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The binary presence or absence of lymph node metastasis or extrathyroidal extension is not associated with survival in papillary thyroid cancers: Implications for staging systems

Hyun-Soo Zhang[a,b], Eun-Kyung Lee[c], Yuh-Seog Jung[c,d], Byung-Ho Nam[e], Boyoung Park[a,*]

[a] Department of Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea
[b] Department of Biomedical Informatics, College of Medicine, Yonsei University, Seoul, Republic of Korea
[c] Center for Thyroid Cancer, Head and Neck Oncology Clinic, National Cancer Center, Goyang, Republic of Korea
[d] Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Republic of Korea
[e] Herings, The Institute of Advanced Clinical and Biomedical Research, Seoul, Republic of Korea

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ABSTRACT

Background: The characteristics of diagnosed papillary thyroid cancer (PTC) have changed over time with the increasing trend of early diagnosis, and the survival impact of conventional prognostic factors such as lymph node metastasis (LNM) and extrathyroidal extension (ETE) is controversial. We investigated PTC prognostic factors for overall survival (OS) and disease specific survival (DSS), focusing on LNM, ETE, and their implications for PTC staging systems.

Methods: We assessed prognostic factors for OS and DSS in a nationwide sample of Korean PTC patients (N = 5192, median follow-up 121 months) using Cox regression. The binary presence or absence of LNM and ETE, as well as other measures of LNM and ETE, were examined for their survival impact. We also evaluated the relative performance of PTC staging systems before and after revising the staging criteria for LNM and ETE.

Results: The binary presence of LNM or ETE was not a prognostic factor for OS or DSS, nor were other various measures of LNM. However, the extent of ETE as none, microscopic, or gross independently influenced survival (OS hazard ratio for gross vs. none: 3.28, 95% confidence interval (CI) 1.97–5.46; DSS hazard ratio for gross vs. none: 3.75, 95% CI 1.59–8.81). The performance of PTC staging systems improved when the extent of ETE and/or location of LNM were used as staging components.

Conclusion: The extent of ETE and/or location of LNM may be better survival indicators than their binary presence or absence, and we propose staging criteria revisions to pertinent staging systems to better reflect the contemporary PTC population.

1. Introduction

Thyroid cancer incidence has increased worldwide over the past few decades, which is largely attributed to the increased detection of small, indolent papillary thyroid cancers (PTCs) [1,2]. Although thyroid cancer generally has a good prognosis, approximately 40,000 people still died from the disease globally in 2012 [1]. Moreover, thyroid cancer is now the third most common cancer in Korea, of which more than 90% are PTCs [3]. Hence, understanding the prognostic factors of PTC [4–10] to pinpoint high-risk patients is important.

The clinicopathological characteristics of diagnosed PTC have changed over time with the increasing trend of early diagnosis [11,12], and tumors are generally smaller (< 1 cm) with less extensive lymph node metastasis (LNM) and extrathyroidal extension (ETE) than before [11,13]. Although older age, larger tumors, and distant metastasis remain major prognostic factors [9,14], recent results demonstrated that

Abbreviations: AMES, age metastasis extent size; CI, confidence interval; DSS, disease-specific survival; EORTC, European Organization for Research and Treatment of Cancer; ETE, extrathyroidal extension; GAMES, grade age metastasis extent size; HR, hazard ratio; KCCR, Korea Central Cancer Registry; LNM, lymph node metastasis; MACIS, metastasis age complete-resection invasion size; NEST, National Epidemiologic Survey of Thyroid cancer; Noguchi, Noguchi thyroid clinic; NTCTCS, National Thyroid Cancer Treatment Cooperative Study; OS, overall survival; OSU, Ohio State University; PTC, papillary thyroid cancer; PVE, proportion of variation explained; TNM, tumor node metastasis; UAB & MDA, University of Alabama & MD Anderson

* Corresponding author at: Department of Medicine, College of Medicine, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul, 04763, Republic of Korea.
E-mail addresses: hszhang@yuhs.ac (H.-S. Zhang), waterfol@ncc.re.kr (E.-K. Lee), jysorl@ncc.re.kr (Y.-S. Jung), byunghonam@heringsglobal.com (B.-H. Nam), hayejine@hanmail.net (B. Park).

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small volume or number of LNM and microscopic ETE rarely affect PTC prognosis [12,15–17]. However, whether the binary presence or absence of these parameters compromise overall survival (OS) or disease specific survival (DSS) in PTC has not been extensively studied.

Additionally, several PTC staging systems, such as the National Thyroid Cancer Treatment Cooperative Study (NTCTCS) and Ohio State University (OSU) staging systems, include the binary presence of LNM or ETE as staging components [18–20]. Given the change in the characteristics of diagnosed PTC and its potential implications to prognostic factors such as LNM or ETE, these previously developed staging systems may not perform as well in populations with higher proportions of early-stage tumors.

In this context, the current study investigated PTC prognostic factors for OS and DSS in a nationwide cohort of Korean PTC patients [21] and examined the independent survival impact of LNM and ETE according to various measures. We also evaluated the performance of the TNM and other PTC staging systems in Korean PTCs and proposed revised staging criteria that may better discriminate survival risk.

2. Materials and methods

2.1. Study population

The current study population is from the Korea Central Cancer Registry (KCCR)'s National Epidemiologic Survey of Thyroid cancer (NEST), which is a nationally representative sample of thyroid cancer patients diagnosed in 1999, 2005, and 2008. Starting in 1999, the thyroid cancer incidence in Korea increased rapidly throughout the years 2005 and 2008 [21]. KCCR-NEST used a two-stage stratified random sampling procedure, which ensured that a proportional number of patients were selected by each region and hospital. The dataset contains demographic, clinicopathological, and treatment information, and is linked to Statistics Korea to identify patients' cause of death. Further details of KCCR-NEST have been described previously [21].

