Sex Disparities in Thyroid Cancer: A SEER Population Study

Peng Li (✉ 837657079@qq.com)

Xiangya Hospital Central South University

Ying Ding

Xiangya Hospital Central South University

Mengyuan Liu

Xiangya Hospital Central South University

Wenlong Wang

Xiangya Hospital Central South University

Xinying Li

Xiangya Hospital Central South University

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Abstract

Background: The incidence and mortality of thyroid cancer vary according to race and sex. Male and female thyroid cancer patients are also given differences in some clinical characteristics, such as tumor size and distant metastasis. However, whether there are sex differences in the prognosis of thyroid cancer remains controversial. Therefore, the present study is intended to explore the relationship between sex and prognosis of patients with thyroid cancer and to provide guidelines for the treatment and management of thyroid cancer patients.

Methods: A retrospective analysis of patients with pathologically proven thyroid cancer from the Surveillance, Epidemiology and End Results database. The sex disparities in the prognosis of different cohorts derived by propensity score matching was investigated using Cox proportional hazards models and Kaplan–Meier functions.

Results: Among 41,270 female and 13,188 male with thyroid cancer, sex was an independent prognostic factor for overall (OS) and cancer-specific (CSS) survival (HR=1.632, 95%CI=1.499-1.777, $P<0.001$; HR= 1.473, 95% CI= 1.245-1.741, $P<0.001$). Male developed a larger tumor size (17.44 vs. 23.51cm) and had a larger proportion of metastasis (lymph nodes: 33.2 vs. 21.0%; distant: 2.3 vs. 0.9%), through female had a higher incidence and were diagnosed with thyroid cancer at an earlier age (47.98 vs. 52.45 years old). Survival month of male patients was significantly lower than that of female patients (72.39 vs. 76.8 months). In Kaplan-Meier analyses of cohorts derived by propensity score matching, OS and CSS declined more sharply for male ($P<0.01$). The mean number (2.0 vs 4.0) and mean ratio (0.192 vs 0.297) of positive nodes supported that male patients have a worse prognosis. Factors including race, age, surgery, histology recode, T, N, M stage and combined summary stage affected the CSS of male and female, plus median income had an extra impact in male ($\geq \$55,000$ versus $< \$55,000$: HR= 0.739, 95% CI= 0.574-0.953, $P= 0.020$).

Conclusion: Thyroid cancer is a tumor with a female prevalence but a male bias in poor prognosis. Sex was an independent prognostic factor for OS and CSS. Other factors including race, age, income, histological type, surgery, T, N, M stage influenced OS of male and female with thyroid cancer. But race had no impact on CSS of thyroid cancer patients and median income only affected male CSS.

Introduction

The incidence of thyroid cancer has been increasing in the last few decades. In the United States, thyroid cancer accounts for 2.9% of new cancer cases and more than 90% of endocrine cancer cases[1]. Thyroid cancer ranks as the fifth most common cancer in females in America[2]. In addition, in recent years, the increase in the incidence of cancer among people aged 15-39 is mainly caused by thyroid cancer[3]. However, different from the high incidence of thyroid cancer, its mortality rate is comparatively low and remains stable. A study showed that the mortality rate of thyroid cancer in the United States was stable between 1975 and 2009 (about 0.5 deaths per 100,000 people)[4]. Also a study revealed that the mortality rate of thyroid cancer increased by 1.1% per year between 1974 and 2013[5]. Papillary thyroid carcinoma (PTC), medullary thyroid carcinoma (MTC), follicular thyroid carcinoma (FTC), and anaplastic thyroid carcinoma (ATC) are the four main types of thyroid carcinoma. PTC and FTC account for over 95% of all thyroid cancers diagnosed annually[6]. Patients with these two types of cancer have a great 5-year survival rate ($>98\%$)[7]. Although MTC and ATC are rare, they are aggressive and progress rapidly and became the main cause of death in patients with thyroid cancer. Unfortunately, the 5-year survival rate of patients with ATC ranges from 0% to 10%, while the median survival is 5-6 months[8].

