Rethinking the 8th AJCC System: Is It Suitable for Patients Aged <55 Years With Stage T4N1M0 Follicular Variant of Papillary Thyroid Carcinoma to Be Placed in Stage I?

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Purpose: The newest (8th) edition of the TNM staging system published in 2017. In this edition, some significant changes happened from the previous edition. As a result, down-staging appeared in nearly one third of DTC patients. However, we don’t know whether the new system predicts the survival of FVPTC patients accurately. Therefore, it is necessary to thoroughly evaluate the correlation between the new system and survival prediction in terms of FVPTC.

Methods: We enrolled 17,662 FVPTC patients from the Surveillance, Epidemiology, and End Results database. Factors associated with survival were identified by Cox regression analyses. The mortality rates per 1,000 person-years were calculated and compared. Cox proportional hazards regression quantified the risk of survival, and survival curves were produced by Kaplan-Meier analyses using log-rank tests.

Results: Age at diagnosis, race, T-stage at diagnosis, distant metastasis, radiation therapy, and surgery were independent factors associated with cancer-specific survival. Patients aged <55 years with stage T4N1M0 FVPTC had higher mortality rates per 1,000 person-years than patients in the same stage according to the 8th AJCC System. Cox proportional hazards regression reflected that patients aged <55 years with stage T1-3, any N, M0 or T4N0M0 disease (p=0.001) and patients aged ≥55 years with T1-2N0M0 disease (p=0.004) had significantly lower risks of cancer-specific survival (CSS) than those aged <55 years with stage T4N1M0 disease. The CSS curve of patients aged <55 years with stage T4N1M0 disease showed a decline on comparison with others belonging to stage I (p<0.001); and the curve was even not different from patients in stage II and stage III (p>0.05).
INTRODUCTION

FVPTC is a major subtype of thyroid cancer, which is the most common endocrine malignancy (1). Some studies have shown that the incidence of thyroid cancer has substantially increased in the last few decades (2, 3). The global thyroid cancer incidence rates have undergone a 3.8-fold increase since the 1970s (3, 4). Approximately 90% of malignant thyroid tumors involve differentiated thyroid cancer (DTC), and DTCs are classified as either papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma based on the histologic pattern (5). PTC, as the most frequent type of thyroid malignancy, has two main subtypes: pure papillary thyroid carcinoma and follicular variant of papillary thyroid carcinoma (FVPTC). FVPTC is composed of follicles lined by cells exhibiting nuclear features of PTC (6).

A variety of staging systems have been used to identify different prognostic groups and predict their survival in terms of DTC; among them, the American Joint Committee on Cancer tumor-node-metastasis (AJCC/TNM) cancer staging system is widely used (7). The newest (8th) edition of the TNM classification (TNM-8th), published in 2017, contained some significant changes from the previous edition (8). In this edition, the age cutoff value increased from 45 to 55 years, and the definitions of primary tumor (T) and regional lymph (N) stages were changed from those in the 7th edition; meanwhile, the AJCC prognostic stage groups underwent a series of adjustments (9, 10). As a result, down-staging appeared in nearly one third of DTC patients (11, 12).

Several studies about the new staging system have shown that its predictive value for survival is better than that of the seventh edition (13, 14). However, we don’t know whether the new system predicts the survival of FVPTC patients accurately; only a few studies have evaluated the relationship between FVPTC and the new classification system. Therefore, it is necessary to thoroughly evaluate the correlation between the new system and survival prediction in terms of FVPTC. In this study, we focused on whether each subgroup of different stages aligns with its newest classification and compared the survival in these subgroups.

More Detailed Staging Groups

Patients with FVPTC were divided into Stage I, Stage II, Stage III, and Stage IV based on the TNM-8th system. Then, Stage I patients were further divided into the following groups: age <55 T1-3, any N, M0 and T4N0M0; group age <55 T4N1M0; and group age ≥55 T1-2N0M0. Stage II patients were further divided into the following groups: age <55 any T, any N, M1; and group age ≥55 T1-2N1M0 and T3, any N, M0.

