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Prognostic Utility of Tumor Stage versus American Thyroid Association Risk Class in Thyroid Cancer

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Abstract

Objective: To evaluate the prognostic strengths of American Joint Committee on Cancer (AJCC) staging and American Thyroid Association (ATA) risk classification in well-differentiated thyroid cancer (DTC), and their implications in guiding medical decision-making and epidemiological study designs.

Methods: The 2004-2017 National Cancer Database was queried for DTC patients. Cox proportional hazards (CPH) and Kaplan-Meier analyses modeled patient mortality and overall survival, respectively. Each CPH model was evaluated by its concordance index, measure of explained randomness (MER), Akaike information criterion (AIC), and area under receiver operating characteristic curve (AUC).

Results: Overall, 134,226 patients were analyzed, with an average age of 48.1±15.1 years (76.9% female). Univariate CPH models using AJCC staging demonstrated higher concordance indices, MERs, and AUCs than those using ATA risk classification (all $p<0.001$). Multivariable CPH models using AJCC staging demonstrated higher concordance indices ($p=0.049$), MERs ($p=0.046$), and AUCs ($p=0.002$) than those using ATA risk classification. The AICs of multivariable AJCC staging and ATA risk models were 7.564×10^4 and 7.603×10^4, respectively. AJCC stage I tumors were associated with greater overall survival than those classified as ATA low risk, while AJCC stages II-III and stage IV tumors demonstrated worse survival than ATA intermediate- and high-risk tumors, respectively (all $p<0.001$).

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Level of Evidence: 4

Conclusion: AJCC staging may be a more predictive system for patient survival than ATA risk. The prognostic utility of these two systems converges when additional demographic and clinical factors are considered. AJCC staging was found to classify patients across a wider range of survival patterns than the ATA risk stratification system.

Keywords

AJCC; TNM; ATA; thyroid cancer; survival; study design

Introduction

Well-differentiated thyroid cancer (DTC), which encompasses the Papillary, Follicular, and Hurthle Cell histological variants, comprises approximately 90% of all diagnosed thyroid carcinomas.[1] Over the past three decades, DTC incidence rates have tripled, reaching as high as 14.7 per 100,000 in 2015.[2] This progressive rise in DTC incidence has been largely attributed to advancing imaging systems and diagnostic protocols that have enabled more sensitive detection of subclinical disease.[3] DTCs are conventionally treated with total thyroidectomy with or without radioiodine therapy and/or thyroid-stimulating hormone suppression therapy. Owing to the growing patient population, there has been increased scrutiny on overtreatment and the underlying staging criteria used to justify therapeutic approaches.[4] To guide treatment and prognostication, DTCs are often stratified by risk according to the American Thyroid Association (ATA) guidelines or TNM stage per the American Joint Committee on Cancer (AJCC) staging manual.[5,6]

First published in 1996, the ATA guidelines broadly outline treatment guidelines for patients with thyroid nodules and DTC. Over the past 25 years, the association has revised its guidelines several times to reflect recent advancements in the field, including improvements in medical diagnostics and treatment strategies. Based on these guidelines, thyroid cancers can be stratified into three risk classes (low, intermediate, and high) according to their risk for structural disease recurrence. Specifically, the ATA defines each risk class by primary tumor size, involvement of regional lymph nodes, and presence of aggressive histological variants, vascular invasion, and distant metastasis.[5,7] Given that approximately 30% of patients with DTC experience tumor recurrence, appropriate management of the disease according to recurrence risk is critical to optimizing patient survival.[8]

In contrast, the AJCC TNM staging system utilizes primary tumor size, degree of local invasion, involvement of regional lymph nodes, and the presence of distant metastasis as markers for designating a composite TNM stage that prognosticates mortality rather than recurrence. In the National Comprehensive Cancer Network (NCCN) guidelines, age and tumor stage are highlighted as two of the most significant clinical factors in influencing patient survival. Furthermore, the NCCN has proposed its application in prospective trials and other epidemiological studies as a tool for patient stratification.[9]

Over the years, researchers have used ATA risk classification and TNM staging as clinical determinants of patient survival in epidemiological studies on DTC.[10–15] Given the widespread use of both systems, especially in the context of a growing DTC patient population, both models' prognostic abilities deserve increased scrutiny to determine if

their interchangeable use in clinical and scientific contexts is warranted. In this study, we aimed to evaluate the abilities of the AJCC staging and ATA risk classification systems in prognosing patient survival to help guide future clinical decision-making and research efforts in this field.