Among the 6846 initially sampled patients, 960 patients for whom corresponding hospitals refused to release information and 90 patients with incomplete medical records were excluded. Among the remaining 5,796 thyroid cancer patients, the current study population included PTC patients who were at least 19 years old without any other cancer at PTC diagnosis (N = 5,192). The clinically relevant variables from previous studies of PTC prognostic factors and staging systems were examined [9,12,18], such as age, sex, tumor size, LNM, ETE, multifocality, distant metastasis, and diagnostic method (Table 1). Missing data for all variables were dummy-coded as "Unknown" to prevent the exclusion of patients without complete variable records. Patient survival was defined as the time-to-event, event being patient death, and the study endpoints were OS and DSS. OS events were deaths due to any cause, and DSS events were deaths due to thyroid cancer (C73). Survival status was followed up until December 31, 2015, and the median follow-up time was 121 months (interquartile range 90–128 months).

All medical records were obtained with patient consent, and the current study was approved by the institutional review board of Hanyang University (HYI-18-199-1). The KCCR-NEST dataset is publicly available upon request (http://kccrsurvey.cancer.go.kr/index.do) [21].

2.2. Statistical analysis

The baseline characteristics of the study population are presented with frequencies and percentages for categorical variables, and with means and standard deviations for the continuous variable age. The Cochran-Armitage test was used to detect changes in the categorical variables over time, and one-way analysis of variance (ANOVA) was used for the continuous variable age. Kaplan-Meier survival curves were plotted to visualize OS and DSS by risk group in PTC staging systems, and Cox proportional hazards regression was used to identify prognostic factors for OS and DSS. Possible time-interaction and violation of the proportional hazards assumption was checked for all variables. Variables that were significant in the univariate analyses (P-value < 0.10) were included in the multivariate analysis to assess their independent impact on OS and DSS.

Other various measures of LNM and ETE were also defined to more closely examine their prognostic significance: "location of LNM" was defined as none (N0), central neck LNM (N1a), or lateral neck LNM (N1b); "number of LNM" was defined as the number of positive lymph nodes; "LNM ratio" was defined as the ratio of the number of positive lymph nodes to the total number of nodes examined; and "extent of ETE" was defined as none, microscopic ETE (limited to perithyroidal soft tissues), or gross ETE (invasion to adjacent structures), based on the collaborative staging manual for thyroid extension [22]. Similar definitions have been used previously [15,23,24].

Among the currently available PTC staging systems, eight of those applicable to KCCR-NEST [18,25] were evaluated for their performance in Korean PTCs: Age, Metastasis, Extent, Size (AMES), European Organization for Research and Treatment of Cancer (EORTC), Grade, Age, Metastasis, Extent, Size (GAMES), Noguchi Thyroid Clinic (Noguchi), NTCTCS, OSU, Tumor, Node, Metastasis (TNM) 8th edition, and University of Alabama and MD Anderson (UAB & MDA); the staging components of these systems are outlined in Supplementary Table 1. The Metastasis, Age, Complete resection, Invasion, Size (MACIS) staging system [18,19] was not included due to the unknown status of complete resection. We used Harrell's C-index [26] and the proportion of variation explained (PVE) [27] to quantify PTC staging system performance. Harrell's C-index is a concordance measure of how well the predicted outcome agrees with the actual outcome, and PVE is a generalized R^2 value that quantifies the degree of association between the outcome and a set of predictors.

All reported *P*-values were two-sided, and a *P*-value < 0.05 was considered statistically significant. We used SAS 9.4 (SAS Institute, Cary, NC, USA) and R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) for all analyses.

3. Results

Table 1 presents the current study population's baseline characteristics in total and by year. The proportion of tumors less than 1 cm changed significantly from 27.4% in 1999 to 66.7% in 2008, and the proportion of patients with distant metastasis decreased significantly over the three time periods. More patients were diagnosed by routine screening over time, and diagnosis by clinical symptoms decreased accordingly.

The prognostic factors for OS and DSS of Korean PTC patients are presented in Table 2. The prognostic factors for OS were age, sex, tumor size, extent of ETE, distant metastasis, diagnostic method, and smoking history in the multivariate analysis. The binary presence or absence of LNM or ETE was non-significant in the univariate analysis. The location of LNM was significantly associated with OS (hazard ratio (HR) 1.64, 95% confidence interval (CI) 1.03–2.60), but became non-significant in multivariate analysis. Other measures of LNM (number of LNM and LNM ratio) were non-significant in the univariate analysis. The extent of ETE was an independent prognostic factor for OS with a HR of 3.28 (95% CI 1.97–5.46) for gross ETE vs. no ETE. Males showed a 2.14 times higher OS hazard (95% CI 1.55–2.96) than females, and PTC diagnosis through clinical symptoms was significant (HR 1.51, 95% CI 1.06–2.15) vs. routine screening.

The prognostic factors for DSS were the same as those for OS, with the exception of smoking history (Table 2). Similar to the OS model, neither the binary presence of LNM or ETE nor other measures of LNM were independently associated with DSS. However, the extent of ETE independently influenced DSS, with a HR of 3.75 (95% CI 1.59–8.81) for gross ETE vs. no ETE.

We also examined how well PTC staging systems classified Korean

Table 1
Baseline characteristics of Korean papillary thyroid cancer (PTC) patients sampled in 1999, 2005, and 2008 (N = 5,192) by year. Values are the mean (standard deviation) for patient age and N (%) for other variables.