Statistical Analysis

Quantitative variables were presented as medians (interquartile range) and categorical variables were expressed as number (%). The factors associated with cancer-specific survival (CSS) and overall survival (OS) were identified by Cox regression analyses, respectively. Then, the hazard ratio (HR) and 95% confidence interval (CI) were calculated. We also calculated and compared cancer-specific mortality (CSM) and all-cause mortality (ACM) rates per 1,000 person-years for each subgroup. Cox proportional hazards regression analyses with adjustment for demographic, pathological, and treatment features were performed to quantify the risk of CSS and OS. Finally, survival curves were produced by Kaplan-Meier analyses using log-rank tests. Statistical significance was defined using a two-sided p<0.05. These analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY), GraphPad Prism version 8 (GraphPad Software Inc., La Jolla, CA), and Stata/SE version 14 (Stata Corp., College Station, TX).

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the 17,662 FVPTC patients are listed in Table 1. The 17,662 patients included 14,013 (79.3%) women and 3,649 (20.7%) men. The median age was 50 (interquartile range, 39–60) years. According
Regarding Stage II, the subgroups age <55 T4N1M0 and stage I (not including age <55 T4N1M0), stage II or even stage III. The HRs for OS are displayed in Table S2. Meanwhile, the adjusted P values for the subgroups of stage II and stage III were all more than 0.05. These data indicated that the group age <55 T4N1M0 differed significantly from the subgroups of stage I but not from those of stage II or even stage III. The HRs for OS are displayed in Table S2, and they showed similar results.

**Kaplan-Meier Analyses Using Log-Rank Tests**

Kaplan-Meier analyses using log-rank tests showed that CSS and OS were significantly different between the groups age <55 T4N1M0 and stage I (not including age <55 T4N1M0), stage II or even stage III.

**Clinicopathological Factors Associated With CSS**

In the univariate Cox regression analysis, age at diagnosis, sex, race, T-stage at diagnosis, lymph node metastasis (LNM), distant metastasis, extrathyroidal extension, and surgery were significant prognostic factors of CSS (all, p < 0.05). Meanwhile, in the multivariate analyses, CSS was associated with age at diagnosis, race, T-stage, distant metastasis, radiation therapy, and surgery (all, p < 0.05). Consequently, LNM may have a combined effect with other factors on CSS (Table S1). Cox analyses of the factors associated with OS showed similar results (Table S1).

**CSM and ACM Rates per 1,000 Person-Years**

The CSM and ACM rates per 1,000 persons-years are shown in Table 4. The CSM in the group age <55 T4N1M0 (3.675, 95% CI: 0.518–26.092) was higher than those in the group age <55 T1-3, any N, M0 or T4N0M0 (0.105, 95% CI: 0.039–0.280) and group age ≥55 T1-2N0M0 (0.115, 95% CI: 0.029–0.461), both of which belonged to stage I; moreover, the CSM in the group age <55 T4N1M0 was even higher than that in a subgroup of stage II (age ≥55 T1-2N1M0 or T3, any N, M0) (1.942, 95% CI: 1.010–3.732). The CSM in the group age <55 T4N1M0 was higher than that in the stage I group and was similar to that in the stage II group. The ACM rates showed similar results.

**Hazard Ratios of Different Subgroups for CSS**

The HRs for CSS of the group age <55 T4N1M0 compared with the other groups are displayed in Table 5. The unadjusted HR of the group age <55 T1-3, any N, M0 or T4N0M0 was 0.028 (95% CI: 0.003–0.252, p=0.001). The HR adjusted for demographic data was 0.028 (95% CI: 0.003–0.256, p=0.002). The HR adjusted for demographic and pathological data was 0.029 (95% CI: 0.003–0.268, p=0.002). The HR adjusted for demographic, pathological, and therapeutic data was 0.021 (95% CI: 0.002–0.198, p=0.001). As to the group age ≥55 T1-2N0M0, the Cox regression HRs for unadjusted, adjusted 1, adjusted 2, and adjusted 3 models were 0.047 (95% CI: 0.005–0.448, p=0.008), 0.046 (95% CI: 0.005–0.441, p=0.008), 0.048 (95% CI: 0.005–0.469, p=0.009), and 0.033 (95% CI: 0.003–0.345, p=0.004), respectively. Meanwhile, the adjusted P values for the subgroups of stage II and stage III were all more than 0.05. These data indicated that the group age <55 T4N1M0 differed significantly from the subgroups of stage I but not from those of stage II or even stage III. The HRs for OS are displayed in Table S2, and they showed similar results.
II, stage III, and stage IV (both, p<0.001). Kaplan–Meier analyses between the group age <55 T4N1M0 and group age <55 T1-3, any N, M0 or T4N0M0 showed significant differences in CSS and OS (both, p <0.001). Meanwhile, compared to the group age ≥55 T1-2N0M0, the group age <55 T4N1M0 showed a significant decline in the CSS curve (p<0.001). Notably, the CSS was not different between the group age <55 T4N1M0 and the subgroups of stage II or even stage III (all, p>0.05). These curves are displayed in Figures 1–6.

