Novel analysis of prognosis of young patients with stage II differentiated thyroid cancer based on AJCC 8.0 and 6.0 criteria to implement the staging system

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Background: The incidence of thyroid cancer among young adults is increasing; however, the clinical challenges specific to this population, such as diagnosis, reduced healthcare access, and inconsistent care, have received limited attention. Here, we conducted a subgroup analysis on a series of relatively young patients with differentiated thyroid carcinomas (DTCs), focusing on those with distant metastases at stage II, to obtain a deeper understanding of the factors influencing survival.

Methods: Information on <45- or <55-year-old patients at any T/N stage with distant metastasis (M1) was extracted from the SEER database according to the staging system in the 6th and 8th American Joint Committee on Cancer (AJCC) editions, respectively. Patient mortality was evaluated using Cox proportional hazards regression analyses and Kaplan-Meier analyses with log-rank tests.

Results: Both cancer-specific and all-cause mortality rates per 1,000 person-years for patients ≥35 years old significantly differed from those of patients <35 years old. DTC-specific survival curves also significantly differed between these age groups, according to both the AJCC 6.0 and 8.0-based analyses (P=0.0017 and P<0.001, respectively), as did patient survival curves (P=0.0003, P<0.001, respectively). The multivariate Cox regression model also revealed that poor OS was strongly predicted by race (P<0.001) in the analysis based on the criteria of 8th AJCC staging system.

Conclusions: Age is a risk factor for disease-specific and overall survival (OS) in young patients with stage II DTC, and young male patients exhibited poorer survival than females. Race also emerged as a potential risk factor for young patients in stage II. These findings offer guidance for improving the older and newer versions of the AJCC staging system.

Keywords: Thyroid cancer; stage II; distant metastasis; prognosis; Surveillance, Epidemiology, and End Results (SEER)

Introduction

Differentiated thyroid carcinomas (DTCs), comprising papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), are widely known as indolent diseases, and their incidence has been increasing more rapidly than that of any other cancer in the US (1,2). As DTCs are generally associated with high overall survival (OS) rates, they are expected to become the third most common cancer among females by 2019 (3,4). According to recent population study, the incidence of thyroid cancer has increased by an average of 3.6% per year in the latest 45 years (5,6). In addition, the most common carcinoma in American adults 16–33 years of age at present is thyroid carcinoma (7). Despite the increased morbidity and incidence of thyroid carcinomas among adolescents and young adults, relatively limited attention has been paid to the specific challenges, including diagnosis, reduced health care access, and inconsistent care, that face this group of patients.

The prognosis of DTC is, to a certain degree, dependent on age, the presence of distant metastases, and the extent and size of the primary tumor (2). Among these relevant factors, the biological characteristics of DTC are most highly dependent on age, with young patients showing a much greater survival rate than older patients (8). Indeed, DTC is the only human malignant tumor for which age is included as part of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system (1). In the eighth edition of the AJCC/tumor, lymph node, metastasis (TNM) cancer staging system, which was officially implemented on January 1, 2018, the age cut-off was raised from 45 years in the older AJCC/TNM cancer staging systems (up to and including the 7th edition) to 55 years (9). Besides the difference in the cut-off point in age, other differences between 6th and 8th edition of AJCC/TNM cancer staging systems including T-stage, N-stage and staging criteria for older patients (≥45/55 years old). The decision for using the age of 45 years as a distinct cut-off point was mainly based on data from the mid-1900s, when a sharp increase in thyroid cancer mortality starting at around the age of 40–50 years was demonstrated (1). Despite this recent switch from the age of 45 years to that of 55 years as the cut-off point, few adjustments have been made to the staging system for young patients. Specifically, all young patients without distant metastases are classified at stage I regardless of tumor size, lymph node status, or extrathyroidal extension. Young patients (<45/55 years old) are only classified at stage

II when they have distant metastases. By contrast, older patients are classified from stages I through IVc, reflecting the fact that younger age can dampen the deleterious effects generally associated with advanced disease to some extent (2). Poor survival in patients with DTC who present with metastatic disease is widely accepted (10). However, as patients <45/55 years old with distant metastases appear to exhibit poorer prognosis than patients in the same age group at stage I, a more thorough understanding of the relationship between the relevant factors and survival in young patients with DTC is needed, especially for those with distant metastases (stage II). In addition, it is necessary to determine the impact that this relationship has on patient outcomes.

In the present study, we conducted a subgroup analysis on a series of patients with DTC at stage II (with distant metastases), who were <45/55 years old, from the Surveillance, Epidemiology, and End Results (SEER) database. The objective of the study was to identify and determine the influence of several risk factors, including age, sex, race, histological type, TN-stage, extension status, radiation treatment, or surgery type, on the prognosis of young patients with stage II DTC with the aim of improving diagnosis and disease management among this group. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-20-46).

Methods

Data sources

The study cohort of patients with DTC was recruited from the SEER database, which is supported by the National Cancer Institute and Centers for Disease Control and Prevention; data collected between 2004 and 2013 were used (11). This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). The SEER database contains information on morbidity, prevalence, mortality, and population-based variables for patients worldwide, as well as details of the primary characteristics of the tumor, including site, spread, and histology where available, along with limited information regarding treatment, excluding chemotherapy (12).

AJCC staging and data preparation

Since SEER is a publicly available database with

anonymized data, no ethical review was required. We examined SEER data collected between 2004 and 2013 and selected patients with a diagnosis of DTC, defined by a combination of the ICD-10 site code of C73.9 (i.e., thyroid) and diagnostic codes of papillary and/or follicular histology, including "papillary carcinoma," "papillary adenocarcinoma," "oxyphilic adenocarcinoma", "follicular adenocarcinoma," "papillary & follicular adenocarcinoma," and "papillary cyst-adenocarcinoma." Patients with missing or unknown data regarding follow-up were excluded from analysis. A total of 99,015 cases were enrolled in this research.