Methods

Study Population

The 2004-2017 National Cancer Database (NCDB) is a deidentified and publicly available database that reports more than 70% of newly diagnosed cancer cases nationwide from over 1500 Commission on Cancer-accredited facilities throughout the U.S.[16] Due to the database's anonymized nature, this study was exempt from University of California Irvine Institutional Review Board approval.

We queried the NCDB for patients diagnosed with DTC using the *International Classification of Disease for Oncology, 3rd Edition* (ICD-O-3) topography code for thyroid (C73.9) and histology/behavior codes for papillary (PTC; 8050/3, 8260/3, 8337/3, 8340-8344/3, 8350/3), follicular (FTC; 8330-8332/3, 8335/3), and Hurthle cell (HTC; 8290/3) thyroid cancer. Patients who did not undergo surgery primarily as part of their treatment course were excluded. Since cases reported tumor staging using varying editions of the AJCC TNM staging system, to avoid confounding results, only cases providing staging data based on the latest AJCC edition (seventh) available in the NCDB were included. Patients who received palliative care or had more than one primary malignancy were excluded. Cases with unknown or missing treatment information were excluded.

Study Variables

All variables used in this study were derived from data in the NCDB. Independent covariates included age, sex, Charlson/Deyo (CD) comorbidity index, cancer histology (PTC, FTC, HTC), AJCC tumor stage, ATA risk class, surgical margins, extent of surgery, radioiodine therapy (RAI), or thyroid-stimulating hormone suppression therapy (THST). The use of chemotherapy was not analyzed, as less than 0.1% of patients in our cohort were reported to have received chemotherapy. CD indices were binarized as 0 and ≥1 to indicate the absence or presence of comorbidities, respectively. Extent of surgery was dichotomized as lobectomy (lobectomy ± isthmectomy) and total thyroidectomy (total, near-total, or subtotal resection) per previously published studies.[17,18] Patients were designated ATA risk classes according to the 2009 ATA guidelines.[19] Of note, among the aggressive histological variants of PTC noted by the ATA (e.g., insular, columnar, hobnail, tall cell, sclerosing), specification of the hobnail variant was unavailable in the NCDB. The primary measured outcome was all-cause mortality starting at the time of diagnosis.

Statistical Analysis

All statistical analyses were performed via R (version 3.6.1; The R Foundation for Statistical Computing) in RStudio (version 1.2.1335). A p-value of <0.05 was considered statistically significant. Unpaired two-sample t-tests were used to evaluate differences in the means of two groups. The association between AJCC stage or ATA risk class and mortality risk was

analyzed via Cox proportional-hazards (CPH) models. Demographic and clinical factors that were statistically significant on univariate CPH analysis were included as covariates in multivariable regression models. The same cohort of patients and covariates were used in all univariate and multivariable analyses. Multivariable CPH models were assessed for multicollinearity by ensuring that all covariates possessed variance inflation factors less than 10.[20] The concordance index, which served as a standard performance measure and represented how well a predicted risk score described an observed series of events, was calculated for each CPH model.[21] Additionally, using the "rsq" R package, we calculated each CPH model's Measure of Explained Randomness (MER), which, similar to the coefficient of determination (R^2) used with uncensored data, served as an explained risk measure in the context of our study's censored data.[22,23] Bootstrapping was performed with 100 bootstrap samples using the "boot" R package in order to determine 95% confidence intervals for calculated concordance indices and MER values.[24] Furthermore, we calculated the Akaike Information Criterion (AIC) to assess relative goodness of fit among CPH models, where a smaller AIC value suggested superior prognostic stratification.[25] The time-dependent area under the receiver operating characteristic curve (AUC) of each CPH model was calculated with the "timeROC" R package. To determine AUC values, 60% percent of the study population was used as the training cohort for developing CPH models that were subsequently applied for calculating the probability of survival in the remaining 40% of patients. The overall predictive performance of each survival model, defined as the average of all calculated time-dependent AUCs, was obtained by determining time-specific AUC values at 3-month intervals for a total of 36 measurements.[26] Finally, using the *ggsurvplot* R package, Kaplan Meier survival curves were generated from the multivariable CPH models and log-rank tests were performed to evaluate the prognostic utility of AJCC stages and ATA risk classes.

Results

Overall, 134,226 patients with DTC between 2004-2017 were analyzed, of which 103,180 (76.9%) were female, with an average age of 48.1±15.1 years. Table 1 lists the demographic and clinical characteristics of this cohort. The prevalence of patients classified as ATA low risk, intermediate risk, or high risk was 57.7%, 33.2%, or 9.1%, respectively. Of this cohort, 95,200 (70.9%), 11,598 (8.6%), 19,137 (14.3%), and 8,291 (6.2%) patients possessed AJCC stage I, stage II, stage III, and stage IV DTC, respectively.

