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ORIGINAL ARTICLE – ENDOCRINE TUMORS

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

Tong Gan, MD[1,3], Bin Huang, DrPH[2,3], Quan Chen, DrPH[3], Heather F. Sinner, MD[1,3], Cortney Y. Lee, MD, FACS[1], David A. Sloan, MD, FACS, FRCSC[1], and Reese W. Randle, MD[1]

[1]Department of Surgery, College of Medicine, University of Kentucky, Lexington, KY; [2]Department of Biostatistics, College of Public Health, University of Kentucky, Lexington, KY; [3]Markey Cancer Center, University of Kentucky, Lexington, KY

ABSTRACT

Background. Differentiated thyroid cancer (DTC) survival is excellent, making recurrence a more clinically relevant prognosticator. We hypothesized that the new American Joint Committee on Cancer (AJCC) 8th edition improves on the utility of the 7th edition in predicting the risk of recurrence in DTC.

Methods. A population-based retrospective review compared the risk of recurrence in patients with DTC according to the AJCC 7th and 8th editions using the Surveillance, Epidemiology, and End Results-based Kentucky Cancer Registry from 2004 to 2012.

Results. A total of 3248 patients with DTC were considered disease-free after treatment. Twenty percent of patients were downstaged from the 7th edition to the 8th edition. Most patients had stage I disease (80% in the 7th edition and 94% in the 8th edition). A total of 110 (3%) patients recurred after a median of 27 months. The risk of recurrence was significantly associated with stage for both editions ($p < 0.001$). In the 7th edition, there was poor differentiation between lower stages and better differentiation between higher stages (stage II hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.39–2.11; stage III HR 3.72, 95% CI 2.29–6.07; stage IV HR 11.66, 95% CI 7.10–19.15; all compared with stage I). The 8th edition better differentiated lower stages (stage II HR 4.06, 95% CI 2.38–6.93; stage III HR 13.07, 95% CI 5.30–32.22; stage IV 11.88, 95% CI 3.76–37.59; all compared with stage I).

Conclusions. The AJCC 8th edition better differentiates the risk of DTC recurrence for early stages of disease compared with the 7th edition. However, limitations remain, emphasizing the importance of adjunctive strategies to estimate the risk of recurrence.

Although thyroid cancer incidence is increasing steadily, deaths from thyroid cancer remain low, with a 5-year survival rate of 98.1%.[1] Of these, differentiated thyroid cancer (DTC) comprises over 90% of all thyroid cancers.[2] Lifelong surveillance for recurrence after treatment is required because the overwhelming majority of patients survive. For this reason, some even suggest that recurrence is a more appropriate prognostic endpoint for DTC.[3] Therefore, staging systems that stratify risk based on recurrence might be better suited to guide clinical management.

Many risk prediction systems exist for DTC. The American Thyroid Association (ATA) risk stratification system uses clinicopathological factors to predict risk of DTC recurrence and to guide adjuvant treatment strategies;[2,4,5] however, pathological variables needed for the ATA system are often not reported and provide inadequate prognostic information. On the other hand, the tumor, node, metastasis (TNM) staging system of the American Joint Commission on Cancer/Union for International Cancer Control (AJCC/UICC) is utilized primarily to differentiate disease based on survival. The variables required for the AJCC system are required to be reported by all pathologists; however, the previous AJCC 7th edition is a poor predictor of recurrence.[4] The revised 8th

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T. Gan, MD
e-mail: tong.gan@uky.edu

edition, implemented in January 2018, demonstrates superior survival stratification, but its ability to prognosticate recurrence is unknown.[6–9] Major changes from the 7th edition include the increase in cut-off age from 45 to 55 years, downgrading regional lymph node metastasis to stage II in older patients, and the removal of minimal extrathyroidal extension (ETE) as an independent determinant of T3 disease.[10] While older age seems equivocal in determining the risk of recurrence,[11–15] regional lymph node positivity[16–20] and minimal ETE[21–23] uniformly increase the risk of recurrence.

The purpose of this study was to evaluate the AJCC 8th edition DTC TNM staging model in stratifying the risk of recurrence compared with the AJCC 7th edition. With the major changes of age, regional lymph node metastasis, and minimal ETE, we hypothesized that the 8th edition improves on the ability for risk stratification of recurrence in the 7th edition.

