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Refining the tumor-node-metastasis staging system for individualized treatment of differentiated thyroid carcinoma

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ABSTRACT

Background: Patients with differentiated thyroid carcinoma (DTC) are staged according to the single age cut point in addition to anatomic extent. A novel staging system is needed to properly show the character and prognosis of DTC by considering age as a continuous variable. We aimed to refine stage and prognostic groups of the eighth edition tumor-node-metastasis (TNM-8) staging system for DTC and to suggest a possible revision.
Methods: We conducted a retrospective data abstraction study of patients with newly diagnosed DTC who were treated at one of two tertiary referral centres in Seoul, Korea between 1994 and 2005. We used recursive partitioning analysis to derive a new staging classification (TNM-RPA) and compared its prediction of cancer-specific survival with that of TNM-8.
Results: The cohort comprised 6342 patients with DTC who were followed up for a median of 11.4 years. Higher TNM-RPA groups were associated with increased risk of death (10-year cancer-specific survival for stages IA, IB, IIA, IIB, III, and IV: 99.6%, 98.1%, 93.0%, 92.4%, 75.1%, and 56.6%, respectively; $P < 0.001$). The C-index values were 0.869 (95% CI, 0.833–0.905) for the TNM-RPA and 0.819 (0.789–0.850) for TNM-8. The proportions of variance explained for the ability of the TNM-RPA and TNM-8 stages to predict cancer-specific survival were 7.1% and 5.7%, respectively.
Conclusion: This study presents a RPA-based TNM stage groupings that incorporate multiple age cutoffs and essential anatomic information, which can be conveniently used to facilitate the individual prediction of long-term cancer-specific survival in patients with DTC.

Introduction

For patients with differentiated thyroid carcinoma (DTC), the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) system is the most widely used indicator of mortality [1,2]. This system has been accepted as a framework that can be used at initial presentation to classify patients at the population level, define prognosis, and determine the best initial treatment approaches. For DTC, unlike most other malignancies, age at diagnosis is the most important prognostic factor. This non-anatomic factor has been used as a dichotomous variable and has been combined with the anatomic tumor extent to stage DTC ever since the initial proposal of TNM stage groups published in 1983 [3,4].

Despite the widespread use of the TNM staging system, some experts question its usefulness in clinical care at the individual patient level. As knowledge of cancer biology evolves, diagnostic tools and treatment

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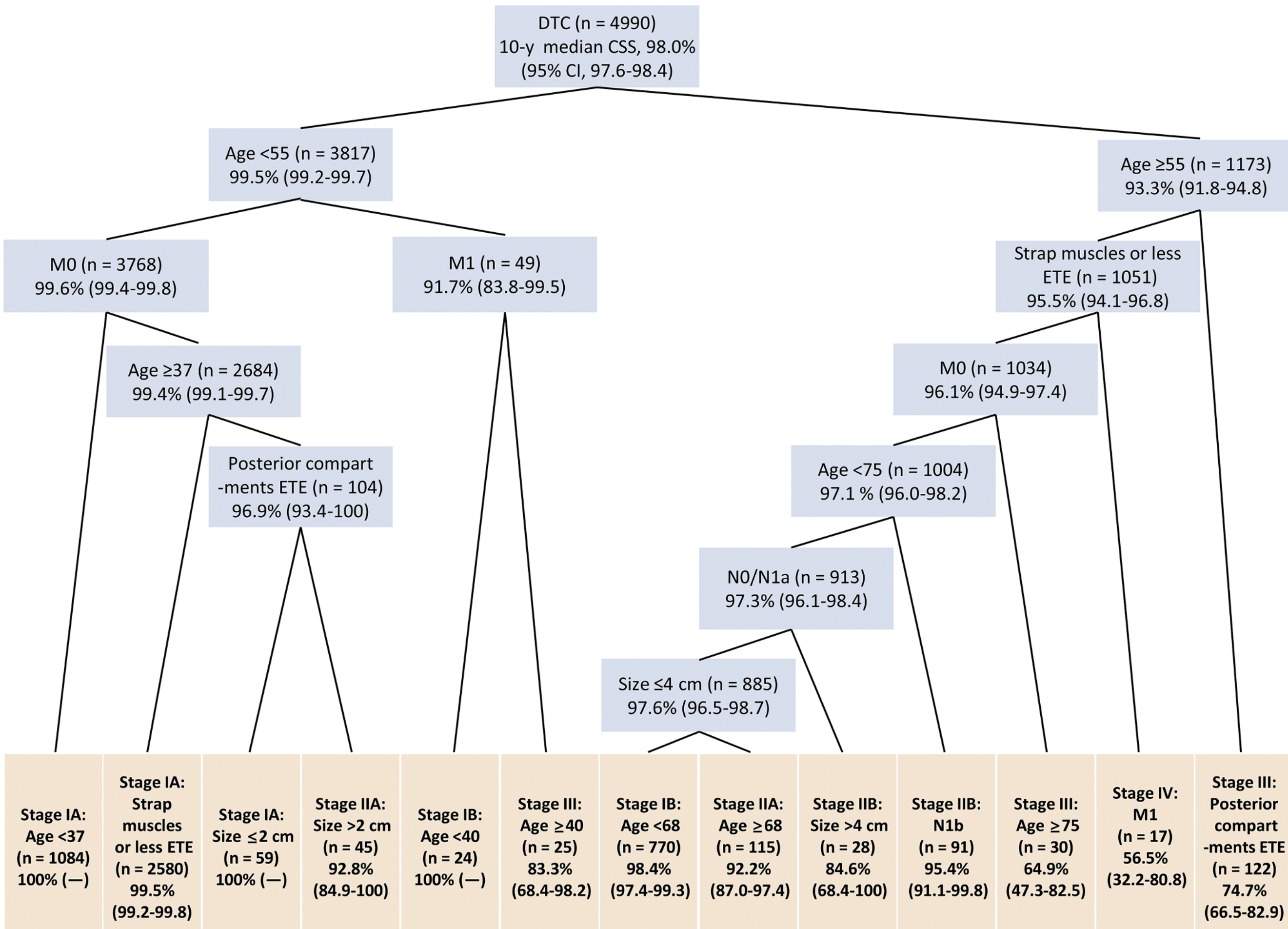

