Ann Surg Oncol (2017) 24:460–468
DOI 10.1245/s10434-016-5594-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Extent of Extrathyroidal Extension as a Significant Predictor of Nodal Metastasis and Extranodal Extension in Patients with Papillary Thyroid Carcinoma

Ji Won Kim, MD[1], Jong-Lyel Roh, MD, PhD[1], Gyungyup Gong, MD, PhD[2], Kyung-Ja Cho, MD, PhD[2], Seung-Ho Choi, MD, PhD[1], Soon Yuhl Nam, MD, PhD[1], and Sang Yoon Kim, MD, PhD[1]

[1]Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

ABSTRACT

Background. Extrathyroidal extension (ETE) and extranodal extension (ENE) indicate poor prognosis for patients with papillary thyroid carcinoma (PTC). The relationships among ETE, ENE, and nodal metastasis (N1) have not been thoroughly studied. In this study, we examined the relationships among the extent of ETE, N1, ENE, and posttreatment recurrence in patients with PTC.

Methods. This study enrolled 1693 consecutive patients with previously untreated PTC who underwent thyroidectomy between 2006 and 2009. The extent of ETE was graded based on intraoperative and pathological findings, and central and lateral neck (N1b) nodal metastases and ENE were pathologically determined. Univariate and multivariate analyses were used to identify the association of clinicopathological factors with recurrence-free survival (RFS) and to define the relationships among the extent of ETE, N1, and ENE.

Results. Of 1693 patients, 1087 (64.2 %) had ETE and 201 (11.9 %) had ENE. Pathologically positive lymph nodes were found in 783 patients (46.2 %), of whom 236 (30.1 %) had N1b. During the median follow-up of 86 months, 90 (5.3 %) patients had recurrences. Multivariate analyses showed that multifocality, ETE, T and N classification, the risk of structural recurrence proposed by the American Thyroid Association, and ENE were independent variables for RFS ($P < .05$). Patients with macroscopic ETE had a 13-fold increased risk of recurrence, and ETE had significant relationships with N1, N1b, and ENE (all $P < .001$).

Conclusions. Local extension, nodal involvement, and ENE contribute to posttreatment recurrence of PTC. Macroscopic ETE predicts nodal metastasis and ENE, which are adverse pathologic features.

Lymph node metastases from papillary thyroid carcinoma (PTC) are not uncommon. It first spreads to the central compartment of the neck and then to the lateral compartment.[1] Prophylactic lymph node dissection for clinically node-negative patients is not usually performed because of the lack of consensus on the prognostic importance of nodal metastasis.[2] However, lymph node metastasis, particularly to the lateral cervical compartment, appears to be associated with a shorter disease-free survival.[3] Additionally, the presence of extranodal extension (ENE) from metastatic lymph nodes has been significantly associated with an increased risk of nodal persistence, distant metastases, and cancer-specific death.[4–7] The presence of ENE is not incorporated into the current staging system proposed by the American Joint Committee on Cancer (AJCC).[8] Once nodal metastasis (N1) and ENE are detected, patients can be treated with a neck dissection procedure to fully resect the cancer followed by postsurgical adjuvant therapy such as radioactive iodine (^{131}I). However, it may be difficult to detect the presence of PTC lymph node metastases and ENE prior to and even during surgery.[9,10]

Electronic supplementary material The online version of this article (doi:10.1245/s10434-016-5594-4) contains supplementary material, which is available to authorized users.

First Received: 5 August 2016;
Published Online: 21 September 2016

J.-L. Roh, MD, PhD
e-mail: rohjl@amc.seoul.kr

Extrathyroidal extension (ETE) has been recognized as an important prognostic factor for PTC.[11,12] The presence of minimal ETE leads to upstaging to T3 in the AJCC staging system, but the prognostic implications of microscopic minimal ETE are currently controversial.[13–15] However, minimal or massive gross ETE are commonly associated with poor treatment outcomes.[16,17] Because macroscopic tumor extension into surrounding tissues is easily identified during surgery and it has an influence on surgical margin positivity, surgeons usually pay attention to it.[14]

Recently, it has been reported that the presence of ETE can predict the presence of ENE.[18] However, the relationships among ETE, ENE, and lymph node metastasis of PTC have been examined in relatively small retrospective cohort studies.[6,18] There was a lack of information on the prognostic differences between minimal and maximal gross ETE as well as between microscopic and macroscopic ETC. Therefore, the differences in prognostic outcomes among patients with microscopic, minimal gross, and maximal gross ETE, and the role of ETE as a predictor of ENE or lymph node metastasis needs to be examined in a large cohort of patients with PTC. This information may improve patient management, minimizing the risk of recurrence, and prolong cancer-specific survival. Therefore, we hypothesized that the extent of ETE affects treatment outcomes and predicts ENE and lymph node metastasis. The purpose of this study was to identify the association of clinicopathological factors with posttreatment recurrence and to examine the relationships among the extent of ETE, nodal metastasis, and ENE.