**DISCUSSION**

In the eighth edition, some significant changes were made in the age cutoff and the definitions of primary tumor (T) and regional lymph node (N), causing a significant number of patients to be down-staged. Although the new staging system has been shown to have better predictive value for survival prognosis, few studies have focused on the specific effect of the TNM-8th system on FVPTC prognosis. Thus, we explored the applicability of the

| Parameters | HR | Univariate HR | Multivariate HR |
|------------|----|---------------|-----------------|
| Age at diagnosis | 1.098 | 1.075 1.122 <0.001* | 1.079 1.055 1.104 <0.001* |
| Year at diagnosis | 2010–2012 2013–2015 | | |
| Sex | Female | 1.018 0.557 1.858 0.955 | 0.788 1.233 0.406 1.530 |
| Race | White | 2.499 1.462 4.273 0.001* | 3.659 2.266 0.670 2.162 |
| T-Stage at diagnosis | T1 | 2.444 0.656 9.102 0.183 | 1.424 0.409 2.111 0.988 |
| Lymph node metastasis | No | 2.570 0.764 3.832 0.192 | 2.734 1.299 0.409 0.988 |
| Distant metastasis | Yes | 2.539 0.630 1.943 0.603 | 1.325 0.517 2.416 |
| Multilocality | No | 1.140 0.669 1.943 0.630 | 1.121 0.592 2.204 0.707 |
| Extrathyroidal extension | Yes | 20.970 4.169 37.612 <0.001* | 23.528 0.993 5.614 1.001* |
| Radiation therapy | None or refused | 0.016 0.005 0.051 <0.001* | 0.169 0.043 0.667 1.011 |
| Surgery | Lobectomy | 0.014 0.002 0.124 <0.001* | 0.138 0.014 1.406 0.094 |
| Total thyroidectomy | 0.018 0.007 0.045 <0.001* | 0.087 0.024 0.317 <0.001* |

*represent the p value <0.05.

