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Modification of the Tumor-Node-Metastasis Staging System for Differentiated Thyroid Carcinoma by Considering Extra-Thyroidal Extension and Lateral Cervical Lymph Node Metastasis

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Background: Concerns have arisen about the classification of extra-thyroidal extension (ETE) and lateral cervical lymph node metastasis (N1b) in the 8th edition of the tumor-node-metastasis staging system (TNM-8). This study evaluated the prognostic validity of a modified-TNM staging system, focusing on ETE and N1b, in differentiated thyroid carcinoma (DTC) patients.

Methods: This multicenter retrospective cohort study included 4,878 DTC patients from five tertiary hospitals. In the modified-TNM, T3b in TNM-8 was down-staged to T2, and stage II was subdivided into stages IIA and IIB. Older patients with N1b were re-classified as stage IIB.

Results: The modified-TNM resulted in staging migration in 540 patients (11%) classified as stage II according to the TNM-8, with 75 (14%), 381 (71%), and 84 patients (16%) classified as stages I, IIA, and IIB, respectively. The 10-year disease-specific survival (DSS) rates in patients classified as stages I, II, III, and IV by TNM-8 were 99.8%, 95.9%, 81.0%, and 41.6%, respectively. The DSS rates of patients classified as stages I, IIA, IIB, III, and IV according to the modified-TNM were 99.8%, 96.4%, 93.3%, 81.0%, and 41.6%, respectively. DSS curves between stages on TNM-8 ($P<0.001$) and modified-TNM ($P<0.001$) differed significantly, but the modified-TNM discriminated better than TNM-8. The proportions of variation explained values of TNM-8 and modified-TNM were 6.3% and 6.5%, respectively.

Conclusion: Modification of the TNM staging system focusing on ETE and N1b could improve the prediction of DSS in patients with DTC. Further researches are needed to validate the prognostic accuracy of this modified-TNM staging system.

Keywords: Lymph nodes; Mortality; Neoplasm staging; Thyroid neoplasms

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INTRODUCTION

Cancer staging plays an important role in patient management and in communications about the prognosis of disease among clinicians and between physicians and their patients [1]. Therefore, accurate tumor staging is critical for treatment decisions and ultimately for patient outcomes [1,2]. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system has been widely used to predict disease mortality in patients with differentiated thyroid carcinoma (DTC) [1-3]. The revised 8th edition of the AJCC TNM staging system (TNM-8) for DTC includes important changes from the 7th edition (TNM-7) [2,3] to minimize over-staging of older patients with low-risk tumors and to provide a more realistic prognosis for patients in high-risk groups [4]. Comparative studies of patients staged by the TNM-7 and TNM-8 showed that the changes incorporated into the TNM-8 could lead to down-staging of approximately 40% of patients with DTC and could better predict patient mortality [5,6]. However, survival discrimination powers were still low in both studies and some aspects of the TNM-8 require improvement [5,6].

Survival outcomes in DTC patients with gross extra-thyroidal extension (ETE) were found to differ according to the direction and extent of ETE [7,8]. Recently, a single center study showed that disease-specific survival (DSS) was better in patients with stage T3b DTC (gross ETE invading only the strap muscles with tumor size ≤4 cm) than for patients with T3a DTC (tumor size >4 cm and limited to the thyroid), with the former having DSS similar to that of patients with T2 DTC [7]. These results suggested the importance of downgrading stage T3b to stage T2 [7]. In addition, modifying TNM-8 by employing N1b classification may better predict survival outcomes [9,10]. The present study investigated whether the TNM-8 classification could be improved by including ETE and N1b in the evaluation of patients with DTC. Specifically, this study compared the prognostic ability of the TNM-8 staging system and a modification of this staging system that included gross ETE and lateral cervical lymph node (LN) metastasis (N1b) to predict DSS in a large, multicenter cohort of patients with DTC.