Variables	Total	Year			
		1999	2005	2008	*P* trend*
Overall N	5192	727	2143	2322	
Mean (SD) age at diagnosis:	46.6 (12.0)	45.5 (13.5)	47.0 (12.2)	46.5 (11.3)	0.008
Sex:					0.024
Male	770 (14.8)	99 (13.6)	287 (13.4)	384 (16.5)	
Female	4422 (85.2)	628 (86.4)	1856 (86.6)	1938 (83.5)	
Tumor size:					< .001
≤1.0 cm	2850 (54.9)	199 (27.4)	1102 (51.4)	1549 (66.7)	
1.1-2.0 cm	1424 (27.4)	222 (30.6)	646 (30.1)	556 (24.0)	
2.1-4.0 cm	566 (10.9)	182 (25.0)	250 (11.7)	134 (5.8)	
> 4.0 cm	105 (2.0)	38 (5.2)	43 (2.0)	24 (1.0)	
Unknown	247 (4.8)	86 (11.8)	102 (4.8)	59 (2.5)	
Lymph node metastasis (LNM):					< .001
No	2240 (43.1)	224 (30.8)	931 (43.4)	1085 (46.7)	
Yes	1889 (36.4)	274 (37.7)	746 (21.8)	869 (37.4)	
Unknown	1063 (20.5)	229 (31.5)	466 (34.8)	368 (15.9)	
Extrathyroidal extension (ETE):					0.074
No	2492 (48.0)	325 (44.7)	1080 (50.4)	1087 (46.8)	
Yes	2378 (45.8)	306 (42.1)	925 (43.2)	1147 (49.4)	
Unknown	322 (6.2)	96 (13.2)	138 (6.4)	88 (3.8)	
Multifocality:					0.320
Unifocal	3439 (66.2)	462 (63.5)	1428 (66.6)	1549 (66.7)	
Multifocal	1542 (29.7)	196 (27.0)	628 (29.3)	718 (30.9)	
Unknown	211 (4.1)	69 (9.5)	87 (4.1)	55 (2.4)	
Distant metastasis:					< .001
No	4870 (93.8)	645 (88.7)	2019 (94.2)	2206 (95.0)	
Yes	15 (0.3)	6 (0.8)	9 (0.4)	0 (0.0)	
Unknown	307 (5.9)	76 (10.5)	115 (5.4)	116 (5.0)	
Diagnostic method:					< .001
Screening	2393 (46.1)	105 (14.4)	997 (46.5)	1291 (55.6)	
Clinical	1584 (30.5)	367 (50.5)	699 (32.6)	518 (22.3)	
Unknown	1215 (23.4)	255 (35.1)	447 (20.9)	513 (22.1)	
Other thyroidal disease:					0.054
None	2975 (57.3)	475 (65.3)	1244 (58.0)	1256 (54.1)	
Hashimoto's thyroiditis	1066 (20.5)	87 (12.0)	430 (20.1)	549 (23.6)	
Other	1086 (20.9)	151 (20.8)	446 (20.8)	489 (21.1)	
Unknown	65 (1.3)	14 (1.9)	23 (1.1)	28 (1.2)	
Family history of thyroid cancer:					0.283
No	4113 (79.2)	516 (71.0)	1728 (80.6)	1869 (80.5)	
Yes	169 (3.3)	18 (2.5)	67 (3.1)	84 (3.6)	
Unknown	910 (17.5)	193 (26.5)	348 (16.3)	369 (15.9)	
Smoking history:					0.283
Never smoked	3785 (72.9)	405 (55.7)	1605 (74.9)	1775 (76.5)	
Ever smoked	303 (5.8)	33 (4.5)	109 (5.1)	161 (6.9)	
Unknown	1104 (21.3)	289 (39.8)	429 (20.0)	386 (16.6)	
Drinking history:					< .001
Nondrinker	3428 (66.0)	386 (53.1)	1449 (67.6)	1593 (68.6)	
Drinker	690 (13.3)	48 (6.6)	273 (12.7)	369 (15.9)	
Unknown	1074 (20.7)	293 (40.3)	421 (19.7)	360 (15.5)	
Surgical extent:					0.004
Total thyroidectomy	4031 (77.7)	532 (73.2)	1646 (76.8)	1853 (79.8)	
Lobectomy	666 (12.8)	84 (11.5)	262 (12.2)	320 (13.8)	
Other	261 (5.0)	72 (9.9)	113 (5.3)	76 (3.3)	
Unknown	234 (4.5)	39 (5.4)	122 (5.7)	73 (3.1)	
Radioactive iodine (RAI):					0.012
No	2785 (53.6)	411 (56.5)	1176 (54.9)	1198 (51.6)	
Yes	2407 (46.4)	316 (43.5)	967 (45.1)	1124 (48.4)	
Events:†					0.002
Overall	**212 (100.0)**	**84 (100)**	**89 (100)**	**39 (100)**	
Thyroid cancer-specific	77 (36.3)	41 (48.8)	26 (29.2)	10 (25.6)	
Other cancer-specific	60 (28.3)	27 (32.1)	21 (23.6)	12 (30.8)	
Other causes-specific	75 (35.4)	16 (19.1)	42 (47.2)	17 (43.6)	

Abbreviations: SD = Standard deviation.

* *P* for trend between increasing year and the variable under consideration using the Cochran-Armitage trend test. The *P* value for the continuous variable age is from one-way analysis of variance (ANOVA), and does not indicate trend.

† Overall event = death due to any cause; Thyroid cancer-specific event = death due to thyroid cancer; Other cancer-specific event = death due to cancer other than thyroid cancer; Other causes-specific event = death due to a cause other than cancer.

Table 2
Papillary thyroid cancer (PTC) prognostic factors for overall survival (OS) and disease-specific survival (DSS) in Korean PTC patients sampled in 1999, 2005, and 2008 (N = 5,192).