**TABLE 4** | Measures of cancer-specific mortality and all-cause mortality of FVPTC.

| Stage | Total Number | Cancer-specific Mortality | All-cause Mortality | Cancer-specific Mortality | All-cause Mortality |
|-------|--------------|----------------------------|---------------------|----------------------------|---------------------|
| No.   | 1,000 Person-Years | % | 95%CI | No. | 1,000 Person-Years | % | 95%CI |
| Stage I | Age <55 T1-3, any N, M0 and T4N0M0 | 10,871 | 4 | 0.037 | 0.105 | 0.039–0.280 | 64 | 0.589 | 1.549 | 1.200–1.999 |
| | Age ≥55 T1-2N0M0 | 5,039 | 3 | 0.060 | 0.115 | 0.029–0.461 | 138 | 2.734 | 7.557 | 6.368–8.969 |
| | Age ≥55 T4N1M0 | 82 | 1 | 1.220 | 3.675 | 0.518–26.092 | 3 | 3.659 | 11.026 | 3.556–34.187 |
| Stage II | Age ≥55 any T, any N, M1 | 52 | 1 | 1.923 | 5.55 | 0.782–39.403 | 2 | 3.846 | 11.101 | 2.776–44.386 |
| | Age ≥55 T1-2N1M0 and T3, any N, M0 | 1,405 | 10 | 0.712 | 1.942 | 1.010–3.732 | 55 | 3.915 | 11.651 | 8.924–15.213 |
| Stage III | Age ≥55 T4a, any N, M0 | 92 | 6 | 6.522 | 21.065 | 9.464–46.888 | 15 | 16.304 | 45.641 | 26.502–78.602 |
obvious in year mortality rate for PTC increased incrementally without an
be upstaged. More aggressive treatments such as radiation therapy and surgery.
extension can be predicted to have a worse prognosis and require
T-stage at diagnosis, LNM, distant metastasis, and extrathyroidal
association with CSS and OS. Patients with older age, higher
hazard regression analyses to identify the prognostic factors
showed similar results. The results indicated that patients aged <55
rates compared to those in stage II. This suggests that the
unadjusted analyses or adjusted analyses. The CSM and ACM
subgroup age <55 T4N1M0 than in the other subgroups in stage I
conformed to their AJCC/TNM stages. Cox proportional hazard
system in FVPTC patients with the aim of improving its
prognosis prediction ability.
In this study, we observed that patients aged <55 years with stage
T4N1M0 disease should be upstaged in the TNM-8th cancer staging system. Among the total patients, Stage I, Stage II, Stage III, and Stage IV accounted for 90.5, 8.2, 0.5, and 0.7% of patients according to the TNM-8th system. Each stage was then divided into detailed groups, and it was determined whether these groups conformed to their AJCC/TNM stages. Cox proportional hazard regression analyses revealed that the risk of CSS was higher in the subgroup age <55 T4N1M0 than in the other subgroups in stage I and actually located between subgroups in stage II, by either unadjusted analyses or adjusted analyses. The CSM and ACM rates per 1,000 person-years for this group were higher than those for stage I and similar to those for stage II. Kaplan-Meier curves showed similar results. The results indicated that patients aged <55 years with stage T4N1M0 showed significantly worse survival than patients in other subgroups in stage I and showed no difference in survival rates compared to those in stage II. This suggests that the subgroup age <55 T4N1M0 should not belong to stage I and needs to be upstaged.
We conducted univariate and multivariate Cox proportional hazard regression analyses to identify the prognostic factors associated with CSS and OS. Patients with older age, higher T-stage at diagnosis, LNM, distant metastasis, and extrathyroidal extension can be predicted to have a worse prognosis and require more aggressive treatments such as radiation therapy and surgery. These analyses partly explained why patients aged <55 years with stage T4N1M0 disease had worse survival and needed to be upstaged.
Yan et al. conducted a retrospective study and found that the 10-year mortality rate for PTC increased incrementally without an obvious inflection point according to age groups <35 years to ≥70 years when analyzing age in 5-year increments (15). Similarly, Adam et al. reported a linear association between age and PTC mortality, without an apparent age cutoff demarcating the difference in survival (16). These studies challenged the appropriateness of age cutoffs in staging systems for FVPTC. Moreover, in the eighth edition of the AJCC/TNM system, the cutoff age used for staging was increased from 45 to 55 years. Hence, we speculate that patients aged 45–55 years need a more thorough classification and evaluation, especially those being down-staged.
The results in Table 3 and Table S1 indicate that stage T4 is associated with a higher mortality risk than T1-3, in terms of either CSM or ACM. In the AJCC system, primary tumor (T) stage is determined by tumor size and extrathyroidal extension. In the newest system, stage T4 includes gross extrathyroidal extension, and the importance of gross extrathyroidal extension in patients without initial distant metastasis has been further emphasized (17–19). Moreover, Lee et al. expressed the same opinion in their study on PTC patients (20). Hence, patients in stage T4 tend to show poor survival.
LNM is also associated with larger odds of adverse outcomes. Schneider et al. demonstrated that LNM did not independently predict survival in their article (p>0.05) (21). Similarly, in our multivariate Cox analyses, LNM was not an independent prognostic factor for CSS but showed a significant influence in univariate analyses. These findings suggest the existence of a synergic effect. Liu et al. pointed out that the synergic effect of gross extrathyroidal extension beyond the strap muscles (stage T4) and LNM may lead to a worse prognosis in DTC patients (22). Thus, we hypothesized that the worse prognosis of patients aged <55 with T4N1M0 disease may be partly due to the synergic effect of stage T4 and LNM. Based on the above evidence, we hypothesize that the combined effect of gross extrathyroidal extension, LNM, and older age is responsible for the poor prognosis in this patient population.
Our study still has several limitations. Selection bias could not be ruled out due to the retrospective design. Moreover, as FVPTC patients have good prognosis, very few adverse events were noted, and only 82 patients aged <55 years were placed in stage T4N1M0. Hence, further research and more clinical trials need to evaluate this stage among patients with FVPTC.

