



Research article

Impacts of the American Joint Committee on Cancer (AJCC) 8th edition tumor, node, metastasis (TNM) staging system on outcomes of differentiated thyroid cancer in Thai patients

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ABSTRACT

Background: In 2018, the American Joint Committee on Cancer (AJCC) 8th edition (AJCC8) was introduced to replace the previous version (AJCC7) due to superiority of AJCC8 over AJCC7 for better prediction of survival from thyroid cancer.

Aim: To compare AJCC staging systems with the American Thyroid Association (ATA) risk classification for the prediction of 5-year disease-free survival (DFS), and 5-year disease-specific survival (DSS) in Thai patients.

Methods: We retrospectively reviewed all patients with histopathologic diagnosis of DTC who were treated at Theptarin Hospital, Bangkok, Thailand from 1987 to 2019.

Results: The study cohort included 262 differentiated thyroid cancer (DTC) patients (papillary thyroid cancer 89.7% with a median time of follow-up 7.8 years). The number (%) of patients within each stage group by AJCC7 and AJCC8 respectively are as follows: Stage I: 173 (66.0%) vs. 232 (88.5%), Stage II: 33 (12.6%) vs. 24 (9.2%), Stage III: 36 (13.7%) vs. 2 (0.8%), Stage IV: 20 (7.7%) vs. 4 (1.5%). The ATA high risk group was found in 24.3% of AJCC7 Stage I compared with 23.7% of AJCC8 Stage I. The 5-year DFS rates in patients classified as stages I, II, III, and IV by AJCC8 were 87.9%, 45.8%, 0% and 25%, respectively. The 5-year DSS rates in patients classified as stages I, II, III and IV by AJCC8 were 98.7%, 100%, 100% and 0%, respectively. AJCC8 was more predictive of DFS rate than AJCC7.

Conclusions: Our study is in accord with previous studies that AJCC8 downstage a significant percentage of patients with DTC and correlated with better prognostic validity. However, even a person at low risk for mortality can be at high risk for recurrence.

1. Introduction

Over the past four decades, the incidence of differentiated thyroid cancer (DTC) has increased over time, predominantly due to the widespread uses of imaging modalities [1]. The diagnosis and management also underwent considerable changes with more evidence-based and consensus-based guidelines [2, 3, 4]. One of the most recent milestones was the 8th edition of the tumor-node-metastasis (TNM) staging system proposed by the American Joint Committee on Cancer (AJCC) which has

been incorporated in the management of DTC since 2018 [5]. Classification system for thyroid cancer provides a basis for mutual communications between clinicians, selection of patients for multiple treatment options and clinical trials. Therefore, its accuracy and reproducibility from diverse geographic location and clinical setting are essential.

The goal of AJCC staging system is to predict DTC survival which differs from the American Thyroid Association (ATA) risk stratification system which focuses on the risk of DTC recurrence. The survival rate of patients is generally favorable with a 5-year survival rate over 98%

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[1]. The current therapeutic strategies are rapidly evolving towards less aggressive treatments. Nevertheless, up to 25% of patients will develop recurrence in both locoregional and distant sites [6]. Therefore, staging system should also stratify the risk of recurrence to provide guidance for treatment planning. The previous AJCC edition in 2010 (the 7th edition, AJCC7) had been criticized mainly for poor survival stratification especially in patients with higher stages and for a poor predictor of recurrence [7]. The revised 8th edition (AJCC8) introduced the new cut-off age for stage I from 45 to 55 years, downgrading regional lymph node metastasis to stage II in older patients, and the removal of microscopic extra-thyroidal extension (ETE) as an indicator of T3 disease [8]. As a result, the revised T3, newly defined as a tumor greater than 4 cm and confined to the thyroid gland (T3a) or gross ETE to the strap muscles (T3b), was the most significant change among TNM staging system.