Fig. 1. Stage groups and 10-y cancer-specific survival (CSS) estimates for differentiated thyroid carcinoma (DTC) based on recursive partitioning analysis in the training cohort. ETE, extrathyroidal extension.

modalities continue to be developed and improved [2]. The prognostic stage groups in the eighth edition of the TNM system (TNM-8) were empirically derived to better reflect the excellent prognosis in most patients with relatively low-risk DTC [3].This led to approximately 40% of patients being down-staged upon reclassification according to TNM-8 compared to the previous edition [5,6]. However, TNM-8 continues to use a single-age threshold of 55 years (revised from 45 years in TNM-7) [7,8]. This oversimplifies the survival deterioration that occurs with increasing age at diagnosis [9] and underestimates the prognosis for younger patients, particularly those aged 45–55 years [10]. Moreover, a major challenge in developing a new TNM classification system is obtaining a comprehensive dataset that covers the full disease spectrum (including early to advanced stages, with at least 100 cancer-specific deaths); for DTC, this mandates more than 10 years of follow-up [11,12].

Recently, researchers have proposed new staging systems for various malignancies based on recursive partitioning analysis (RPA), a statistical methodology which creates a decision tree according to the optimized binary partition of multiple prognostic factors using splitting, pruning, and final tree structure selection algorithms. The alternative staging systems performed better than TNM systems in human papillomavirus-related oropharyngeal cancer, lung cancer, and medullary thyroid cancer [13–15]. Therefore, we aimed to do a multicentre study to develop an RPA-based prognostic system (TNM-RPA) that would predict cancer-specific survival (CSS) in individual patients with DTC more effectively than TNM-8.

Materials and methods

Study population

This was a retrospective data abstraction study of consecutive patients with newly diagnosed, histologically confirmed DTC [papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), including Hürthle cell thyroid carcinoma] who were treated at Samsung Medical Center and Asan Medical Center in Seoul, Korea between 1994 and 2005. The study protocol was approved by the institutional review boards of both institutions. Patients with poorly differentiated thyroid carcinoma were excluded. Collected patient data included gender, age at diagnosis, histologic subtype, pathologic tumor size, pathologic lymph node involvement status, and presence of distant metastases. Presence of extrathyroidal extension (ETE) was ascertained either by operative record or pathologic report. We based the initial staging on TNM-8 [3]. Treatment data were also extracted, including the extent of thyroidectomy and cumulative activities of radioiodine ablation. Postoperatively, patients were followed at regular intervals. The time to last follow-up, survival status, and date and cause of death were recorded. CSS was defined as the time from initial surgery to final follow-up or death caused by DTC, as described previously [6,7].