Evaluating Predictive Model Performance

On univariate CPH analysis (Table 2), the concordance index of the survival model using AJCC staging (0.710±0.038) was significantly greater than that using ATA risk classification (0.641±0.048; $p<0.001$). Similarly, the MER of the AJCC staging model (0.529±0.133) was significantly greater than that of the ATA risk model (0.336±0.140; $p<0.001$). Moreover, the AUC of the AJCC staging model (0.712±0.036) was significantly larger than that of the ATA risk model (0.645±0.051, $p<0.001$). Additionally, the AIC values of the AJCC staging and ATA risk models were found to be 9.592×10^4 and 9.743×10^4, respectively.

On multivariable CPH analysis (Table 2), the concordance index of the AJCC staging model (0.813 ± 0.038) was significantly greater than that of the ATA risk model (0.803±0.033; p=0.049). Additionally, the MER of the multivariable AJCC staging model (0.772±0.079) was significantly greater than that of the multivariable ATA risk model (0.743±0.110; p=0.046). Moreover, the AUC of the multivariable AJCC staging model (0.815±0.020) was significantly larger than that of the multivariable ATA risk model (0.808±0.019, p=0.002). Additionally, the AIC values of the multivariable AJCC staging and ATA risk models were determined to be 7.564×10^4 and 7.603×10^4, respectively.

Survival Analysis by AJCC Staging and ATA Risk Classification

Associations between AJCC stage or ATA risk class and all-cause mortality were evaluated using univariate and multivariable CPH analyses and are listed in Table 3. On multivariable CPH analysis, AJCC stage II (HR 1.523; 95% CI, 1.359-1.707; p<0.001), stage III (HR 1.725; 95% CI, 1.570-1.895; p<0.001), and stage IV (HR 4.879; 95% CI, 5.374; p<0.001) were associated with increased mortality risk than stage I DTC. Moreover, ATA intermediate (HR 1.432; 95% CI, 1.317-1.556; p<0.001) and high risk (HR 4.077; 95% CI, 3.627-4.583; p<0.001) patients were found to be associated with increased mortality than ATA low risk patients.

Kaplan Meier survival curves were generated to evaluate differences in survival outcomes among AJCC stage- and ATA risk-stratified patients (Figure 1). AJCC stage I patients were associated with greater overall survival (OS) than ATA low risk patients (Figure 1A, p<0.001). However, AJCC stages II and III tumors were associated with decreased OS compared to those classified as ATA intermediate risk (Figure 1B, both p<0.001). Similarly, AJCC stage IV patients were associated with lower OS than ATA high risk patients (Figure 1C, p<0.001).

Discussion

In this population-based study, we utilized a cohort of 134,226 patients with DTC to evaluate the prognostic abilities of the AJCC staging and ATA risk systems. Performance measures from univariate and multivariable CPH models demonstrated that the AJCC staging system was more precise in predicting overall survival. Further analysis indicated that patients with AJCC stage I tumors were associated with greater OS than those classified as ATA low risk. Conversely, patients with AJCC stages II-III and stage IV cancers were found to be associated with worse OS than those classified as ATA intermediate and high risk, respectively. As a whole, these findings suggest that the AJCC staging system may generally be more useful for clinicians in prognosing patient survival and for medical scientists in designing survival-based outcome studies.

The statistically significant differences in performance and hazard ratios between the two tumor stratification systems (TSSs) were most pronounced in the univariate CPH models, suggesting that when considered alone, AJCC predicts patient survival with much greater accuracy than ATA. It is, therefore, important to recognize this difference in model behavior when designing studies or stratifying patients on the basis of TNM stage or ATA risk. However, these differences narrow in the multivariable models, implying that if multiple

demographic and clinical factors are incorporated into the decision process, studies may be able to predict patient prognosis using either TSS interchangeably with minimal differences in accuracy. Yet, differences in the Kaplan-Meier survival curves of the four AJCC stage and three ATA risk strata suggest caution when drawing direct comparisons between the two. Neither system was seen to be universally more or less conservative than the other, allowing potential for situational applications of each TSS. For example, while the ATA low risk classification was significantly more conservative in OS prognosis than that of AJCC stage I, the ATA intermediate risk classification was observed to be significantly less conservative than both AJCC stages II and III. Furthermore, the ATA high risk category similarly predicted higher survival probability than did AJCC stage IV. Taken together, these observations suggest that AJCC staging stratifies patients across a wider range of survival patterns than the ATA risk system, thereby suggesting that it may be more useful in stratifying DTC patients at either end of the prognostic spectrum. This can be partly attributed to the AJCC TSS' inherent ability to stage patients into more strata compared to the ATA TSS.