METHODS

Study Population

This retrospective study was conducted through reviews of the electronic medical records of patients who underwent thyroidectomy at the Department of Otolaryngology of our tertiary referral center between 2006 and 2009. Patients who underwent thyroidectomy for previously untreated PTC and were followed up for at least 2 years after surgery were included. Patients with a prior history of cancer treatment ($n = 39$) and those with incomplete follow-up information ($n = 33$) were excluded. A total of 1693 patients were eligible for the final analyses. Preoperatively, all patients underwent ultrasonography (US) and US-guided fine needle aspiration biopsy (FNAB).

Based on intraoperative and pathological findings, the extent of ETE was classified into 4 groups: G0, no ETE; G1, microscopic ETE; G2, minimal macroscopic ETE; and G3, massive macroscopic ETE. Tumor and nodal size, multifocality and bilaterality, number of lymph nodes harvested and number positive, and ENE were determined from the pathological examinations.[19] The lymph node ratio (LNR) was calculated from the number of positive lymph nodes divided by the total number of lymph nodes harvested.[20,21] Tumors were pathologically staged using the tumor-node-metastasis (TNM) staging system of the AJCC (7th ed.).[8] The risk stratification of structural disease recurrence recently proposed by the American Thyroid Association (ATA) was also used.[12] This study was approved by our institutional review board, and informed consent from each patient was waived.

Treatment and Follow-Up

All study patients underwent tumor extirpation with the intent of macroscopic complete resection. An ipsilateral lobectomy was performed for small (<1 cm) unifocal malignant nodules and all others underwent total thyroidectomy. Therapeutic lateral compartment lymph node dissection (LND) was performed in the lateral neck, along with central compartment lymph node dissection (CND). Regardless of clinical nodal involvement, our institutional protocol includes prophylactic CND in the ipsilateral or bilateral side of the central neck compartment. Patients with completion thyroidectomy were considered to have undergone a total thyroidectomy. All surgical specimens from the thyroids and lymph nodes were carefully examined by surgeons and pathologists. Microscopic and macroscopic invasion to surround tissues or organs, and nodal involvement and its extension, were reported.

Postoperatively, most of the study patients with total thyroidectomy received radioactive iodine (RAI) ablation of 30–200 mCi, depending on the clinicopathological findings, while the low-risk patients with unifocal microcarcinoma or a lobectomy did not receive RAI ablation.

During follow-up, all patients were regularly followed by clinical and US examinations, measurement of serum thyroglobulin (Tg), whole-body iodine scanning, and chest radiography after surgery and RAI ablation. Any lesions identified during follow-up imaging that raised the suspicion of recurrence in the remnant thyroid, resection bed, or lymph nodes were histologically confirmed by FNAB examination and reoperation. Clinical posttreatment recurrence was defined as the reappearance of pathologically proven tumors in the resection bed or neck, and/or the appearance of metastatic lesions in distant sites.

Statistical Analysis

The primary endpoint was recurrence-free survival (RFS), defined as the time from surgery until the first evidence of any recurrence. A Cox proportional hazards regression model was used for the analyses of the relationships among clinicopathological variables and RFS.

Binary logistic regression analyses were also used to find variables with significant relationships among ENE, lymph node metastasis, and ENE. Multivariate analyses were performed with backward elimination including variables with P values <.05 on univariate analyses. The estimated hazard ratios (HRs), odds ratios (ORs), and their 95 % confidence intervals (95 % CIs) were calculated. The Kaplan-Meier estimates were used to depict survival curves, and their statistical differences were calculated using the log-rank test. Statistical differences of categorical data were assessed using the χ^2 test or Fisher exact test. A 2-sided P value <.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS software version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Patient Characteristics

The study patients consisted of 352 men and 1341 women, with a median age of 55 years (range 18–86 years), and the majority (80.6 %) were ≥45 years (Table 1). On pathological review, 1089 (64.4 %) had advanced T3–T4 stage, 783 (46.2 %) had nodal positivity (pN+), and 1015 (60.0 %) had advanced overall stage III–IV. Median size of the tumors was 1.1 cm, and tumors >2 cm were found in 216 patients (12.8 %). Multifocal tumors were found in 536 patients (31.7 %), and 1087 patients (35.8 %) had ETE: G1 in 645 patients (38.1 %), G2 in 368 patients (21.7 %), and G3 in 74 patients (4.4 %). The median number of lymph nodes harvested and involved were 12 (range 0–144) and 2 (range 0–50), respectively. ENE was found in 201 patients (11.9 %).