The incidence and mortality of thyroid cancer vary between different races and sex. Studies showed that the incidence of thyroid cancer in whites is considerably higher than in other racial groups such as blacks, Asians, and Hispanics[9]. Well-differentiated thyroid cancer is 3 times more common in females, while the incidence of poorly differentiated thyroid cancer in males and females is similar[10]. In addition, male and female thyroid cancer patients also have differences in some clinical characteristics, such as tumor size and histological type. Wang et al. found that sex was not an independent risk factor for distant metastasis[11, 12]. However, whether there are sex differences in the prognosis of thyroid cancer remains controversial. A meta-analysis showed that the prognosis of male PTC patients is worse, and the risk of recurrence is 1.53 times that of

females[13]. Besides, Fang and Liu et al. found that in papillary thyroid carcinoma, men get a poorer prognosis than women[14, 15]. Likewise, Kruijff, S. et al. demonstrated the risk of structural recurrence in men is 2.44 times that of women[16]. On the contrary, Nilubol et al. reported that sex does not constitute an independent prognostic factor for disease-specific survival in thyroid cancer[17]. Meanwhile, Oyer, S and Grogan, R. H. et al. also reached similar conclusions[18, 19] and there is no significant sex difference in the prognosis of ATC patients[8]. These conflicting results caused problems in the treatment and management of thyroid cancer patients. Therefore, we need further research to establish whether there are sex differences in the prognosis of thyroid cancer.

In this retrospective study, we collected thyroid cancer data from 2004 to 2018 (54458 patients) through the Surveillance, Epidemiology, and End Results (SEER) database and used the propensity score matching (PSM) method to explore the relationship between the sex and prognosis of patients with thyroid cancer.

Methods

Data Selection

Patients with thyroid cancer (primary site coded as C73.9—thyroid gland) between 2004 and 2018 were obtained from the SEER database: Incidence - SEER Research Data, 9 Registries, Nov 2020 Sub (1975-2018). Race recode, Sex, Year of diagnosis, AYA site recode 2020 Revision, Laterality, Diagnostic Confirmation, Combined Summary Stage, Derived AJCC T, Derived AJCC N, Derived AJCC M, Reason no cancer-directed surgery, regional nodes examined, regional nodes positive, CS tumor size, COD to site recode, SEER cause-specific death classification, Survival months, Age recode with single ages and 85+, Median household income, we obtained the patient information under the above items from the SEER database.

In this large cohort, microscopic confirmed thyroid cancer patients whose pathological type was limited to '9.1.1 Medullary, 9.1.2 Hurthle cell carcinoma, 9.1.3 Papillary, 9.1.4 Follicular, 9.1.5 Papillary with follicular variant' from AYA site recode 2020 Revision were included. And all of their Behavior code ICD-O-3 was 'malignant'. Data on regional lymph nodes were collected from regional nodes examined (1988+) and regional nodes positive (1988+). Patients with incomplete information were excluded (Fig. 1). We also excluded patients whose age of diagnosis was marked as 85+ without knowing the exact value. Then we re-staged all these patients according to the 7th AJCC T/N/M staging system to avoid confusion[20, 21].

Statistical Analyses

Continuous variables are described as the means, and categorical variables are described as frequencies and percentages, compared respectively using t-test and Pearson's chi-squared test. Univariate and multivariable survival analyses using Cox proportional hazards models to calculate hazard ratios (HRs). Survival curves were derived by Kaplan–Meier method and compared using log-rank test. Then we introduced propensity score matching into our study[22]. All of the statistical analyses were carried out using SPSS Statistical Software version 22.0 (IBM Corp.). A two-sided p value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the SEER cohort

In total, 41,270 female and 13,188 male patients (female to male ratio was 3.13) obtained from the SEER database met the inclusion criteria (Table 1). Female patients are typically diagnosed at an earlier age than males on average (47.98 vs. 52.45 years old). On the ethnic level, there are more female cases in the white and black population. Compared with female patients, male patients developed a larger tumor size (17.44 vs. 23.51cm) and had a larger proportion of lymph node metastasis (33.2 vs. 21.0%) and distant metastasis (2.3 vs. 0.9%), consistent with the distribution of combined summary stage (Regional 36.1 vs. 26.1%, Distant 4.0 vs. 1.9%). A rare pathological type, medullary carcinoma, occurred more frequently in male patients than in female patients (2.9 vs. 1.2%). And survival month of male patients was significantly lower than that of female patients (72.39 vs. 76.8 months). Male seems to have a worse prognosis, considering that thyroid cancer caused more specific death

(2.9 vs. 1.1%) in them. We found sex differences in whether surgery performed or not (surgery performed Male: Female = 98.7%: 99.4%) which might be attributed to tumor progression and malignancy. Median income was also different in female and male ($P<0.001$). But the difference between laterality of male and female was non-significant ($P=0.376$). These findings revealed a large sex disparity in clinical characteristics of thyroid cancer.