METHODS

Patients

In this retrospective, multicenter cohort study, 4,878 patients with DTC who underwent thyroid surgery between 1996 and 2005 at five tertiary hospitals in Korea were included: Asan Medical Center (n=3,176), Chonnam National University Hwasun Hospital (n=691), Pusan National University Hospital (n=552), Ulsan University Hospital (n=345), and Chungnam National University Hospital (n=114). All the included patients were pathologically proven to have papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma (FTC). The research protocol was approved by the Institutional Review Board of each institution: Asan Medical Center, 2016-1301; Chonnam National University Hwasun Hospital, CNUHH-2017-053; Pusan National University Hospital, 1701-014-051; Ulsan University Hospital, 2016-12-031; and Chungnam National University Hospital, CNUH 2017-01-018. Informed consent was waived due to the retrospective design of this study [10].

The clinical and pathological data obtained from electronic medical records included age at the time of diagnosis, sex, primary tumor size, pathologic subtype, extent of ETE, presence and location of cervical LN metastases, presence of distant metastases, extent of surgery, and use of radioactive iodine ablation. The survival status, last follow-up time, and causes of death were also collected.

Definition of modified-TNM

Patients categorized according to the TNM-8 [3] were subsequently reclassified using a modified-TNM staging system (Table 1). Patients were reclassified into different T and TNM stages by the modified-TNM staging system. Patients classified as T3b (gross ETE invading only strap muscles with tumor size ≤ 4 cm) according to the TNM-8 were reclassified as T2 according to the modified-TNM, and stage II on the TNM-8 was subdivided into stages IIA and IIB on the modified-TNM. Older patients (≥55 years) with N1b disease were reclassified as stage IIB on the modified-TNM, whereas the remaining patients were classified into stage IIA.

Primary outcome

The TNM staging system is useful for predicting disease mortality and therefore recommended for staging of patients with DTC [3]. Therefore, the primary outcome of this study was DSS, defined as the time interval from the date of the initial thyroidectomy to the date of last censor or death due to DTC.

Statistics

Data were analyzed using R version 3.5.1 software and the R libraries (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). Categorical variables were presented as numbers with percentages and continuous variables

Table 1. Prognostic Stages and Stage Groups According to the TNM-8 and the Modified-TNM

	TNM-8	Modified-TNM
T category		
TX	Primary tumor cannot be assessed	Same as 8th edition
T0	No evidence of primary tumor	Same as 8th edition
T1	Tumor size ≤2 cm, limited to the thyroid	Same as 8th edition
T2	Tumor size >2 cm and ≤4 cm, limited to the thyroid	Tumor size >2 cm and ≤4 cm, limited to the thyroid, or gross extrathyroidal extension invading only strap muscles with tumor size ≤4 cm
T3a	Tumor size >4 cm, limited to the thyroid	Tumor size >4 cm, limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles from a tumor of any size	Gross extrathyroidal extension invading only strap muscles with tumor size >4 cm
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve	Same as 8th edition
T4b	Gross extrathyroidal extension invading prevertebral fascia, encasing the carotid artery, or mediastinal vessels	Same as 8th edition
The definitions of N and M categories are identical		
Stage group		
	I: Tx Nx M0 <55 yr T1-2 N0/NX M0 ≥55 yr	I: Tx Nx M0 <55 yr T1-2 N0/NX M0 ≥55 yr
	II: Tx Nx M1 <55 yr T1-2 N1 M0 ≥55 yr T3a/T3b Nx M0 ≥55 yr	IIA: Tx Nx M1 <55 yr T1-2 N1a M0 ≥55 yr T3a/T3b N0-1a M0 ≥55 yr
		IIB: T1-2 N1b M0 ≥55 yr T3a/T3b N1b M0 ≥55 yr
	III: T4a Nx M0 ≥55 yr	III: T4a Nx M0 ≥55 yr
	IVA: T4b Nx M0 ≥55 yr	IVA: T4b Nx M0 ≥55 yr

TNM-8, 8th edition of the AJCC TNM staging system; TNM, tumor-node-metastasis.

were as means with standard deviations. We plotted DSS curves using the Kaplan-Meier method and compared them using log-rank test. We evaluate the impact of TNM stage groupings on DSS based on the Cox-proportional hazard model. Relative risks of survival are reported as hazard ratios (HRs), 95% confidence interval (CI), and *P* value.

