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# Development of a New Clinical Severity Staging System for Patients With Nonmetastatic Papillary Thyroid Carcinoma

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**IMPORTANCE** The inclusion of patient features in addition to tumor morphology provides a more holistic staging system.

**OBJECTIVE** To identify prognostically important variables in papillary thyroid carcinoma (PTC) to incorporate into a comprehensive functional severity staging system (FSSS) and clinical severity staging system (CSSS) and to validate the model using a multi-institutional database.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective cohort study of adults 18 years or older newly diagnosed or treated for nonmetastatic PTC at the Siteman Cancer Center from 1995 through 2012. Binary logistic regression was used to explore the association between 5-year survival and age, comorbidities, and tumor morphologic features. Conjunctive consolidation was used to create staging systems that incorporated important patient and tumor information. The created FSSS and CSSS were compared with the current AJCC staging system and externally validated using the National Cancer Database (NCDB).

**MAIN OUTCOMES AND MEASURES** Five-year survival.

**RESULTS** The cohort consisted of 774 eligible patients with PTC. There were 119 (15%) deaths in the cohort and a 90% 5-year survival rate. The median age of the patients was 51 years (range, 18-91); 562 (73%) were women. Conjunctive consolidation combined age, comorbidity, and T stage to create a new CSSS with 3 categories where 5-year survival rates (95% CI) were as follows: stage A (n = 612), 95% (94%-97%); stage B (n = 131), 74% (67%-82%); and stage C (n = 31), 58% (41%-75%). The performance of the FSSS and CSSS was validated using the NCDB data. The new staging system indicates that patients with nonmetastatic disease, patients younger than 40 years, or patients without comorbidity regardless of age have a very high 5-year survival rate.

**CONCLUSIONS AND RELEVANCE** The FSSS and CSSS had better predictive results than the current AJCC staging system. The addition of patient features to tumor morphology provides a more comprehensive staging system that improves prognostic accuracy. These comprehensive staging systems can improve scientific reporting of disease outcomes, support comparative effectiveness studies, and guide clinical care by defining prognosis for newly diagnosed patients.

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Supplemental content

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The American Joint Committee on Cancer (AJCC) staging system has many uses, which are crucial for proper understanding of cancer statistics, scientific communication, and patient management. The most important use of the AJCC staging system according to members of the American Society for Head and Neck Surgery is comparing end results.[1] The implications of a more prognostically accurate cancer staging system are enhanced patient management and more meaningful scientific research.[1,2]

In the past 30 years, the incidence of thyroid cancer has tripled,[3] making thyroid cancer the eighth most commonly diagnosed cancer.[4,5] Of the 4 main types of thyroid cancer, papillary thyroid carcinoma (PTC) is the most common, representing 81% of newly diagnosed thyroid cancer cases.[6] The rise in incidence of thyroid cancer is heavily due to the rise in incidence of PTC.[7] Overall, PTC has a 97% 5-year survival rate[4,8] and a 93% 10-year survival rate.[9] The PTC epidemic occurring in the United States is more accurately classified as an epidemic of overdiagnosis rather than an epidemic of disease.[3,7,10-12]

The current AJCC staging system for PTC is based on the patient age and morphologic spread of the tumor as described by the tumor, node, and metastasis (TNM) system.[13] This system fails to incorporate other prognostically important variables, such as patient burden of comorbidity.[14-20] Clinical severity staging systems (CSSS) incorporating burden of comorbidities have been created for cancers of the oral cavity,[21] oropharynx,[22] larynx,[18] lung,[16] rectum,[14,15] breast,[23] and prostate.[17]

There is conflicting evidence in the literature regarding the prognostic impact of age,[24-27] sex,[25-27] burden of comorbidity,[2,19,28] and morphologic spread of tumor.[24,25,27] The purpose of the present study is to (1) explore prognostically important variables in PTC at our institution; (2) develop a comprehensive functional severity staging system (FSSS) and CSSS using the identified variables; and (3) validate the model.

### Key Points

**Question** Does incorporation of patient demographic, clinical, and morphologic information into a cancer staging system improve prognostic accuracy for nonmetastatic papillary thyroid carcinoma (PTC)?