In the past 5 years after its introduction, several comparative studies from established DTC patient cohorts worldwide demonstrated the superiority of AJCC8 over AJCC7 for prediction of the survival and recurrence rate [9, 10, 11, 12, 13]. A recent meta-analysis showed that stage migration patterns were observed mostly from stage II to stage I (varied from 66–85%) in each study [14]. However, the impact of this revised staging system differed by race and ethnicity, with the least impact found in Hispanics and Asian-Pacific Islanders [15]. There has also been a paucity of data on the comparison between the revised AJCC and other prognostic tools to predict the outcomes of DTC. The MACIS (Metastases, Age, Completeness of resection, Invasion, Size) prognostic system which had been used effectively in papillary thyroid carcinoma (PTC) for more than 3 decades [16] was recently demonstrated to be inferior to the AJCC8 in the survival outcome [17]. However, no comparison of recurrence outcomes between the MACIS and AJCC8 had been done. Therefore, the aim of this study was 1) to assess quantitatively how changing the AJCC staging system affected the stage migration patterns 2) to examine the long-term outcomes between both AJCC7 and AJCC8 3) to compare the revised AJCC with the MACIS prognostic system in patients with PTC for predicting the risk of recurrence in a cohort of Thai patients in order to provide a more generalizable use of this revised staging system in underrepresented population.

2. Materials and methods

2.1. Data sources

All consecutive patients with a histological diagnosis of DTC who had been treated at Theptarin Hospital, Bangkok, Thailand from 1987 to 2019 were retrospectively reviewed. They were categorized in accordance with the ATA risk of recurrence stratification system [2]. Patients with one or more of the following features were excluded: age <15 years, non-DTC diagnosis (poorly differentiated thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer, and other thyroid cancers), incomplete data for staging system, and follow-up time less than 6 months. Duration of follow-up period was defined as the time between the initial surgery and the last visit.

2.2. Surgical treatment and adjuvant therapy

At our institution, we performed total thyroidectomy for tumors size more than 1.0 cm preoperatively on ultrasound. Patients with tumors size ≤1 cm in size underwent total or hemithyroidectomy at the discretion of the treating surgeon. Central neck dissection was performed only when suspicious nodes were identified on preoperative imaging or by intraoperative finding. Dissection of the lateral neck was performed only in patients with confirmed lateral neck nodal metastases based on either preoperative fine-needle aspiration biopsy or intraoperative frozen section. All of operations were limited to 5 high-volume surgeons (experienced with ≥25 cases per year) during the study period. Most patients with total thyroidectomy received postoperative radioactive iodine (RAI) ablation. Our ablation protocol used RAI activities prescribed at the

attending physicians' discretion (generally 100–200 millicurie). Follow-up consisted of clinical history, examination, serum thyroglobulin (Tg) level and anti-thyroglobulin (anti-Tg) antibodies monitoring, and structural imaging using neck ultrasound.

Final disease status was determined based on the last clinical visit during study period. Disease-specific survival (DSS) was defined as the time from the date a patient was diagnosed and ended at the time of death from DTC or at the last visit. Disease-free survival (DFS) was defined as the time from the date a patient was diagnosed to the date of recurrence or at the last visit. Comparison between group stratification based on AJCC7 and AJCC8 was performed in regarding to ATA risk classification, the 5-year DSS and the 5-year DFS. In patients with PTC, the 5-year DFS was compared between the revised AJCC and the MACIS scores. This study was approved by the Ethics Committee of Theptarin Hospital (EC No.2–2019). No informed consent to participate was required as a retrospective study.