These findings support that the respective original intents behind the development of each TSS – AJCC TNM to prognosticate mortality and ATA risk to predict disease recurrence – are still clinically meaningful today.[27] Nonetheless, several studies in the past have attempted to assess and extend the utility of ATA risk status to evaluate risk of mortality in addition to recurrence, with some success.[12,28,29] Still, other authors have suggested that both AJCC and ATA TSSs are insufficient when used alone and should be strategically combined and/or supplemented by demographic or other clinical factors to improve DTC prognostic predictions. In 2018, Ghaznavi *et al.* described a six-category subclassification system that used ATA criteria as well as age to further stratify disease-specific survival prognoses for patients that had AJCC stage I or II DTC.[30] An advantage of this highly personalized, combined risk estimation system was the use of clinicopathologic information routinely collected for AJCC and ATA TSSs.[30] Song *et al.* found that inclusion of the mutation status of the promoter of the gene encoding telomerase reverse transcriptase (*TERT*) in the risk stratification decision process overcame certain limitations of both the mortality and recurrence predictiveness of both the AJCC and ATA TSSs.[31] Interestingly, they extended this analysis to the older Age, Metastasis, Extent, and Size (AMES) TSS, established in 1988 with two risk levels and used traditionally to decide between partial or total thyroidectomy, and the Metastasis, Age, Completeness of Resection, Invasion, and Size (MACIS) system, developed in 1993 for the prognostication of PTC, and found utility in considering *TERT* mutations for patients categorized as high-risk under these scoring systems as well.[31–33] Combinatory, multifactorial risk stratification protocols have also been used internationally. With the release of the 2015 revision of ATA guidelines, the Korean Thyroid Association responded by "flexibly and selectively" adopting guidelines for active surveillance and surgical extent while still relying on the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) for sonograph-informed fine needle aspiration.[34,35] Recently, Italian researchers demonstrated that a high neutrophil-to-lymphocyte ratio was predictive of recurrence in patients categorized as low-risk under the ATA criteria, and may be informative in follow-up protocols and management of this subgroup of patients.[36] Additionally, Kelly *et al.* suggested the utility of pre-ablation stimulated thyroglobulin levels

as an important factor predictive of survival complementary to the 8th edition AJCC staging system.[29]

While the updated 2015 ATA risk criteria have been demonstrated to possess some utility in prognosticating mortality, recent studies have also suggested that, likewise, the 8th edition AJCC staging system exhibits promising predictiveness of recurrence. Notably, a 2017 population-based study of papillary thyroid cancer patients reported that 8th edition AJCC staging predicted recurrence with higher accuracy than both the 2009 and 2015 ATA risk criteria.[37] Park *et al.* attributed this partly to the modification of the extrathyroidal extension (ETE) criteria within the 8th edition AJCC staging guidelines, finding that designating gross ETE to only the strap muscles under the new T3b category provided prognostic information about long-term recurrence.[38] Gan *et al.* reiterated the increasing clinical relevance of recurrence as a prognosticator with DTC survival on the rise, and demonstrated that the 8th edition AJCC TSS better differentiated recurrence risk in early stages of DTC compared to its previous edition.[39] Therefore, whether the 8th edition AJCC staging system has overtaken the 2015 ATA risk criteria in its ability to prognose recurrence risk in DTC is certainly worth further investigation in future studies.

Guidelines from the NCCN regarding the AJCC edition used in the present study, the 7th edition, maintain that tumor stage and age are two of the strongest variables affecting mortality among DTC patients.[9] However, it is worthy to note that they also clearly state their stance against the use of composite TNM stages as the primary guide to approaching DTC management, and instead use many of the individual tumor and patient characteristics considered in TNM staging as the primary determinants of NCCN treatment recommendations.[9] Despite this digression from TNM-stage-informed DTC management, the NCCN does endorse the use of 7th edition AJCC staging guidelines when stratifying and prognosticating patients for prospective trials or epidemiological studies.[9]

To our knowledge, this is one of the first studies to compare the prognostic performances of the AJCC staging and ATA risk classification systems in DTC patients. A better understanding of the prognostic capabilities of these two stratification systems can not only aid physicians in medical decision-making and patient counseling, but can also help in shaping the study designs of future research efforts for DTC. Despite great care in analyzing the data, there are, however, limitations to this study to consider, much of which were a consequence of using a large administrative database. Since patients were extracted from a de-identified national database, the data may be susceptible to selection and information bias that may impact interpretations of patient mortality.[40] Furthermore, we were restricted to using overall survival as our main outcome variable and could not evaluate patient prognosis on the basis of recurrence-free or disease-free survival. Additionally, it is possible that the use of 4 categories in TNM staging compared to 3 categories in ATA risk classification enabled a more favorable distribution for modeling mortality. The presence and magnitude of such an effect would require more advanced statistical examination; thus, future study and consideration of this effect may be warranted. Lastly, due to NCDB limitations, we were unable to analyze more recent variants of the studied stratifications systems, including the 8th edition of the AJCC staging system and the 2015 ATA risk classification system. However, the ATA's 2015 revision of its risk stratification system was largely similar to