Differences in the survival of female and male patients in the SEER cohort

During the time period 1975-2018, the age-adjusted incidence rate of thyroid cancer is 9.2 (4.9 in male, 13.3 in female) per 100,000. From 2010 to 2016, the incidence has been at a stable level. Female were still affected 3 times more than male, although the curves shifted downward during 2017-2018 (Fig. 2a). Compared with female patients in the same period, male diagnosed with thyroid cancer each year seems to have a higher potential of specific death (Fig. 2b). Considering that the proportion of patients died of thyroid cancer among mortality generally rose up (Fig. 2c). Thyroid cancer still threatens human health, especially female due to the higher incidence. As showed in Kaplan-Meier analysis of the SEER cohort, OS declined more sharply for male (Log-rank test, $p<0.001$) (Fig. 3a). Similar results were observed for CSS (Log-rank test, $p<0.001$) (Fig. 3b). Namely, female had better OS and CSS prognosis compared with the male. In the univariate and multivariate analyses of OS and CSS in the SEER cohort, there was significant difference between male and female with different tumor size, age or median income subgroups, and the male versus female HRs were > 1.000 (Table S1 and S2, Additional File 1).

Additionally, we observed sex differences in nodal ratio. The number of metastatic lymph node number and metastatic lymph node ratio could be prognostic metrics for thyroid cancer[23-25], and can improve predictive ability in a novel N staging system compared with the AJCC system[26]. In this process, 21,825 female and 7,256 males were collected after excluding patients with unknown/not stated regional nodes. The mean number of positive nodes was 2.0 in female, whereas the mean number of positive nodes was 4.0 in male. Nodal Ratio (NR) is defined as the number of positive lymph nodes out of the number of total lymph nodes in the specimen. Mean NR of female and male was 0.192 and 0.297, respectively (Table S3, Additional File 2). Lebourneux et al. demonstrated that the number of positive LNs is related to a significantly higher 10-year risk of recurrence: 3% for <5 LN metastases [27]. Nam et al. demonstrated that $NR>0.3$ was associated with higher rates of any site and nodal recurrence[28]. Taking into account the results of previous studies, our results on the positive number and positive ratio of cervical lymph nodes in patients with thyroid cancer support the conclusion that male patients have a worse prognosis to a certain extent. Together, these results demonstrated male thyroid cancer associated with a worse prognosis.

Differences in the survival of female and male patients in cohorts after propensity score matching

To eliminate selection bias in observational non-randomized controlled trials, male and female patients diagnosed with thyroid cancer between 2004 and 2018 were matched via PSM. We conducted several matchings including different factors to confirm our conclusion. OS and CSS functions after propensity score matching indicated the sex disparity of prognosis on different levels (Fig. 4).

After 1:1 matching including all the factors, 12779 male and 12779 female patients were collected to form a new post-PSM cohort (Table S4, Additional File 1). Survival months were longer (74.14 ± 49.14 vs 72.68 ± 49.23 , $P=0.018$) in the female. There is more overall and specific death in male (overall death: 10.6 vs. 6.9%, specific death: 2.5 vs. 1.9%, $P<0.001$, respectively).

Kaplan-Meier curves of OS and CSS for male and female patients in the post-PSM cohort supported the same conclusion as in the SEER cohort (Fig. 5a, b). Compared with female patients, the hazard ratio (HR) for all-cause death in male patients was 1.62 (95%CI=1.514-1.734, $P<0.001$), and the HR for cancer-specific death was 1.437 (95%CI=1.248-1.654, $P<0.001$) (Table 2, 3). After adjustment for clinical basic data, these HRs for all-cause and cancer-specific death became 1.632 (95%CI=1.499-1.777, $P<0.001$) and 1.473 (95% CI=1.245-1.741, $P<0.001$) (Table 2, 3), respectively.