METHODS

Registry Data

The University of Kentucky Office of Research Integrity Institutional Review Board approved this study with an exempt status (Protocol ID: 43058). The Kentucky Cancer Registry (KCR) provided a Data Use Agreement and access to registry data, on 27 April 2018. The KCR is a population-based central cancer registry in Kentucky, established in 1990 and added as an expansion registry to the Surveillance, Epidemiology, and End Results (SEER) database in 2000. It has been recognized annually by the North American Association of Central Cancer Registries for its completeness and accuracy.[24] The KCR collects the clinical and pathological data necessary for the TNM staging system, as well as disease state and date of recurrence, which are lacking in many national databases.

The KCR began incorporating the AJCC staging in 2004 and defined recurrence as the return of DTC (new disease with the same histology code as previous disease) after a disease-free state was achieved. Coders abstracted recurrence from clinical documentation, but the KCR does not differentiate between structural and biochemical recurrence. Disease-free survival (DFS) was defined as the period of time from the date a patient was diagnosed to the date of recurrence.

Study Population

We identified KCR patients with DTC from 2004 to 2012 using the SEER site-specific code C739 and International Classification of Diseases for Oncology, Third Revision (ICD-O-3) histology codes 8050/3 (papillary carcinoma, not otherwise specified [NOS]), 8260/3 (papillary adenocarcinoma, NOS), 8330/3 (follicular adenocarcinoma, NOS), 8331/3 (follicular adenocarcinoma, well-differentiated), 8332/3 (follicular adenocarcinoma, trabecular), 8335/3 (follicular carcinoma, minimally invasive), 8340/3 (papillary carcinoma, follicular variant), 8341/3 (papillary microcarcinoma), 8342/3 (papillary carcinoma, oxyphilic cell), 8343/3 (papillary carcinoma, encapsulated), and 8344/3 (papillary carcinoma, columnar cell). We excluded patients for whom we could not confidently evaluate recurrence, such as those diagnosed at autopsy or on death certificate, those with metastatic disease, those with no or unknown operative management, those who were never considered disease free, and those missing recurrence data. Since we were comparing recurrence based on staging systems, we excluded those with incomplete staging. We also excluded children (aged < 18 years) and patients with other malignancies.

Data Analysis

Staging criteria for the 7th and 8th editions was applied separately to the same population based on the AJCC criteria to create two groups. The Kaplan–Meier method estimated DFS, and log-rank tests compared DFS by stage. Cox regression identified risk factors for recurrence to determine which components of the 8th edition influenced accurate prediction of recurrence. Selective multivariate analyses included age, sex, and all factors significantly associated with recurrence from the univariate analyses. Cox proportional hazard regression provided hazard ratios (HR) and confidence intervals (CIs) by stage. An α of 0.05 defined statistical significance. We used SAS/STAT version 9.4 (SAS Institute, Cary, NC, USA) for all analyses.

RESULTS

Patient Characteristics

Overall, 4676 patients were diagnosed with DTC in Kentucky from 2004 to 2012. Of these, 3248 formed the final study cohort. A total of 1428 patients were excluded for the following reasons: age < 18 years ($n = 51$), M1 disease ($n = 52$), never considered disease-free ($n = 469$), other cancer diagnosis ($n = 607$), diagnosis on autopsy or death ($n = 3$), missing recurrence data ($n = 323$), none or unknown surgical management ($n = 179$), and unknown or incomplete staging ($n = 219$). The median age was 48 years and the majority of patients were female ($n = 2591$, 80%) and Caucasian ($n = 3031$, 93%)

TABLE 1 Study population demographics and clinicopathological factors

Patient characteristics	KY DTC 2004–2012 [*n* = 3248] (%)
Age, years	
< 45	1342 (41)
45–54	818 (25)
55–74	970 (30)
75+	118 (4)
Sex	
Female	2591 (80)
Male	657 (20)
Race	
White	3031 (93)
Black	164 (5)
Other	34 (2)
Insurance	
Not insured	107 (3)
Insured	3093 (95)
Unknown	48 (2)
Histology	
Papillary cancer	3056 (94)
Follicular cancer	192 (6)
Focality	
Solitary	2019 (62)
Multifocal	1157 (36)
Unknown	72 (2)
Extrathyroidal extension	
Absent	2928 (90)
Present	320 (10)
Surgical approach	
Lobectomy	686 (21)
Total thyroidectomy	2523 (78)
Thyroidectomy, NOS	39 (1)
Adjuvant radiation	
External beam	14 (< 1)
Radioisotope	1603 (49)
None	1432 (44)
Other	199 (6)
T stage[a]	
0	7 (< 1)
1	1826 (56)
2	487 (15)
3	357 (11)
4	47 (2)
Unknown	512 (16)