Statistical analysis

Candidates for overall prognostic stage groups were developed in conjunction with the proposed changes to the T, N, and M categories in TNM-8 [3]. Notably, we decomposed the components of T, pathologic tumor size and ETE, and treated them as individual variables, because a previous study showed that the mortality risk conferred by the existence of gross invasion into strap muscles (T3b) did not differ from that of T1 tumors [6,16]. The existing N and M descriptors were validated [6], so no changes were proposed. Age at diagnosis was treated as a continuous variable to establish multiple age cutoffs, to improve the staging system.

The staging system was developed using a randomly selected training cohort comprising three-quarters of the total cohort ($n = 4990$), with 1352 patients reserved for subsequent internal validation (the validation cohort). The random selection process was stratified by size, histology, cancer centre (Samsung Medical Center/Asan Medical Center), and year of surgery (1994–1999/2000–2003/2004–2005). The components of TNM-8 were then applied to the training dataset. Candidate stage grouping schemes were initially developed using a recursive partitioning algorithm [14,15], which generated a tree-based model for survival data using likelihood-based splitting criteria for recursive partitioning (Fig. 1). The analysis grouped cases on the basis of CSS after determining the best split points using an ordered variable for the M (M0/M1), ETE [no/microscopic/strap muscles (T3b)/T4a/T4b], size (≤2.0 cm/ > 2.0 ≤ 4.0 cm/ > 4.0 cm), and N (N0/N1a/N1b) descriptors and continuous variables for age. In addition, the relative contribution to the CSS prediction for each variable was evaluated based on 'variable importance depth' in a random forest algorithm. The analysis was conducted using the statistical package R (v. 3.4.3; The R Foundation, Vienna, Austria; http://www.R-project.org/).

An ordered list of groupings was developed from the terminal nodes of the survival tree. With this list as a frame, the TNM-RPA with six proposed stage groupings was developed by combining adjacent groups based on their statistical properties, taking into account minimal hazard difference and sample size balance between the prognostic groups and relevance to clinical practice. Contrasts between adjacent stage groups were evaluated by Cox regression analysis in the training and validation cohorts, adjusting for baseline factors (histology, extent of surgery, radioiodine ablation, cancer centre, and year of surgery).

To estimate how well each of the two staging systems predicted the outcome of CSS, we computed the proportions of variance explained (PVEs) in Cox proportional regression models [17]. PVE (%) ranges from 0 to 100, with larger numbers suggesting better predictability. To estimate the discriminatory ability of the TNM-8 and TNM-RPA stages, we calculated the C-index for a model containing the stage as the sole independent variable [18]. The null value for the C-index was 0.5, with a maximum of 1.0; a larger C-index indicates a better model for discriminating the outcome. The area under the receiver operating characteristic curve was also used to examine the discriminatory ability for CSS outcome at 10 years. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

We identified 6352 consecutive patients with DTC at the two participating centres between 1994 and 2005. Ten patients were excluded owing to an absence of follow-up information after initial surgery, meaning that 6342 patients were enrolled in the study. The patient characteristics are shown in Table 1. All patients were Korean, 86.9% were women, and the median age at diagnosis was 46.0 (interquartile range, 37.9–54.6). Almost all patients had PTC. The mean size of the primary tumor was 1.6 cm, and 348 patients (5.5%) had gross ETE into posterior neck compartments (T4a or T4b, according to the T categories in TNM-8). Cervical lymph node metastases were present in 42.5% of patients, and 1.6% (100 patients) had distant metastases. The proportions of patients with a TNM stage of I, II, III, IVA, and IVB were 83.3% ($n = 5280$), 14.0% ($n = 890$), 2.1% ($n = 132$), 0% ($n = 3$), and 0.6% ($n = 37$), respectively. Most patients underwent a total thyroidectomy and radioiodine ablation. The median follow-up period until censoring or death was 11.4 years; 159 (2.5%) cancer-specific deaths were recorded. No important baseline differences existed between patients in the training and validation cohorts.

Table 1
Patient characteristics.