Variable	Category	Overall survival (OS)				Disease-specific survival (DSS)			
		Univariate* HR (95% CI)	*P*-val.	Multivariate† HR (95% CI)	*P*-val.	Univariate* HR (95% CI)	*P*-val.	Multivariate† HR (95% CI)	*P*-val.
Age		1.13 (1.12-1.15)	< .001	**1.12 (1.11-1.14)**	**< .001**	1.16 (1.13-1.19)	< .001	**1.13 (1.11-1.16)**	**< .001**
Sex	Female	1.0		1.0		1.0		1.0	
	Male	2.43 (1.80-3.28)	< .001	**2.14 (1.55-2.96)**	**< .001**	3.12 (1.97-5.08)	< .001	**2.94 (1.81-4.80)**	**< .001**
Tumor size (cm)	≤1.0	1.0		1.0		1.0		1.0	
	1.1-2.0	0.99 (0.68-1.48)	0.996	0.79 (0.53-1.18)	0.254	1.28 (0.57-2.89)	0.550	0.91 (0.39-2.09)	0.819
	2.1-4.0	2.04 (1.37-3.05)	< .001	0.93 (0.60-1.45)	0.753	5.47 (2.73-10.96)	< .001	1.94 (0.91-4.15)	0.088
	> 4.0	6.51 (4.48-9.45)	< .001	**2.02 (1.13-3.60)**	**0.017**	16.11 (7.12-36.45)	< .001	**4.79 (1.97-11.64)**	**0.001**
Presence of LNM	No	1.0				1.0		1.0	
	Yes	1.18 (0.83-1.67)	0.348			2.02 (1.14-3.61)	0.017	1.12 (0.60-2.09)	0.731
Location of LNM‡	*None*	*1.0*		*1.0*		*1.0*		*1.0*	
	Central neck	*1.24 (0.80-1.94)*	*0.339*	*1.30 (0.82-2.05)*	*0.262*	*1.55 (0.71-3.35)*	*0.269*	*1.34 (0.60-2.98)*	*0.474*
	Lateral neck	*1.64 (1.03-2.60)*	*0.038*	*0.81 (0.49-1.36)*	*0.434*	*4.24 (2.20-8.16)*	*< .001*	*1.51 (0.72-3.18)*	*0.273*
Number of LNM‡		*1.02 (0.98-1.05)*	*0.431*			*1.02 (0.97-1.08)*	*0.415*		
LNM ratio‡		*1.26 (0.68-2.31)*	*0.463*			*2.49 (0.97-6.42)*	*0.059*		
Presence of ETE	No	1.0		1.0		1.0		1.0	
	Yes	1.56 (1.14-2.13)	0.006	1.11 (0.80-1.55)	0.535	2.49 (1.39-4.48)	0.002	1.37 (0.73-2.55)	0.327
Extent of ETE‡	*None*	*1.0*		*1.0*		*1.0*		*1.0*	
	Microscopic	*1.25 (0.89-1.75)*	*0.189*	*0.94 (0.66-1.33)*	*0.722*	*1.88 (1.01-3.50)*	*0.048*	*1.13 (0.59-2.18)*	*0.716*
	Gross	*5.69 (3.56-9.08)*	*< .001*	***3.28 (1.97-5.46)***	***< .001***	*11.04 (5.12-23.81)*	*< .001*	***3.75 (1.59-8.81)***	***0.002***
Presence of multifocality	No	1.0				1.0			
	Yes	1.06 (0.77-1.48)	0.706			1.04 (0.59-1.84)	0.897		
Distant metastasis	No	1.0		1.0		1.0		1.0	
	Yes	14.15 (6.63-30.18)	< .001	**4.33 (1.84-10.21)**	**0.001**	37.51 (16.1-87.42)	< .001	**10.98 (4.06-29.67)**	**< .001**
Other thyroidal disease	None	1.0		1.0		1.0		1.0	
	Hashimoto's thyroiditis	0.30 (0.17-0.52)	< .001	0.57 (0.32-1.02)	0.059	0.15 0.05-0.49)	0.002	0.43 (0.13-1.42)	0.167
	Other	1.08 (0.79-1.49)	0.620	1.01 (0.72-1.42)	0.963	0.62 (0.34-1.12)	0.114	0.77 (0.40-1.46)	0.419
Diagnostic method	Screening	1.0		1.0		1.0		1.0	
	Clinical	2.04 (1.45-2.87)	< .001	**1.51 (1.06-2.15)**	**0.023**	4.08 (2.07-8.05)	< .001	**2.71 (1.32-5.53)**	**0.006**
Smoking history	No	1.0		1.0		1.0		1.0	
	Yes	2.36 (1.52-3.67)	< .001	**1.81 (1.11-2.97)**	**0.018**	2.66 (1.30-5.43)	0.007	1.25 (0.55-2.84)	0.600

Abbreviations: CI = Confidence interval; ETE = Extrathyroidal Extension; HR = Hazard ratio; LNM = Lymph node metastasis.

* Univariate analysis was conducted using a cut-off *P*-value < 0.10, and results are presented for all significant variables with the exception of LNM, ETE, and multifocality variables, for which univariate analysis results are presented regardless of statistical significance.

† All statistically significant variables in the univariate analysis (*P*-value < 0.10) were included in the multivariate model, and the statistically significant multivariate analysis results (*P*-value < 0.05) are presented in bold.

‡ Univariate and multivariate analysis results are italicized for the variables "location of LNM", "number of LNM", "LNM ratio", and "extent of ETE", which are other measures of LNM and ETE, examined for their impact on survival in Korean PTC patients.

Table 3
Risk group classification by 8 papillary thyroid cancer (PTC) staging systems for Korean PTC patients sampled in 1999, 2005, and 2008 (N = 5,192). All values are N (%).

Risk group*	AMES	EORTC	GAMES	Noguchi	NTCTCS	OSU	TNM 8th	UAB &MDA
Stage I or Low	3799 (73.2)	798 (15.4)	2062 (39.7)	3816 (73.5)	2664 (51.3)	1266 (24.4)	4386 (84.5)	3029 (58.3)
Stage II	–	1948 (37.5)	–	–	1301 (25.0)	1321 (25.4)	403 (7.8)	–
Stage III or Intermed.	–	1612 (31.1)	2630 (50.6)	866 (16.7)	1029 (19.8)	2404 (46.3)	29 (0.6)	1841 (35.5)
Stage IV	–	370 (7.1)	–	–	12 (0.2)	15 (0.3)	27 (0.5)	–
Stage V or High	1049 (20.2)	7 (0.1)	107 (2.1)	90 (1.7)	–	–	–	15 (0.3)
Unknown	344 (6.6)	457 (8.8)	393 (7.6)	420 (8.1)	186 (3.6)	186 (3.6)	347 (6.7)	307 (5.9)
Total	5192 (100.0)	5192 (100.0)	5192 (100.0)	5192 (100.0)	5192 (100.0)	5192 (100.0)	5192 (100.0)	5192 (100.0)

Abbreviations: AMES = Age, Metastasis, Extent, Size; EORTC = European Organization for Research and Treatment of Cancer; GAMES = Grade, Age, Metastasis, Extent, Size; Noguchi = Noguchi thyroid clinic; NTCTCS = National Thyroid Cancer Treatment Cooperative Study; OSU = Ohio State University; TNM = Tumor, Node, Metastasis; UAB & MDA = University of Alabama and MD Anderson.