KY Kentucky, *DTC* differentiated thyroid cancer, *NOS* not otherwise specified, *AJCC* American Joint Committee on Cancer

[a]According to the AJCC 8th edition

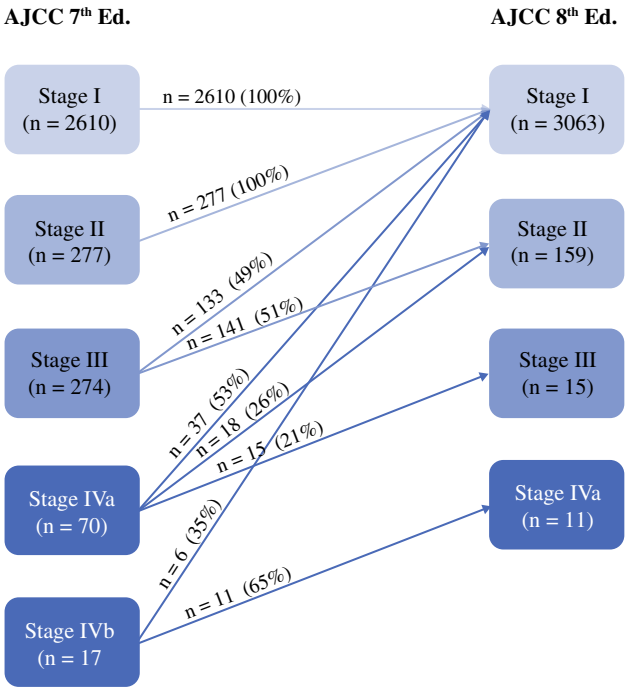

FIG. 1 Restaging and migration of the study population from the AJCC 7th edition to the 8th edition. The study population was previously staged based on the 7th edition criteria. Utilizing the major changes to the revised 8th edition, an algorithm was generated that allowed restaging according to the 8th edition. A large proportion of the stage I patients remained stage I; all other stages were downstaged, and no patients remained in the same stage or were upstaged. *AJCC* American Joint Committee on Cancer

[Table 1]. The median follow-up time for all patients was 88.9 months (interquartile range [IQR] 65.2–118.1). There were 110 (3%) patients whose disease recurred by the end of the study period; the median time to first recurrence was 27.5 months (IQR 13.6–53.4).

According to AJCC staging for either edition, most patients had stage I disease (80% in the 7th edition and 94% in the 8th edition), and almost all patients had either stage I or II disease (89% in the 7th edition and 99% in the 8th edition). In comparing the two cohorts, we identified that 20% of patients were downstaged from the 7th edition to the 8th and no patients were upstaged (Fig. 1). In fact, all patients staged II–IV were downstaged at least one stage from the 7th edition to the 8th edition.

Disease-Free Survival

Both the AJCC 7th and 8th edition staging models significantly stratified the risk of recurrence (Fig. 2). When comparing between the two editions, DFS was similar for stage I patients regardless of the particular edition (Table 2). This finding demonstrated the cases that were

