscopic positive margin	1.079 (0.690–1.687)	.140
Nodal stage		
N0 (reference)	NA	NA
N1a	2.719 (1.865–3.964)	<.001
N1b	5.142 (3.389–7.801)	<.001
Adjuvant radioactive iodine		
Absent	NA	NA
≤30	0.905 (0.429–1.908)	.793
30–100	0.962 (0.508–1.824)	.906
>100	1.317 (0.684–2.536)	.411

PTC, papillary thyroid carcinoma; HR, hazard ratio; CI, confidence interval; NA, not available.

locoregional recurrence in PTC patients (adjusted HR = 1.079, $P = .140$). As described in the guidelines, older age, tumor size, TSH suppression, and nodal stage were important prognostic factors in PTC patients. In our study, 96.8% of patients with a positive microscopic margin received RAI, and they received a greater dose of RAI compared with those patients in the margin-negative group. We found that this might have led to selection bias. Therefore, we performed further statistical analysis to minimize the adjuvant role of RAI in PTC patients with microscopically positive margins (Tables IV, V). With this adjusted analysis, a microscopically positive margin did not increase the risk of locoregional recurrence and recurrence-free survival in any other conditions (Table V, Fig 1).

Prognostic impact of the location of the involved margin on locoregional recurrence in PTC patients

The recurrence-free survival rate in the positive anterior margin group was 96.3% at 5 years, 91.2% at 10 years, and 88.8% at 15 years, and that in the posterior positive posterior margin group, the recurrence-free survival rate was 93.1% at 5 years, 91.1% at 10 years, and 90.3% at 15 years ($P = .77$). After adjustment for clinicopathologic characteristics in the Cox proportional hazard model (Table VI), a positive posterior margin did not increase the risk of locoregional recurrence in PTC patients compared with those patients with a positive anterior margin (adjusted HR = 1.24, $P = .672$). In the propensity score-match analysis, the locations of the

Table IV
Propensity score matching for relationships between clinicopathologic characteristics and margin status according to RAI status in 626 PTC patients

	Microscopic margin (–)	Microscopic margin (+)	P value
Total	5,980 (95.0)	313 (5.0)	NA
Sex			.012
Female	62 (19.8)	275 (87.9)	
Male	251 (80.2)	38 (12.1)	
Age (y)			.002
Mean ± SD	46.9 ± 11.7	44.0 ± 11.8	
<45	122 (39.0)	156 (49.8)	
≥45	191 (61.0)	157 (50.2)	.008
<55	226 (72.2)	257 (82.1)	
≥55	87 (27.8)	56 (17.9)	.004
BRAF mutation*†			.617
Negative	13 (15.3)	8 (19.0)	
Positive	72 (84.7)	34 (81.0)	
Surgical approach			.432
Open	297 (94.9)	302 (96.5)	
Oncoplastic (endoscopic or robotic)	16 (5.1)	11 (3.5)	
Neck dissection			<.001
No	53 (16.9)	102 (32.6)	
Central	202 (64.5)	166 (53.0)	
Lateral	58 (18.5)	45 (14.4)	
TSH			.003
Mean ± SD	2.0 ± 1.7	1.6 ± 1.5	
Tumor size (cm)			<.001
Mean ± SD	1.3 ± 1.0	1.5 ± 1.0	
≤0.5	62 (24.4)	23 (7.3)	
0.5–1.0	104 (35.6)	102 (32.6)	
1.0–2.0	98 (30.3)	113 (36.1)	
2.0–4.0	43 (8.5)	71 (22.7)	
>4.0	6 (1.2)	4 (1.3)	
Extrathyroidal extension			<.001
Absent	114 (36.4)	17 (5.4)	
Microscopic	199 (63.6)	296 (94.6)	
Chronic lymphocytic thyroiditis			.003
Absent	238 (76.0)	268 (85.6)	
Present	75 (24.0)	45 (14.4)	
T stage (AJCC 7th)			<.001
T1	100 (31.9)	16 (5.1)	
T2	13 (4.2)	1 (0.3)	
T3	200 (63.9)	296 (94.6)	
T4	NA	NA	
Nodal stage			.179
N0	125 (39.9)	148 (47.3)	
N1a	140 (44.7)	124 (39.6)	
N1b	48 (15.3)	41 (13.1)	
Location of the involved margin			1.000
Anterior positive margin	NA	85 (27.2)	
Posterior positive margin	NA	228 (72.8)	

PTC, papillary thyroid carcinoma; SD, standard deviation; NA, not available.