**Findings** In this cohort study of 774 adults with PTC, age, comorbidity, and tumor stage were all statistically and clinically important variables that affected prognosis. These variables were combined using the conjunctive consolidation method to create a functional and clinical severity staging system for PTC that was more predictive of survival than the current AJCC staging system.

**Meaning** The incorporation of patient demographic, clinical, and morphologic information can create a more prognostically accurate cancer staging system for PTC.

## Methods

### Collection of Data

Certified tumor registrars (CTRs) of the Oncology Data Services at Siteman Cancer Center prospectively capture patient, tumor, and treatment information for all patients diagnosed with PTC. Cancer registers collect information according to the data exchange standards and record description guidelines of the North American Association of Central Cancer Registries (NAACCR) Uniform Data Standards Committee.[29] The NAACCR data standards are used for cancer registration by central (eg, state) registries, hospital-based registries (eg, National Cancer Database [NCDB]), and other groups (eg, the National Cancer Institute Surveillance, Epidemiology, and End Results Program and the Centers for Disease Control and Prevention National Program of Cancer Registries) in North America. All NCDB data undergo a battery of data integrity checks.[30]

### Study Population

Patients diagnosed with or treated for PTC at the Siteman Cancer Center between January 1, 1995, and December 31, 2012, were eligible for inclusion in the study. The study was declared exempt from review by the institutional review board at Washington University. This time span was chosen because CTRs first began collecting comorbid health condition data in 1995, and 2012 provides sufficient time for 5-year follow up. Exclusion criteria included age younger than 18 years; histologic findings other than PTC; metastatic disease; and cases with missing comorbidity, morphologic, or 5-year survival information.

### Classification of Data

Initial *zero time*[16,18,31] was defined as the date of PTC diagnosis. This date was chosen because diagnosis of thyroid carcinoma during the study time period is stable and thus would be minimally susceptible to "zero-time shift."[32] Prezero interval information included demographic and comorbid health information. Race information was recorded by CTRs. Zero-time information included diagnosis date, histologic code, and morphologic extent of tumor. Postzero interval information included outcome information such as duration of follow-up and vital status.

### Classification of Patient Age and Morphological Stage

The current AJCC staging system incorporates age as a dichotomous variable based on previous research demonstrating the difference in survival in patients above and below the fifth decade of life.[25,33-37] Other literature suggests that survival declines with increasing age beyond a dichotomized point break.[26,27,38] The present study investigates age as a 5-category ordinal variable, created based on univariable binary regression of various age groupings.

In the present study, we create a new classification of pathology based on the described conjunctive consolidation method. Morphologic stage was classified by primary tumor stage alone without nodal information because nodal stage provided little additional value to the tumor stage.

### Comorbidity

Comorbidity was classified according to the Adult Comorbidity Evaluation-27 (ACE-27) index. The ACE-27 index is a validated instrument that captures comorbidities and grades severity for adult patients with cancer.[39,40] Comorbidity information was captured prospectively by CTRs who successfully completed a short online training program. If the tumor registry did not contain individual patient comorbid information, the primary author (O.A.K.) conducted a manual review of the patient medical records to obtain missing comorbidity data.

### Therapeutic Nil Hypothesis

The "nil hypothesis" assumes that the best therapy option for each patient was selected, and different treatment courses would have had no impact on clinical outcome. With this assumption, clinical, demographic, and tumor characteristics were examined in relation to survival, regardless of treatment modality. The exclusion of effect from actual treatment is a necessary approach to create a pretreatment prognostic staging system.[41-44]

### Follow-up and Outcome

Follow-up information was obtained from the cancer registry. The duration of time between date of diagnosis and date of last patient contact or date of death defined the length of follow-up. Vital status was defined as alive or dead.