2.3. Statistical analysis

Descriptive data was reported in mean with standard deviation, median with interquartile range (IQR), and number with percentage. Qualitative variables were compared using Pearson chi-square and Fisher tests. Quantitative variables were analyzed using Student's t test for independent samples. Agreement for categorical data was evaluated by using the Cohen's kappa coefficient. Survival analysis was performed using univariate and multivariate Cox proportional hazards regression models. Survival curves were generated by the Kaplan-Meier method and log-rank tests were used to compare survival rates between stages. Differences in survival between AJCC editions were also assessed by using Stage I as a reference group and represented as hazard ratios (HRs) and 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS Statistical Package, version 24.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

The study cohort consisted of 262 DTC patients (female 81.3%, mean age 42.6 ± 14.5 years, papillary thyroid cancer 89.7%, the median tumor size of 2.0 cm (IQR 1.3, 3.0 cm) with the median time of follow-up 94 months (IQR 35, 175 months). Most patients underwent total thyroidectomy (89.3%) as shown in Table 1. Recurrence, death from DTC, and death from other causes occurred in 60 (22.9%), 4 (1.5%), and 8 (3.1%) of the patients, respectively. The overall 5-year DFS and DSS rates of the patients were 78.0% and 97.4%, respectively.

3.2. Stage migration patterns from AJCC staging system 7th to 8th edition

As shown in Figure 1, use of AJCC8 shifted classification to earlier stages: stage I from 66.0% to 88.5%; stage II from 12.6% to 9.2%; stage III from 13.7% to 0.8%; stage IV from 7.7% to 1.5%. In the overall cohort, 20% of patients were downstaged from the AJCC7 to AJCC8 and no patients were upstaged. When analyzing pathological tumor stage (T classifications) from TNM staging, of 77 patients classified as having T3 disease on the AJCC7, 34 (44.2%) patients were downgraded to the T1 category on the AJCC8 and 19 (24.7%) patients were downgraded to the T2 category. The revised T3 reduced the number of patients sharply when compared with the T3 from AJCC7 (Figure 2).

3.3. The impact of the revised AJCC staging system on ATA risk classification

Applying the AJCC8, stage I patients were stratified as low-risk in 58.6%, as intermediate-risk in 17.7% and as high-risk in 23.7%. Those in stage II were classified as low-risk in 16.7%, as intermediate-risk in

Table 1. Clinical characteristics and pathological details of patients with differentiated thyroid carcinoma.

	Total (n = 262)
Age at diagnosis (years)	42.6 ± 14.5
<45	153 (58.4)
45-54	56 (21.4)
55-74	48 (18.3)
≥75	5 (1.9)
Female (%)	213 (81.3)
Pathology (%)	
Papillary Thyroid Carcinoma	235 (89.7)
Follicular Thyroid Carcinoma	20 (7.6)
Others	7 (2.7)
Tumor size (cm)	2.0 (IQR 1.3,3.0)
<2	107 (40.8)
2-4	128 (48.9)
>4	27 (10.3)
Extra-thyroidal extension (%)	
No ETE	200 (76.3)
Microscopic ETE	42 (16.0)
Gross ETE	20 (7.7)
Multifocality (%)	65 (24.8)
Lymph node metastasis (N1)	62 (23.7)
Distant metastasis (%)	14 (5.3)
Total thyroidectomy (%)	234 (89.3)
RAI treatment (%)	258 (98.5)
RAI activity (millicurie)	130 ± 40.9

Data are expressed as the mean ± SD, median (percentiles 25–75).
RAI: radioactive iodine.

16.7% and as high-risk in 66.6%. All stage III and stage IV patients were classified as high-risk as shown in Table 2. The magnitude of reclassifications in ATA low-and intermediate-risk patients led to a weak level of agreement between AJCC7 and AJCC8 (kappa 0.08 and 0.16, respectively; $p < 0.05$ for both comparisons). However, In ATA high-risk

patients, the agreement between the two classifications was considered moderate (kappa 0.45, $p < 0.001$).

3.4. Disease-free survival (DFS) and disease-specific survival (DSS) from AJCC staging system 7th to AJCC 8th edition

As shown in Figure 3 and Figure 4, the Kaplan-Meier plot for stage-dependent DFS and DSS showed a statistically significant value for both editions. However, DFS had a more significant p -value using the AJCC8 than the AJCC7 edition. The 5-year DFS rates in patients classified as stages I, II, III, and IV by AJCC8 were 87.9%, 45.8%, 0% and 25%, respectively. The 5-year DSS rates in patients classified as stages I, II, III and IV by AJCC8 were 98.7%, 100%, 100% and 0%, respectively. The AJCC8 better stratified the 5-year DFS among stages by showing higher HRs when compared with Stage I as a reference group (Table 3).