* BRAF mutation analysis was started in 2008.

† Counted only in administered patients.

positive margin was not associated with locoregional recurrence nor recurrence-free survival (Table V, Fig 2).

Discussion

The incidence of a microscopically positive margin has been reported as 6.1%–14.1% in patients after a thyroidectomy for PTC.^{16,18–20} The incidence of a microscopically positive margin in this study was 5.6%. This relatively low incidence may be explained by our exclusion of multifocal tumors and inclusion in this study of a large portion of papillary microcarcinomas (tumor size less than 1 cm). A microscopically positive margin did not in this study increase the risk of locoregional recurrence in PTC patients after adjustment for other clinicopathologic factors. In the propensity score–match analysis (Table V), the results were not changed after controlling for RAI, including well-known major risk factors for

recurrence, such as age, T stage, and nodal stage as reported by several guidelines.

Our results were consistent with those of earlier studies^{18–21} except for the posterior margin reported by Lang et al,¹⁶ who noted that a microscopically positive margin was not an independent risk factor for disease-free survival and did not increase recurrence. In contrast a positive posterior margin did increase the rate of disease-free survival.¹⁶ In this study, however, we showed that a positive posterior margin did not increase the risk of locoregional recurrence. Furthermore, a positive posterior margin had no adverse effect on recurrence-free survival rates in PTC patients compared with those with a positive anterior margin.

Hong et al¹⁶ and Lang et al²⁰ reported that the site of recurrence was not in the thyroid bed but in the regional nodes. For this reason, they recommended that PTC patients with a microscopically positive margin be required to undergo a more meticulous evaluation

Table V

Cox proportional hazards regression analysis of matched paired data for relationships between clinicopathologic characteristics and recurrence according to RAI status in 626 PTC patients

	Locoregional recurrence Adjusted HR (95 % CI) (95% CI)	P value
Sex		.147
Female	Ref	
Male	0.40 (0.109–1.393)	
Age (y)		
<45	Ref	
≥45	0.426 (0.158–1.154)	.093
<55	Ref	
≥55	2.568 (0.851–7.754)	.094
Surgical approach		.770
Open	Ref	
Oncoplastic(endoscopic or robotic)	1.360 (0.174–10.647)	
Neck dissection		
No	Ref	
Central	1.463 (0.560–3.827)	.438
Lateral	1.789 (0.161–19.855)	.636
TSH	0.624 (0.436–0.895)	.010
Tumor size (cm)	1.589 (1.233–2.048)	<.001
Chronic lymphocytic thyroiditis		.222
Absent	Ref	
Present	1.584 (0.757–3.316)	
T stage (AJCC 7th)		
T1	Ref	.251
T2	4.166 (0.349–49.713)	.259
T3	11.908 (1.061–133.654)	.045
T4	NA	NA
Nodal stage		
N0	Ref	
N1a	1.796 (0.753–4.279)	
N1b	2.422 (0.262–22.429)	
Microscopic positive margin	NA	.916
Location of the involved margin		
Anterior positive margin	Ref	
Posterior positive margin	1.137 (0.481–2.691)	.770

PTC, papillary thyroid carcinoma; SD, standard deviation; HR, hazard ratio; CI, confidence interval; NA, not available; Ref, reference.