	Total ($n = 6342$)	Training cohort ($n = 4990$)	Validation cohort ($n = 1352$)
Follow-up, years	11.4 (9.5–13.3)	11.3 (9.4–13.3)	11.5 (9.6–13.4)
Gender			
Female	5513 (86.9)	4344 (87.1)	1169 (86.5)
Male	829 (13.1)	646 (12.9)	183 (13.5)
Age at diagnosis, years	46.0 (37.9–54.6)	46.1 (37.8–54.8)	45.9 (38.0–54.0)
Histology			
Papillary thyroid carcinoma	6141 (96.8)	4836 (96.9)	1305 (96.5)
Follicular thyroid carcinoma	201 (3.2)	154 (3.1)	47 (3.5)
T component			
Size, cm	1.6 ± 1.3	1.6 ± 1.3	1.7 ± 1.3
≤ 2.0 cm	4792 (75.6)	3785 (75.9)	1007 (74.5)
> 2.0 ≤ 4.0 cm	1265 (19.9)	980 (19.6)	285 (21.1)
> 4.0 cm	285 (4.5)	225 (4.5)	60 (4.4)
Extrathyroidal extension			
No/microscopic	5319 (83.9)	4191 (84.0)	1128 (83.4)
Strap muscles	675 (10.6)	527 (10.6)	148 (10.9)
Posterior compartments	348 (5.5)	272 (5.5)	76 (5.6)
N component			
N0	3649 (57.5)	2869 (57.5)	780 (57.7)
N1a	2009 (31.7)	1587 (31.8)	422 (31.2)
N1b	684 (10.8)	534 (10.7)	150 (11.1)
Distant metastases			
No, M0	6242 (98.4)	4913 (98.5)	1329 (98.3)
Yes, M1	100 (1.6)	77 (1.5)	23 (1.7)
TNM-8 stage			
I	5280 (83.3)	4146 (83.1)	1134 (83.9)
II	890 (14.0)	703 (14.1)	187 (13.8)
III	132 (2.1)	110 (2.2)	22 (1.6)
IVA	3 (0.0)	3 (0.1)	0 (0.0)
IVB	37 (0.6)	28 (0.6)	9 (0.7)
Extent of surgery			
Total thyroidectomy	5416 (85.4)	4252 (85.2)	1164 (86.1)
Lobectomy	926 (14.6)	738 (14.8)	188 (13.9)
Radioiodine ablation			
Yes	5159 (81.3)	4051 (81.2)	1108 (82.0)
No	1183 (18.7)	939 (18.8)	244 (18.0)

Data are the median (interquartile range), number of patients (%), or mean ± standard deviation.

In RPA with the anatomic and age variables for DTC, we found that age was the most important, followed by M, ETE, and size. The N categories had the smallest effect on the stage grouping (results not shown). Fig. 1 shows prognostic subsets based on RPA that used the five aforementioned variables with 10-year CSS estimates. We propose dividing patients with stage I and II diseases into two subgroups for each: stage IA (defined as age < 37, M0; age ≥ 37 < 55, M0; ETE of strap muscles or less regardless of size or ETE of posterior compartments; and size < 2 cm); stage IB (age < 40, M1; age ≥ 55 < 68, M0; ETE of strap muscles or less; size ≤ 4 cm, N0/N1a); stage IIA (age ≥ 37 < 55, M0; ETE of posterior compartments, size > 2 cm; age ≥ 68 < 75, M0; ETE of strap muscles or less, size ≤ 4 cm, N0/N1a), and IIB (age ≥ 55 < 75, M0; ETE of strap muscles or less, size > 4 cm and N0/N1a or any size with N1b). Stage III would be defined as age ≥ 40 < 55, M1; age ≥ 55, ETE of posterior compartments, age ≥ 75, M0, and ETE of strap muscles or less. Stage IV would be age ≥ 55, M1, and ETE of strap muscles or less. These six groups are well balanced with respect to the number of patients in each group, and differ from each other with respect to the CSS rate, whereas there were no significant differences in the mortality risk within the stage groups.

Table 2
Hazard ratios for risk of death in the training and validation cohorts for the TNM-8 and proposed TNM-RPA stages.