3.5. Disease outcomes at the last follow-up according to AJCC7 and AJCC8

After the median follow-up of 7.8 years, the rate of excellent response was obtained in 66.4% of all patients. As shown in Table 4, the rate of structural incomplete and biochemical incomplete response differed greatly between both editions and those differences were mainly observed in the higher stages. The agreement between the two classifications in relationship to disease outcomes was considered low.

3.6. Comparison of DFS between the AJCC8 and the MACIS score

The results of the Kaplan–Meier analysis demonstrated the poorer performance of the MACIS score when compared with the AJCC8 as shown in Figure 5. While the AJCC8 could identify the risk of recurrence at lower stage (stage I versus II), the MACIS score at less than 6.99 performed worse in predicting the 5-year DFS as shown in Table 5.

4. Discussion

This study comprehensively analyzed the clinical impact of revised AJCC staging system in the stage reclassification and long-term outcomes

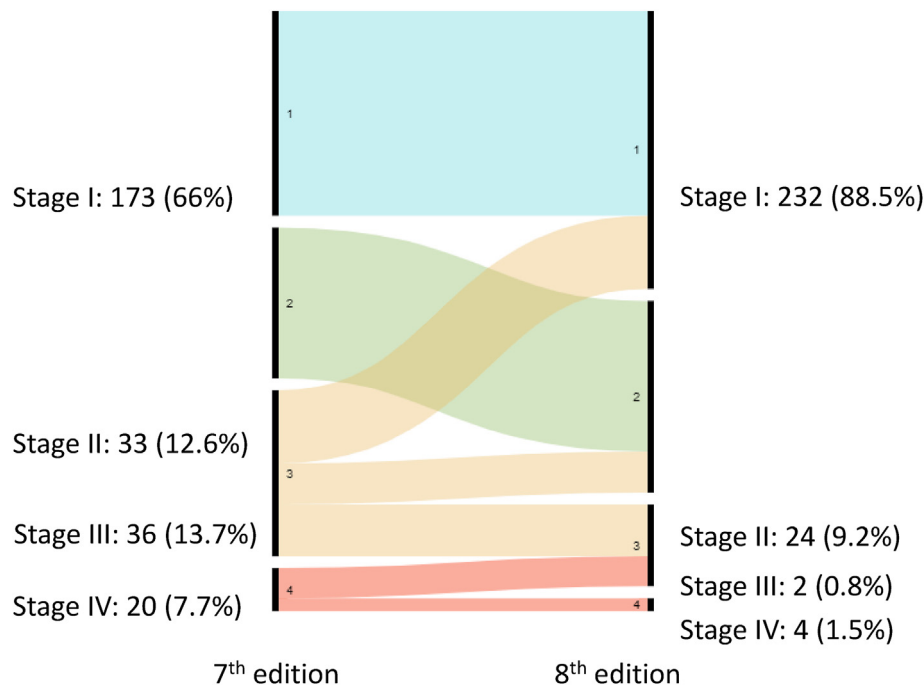


Figure 1. Alluvial diagram of TNM stage migration with AJCC7 and AJCC8.