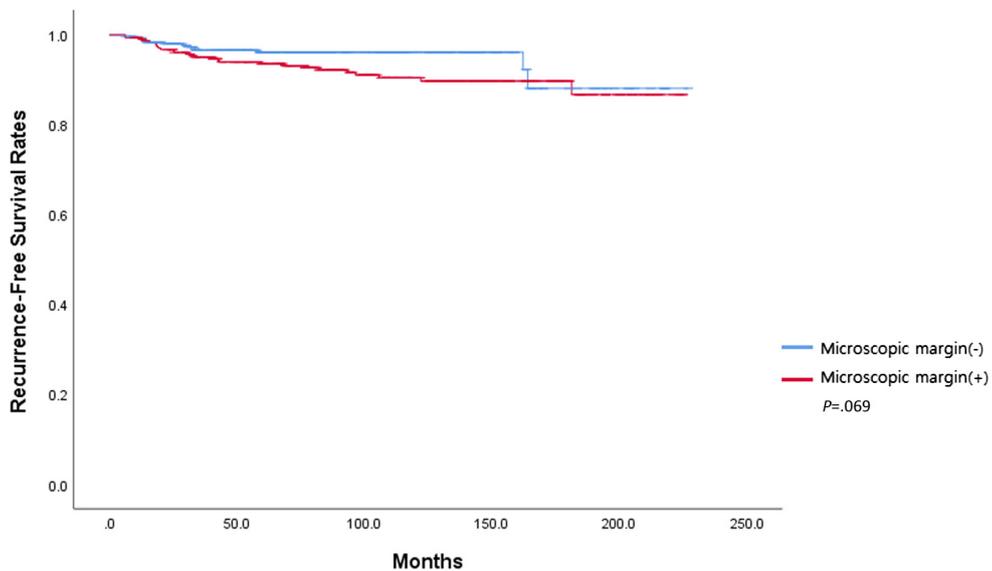


Fig 1. Recurrence-free survival in 626, propensity score-matched PTC patients according to a microscopic margin status. PTC, papillary thyroid carcinoma.

Table VI

Cox proportional hazards model for locoregional recurrence in 313 PTC patients with a microscopically positive margin according to location of the involved margin

Location of the involved margin	Locoregional recurrence	
	Adjusted HR (95 % CI) [*]	P value
Positive anterior margin (<i>reference</i>)	NA	NA
Positive posterior margin	1.24 (0.464–3.288)	0.672

PTC, papillary thyroid carcinoma; HR, hazard ratio; CI, confidence interval.

^{*} Adjusted for sex, age, operative approach (open or oncologic), neck dissection (absent, central, or lateral), tumor size, extrathyroidal extension (absent, microscopic), chronic lymphocytic thyroiditis, TSH, nodal stage (N0, N1a, or N1b), and adjuvant radioactive iodine.

postoperatively for the areas not planned to be included in the operative specimen.^{16,20} Our results showed recurrence in the regional LNs rather than the primary tumor site in 90.6% of recurrent patients. Therefore, we agree that a more meticulous postoperative evaluation with imaging focused not on regional LNs with no ignorance of the thyroidectomy site is needed. In addition, we suppose that the relatively high recurrence rate (9.4%) in the bed of the thyroid resulted from the larger cohort of this study compared with earlier ones.

Although microscopic ETE on the final pathology was included in the T3 stage in the AJCC 7th edition, ETE was removed from the definition of T3 stage in the AJCC 8th edition, leaving only patients with macroscopic ETE invading the strap muscle at diagnosis.¹⁵ Microscopic ETE has no impact on overall stage.¹⁵ In this respect, although we only investigated recurrence (not survival), our results supported the new AJCC classification, which notes that patients with a positive microscopic margin may be classified as T1 or T2 according only to tumor size and regardless of margin involvement.

In our study, 96.8% of patients with a microscopically positive margin received RAI, but it was unclear whether RAI affected recurrence, because most of our cohort was considered low risk (Table 1). The majority (76%) of patients with an ATA low and intermediate risk did not receive additional therapy after curative TT, and there was no recurrence in either group.⁵ Thus, the effects of RAI suggested by ATA were primarily targeted at a high-risk group,

and there is no clear evidence that RAI decreased recurrence in the low-risk group with a positive microscopic margin.