The proportion of variation explained (PVE) in the Cox-proportional hazard model was calculated to estimate how well each of the staging systems predicted the outcome of DSS. PVE, which ranges from 0 to 100, was calculated using the formula: $PVE = 1 - \exp(-G^2/n)$, in which G^2 is the maximum likelihood ratio determined by analysis using the chi-square test associated with the null hypothesis, and n is the total number of valid patients in the study [11]. All *P* values were two-sided, and *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

The baseline clinical and pathological characteristics of the 4,878 patients with DTC are illustrated in Table 2. Mean patient age was 45.9±12.2 years, and 87% were women. Most patients (n=4,704, 96%) were diagnosed with PTC. The mean primary tumor size was 1.7±1.3 cm, and 3,534 (72%), 1,116 (23%), and 228 patients (5%) had primary tumor sizes ≤2, 2 to 4, and >4 cm, respectively. Of the 4,878 patients, 1,407 (29%), 577 (12%), and 267 (5%) showed microscopic ETE, gross ETE invading the strap muscles alone, and gross ETE invading areas other than the strap muscles, respectively. Of the 577 patients with gross ETE invading only the strap muscles, 530 (92%) had primary tumors ≤4 cm in size and 47 (8%) had tumors >4 cm. Cervical LN metastases were identified in 2,116 patients (43%), including 1,624 (33%) with N1a and 492 (10%) with N1b dis-

Table 2. Baseline Clinical and Pathological Characteristics of Patients with Differentiated Thyroid Carcinoma

Characteristic	Value
Number	4,878
Age, yr	45.9±12.2
Female sex	4,226 (87)
Pathology	
PTC	4,704 (96)
FTC	174 (4)
Primary tumor size, cm	1.7±1.3
≤2	3,534 (72)
2–4	1,116 (23)
>4	228 (5)
Extra-thyroidal extension	
Microscopic	1,407 (29)
Gross, invading only strap muscle	577 (12)
With primary tumor size ≤4 cm	530
With primary tumor size >4 cm	47
Gross, invading other than strap muscle	267 (5)
Cervical LN metastasis	
N1a	1,624 (33)
N1b	492 (10)
Distant metastasis	74 (2)
Total thyroidectomy	3,891 (80)
RAI treatment	3,140 (64)

Values are expressed as mean±standard deviation or number (%).
PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; LN, lymph node; RAI, radioactive iodine.