### Development of the FSSS and CSSS

The model building process mirrors that used in the development of CSSS for cancers previously.[14-18,21-23,45] Prognostically significant variables were identified using binary logistic regression. The prognostically significant variables were combined through a cross-table analysis process known as conjunctive consolidation.[46] This method allows grouping of variables according to statistical isometry and biologic coherence.[16]

### Performance of the Prognostic Models

The performance of the FSSS and CSSS were compared with the AJCC staging system based on measures of clinical sensibility and statistical evaluation.[43,44] The 3 staging systems were compared using tonicity of survival curves, survival gradient range, discriminative power, log rank for linear trend, and variance reduction score.[16,41-43]

### Validation

Internal validation was conducted using a bootstrap validation approach with resampling for 100 bootstrap samples to correct for optimism of the C statistic. The bootstrapping approach allows for the calculation of standard errors and is a reliable method of internally validating a model.[47-50]

External validation was achieved using the NCDB, which is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Established in 1989, the NCDB is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignant conditions in the United States annually. The FSSS and CSSS were applied to this national data, and the same model performance measures, detailed prior, were used to calibration, discrimination, and overall accuracy of the models. The NCDB classifies comorbidity according to the Deyo adaption of the Charlson Comorbidity Index (CCI),[51] which uses the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes reported in the studied registry to create a weighted index of comorbidity.[52] Therefore, a different comorbidity instrument was used during the assessment of the validation of the FSSS and CSSS in the NCDB.

### Statistical Analysis

Analysis was conducted on SAS 9.4 software (SAS Institute Inc) and IBM SPSS Statistics for Windows, version 24.0 (IBM Corp). A 2-sided α with threshold of .05 was used. Basic descriptive statistics, univariable and multivariable binary logistic regression, and Kaplan-Meier survival analysis were used.

## Results

### Baseline Characteristics and 5-Year Survival Results of Siteman Registry

From the Siteman registry, 1483 eligible patients were identified. Missing information excluded 709 patients, leaving 774 patients included for analysis. In all, 562 (73%) were women. The median age was 51 years (range, 18-91 years). The median follow-up time was 92 months (range, 2-242 months). Overall, there were 119 (15%) patients who died, and a 90% 5-year survival.

Zero time, prezero interval, and 5-year survival information are provided in **Table 1**. Sex, age, presence of severe comorbidity, and T stage were prognostically significant variables on univariable binary logistic regression. Age, comorbidity, and T stage resulted in distinct survival gradients.

The prognostically significant zero and prezero variables identified in the univariable binary logistic regression were used in a multivariable binary logistic regression as seen in Table 1. Age, comorbidity, and T stage were prognostically significant variables associated with 5-year survival.

### Conjunctive Consolidation of Age and Comorbidity Into the Functional Severity Staging System

In **Table 2** the combined impact of age and comorbidity on 5-year survival is listed. The prognostic gradients of age and comorbidity are listed in the last row and column, respectively (each labelled "Total"). The prognostic gradient for age extends from 99% to 77% from the youngest to the oldest categories, respectively, and the prognostic gradient for comorbidity extends from 98% to 75% from those without comorbidity to those with moderate to severe comorbidity, respectively. Importantly, each additional decade of age had an impact on 5-year survival, and no dichotomous age break (ie, 45 years) was apparent in the data. As can be seen, within most categories of age, comorbidity severity defines

Table 1. Association of Baseline Demographic, Clinical, and Tumor Characteristics With Overall Survival