Factors affecting the prognosis of female and male thyroid cancer

The statistically significant factors affecting OS of female thyroid cancer (Table 4) were race (white versus black: HR= 0.736, 95% CI= 0.636-0.852, $P<0.001$, other versus black: HR= 0.682, 95%CI= 0.565-0.822, $P<0.001$), age of diagnosis (<55 versus ≥ 55

years old: HR= 6.195, 95%CI= 5.612-6.838, $P<0.001$), median income ($\geq \$55,000$ versus $< \$55,000$: HR= 0.841, 95% CI= 0.753-0.940, $P<0.001$), surgery (versus not performed: HR= 0.134, 95% CI= 0.108-0.167, $P<0.001$), distant in combined summary stage (versus localized: HR= 2.133, 95% CI= 1.671-2.723, $P<0.001$) T stage, M stage and histology recode (versus medullary: HR= 0.892, 95% CI= 0.853-0.933, $P<0.001$). The risk of death increases with upgrading of T, M stage. Similar results were found in analysis of OS for male patients (Table 5). As for CSS, the factors for female (Table 6) were tumor size ($>1\text{cm}$ versus $\leq 1\text{cm}$: HR= 1.578, 95% CI= 1.199-2.077, $P<0.001$), age of diagnosis (<55 versus ≥ 55 years old: HR= 7.054, 95%CI= 5.562-8.946, $P<0.001$), surgery (versus not performed: HR= 0.153, 95% CI= 0.109-0.217, $P<0.001$), histology recode (versus medullary, HR= 0.750, 95% CI= 0.696-0.809) and the risk of death increased with upgrading of T, N, M and combined summary stage. In male patients, median income ($\geq \$55,000$ versus $< \$55,000$: HR= 0.739, 95% CI= 0.574-0.953, $P= 0.020$) had an extra impact compared with female (Table 7). These findings implicated race, age of diagnosis, median income, surgery, tumor size, and histology recode, T, N, M and combined summary stage contributed to the prognosis of thyroid cancer.

Discussion

Based on a large population from the SEER database, this retrospective study was conducted to explore the differences of clinical features and prognostic factors in male and female thyroid cancer patients. Different from previous studies, our sample size is larger and follow-up is longer. Moreover, we conducted several PSM including diverse factors to confirm our conclusions. Furthermore, stratified survival analysis in all primary clinical characteristics was conducted in our study. In the present study, we found that tumor sizes of male patients were larger than that of female patients and the tumor grade of male patients was worse than that of female patients. More importantly, males had significantly poorer OS and CSS than females. Besides, we found that male and female patients had different prognostic risk factors. Unlike in female patients, median income affected CSS in male patients. What's more, race only had an impact on the OS and not CSS in patients with thyroid cancer. Interestingly, after stratified for clinical features, we found that only white patients and PTC patients had a significant sex difference in CSS compared to other races and histological types of thyroid cancer, and that the difference in prognosis between male and female patients seemed to be gradually shrinking with the progression of tumor. This might be due to insufficient number of cases in other subgroups after stratified by clinical characteristics. Therefore, a larger number of cases and longer follow-up are necessary to clarify the results.

Numerous studies have tried to explain the sex differences in thyroid cancer. For example, high estrogen levels¹⁸, methylation of X chromosome promoter[29], and over-expression and mutations in related genes such as EZH2, KDM5C, and IL7R seem to be associated with a higher incidence of thyroid cancer in women[30-32]. In addition, Hashimoto's thyroiditis (HT), which is more prevalent in women, also appears to be closely associated with thyroid cancer[33]. Some studies have shown that although the incidence of thyroid cancer is higher in women, the overall mutation burden is higher in men[34], and that testosterone promotes the progression of FTC in mice, which is consistent with the more aggressive FTC observed in men[35], and these may be associated with poor prognosis in men. However, it has also been found that the TFRC, which is associated with tumor progression and poor prognosis, is over-expression in women[36]. In addition, it has been suggested that higher ESR1 expression and higher ESR ratio in female PTC patients are associated with invasive prognostic factors and poorer OS[37]. Our research provides a piece of evidence for systematically incorporating sex differences into the paradigms for laboratory and clinical cancer research, and the current emphasis on developing personalized approaches to cutting-edge cancer treatment.

Our research is not without limitations, so some inherent limitations must be considered when interpreting our results. We are subject to restrictions related to the SEER database, including covering only one-third of the population in the United States, incomplete data collection (no data on recurrence of thyroid cancer, family history, weight and height, and medical comorbidities), information inaccurate input and inconsistent tumor classification may be caused by changes in the staging angle. These issues may have caused potential deviations in our analysis. In addition, in this study, we did not evaluate the impact of social status and medical insurance on the prognosis of patients with thyroid cancer.

