Is a simplified TNM staging system more clinically relevant than the American Joint Committee on Cancer system for the follicular variant of papillary thyroid cancer?

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Background: Despite the recent release of the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual, risk stratification for the follicular variant of papillary thyroid cancer (FVPTC), which is the second common variant of papillary thyroid carcinoma (PTC) after classical PTC, remains controversial. This study aimed to develop a more accurate and relevant staging system specifically for FVPTC.

Methods: Patients with FVPTC who were included in the Surveillance, Epidemiology, and End Results (SEER) open database between 2010 and 2015 were divided into 47 groups according to their TNM classifications and age. Subsequently, these 47 groups were categorized into appropriate stages based on Kaplan-Meier survival curves, mortality analyses, a Cox proportional hazards model, and clinical considerations.

Results: Our retrospective analysis of 17,628 cases yielded the following new staging classification: stage I, defined as age <55 years and any T/N/M or age ≥55 years and T1-3/any N/M0 (n=17,427, 98.85%); stage II, age ≥55 and T4/any N/M0 or age ≥55 and any T/N0/M1 (n=173, 0.99%); and stage III, age ≥55 and any T/N1/M1 (n=28, 0.16%). The overall mortality rates per 1,000-person-years were 4.135 [95% confidence interval (CI): 3.653–4.681], 71.193 (95% CI: 51.354–98.697), and 199.744 (95% CI: 115.983–343.997) for our new stages I, II, and III, respectively. The hazard ratios for the new stages II and III (reference: stage I) were 5.081 (95% CI: 3.110–8.301) and 21.690 (95% CI: 11.402–41.258), respectively.

Conclusions: Compared to the 8th edition of the AJCC staging system, our newly proposed system provided more accurate risk stratification for patients with FVPTC, as demonstrated by actual survival and mortality outcomes. This new model may thus help guide more personalized treatment for these patients.

Keywords: Follicular variant of papillary thyroid carcinoma (FVPTC); Surveillance, Epidemiology, and End Results (SEER); American Joint Committee on Cancer (AJCC); staging system; risk stratification

Submitted Nov 29, 2019. Accepted for publication Feb 17, 2020.

doi: 10.21037/atm.2020.03.111

View this article at: http://dx.doi.org/10.21037/atm.2020.03.111

Introduction

The follicular variant of papillary thyroid carcinoma (FVPTC) is histologically characterized by follicular cell growth patterns and the presence of nuclear features of classical PTC (CPTC) (1,2). FVPTC is the most common subtype of malignant papillary thyroid tumor apart from CPTC, accounting for up to 23% of all PTCs (2,3). Recent statistics have suggested that the incidence of FVPTC is increasing steadily, especially in Western countries (4-6), which has drawn increased attention for the diagnosis, management, and prognosis of FVPTC.

The current consensus among thyroid academics is that there are only a few differences between FVPTC and CPTC; moreover, the overall management of the two malignancies are similar, and patients with FVPTC and CPTC have identical long-term outcomes (7-12). However, research have shown that despite these similarities, patients with FVPTC present clinically with more favorable clinicopathologic features and are stratified into lower and less-aggressive tumor risk categories (13). For example, a recent largescale multinational study suggested that FVPTC was associated with lower rates of extrathyroidal invasion, lymph node metastasis, disease recurrence, and mortality when compared with CPTC (14). However, there was no difference between CPTC and FVPTC in the use of clinical radioiodine-131 treatment (14), despite the potentially poorer prognosis typically associated with this therapy. Therefore, patients with FVPTC might expect better prognosis with tailored disease management.

According to the American Thyroid Association Management guidelines, the goals of initial therapy for patients with PTC include accurate disease staging and risk stratification, the minimization of adverse and unnecessary therapy, and the achievement of a favorable prognosis (15). Despite these recommended goals, the most recent 8th edition of the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system, which is the most widely used risk stratification system, does not distinguish FVPTC from PTC (16). Thus, the present study aimed to develop a more accurate and clinically relevant TNM staging system for patients with FVPTC.

Methods

Patients and database

For this study, we obtained the data of patients with FVPTC who were included in the openly accessible Surveillance, Epidemiology, and End Results (SEER) database (National Cancer Institute, Bethesda, MD, USA) between 2010 and 2015. Since SEER is a publicly available database with anonymized data, no ethical review was required. Additionally, a data use agreement was signed for this project.

Accounting for the favorable prognosis of FVPTC, we selected overall survival (OS) data, rather than cancer-specific survival (CSS). Furthermore, we excluded 644 cases in the following manner: 632 cases with recorded categories of T0, TX, NX, N1NOS, or T4NOS (In SEER database, a status described as "N1NOS" or "T4NOS" is distinguished, but it does not exist in the TNM criteria defined in the TNM/AJCC staging system. Thus, we excluded cases that recorded categories of N1NOS or T4NOS), 11 cases with unclear survival duration, and 1 case in which the patient died during the 83rd month of follow-up of an unknown cause. The following data were collected for all patients: age at diagnosis, year of diagnosis, sex, race, T/N/M category, TNM stage according to the 8th edition of AJCC, tumor size, number of tumor foci, extension, radiation status, and surgical modality. Missing or unclear data were treated as user missing values.