The study patients were followed for a median of 86 months (range, 24–119 months). A total of 90 patients (5.3 %) had recurrences at a median of 26 months (range, 6–103 months) after treatment: 13 (0.8 %) in the thyroid remnant or bed, 23 (1.4 %) in central compartment lymph nodes, 47 (2.8 %) in lateral compartment lymph nodes, and 13 (0.8 %) in distant sites. At last follow-up, only 8 patients (0.5 %) had died of PTC and 22 patients (1.3 %) died of other causes.

Risk Factors for Posttreatment Recurrences

In all study patients, univariate analyses showed that age (<45 years), sex (male), tumor size (>2 cm), multifocality, ETE (any grades), positive resection margin, T and N classifications, overall TNM stage (IV), the ATA risk group for structural disease recurrence, ENE, and MACIS score (≤5) were significant variables predictive of any site of recurrence after treatment (all $P < .05$) (Table 2). Multivariate analyses showed that multifocality, ETE (G3), T (pT4) and N (N1a and N1b) classifications, the ATA risk group, and ENE were independent variables predictive of posttreatment recurrence (all $P < .05$) (Table 2 and Fig. 1).

Relationships Among ETE and N1, N1b, and ENE

The Supplementary Table S1 shows the results of relationships among clinicopathological variables and N1, N1b, and ENE. For pathological nodal involvement (pN+), univariate analyses showed that age (<45 years), sex (male), tumor size (>2 cm), the palpability of malignant thyroid nodules, multifocality, bilaterality, and ENE were significantly associated with pN+ (all $P < .05$). Multivariate analyses showed that age, sex, tumor size, multifocality, and ETE were independent variables predictive of pN+ (all $P < .05$) (Table 3). For N1b and ENE, univariate analyses showed that sex (male), tumor size, tumor palpability, multifocality, bilaterality, ETE, central neck involvement, and LNR (>0.2) were significant risk factors (all $P < .05$). In addition, age was a significant variable for N1b, while lateral neck involvement and ≤3 involved lymph nodes were significant variables for ENE (all $P < .05$). Multivariate analyses showed that age, tumor size, palpability, multifocality, ETE, and central neck involvement were independent predictors of ENE, while ETE, central and lateral neck involvement, number of positive lymph nodes, and LNR were independent predictors for ENE (all $P < .05$). Table 4 shows the crosstab analysis between the extent of ETE and pN+, N1b, and ENE. The extent of ETE was significantly related to nodal metastasis, N1b, and ENE ($P < 0.001$ for all).

DISCUSSION

The present study demonstrated a relationship between ETE extent, nodal metastasis, ENE, and posttreatment recurrence. Among the factors affecting the prognosis of PTC, significant ETE, multifocality, advanced T and N classifications, and ENE have been highlighted in our study, consistent with previous reports.[22] In our study, the incidence of ETE (64 %) was higher than in previous reports (5 %–45 %).[13,15,16,18] This might be because we performed careful pathological examinations of thyroid specimens, revealing the presence of microscopic ETE in a high proportion (38 %) of our study population. On the other hand, the incidences of lymph node metastasis and ENE found in our study are consistent with incidences reported previously.[7,9,16,18,22]

As a prognostic indicator of recurrence and survival in differentiated thyroid cancer (DTC), ENE has been

TABLE 1 Clinical characteristics of study patients ($n = 1693$)