### Table 5: Hazard ratios of AJCC Cancer Staging (8th Edition) for cancer-specific survival.

| Stage at diagnosis | Stage based on TNM-8th system | Unadjusted Cox regression | Adjusted 1 Cox regression | Adjusted 2 Cox regression | Adjusted 3 Cox regression |
|--------------------|-------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                    |                               | Hazard Ratio (95% CI)    | p-value                  | Hazard Ratio (95% CI)    | p-value                  | Hazard Ratio (95% CI)    | p-value                  |
| Age <55 T4N1M0     | 1                             | ref                      |                          | ref                      |                          | ref                      |                          |
| Age <55 T1-3, any N, M0 and T4N0M0 | I | 0.028(0.003–0.252)          | 0.001*                   | 0.028(0.003–0.256)       | 0.002*                   | 0.029(0.003–0.268)       | 0.001*                   |
| Age ≥55 T1-2N0M0   | 1                             | 0.047(0.005–0.448)       | 0.008*                   | 0.046(0.005–0.441)       | 0.008*                   | 0.048(0.005–0.469)       | 0.009*                   |
| Age <55 any T, any N, M1 | II | 1.467(0.092–23.463)          | 0.786                    | 1.421(0.089–22.753)      | 0.804                    | 1.455(0.091–23.335)      | 0.791                    |
| Age ≥55 T1-2N1M0 and T3, any N, M0 | II | 0.577(0.074–4.504)          | 0.599                    | 0.577(0.071–4.363)       | 0.578                    | 0.581(0.074–4.576)       | 0.606                    |
| Age ≥55 T4a, any N, M0 | III | 5.501(0.662–45.703)         | 0.115                    | 5.628(0.674–46.983)      | 0.111                    | 0.029(0.003–0.268)       | 0.002*                   |

*Represent the p-value <0.05.
FIGURE 1 | Kaplan–Meier curves for cancer-specific survival (A) and overall survival (B) between FVPTC patients in stage I (not including age <55 T4N1M0), II, III, IV and those aged <55 years with stage T4N1M0 disease.

FIGURE 2 | Kaplan–Meier curves for cancer-specific survival (A) and overall survival (B) between FVPTC patients aged <55 years with stage T1-3, any N, M0 or T4N0M0 disease and patients aged <55 years with stage T4N1M0 disease.
A FIGURE 3 | Kaplan–Meier curves for cancer-specific survival (A) and overall survival (B) between FVPTC patients aged ≥55 years with stage T1-2N0M0 disease and patients aged <55 years with stage T4N1M0 disease.

B FIGURE 4 | Kaplan–Meier curves for cancer-specific survival (A) and overall survival (B) between FVPTC patients aged <55 years with stage any T, any N, M1 disease and patients aged <55 years with stage T4N1M0 disease.
FIGURE 5 | Kaplan–Meier curves for cancer-specific survival (A) and overall survival (B) between FVPTC patients aged ≥55 years with stage T1-2N1M0 or T3, any N, M0 disease and patients aged <55 years with stage T4N1M0 disease.

FIGURE 6 | Kaplan–Meier curves for cancer-specific survival (A) and overall survival (B) between FVPTC patients aged ≥55 years with stage T4a, any N, M0 disease and patients aged <55 years with stage T4N1M0 disease.
In conclusion, FVPTC patients aged <55 years in stage T4N1M0 have a worse prognosis than stage I patients and have comparable prognosis compared to stage II patients. Therefore, they should be upstaged and receive a more accurate prognosis prediction. Meanwhile, we recommend more aggressive treatments for older patients with a high T-stage and LNM.

DATA AVAILABILITY STATEMENT
Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

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AUTHOR CONTRIBUTIONS
LG and ZL provided design of the study. SC, WZe, JH, and YYH organized the database. WL, DH, and LZ performed the statistical analysis. WL wrote the first draft of the manuscript. YHH, ML, WW, CZ, and MW contributed to manuscript revision. All authors read and approved the submitted version.

SUPPLEMENTARY MATERIAL
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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