	Training cohort (n = 4990)		Validation cohort (n = 1352)	
	Hazard ratio (95% CI)	n	Hazard ratio (95% CI)	n
TNM-8 stage				
I	1.00	4146	1.00	1134
II	12.66 (7.82–20.50)	703	14.08 (6.13–32.34)	187
III	62.88 (36.81–107.39)	110	21.83 (6.51–73.15)	22
IVA	13.65 (1.67–111.70)	3	NA	0
IVB	107.53 (56.86–203.34)	28	69.99 (19.79–247.55)	9
TNM-RPA stage				
IA	1.00	3723	1.00	1025
IB	4.49 (2.21–9.13)	794	12.57 (4.25–37.15)	198
IIA	20.11 (9.67–41.79)	160	11.25 (2.12–59.78)	50
IIB	32.06 (16.03–64.13)	119	33.22 (10.17–108.49)	38
III	89.66 (51.41–156.37)	177	56.62 (18.17–176.46)	34
IV	114.81 (49.80–264.70)	17	87.21 (19.69–386.17)	7

Data are the hazard ratios (95% CI) and number of patients. Hazard ratios were adjusted for histology, extent of surgery, radioiodine ablation, cancer centre (Samsung Medical Center, Asan Medical Center), and year of surgery (1994–1999, 2000–2003, and 2004–2005). TNM-8, eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control tumor-node-metastasis (TNM) staging system; RPA, recursive partitioning analysis; CI, confidence interval.

In the multivariate Cox regression, risk of death increased significantly with each successive stage group after adjustment, in both TNM-8 and the more finely parsed proposed TNM-RPA (Table 2 and Fig. S1). Compared with patients who had TNM-RPA stage IA disease, those who had TNM-RPA stage III and IV diseases had approximately one hundred times the risk of death (adjusted HR, 89.66 and 114.81, respectively). These results were consistent in the validation cohort.

Next, we calculated the 10- and 15-year CSS rates and adjusted the HRs for the risk of death using the TNM-8 and TNM-RPA stages for the entire cohort (Table 3 and Fig. 2). The overlap in the TNM survival curves in Fig. 2A may be partly due to the lack of cases with T4b in the Asan Medical Center, despite the attempt to correct for this by adjusting for centre. Adjusted HRs for TNM-RPA showed good coherence, with a declining outcome as the TNM-RPA categories increased, which was better than that of TNM-8. Table 4 summarizes the proposed TNM-RPA stage group tabulation scheme.

The TNM-RPA had a higher C-index of 0.869 (95% CI 0.833–0.905) compared with 0.819 (0.789–0.850) for TNM-8 ($P < 0.001$). The area under the receiver operating characteristic curve at 10 years showed a significant difference ($P = 0.001$) between the TNM-RPA (0.882; 0.840–0.923) and TNM-8 (0.826; 0.779–0.874). These patterns were consistently observed in the test cohort and, internally, supported the better discrimination ability of the TNM-RPA. Moreover, the TNM-RPA had a higher PVE value (7.1%) for the risk of cancer-specific death than TNM-8 (5.7%). Based on the proposed TNM-RPA, the entire cohort was allocated into stage IA (n = 4748, 74.9%), IB (n = 992, 15.6%), IIA (n = 210, 3.3%), IIB (n = 157, 2.5%), III (n = 211, 3.3%), and IV (n = 24, 0.4%). Accordingly, 608 (9.6%) patients were down-staged and 185 (2.9%) patients were up-staged as a result of the proposed TNM-RPA stage grouping reclassification (Table S1).

Discussion

This large cohort study supports the use of a modified TNM prognostic stage grouping that contains multiple age cutoffs within the current UICC framework for DTC [19]. The proposed stage and prognostic groupings were derived from databases from two institutions that have served patients with DTC nationwide, as tertiary referral cancer centres, since the early 1990s. Although internal validation was performed with sophisticated statistical modelling methods, external validation is encouraged, using high-fidelity cancer registry-level data. These data can be used to confirm the prognostic observations identified in institutional datasets, which often lack essential factors that are required to determine the anatomic extent of DTC at presentation according to TNM-8 [3].