Variable	*N*	%
Sex, male/female	352/1341	20.8/79.2
Age at diagnosis, median (range), years	55 (18–86)	
≥45 years	1364	80.6
pTNM stage		
pT1a/T1b/T2/T3/T4	461/117/26/1015/74	27.2/6.9/1.5/60.0/4.4
pN0/N1a/N1b	910/547/236	53.8/32.3/13.9
M0/M1	1688/5	99.7/0.3
Overall I/II/III/IV	669/9/807/208	39.5/0.5/47.7/12.3
ATA risk group[a]		
Low/intermediate/high	559/1029/95	33.6/60.8/5.6
MACIS score, median (range)	4.82 (2.70–10.83)	
≥5	729	43.1
Pathologic tumor size, median (range), cm	1.1 (0.1–10.8)	
>2	216	12.8
Multifocality	536	31.7
Extrathyroidal extension		
No/microscopic/macroscopic/massive	606/645/368/74	35.8/38.1/21.7/4.4
Extranodal extension	201	11.9
Surgery		
Lobectomy/total thyroidectomy	68/1625	4.0/96.0
CND/CND plus LND	1290/261	76.2/15.4
Resection margin involved	315	18.6
Postoperative RAI	1538	90.8
First relapse[b]	90	5.3
Thyroid remnants or bed	13	0.8
Central compartment LN	23	1.4
Lateral compartment LN	47	2.8
Distant sites	13	0.8
Median time to first relapse (range), months	26 (6–103)	
Follow-up information		
Median follow-up (range), months	86 (24–119)	
Death (index cancer/other causes)	8/22	0.5/1.3

CND central compartment neck dissection, *MACIS score* distant metastasis, patient age, completeness of resection, local invasion, and tumor size score, *LN* lymph node, *LND* lateral compartment neck dissection, *pTNM* pathologic tumor-node-metastasis stage (AJCC, 7th ed.), *RAI* radioactive iodine (I^{131}) therapy, *RT* radiotherapy

[a] The risk of structural disease recurrence proposed by the American Thyroid Association (ATA)[12]

[b] Including mutually overlapping recurrences

emphasized rather than ETE.[18] Therefore, it would be better to identify the presence of ENE for appropriate nodal management, prior to or during surgery. Our study indicated the degree of ETE was significantly associated with recurrence and, moreover, might predict the ENE as well as lymph node metastasis to all sites and to the lateral neck. Our study implies that the intraoperative observation of tumor local invasion might lead to proper neck management that can minimize recurrence.

Several studies have examined the prognostic role of ETE in DTC and found the extent of ETE affects patient prognosis.[14,15] Ito et al. suggested against the use of minimal ETE as an indicator of a poor prognosis because it had no association with RFS, unlike macroscopic ETE.[23] Arora et al. reported a 33.4 % (71 of 212) incidence of ETE (10.8 % macroscopic vs. 22.6 % microscopic), and only macroscopic ETE was associated with a 6.4-fold increased relative risk of recurrence.[13] Nixon et al. included 984 cT1/

TABLE 2 Relationships between clinicopathologic variables and recurrence-free survival

Variable	Univariate		Multivariate	
	HR (95 % CI)	*P* value	HR (95 % CI)[a]	*P* value
Age, <45 years	1.62 (1.02–2.57)	.040		
Sex, male/female	2.07 (1.34–3.19)	.001		
Tumor size, >2 cm	3.35 (2.15–5.22)	<.001		
Multifocality	2.71 (1.79–4.10)	<.001	1.95 (1.28–2.97)	.002
Extrathyroidal extension				
No (G0)	1		1	.033
Microscopic (G1)	2.70 (1.40–5.21)	.002	1.79 (0.92–3.88)	.081
Minimal macroscopic (G2)	3.69 (1.87–7.29)	<.001	1.71 (0.82–3.48)	.164
Massive macroscopic (G3)	13.36 (6.38–27.98)	<.001	3.05 (1.32–7.58)	.008
Positive resection margin	2.49 (1.62–3.84)	<.001		
T classification				
pT1–T2	1	<.001	1	.042
pT3	3.06 (1.65–5.68)	<.001	1.65 (0.92–3.55)	.086
pT4	12.37 (5.91–25.91)	<.001	2.65 (1.23–6.44)	.014
N classification				
pN0	1	<.001	1	.002
pN1a	3.36 (1.81–6.25)	<.001	2.00 (1.04–3.83)	.038
pN1b	12.52 (6.98–22.47)	<.001	3.71 (1.79–7.69)	<.001
Overall pTNM stage				
I–II	1	<.001		
III	1.20 (0.72–2.01)	.483		
IV	3.77 (2.28–6.24)	<.001		
ATA risk group[b]				
Low	1	<.001	1	.002
Intermediate	4.79	<.001	2.48 (1.10–5.62)	.029
High	22.87	<.001	5.00 (1.97–12.74)	.001
Extranodal extension	7.54 (4.99–11.41)	<.001	2.60 (1.55–4.35)	<.001
MACIS score ≥ 5	1.93 (1.27–2.93)	.002		