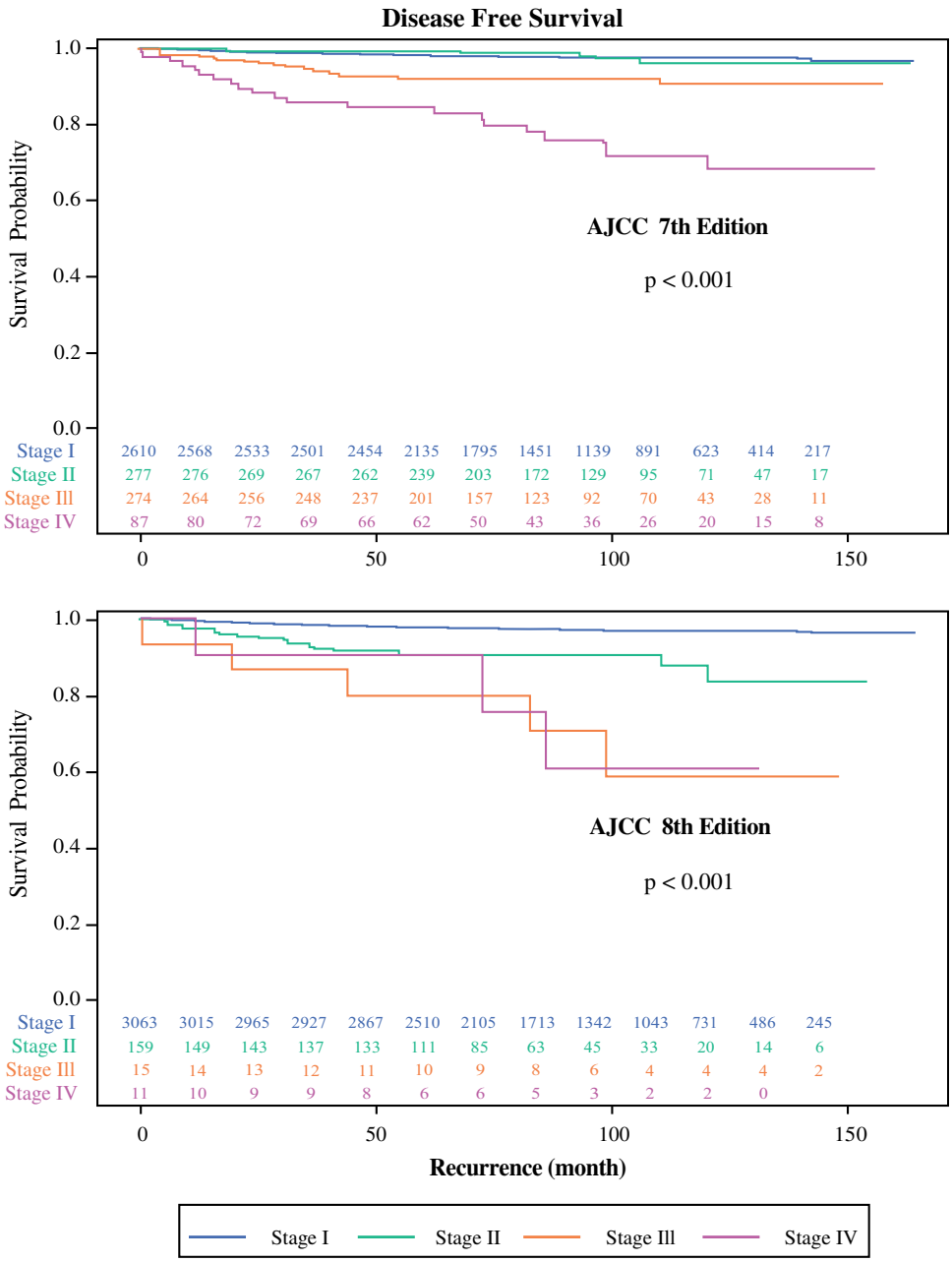

FIG. 2 Comparison of disease-free survival between the AJCC 7th and 8th editions. Disease-free survival was plotted using the Kaplan–Meier method, comparing stages I–IV in both editions. Both comparisons were statistically significant. *AJCC* American Joint Committee on Cancer

downstaged to stage I in the 8th edition represented low-risk disease. Stage II and III disease conferred a greater risk of recurrence in the 8th edition compared with the 7th edition, but stage IV disease did not.

When comparing between stages within each edition, the 7th edition had poor differentiation of lower stages and better differentiation of higher stages (Table 3). The risk of recurrence was not different between stages I and II in the 7th edition, but increased stage, from II to III and III to IV, was associated with a higher risk of recurrence. In contrast, the 8th edition better differentiated the risk of recurrence at lower stages. Stage II had a significantly higher risk of recurrence than stage I, but stage IV disease was not associated with a greater risk of recurrence compared with stage II or III disease.

Patient Characteristics Relating to Recurrence

We performed univariate and multivariate Cox regression to identify the components of the 8th edition staging system that impacted its ability to stratify the risk of recurrence (Table 4). Our multivariate model included age (a cut-off age of 55 years was used in the 8th edition), sex, and any significant variables from the univariate analyses. After adjusting for sex, disease characteristics (focality, ETE, T stage, nodal status), and treatment variation (extent

TABLE 2 Comparison of 5- and 10-year DFS between the AJCC 7th and 8th editions

Stage	Year	AJCC 7th edition		AJCC 8th edition		*p* value
		DFS (%)	95% CI	DFS (%)	95% CI	
I	5	98.0	97.4–98.5	97.7	97.1–98.2	NS
II		99.3	97.1–99.8	90.1	84.7–94.4	< 0.001
III		92.0	88.1–94.7	79.4	48.8–92.9	NS
IV[a]		84.5	74.7–90.7	90.1	50.8–98.7	NS
I	10	97.5	96.8–98.1	96.8	96.1–97.5	NS
II		96.6	91.8–98.5	84.1	71.2–91.5	0.018
III		90.4	84.8–94.0	57.8	23.9–81.0	0.037
IV[a]		68.1	54.0–78.6	58.9	17.1–85.4	NS

