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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

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Abstract

Background: Differentiated thyroid cancer (DTC) survival is excellent, making recurrence a more clinically relevant prognosticator. We hypothesize that the new American Joint Committee on Cancer (AJCC) 8th edition improves upon 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 SEER based Kentucky Cancer Registry from 2004–2012.

Results: A total of 3248 patients with DTC were considered disease free after treatment. Twenty percent of patients were down-staged from the 7th 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. 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 HR 0.91, 95%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: AJCC 8th edition better differentiates risk of DTC recurrence for early stages compared to the 7th edition. Limitations remain, however, emphasizing the importance of adjunctive strategies to estimate risk of recurrence.

Keywords

Differentiated Thyroid Cancer; Recurrence; AJCC 8th Edition

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Introduction:

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 end point 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 American Joint Commission on Cancer/Union for International Cancer Control's Tumor, Nodes, Metastasis (AJCC) staging system is utilized primarily to differentiate disease based on survival. The variables required for the AJCC system is required to be reported by all pathologists. Yet, the previous AJCC 7th edition is a poor predictor of recurrence.[4] The revised 8th 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 of age cutoff from 45 to 55, downgrading regional lymph node metastasis to stage II in older patients, and the removal of minimal extra-thyroidal 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 is to evaluate the AJCC 8th edition DTC TNM staging model in stratifying the risk of recurrence compared to the AJCC 7th edition. With the major changes of age, regional lymph node metastasis, and minimal ETE, we hypothesize that the 8th edition improves upon the ability for risk stratification of recurrence in the 7th edition.

Methods:

Registry Data:

This University of Kentucky Office of Research Integrity Institutional Review Board approved this study with the exempt status (Protocol ID: 43058). The Kentucky Cancer Registry (KCR) provided a data use agreement and access to registry data on April 27, 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 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 pathologic data necessary for TNM staging system as well as disease state and date of recurrence, which is lacking in many national databases.

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

Study Population:

We identified KCR patients with DTC from 2004 – 2012 using SEER site specific code C739 and 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 (age less than 18) and patients with other malignancies.

Data Analysis:

Staging criteria for the 7^{th} and 8^{th} edition was applied separately to the same population based on the AJCC criteria to create two groups. The Kaplan Meier method estimated DFS. Log rank tests compared DFS by stage. Cox regression identified risk factors for recurrence to determine which components of the 8^{th} 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 by stage. An α of 0.05 defined statistical significance. We used SAS/STAT version 9.4 (Cary, NC) for all analyses.

Results:

Patient characteristics:

There were 4676 patients 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 less than 18 (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), unknown or incomplete staging (n = 219). The median age was 48 years and the majority were female (n = 2591, 80%) and Caucasian (n = 3031, 93%; Table 1). The median follow-up time for all patients was 88.9 months (IQR 65.2 – 118.1 months). 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 months).

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 down-staged from the 7th edition to the 8th and no patients were upstaged (Figure 1). In fact, all patients staged II - IV were down-staged at least one stage from the 7th to the 8th edition.

Disease Free Survival:

Both the AJCC 7th and 8th edition staging models significantly stratified the risk of recurrence (Figure 2). When comparing between editions, DFS was similar for stage I patients regardless of the particular edition (Table 2a). This finding demonstrated the cases that were down-staged 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 compared to 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 2b). Risk of recurrence was not different between stage 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 significantly higher risk of recurrence than stage I, but stage IV disease was not associated with a greater risk of recurrence compared to 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 3). Our multivariate model included age (55-year cut-off 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 of surgery, adjuvant radiation), higher recurrence rates were independently associated with age 55 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 to that of the 7th edition using population based data from the state of Kentucky. Stage escalation conferred 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 stage I and II for 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 to 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 age cutoff from 45 to 55, 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 down-staging (20%) in the current study is comparable to prior studies (12%−27%).[6,7,12,25]

Interestingly, age 55 or greater conferred a higher risk of recurrence in the current study after adjusting for other factors predictive of recurrence. Historically, age 55 years or greater reliably indicated worse survival for patients with DTC, but its impact on recurrence have been unclear.[12] Cho *et al.*[11] demonstrated age greater than 62.5 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 less than 45 was highly associated with recurrence.[26] Nevertheless, our data indicate that increasing the age cut-off to 55 appropriately allocates 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 was younger than 55 years and are classified with stage I disease regardless of nodal status. For the third of patients who were 55 years or older, those with positive nodes in the absence of T4 disease were down-staged to stage II from stage III. This change may account for the increased risk of recurrence for stage II patients according to the 8th edition compared to 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 upon 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 to no ETE, but does not correlate with survival.[21–23] In a metanalysis by Diker-Cohen *et* al,[23] minimal ETE was associated with increased recurrence in those without lymph node disease. Yet, 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 which moved tumors less than 4cm 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 United States, but systematic differences in disease or treatment in Kentucky is

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 which includes metastatic disease, we would expect the DFS to be similar as it cannot be measured in those with metastatic disease. Further, the large confidence interval 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. These include 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 by 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 to 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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Synopsis:

The 8th edition's ability to predict risk of recurrence in Differentiated Thyroid Cancer was evaluated. The 8th edition differentiates lower staged disease better than the 7th, providing a more useful clinical tool for the majority of patients.