95 % CI 95 % confidence interval, *HR* hazard ratio, *MACIS score* distant metastasis, patient age, completeness of resection, local invasion, and tumor size score, *pTNM* pathologic tumor-node-metastasis stage (AJCC, 7th ed.), *RFS* recurrence-free survival

[a] Cox proportional hazard regression analyses were performed with backward elimination from variables with *P* values <.05 on univariate analyses

[b] The risk of structural disease recurrence proposed by the American Thyroid Association (ATA)[12]

T2N0 PTC patients, among whom 115 (11.7 %) were upstaged to pT3; however, there was no difference in 10-year RFS compared with patients with pT1–T2 tumors (95 vs 98 %; $P = .188$).[24]

The prognostic value of local disease extent was reconfirmed by a recent study showing the different oncological outcomes between gross and microscopic ETE.[15] However, microscopic ETE, particularly tumors ≥1 cm, might be related to lymph node metastasis, and the presence of ENE may be a marker for a more aggressive disease biology.[16,18] Our current study supported the previous findings of microscopic ETE (G1) as not being a significant prognostic indicator. We also divided the patients with gross ETE into minimal macroscopic (G2) and massive macroscopic (G3) ETE groups. Our study showed that the presence of G2 ETE was not an independent predictive factor of RFS, unlike G3 ETE, which was associated with poor RFS outcomes. Therefore, the present study results suggest that minimal macroscopic ETE should be distinguished from massive macroscopic ETE as a separate clinical entity.

The significance of ENE has been frequently reported in the literature. In 1989, Spires et al. first reported ENE in thyroid cancer, but they did not recognize this as a significant

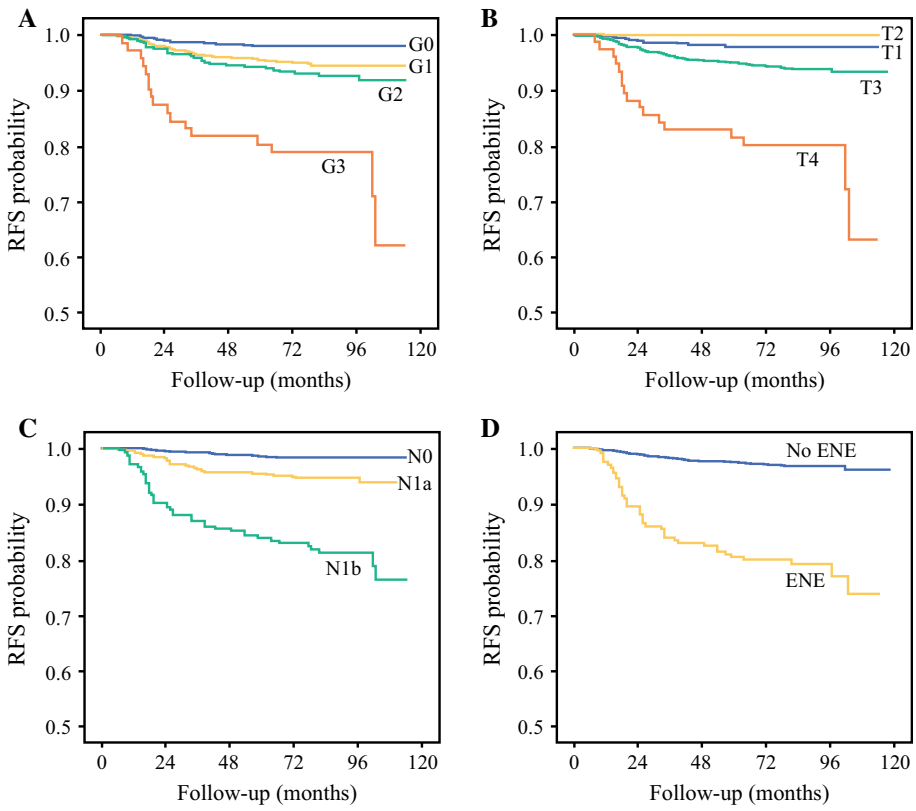

FIG. 1 Kaplan-Meier estimates showing recurrence-free survival (RFS) according to the extent of extrathyroidal extension (G0–G3) (**a**), T and N classifications (**b**, **c**), and presence of extranodal extension (ENE) (**d**). Log-rank test, $P < .001$

TABLE 3 Multivariate analyses on relationships between the clinicopathologic factors and pN+, N1b, or ENE