* The AMES staging system classifies patients into either low- or high-risk groups, and GAMES, Noguchi, and UAB & MDA staging systems classify patients into low-, intermediate-, or high-risk groups. Other staging systems classify patients into stages I through IV (NTCTCS, OSU, TNM 8th) or groups I through V (EORTC).

PTC survival risk (Tables 3, 4 and Fig. 1). The number of patients included in the highest stage or risk group for EORTC, NTCTCS, OSU, TNM 8th, and UAB & MDA staging ranged from only 7 to 27 patients (Table 3). AMES staging classified a large proportion of patients as high risk (20.2%), with the binary presence of ETE upstaging patient risk. The proportion of stage III patients in NTCTCS and OSU staging was large (19.8% and 46.3%, respectively), mainly because the binary presence of LNM or ETE upstaged patient risk. The TNM 8th edition seemed to greatly downstage patient risk overall, classifying 84.5% of patients as stage I.

Fig. 1 shows OS and DSS Kaplan-Meier survival curves for each staging system. EORTC, Noguchi, and GAMES staging performed relatively well and showed a distinct separation of survival curves. The survival difference between stage III and IV patients of the TNM 8th edition was unclear after the first 90 months of follow-up. NTCTCS and OSU staging performed relatively poorly in stratifying the survival risk

Table 4
Harrell's C-index, proportion of variation explained (PVE, %), and their respective rankings for 8 papillary thyroid cancer (PTC) staging systems applied to Korean PTC patients sampled in 1999, 2005, and 2008 (N = 5,192).

StagingSystem*	Overall survival (OS)				Disease-specific survival (DSS)			
	C-index (95% CI)	PVE	C-index Ranking	PVE Ranking	C-index (95% CI)	PVE	C-index Ranking	PVE Ranking
EORTC	0.779 (0.732-0.826)	12.6	1	1	0.851 (0.767-0.935)	16.1	1	1
Noguchi	0.742 (0.707-0.777)	9.0	2	2	0.821 (0.762-0.880)	12.8	2	2
GAMES	0.704 (0.661-0.747)	6.8	4	3	0.791 (0.718-0.864)	12.7	3	3
TNM 8th	0.634 (0.610-0.658)	5.3	7	5	0.728 (0.687-0.769)	9.7	7	4
UAB & MDA	0.710 (0.671-0.749)	6.7	3	4	0.754 (0.689-0.819)	8.7	4	5
AMES	0.670 (0.637-0.703)	4.4	6	6	0.751 (0.694-0.808)	7.7	5	6
NTCTCS	0.676 (0.635-0.717)	3.7	5	7	0.751 (0.682-0.820)	6.9	6	7
OSU	0.564 (0.521-0.607)	1.3	8	8	0.637 (0.566-0.708)	4.0	8	8

Abbreviations: AMES = Age, Metastasis, Extent, Size; EORTC = European Organization for Research and Treatment of Cancer; GAMES = Grade, Age, Metastasis, Extent, Size; Noguchi = Noguchi thyroid clinic; NTCTCS = National Thyroid Cancer Treatment Cooperative Study; OSU = Ohio State University; TNM = Tumor, Node, Metastasis; UAB & MDA = University of Alabama and MD Anderson.

* Staging systems are ordered by PVE ranking for disease-specific survival.

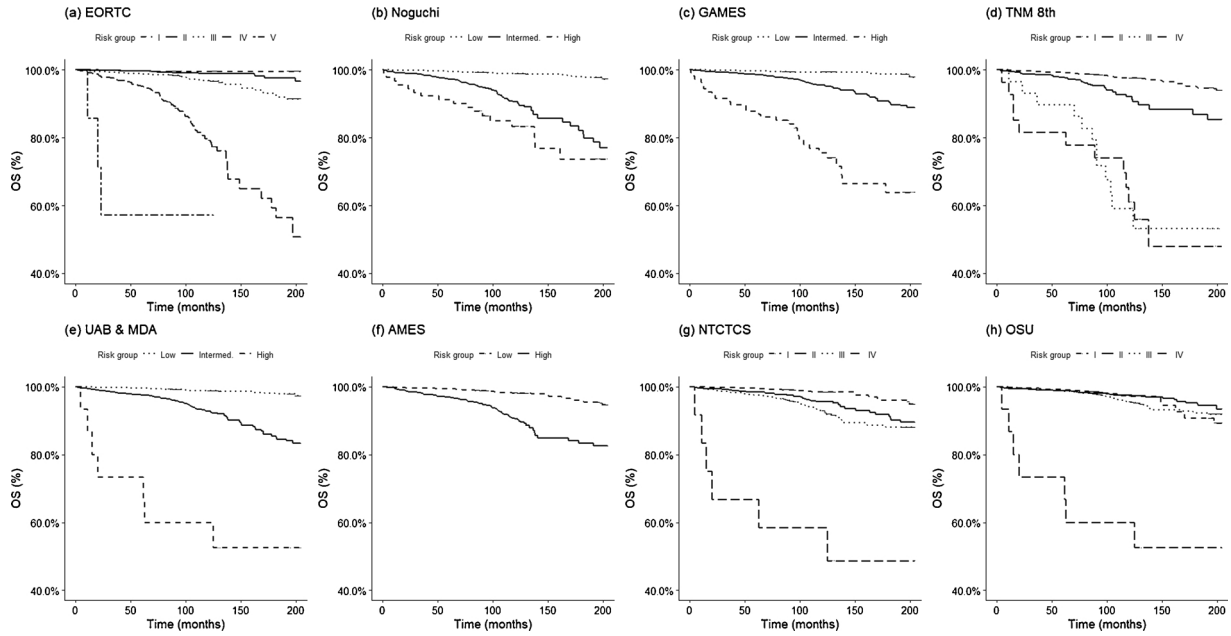

Fig. 1. Kaplan-Meier overall survival (OS) curves by risk group for 8 papillary thyroid cancer (PTC) staging systems applied to Korean PTC patients sampled in 1999, 2005, and 2008 (N = 5,192, overall events = 212).

of Korean PTCs.