The SEER system indicates disease stages using AJCC 6.0 for data from 2004 to 2013. At the time of this analysis, the new 8th AJCC edition had not been implemented; therefore, we applied the AJCC 8.0 criteria to restage all cases of DTC in the SEER dataset 18 from 2004 to 2013 with available TNM information. The selection process is described in detail under Supplementary. We extracted information for patients at any T/N stage with distant metastasis (M1) who were <45 years of age, based on the staging system of the 6th AJCC edition, as well as for patients at any T/N stage with distant metastasis (M1) who were <55 years of age, using the staging system of the 8th AJCC edition for further comparison.

Statistical analyses

According to Oyer et al. (13), an increase in age was associated with a significant decrease in disease-specific survival (DSS) for each decade. Specifically, patients who were 35–44 years of age showed a statistically significant decrease in DSS compared with those that were 25–34 years old. Based on these findings, we chose 35 years of age as a cut-off point to regroup patients <45/55 years old (<45 or <55 years old according to the 6th and 8th editions, respectively) with distant metastases for survival analyses. The follow-up data for selected patients were evaluated to calculate the rates of cancer-specific survival (CSS) and OS, as well as the mortality rates per 1,000 person-years. In addition, the mortality rates per 1,000 person-years among different groups were compared, with consideration of relevant factors. Hazard ratios (HRs) were used to determine the magnitude of the effect of disease stage on DTC-specific patient mortality, and 95% confidence intervals (CIs) were used to indicate the significance of the risk. Univariate and multivariate Cox regression analyses were performed to examine whether DSS and OS were associated with age, sex, race, histological type, TNM stage, extension status, radiation treatment, or surgery type. Patient survival curves were analyzed by Kaplan-Meier analyses with log-rank tests, and with Cox proportional hazards regression analyses.

Results

General findings

The distribution of patients in each stage classified according to the 6th and 8th AJCC staging system is summarized in *Table S1*. The proportion of patients classified in stage II based on the criteria of the 6th edition (7.64%) and 8th edition (7.54%) was similar. Moreover, there was a greater risk in younger patients (<45 or <55 years old according to the 6th and 8th editions, respectively) than in those ≥45 or ≥55 years old (*Table S2*). The flow diagram in *Figure 1* shows the total number of patients extracted from the database, how all of the patients were categorized, and how many patients were excluded from analysis under the staging system in the 6th and 8th AJCC editions. Overall, there were 276 patients in the <45-year-old group and 461 patients in the <55-year-old group. The other demographic characteristics of these two groups are shown in *Table 1*.

Clinicopathological parameters that affect CSS and OS

Univariate Cox regression analyses revealed that the CSS of patients classified according to both the 6th and 8th editions of the AJCC staging systems was significantly associated with age at diagnosis (P=0.01, P<0.001, respectively), sex (P=0.006, P=0.001), histological type (P=0.04, P=0.001), and T-stage (P=0.008, P<0.001) (*Table 2*); a similar result was observed for OS (*Table 3*). Patients who were ≥35 years old (P=0.001, P<0.001), at stage T4 (P=0.002, P<0.001), or male (P=0.018, P<0.001) exhibited poorer OS under both staging systems. However, multivariate Cox regression analyses showed that only age at diagnosis and race were associated with CSS under the 8th edition staging system, in which patients diagnosed at ≥35 years old (P=0.001) and black patients (P<0.001) had significantly poorer CSS (*Table 4* and *Table S3*). The multivariate Cox regression model also revealed that poor OS was predicted by age (P=0.003) and surgery type (P=0.007) based on analysis using the 6th AJCC edition, and most strongly predicted by age (P<0.001), sex (P=0.013), and race (P<0.001) based on
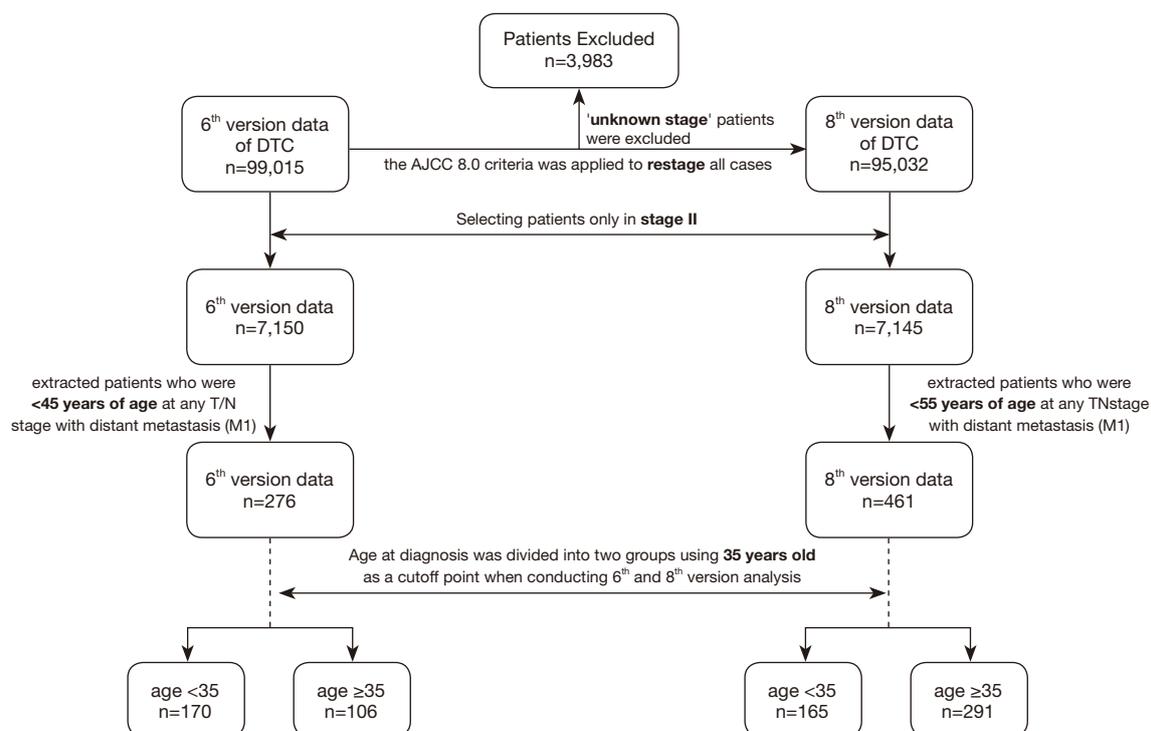
Figure 1 The flow diagram of the selection process, showing the total number of patients extracted from the database and how many patients were excluded from analysis under the staging system in the 6th and 8th AJCC editions (five patients lacked the information of age in the 8th version data).