Variable	pN+		N1b		ENE	
	OR (95 % CI)[a]	*P* value	OR (95 % CI)[a]	*P* value	OR (95 % CI)[a]	*P* value
Age <45 years	1.80 (1.38–2.35)	<.001	1.50 (1.04–2.17)	.030	–	
Sex, male/female	2.35 (1.80–3.07)	<.001	–		–	
Tumor size >2 cm	3.00 (2.08–4.33)	<.001	2.19 (1.47–3.25)	<.001	–	
Tumor palpability	–		1.49 (1.05–2.13)	.027	–	
Multifocality	1.45 (1.05–1.99)	.023	1.42 (1.03–1.95)	.035	–	
Bilaterality	1.65 (1.16–2.36)	.006			–	
ETE						
No	1	<.001	1	<.001	1	.001
Microscopic	1.93 (1.52–2.47)	<.001	1.67 (1.06–2.62)	.027	1.40 (0.81–2.41)	.233
Minimal gross	3.44 (2.56–4.62)	<.001	2.69 (1.68–4.29)	<.001	2.06 (1.19–3.58)	.010
Massive gross	13.71 (5.99–31.36)	<.001	6.23 (3.28–11.84)	<.001	3.77 (1.83–7.79)	<.001
Nodal involvement						
Central neck	–		8.52 (5.55–13.10)	<.001	3.37 (1.69–6.72)	.001
Lateral neck	–		–		7.45 (4.75–11.68)	<.001
No. LN+ ≥3	–		–		2.68 (1.54–4.68)	.001
LNR >0.2	–		–		2.68 (1.66–4.33)	<.001

95 % CI 95 % confidence interval, *ENE* extranodal extension, *ETE* extrathyroidal extension, *LN+* positive lymph node, *LNR* lymph node ratio, *N1b* nodal metastasis to lateral neck compartment, *OR* odds ratio, *pN+* pathological nodal involvement

[a] Binary logistic regression analyses were performed with backward elimination from variables with *P* values <.05 on univariate analyses

TABLE 4 Crosstab analysis between the extent of ETE and pN+, N1b, or ENE

ETE	pN+			N1b			ENE		
	No	Yes	*P* value	No	Yes	*P* value	No	Yes	*P* value
No	422 (69.6)	184 (30.4)	<.001	573 (94.6)	33 (5.4)	<.001	580 (95.7)	26 (4.3)	<.001
Microscopic	346 (53.6)	299 (46.4)		571 (88.5)	74 (11.5)		582 (90.2)	63 (9.8)	
Minimal gross	135 (36.7)	233 (63.3)		278 (75.5)	90 (24.5)		291 (79.1)	77 (20.9)	
Massive gross	7 (9.5)	67 (90.5)		35 (47.3)	39 (52.7)		39 (52.7)	35 (47.3)	

ENE extranodal extension, *ETE* extrathyroidal extension, *N1b* nodal metastasis to lateral neck compartment, *pN+* pathological nodal involvement

indicator of a poor prognosis.[25] The prognostic importance of ENE was first identified by Yamashita et al. in 1997 and Sugitani et al. in 1998, who reported the significant association of ENE with distant metastases and a poor prognosis.[5,26] All of Sugitani et al.'s cases of papillary thyroid microcarcinoma with ENE developed distant metastases.[26] Subsequently, multiple studies have reported that ENE predicts recurrence and worse cancer-specific survival.[6,7,10,18,22,27,28] Recent reports further examined the role of ENE as a significant predictor of neck level V metastases as well as disease persistence and systemic disease progression.[6,10] The present study supports the previous findings that the presence of ENE reflects a significant association with poor RFS outcomes. A considerable number of PTC patients might have clinically relevant, adverse histologic features in clinically negative central nodes, such as a large number of occult positive central nodes and occult nodes with ENE.[9] Intraoperative inspection and palpation are unable to reliably identify metastatic nodes and ENE, regardless of the experience of the surgeon.[9] Therefore, nodal metastasis or ENE might be better predicted by other clinical or intraoperative findings.[16,18]

The present study also showed a relationship among ETE, nodal metastasis, and ENE in PTC patients. Recently, Clain et al. showed the clinical significance of ETE for prediction of ENE in a retrospective cohort of 193 DTC patients with pathologically metastatic lymph nodes.[18] DTC with ETE had a 12-fold higher incidence of ENE than tumors confined within the thyroid gland, and after exclusion of T4 cases, tumors with minimal ETE had a 13-fold increased incidence of ENE compared with tumors without ENE (39 of 66 [59 %] vs 12 of 121 [10 %]; $P < .001$). Primary tumors with ETE and ENE were also larger than those without ETE and ENE (mean 2.3 vs 1.4 cm; $P = .004$). Their additional study suggested that small lymph nodes could have ENE, showing that 59 % of the metastatic nodes with ENE were smaller than the size of 1.5 cm that was previously reported by Ito et al. as a threshold size for disease recurrence.[28,29]