Table 4 quantifies the performance of the eight staging systems in terms of concordance (Harrell's C-index) and PVE. EORTC staging showed the highest C-index and PVE with 0.779 (0.732-0.826) and 12.6% for OS, and 0.851 (0.767-0.935) and 16.1% for DSS, respectively. As their poorly separated survival curves indicate, NTCTCS and OSU staging showed the worst C-index and PVE when applied to Korean PTC (Fig. 1, Fig. 2).

After revising the binary presence of LNM and/or ETE criteria in NTCTCS and OSU staging to the location of LNM (none, central neck, or lateral neck) and/or the extent of ETE (none, microscopic, or gross), their predictive performances generally improved in terms of C-index and PVE percentage changes (Table 5). The supplementary figures show the shows survival curves before vs. after staging system revision, where stages I to III curves became markedly more distinguishable after revision.

4. Discussion

In the current study, the prognostic factors for OS in Korean PTC patients were older age, male sex, larger tumor size, gross ETE, distant metastasis, diagnosis through clinical symptoms, and positive smoking history, while the prognostic factors for DSS were identical to those for OS with the exception of smoking history. The binary presence or absence of LNM or ETE was not a prognostic factor for survival, and other measures of LNM (location, number, and ratio of metastatic lymph nodes) were also not associated with survival. However, the extent of ETE as none, microscopic, or gross was an independent predictor of OS and DSS. When we compared the performance of different PTC staging systems in Korean PTCs, NTCTCS and OSU staging that used the binary presence of LNM and/or ETE as staging components performed relatively poorly, and instead using the location of LNM and/or the extent of ETE improved their performance.

Although LNM is an established prognostic factor for PTC recurrence [13,23], its association with survival is controversial. Some studies showed that the binary presence of LNM itself was linked to worse survival [6,8], while others reported that only the more severe lateral neck LNM (N1b), but not central neck LNM (N1a), affected survival [4,14], and still others stated that LNM was not associated with survival at all [7,9]. In the current study, lateral neck LNM and the binary presence of LNM, were not associated with OS or DSS. Additionally, the number of LNM and LNM ratio were not associated with survival in our

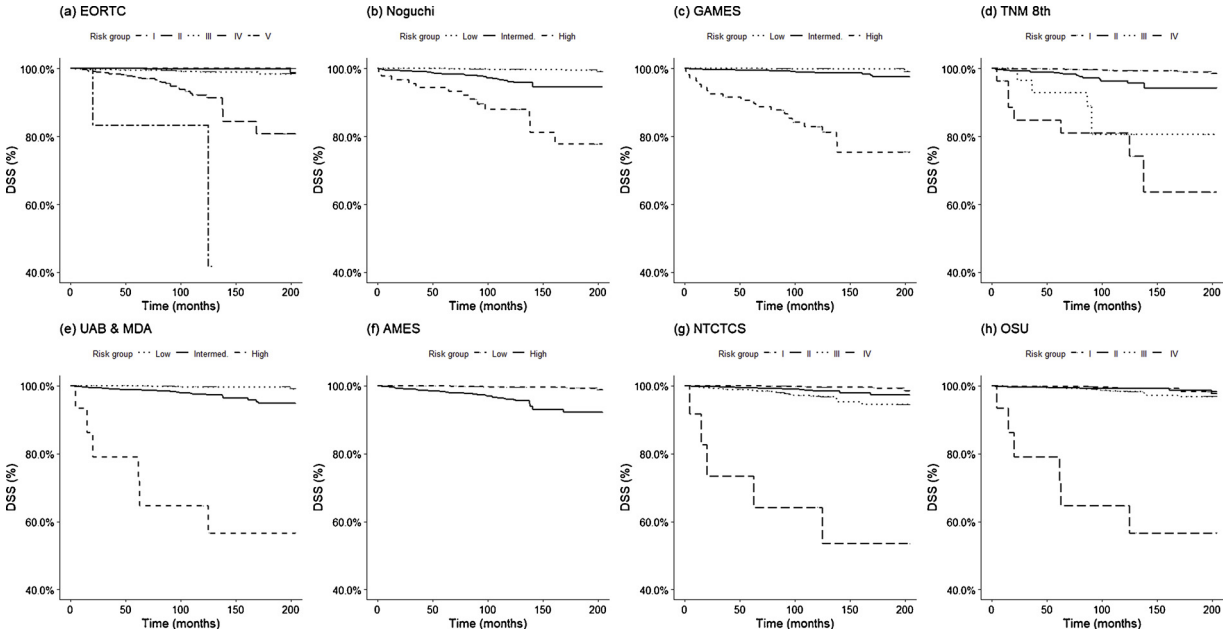

Fig. 2. Kaplan-Meier disease-specific survival (DSS) curves by risk group for 8 papillary thyroid cancer (PTC) staging systems applied to Korean PTC patients sampled in 1999, 2005, and 2008 (N = 5,192, thyroid cancer-specific events = 77).

study, which was in contrast to some studies that showed compromised survival by these variables [24,28]. Our results are compatible with a recent review that LNM is not associated with DSS in PTCs [12] and with the TNM 8th edition, where the binary presence of LNM no longer upstages a patient to stage III, and lateral neck LNM does not upstage a patient to stage IV [25].

ETE is a more concrete prognostic factor for PTC survival, but its degree of impact is still controversial. While some reported worse survival in those with any ETE [4,6,7,29], other studies further divided ETE into microscopic or gross ETE and showed no survival risk for microscopic ETE [15,16,30,31]. The proportion of gross ETE in our study decreased from 12.7% in 1999 to only 3.6% in 2008, and the overall presence of ETE became a less severe condition for patients over time. Accordingly, the binary presence of ETE had no impact on either OS or DSS in our study. However, when ETE was divided into none, microscopic or gross, gross ETE showed compromised OS and DSS compared to none, while microscopic ETE did not. Since survival differences existed even within gross ETE by the degree and site of extension [30], the extent of ETE may be more useful in discriminating survival risk than its binary presence or absence. The TNM 8th edition seems to accurately reflect this situation, with only gross ETE upstaging a patient's survival risk [25].