Development process

We initially divided all cases into 2 groups using the cut-off age of 55 years. Next, we divided the total patient sample into 47 groups according to the T, N, and M categories. In this step, we excluded groups which contained cases below 10 and with no mortality as follows: age <55: T1N1aM1 (n=1), T1N1bM1 (n=2), T2N0M1 (n=1), T2N1aM1 (n=1), T2N1bM1 (n=1), T3N1aM1 (n=4), T4N0M1 (n=3), T4N1aM1 (n=1); age ≥55: T4N1bM1 (n=9), T1N1aM1 (n=6), T1N1bM1 (n=2), T2N1bM1 (n=4). After filtering out 679 cases from the total data, 17,628 patients were included in the study.

Then, we divided these groups into three new proposed stages based on the results of the clinical experiences and Kaplan-Meier (K-M) survival curves. Furthermore, we calculated the probability of mortality per 1,000-person-years. Cox proportional hazards models were used to assess the variables associated with prognosis in the three final stages after adjusting for age at diagnosis, year of diagnosis, sex, race, tumor size, number of tumor foci, tumor extension, radiation, and surgical modality.

Table 1 Demographics and clinical characteristics of 17,628 patients with FVPTC identified in the SEER database between 2010 and 2015

Variable	N (%)
Gender	
Female	13,991 (79.36)
Male	3,637 (20.64)
Race	
White	14,173 (81.57)
Black	1,604 (9.23)
Other	1,598 (9.20)
Age at diagnosis	
<55	10,982 (62.30)
≥55	6,646 (37.70)
Year of diagnosis	
2010–2012	7,895 (44.79)
2013–2015	9,733 (55.21)
Tumor size, mean (SD), mm	29.34 (101.28)[a]
Number of tumor foci	
1	9,317 (53.18)
≥2	8,203 (46.82)
Extension	
No	15,729 (89.43)
Yes	1,858 (10.57)
T category	
T1	10,685 (60.61)
T2	3,523 (19.98)
T3	3,143 (17.84)
T4	277 (1.57)
N category	
N0	15,436 (87.57)
N1a	1,372 (7.78)
N1b	820 (4.65)
M category	
M0	17,525 (99.41)
M1	103 (0.59)
Radiation	
None/refused	9,596 (54.43)
Yes	8,032 (45.57)
Surgical procedure	
Biopsy	44 (0.25)
Lobectomy	2,671 (15.23)
Subtotal or near-total thyroidectomy	392 (2.24)
Total thyroidectomy	14,430 (82.28)

[a], standard deviation. FVPTC, follicular variant of papillary thyroid carcinoma; SEER, Surveillance, Epidemiology, and End Results; SD, standard deviation.

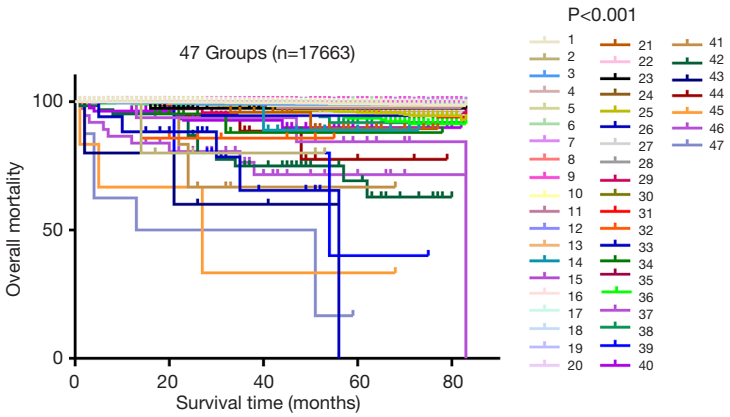
Statistical analysis

The demographic and clinical information are summarized as frequencies, proportions, and mean values ± standard deviations, as appropriate. As noted above, K-M curves, Cox proportional hazards models, and mortality per 1,000-person-year were used in the survival analyses. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 22.0 (IBM Corp., Armonk, NY, USA), Stata/SE version 15 (Stata Corp, College Station, TX, USA), GraphPad Prism version 7 (GraphPad Software Inc., La Jolla, CA, USA), or MATLAB version 2018a (MathWorks, Cambridge University Press, Cambridge, UK).

Results

Patient demographics

The demographic and clinical characteristics of the included patients are summarized in *Table 1*. The 17,628 cases included 13,991 female and 3,637 male patients (approximate female:male ratio, 3.85:1). At diagnosis, 10,982 patients were younger than 55 years, and 6,646 were 55 years or old (approximate ratio, 1.65:1). Moreover, 10,685, 3,523, 3,143, and 277 patients had T1, T2, T3, or T4 diseases, respectively; 15,436, 1,372, and 820 patients had N0, N1a, or N1b disease, respectively; and 17,525 and 103 patients had M0 or M1 disease, respectively.