Our study confirmed the previous findings that extent of ETE predicts the presence of ENE as well as PTC outcomes.[15,16,18] In our study, gross but not microscopic ETE might predict pathological ENE. Furthermore, the present study provides clinically useful information on the prediction of lymph node metastases in addition to the presence of ENE, both predictors of an adverse outcome of PTC. Any tumors with microscopic or gross ETE were more likely to have nodal metastases in the central or lateral neck compartments. Gross ETE is easily detected during surgery, and its presence could be used to guide surgical extent in the neck. Our study suggests that when gross ETE is present, the thyroid gland, including malignant nodules, should be completely extirpated with combined neck dissection in the central neck to remove any nodal disease with potentially adverse pathologic features. Consistent with our findings, the new ATA management guidelines announced in 2015 recommend prophylactic CND in cases of PTC with cN0 T3 or T4 or cN1b, if the nodal information will be used to plan further therapeutic steps.[12]

The retrospective design is a major limitation that may have introduced potential biases that affected the results. Various pathologic subtypes were not considered in our analyses because of their very rare occurrence. Furthermore, most of our cases were clinically low-risk T1 tumors $\leq$2 cm that were surgically treated without a clinical observational trial.[30,31] The increased use of thyroid cancer screening in our country has contributed to the 15-fold increase in the rates of thyroid cancer diagnosis over the past 20 years.[32] Nonetheless, a high proportion of our cases had microscopic (38 %) or macroscopic (26 %) ETE, lymph node metastasis (56 %), and ENE (12 %), despite being small PTCs. Our study showing the relationship between the extent of ETE and nodal metastasis and ENE could be clinical useful information on the proper management of these patients.

In conclusion, our study showed that significant ETE, multifocality, nodal metastasis, and ENE are associated

with an increased risk of recurrence. The extent of ETE is important: Only massive macroscopic ETE but not microscopic or minimal macroscopic ETE is significantly associated with recurrence. In PTC patients with no clinical evidence of nodal metastasis or ENE, it is difficult to identify adverse pathological features prior to or during surgery. This study might provide clinically useful information in the intraoperative observation of gross ETE predicting nodal metastasis and ENE, and this information may be helpful in making decisions about the combined neck dissection of patients with PTC.

ACKNOWLEDGMENT This study was supported by a Grant (No. 2015R1A2A1A15054540) from the Basic Science Research Program through the National Research Foundation of Korea (NRF), Ministry of Science, ICT, and Future Planning and a Grant (No. HI15C2920) from the Korean Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), Ministry of Health & Welfare, Seoul, Republic of Korea (J.L. Roh).

DISCLOSURE The authors have declared no conflicts of interest.