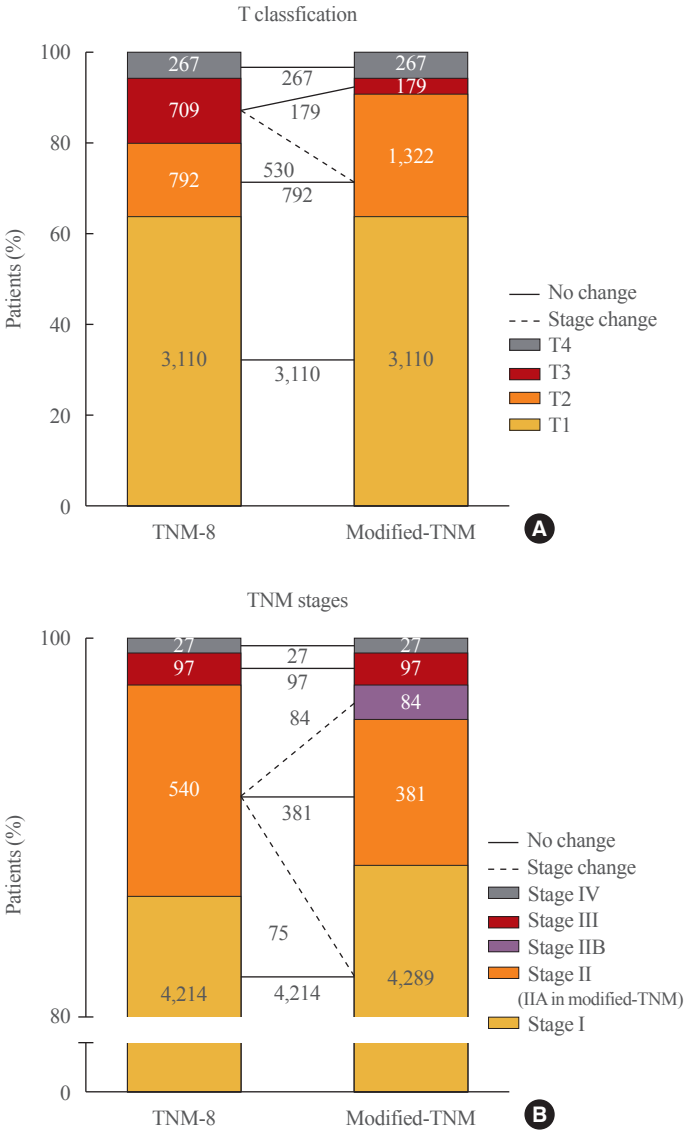

Fig. 1. Distribution of patients according to (A) T classifications and (B) tumor-node-metastasis (TNM) stages, as determined by the 8th edition of the TNM staging system (TNM-8) and the modified-TNM staging system.

ease. Distant metastasis at diagnosis was found in 74 patients (2%). The median follow-up period until censoring or death was 10.2 years (interquartile range, 7.8 to 12.0).

Distribution of patients per stage according to the TNM-8 and the modified-TNM

Fig. 1 shows the migration of staging from the TNM-8 to the modified-TNM. Of 709 patients classified as having T3 disease on the TNM-8, 530 (75%) with T3b (gross ETE invading only strap muscles with tumor size ≤4 cm) disease were down-graded to the T2 category (Fig. 1A). The TNM-8 classified 4,214 patients (86%) as having stage I tumors, 540 (11%) as having stage II, 97 (2%) as having stage III, and 27 (1%) as having stage VI (Fig. 1B). Application of the modified-TNM to the 540 patients classified as stage II according to the TNM-8 resulted in 75 (14%) of these patients being down-staged to stage I, with the remaining 381 (71%) and 84 patients (16%) reclassified as stages IIA and IIB, respectively. Among the 75 patients being down-staged to stage I, there were 72 classical PTC, two follicular variant PTC, and one FTC. Patients with stages III and IV tumors according to the TNM-8 showed no changes when classified according to the modified-TNM.

DSS according to the TNM-8 and modified-TNM

DSS in patients with DTC was evaluated according to the TNM-8 and modified-TNM staging systems (Table 3, Fig. 2).

Table 3. Relative Risk of DSS and Prognostic Validity According to the TNM-8 and the Modified-TNM

Variable	No. (%)	10-yr DSS rates, %	HR	95% CI	*P* value	PVE, %
TNM-8						6.3
Stage I	4,214 (86)	99.8	1.0	Reference		
Stage II	540 (11)	95.9	23.0	11.6–45.6	<0.001	
Stage III	97 (2)	81.0	143.0	68.8–297.5	<0.001	
Stage IV	27 (1)	41.6	366.7	173.8–744.0	<0.001	
Modified-TNM						6.5
Stage I	4,289 (88)	99.8	1.0	Reference		
Stage IIA	381 (8)	96.4	16.7	8.1–34.0	<0.001	
Stage IIB	84 (2)	93.3	38.6	17.4–85.4	<0.001	
Stage III	97 (2)	81.0	121.1	60.5–242.5	<0.001	
Stage IV	27 (1)	41.6	313.2	154.1–636.8	<0.001	

DSS, disease-specific survival; TNM-8, 8th edition of the AJCC TNM staging system; TNM, tumor-node-metastasis; HR, hazard ratio; CI, confidence interval; PVE, proportion of variation explained.