Note: age<55, 1-24; 1, T1N0M0; 2, T1N0M1; 3, T1N1aM0; 4,T1N1aM1; 5, T1N1bM0; 6, T1N1bM1; 7, T2N0M0; 8, T2N0M1; 9, T2N1aM0; 10, T2N1aM1; 11, T2N1bM0; 12, T2N1bM1; 13, T3N0M0; 14, T3NOM1; 15, T3N1aM0; 16, T3N1aM1; 17, T3N1bM0; 18, T3N1bM1; 19, T4N0M0; 20, T4N0M1; 21, T4N1aM0; 22, T4N1aM1; 23, T4N1bM0; 24, T4N1bM1; age≥55, 25-47; 25, T1N0M0; 26, T1N0M1; 27, T1N1aM0; 28,T1N1aM1; 29, T1N1bM0; 30, T1N1bM1; 31, T2N0M0; 32, T2NOM1; 33, T2N1aM0; 34, T2N1bM0; 35, T2N1bM1; 36, T3N0M0; 37, T3N0M1; 38, T3N1aM0; 39, T3N1aM1; 40, T3N1bM0; 41, T3N1bM1; 42, T4NOM0; 43, T4N0M1; 44, T4N1aM0; 45, T4N1aM1; 46, T4N1bM0; 47, T4N1bM1.

Figure 1 Kaplan-Meier curves for estimated survival among 47 groups of FVPTC patients divided according to TNM categories and an age of 55 years. FVPTC, follicular variant of papillary thyroid cancer; TNM, tumor, node, and metastasis.

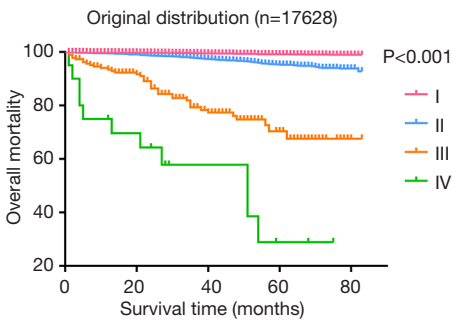


Figure 2 Kaplan-Meier curves for estimated survival after dividing the 47 groups into four stages.

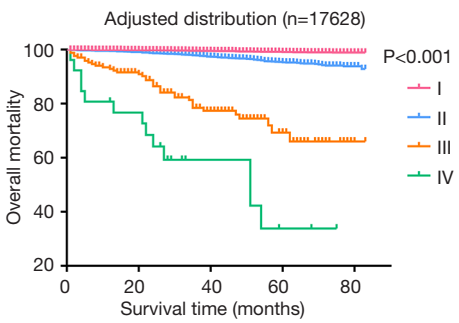


Figure 3 Adjusted Kaplan-Meier curves for estimated survival based on the original distribution.

The proposed TNM staging system

Patients were divided into 47 groups, as described in the materials and methods section (see *Table S1*). *Figure 1* presents the survival status of all the patients based on the distribution into these 47 groups. After excluding groups that contained cases below 10 and no mortality, we then used the survival trends to classify the remaining groups into four stages (*Figure 2*), which we termed "original distribution". However, a few groups with fewer than 10 cases and with mortality were included because of the clinical and statistical significance.

Additionally, the statistical results of the group of patients <55 years with T3/N0/M1 and containing ten cases, were inconsistent with the clinical prognosis because patients in this group had a more favorable prognosis than those in the stage II groups in clinical settings, which might be attributable to an insufficient number of cases. We then used the clinical experiences to adjust this distribution, treating those aged <55 years with T3/N0/M1 disease as stage I, which we termed "adjusted distribution", as shown in *Figure 3*. We considered patient aged ≥55 years and with a distant metastasis as high-risk factor. We assigned patients who met those criteria to stage IV. As shown in *Figure 4*, however, this division decreased the difference between stages III and IV when compared with the adjusted distribution.

As shown in *Figure 3*, we observed few differences between stage I, which was composed of groups of age <55 and any T/any N/M0, and stage II, which consisted of groups from age <55 and any T/any N/M1 or age ≥55 and T1-3/any N/M0. Then, we analyzed the shape of

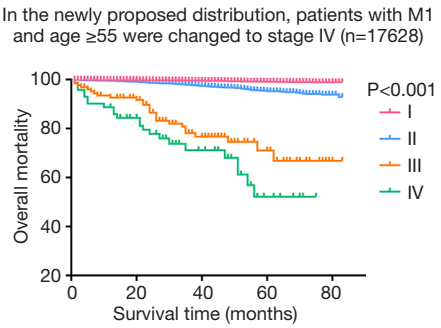


Figure 4 Kaplan-Meier curves for estimated survival among patients aged ≥55 years and M1 categories as stage IV.