| Characteristic | Siteman Cancer Center Registry | | | | NCDB Patients, No. (%) | |
|---|---|---|---|---|---|---|
| | Patients, No. (%) | | Odds Ratio (95% CI) | | | |
| | Frequency (n = 774) | Alive at 5 Years (n = 699) | Univariable (n = 774) | Multivariable (n = 774)[a] | Frequency (n = 104 788) | Alive at 5 Years (n = 97 118) |
| Sex | | | | | | |
| Women | 562 (73) | 520 (93) | 1 [Reference] | 1 [Reference] | 80 871 (77) | 76 228 (94) |
| Men | 212 (27) | 179 (84) | 0.44 (0.27-0.71) | 0.64 (0.37-1.09) | 23 917 (23) | 20 890 (87) |
| Age, y | | | | | | |
| 18-39 | 198 (26) | 197 (99.5) | 1 [Reference] | 1 [Reference] | 26 760 (26) | 26 412 (99) |
| 40-49 | 165 (21) | 156 (95) | 0.09 (0.01-0.70) | 0.11 (0.01-0.92) | 25 370 (24) | 24 624 (97) |
| 50-59 | 189 (24) | 169 (89) | 0.04 (0.01-0.32) | 0.09 (0.01-0.67) | 24 552 (23) | 23 119 (94) |
| 60-69 | 131 (17) | 107 (82) | 0.02 (<0.01-0.17) | 0.05 (0.01-0.42) | 16 276 (16) | 14 370 (88) |
| >69 | 91 (12) | 70 (77) | 0.02 (<0.01-0.13) | 0.04 (0.01-0.32) | 11 830 (11) | 8593 (73) |
| Race | | | | | | |
| White or other | 684 (88) | 621 (91) | 1 [Reference] | NA | 95 124 (91) | 88 171 (93) |
| Black | 81 (11) | 69 (85) | 0.58 (0.30-1.14) | NA | 6769 (7) | 6169 (91) |
| Unknown | 9 (1) | NA | NA | NA | 2895 (2) | NA |
| Tobacco use | | | | | | |
| None | 416 (54) | 383 (92) | 1 [Reference] | NA | NA | NA |
| Current | 115 (15) | 95 (83) | 0.41 (0.23-0.75) | NA | NA | NA |
| Previous | 128 (17) | 112 (88) | 0.60 (0.32-1.14) | NA | NA | NA |
| Unknown | 115 (14) | NA | NA | NA | NA | NA |
| Alcohol use | | | | | | |
| None | 331 (43) | 300 (91) | 1 [Reference] | NA | NA | NA |
| Current | 282 (36) | 254 (90) | 0.94 (0.55-1.61) | NA | NA | NA |
| Previous | 28 (4) | 24 (86) | 0.62 (0.20-1.90) | NA | NA | NA |
| Unknown | 133 (17) | NA | NA | NA | NA | NA |
| Comorbidity[b] | | | | | | |
| None | 328 (42) | 321 (98) | 1 [Reference] | 1 [Reference] | 88 963 (84) | 83 869 (94) |
| Mild | 252 (33) | 232 (92) | 0.25 (0.11-0.61) | 0.41 (0.16-1.02) | 13 206 (13) | 11 438 (87) |
| Moderate/severe | 194 (25) | 146 (75) | 0.07 (0.03-0.15) | 0.12 (0.05-0.28) | 2619 (3) | 1811 (69) |
| Pathologic T stage | | | | | | |
| T1 or T2 | 549 (71) | 507 (92) | 1 [Reference] | 1 [Reference] | 66 464 (63) | 62 495 (94) |
| | | | | | 17 241 (17) | 16 256 (94) |
| T3 | 159 (21) | 139 (87) | 0.58 (0.33-1.01) | 0.55 (0.29-1.02) | 16 603 (16) | 15 022 (91) |
| T4 | 66 (9) | 53 (80) | 0.34 (0.17-0.67) | 0.34 (0.16-0.74) | 4480 (4) | 3345 (75) |
| AJCC TNM pathological stage | | | | | | |
| 1 | 519 (67) | 486 (94) | 1 [Reference] | NA | 64 602 (62) | 61 584 (95) |
| 2 | 61 (8) | 53 (87) | 0.45 (0.20-1.02) | NA | 7034 (7) | 6476 (92) |
| 3 | 131 (17) | 110 (84) | 0.36 (.20-0.64) | NA | 12 298 (12) | 10 958 (89) |
| 4 | 46 (6) | 36 (78) | 0.24 (0.11-0.54) | NA | 6096 (6) | 4531 (74) |
| Unknown | 17 (2) | NA | NA | NA | 14 758 (14) | NA |

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27[39,40]; AJCC, The American Joint Committee on Cancer; CCI, Charlson Comorbidity Index[51]; NA, not applicable; NCDB, National Cancer Database; TNM, tumor, node, and metastasis.

[a] Included variables on multivariable binary logistic regression were statistically significant on univariable binary logistic regression.

[b] The instrument used to measure comorbidity in the Siteman cancer registry was ACE-27 index, and the instrument used to measure comorbidity in the NCDB was CCI.

unique prognostic gradients. Likewise, within each category of comorbidity, age defines unique prognosis. This dual impact of age and comorbidity on survival is referred to as a "double-gradient." Conjoined categories of age and comorbidity were combined based on statistical isometry for 5-year survival rates and clinical sensibility into the 3-category FSSS. The resulting 3-stage FSSS had a 5-year survival (95% CI) of 99% (97%-100%) for stage α (n = 417), 85% (81%-90%) for stage β (n = 268), and 66% (57%-76%) for stage γ (n = 89). The prognostic gradient of the FSSS is wider than both the prognostic gradients of age and comorbidity by approximately 10%.