that of its 2009 version, with only a few additional prognostic variables, whose incremental benefits, per the ATA, have not yet been established.[41,42] On the other hand, recent reports have suggested that the 8th edition of the AJCC staging system may provide even better predictability of mortality and tumor recurrence than its predecessor.[14,43,44] Therefore, future studies with carefully crafted variable and outcome measures may be warranted to further elucidate the relative prognostic abilities of these two stratification models in their most recent editions.

Conclusion

AJCC staging serves as a more prognostic model for patient survival compared to ATA risk classification. The greater predictive strength of AJCC staging becomes less pronounced when multiple additional demographic and clinical factors are considered. Additionally, AJCC staging represents patients across a wider range of survival patterns than ATA risk classification and may be more useful in certain outcomes-based studies where more precise stratification of DTC patients according to their survival patterns is desired.

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References

1. Nguyen QT, Lee EJ, Huang MG, Park YI, Khullar A, Plodkowski RA. Diagnosis and treatment of patients with thyroid cancer. Am Heal drug benefits. 2015;8(1):30–40.
2. SEER stat fact sheets: thyroid cancer. National Cancer Institute. Published 2021. Accessed April 22, 2021. https://seer.cancer.gov/statfacts/html/thyro.html
3. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014;140(4):317–322. doi:10.1001/jamaoto.2014.1 [PubMed: 24557566]
4. Stewart LA, Kuo JH. Advancements in the treatment of differentiated thyroid cancer. Ther Adv Endocrinol Metab. 2021;12:20420188211000252. doi:10.1177/20420188211000251
5. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015;26(1):1–133. doi:10.1089/thy.2015.0020
6. Edge S, Byrd D, Compton C, Fritz A, FL G, A T, eds. AJCC Cancer Staging Manual. 7th ed. American Joint Committee on Cancer; 2010. https://cancerstaging.org/references-tools/
7. Grani G, Zatelli MC, Alfò M, et al. Real-World Performance of the American Thyroid Association Risk Estimates in Predicting 1-Year Differentiated Thyroid Cancer Outcomes: A Prospective Multicenter Study of 2000 Patients. Thyroid. 2021;31(2):264–271. doi:10.1089/thy.2020.0272 [PubMed: 32475305]
8. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97(5):418–428. doi:10.1016/0002-9343(94)90321-2 [PubMed: 7977430]
9. Haddad R, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma Version 1. National Comprehensive Cancer Network, Inc. Accessed April 22, 2021. NCCN.org
10. Vargas-Pinto S, Romero Arenas MA. Lobectomy Compared to Total Thyroidectomy for Low-Risk Papillary Thyroid Cancer: A Systematic Review. J Surg Res. 2019;242:244–251. doi:10.1016/j.jss.2019.04.036 [PubMed: 31103828]