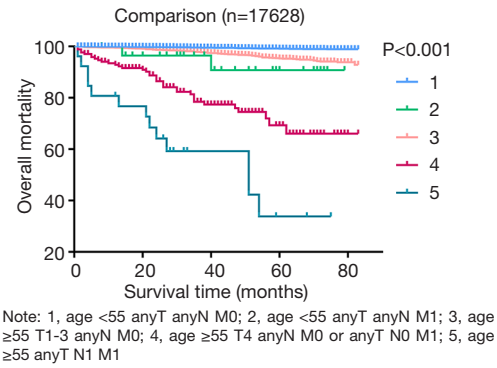


Figure 5 Kaplan-Meier curves for estimated survival curves according to the following stages: age <55 years, any T/any N/M0; age <55 years, any T/any N/M1; age ≥55 years, T1-3/any N/M0; age ≥55 years, T4/any N/M0 or any T/N0/M1; age ≥55 years, any T/N1/M1.

Figure 5, which revealed that the trends of curves of those three groups were similar. This indicated to us that those three groups share similar mortality rates, and the adjusted Cox analysis and mortality per 1,000-person-year of these three groups are shown in Table S2 and S3, respectively. Overall mortality per 1,000-person-year of all 47 groups is also available in *Table S4*. Therefore, our newly proposed staging system combines stages I and II in the adjusted distribution as new stage I. In our new system, stage I is defined as an age <55 years and any T/N/M or an age ≥55 years and T1-3/any N/M0. Stage II is defined as an age ≥55 years and T4/any N/M0 or any T/N0/M1. Stage III is defined as aged ≥55 years and any T/N1/M1. A comparison of the group distribution of original distribution, adjusted distribution, and the newly proposed staging system is shown in *Table 2*.

Predictive ability of the new proposed TNM staging system

After formatting our newly proposed TNM staging system, we verified its accuracy by comparing the K-M curves of the estimated OS, and CSS generated from the data stratified by the 8th edition of AJCC and our newly proposed staging system (*Figures 6* and *7*), respectively. The downward trends of all the curves based on the new proposed staging system were more even and distinctive. The distributions and frequencies of cases are shown in *Table 3* and *Figure 8*. Stage I, II, and III in the newly proposed system included 17,427, 173, and 28 patients, respectively. Accordingly, the new proposed system provided a superior representation of the gradient of disease classification.

Tables 4 and *5* present a comparison of the overall mortality rate per 1,000-person-year and the results of Cox analysis based on the 8th edition AJCC staging system, adjusted distribution, and newly proposed system. The overall mortality rates per 1,000-person-year for new stage I, II, and III were 4.135 [95% confidence interval (CI): 3.653–4.681], 71.193 (95% CI: 51.354–98.697), and 199.744 (95% CI: 115.983–343.997), respectively. The adjusted hazard ratios (HRs) for the new II, and III (reference: stage I) were 5.081 (95% CI: 3.110–8.301; P<0.001) and 21.690 (95% CI: 11.402–41.258, P<0.001), respectively. Furthermore, comparison of cancer-specific mortality per 1,000-person-year based on 8th edition AJCC staging system, adjusted distribution, and newly proposed system were shown in *Table S5*. *Table S6* presents the results based on CSS data.

Discussion

The AJCC staging system is used for the risk stratification of various carcinomas. This system is primarily based up on the anatomic extent of cancer and is continuously updated to remain relevant to current clinical practice and advances in cancer prognosis (17). However, this system is suboptimal for the risk stratification of FVPTC, despite the status of this malignancy as the second common PTC subtype. Accordingly, the AJCC system has failed to adapt to the concept of precision medicine advocated by the ATA, wherein the need for adequate treatment is balanced against the risk of overtreatment (15). Accordingly, we proposed a new staging system for patients with FVPTC.

In this study, we used a sample of patients included in the SEER database, which has been recognized annually by the North American Association of Central Cancer Registries for its completeness and accuracy (18), as well

Table 2 Comparison of three different distributions of 47 groups of patients with FVPTC based on the TNM stages and an age cut-off of 55 years

Group	Stage	Original distribution	Adjusted distribution	New proposed
1	T1N0M0	Age <55	Age <55	Age <55
3	T1N1aM0	T1 anyN M0	AnyT anyN M0	Age ≥55
5	T1N1bM0	T2 anyN M0		T1-3 anyN M0
7	T2N0M0	T3 anyN M0		
9	T2N1aM0	T3N1bM1		
11	T2N1bM0	T4 N0/1b M0		
13	T3N0M0			
15	T3N1aM0			
17	T3N1bM0			
18	T3N1bM1			
19	T4bN0M0			
23	T4aN1bM0			
2	T1aN0M1	Age <55	Age <55	
21	T4aN1aM0	T1aN0M1	AnyT anyN M1	
25	T1N0M0	T4aN1aM0	Age ≥55	
27	T1N1aM0	Age ≥55	T1-3 anyN M0	
29	T1N1bM0	T1 anyN M0		
31	T2N0M0	T2 anyN M0		
33	T2N1aM0	T3 anyN M0		
34	T2N1bM0			
36	T3N0M0			
38	T3N1aM0			
40	T3N1bM0			
14	T3N0M1	Age <55	Age ≥55	Age ≥55
26	T1N0M1	T3N0M1	T4 anyN M0	T4 anyN M0
32	T2N0M1	Age ≥55	AnyT N0 M1	AnyT N0 M1
37	T3N0M1	T1-4N0M1		
41	T3N1bM1	T3N1bM1		
42	T4N0M0	T4 anyN M0		
43	T4N0M1			
44	T4N1aM0			
46	T4N1bM0			
45	T4N1aM1	Age ≥55	Age ≥55	Age ≥55
39	T3N1aM1	T4N1M1	AnyT N1 M1	AnyT N1 M1
47	T4N1bM1	T3N1aM1		