analysis using the 8th edition of the AJCC (*Table 5*).

Cancer-specific and all-cause mortality rates

During the follow-up period, substantially higher rates of cancer-specific deaths and all-cause mortality deaths were observed under the AJCC 8.0-based analysis than under the AJCC 6.0-based analysis (*Table 6*). Given the associations of age at diagnosis, sex, race, and surgery type with CSS and OS based on the univariate and multivariate Cox analyses described above, we further calculated the cancer-specific and all-cause mortality rates in different groups based on these factors. As shown in *Table 7*, both the cancer-specific and all-cause mortality rates per 1,000 person-years of patients aged ≥35 years significantly differed from those of patients <35 years old.

Patient and DTC-specific survival curves

Kaplan-Meier analyses revealed a significant difference in the DTC-specific survival curves between patients diagnosed at <35 and ≥35 years old under both the AJCC 6.0 and 8.0-based analyses (P=0.0017 and P<0.0001, respectively; *Figure 2A,B*). However, there was no difference in DTC-specific survival curves according to race according to the AJCC 6.0-based analysis (P=0.1178, *Figure 3*): all curves were flat, with only a minimal decline. A similar difference between age groups was found for patient survival curves (6th edition P=0.0003, 8th edition P<0.0001; *Figure 4A,B*). However, the decline of the patient survival curve in both analyses was sharper for male patients than for female patients (6th edition P=0.0159, *Figure 5A*; 8th edition P=0.0003, *Figure 5B*). Similar to the DTC-specific curves, there was no influence of race on patient survival curves (P=0.2069, *Figure 6*). Moreover, the patient survival curves did not differ significantly between surgery types according to either the AJCC 6.0-based analysis (P=0.7050) or AJCC 8.0-based analysis (P=0.4334) (*Figure 7A,B*).

Discussion

Papillary and follicular carcinomas are DTCs that account

Table 1 Characteristics of patients at any T/N stage with distant metastasis (M1) and were <45 years of age according to the staging system of the 6[th]AJCC edition, as well as patients at any T/N stage with distant metastasis (M1) who were <55 years of age according to the staging system of the 8th AJCC edition (the proportion is presented with effective percentage)

Covariate	Level	6th edition		8th edition	
		N	%	N	%
Age at diagnosis	<35	170	61.60	165	36.18
	≥35	106	38.40	291	63.82
Year of diagnosis	2004–2008	140	50.70	220	47.70
	2009–2013	136	49.30	241	52.30
Sex	Female	175	63.40	272	59.00
	Male	101	36.60	189	41.00
Race	White	222	81.02	356	77.56
	Black	24	8.76	43	9.37
	Other	28	10.22	60	13.07
Histological types	Papillary	254	92.70	405	89.01
	Follicular	20	7.30	50	10.99
T stage	T1/T2/T3	165	70.82	258	65.65
	T4	68	29.18	135	34.35
N-stage	N0	61	23.28	134	30.88
	N1	201	76.72	300	69.12
Multifocality	No	86	37.72	161	41.07
	Yes	142	62.28	231	58.93
Extension	No	100	42.19	160	40.20
	Yes	137	57.81	238	59.80
Radiation	None or refused	61	22.51	112	24.83
	Radiation beam or radioactive implants	23	8.49	55	12.20
	Radioisotopes or radiation beam plus isotopes or implants	187	69.00	284	62.97
Surgery	Lobectomy	14	5.71	19	4.81
	Subtotal or near-total thyroidectomy	7	2.86	17	4.30
	Total thyroidectomy	224	91.43	359	90.89
Survival months (month)		52.685±34.4997		46.93±33.919	
CSS	Alive	261	94.60	391	84.80
	Death	15	5.40	70	15.20
OS	Alive	244	88.40	363	78.70
	Death	32	11.60	98	21.30

Table 2 Univariate analyses results for clinicopathologic parameters associated with the cancer-specific survival