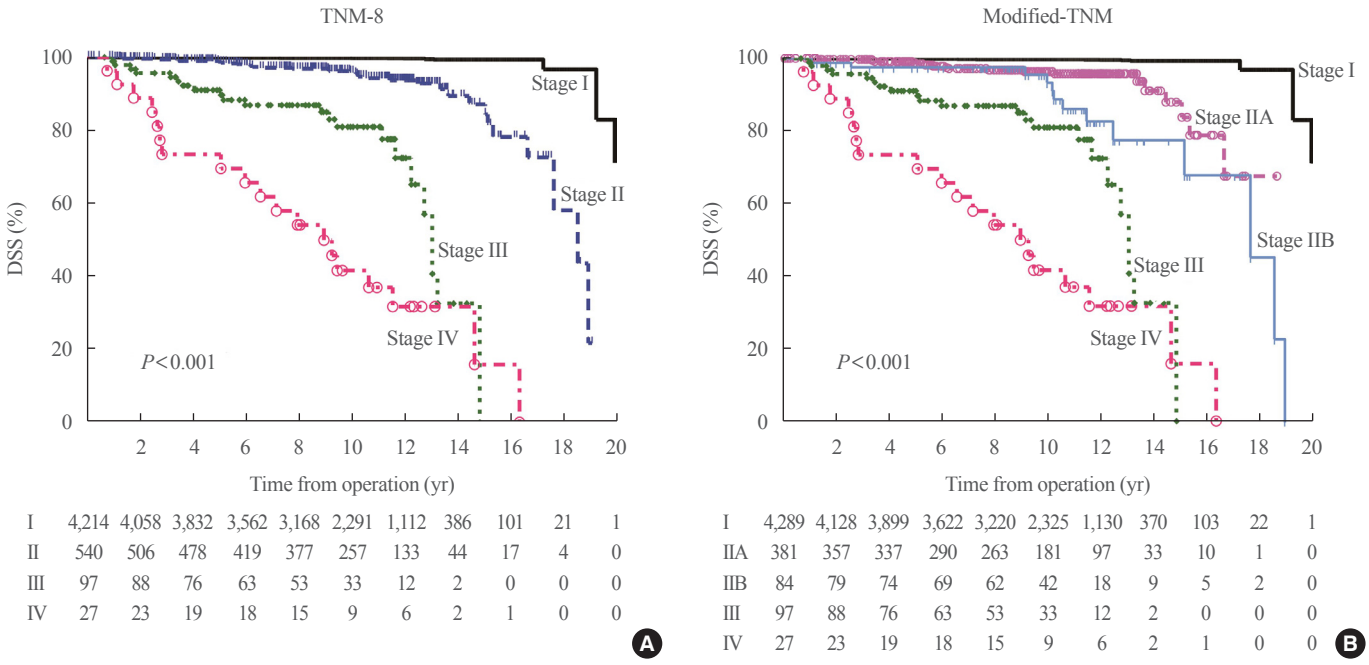

Fig. 2. Kaplan-Meier analysis of disease-specific survival (DSS) in patients with differentiated thyroid carcinoma classified according to (A) the 8th edition of the tumor-node-metastasis (TNM) staging system (TNM-8) and (B) the modified-TNM staging system.

DSS was associated significantly with stage at diagnosis, as determined by the TNM-8 ($P<0.001$) (Fig. 2A) and modified-TNM ($P<0.001$) (Fig. 2B) staging systems. However, differences in DSS between stage groups appeared to be more distinct when patients were staged by the modified-TNM than the TNM-8 (Fig. 2).