Original distribution, based on 47 groups without adjustment; adjusted distribution, based on 47 groups with adjustment; new proposed, adjusted based on the adjusted distribution together with clinical experiences. FVPTC, follicular variant of papillary thyroid carcinoma; TNM, tumor, node, and metastasis.

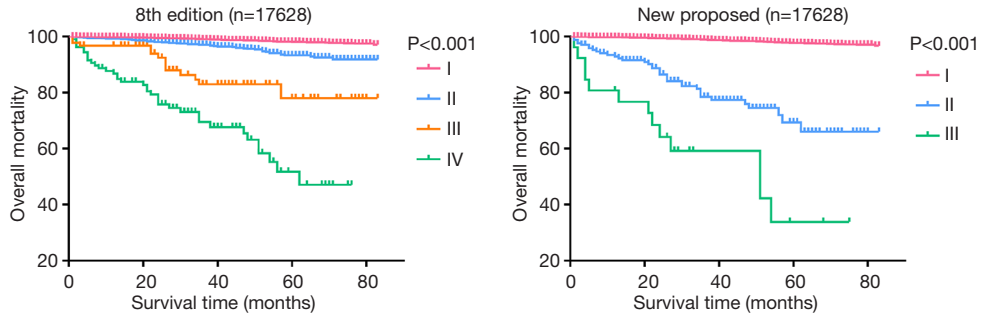


Figure 6 Kaplan-Meier curves for estimated survival curves according to the 8th edition AJCC system and the new proposed TNM staging system. Curves are based on overall mortality data. AJCC, the American Joint Committee on Cancer; TNM, tumor, node, and metastasis.

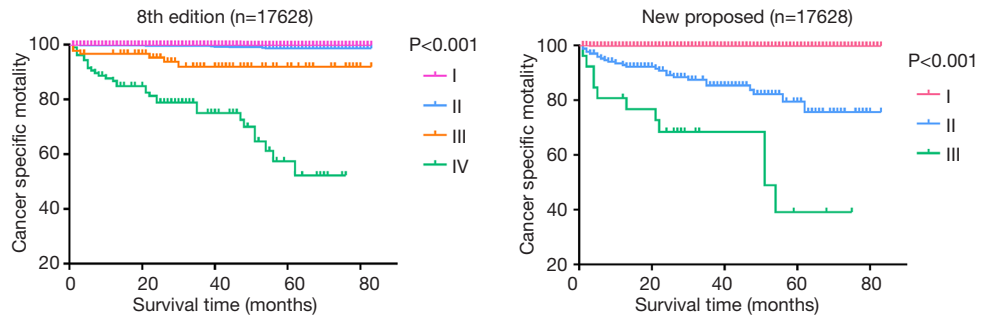


Figure 7 Kaplan-Meier survival curves for estimated survival according to the 8th edition AJCC system and the new proposed TNM staging system. Curves are based on cancer- specific mortality data. AJCC, the American Joint Committee on Cancer; TNM, tumor, node, and metastasis.

Table 3 Comparison of the distribution of patients with FVPTC between the 8th edition of the AJCC staging manual[a] and the new proposed TNM staging system

Stage	8th edition		New proposed	
	Distribution	N (%)	Distribution	N (%)
I	Age <55 anyT anyN M0, age ≥55 T1-2 N0 M0	15,993 (90.72)	Age <55 any T/N/M, age ≥55 T1-3 anyN M0	17,427 (98.85)
II	Age <55 anyT anyN M1, age ≥55 T1-2 N0 M0, T3 anyN M0	1,434 (8.14)	Age ≥55 T4 anyN M0, anyT N0 M1	173 (0.99)
III	Age ≥55 T4a anyN M0	92 (0.52)	Age ≥55 anyT N1 M1	28 (0.16)
IV	Age ≥55 T4b anyN M0, anyT anyN M1	109 (0.62)	–	–

[a], staging was based on the American Joint Committee on Cancer 8th edition. FVPTC, follicular variant of papillary thyroid carcinoma; AJCC, the American Joint Committee on Cancer; TNM, tumor, node, and metastasis.

as various statistical methods and clinical factors. After various calculations, comparisons and modeling, we hereby propose a new three-stage system for FVPTC, as described in the Results. This new proposed simplified staging system provides better stratification of low-, medium-, and high-risk patients than that of the AJCC staging system. The conversion of a four-stage system to a three-stage system is the most significant change proposed in this work. Our proposed system is consistent with an earlier observation by Jukkola *et al.* indicating that the AJCC TNM staging system