Parameters	Level	6th edition univariate				8th edition univariate			
		HR	95 % CI		P value	HR	95 % CI		P value
			Lower	Higher			Lower	Higher	
Year of diagnosis	2004–2008	ref				ref			
	2009–2013	0.724	0.241	2.179	0.566	0.93	0.553	1.562	0.784
Age at diagnosis	<35	ref				ref			
	≥35	4.5	1.433	14.135	0.01	10.706	3.901	29.384	<0.001
Sex	Female	ref				ref			
	Male	4.926	1.568	15.47	0.006	2.214	1.376	3.564	0.001
Race	White	ref				ref			
	Black	2.278	0.642	8.08	0.202	2.6	1.404	4.813	0.002
	Other	–	–	–	–	1.071	0.541	2.121	0.845
Histological types	Papillary	ref				ref			
	Follicular	3.819	1.064	13.703	0.04	2.523	1.443	4.414	0.001
T-stage	T1/T2/T3	ref				ref			
	T4	5.049	1.519	16.782	0.008	4.005	2.323	6.903	<0.001
N-stage	N0	ref				ref			
	N1	3.518	0.457	27.067	0.227	1.232	0.706	2.149	0.463
Extension	Yes	ref				ref			
	No	3.527	0.772	16.103	0.104	1.99	1.106	3.583	0.022
Multifocality	Yes	ref				ref			
	No	1.756	0.475	6.489	0.398	1.014	0.589	1.745	0.961
Radiation	None or refused	ref				ref			
	Radiation beam or radioactive implants	5.456	1.361	21.869	0.017	1.813	0.986	3.333	0.055
	Radioisotopes or radiation beam plus isotopes or implants	0.57	0.143	2.283	0.428	0.382	0.219	0.666	0.001
Surgery	Lobectomy	ref				ref			
	Subtotal or near total thyroidectomy	–	–	–	–	0.833	0.186	3.727	0.812
	Total thyroidectomy	0.595	0.077	4.618	0.62	0.488	0.175	1.365	0.172

1250

Huang et al. Prognosis for young patients with DTC stage II

Table 3 Univariate analyses results for clinicopathologic parameters associated with the overall survival

Parameters	Level	6th edition univariate				8th edition univariate			
		HR	95 % CI		P value	HR	95 % CI		P value
			Lower	Higher			Lower	Higher	
Year of diagnosis	2004–2008	ref				ref			
	2009–2013	1.03	0.481	2.204	0.939	0.933	0.598	1.457	0.761
Age at diagnosis	<35	ref				ref			
	≥35	3.547	1.679	7.491	0.001	5.677	2.949	10.927	<0.001
Sex	Female	ref				ref			
	Male	2.323	1.154	4.676	0.018	2.15	1.436	3.217	<0.001
Race	White	ref				ref			
	Black	1.439	0.502	4.129	0.498	2.173	1.261	3.746	0.005
	Other	0.232	0.031	1.712	0.152	0.777	0.411	1.468	0.437
Histological types	Papillary	ref				ref			
	Follicular	2.151	0.75	6.168	0.154	2.105	1.273	3.481	0.004
T-stage	T1/T2/T3	ref				ref			
	T4	3.467	1.591	7.556	0.002	3.144	2.001	4.939	<0.001
N-stage	N0	ref				ref			
	N1	1.128	0.458	2.777	0.794	1.145	0.72	1.82	0.568
Extension	Yes	ref				ref			
	No	1.873	0.787	4.46	0.156	1.689	1.04	2.746	0.034
Multifocality	Yes	ref				ref			
	No	3.071	1.054	8.949	0.04	1.316	0.81	2.138	0.268
Radiation	None or refused	ref				ref			
	Radiation beam or radioactive implants	1.55	0.606	3.963	0.36	1.149	0.668	1.977	0.616
	Radioisotopes or radiation beam plus isotopes or implants	0.271	0.121	0.609	0.002	0.31	0.197	0.488	<0.001
Surgery	Lobectomy	ref				ref			
	Subtotal or near total thyroidectomy	–	–	–	–	0.901	0.242	3.36	0.877
	Total thyroidectomy	0.545	0.127	2.332	0.413	0.526	0.21	1.316	0.17

Table 4 Multivariate analyses results for clinicopathologic parameters associated with the cancer-specific survival in 8.0-based analysis

Parameters	Level	8th edition multivariate			
		HR	95 % CI		P value
			Lower	Higher	
Year of diagnosis	2004–2008	ref			
	2009–2013	1.174	0.58	2.377	0.656
Age at diagnosis	<35	ref			
	≥35	34.06	4.493	258.208	0.001
Sex	Female	ref			
	Male	1.885	0.962	3.696	0.065
Race	White	ref			
	Black	9.632	3.746	24.77	<0.001
	Other	0.904	0.331	2.472	0.844
Histological types	Papillary	ref			
	Follicular	1.862	0.745	4.655	0.183
T-stage	T1/T2/T3	ref			
	T4	1.951	0.835	4.555	0.123
N-stage	N0	ref			
	N1	2.132	0.861	5.277	0.102
Extension	Yes	ref			
	No	1.34	0.488	3.682	0.57
Multifocality	Yes	ref			
	No	1.353	0.661	2.771	0.408
Radiation	None or refused	ref			
	Radiation beam or radioactive implants	1.648	0.631	4.309	0.308
	Radioisotopes or radiation beam plus isotopes or implants	0.858	0.389	1.891	0.704
Surgery	Lobectomy	ref			
	Subtotal or near total thyroidectomy	0.644	0.113	3.653	0.619
	Total thyroidectomy	0.273	0.073	1.022	0.054

1252

Huang et al. Prognosis for young patients with DTC stage II

Table 5 Multivariate analyses results for clinicopathologic parameters associated with the overall survival