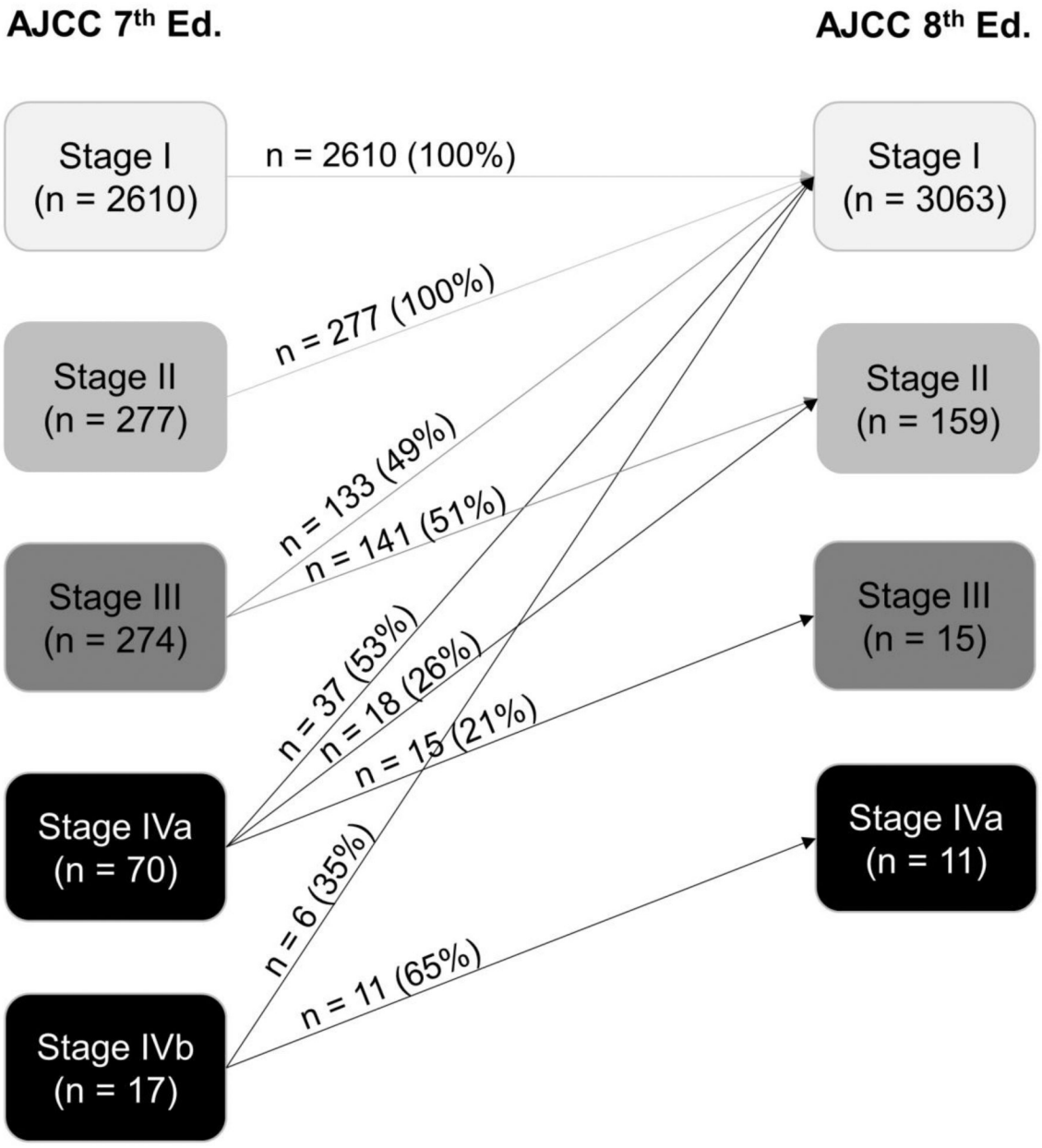

Figure 1. The Restaging and Migration of the Study Population From the AJCC 7th Edition to the 8th Edition.

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 down-staged, no patients remained in the same stage nor were upstaged.