Table 2. Conjunctive Consolidation of Comorbidity and Age Into the FSSS[a]

| Comorbidity[b] | Patient Age, y[c] | | | | | Total |
|---|---|---|---|---|---|---|
| | 18-39 | 40-49 | 50-59 | 60-69 | >69 | |
| None | 137/137 (100) | 94/97 (97) | 56/56 (100) | 22/23 (96) | 12/15 (80)[d] | 321/328 (98) |
| Mild | 42/42 (100) | 42/43 (98) | 64/72 (89)[d] | 47/53 (89)[d] | 37/42 (88)[d] | 232/252 (92) |
| Moderate/severe | 18/19 (95) | 20/25 (80)[c] | 49/61 (80)[d] | 38/55 (69)[e] | 21/34 (62)[e] | 146/194 (75) |
| Total | 197/198 (99) | 156/165 (95) | 169/189 (89) | 107/131 (82) | 70/91 (77) | 699/774 (90) |

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; FSSS, functional severity staging system.

[a] All data reported as number of patients alive at 5 years/total number of patients in the category (5-year survival rate as percentage).

[b] Comorbidity was measured by the ACE-27 index.[39,40]

[c] Unless otherwise indicated, all data represent FSSS stage α disease.

[d] FSSS stage β disease.

[e] FSSS stage γ disease.

Table 3. Conjunctive Consolidation of the FSSS and T Stage Into the CSSS[a]

| FSSS Stage | T Stage[b] | | | Total |
|---|---|---|---|---|
| | T1 and T2 | T3 | T4 | |
| α | 293/296 (99) | 89/90 (99) | 29/31 (94) | 411/417 (99) |
| β | 173/195 (89) | 34/45 (76)[c] | 22/28 (79)[c] | 229/268 (85) |
| γ | 41/58 (71)[c] | 16/24 (67)[d] | 2/7 (29)[d] | 59/89 (66) |
| Total | 507/549 (92) | 139/159 (87) | 53/66 (80) | 699/774 (90) |

Abbreviations: CSSS, clinical severity staging system; FSSS, functional severity staging system.

[a] All data reported as number of patients alive at 5 years/total number of patients in the category (5-year survival rate as percentage).

[b] Unless otherwise indicated, all data represent CSSS stage A disease.

[c] CSSS stage B disease.

[d] CSSS stage C disease.

Table 4. Five-Year Survival Rates Stratified by the Evaluated Staging Systems and Applied to the NCDB Data[a]

| Disease Severity[b] | Staging System | | | | | |
|---|---|---|---|---|---|---|
| | AJCC | | FSSS | | CSSS | |
| | Stage | 5-Year Survival | Stage | 5-Year Survival | Stage | 5-Year Survival |
| 1 | 1 | 95 (95.1-95.5) | α | 96 (95.9-96.3) | A | 94 (94.1-94.5) |
| 2 | 2 | 92 (91.5-92.7) | β | 80 (78.9-80.1) | B | 67 (65.9-68.3) |
| 3 | 3 | 89 (88.5-89.7) | γ | 57 (54.8-59.8) | C | 45 (40.1-50.3) |
| 4 | 4 | 74 (73.1-75.5) | NA | NA | NA | NA |

Abbreviations: AJCC, The American Joint Committee on Cancer; CSSS, clinical severity staging system; FSSS, functional severity staging system; NA, not applicable; NCDB, National Cancer Database.

[a] Data reported as survival rate (95% CI) in percentages.

[b] The higher the number, the greater the disease severity.

### Conjunctive Consolidation of FSSS and TNM Pathological Stage Group Into a CSSS

**Table 3** summarizes the consolidation of the FSSS with T stage. The prognostic impact of the FSSS remains within each T stage. Regardless of tumor stage, those in the first functional severity stage had the highest 5-year survival rate. The resulting 3-stage CSSS had a 5-year survival (95% CI) of 95% (94%-97%) for stage A (n = 612), 74% (67%-82%) for stage B (n = 131), and 58% (41%-75%) for stage C (n = 31). This increases the range of the survival gradient observed by the FSSS by 4%.