Parameters	Level	6th edition multivariate				8th edition multivariate			
		HR	95 % CI		P value	HR	95 % CI		P value
			Lower	Higher			Lower	Higher	
Year of diagnosis	2004–2008	ref				ref			
	2009–2013	3.089	0.965	9.885	0.057	1.186	0.634	2.217	0.594
Age at diagnosis	<35	ref				ref			
	≥35	8.591	2.092	35.28	0.003	13.958	4.165	46.771	<0.001
Sex	Female	ref				ref			
	Male	2.49	0.831	7.454	0.103	2.113	1.174	3.801	0.013
Race	White	ref				ref			
	Black	–	–	–	0.988	8.421	3.627	19.553	<0.001
	Other	0.267	0.028	2.539	0.25	0.733	0.3	1.792	0.496
Histological types	Papillary	ref				ref			
	Follicular	0.394	0.04	3.866	0.424	1.321	0.548	3.182	0.535
T-stage	T1/T2/T3	ref				ref			
	T4	3.394	0.881	13.073	0.076	2.092	0.989	4.426	0.054
N-stage	N0	ref				ref			
	N1	1.436	0.256	8.051	0.681	1.884	0.85	4.174	0.119
Extension	Yes	ref				ref			
	No	0.431	0.095	1.951	0.274	1.022	0.433	2.413	0.96
Multifocality	Yes	ref				ref			
	No	4.578	0.826	25.362	0.082	1.789	0.932	3.436	0.08
Radiation	None or refused	ref				ref			
	Radiation beam or radioactive implants	5.053	0.871	29.314	0.071	1.339	0.567	3.162	0.505
	Radioisotopes or radiation beam plus isotopes or implants	1.196	0.25	5.735	0.823	0.743	0.379	1.455	0.386
Surgery	Lobectomy	ref				ref			
	Subtotal or near total thyroidectomy	–	–	–	0.988	0.5	0.089	2.796	0.43
	Total thyroidectomy	0.027	0.002	0.376	0.007	0.319	0.088	1.162	0.083

Table 6 Cancer-specific mortality and all-cause mortality for the cancer specific deaths and all cause deaths of thyroid cancer in 6.0- and 8.0-based analysis

Extension	Cancer-specific mortality		Cancer-specific mortality		All-cause mortality		All-cause mortality	
	No.	%	1,000 person-years	95% CI	No.	%	1,000 person-years	95% CI
6th edition	15	5.40	11.55	6.843–19.508	32	11.60	24.76	17.310–35.4096
8th edition	70	15.20	37.24	29.314–47.321	98	21.30	51.70	42.190–63.349

Table 7 Cancer-specific mortality and all-cause mortality of several relevant factors for the cancer specific deaths and all cause deaths of thyroid cancer in 6.0- and 8.0-based analysis

Classification	Parameters	Level	Cancer-specific mortality		Cancer-specific mortality		All-cause mortality		All-cause mortality	
			No.	%	1,000 person-years	95% CI	No.	%	1,000 person-years	95% CI
6th edition	Age at diagnosis	<35	4	2.4	4.01	1.295–12.445	10	5.9	12.04	6.265–23.143
		≥35	11	10.4	23.69	13.119–42.776	22	20.8	45.23	29.488–69.364
	Sex	Female	4	2.3	5.17	1.940–13.772	14	8	16.80	9.755–28.932
		Male	11	10.9	22.84	12.286–42.440	18	17.8	38.82	24.133–62.446
	Race	White	12	5.4	11.63	6.443–21.008	27	12.2	26.44	17.867–39.131
		Black	3	12.5	33.15	10.691–102.781	4	16.7	44.20	16.589–117.764
		Other	0	0	–	–	1	3.6	6.07	0.855–43.112
	Surgery	Lobectomy	1	7.1	17.99	2.534–127.719	2	14.3	17.99	2.534–127.719
		Subtotal or near-total thyroidectomy	0	0	–	–	0	0	–	–
		Total thyroidectomy	11	4.9	10.86	6.013–19.605	21	9.4	20.73	13.514–31.790
8th edition	Age at diagnosis	<35	4	2.4	4.16	1.341–12.894	10	6.1	12.48	6.491–23.977
		≥35	66	22.7	60.87	47.640–77.763	88	30.2	79.89	64.505–98.934
	Sex	Female	29	10.7	26.09	18.132–37.548	42	15.4	35.99	26.399–49.065
		Male	41	21.7	55.27	40.219–75.962	56	29.6	77.09	58.895–100.908
	Race	White	47	13.2	32.24	23.990–43.318	70	19.7	48.35	37.989–61.548
		Black	13	30.2	97.14	56.402–167.286	17	39.5	119.55	73.241–195.144
		Other	10	16.7	34.59	18.612–64.291	11	18.3	38.05	21.073–68.710
	Surgery	Lobectomy	4	21.1	55.75	20.924–148.538	5	26.3	55.75	20.924–148.538
		Subtotal or near-total thyroidectomy	3	17.6	50.00	16.126–155.029	4	23.5	66.67	25.021–177.627
		Total thyroidectomy	41	11.4	27.76	20.443–37.706	56	15.6	37.92	29.183–49.275

for more than 90% of the nearly 50,000 cases of thyroid cancers diagnosed in the US every year (7). Age is known to be an important prognostic factor for DTC patients, although far less attention has been paid to younger patients owing to their better survival relative to older patients. However, thyroid cancer has become the most common cancer in 16–33-year-old American individuals. Despite this increase in thyroid cancer incidence among young patients, there are many clinical challenges facing this group in terms