When staged according to the TNM-8, the 10-year DSS rates for patients with stages I, II, III, and IV DTCs were 99.8%, 95.9%, 81.0%, and 41.6%, respectively (Table 3). When staged according to the modified-TNM, the 10-year DSS rates for patients with stages I, IIA, IIB, III, and IV DTCs were 99.8%, 96.4%, 93.3%, 81.0%, and 41.6%, respectively. Using modified-TNM stage I as the reference, patients with stage IIA (HR, 16.7; 95% CI, 8.1 to 34.0; $P<0.001$) and stage IIB (HR, 38.6;

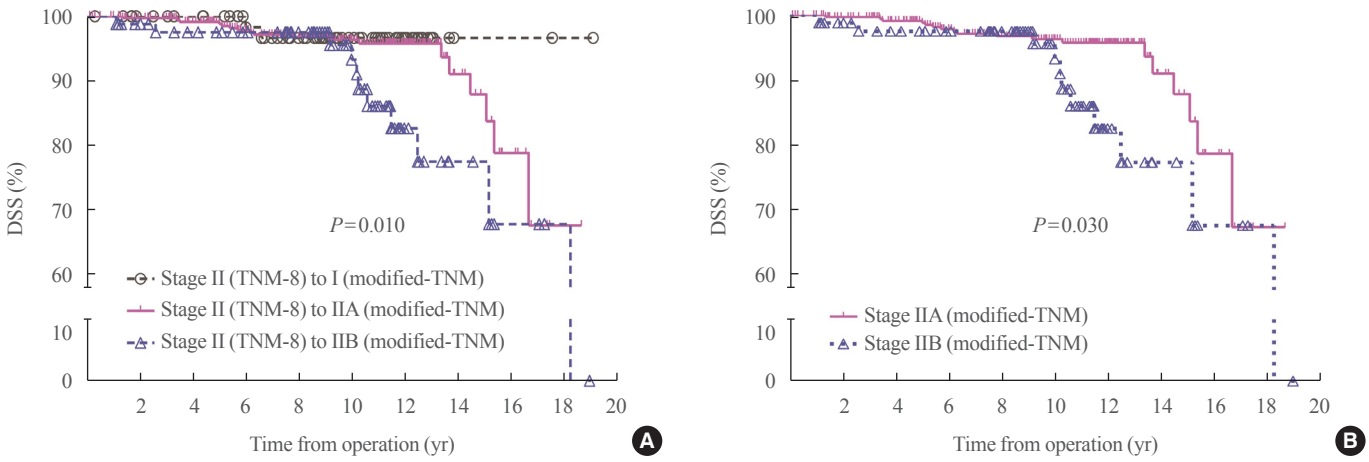

Fig. 3. Kaplan-Meier analysis of disease-specific survival (DSS) in patients who showed (A) stage migration after applying the modified-tumor-node-metastasis (TNM) staging system and (B) patients classified as stages IIA and IIB according to the modified-TNM. TNM-8, the 8th edition of the TNM staging system.

95% CI, 17.4 to 85.4; $P<0.001$) had significantly poorer DSS. The value of the PVE of the modified-TNM system was 6.5% and that of the TNM-8 was 6.3%.

DSS in patients with stage migration after applying the modified-TNM

Patients classified as stage II according to the TNM-8 were reclassified as stages I, IIA, and IIB according to the modified-TNM. Following stage migration, the DSS curves of these three groups differed significantly ($P=0.010$) (Fig. 3A), with their 10-year DSS rates being 96.7%, 96.4%, and 93.3%, respectively. DSS rates also differed significantly between stages IIA and IIB ($P=0.030$) (Fig. 3B), with patients classified as stage IIB having a 2.3-fold poorer DSS than those reclassified as stage IIA (95% CI, 1.1 to 4.8; $P=0.035$).