AJCC American Joint Committee on Cancer, *DFS* disease-free survival, *CI* confidence interval, *NS* non-significant

[a]Stage IV disease excludes all metastatic disease

TABLE 3 Comparison of the risk of recurrence between individual stages in the AJCC 7th and 8th editions

Stage	AJCC 7th edition			AJCC 8th edition		
	HR	95% CI	*p* value	HR	95% CI	*p* value
I	Ref	–	–	Ref	–	–
II	0.91	0.39–2.11	0.827	4.06	2.38–6.93	< 0.001
III	3.72	2.29–6.07	< 0.001	13.07	5.30–32.22	< 0.001
IV[a]	11.66	7.10–19.15	< 0.001	11.88	3.76–37.59	< 0.001

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

[a] Stage IV disease excludes all metastatic disease

of surgery, adjuvant radiation), higher recurrence rates were independently associated with age 55 years and older, higher T stage (8th edition), and lymph node positivity. Interestingly, ETE, focality, surgical extent, and adjuvant therapy were no longer associated with recurrence.

DISCUSSION

While the AJCC 7th edition TNM staging system effectively predicted survival for patients with DTC, it poorly stratified the risk of recurrence.[2,5] We compared the ability of the new AJCC 8th edition to prognosticate the risk of recurrence with that of the 7th edition using population-based data from the state of Kentucky. Stage escalation conferred a significantly higher risk of recurrence according to each edition overall, but the 8th edition provided better risk differentiation at lower stages than the 7th edition. Considering stage I and II disease accounts for the overwhelming majority of patients with DTC, the ability to distinguish the risk of recurrence between lower stages is paramount. The risk of recurrence was similar between stages I and II in the 7th edition, but significantly higher for stage II compared with stage I in the 8th edition. This demonstrates that the 8th edition more appropriately places lower-risk patients into stage I and higher-risk patients into stage II when compared with the 7th edition. Therefore, the 8th edition appears more clinically useful in its ability to stratify patients according to the risk of DTC recurrence, even though it did not stratify the risk of recurrence of higher stages as well as the previous edition.

The 8th edition increased the staging cut-off age from 45 to 55 years, condensed lymph node positivity to stage II in older patients, and removed minimal ETE as a determinate of T stage in older patients.[10] Even though our study excluded patients with metastatic disease for the purpose of accurately detecting recurrence, the resulting downstaging (20%) in the current study is comparable to prior studies (12–27%).[6,7,12,25]

Interestingly, age 55 years or older conferred a higher risk of recurrence in the current study after adjusting for other factors predictive of recurrence. Historically, age 55 years or older reliably indicated worse survival for patients with DTC, but its impact on recurrence have been unclear.[12] Cho et al.[11] demonstrated age > 62.5 years is associated with significantly higher recurrence risk in DTC; however, other investigations failed to demonstrate an association between older age and recurrence.[13–15] In fact, a meta-analysis demonstrated that age < 45 years was highly associated with recurrence.[26] Nevertheless, our data indicate that increasing the cut-off age to 55 years appropriately allocates a higher risk of recurrence based on age to higher-staged disease.

Positive lymph nodes conferred worse DFS in the current study, but the overall impact of nodal status on risk stratification according to the 8th edition is unclear. Nearly two-thirds of the study cohort were younger than 55 years of age and were classified with stage I disease regardless of