11. Liu J, Zhang Z, Huang H, et al. Total thyroidectomy versus lobectomy for intermediate-risk papillary thyroid carcinoma: A single-institution matched-pair analysis. Oral Oncol. 2019;90:17–22. doi:10.1016/j.oraloncology.2019.01.010 [PubMed: 30846171]
12. van Velsen EFS, Stegenga MT, van Kemenade FJ, et al. Evaluating the 2015 American Thyroid Association Risk Stratification System in High-Risk Papillary and Follicular Thyroid Cancer Patients. Thyroid. 2019;29(8):1073–1079. doi:10.1089/thy.2019.0053 [PubMed: 31140385]
13. Pontius LN, Oyekunle TO, Thomas SM, et al. Projecting Survival in Papillary Thyroid Cancer: A Comparison of the Seventh and Eighth Editions of the American Joint Commission on Cancer/Union for International Cancer Control Staging Systems in Two Contemporary National Patient Cohorts. Thyroid. 2017;27(11):1408–1416. doi:10.1089/thy.2017.0306 [PubMed: 28891405]
14. Nam SH, Bae MR, Roh J-L, et al. A comparison of the 7th and 8th editions of the AJCC staging system in terms of predicting recurrence and survival in patients with papillary thyroid carcinoma. Oral Oncol. 2018;87:158–164. doi:10.1016/j.oraloncology.2018.11.003 [PubMed: 30527232]
15. Yang Q, Zhao Z, Zhong G, Jin A, Yu K. Effect of adjuvant radioactive iodine therapy on survival in rare oxyphilic subtype of thyroid cancer (Hürthle cell carcinoma). PeerJ. 2019;7:e7458. doi:10.7717/peerj.7458 [PubMed: 31523497]
16. National Cancer Database. American College of Surgeons. Published 2020. https://www.facs.org/Quality-Programs/Cancer/NCDB
17. Bilimoria KY, Bentrem DJ, Linn JG, et al. Utilization of total thyroidectomy for papillary thyroid cancer in the United States. Surgery. 2007;142(6):902–906. doi:10.1016/j.surg.2007.09.002
18. Adam MA, Pura J, Goffredo P, et al. Impact of extent of surgery on survival for papillary thyroid cancer patients younger than 45 years. J Clin Endocrinol Metab. 2015;100(1):115–121. doi:10.1210/jc.2014-3039 [PubMed: 25337927]
19. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2009;19(11):1167–1214. doi:10.1089/thy.2009.0110 [PubMed: 19860577]
20. Yoo W, Mayberry R, Bae S, Singh K, Peter He Q, Lillard JW Jr. A Study of Effects of MultiCollinearity in the Multivariable Analysis. Int J Appl Sci Technol. 2014;4(5):9–19. https://pubmed.ncbi.nlm.nih.gov/25664257 [PubMed: 25664257]
21. Longato E, Vettoretti M, Di Camillo B. A practical perspective on the concordance index for the evaluation and selection of prognostic time-to-event models. J Biomed Inform. 2020;108:103496. doi:10.1016/j.jbi.2020.103496 [PubMed: 32652236]
22. Honerkamp-Smith G, Xu R. Three measures of explained variation for correlated survival data under the proportional hazards mixed-effects model. Stat Med. 2016;35(23):4153–4165. doi:10.1002/sim.6993 [PubMed: 27241815]
23. Heller G A measure of explained risk in the proportional hazards model. Biostatistics. 2012;13(2):315–325. doi:10.1093/biostatistics/kxr047 [PubMed: 22190711]
24. DiCiccio TJ, Efron B. Bootstrap confidence intervals. Stat Sci. 1996;11(3):189–228. doi:10.1214/ss/1032280214
25. Yoon HM, Ryu KW, Nam BH, et al. Is the new seventh AJCC/UICC staging system appropriate for patients with gastric cancer? J Am Coll Surg. 2012;214(1):88–96. doi:10.1016/j.jamcollsurg.2011.09.018 [PubMed: 22036661]
26. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: current methods and applications. BMC Med Res Methodol. 2017;17(1):53. doi:10.1186/s12874-017-0332-6 [PubMed: 28388943]
27. Tuttle RM, Alzahrani AS. Risk Stratification in Differentiated Thyroid Cancer: From Detection to Final Follow-Up. J Clin Endocrinol Metab. 2019;104(9):4087–4100. doi:10.1210/jc.2019-00177 [PubMed: 30874735]
28. Robenshtok E, Nachalon Y, Benbassat C, et al. Disease Severity at Presentation in Patients with Disease-Related Mortality from Differentiated Thyroid Cancer: Implications for the 2015 ATA Guidelines. Thyroid. 2017;27(9):1171–1176. doi:10.1089/thy.2017.0040 [PubMed: 28791923]
29. Kelly A, Barres B, Kwiatkowski F, et al. Age, thyroglobulin levels and ATA risk stratification predict 10-year survival rate of differentiated thyroid cancer patients. PLoS One. 2019;14(8):e0221298. doi:10.1371/journal.pone.0221298 [PubMed: 31425569]

30. Ghaznavi SA, Ganly I, Shaha AR, English C, Wills J, Tuttle RM. Using the American Thyroid Association Risk-Stratification System to Refine and Individualize the American Joint Committee on Cancer Eighth Edition Disease-Specific Survival Estimates in Differentiated Thyroid Cancer. Thyroid. 2018;28(10):1293–1300. doi:10.1089/thy.2018.0186 [PubMed: 29897011]

31. Song YS, Lim JA, Choi H, et al. Prognostic effects of TERT promoter mutations are enhanced by coexistence with BRAF or RAS mutations and strengthen the risk prediction by the ATA or TNM staging system in differentiated thyroid cancer patients. Cancer. 2016;122(9):1370–1379. doi:10.1002/cncr.29934 [PubMed: 26969876]

32. Haigh PI, Urbach DR, Rotstein LE. AMES prognostic index and extent of thyroidectomy for well-differentiated thyroid cancer in the United States. Surgery. 2004;136(3):609–616. doi:10.1016/j.surg.2003.12.009 [PubMed: 15349109]

33. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993;114(6):1050–1058. [PubMed: 8256208]

34. Yi KH. The Revised 2016 Korean Thyroid Association Guidelines for Thyroid Nodules and Cancers: Differences from the 2015 American Thyroid Association Guidelines. Endocrinol Metab (Seoul, Korea). 2016;31(3):373–378. doi:10.3803/EnM.2016.31.3.373

35. Migda B, Migda M, Migda MS, Slapa RZ. Use of the Kwak Thyroid Image Reporting and Data System (K-TIRADS) in differential diagnosis of thyroid nodules: systematic review and meta-analysis. Eur Radiol. 2018;28(6):2380–2388. doi:10.1007/s00330-017-5230-0 [PubMed: 29294156]

36. Offi C, Romano RM, Cangiano A, Candela G, Docimo G. Clinical significance of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio and prognostic nutritional index in low-risk differentiated thyroid carcinoma. Acta Otorhinolaryngol Ital. 2021;41(1):31–38. doi:10.14639/0392-100X-N1089 [PubMed: 33746220]

37. Suh S, Kim YH, Goh TS, et al. Outcome prediction with the revised American joint committee on cancer staging system and American thyroid association guidelines for thyroid cancer. Endocrine. 2017;58(3):495–502. doi:10.1007/s12020-017-1449-4 [PubMed: 29030773]

38. Park SY, Kim HI, Kim J-H, et al. Prognostic significance of gross extrathyroidal extension invading only strap muscles in differentiated thyroid carcinoma. Br J Surg. 2018;105(9):1155–1162. doi:10.1002/bjs.10830 [PubMed: 29663333]

39. Gan T, Huang B, Chen Q, et al. Risk of Recurrence in Differentiated Thyroid Cancer: A Population-Based Comparison of the 7th and 8th Editions of the American Joint Committee on Cancer Staging Systems. Ann Surg Oncol. 2019;26(9):2703–2710. doi:10.1245/s10434-019-07275-1 [PubMed: 30830539]

40. Kumar A, Guss ZD, Courtney PT, et al. Evaluation of the Use of Cancer Registry Data for Comparative Effectiveness Research. JAMA Netw open. 2020;3(7):e2011985. doi:10.1001/jamanetworkopen.2020.11985 [PubMed: 32729921]

41. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1–133. doi:10.1089/thy.2015.0020 [PubMed: 26462967]

42. Haugen BR. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: What is new and what has changed? Cancer. 2017;123(3):372–381. doi:10.1002/cncr.30360 [PubMed: 27741354]

43. Kim TH, Kim YN, Kim HI, et al. Prognostic value of the eighth edition AJCC TNM classification for differentiated thyroid carcinoma. Oral Oncol. 2017;71:81–86. doi:10.1016/j.oraloncology.2017.06.004 [PubMed: 28688696]

44. Kim M, Kim WG, Oh H-S, et al. Comparison of the Seventh and Eighth Editions of the American Joint Committee on Cancer/Union for International Cancer Control Tumor-Node-Metastasis Staging System for Differentiated Thyroid Cancer. Thyroid. 2017;27(9):1149–1155. doi:10.1089/thy.2017.0050 [PubMed: 28635571]

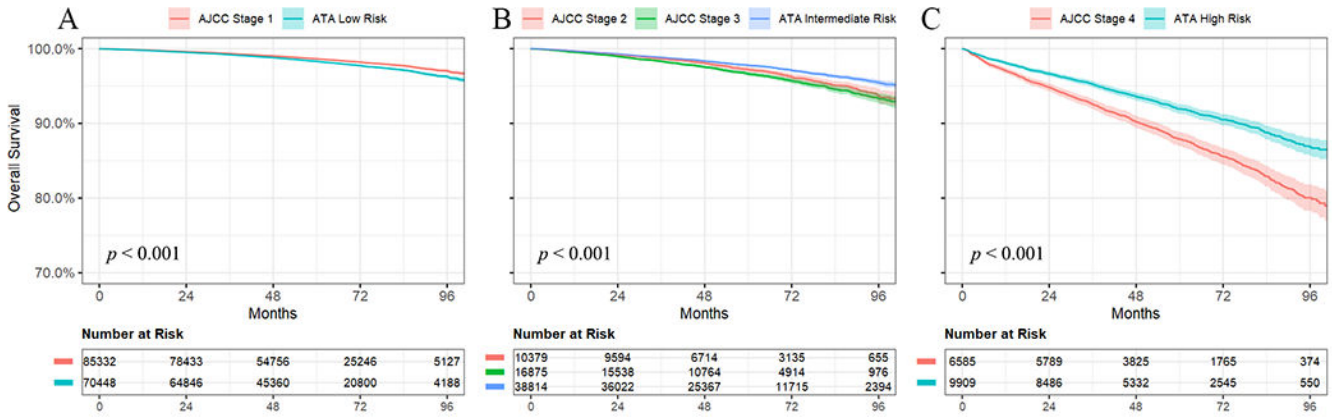

Figure 1:

Kaplan-Meier survival curves of patients with well-differentiated thyroid cancer, stratified by (A) AJCC Stage 1 vs. ATA low risk, (B) AJCC Stage 2 vs. AJCC Stage 3 vs. ATA intermediate risk, and (C) AJCC Stage 4 vs. ATA high risk. Shaded areas represent 95% confidence intervals.

Table 1:

Sociodemographic and clinical factors among patients with well-differentiated thyroid cancer (N= 134,226).

Variable	No. (%)
Age, yr	
< 55	88,005 (65.6)
≥ 55	46,221 (34.4)
Sex	
Male	31,046 (23.1)
Female	103,180 (76.9)
Charlson/Deyo Score	
0	111,782 (83.3)
≥ 1	22,444 (16.7)
Histology	
Papillary	125,829 (93.7)
Follicular	5,953 (4.4)
Hurthle Cell	2,444 (1.8)
AJCC Stage	
I	95,200 (70.9)
II	11,598 (8.6)
III	19,137 (14.3)
IV	8,291 (6.2)
ATA Classification	
Low Risk	77,456 (57.7)
Intermediate Risk	44,611 (33.2)
High Risk	12,159 (9.1)
Extent of Surgery	
Lobectomy	16,774 (12.3)
Total Thyroidectomy	119,310 (87.7)
Surgical Margins	
Negative	114,973 (86.7)
Positive	17,561 (13.3)
RAI Therapy	
No	64,924 (50.3)
Yes	64,062 (49.7)
TSH Suppression Therapy	
No	43,531 (33.0)
Yes	88,246 (67.0)

AJCC: American Joint Committee on Cancer; ATA: American Thyroid Association; RAI: Radioactive Iodine; TSH: Thyroid-Stimulating Hormone

Not all cases reported values for the collected variables, thus the percentages reflect the number of cases with available data.

Table 2:

Comparisons of the goodness-of-fit and predictive power of univariate and multivariable Cox proportional hazard models using ATA risk classification versus AJCC staging.

	Univariate Regression			Multivariable Regression		
Measure	**ATA Classification**	**AJCC Staging**	***P*-Value**	**ATA Classification**	**AJCC Staging**	***P*-Value**
C-Index	0.641 ± 0.048	0.710 ± 0.038	<0.001 *	0.803 ± 0.033	0.813 ± 0.038	0.049 *
MER	0.336 ± 0.140	0.529 ± 0.133	<0.001 *	0.743 ± 0.110	0.772 ± 0.079	0.046 *
AIC	9.743×10^4	9.592×10^4	~	7.603×10^4	7.564×10^4	~
AUC	0.645 ± 0.051	0.712 ± 0.036	<0.001 *	0.808 ± 0.019	0.815 ± 0.020	0.002 *

ATA: American Thyroid Association; AJCC: American Joint Committee on Cancer; C-Index: Concordance Index; MER: Measure of Explained Randomness; AIC = Akaike Information Criterion; AUC: Area Under Curve

* Statistically significant, $p<0.05$

Table 3:

Univariate and multivariable Cox proportional hazard regressions of patients with well-differentiated thyroid cancer using ATA Risk Class versus AJCC Stage as covariates.

Prognostic Variable	Univariate		Multivariable†	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
AJCC Stage				
I	1 [Reference]		1 [Reference]	
II	2.268 (2.046-2.514)	<0.001*	1.541 (1.374-1.728)	<0.001*
III	2.798 (2.582-3.032)	<0.001*	1.722 (1.566-1.894)	<0.001*
IV	10.160 (9.454-10.919)	<0.001*	4.828 (4.378-5.325)	<0.001*
ATA Risk Class				
Low	1 [Reference]		1 [Reference]	
Intermediate	1.159 (1.078-1.245)	<0.001*	1.428 (1.313-1.553)	<0.001*
High	5.163 (4.810-5.542)	<0.001*	3.997 (3.550-4.500)	<0.001*

HR: Hazard Ratio; CI: Confidence Interval; AJCC: American Joint Committee on Cancer; ATA: American Thyroid Association

†Results are representative of two separate regressions, as multivariable models only included either AJCC Stage or ATA Risk Class as a covariate.

*Statistically significant, $p<0.05$