Older age, larger tumor size, distant metastasis, and male sex are well-known prognostic factors for PTC survival [4,9,10], and their prognostic significance was confirmed in our study (Table 2). The significant influence of sex on PTC survival in our study is noteworthy, where males had a higher OS and DSS hazard than females, which has been confirmed in some studies [4,6,14] but not others [7,8,10]. Regarding tumor multifocality, our results showed no association between the binary presence of multifocality and patient survival, while another study reported that an increased number of tumor foci (the extent of multifocality) was linked to worse cancer-specific survival [32].

Among PTC staging systems applied to Korean PTCs, EORTC staging showed the best performance, with the highest C-index and PVE (Table 4). EORTC staging also incorporated male sex as a staging component, which was a good fit for the significantly worse survival of male patients in the current study. In previous studies, MACIS, TNM, and EORTC were the best performers in 589 Chinese PTC patients [18], and the three also performed the best in 293 Austrian PTC patients [19]. The recently updated TNM 8th edition showed worse discrimination compared to other staging systems such as EORTC staging (Table 4), which was surprising considering that the TNM 8th edition staging criteria for LNM and ETE were very much in agreement with our study results. Fewer patients were classified as high risk (stages III or IV) by the TNM 8th edition compared to other staging systems (Table 3), which may indicate that some high-risk patients were overly

Table 5
Harrell's C-index, proportion of variation explained (PVE, %), and their respective percentage changes after staging system revisions from using the binary presence of LNM and/or ETE to using the location of LNM and/or the extent of ETE as staging components for the NTCTCS and OSU papillary thyroid cancer (PTC) staging systems, applied to Korean PTC patients sampled in 1999, 2005, and 2008 (N = 5,192).

Revised Staging system*	C-index and PVE after staging system revision				% Change of C-index and PVE after staging system revision			
	Overall survival		Disease-specific survival		Overall survival		Disease-specific survival	
	C-index (95% CI)	PVE	C-index (95% CI)	PVE	C-index % change	PVE% change	C-index % change	PVE% change
NTCTCS	0.678 (0.637-0.719)	4.3	0.787 (0.720-0.854)	9.6	0.3	16.1	4.8	38.2
OSU	0.596 (0.555-0.637)	3.2	0.713 (0.644-0.782)	7.8	5.7	141.3	11.9	97.4

Abbreviations: ETE = Extrathyroidal Extension; LNM = Lymph node metastasis; NTCTCS = National Thyroid Cancer Treatment Cooperative Study; OSU = Ohio State University.

* The NTCTCS staging component "binary presence of LNM" was replaced by the "location of LNM", and the OSU staging components "binary presence of LNM" and "binary presence of ETE" were replaced by the "location of LNM" and the "extent of ETE".

downstaged. For example, the TNM 8th edition classified patients aged ≥55 with tumors > 4 cm but without gross ETE as stage II (N = 26, among which 9 experienced an OS event), whereas EORTC staging classified such patients as stages III (N = 7 and no events) or IV (N = 19 and 9 OS events). While some Korean studies showed that the TNM 8th edition predicted DSS of differentiated thyroid cancers better than the 7th edition [33,34], further studies are needed to evaluate its prognostic value in PTCs.

Among other staging systems, NTCTCS and OSU staging performed relatively poorly. The two staging systems commonly applied the binary presence of LNM and/or ETE as staging components; however, using the location of LNM and/or the extent of ETE instead generally improved their performance (Table 5). Although the location of LNM was not an independent prognostic factor for survival in our study, it discriminated patient survival better than the binary presence or absence of LNM when applied to NTCTCS staging. Other studies have shown that lateral neck LNM significantly reflected worse DSS and disease-free survival (*P*-value < .0001) whereas central neck LNM did not [4,14]. Accordingly, upstaging only those with the more severe lateral neck LNM may enable better survival discrimination. We must also consider that NTCTCS and OSU staging were developed in the 1990s (1998 and 1994, respectively) [18–20] when palpation by hand was a common diagnostic method, in contrast to today's detection of microcarcinomas via ultrasound imaging. Hence, the binary presence of LNM and/or ETE usually reflected larger macroscopic disease of more clinical relevance and including these binary variables as staging components made much more sense at that time. In other words, these staging systems were developed at a time when PTC presentation was very different with larger primaries and more advanced nodal disease, and thus may not apply very well to current clinical experience.

This is the first nationwide study on prognostic factors for PTC survival in Korea, but has some inherent limitations. First, no recurrence information was included in KCCR-NEST, so we were unable to examine prognostic factors for recurrence. Additionally, no information was available on histological subtypes (tall cell, columnar cell, etc.) or molecular markers (BRAF, TERT, etc.). Third, the small number of thyroid cancer-specific events resulted in less precise estimates of prognostic factors and staging system performance for DSS. Fourth, KCCR-NEST has a higher proportion of missing values regarding LNM status (20.5%), so the assessment of LNM as a prognostic factor for survival may be relatively limited. Regarding a generally decreasing proportion of missing values over time, sensitivity analyses were conducted comparing different time periods (1999, 2005, and 2008) under the missing at random (MAR) assumption to ensure that the effect estimates of LNM and ETE on PTC survival were qualitatively similar.

Conclusively, in a nationwide cohort of Korean PTC patients, the binary presence or absence of LNM or ETE were not prognostic factors for survival, nor were the location of LNM, number of LNM, or LNM ratio. However, the extent of ETE as none, microscopic, or gross was an independent prognostic factor for both OS and DSS. Among PTC staging systems, NTCTCS and OSU staging systems that use the binary presence of LNM and/or ETE as staging criteria performed poorly compared to others, and using the location of LNM and/or the extent of ETE instead improved their performance. Therefore, the extent or severity of LNM and/or ETE may be better predictors of PTC survival than their binary presence or absence, and we propose staging criteria revisions to pertinent staging systems to better assess survival risk in today's PTC population. Our study demonstrates the need for PTC staging systems to be adjusted periodically as patient characteristics change over time. Although the TNM system is periodically updated, the 8th edition may have overly downstaged some high risk patients in the current study, and further validation of its predictive performance would be beneficial.

Authorship contribution statement

Hyun-Soo Zhang analyzed and interpreted the data and wrote the manuscript. Eun-Kyung Lee and Yu-Seog Jung interpreted the study results, provided critical feedback, and revised the Discussion section of the manuscript. Byung-Ho Nam provided statistical expertise in the Methods section and critically revised the Results section of the manuscript. Boyoung Park conceived the study design and wrote and reviewed the manuscript. All authors read and approved the final version of the manuscript submitted.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101589.