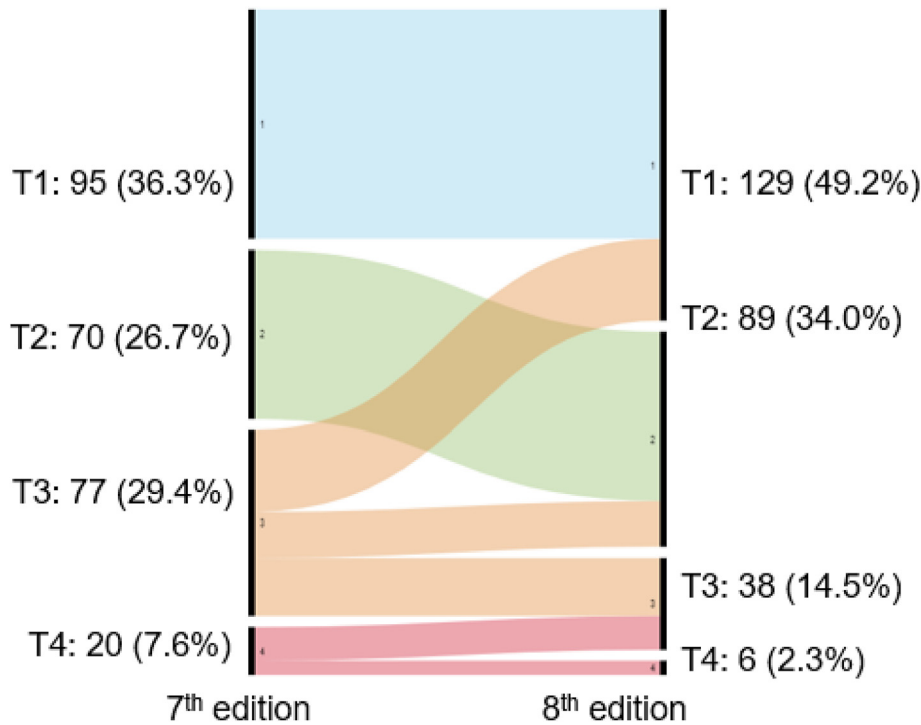


Figure 2. Alluvial diagram of tumor staging migration with AJCC7 and AJCC8.

Table 2. Comparison of ATA risk according to the AJCC7 and AJCC8.

ATA risk	AJCC 7 th edition n (%)				AJCC 8 th edition n (%)				Kappa	P-value
	I	II	III	IV	I	II	III	IV		
Low	100 (57.8)	22 (66.6)	17 (47.2)	1 (5.0)	136 (58.6)	4 (16.7)	0	0	0.08	0.029
Intermediate	31 (17.9)	2 (6.1)	10 (27.8)	2 (10.0)	41 (17.7)	4 (16.7)	0	0	0.16	0.017
High	42 (24.3)	9 (27.3)	9 (25.0)	17 (85.0)	55 (23.7)	16 (66.6)	2 (100.0)	4 (100.0)	0.46	<0.001

ATA: American Thyroid Association, AJCC: American Joint Committee on Cancer.

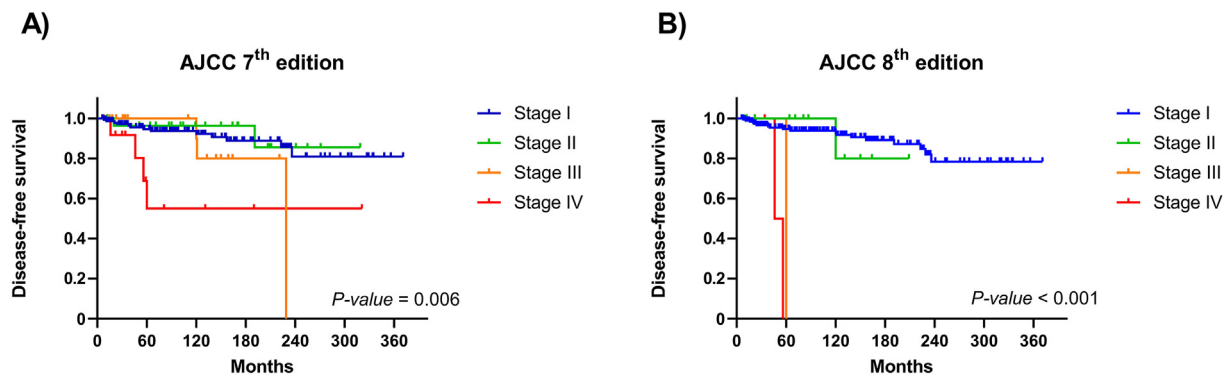


Figure 3. Kaplan-Meier analysis of disease-free survival (DFS) in patients with differentiated thyroid carcinoma classified according to A) the 7th edition of AJCC B) the 8th edition of AJCC.

among Thai patients with DTC. Consistent with previous published studies [10, 11, 12, 13, 14], our data supported that AJCC8 more accurately predicted survival and better identified the risk of recurrence when compared with the previous edition. Moreover, the AJCC8 could also identify the risk of recurrence at lower stage better than the MACIS score.