### External Validation

Demographic, clinical, and tumor characteristics from the NCDB are reported in Table 1. The variables in the NCDB were grouped the same as the variables in the Siteman cancer registry. The FSSS and CSSS were created by the same combination of variables as reported in Tables 2 and 3, but with a different comorbidity instrument. **Table 4** lists the resulting 5-year survival rates within each category of the AJCC, FSSS, and CSSS staging systems. All 3 systems demonstrated a consistent decrease in 5-year survival across each stage, as seen in the eFigure in the Supplement.

### Performance and Quantitative Evaluation of Staging System

**Table 5** summarizes the performance of the 3 staging systems based on the Siteman and NCDB data. For the Siteman data, the CSSS outperformed the FSSS and the AJCC staging systems in every aspect except for the C statistic. For the NCDB data, the CSSS had the largest overall survival gradient, but in all other measures, the FSSS performed the best.

## Discussion

In this study, we identified age, comorbidity, and tumor stage as prognostically significant variables in the Siteman registry

Table 5. Quantitative Evaluation of Staging Systems Stratified by Data Set

| | Siteman Registry Data | | | NCDB Data | | |
|---|---|---|---|---|---|---|
| Category of Evaluation | AJCC | FSSS | CSSS | AJCC | FSSS | CSSS |
| Monotonicity of survival gradient | Yes | Yes | Yes | Yes | Yes | Yes |
| Overall survival gradient, % | 16 | 33 | 37 | 21 | 39 | 49 |
| Variance reduction score | 0.05 | 0.13 | 0.21 | 0.08 | 0.15 | 0.11 |
| Log rank for linear trend | 28.38 | 142.77 | 151.77 | 4268.83 | 14 375.62 | 11 457.96 |
| C statistic (95% CI) | 0.63 (0.56-0.71) | 0.80 (0.75-0.85) | 0.74 (0.67-0.81) | 0.66 (0.65-0.66) | 0.71 (0.70-0.72) | 0.62 (0.61-0.62) |

Abbreviations: AJCC, The American Joint Committee on Cancer; CSSS, clinical severity staging system; FSSS, functional severity staging system; NCDB, National Cancer Database.

and validated their importance in the NCDB data. The prognostic importance of age was realized across the entire age spectrum and was not captured as a dichotomized point. By combining different categories of age, comorbidity, and T stage, through the process known as conjunctive consolidation, we developed 2 new composite staging systems—the FSSS and CSSS. We quantitatively compared the prognostic accomplishments of the new FSSS and CSSS with the AJCC staging system and demonstrated that combinations of age, comorbidity, and T stage used in the Siteman data set also were able to define unique prognostic subgroups within the NCDB data set. Our results demonstrate that both the CSSS and FSSS are more prognostically accurate than the current AJCC staging system.

The incidence of thyroid cancer is dramatically increasing largely due to the increase in PTC incidence, which has nearly tripled from 1973 to 2009.[53] Yet despite the increase in incidence, overall survival for PTC remains high.[53-55] Furthermore, PTC has a large reservoir of subclinical disease demonstrated through previous studies that report PTC as a common histological finding on autopsy without previous symptoms.[7,56,57] A study performed by Morris et al[58] identified a strong correlation between several markers of health care access and papillary thyroid cancer incidence rate, which suggests that the increase in health care activity is contributing to the detection of the reservoir of subclinical PTC. Overall, the accumulation of an increase of incidence without increase of mortality, a large reservoir of disease, and the increase of detection of the disease suggest an epidemic of overdiagnosis.[3,7,10,12]

The concern with an overdiagnosis phenomenon is the uncertainty of knowing which cancer is "overdiagnosed" and which cancer is in need of attention.[10] The uncertainty causes patients to undergo potentially unnecessary follow-up examinations, imaging, biopsies, surgery, irradiation, and/or chemotherapy.[11] Exposing patients to treatment for a subclinical disease subjects patients to the adverse effects of treatment without offering the same benefits.[3,10,11] The repercussions of an overdiagnosed cancer can affect the patient emotionally, physically, and mentally.[11] Therefore, the ability to differentiate between subclinical disease, which is unlikely to progress and cause harm, and progressive disease is the cogent clinical question of our time.[10,11]