REFERENCES

1. Roh JL, Kim JM, Park CI. Lateral cervical lymph node metastases from papillary thyroid carcinoma: pattern of nodal metastases and optimal strategy for neck dissection. *Ann Surg Oncol.* 2008;15:1177–82.
2. Viola D, Materazzi G, Valerio L, et al. Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study. *J Clin Endocrinol Metab.* 2015;100:1316–24.
3. de Meer SG, Dauwan M, de Keizer B, Valk GD, Borel Rinkes IH, Vriens MR. Not the number but the location of lymph nodes matters for recurrence rate and disease-free survival in patients with differentiated thyroid cancer. *World J Surg.* 2012;36: 1262–7.
4. Asanuma K, Kusama R, Maruyama M, Fujimori M, Amano J. Macroscopic extranodal invasion is a risk factor for tumor recurrence in papillary thyroid cancer. *Cancer Lett.* 2001;164: 85–9.
5. Yamashita H, Noguchi S, Murakami N, Kawamoto H, Watanabe S. Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. *Cancer.* 1997;80:2268–72.
6. Lango M, Flieder D, Arrangoiz R, et al. Extranodal extension of metastatic papillary thyroid carcinoma: correlation with biochemical endpoints, nodal persistence, and systemic disease progression. *Thyroid.* 2013;23:1099–105.
7. Park CH, Song CM, Ji YB, et al. Significance of the extracapsular spread of metastatic lymph nodes in papillary thyroid carcinoma. *Clin Exp Otorhinolaryngol.* 2015;8:289–94.
8. Edge SB BD, Compton CC, Fritz AG, Greene FL, Trotti A. *The American Joint Committee for Cancer (AJCC) Cancer Staging Manual. 7th ed.*: New York: Springer; 2010:87–96.
9. Scherl S, Mehra S, Clain J, et al. The effect of surgeon experience on the detection of metastatic lymph nodes in the central compartment and the pathologic features of clinically unapparent metastatic lymph nodes: what are we missing when we don't perform a prophylactic dissection of central compartment lymph nodes in papillary thyroid cancer? *Thyroid.* 2014;24:1282–8.
10. Shim MJ, Roh JL, Gong G, et al. Preoperative detection and predictors of level V lymph node metastasis in patients with papillary thyroid carcinoma. *Br J Surg.* 2013;100:497–503.
11. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19:1167–214.
12. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2016;26: 1–133.
13. Arora N, Turbendian HK, Scognamiglio T, Wagner PL, Goldsmith SJ, Zarnegar R, Fahey TJ 3rd. Extrathyroidal extension is not all equal: implications of macroscopic versus microscopic extent in papillary thyroid carcinoma. *Surgery.* 2008;144:942–7; discussion 947–8.
14. Rivera M, Ricarte-Filho J, Tuttle RM, et al. Molecular, morphologic, and outcome analysis of thyroid carcinomas according to degree of extrathyroid extension. *Thyroid.* 2010;20:1085–93.
15. Radowsky JS, Howard RS, Burch HB, Stojadinovic A. Impact of degree of extrathyroidal extension of disease on papillary thyroid cancer outcome. *Thyroid.* 2014;24:241–4.
16. Lee HS, Park C, Kim SW, Park T, Chun BK, Hong JC, Lee KD. Correlation of minimal extrathyroidal extension with pathologic features of lymph node metastasis in patients with papillary thyroid carcinoma. *J Surg Oncol.* 2015;112:592–6.
17. Chereau N, Buffet C, Tresallet C, Tissier F, Golmard JL, Leenhardt L, Menegaux F. Does extracapsular extension impact the prognosis of papillary thyroid microcarcinoma? *Ann Surg Oncol.* 2014;21:1659–64.
18. Clain JB, Scherl S, Dos Reis L, et al. Extrathyroidal extension predicts extranodal extension in patients with positive lymph nodes: an important association that may affect clinical management. *Thyroid.* 2014;24:951–7.
19. So YK, Kim MW, Son YI. Multifocality and bilaterality of papillary thyroid microcarcinoma. *Clin Exp Otorhinolaryngol.* 2015;8:174–8.
20. Vas Nunes JH, Clark JR, Gao K, et al. Prognostic implications of lymph node yield and lymph node ratio in papillary thyroid carcinoma. *Thyroid.* 2013;23:811–6.
21. Choi SY, Cho JK, Moon JH, Son YI. Metastatic lymph node ratio of central neck compartment has predictive values for locoregional recurrence in papillary thyroid microcarcinoma. *Clin Exp Otorhinolaryngol.* 2016;9:75–9.
22. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid.* 2012;22:1144–52.
23. Ito Y, Tomoda C, Uruno T, et al. Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival. *World J Surg.* 2006;30:780–6.
24. Nixon IJ, Ganly I, Patel S, et al. The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. *Surgery.* 2011;150:1242–9.
25. Spires JR, Robbins KT, Luna MA, Byers RM. Metastatic papillary carcinoma of the thyroid: the significance of extranodal extension. *Head Neck.* 1989;11:242–6.
26. Sugitani I, Yanagisawa A, Shimizu A, Kato M, Fujimoto Y. Clinicopathologic and immunohistochemical studies of papillary thyroid microcarcinoma presenting with cervical lymphadenopathy. *World J Surg.* 1998;22:731–7.

27. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab.* 2005;90:5723–9.
28. Ito Y, Higashiyama T, Takamura Y, et al. Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. *World J Surg.* 2007;31:2085–91.
29. Alpert EH, Wenig BM, Dewey EH, Su HK, Dos Reis L, Urken ML. Size distribution of metastatic lymph nodes with extranodal extension in patients with papillary thyroid cancer: a pilot study. *Thyroid.* 2015;25:238–41.
30. Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg.* 2010;34:28–35.
31. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg.* 2010;34:1222–31.
32. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"—screening and overdiagnosis. *N Engl J Med.* 2014;371:1765–7.