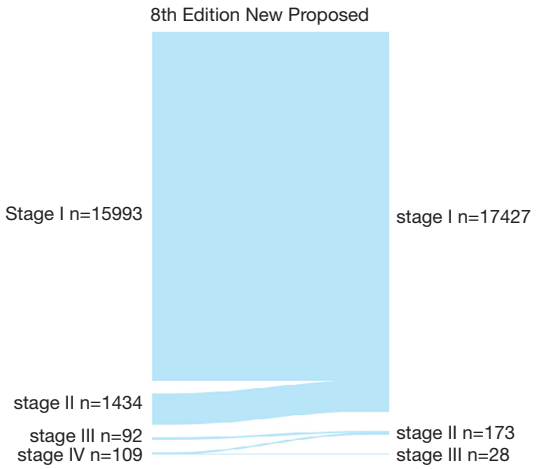


Figure 8 Alluvial flow diagram representing the SEER patients from the 8th edition of the AJCC system to the new proposed staging system. SEER, Surveillance, Epidemiology, and End Results; AJCC, the American Joint Committee on Cancer.

adequately distinguishes stages I and IV, but less clearly distinguishes the intermediate-risk groups (stages II and III) (19). Jukkola *et al.* found that the relevance of the TNM classification improved after combining stages I and II (19). Similarly, we pooled stage I and II into our new stage I.

We additionally classified all patients younger than 55 years into stage I, regardless of their N or M category. This was consistent with an earlier observation by Zaydfudim *et al.* that patients with PTCs younger than 45-year-old did not affect survival rates (20). Kim *et al.* compared three subtypes of FVPTC and suggested that the clinicopathologic behavior of noninvasive encapsulated FVPTC was similar to that of invasive encapsulated FVPTC but distinct from that of infiltrative FVPTC. Their observation indicated that the combination of lymph node and distant metastases might indicate a worse prognosis than those of either alone (21), consistent with our

Table 4 Comparison of overall mortality per 1,000-person-year between the 8th edition, adjusted distribution and new proposed TNM staging system

Stage	8th edition			Adjusted distribution			New proposed		
	Fail	Rate	95% CI	Fail	Rate	95% CI	Fail	Rate	95% CI
I	206	3.483	3.025–4.009	67	1.616	1.260–2.073	263	4.135	3.653–4.681
II	57	11.806	9.086–15.341	196	8.513	7.379–9.821	38	71.193	51.354–98.697
III	15	46.777	27.161–80.558	38	71.193	51.354–98.697	15	199.744	115.983–343.997
IV	38	122.937	88.678–170.431	15	199.744	115.983–343.997	–	–	–

CI, confidence interval; TNM, tumor, node, and metastasis.

Table 5 Adjusted* Cox analysis and comparison of overall mortality among patients with FVPTC between the 8th edition, adjusted distribution and new proposed TNM staging system

Stage	8th edition			Adjusted distribution			New proposed		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
I	Ref			Ref			Ref		
II	1.319	0.910–1.912	0.144	0.771	0.507–1.171	0.222	5.081	3.110–8.301	<0.001
III	3.512	1.636–7.541	0.001	3.940	2.079–7.468	<0.001	21.690	11.402–41.258	<0.001
IV	12.776	7.637–21.373	<0.001	17.707	8.626–36.350	<0.001	–	–	–

*, adjusted for age at diagnosis, year of diagnosis, gender, race, tumor size, extension, multifocality, radiation, surgery method. FVPTC, follicular variant of papillary thyroid carcinoma; TNM, tumor, node, and metastasis; CI, confidence interval; HR, hazard ratio.

proposed stage III. Furthermore, patients categorized as our new stage III, aged ≥55 years with lymph node and distant metastases, also corresponded to the high-risk category and were recommended to undergo radioactive iodine therapy remnant ablation. In contrast, patients classified as stage I may undergo simple lobectomy (15,22). In summary, our newly proposed TNM staging system is more clinically practical than the existing system.

The MACIS staging system considers metastasis, age, completeness of resection, invasion, and size when predicting the mortality of patients with PTC after primary surgery (23). The QTNM staging system aims to provide a simple risk stratification method but may not contain a sufficient number of effective factors (24,25). In contrast, our newly proposed staging system is based on the existing AJCC TNM staging system and the overall mortality associated with FVPTC. The advantages of this system include its simplicity and clinical practical, as well as the ability to provide a risk classification at the initial diagnosis. Consequently, this system could be highly valuable when estimating the subsequent management and prognosis.

Despite the aforementioned advantages, our study had some limitations. Genetic, environmental, and biological factors should be considered in staging models. However, the importance of these factors remains controversial. Accordingly, we aim to follow the mainstream consensus regarding thyroid carcinoma and will add additional relevant factors to our staging system in a stepwise manner over time to continue the facilitation of risk stratification, management, and prognosis for FVPTC. We also note that our newly proposed staging system is based on the SEER database, which includes a primarily North American population. This may affect the generalizability of our system.