Conclusion

In summary, we found that although thyroid cancer was more common in women than in men, when diagnosed with thyroid cancer male patients had larger tumors and higher TNM stage. And males had significantly poorer OS and CSS than females. In addition, this study showed that male and female patients had different prognostic risk factors. Unlike in female patients, median income affected CSS in male patients. What's more, race only had an impact on the OS and not CSS in patients with thyroid cancer.

Abbreviations

SEER: the Surveillance, Epidemiology, and End Results database;

PTC: Papillary thyroid carcinoma;

MTC: Medullary thyroid carcinoma;

FTC: Follicular thyroid carcinoma;

ATC: Anaplastic thyroid carcinoma;

PSM: Propensity score matching;

OS: Overall survival;

CSS: Cancer-specific survival;

NR: Nodal ratio;

LN: Lymph node;

HR: Hazard ratio;

Declarations

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Authors' contributions

PL, YD and WW conceptualized the project. XL and WW were responsible for the whole administration. PL, YD and ML analyzed data and wrote the manuscript. All authors have read, edited and approved the manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are available in the SEER repository, (<https://seer.cancer.gov/>).

Competing interests

The authors declare that they have no conflict of interest.

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Tables

Table 1. Baseline Characteristics of the SEER Cohort (Patients with Thyroid Cancer from the Surveillance, Epidemiology, and End Results Database(2004-2018))

Characteristics	Variable	Female	Male	P
		n=41270	n=13188	
Age ^a	Mean± SD	47.98±14.93	52.45±15.04	<0.001
	<55	27279(66.1)	6950(52.7)	<0.001
	≥55	13991(33.9)	6238(47.3)	
Race	White	32930(79.8)	11151(84.6)	<0.001
	Black	3033(7.3)	661(5.0)	
	Other	5307(12.9)	1376(10.4)	
Tumor Size ^b	Mean± SD	17.44±18.05	23.51±24.56	<0.001
	≤1.0cm	16797(40.7)	4062(30.8)	<0.001
	>1.0cm	24473(59.3)	9126(69.2)	
T Stage	Tx	35(0.1)	18(0.1)	<0.001
	T0	54(0.1)	42(0.3)	
	T1	26039(63.1)	6474(49.1)	
	T2	7140(17.3)	2547(19.3)	
	T3	7031(17.0)	3549(26.9)	
	T4	971(2.4)	558(4.2)	
N Stage	Nx	1169(2.8)	353(2.7)	<0.001
	N0	31438(76.2)	8461(64.2)	
	N1	8663(21.0)	4374(33.2)	
M Stage	M x	291(0.7)	86(0.7)	<0.001
	M0	40594(98.4)	12794(97.0)	
	M1	385(0.9)	308(2.3)	
Combined Summary Stage	Localized	29701(72.0)	7898(59.9)	<0.001
	Regional	10773(26.1)	4765(36.1)	
	Distant	796(1.9)	525(4.0)	
Surgery Performed	No	260(0.6)	169(1.3)	<0.001
	Yes	41010(99.4)	13019(98.7)	
Histology Recode /Pathological Type	Medullary	510(1.2)	379(2.9)	<0.001
	Hurthle cell carcinoma	827(2.0)	372(2.8)	
	Papillary	26990(65.4)	8477(64.3)	
	Papillary with follicular variant	10995(26.6)	3129(23.7)	
	Follicular	1948(4.7)	831(6.3)	
Laterality ^c	Bilateral	202(0.5)	78(0.6)	0.376

	Not paired Site	41055(99.5)	13108(99.4)	
Median Income	< \$35,000	121(0.3)	44(0.3)	<0.001
	\$35,000-\$54,999	6308(15.3)	1900(14.4)	
	\$55,000-\$74,999	18693(45.3)	5831(44.2)	
	≥\$75,000	16148(39.1)	5413(41.0)	
All-cause Death	Alive	39136(94.8)	11731(89.0)	<0.001
	Dead	2134(5.2)	1457(11.0)	
Cancer-specific Death	Alive	40817(98.9)	12810(97.1)	<0.001
	Dead	453(1.1)	378(2.9)	
Survival Months	Mean± SD	76.8±49.59	72.39±49.25	<0.001
a.Age at diagnosis was grouped into <55 and ≥55 years old based on the 8th AJCC staging system;				
b.Tumor size was grouped into ≤1.0cm and >1.0cm based on the definition of micro-thyroid carcinoma;				
c.the laterality of where the thyroid cancer originated.				