of diagnosis, reduced healthcare access, and inconsistent care. Thus, this population requires closer attention in regard to the resolution of the challenges hindering favorable patient outcomes (10). Although DTC is a disease with a generally good outcome, patients presenting with distant metastatic disease have less favorable outcomes (14). Poor survival in patients with DTC that present with metastatic disease has been demonstrated previously and is not disputed (15). Thus, we conducted a subgroup analysis
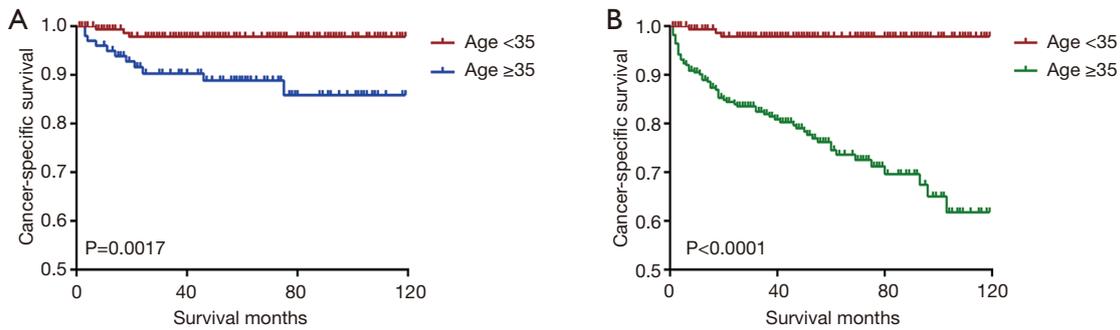
Figure 2 Kaplan Meier curves for cancer-specific survival among patients stratified by age for 6.0-based analysis (A) and 8.0-based analysis (B).
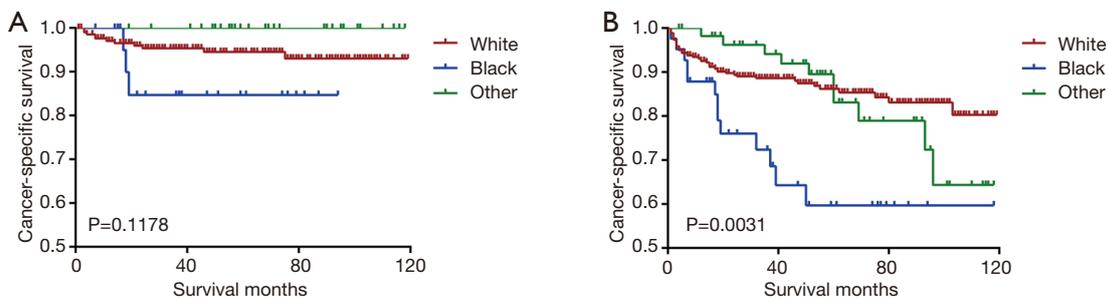

Figure 3 Kaplan Meier curves for cancer-specific survival among patients stratified by race for 6.0-based analysis (A) and 8.0-based analysis (B).
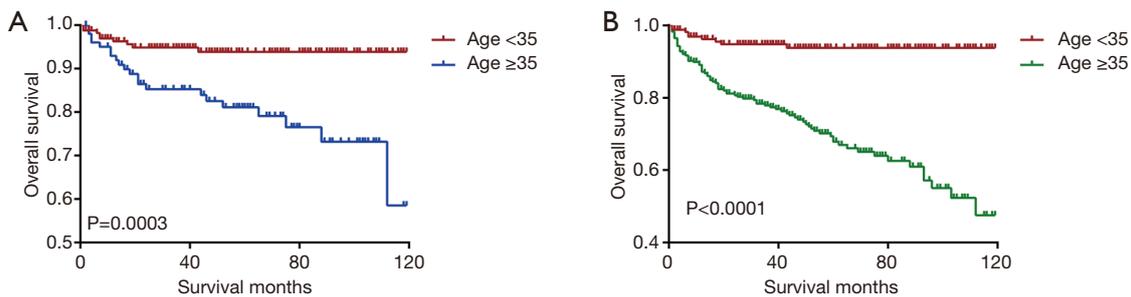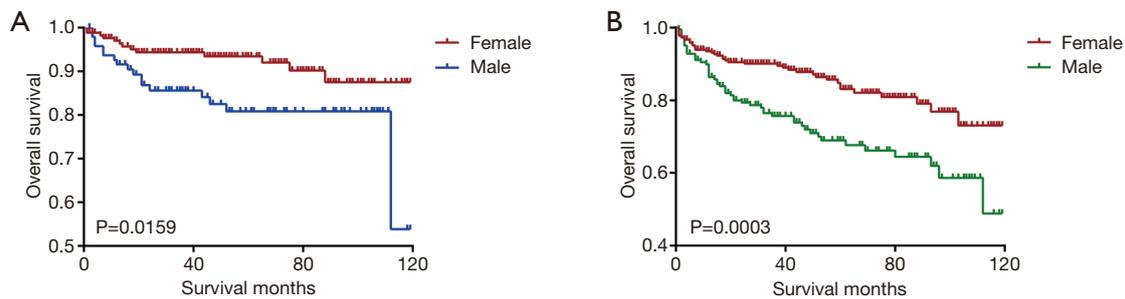

Figure 4 Kaplan Meier curves for overall survival among patients stratified by age for 6.0-based analysis (A) and 8.0-based analysis (B).

on a series of patients who were under the cut-off age and in stage II.

The current staging system for DTCs emphasizes the importance of patient age to the prognosis of these cancers by creating two dichotomous patient groups based on an assigned cut-off of age (13). Age first appeared as a prognostic factor in the second edition of the AJCC Cancer Staging Manual published in 1983, in which patients were grouped according to an age of less than 45 years or above 45 years; this grouping system was maintained until publication of the 8th edition (16). Using an evidenced-

based approach, a multidisciplinary committee of thyroid cancer experts made several substantial modifications to the seventh edition of the AJCC/TNM staging system that are now embodied in the new eighth edition staging system, including changing the cut-off point for age in the staging system from 45 to 55 years. According to this system, all patients younger than 55 years of age are considered to have stage I disease (regardless of tumor size, lymph node status, histologic subtype, or the presence/absence of extrathyroidal extension) unless they have distant metastases, in which case their disease is considered to be at stage II (9). In order