Patient age at the initial diagnosis of thyroid cancer was a very strong predictor for the outcomes [18]. Therefore, the cut-off threshold for the age at the diagnosis plays a central role of TNM staging. Guidelines all

over the world in the last decade advocated treatment de-escalation in the low-risk thyroid cancer. To support these recommendations, published data repeatedly confirmed that the shift in age threshold from 45 to 55 years within the AJCC criteria better correlated with the survival rate [19, 20]. For patients over 55 years old, the ETE extension into the adjacent tissues or organs is considered the most important prognostic factor for disease recurrence and also tends to have more aggressive histological subtypes. The severity of locally advanced thyroid cancer

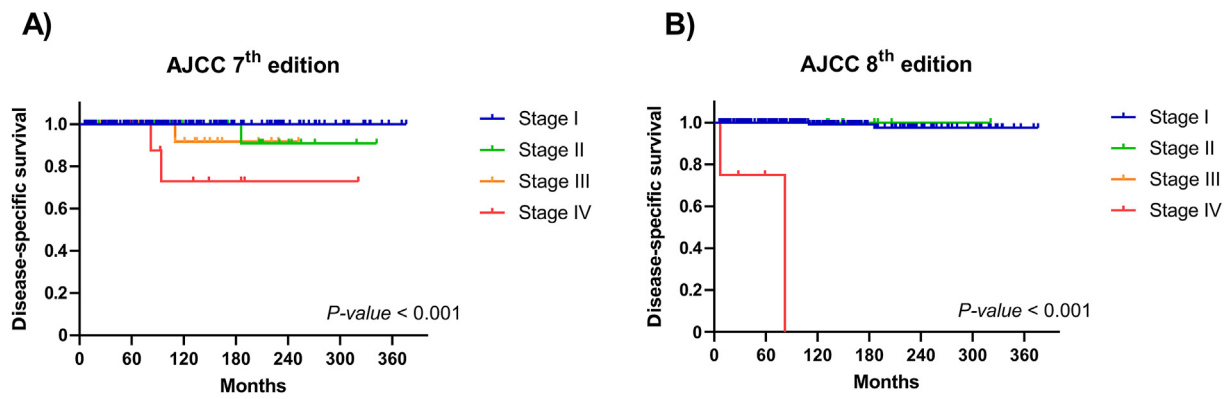


Figure 4. Kaplan-Meier analysis of disease-specific survival (DSS) in patients with differentiated thyroid carcinoma classified according to A) the 7th edition of AJCC B) the 8th edition of AJCC.

Table 3. Comparison of disease-free survival (DFS) between individual stages in the AJCC7 and AJCC8.

Stage	AJCC 7 th edition			AJCC 8 th edition		
	HR	95%CI	P-value	HR	95%CI	P-value
I	Reference	-	-	Reference	-	-
II	1.26	0.55–2.89	0.581	3.93	2.09–7.41	<0.001
III	2.89	1.49–5.63	0.002	7.55	1.81–31.46	0.005
IV	4.74	2.39–9.38	<0.001	5.64	1.73–18.39	0.004

AJCC: American Joint Committee on Cancer, CI: confidence interval, HR: hazard ratio.

Table 4. Comparison of disease outcomes at the last follow-up according to each stage in the AJCC7 and AJCC8.