In conclusion, the present study aimed to develop a new staging system that could be used for risk stratification of FVPTC. Compared to the 8th edition of the AJCC staging system, our newly proposed system ca provided more accurate risk stratification for patients with FVPTC, as demonstrated by actual survival and mortality outcomes. This new model may thus help guide more personalized treatment for these patients. However, this preliminary study leaves some questions to be answered, and extensive trials with more diverse patient populations are needed to verify our conclusions.

Acknowledgments

Funding: The authors are sponsored by the Shanghai Pujiang Program (2019PJD040) and the Pandeng Program of Shanghai Tenth People's Hospital (2018SYPDRC018).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.111). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Hu D, Huang Y, Zeng W, Chen S, Huang Y, Li M, Long W, Huang J, Wei W, Zhang C, Liu Z, Guo L. Is a simplified TNM staging system more clinically relevant than the American Joint Committee on Cancer system for the follicular variant of papillary thyroid cancer? Ann Transl Med 2020;8(7):463. doi: 10.21037/atm.2020.03.111

Supplementary

Table S1 Distribution of patients and events in the 47 group according to the original data

Group	Age	Stage	Total	Overall mortality	Cancer-specific mortality
1	<55	T1N0M0	5,744	38	0
2		T1N0M1	5	1	0
3		T1N1aM0	426	4	0
4		T1N1aM1	1	0	0
5		T1N1bM0	191	2	0
6		T1N1bM1	2	0	0
7		T2N0M0	2,199	8	1
8		T2N0M1	1	0	0
9		T2N1aM0	191	0	0
10		T2N1aM1	1	0	0
11		T2N1bM0	81	1	1
12		T2N1bM1	1	0	0
13		T3N0M0	1,417	10	1
14		T3N0M1	10	1	1
15		T3N1aM0	327	1	1
16		T3N1aM1	4	0	0
17		T3N1bM0	249	0	0
18		T3N1bM1	14	0	0
19		T4N0M0	46	0	0
20		T4N0M1	3	0	0
21		T4N1aM0	38	2	1
22		T4N1aM1	1	0	0
23		T4N1bM0	44	1	0
24	≥55	T4N1bM1	9	0	0
25		T1N0M0	4,068	115	1
26		T1N0M1	17	5	4
27		T1N1aM0	146	4	0
28		T1N1aM1	6	0	0
29		T1N1bM0	88	3	0
30		T1N1bM1	2	0	0
31		T2N0M0	972	24	2
32		T2N0M1	8	1	0
33		T2N1aM0	51	2	0
34		T2N1bM0	21	2	0
35		T2N1bM1	4	0	0
36		T3N0M0	863	33	4
37		T3N0M1	15	2	2
38		T3N1aM0	156	5	1
39		T3N1aM1	6	2	2
40		T3N1bM0	80	6	5
41		T3N1bM1	6	2	1
42		T4aN0M0	66	16	8
43		T4bN0M1	6	2	2
44		T4aN1aM0	24	3	2
45		T4bN1aM1	7	4	3
46		T4aN1bM0	37	9	7
47		T4bN1bM1	9	7	6

Table S2 Adjusted Cox analysis of overall mortality in patients with FVPTC staged age <55 years, any T/any N/M0; age <55 years, any T/any N/M1; age ≥55 years, T1-3/any N/M0

Variable	HR	95% CI	P value
Age at diagnosis	1.085	1.070–1.099	<0.001
Race			
White	Ref		<0.001
Black	2.022	1.483–2.756	<0.001
Other	0.778	0.487–1.242	0.293
Gender	1.735	1.364–2.207	<0.001
Year of diagnosis	0.708	0.536–0.935	0.015
Tumor size	1.001	1.000–1.002	0.057
Extension	1.680	1.161–2.430	0.006
Number of tumor foci	0.907	0.714–1.152	0.424
Age <55 anyT anyN M0	Ref		
Age <55 anyT anyN M1	9.433	2.281–39.015	0.002
Age ≥55 T1-3 anyN M0	0.732	0.481–1.113	0.145
Age ≥55 T4 anyN M0, anyT N0 M1	3.835	2.020–7.281	<0.001
Age ≥55 anyT N1 M1	17.521	8.527–36.004	<0.001
Radiation			
None/refused	Ref		
Yes	0.522	0.400–0.683	<0.001
Surgical procedure			
Biopsy	Ref		
Lobectomy	0.130	0.061–0.277	<0.001
Subtotal or near-total thyroidectomy	0.091	0.032–0.256	<0.001
Total thyroidectomy	0.101	0.049–0.212	<0.001

FVPTC, follicular variant of papillary thyroid carcinoma; CI, confidence interval; HR, hazard ratio.

Table S3 Analysis of overall mortality per 1,000-person-year in patients staged age <55 years, any T/any N/M0; age <55 years, any T/any N/M1; age ≥55 years, T1-3/any N/M0; age ≥55 years, T4/any N/M0 or any T/N0/M1; age ≥55 years, any T/N1/M1

Stage	Fail	Rate	95% CI
Age <55 anyT anyN M0	67	0.130	0.054–0.313
Age <55 anyT anyN M1	2	9.210	1.297–65.379
Age ≥55 T1-3 anyN M0	194	0.501	0.277–0.903
Age ≥55 T4 anyN M0, anyT N0 M1	38	71.193	51.354–98.697
Age ≥55 anyT N1 M1	15	199.744	115.983–343.997

CI, confidence interval.