TNM-8 maintains the worldwide acceptability of the traditional TNM staging paradigm and appears to be satisfactory. However, for predicting disease mortality, TNM-8 recommends a single age cutoff of 55 years for all patients with DTC, which polarizes risk stratification. When facing a patient who has been newly diagnosed with DTC, a clinician's foremost task is to make a judgment in regard to personalized survival outcome as well as a tailored decision for the most effective course of treatment using the essential prognostic information available. Recent studies by independent researchers have shown that the mortality risk conferred by increasing age at diagnosis has log-linear characteristics, becoming greatly more important as patients age [7,9]. This phenomenon means that a single age cutoff is irrelevant, answering an easier heuristic question instead [20], no matter how the threshold is raised or lowered. Multiple age cutoffs for older age groups should therefore be adopted, and a corresponding scheme should be developed for the optimal incorporation of the anatomic disease extent for individual risk prediction. The C-index and PVE values were higher

Table 3
Hazard ratios for risk of death and cancer-specific survival for the TNM-8 and proposed TNM-RPA stages for the entire cohort.

	No. of patients (%)	No. of deaths (%)	Cancer-specific survival		Hazard ratio (95% CI)	P
			10 year (%)	15 year (%)		
TNM-8 stage						
I	5280 (83.3)	38 (0.7)	99.4	99.1	Reference	
II	890 (14.0)	65 (7.3)	94.8	89.9	12.45 (8.25–18.80)	< 0.001
III	132 (2.1)	34 (25.8)	79.1	51.1	51.74 (32.13–83.31)	< 0.001
IVA	3 (0.0)	1 (33.3)	66.7	66.7	14.39 (1.84–112.39)	0.011
IVB	37 (0.6)	21 (56.8)	51.2	34.4	94.29 (53.40–166.48)	< 0.001
TNM-RPA stage						
IA	4748 (74.9)	22 (0.5)	99.6	99.5	Reference	
IB	992 (15.6)	24 (2.4)	98.1	95.7	6.09 (3.41–10.90)	< 0.001
IIA	210 (3.3)	15 (7.1)	93.0	91.9	17.67 (9.10–34.29)	< 0.001
IIB	157 (2.5)	23 (14.6)	92.4	81.2	31.92 (17.60–57.87)	< 0.001
III	211 (3.3)	63 (29.9)	75.1	52.7	84.35 (51.48–138.23)	< 0.001
IV	24 (0.4)	12 (50.0)	56.6	51.0	104.25 (50.18–216.57)	< 0.001

Hazard ratios were adjusted for histology, extent of surgery, radioiodine ablation, cancer centre (Samsung Medical Center, Asan Medical Center), and year of surgery (1994–1999, 2000–2003, and 2004–2005). TNM-8, eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control tumor-node-metastasis (TNM) staging system; RPA, recursive partitioning analysis; CI, confidence interval.