Figure 5 Kaplan Meier curves for overall survival among patients stratified by sex for 6.0-based analysis (A) and 8.0-based analysis (B).
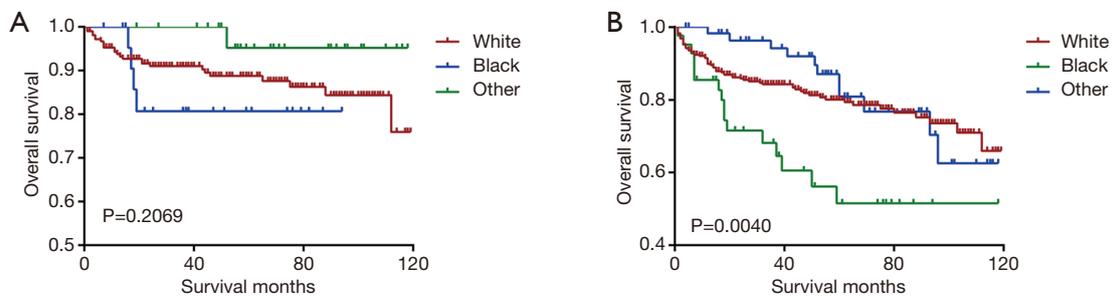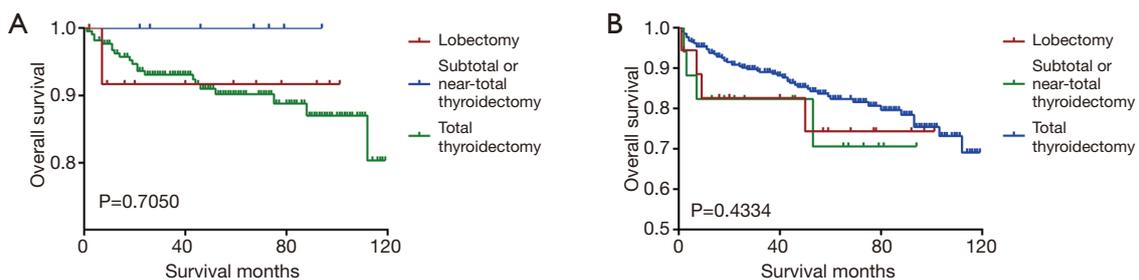

Figure 6 Kaplan Meier curves for overall survival among patients stratified by race for 6.0-based analysis (A) and 8.0-based analysis (B).

Figure 7 Kaplan Meier curves for overall survival among patients stratified by surgery for 6.0-based analysis (A) and 8.0-based analysis (B).

to explore the differences between the application of these two versions of the standard, we applied the cut-off ages for both staging systems in our subgroup analysis, which revealed similar proportions of stage II patients under both criteria.

Our Kaplan-Meier analyses showed a significant difference in DTC-specific and patient survival curves between patients below and above 35 years old under both AJCC 6.0- and 8.0-based analyses. Overall, regardless of the edition the standard was based on, patients ≥35 years old had worse outcomes than patients <35 years old for both CSS and OS, which is consistent with the results of Oyer

et al. (13) Moreover, it is noteworthy that both the cancer-specific and all-cause mortality rates per 1,000 person-years of patients aged ≥35 years old remarkably differed from those of patients <35 years old. Tran Cao *et al.* (2). proposed that under the current AJCC staging guidelines for DTC, the protective effects of age may be overestimated, especially in the setting of metastatic disease, resulting in the under-staging of young patients. Thus, further detailed investigations are needed to determine whether the age cut-off point in the staging system for young patients should be refined.

Nilubol *et al.* (17) reported that male patients are more

1256

Huang et al. Prognosis for young patients with DTC stage II

likely to have more advanced disease; however, they did not identify sex as an independent prognostic factor for DSS. Jonklaas *et al.* (15) conducted an in-depth analysis of the impact of age and sex on survival in patients with PTC and noted that, among younger patients, females had better outcomes (<55 years). In our subgroup analysis, sex emerged as a risk factor for OS in young patients at stage II: being male was associated with a statistically significant increase in overall mortality according to both the AJCC 6.0- and 8.0-based analyses. However, race only emerged as a risk factor for CSS and OS when we applied the 8th edition criteria, while the result for the AJCC 6.0-based analysis showed the reverse pattern. Thus, the effect of race was associated with the classification accuracy of age, indicating the need for additional studies to determine whether race should be considered a risk factor for young patients with stage II DTC based on the 8th edition AJCC staging system.

It must also be noted that databases such as the SEER registry have inherent limitations that should be taken into consideration when interpreting our results. First, we were unable to distinguish between patients at T1/T2/T3 stages in the 8.0-based analysis because of coding overlaps. Thus, we used a unified standard, defining patients in the T1/T2/T3 stages as a single group in the analyses based on both editions. Furthermore, information regarding family history, vascular invasion, or other histologic findings was not evaluated or included in our dataset. Third, we did not account for recurrence and surgery-related comorbidities in our analyses. The SEER database does not include information regarding whether the patients underwent repeated surgery, and this lack of information may have biased our findings.

Despite these several inherent weaknesses of the use of national retrospective databases, the strengths of the present work are derived from the fact that the population data were gathered across varied regions and hospital settings. As the study period spans several decades, the workup and management of patients with regional and distant metastases undoubtedly changed over this time. To account for these chronological trends as potential confounders, the exact year of diagnosis should be incorporated into the multivariate model to account for changes in practice patterns over time.

Conclusions

In summary, our analyses demonstrate that age is a risk factor for CSS and OS in young patients with stage II

DTC, and that young male patients appear to have poorer survival than young female patients. Race also appears to be a potential risk factor for young patients in stage II, which may lead to new perspectives and improvements in applying both the older and newer versions of the AJCC staging system; however, additional evidence is required to validate these results.

Acknowledgments

Footnote

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Materials and methods

Here is some summaries about these process.