Table S4 Comparison of overall mortality per 1,000-person-year in the 47 groups

Group	Age	Stage	Total	Overall mortality	Rate	95% CI
1	<55	T1N0M0	5,744	38	1.612	1.146–2.267
2		T1N0M1	5	1	75.000	10.565–532.430
3		T1N1aM0	426	4	2.706	1.016–7.210
4		T1N1aM1	1	0	–	–
5		T1N1bM0	191	2	2.811	0.703–11.239
6		T1N1bM1	2	0	–	–
7		T2N0M0	2,199	8	1.040	0.520–2.080
8		T2N0M1	1	0	–	–
9		T2N1aM0	191	0	–	–
10		T2N1aM1	1	0	–	–
11		T2N1bM0	81	1	3.412	0.481–24.222
12		T2N1bM1	1	0	–	
13		T3N0M0	1,417	10	2.102	1.131–3.907
14		T3N0M1	10	1	22.814	3.214–161.956
15		T3N1aM0	327	1	0.930	0.131–6.609
16		T3N1aM1	4	0	–	–
17		T3N1bM0	249	0	–	–
18		T3N1bM1	14	0	–	–
19		T4N0M0	46	0	–	–
20		T4N0M1	3	0	–	–
21		T4N1aM0	38	2	15.404	3.853–61.593
22		T4N1aM1	1	0	–	–
23		T4N1bM0	44	1	7.030	0.990–49.906
24	≥55	T4N1bM1	9	0	–	–
25		T1N0M0	4,068	115	7.715	6.389–9.316
26		T1N0M1	17	5	114.504	47.660–275.099
27		T1N1aM0	146	4	8.962	3.364–23.878
28		T1N1aM1	6	0	–	–
29		T1N1bM0	88	3	10.686	3.446–33.132
30		T1N1bM1	2	0	–	–
31		T2N0M0	972	24	7.181	4.813–10.713
32		T2N0M1	8	1	47.244	6.655–335.389
33		T2N1aM0	51	2	12.827	3.208–51.289
34		T2N1bM0	21	2	27.650	6.915–110.556
35		T2N1bM1	4	0	–	–
36		T3N0M0	863	33	10.960	7.751–15.499
37		T3N0M1	15	2	47.182	15.217–146.292
38		T3N1aM0	156	5	9.940	4.137–23.882
39		T3N1aM1	6	2	109.589	27.408–438.185
40		T3N1bM0	80	6	23.369	10.499–52.017
41		T3N1bM1	6	2	117.073	29.280–468.110
42		T4N0M0	66	16	72.696	43.054–122.745
43		T4N0M1	6	2	164.384	41.112–657.278
44		T4N1aM0	24	3	39.560	12.759–122.660
45		T4N1aM1	7	4	246.575	79.526–764.524
46		T4N1bM0	37	9	93.103	48.443–178.937
47		T4N1bM1	9	7	341.232	153.302–759.542

CI, confidence interval.

Table S5 Comparison of cancer-specific mortality per 1,000-person-year between the 8th edition AJCC TNM staging system, adjusted distribution and the new proposed TNM staging system

Stage	8th edition			Adjusted distribution			New proposed		
	Fail	Rate	95% CI	Fail	Rate	95% CI	Fail	Rate	95% CI
I	8	0.126	0.060–0.264	5	0.130	0.054–0.313	19	0.281	0.175–0.452
II	11	2.108	1.134–3.918	14	0.543	0.309–0.957	25	51.417	35.009–75.517
III	6	21.589	9.699–48.055	25	51.417	35.009–75.517	12	169.014	93.600–305.190
IV	31	105.862	74.449–150.530	12	169.014	93.600–305.190	–	–	–

AJCC, the American Joint Committee on Cancer; TNM, tumor, node, and metastasis; CI, confidence interval.

Table S6 Adjusted* Cox analysis of the comparison of cancer-specific mortality in patients with follicular variant-papillary thyroid cancer (FVPTC) according to the 8th edition AJCC TNM staging system, adjusted distribution and new proposed TNM staging system

Stage	8th edition			Adjusted distribution			New proposed		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
I	Ref			Ref			Ref		
II	8.766	2.935–26.176	0.319	1.714	0.467–6.294	0.417	28.616	10.448–78.377	<0.001
III	49.165	10.641–231.731	<0.001	46.310	9.910–216.411	<0.001	119.844	40.563–354.082	<0.001
IV	301.059	97.196–978.165	<0.001	180.784	40.919–798.722	<0.001	–	–	–

*, adjusted for age at diagnosis, year of diagnosis, gender, race, tumor size, extension, multifocality, radiation, surgery method. AJCC, the American Joint Committee on Cancer; TNM, tumor, node, and metastasis; CI, confidence interval; HR, hazard ratio.