DISCUSSION

This multicenter cohort study evaluated whether and how the prognostic predictability of the TNM-8 staging system for patients with DTC could be improved by modifications focusing on both gross ETE and lateral cervical LN metastasis. Application of the modified-TNM staging system resulted in stage migration only in patients classified as stage II according to the TNM-8. About 14% of these patients were down-staged to stage I, whereas 71% and 16% were reclassified as stages IIA and IIB, respectively. The modified-TNM staging system appeared to better discriminate among stages and to better predict DSS than the TNM-8. Potential modifications, including the down-grading of patients with T3b (gross ETE invading only strap muscles with tumor size ≤4 cm) to T2 and the upgrading of older patients with N1b disease from stage II, may better predict DSS in patients with DTC.

In the modified-TNM, tumors with gross ETE measuring ≤4 cm are down-staged to T2 disease. This change is based on the findings of previous studies, which showed that gross ETE invading only the strap muscles did not affect survival outcome in patients with DTC, especially in patients with tumors ≤4 cm in size [7,8,12]. In addition, patients with gross ETE invading only the strap muscles and tumor size ≤4 cm showed no difference in DSS compared to patients with T2 disease, but rather showed significantly better DSS compared to patients with T3a disease [7]. ETE has been considered as a prognostic factor in patients with DTC and is observed in 5% to 45% of these patients [13]. Beginning with the sixth edition of the AJCC TNM staging system, the presence of ETE has been divided into two grades, minimal and massive ETE, affecting the T category [2]. Many studies have shown that DTC patients with massive ETE have a much poorer survival outcome than those with minimal ETE [13,14], and that DTC patients with minimal and no ETE have similar survival outcomes [15,16]. For this reason, the revised TNM-8 ascribed high importance to gross ETE but eliminated minimal ETE in T staging [3]. However, it was unclear whether patients having tumors ≤4 cm with gross ETE invading the strap muscles alone also have a poor prognosis, and whether it is appropriate for these patients to be upgraded to a higher T

grade. Although 75% of patients in this study with T3 disease were down-graded to T2, the 10-year DSS rate of patients classified as stage T2 by the modified-TNM was excellent (98.9%, data not shown).

The TNM-8 classification of patients with DTC does not consider the location of metastatic LNs in stage grouping [3]. Consequently, the TNM-8 downstages a large number of patients with N1b disease. However, there is evidence that N1b disease is a significant prognostic factor in patients with DTC, and that survival outcomes are worse for DTC patients with N1b than with N1a [9,17,18]. This study found that older patients with N1b disease were predicted to have a significantly lower 10-year DSS rate than those with N0 or N1a disease, emphasizing the prognostic significance of N1b in older patients with DTC, and suggesting that N1b should not be treated as equivalent to N0 or N1a. Further research is needed to assess the prognostic value of N1b disease according to the modified-TNM staging system for patients with DTC.

This study had limitations because of its retrospective design. There may be variations in the intensity of treatment and the frequency of follow-up. However, our findings are based on data from a large multicenter cohort population with a relevant number of disease-specific death events during a median 10.2 years of follow-up.

In conclusion, this study provided valuable information about the suitability of the TNM-8 for staging DTC and suggested that modifications based on ETE and N1b may improve its accuracy. Differences in DSS between each pair of stages on the modified-TNM appeared greater than those between each pair of stages on the TNM-8. In addition, the modified-TNM grouping appeared to be a better predictor of DSS than the TNM-8. These findings indicate that the modified-TNM grouping proposed here may better predict outcomes and improve treatment selection for patients with DTC. Further researches are needed to valid the prognostic accuracy of these modifications.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: M.K., W.G.K., M.J.J., H.C.K., T.Y.K. Acquisition, analysis, or interpretation of data: M.K., M,J.J., H.S.Y., E.S.K., H.C.K. Drafting the work or revising: M.K., T.Y.K. Final approval of the manuscript: M.K., W.G.K., M.J.J., H.K.K., H.S.Y., E.S.K., B.H.K., W.B.K., Y.K.S., H.C.K., T.Y.K.

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