References

[1] C. La Vecchia, et al., Thyroid cancer mortality and incidence: a global overview, Int. J. Cancer 136 (9) (2015) 2187–2195.
[2] S. Franceschi, S. Vaccarella, Thyroid cancer: an epidemic of disease or an epidemic of diagnosis? Int. J. Cancer 136 (11) (2015) 2738–2739.
[3] K.W. Jung, et al., Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2015, Cancer Res. Treat. 50 (2) (2018) 303–316.
[4] M.J. Jeon, et al., Disease-specific mortality of differentiated thyroid cancer patients in Korea: a multicenter cohort study, Endocrinol. Metab. (Seoul) 32 (4) (2017) 434–441.
[5] H. Choi, et al., Secular trends in the prognostic factors for papillary thyroid cancer, Eur. J. Endocrinol. 171 (5) (2014) 667–675.
[6] X.M. Yu, et al., Should all papillary thyroid microcarcinomas be aggressively treated? An analysis of 18,445 cases, Ann. Surg. 254 (4) (2011) 653–660.
[7] B.H. Lang, et al., Prognostic factors in papillary and follicular thyroid carcinoma: their implications for cancer staging, Ann. Surg. Oncol. 14 (2) (2007) 730–738.
[8] C. Passler, et al., Prognostic factors of papillary and follicular thyroid cancer: differences in an iodine-replete endemic goiter region, Endocr. Relat. Cancer 11 (1) (2004) 131–139.
[9] A.R. Shaha, Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer, Laryngoscope 114 (3) (2004) 393–402.
[10] J.P. Shah, et al., Prognostic factors in differentiated carcinoma of the thyroid gland, Am. J. Surg. 164 (6) (1992) 658–661.
[11] B.Y. Cho, et al., Changes in the clinicopathological characteristics and outcomes of thyroid cancer in Korea over the past four decades, Thyroid 23 (7) (2013) 797–804.
[12] S.L. Gillanders, J.P. O'Neill, Prognostic markers in well differentiated papillary and follicular thyroid cancer (WDTC), Eur. J. Surg. Oncol. 44 (3) (2018) 286–296.
[13] M.J. Jeon, et al., Recent changes in the clinical outcome of papillary thyroid carcinoma with cervical lymph node metastasis, J. Clin. Endocrinol. Metab. 100 (9) (2015) 3470–3477.
[14] Y. Ito, A. Miyauchi, Prognostic factors and therapeutic strategies for differentiated carcinomas of the thyroid, Endocr. J. 56 (2) (2009) 177–192.
[15] I.D. Hay, et al., Minimal extrathyroid extension in papillary thyroid carcinoma does not result in increased rates of either cause-specific mortality or postoperative tumor recurrence, Surgery 159 (1) (2016) 11–19.
[16] Z. Al-Qurayshi, et al., Minimal extrathyroidal extension does not affect survival of well-differentiated thyroid cancer, Endocr. Relat. Cancer 24 (5) (2017) 221–226.
[17] Y. Ito, A. Miyauchi, Prognostic factors of papillary and follicular carcinomas in

Japan based on data of kuma hospital, J. Thyroid Res. (2012) 973497.
[18] B.H. Lang, et al., Staging systems for papillary thyroid carcinoma: a review and comparison, Ann. Surg. 245 (3) (2007) 366–378.
[19] C. Passler, et al., Application of staging systems for differentiated thyroid carcinoma in an endemic goiter region with iodine substitution, Ann. Surg. 237 (2) (2003) 227–234.
[20] J.D. Brierley, et al., A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example, Cancer 79 (12) (1997) 2414–2423.
[21] S. Park, et al., Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study, BMJ 355 (2016) i5745.
[22] Collaborative Stage Data Set, Thyroid CS Extension. http://web2.facs.org/cstage0205/thyroid/Thyroid_bby.html, 2013, (Accessed 23 July 2019).
[23] Y. Hwangbo, et al., Long-term recurrence of small papillary thyroid cancer and its risk factors in a Korean multicenter study, J. Clin. Endocrinol. Metab. 102 (2) (2017) 625–633.
[24] D.F. Schneider, H. Chen, R.S. Sippel, Impact of lymph node ratio on survival in papillary thyroid cancer, Ann. Surg. Oncol. 20 (6) (2013) 1906–1911.
[25] R.M. Tuttle, B. Haugen, N.D. Perrier, Updated american joint committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid Cancer (eighth edition): what changed and why? Thyroid 27 (6) (2017) 751–756.
[26] F.E. Harrell Jr., K.L. Lee, D.B. Mark, Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors, Stat. Med. 15 (4) (1996) 361–387.
[27] M. Schemper, J. Stare, Explained variation in survival analysis, Stat. Med. 15 (19) (1996) 1999–2012.
[28] M.A. Adam, et al., Presence and number of lymph node metastases are associated with compromised survival for patients younger than age 45 years with papillary thyroid cancer, J. Clin. Oncol. 33 (21) (2015) 2370–2375.
[29] L.M. Youngwirth, et al., Extrathyroidal extension is associated with compromised survival in patients with thyroid cancer, Thyroid 27 (5) (2017) 626–631.
[30] M. Hotomi, et al., A novel definition of extrathyroidal invasion for patients with papillary thyroid carcinoma for predicting prognosis, World J. Surg. 36 (6) (2012) 1231–1240.
[31] I.J. Nixon, et al., The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer, Surgery 150 (6) (2011) 1242–1249.
[32] N. Qu, et al., Number of tumor foci predicts prognosis in papillary thyroid cancer, BMC Cancer 14 (2014) 914.
[33] T.H. Kim, et al., Prognostic value of the eighth edition AJCC TNM classification for differentiated thyroid carcinoma, Oral Oncol. 71 (2017) 81–86.
[34] M. Kim, et al., Comparison of the seventh and eighth editions of the American joint committee on cancer/union for international cancer control tumor-node-metastasis staging system for differentiated thyroid cancer, Thyroid 27 (9) (2017) 1149–1155.