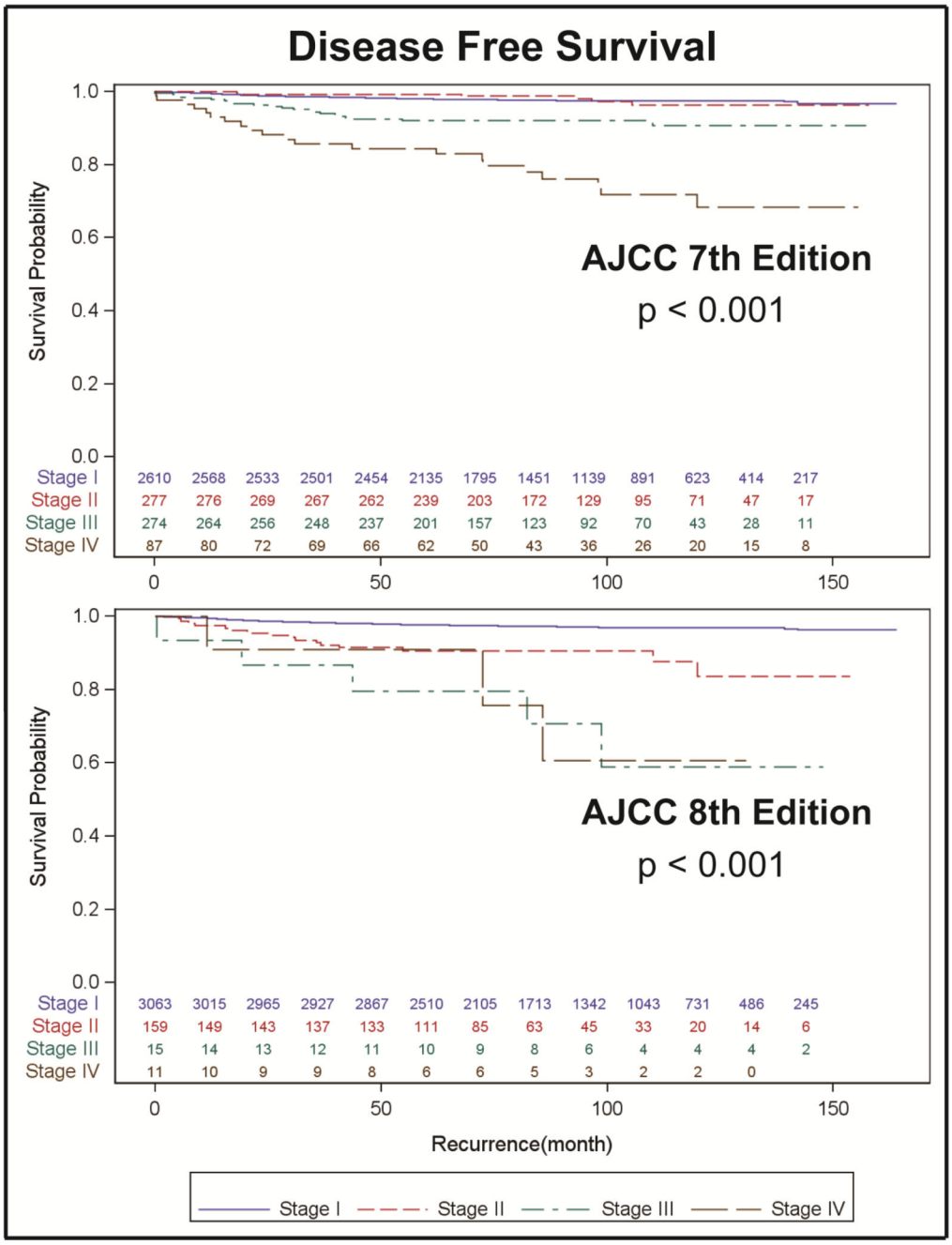

Figure 2. Comparison of Disease Free Survival between the AJCC 7th and 8th Editions.

Disease free survival was plotted by the Kaplan Meier method comparing Stage I - IV in both editions. Both comparisons were statistically significant.

Table 1.

Study Population Demographics and Clinicopathological Factors.

Patient Characteristics	KYDTC 2004–2012 (n = 3248)
Age	
<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%)

Patient Characteristics	KYDTC 2004–2012 (n = 3248)
2	487 (15%)
3	357 (11%)
4	47 (2%)
Unknown	512 (16%)

[a]According to the AJCC 8th Edition. *KY* Kentucky, *DTC* Differentiated Thyroid Cancer, *NOS* Not Otherwise Specified

Table 2
Comparison of Recurrence Risk Between the AJCC 7th and 8th Editions.

a) Comparison of 5 and 10 year DFS between the two editions. b) Comparison of the Risk of Recurrence Between Individual Stages in the AJCC 7th and 8th Editions.

a)	*Stage*	*Year*	AJCC 7th Ed		AJCC 8th Ed		*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

b)	*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

[a]Stage IV disease excludes all metastatic disease. *DFS* Disease Free Survival, *95%CI* 95% Confidence Interval, *HR* Hazard Ratio.

Table 3.

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	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 None	0.57	(0.25–1.29)	NS	-	-	-
Unknown vs None	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)	0.0213
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						
Pos vs Neg	5.10	(3.20–8.14)	< 0.001	3.39	(2.02–5.68)	< 0.001
None Examined vs Neg	0.67	(0.41–1.11)	NS	0.68	(0.41–1.14)	NS
Adjuvant Therapy						
XRT vs None	6.54	(2.51–17.09)	< 0.001	1.63	(0.57–4.67)	NS
I^{131} vs None	2.84	(1.81–4.46)	< 0.001	1.55	(0.93–2.58)	NS

[a]According to the AJCC 8th Edition. *ETE* extrathyroidal extension, *LN* Lymph node, *XRT* External Beam Radiation, *I131* Radioactive iodine.