Treatment response	AJCC 7 th edition n (%)				AJCC 8 th edition n (%)				Kappa	P-value
	I	II	III	IV	I	II	III	IV		
Structural incomplete	9 (5.2)	6 (18.2)	2 (5.5)	7 (35.0)	15 (6.5)	6 (25.0)	1 (50.0)	2 (50.0)	0.45	<0.001
Biochemical incomplete	30 (17.3)	3 (9.1)	10 (27.8)	2 (10.0)	37 (15.9)	8 (33.3)	0	0	0.34	<0.001
Indeterminate	18 (10.4)	2 (6.1)	4 (11.1)	3 (15.0)	26 (11.2)	1 (4.2)	0	0	0.06	0.333
Excellent	116 (67.1)	22 (55.6)	20 (55.6)	8 (40.0)	154 (66.4)	9 (37.5)	1 (50.0)	2 (50.0)	0.19	<0.001

AJCC: American Joint Committee on Cancer.

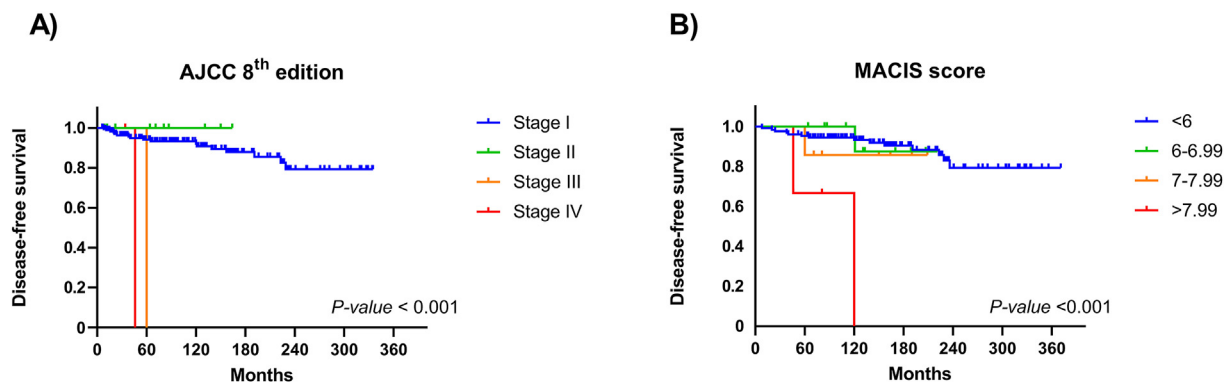


Figure 5. Kaplan-Meier analysis of disease-free survival (DFS) in patients with papillary thyroid carcinoma classified according to A) the 8th edition of AJCC B) the MACIS prognostic system.

based on the involved anatomical structures had been addressed clearly in the revised AJCC staging [21]. However, the effect of revised staging criteria toward the recurrence rate has been less well-studied in the public use databases due to their insufficient data to obtain the recurrence rate. Therefore, each region's own database should be used to

examine the generalizability of universal staging systems. Our data also confirmed the greater accuracy of the revised age threshold in predicting long-term outcomes. Each edition of AJCC intended to apply for tumor staging at least 5–10 years until enough additional data were available to change their recommendations. As mortality from DTC increases

Table 5. Comparison of disease-free survival (DFS) between MACIS prognostic score and AJCC8.

MACIS				AJCC 8 th edition			
Score	HR	95%CI	P-value	Stage	HR	95%CI	P-value
<6	Reference	-	-	I	Reference	-	-
6–6.99	2.02	0.96–4.24	0.064	II	3.93	2.09–7.41	<0.001
7–7.99	3.18	1.40–7.22	0.006	III	7.55	1.81–31.46	0.005
>7.99	6.66	3.04–14.61	<0.001	IV	5.64	1.73–18.39	0.004

MACIS: distant Metastasis, patient Age, Completeness of resection, local Invasion, and tumor Size.

progressively with advancing age, the concept of ‘age’ as a continuous variable, not a cut-off threshold might be adopted in the future if sophisticated methods of gathering data were available.