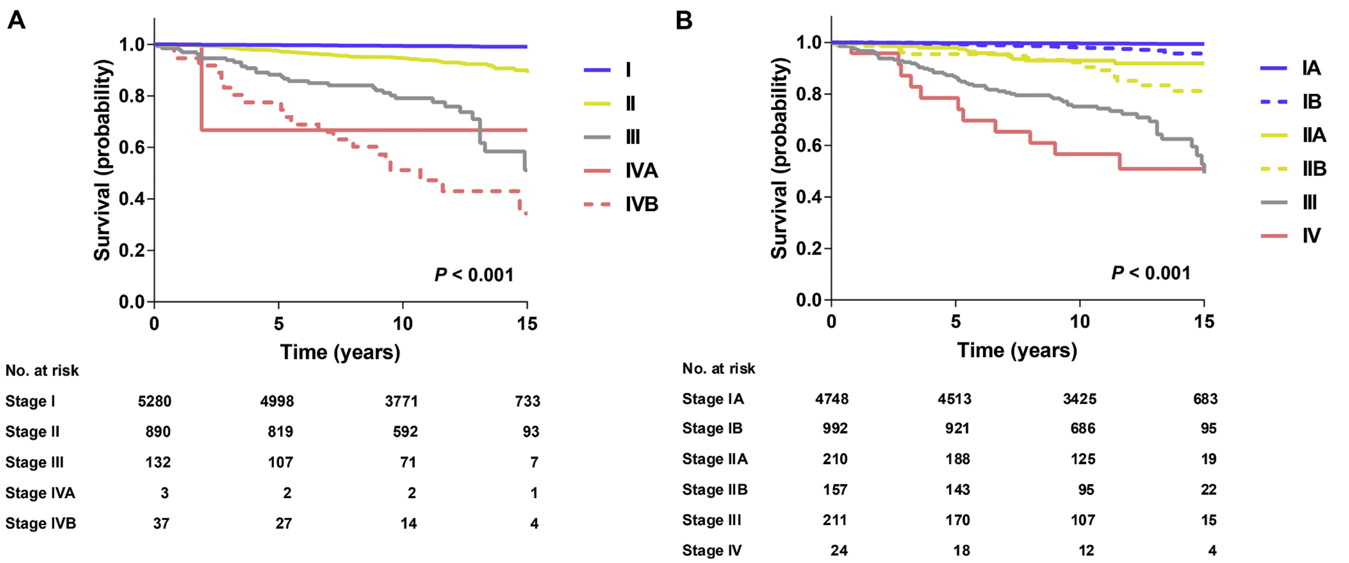

Fig. 2. Kaplan–Meier cancer-specific survival curves according to (A) the TNM-8 and (B) the proposed TNM-RPA stage derived by recursive partitioning analysis for the entire cohort.

Table 4
Proposed TNM-RPA stage derived by recursive partitioning analysis.

Group	Age	M	T		N
			ETE	Size	
IA	< 37	M0	Any ETE	Any size	Any N
	≥37 < 55	M0	Strap muscles or less	Any size	Any N
	≥37 < 55	M0	Posterior compartments	≤2 cm	Any N
IB	< 40	M1	Any ETE	Any size	Any N
	≥55 < 68	M0	Strap muscles or less	≤4 cm	N0/N1a
IIA	≥37 < 55	M0	Posterior compartments	> 2 cm	Any N
	≥68 < 75	M0	Strap muscles or less	≤4 cm	N0/N1a
IIB	≥55 < 75	M0	Strap muscles or less	> 4 cm	N0/N1a
	≥55 < 75	M0	Strap muscles or less	Any size	N1b
III	≥40 < 55	M1	Any ETE	Any size	Any N
	≥55	Any M	Posterior compartments	Any size	Any N
	≥75	M0	Strap muscles or less	Any size	Any N
IV	≥55	M1	Strap muscles or less	Any size	Any N

Definitions of the T and N components are based on the eighth edition TNM staging system. ETE, extrathyroidal extension.

in the proposed TNM-RPA, suggesting that, as a result of the changes in the age cutoff points and decomposition of T components, the revised prognostic stage grouping was superior to TNM-8.

The alternative prognostic groups presented here are consistent with the recent changes in the eighth edition of AJCC/UICC staging manuals for various other cancers, which include relevant non-anatomic factors in pursuit of a more personalized approach rather than the population-based TNM classification [2,19] (for example, prostate specific antigen in prostate carcinoma, carcinoembryonic antigen in colorectal carcinoma, and human papillomavirus status in oropharyngeal carcinoma).

Several mechanisms are involved in the aggressive phenotype of DTC in older patients, such as decreased avidity and response to radioiodine ablation [21], higher frequency of the *BRAF*^{V600E} and *TERT* promoter mutations [22–24], declining immune surveillance against cancer [25], and age-related TSH elevation, which may promote thyrocyte proliferation [26,27]. In addition, the FTC to PTC ratio increases with age: PTC incidence peaks between 30 and 54 years and decreases thereafter, whereas the incidence of FTC and less differentiated thyroid carcinoma generally increases with age [28].

Using our proposed TNM-RPA, we were capable of sub-classifying patients with metastatic DTC (M1) into stage IB (age < 40), III (≥40 < 55), and IV (≥55), mainly according to age thresholds, rather than dichotomizing them as stage II or IVB by the single age cutoff as per TNM-8. Similarly, a recent Israeli study indicated that the severity of DTC in the 45–55-year-old age group should not be underestimated, although mortality among metastatic cases could not be assessed due to the small sample size [10]. Regarding the ETE variables of the TNM-RPA classification, survival estimates were consistently demarcated by the presence or absence of a posterior neck compartment extension that includes vital structures such as the trachea, larynx, oesophagus, and recurrent laryngeal nerves. ETE in only strap muscles or a microscopic extension was not taken into account when splitting the survival outcome, consistent with preexisting evidence [6,16,29].

In conclusion, this large cohort study presents an RPA-based staging scheme that incorporates multiple age cutoffs and essential information about the anatomic disease extent to help predict long-term CSS in individual patients with DTC.

Conflict of interest

None declared.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2018.12.014.

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