Recent literature on the management of overdiagnosed cancer[10,11] and PTC[7,54,59] suggests the use of active surveillance, rather than immediate treatment, of asymptomatic patients with newly diagnosed PTC detected through screening. Prospective trials assessing the use of active surveillance in PTC report success in the use of this alternative treatment approach.[59-61] The new FSSS and CSSS staging systems are tools that might aid the scientific community in furthering our understanding of PTC by identifying which patients could likely be considered for active surveillance and by improving comparative treatment effectiveness analysis.

The FSSS and CSSS staging systems may be used to estimate prognostic information using pretreatment characteristics, thus helping to identify patients that have favorable outcomes. The patients with favorable predicted outcomes may benefit the most from an initial active surveillance. This hypothesis would need to be tested by prospective studies. Our data indicate that for patients with nonmetastatic disease, patients 40 years or younger or patients, regardless of age, with no comorbidity have a very high 5-year survival rate. Therefore, these patients may be the ones most likely to benefit from an active surveillance approach for tumors diagnosed through screening. Furthermore, as different courses of management for PTC are being explored, the FSSS and CSSS can be used to allow better methods of comparative treatment effectiveness through more precise prognostic modeling.

## Limitations

This study should serve as the next step in the effort to improve cancer staging systems through the inclusion of multiple prognostic variables and the use of sophisticated predictive analytic approaches such as nomograms. In the development of this model, there were a few obstacles that likely can be improved on. Importantly, we were unable to investigate the iatrotropic stimulus—that is the event or stimulus that provokes a patient to visit a physician.[31,62,63] The iatrotropic stimulus is a crucial piece of information that can be used as a marker for prognosis. Patients who present asymptomatically with an incidentally diagnosed cancer will likely have a better prognosis than those who present symptomatically and whose thyroid tumors are diagnosed through case finding.[60,64] During manual collection of ACE-27 data through chart review, we found a recurring theme throughout many initial evaluations of PTC to be the "incidental" diagnoses of PTC by various diagnostic procedures in patients without signs and symptoms of thyroid dysfunction. In light of the overdiagnosis phenomenon, we believe that iatrotropic stimulus in the case of PTC would provide additional information that strengthens a cancer staging system to distinguish cancers that

are indolent and unlikely to progress from those in need of urgent attention and guide sensible treatment.

A second limitation is that the model created using the Siteman cancer registry was not exactly reproducible in the NCDB data because comorbidity information in the NCDB is collected according to the Deyo adaption of the CCI.[51] In the Siteman registry, comorbidity is collected by both the Deyo adaption of CCI and the ACE-27 instrument. We chose to use the ACE-27 comorbidity index[39,40] because it is more complete in the description of unique prognostic subgroups. Under CCI classification, approximately 10% of the cohort was coded as having comorbidity, with the remaining 90% coded as having no comorbidity. However, by the ACE-27 instrument, approximately 58% of the cohort was coded as having comorbidity. A previous study within this department[65] similarly identified, in a cohort of 6135 patients, that 67% of patients coded as not having comorbidity by CCI were coded has having comorbidity by ACE-27, with approximately 27% coded has having moderate to severe comorbidity.

Another limitation of the study is the inclusion of Siteman Cancer Center in the NCDB registry. It is potentially a bias to externally validate using a cohort that includes the cohort used to develop the model. However, given the large number of patients in the NCDB cohort, and the relatively small number of patients in the Siteman cohort, the impact is likely to be minimal.

## Conclusions

The addition of patient factors to the morphologic description of primary tumor created a better prognostic staging system. The FSSS and CSSS staging systems, compared with the AJCC, may improve the scientific reporting of disease outcomes and guide clinical care by improving classification of patients in clinically meaningful strata. In light of the overdiagnosis phenomenon, both the FSSS and CSSS can be useful tools to support comparative effectiveness studies and facilitate patient involvement in decision making.


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