Regarding the patterns of stage migration, our study confirmed earlier studies that downstaging mainly found in patients with advanced stages. However, the differences of migrating patterns between stages were observed in our cohort. In contrast to a recent meta-analysis which reported that more than three-fourths of patients with stage II migrated to stage I [14], our data showed that only one-fourth of patients with stage II migrated to stage I. On the other hand, more than three-fourths of patients originally in stage III moved to stage I. Significant differences in cancer characteristics between studies likely affected variation in stage migration. Our data were more like Korean studies than Caucasian patients [9, 22]. When analyzing the T component of TNM staging, almost half of the original T3 category downgraded to T1 category. The AJCC8 edition placed an important milestone for gross ETE invading strap muscles from the viewpoint of survival predictor. ETE has been observed in 5%–45% of all DTC patients in which majority of them were microscopic ETE [4]. In a recent Korean study, further ETE modifications by limiting gross ETE invading only strap muscles with tumor size >4 cm only to regard as T3 category showed better accuracy to predict DSS [23]. Therefore, further research should be done to assess the prognostic value of gross ETE in various tumor sizes in different population to validate the interesting findings from the Korean study.

In 2006, the ATA recognized that the risk of DTC recurrence was poorly predicted by AJCC 6th edition, the guideline committees intervened to propose a newly three-tier stratification system known as the ATA Initial Risk Stratification System which had been used since 2009 [24]. However, further amendments were constantly proposed with suggestions to adopt tumor genetic biomarkers to refine its predictability [25]. In this regard, even a person at low risk for mortality can be at high risk for recurrence as revealed by ATA high-risk group up to one-fourth of Stage I patients. It should be emphasized that downstaging could prevent overtreatment in patients with good prognosis for cancer death but patients with high-risk features for recurrence should receive appropriate treatments to prevent morbidity from recurrence disease.

With the difficulties of predicting risk of death, recurrence, and the response to treatment throughout a patient's DTC course from a single prognostic system, integrating the approaches with the concept of dynamic risk stratification proposed by ATA might be a practical way to follow-up DTC patients [26]. In addition to disease-specific mortality, local disease recurrence remains a significant challenge for patients with DTC and their clinicians. With the better DFS prediction outcomes from AJCC8, confirmed by our present data and others, the AJCC8 could serve as a simple initial predictor for recurrence if detailed information required for the MACIS or ATA risk stratification could not be reached in the busy clinic settings.

There is a few limitations of this study. First, the relatively short follow-up period of less than 10 years prevented us from analyzing 10-year DFS and DSS. Second, the protocol treatment in our institute had not been updated with the current trend of less aggressive treatments in both surgery and RAI ablation. Therefore, patients with higher T stage and microscopic ETE may have received more aggressive treatment and surveillance, which may influence the results of recurrence rate. Third,

our study population had the exceptionally low mortality rate which could have affected the impact of staging system on DSS. Finally, all pathological reports were reviewed from medical records only. The quality and completeness of pathological reports might affect the accuracy of designated staging category. However, our data were retrieved from a tertiary thyroid center for DTC patients in Thailand and is one of the first cohort in Southeast Asia to validate both AJCC editions for thyroid cancer.

5. Conclusion

Our study in Thai patients with DTC is in accord with previous studies that AJCC8 downstage a significant percentage of patients and correlated with better prognostic validity. These data are evidence that the revised AJCC stages are generalizable to Southeast Asian patients.

Declarations

Author contribution statement

Yotsapon Thewjitcharoen and Waralee Chatchomchuan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Krittadhee Karndumri: Conceived and designed the experiments; Analyzed and interpreted the data.

Siriwan Butadej and Soontaree Nakasatien: Conceived and designed the experiments.

Veekij Veerasomboonsin: Performed the experiments; Analyzed and interpreted the data.

Sriurai Porramatikul, Sirinate Krittiyawong, Ekgluck Wanothayaroj, Rajata Rajatanavin and Thep Himathongkam: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Auchai Kanchanapituk: Analyzed and interpreted the data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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