(I) Restaging of the cases of DTC in the data of SEER 18 from 2004 to 2013 was performed using the criteria of AJCC 8.0. For patients under 55 years old, stage can be assigned directly according to the M-status. But for patients older than 55 years which are at T3 in AJCC 6th edition, their T categories need to re-assigned. If the tumor size is larger than 4 cm or patients have lymph node metastasis, it will be assigned stage II. If this patient has distant metastasis, it will be assigned stage IVB. For the patients, whose tumor size ≤4 cm, and no lymph node and distant metastasis, it is hard to identifying whether minimum or gross extra thyroid extension exists in these patients (T1/T3 or T2/T3), therefore it is hard to assigned the stage (I or II). There patients will be excluded for our analysis.

(II) Additionally, 209 patients were found with T0, whose tumor size is 0. But some of them have lymph node metastasis or even distant metastasis. If the age <55, it is easy to identify the stage I or II based on the M1 status. For patients with age ≥55, if patients have lymph node metastasis, it will be assigned stage II. If this patient has distant metastasis, it will be assigned stage IVB. But if the patient is T0, N0/NX and M0, it is hard to identify the stage, here I used 'unknown stage'.

(III) At the same time, 3,958 patients were found with TX, whose tumor size is unknown or thyroid extension is unknown. If the age <55, it is easy to identify the stage I or II based on the M1 status. For patients with age ≥55, if this patient has distant metastasis M1, it will be assigned stage IVB. But for others, it is hard to identify the stage without the T category (Stage I, II, III or IVA), and here I used 'unknown stage'.

(IV) Also, 45 patients were found at T4, but could not identifying whether T4a or T4b. If the age <55, it is easy to identify the stage I or II based on the M1 status. For patients with age ≥55, if this patient has distant metastasis M1, it will be assigned stage IVB. But for others, it is hard to identify the stage (III or IVA), and here I used 'unknown stage'.

(V) Finally, 3,983 patients are 'unknown stage' patients, and 95,032 patients have new AJCC 8th edition stage information.

Table S1 Characteristics of patients with differentiated thyroid cancer from the Surveillance, Epidemiology, and End Results Database (SEER) [2004–2013] stratified by 6.0 and 8.0 edition AJCC staging system

Patient characteristics	AJCC Version 6		AJCC Version 8	
	n	%	n	%
Sex				
Female	72,135	77.04	72,928	76.95
Male	21,504	22.96	21,847	23.05
Age				
<45/55[a]	37,144	39.67	62,019	65.44
≥45/55[a]	56,495	60.33	32,756	34.56
AJCC stage at diagnosis				
I	68,600	73.26	84,828	89.5
II	7,150	7.64	7,145	7.54
III	11,606	12.39	1,123	1.18
IV	6,283	6.71	1,679	1.77

[a], 45 years old in the 6th edition analysis and 55 years old in 8th edition analysis, respectively.

Table S2 Differentiated thyroid cancer-specific deaths and hazard ratios of mortality in patients with different disease stages stratified by 6.0 and 8.0 edition AJCC staging system

Versions	Stages	Deaths		Deaths per 1,000 person-years		Hazard ratios	
		No.	%	Value	95% CI	Value	95% CI
AJCC TNM system (Version 6) (n=93,639)	Stage I	72	0.1	0.23	0.18–0.29	1	–
	Stage II (<45 years)	14	5.13	10.8	6.27–18.60	46.95	26.468–83.298
	Stage II (≥45 years)	36	0.52	1.23	0.89–1.71	4.95	3.317–7.397
	Stage III	109	0.94	2.37	1.96–2.87	9.82	7.279–13.241
	Stage IVA	232	5.42	13.97	12.25–15.92	57.37	43.969–74.849
	Stage IVB	164	21.08	52.92	45.16–62.00	222.1	168.111–293.430
	Stage IVC	410	33.4	116.85	105.64–129.24	468.68	360.26–609.74
AJCC TNM system (Version 8) (n=94,775)	Stage I	182	0.21	0.49	0.43–0.57	1	–
	Stage II (<55 years)	70	15.22	37.17	29.25–47.22	75.16	57.046–99.015
	Stage II (≥55 years)	144	2.15	5.71	4.84–6.73	11.23	9.020–13.975
	Stage III	156	13.89	34.62	29.50–40.62	69.45	56.075–86.020
	Stage IVA	161	25.04	65.72	55.94–77.21	134.94	109.138–166.838
	Stage IVB	352	33.98	122.47	109.84–136.56	235.7	196.646–282.505

Table S3 Multivariate analyses results for clinicopathologic parameters associated with the cancer-specific survival in 6.0-based analysis

Parameters	Category	HR	6th edition multivariate		
			95 % CI		P value
Year of diagnosis	2004–2008	ref			
	2009–2013	3.418	0.596	1.96E+01	0.168
Age at diagnosis	<35	ref			
	≥35	5,969.697	0	1.31E+19	0.63
Sex	Female	ref			
	Male	2.255	0.396	1.28E+01	0.36
Race	White	ref			
	Black	0.058	0	0.001	0.994
	Other	0	0	5.89E+59	0.834
Histological types	Papillary	ref			
	Follicular	1.041	0.102	1.07E+01	0.973
T-stage	T1/T2/T3	ref			
	T4	1.06	0.196	5.73E+00	0.946
N-stage	N0	ref			
	N1	5,818.328	0	7.92E+33	0.807
Extension	Yes	ref			
	No	0.592	0.082	4.30E+00	0.605
Multifocality	Yes	ref			
	No	1.384	0.221	8.66E+00	0.728
Radiation	None or refused	ref			
	Radiation beam or radioactive implants	33,6341.8	0	1.01E+123	0.927
	Radioisotopes or radiation beam plus isotopes or implants	42,833.5	0	1.28E+122	0.938
Surgery	Lobectomy	ref			
	Subtotal or near total thyroidectomy	–	–	–	–
	Total thyroidectomy	–	–	3.08E+10	0.533