Despite ample studies on the prognosis of PTC patients with incomplete resection and grossly positive margins, there are few recommendations or guidelines for management of PTC patients with a microscopically positive margin. According to 2009 ATA guidelines, patients with residual tumor should receive a greater dose of RAI (100–200 mCi), and patients with grossly involved margins should consider external beam irradiation. This suggestion, however, was based on expert opinions, and there is still a lack of clear evidence. Therefore, we conducted this study to compensate for the limitations of earlier studies by providing additional evidence on this margin subject.

Our study had several limitations. The first is a statistical limitation, because this was a retrospective study conducted in a single center. Second, there were certain inabilities to determine the exact therapeutic value of RAI. The additional therapeutic decisions also depended on the preferences of clinicians or patients, so that RAI treatment failed to be applied evenly to all patients. The adjuvant role of RAI in PTC patients with a microscopically positive margin should be elucidated in a future study. Third, the recently published 8th edition of the AJCC/TNM cancer staging system has been in place since January 1, 2018. Unfortunately, we collected patients up until 2015, and the study was unable to apply the new AJCC guidelines. The long-term follow-up for PTC patients graded with a new staging system should be carried out. Finally, additional multicenter and long-term follow-up studies might be necessary to ensure the real meaning of a microscopically margin positivity. Nevertheless, the strength of our study is that we tried to increase statistical reliability by using a larger cohort and more effective statistical analyses than did earlier studies.

In conclusion, the presence and location (especially posteriorly) of a microscopically positive margin did not increase the risk of locoregional recurrence in PTC patients. Furthermore, an involved margin may not be an independent prognostic factor in recurrence-free survival rates. Clinicians should carefully consider the value of adjuvant treatment or surveillance after curative thyroid surgery when treating PTC patients with a microscopically positive margin status.

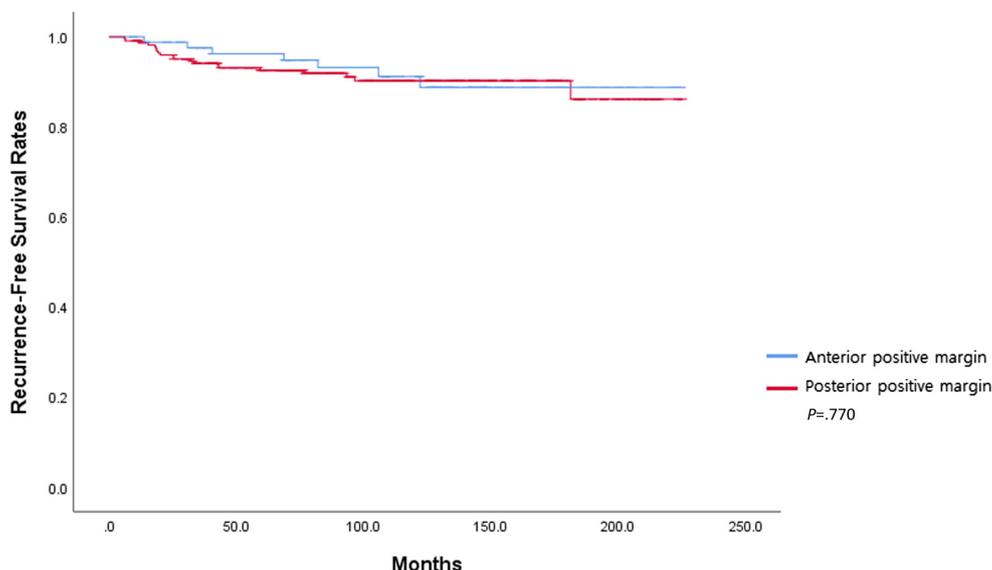


Fig 2. Recurrence-free survival curve in 626, propensity score–matched PTC patients with a microscopically positive margin according to location of the involved margin. PTC, papillary thyroid carcinoma.

Funding/Support

The authors have no specific funding to declare for this work.

Conflict of interest/Disclosure

The authors have no conflicts of interest to declare.

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