TABLE 4 Univariate and multivariate analysis of predictors of recurrence

Independent variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age ≥ 55 vs. < 55 years	1.24	0.84–1.83	NS	1.68	1.12–2.51	0.011
Female vs. male	0.58	0.39–0.87	0.009	0.81	0.53–1.23	NS
Race						
Black vs. white	1.62	0.83–3.25	NS	–	–	–
Other vs. white	2.02	0.50–8.18	NS	–	–	–
Insurance status						
Insured vs. no insurance	0.57	0.25–1.29	NS	–	–	–
Unknown vs. no insurance	0.32	0.04–2.68	NS	–	–	–
Tumor (T) stage[a]						
T2 vs. T1	1.57	0.95–2.60	NS	1.14	0.68–1.91	NS
T3 vs. T1	3.87	2.42–6.20	< 0.001	2.04	1.12–3.69	0.019
T4 vs. T1	8.12	4.32–15.27	< 0.001	2.72	1.16–6.36	0.021
ETE vs. no ETE	4.38	2.92–6.57	< 0.001	1.06	0.57–1.96	NS
Multifocal vs. solitary	2.12	1.45–3.09	< 0.001	1.38	0.93–2.05	NS
Lobectomy vs. total	0.48	0.27–0.86	0.013	0.98	0.53–1.82	NS
LN examination						
Positive vs. negative	5.10	3.20–8.14	< 0.001	3.39	2.02–5.68	<0.001
None examined vs. negative	0.67	0.41–1.11	NS	0.68	0.41–1.14	NS
Adjuvant therapy						
XRT vs. no XRT	6.54	2.51–17.09	< 0.001	1.63	0.57–4.67	NS
I^{131} vs. no I^{131}	2.84	1.81–4.46	< 0.001	1.55	0.93–2.58	NS

[a] According to the AJCC 8th edition

HR hazard ratio, *CI* confidence interval, *ETE* extrathyroidal extension, *LN* lymph node, *XRT* external beam radiation, I^{131} radioactive iodine, *NS* non-significant, *AJCC* American Joint Committee on Cancer

nodal status. For the one-third of patients who were aged 55 years or older, those with positive nodes in the absence of T4 disease were downstaged from stage III to stage II. This change may account for the increased risk of recurrence for stage II patients according to the 8th edition compared with that for stage II in the 7th edition. Although other literature indicates that regional lymph node metastasis may have minor impacts on survival, node positivity consistently incurs a higher risk of recurrence.[10,13,16–20]

Higher T stage, now based entirely on tumor size and gross local invasion, correlates with higher recurrence rates in our current study. In the previous edition, minimal ETE automatically equated to T3 disease. Similar to node positivity, minimal ETE is associated with higher recurrence rates compared with no ETE, but does not correlate with survival.[21–23] In a meta-analysis by Diker-Cohen et al.,[23] minimal ETE was associated with increased recurrence in those subjects without lymph node disease; however, due to its low impact on survival, the AJCC removed minimal ETE from the 8th edition staging criteria.[10] Interestingly, our results demonstrate, after adjusting for age, sex, T stage, and extent of surgery, ETE was no longer a significant predictor of recurrence. Despite the change that moved tumors < 4 cm in size from T3 classification to T1 or T2, T3 disease still confers at least twice the risk of recurrence as T1 in the 8th edition.

This study represents a large population-based comparative cohort, but it does have some limitations. Kentucky captures both rural and urban populations and may be generalizable to the greater US, but systematic differences in disease or treatment in Kentucky are possible. We excluded patients who had metastatic disease as these patients were never disease-free to have a recurrence. Although our stage IV group likely does not have the same survival as the general population that includes metastatic disease, we would expect the DFS to be similar as it cannot be measured in those with metastatic disease. Furthermore, the large CI is likely due to the small sample size of the remaining stage III and IV 8th edition population. Although the KCR is quite accurate and captures recurrence, patients who move outside of Kentucky would be lost to follow-up; however, if patients remain in Kentucky, even if they change physicians or treatment locations, their data would not be lost. Excluding patients without recurrence data narrowed our sample population, but it also allowed us to confidently identify groups with and without

recurrence. Additionally, any unknown selection bias resulting from the identification of our sample population would minimally affect our results because we compared staging systems using the same population. Another limitation involves the follow-up time. Although, the median follow-up time was relatively long at 91 months, late recurrences are possible. However, since most DTC recurrence occurs in the first 3–4 years, the shorter follow-up time may have minimal effects on this study.[27,28] Lastly, there are limitations that are inherent to the use of large databases, including inaccurate and incomplete data entered by the registrar. However, this is less likely to occur with KCR due to its excellent record for its completeness and accuracy as per the North American Association of Central Cancer Registries.[24]

CONCLUSIONS

This population-based study evaluated the ability of the revised AJCC 8th edition to stratify DTC recurrence compared with the previous edition. The ability of the 8th edition to predict recurrence correlates with the substantial downstaging of patients from the 7th edition. The 8th edition is more clinically useful because it better differentiates the risk of recurrence between lower-stage disease, where the majority of patients fall. Despite this improvement, supplemental risk stratification systems remain important to guide surveillance and adjunctive therapies.

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