Table 2. Hazard Ratios of Sex for All-cause Death of Thyroid Cancer									
Characteristic	Sex	Unadjusted				Adjusted			
		All-cause Death	HR	95%CI	P	All-cause Death	HR	95%CI	P
All thyroid carcinoma	Female	2134 [41270]	1(reference)	-	-	882(12779)	1(reference)	-	-
	Male	1457 [13188]	1.62	1.514-1.734	<0.001	1349(12779)	1.632	1.499-1.777	<0.001

Table 3. Hazard Ratios of Sex for Cancer-specific Death of Thyroid Cancer									
Characteristic	Sex	Unadjusted				Adjusted			
		Cancer-specific death	HR	95%CI	P	Cancer-specific Death	HR	95%CI	P
All thyroid carcinoma	Female	453 [41270]	1(reference)	-	-	239(12779)	1(reference)	-	-
	Male	378 [13188]	1.437	1.248-1.654	<0.001	323(12779)	1.473	1.245-1.741	<0.001

Table 4. Univariate and Multivariate Cox Regression Analyses of Overall Survival in Female Thyroid Cancer.					
Characteristics	Variable	Univariate Analysis		Multivariate Analysis	
		HR[95%CI]	P	HR[95%CI]	P
Tumor Size	≤1cm	1	-	1	-
	>1cm	1.238[1.133-1.352]	<0.001	1.030[0.934-1.137]	0.55
Race	black	1	-	1	-
	white	0.703[0.608-0.813]	<0.001	0.736[0.636-0.852]	<0.001
	other	0.729[0.598-0.864]	<0.001	0.682[0.565-0.822]	<0.001
Age	<55	1	-	1	-
	≥55	6.622[6.004-7.304]	<0.001	6.195(5.612-6.838)	<0.001
Median Income	<\$55,000	1	-	1	-
	≥\$55,000	0.717[0.642-0.800]	<0.001	0.841(0.753-0.940)	<0.001
Surgery Performed	No	1	-	1	-
	Yes	0.075[0.061-0.092]	<0.001	0.134(0.108-0.167)	<0.001
Histology Recode /Pathological Type	Medullary	1	-	1	-
	HCC ^a	0.773[0.570-1.050]	0.099	0.949[0.695-1.296]	0.743
	Fillicular	0.526[0.396-0.699]	<0.001	0.750[0.564-0.998]	0.048
	Pap with Fv ^b	0.344[0.268-0.442]	<0.001	0.626[0.484-0.810]	<0.001
	Papillary	0.328[0.257-0.418]	<0.001	0.618[0.481-0.793]	<0.001
T Stage	Tx	0.607[0.226-1.632]	0.323	0.206[0.075-0.562]	0.002
	T0	0.894[0.475-1.685]	0.729	0.307[0.160-0.591]	<0.001
	T1	0.186[0.161-0.214]	<0.001	0.354[0.288-0.436]	<0.001
	T2	0.178[0.149-0.211]	<0.001	0.347[0.279-0.431]	<0.001
	T3	0.296[0.253-0.347]	<0.001	0.470[0.395-0.560]	<0.001
	T4	1	-	1	-
N Stage	Nx	1.479[1.109-1.973]	0.008	1.144[0.848-1.542]	0.379
	N0	0.915[0.823-1.017]	0.099	1.004[0.872-1.157]	0.954
	N1	1	-	1	-
M Stage	Mx	0.107[0.071-0.161]	<0.001	0.207[0.135-0.319]	<0.001
	M0	0.086[0.072-0.101]	<0.001	0.266[0.211-0.335]	<0.001
	M1	1	-	1	-
Combined Summary Stage	Localized	1	-	1	-
	Regional	1.118[1.010-1.237]	0.031	0.994[0.879-1.124]	0.92
	Distant	7.644[6.673-8.755]	<0.001	2.133[1.671-2.723]	<0.001
a. HCC: Hurthle cell carcinoma;					

Table 5. Univariate and Multivariate Cox Regression Analyses of Overall Survival in Male Thyroid Cancer.

Characteristics	Variable	Univariate Analysis		Multivariate Analysis	
		HR[95%CI]	P	HR[95%CI]	P
Tumor Size	≤1cm	1	-	1	-
	>1cm	1.213[1.081-1.361]	0.001	0.984[0.864-1.120]	0.802
Race	black	1	-	1	-
	white	0.675[0.550-0.828]	<0.001	0.776[0.630-0.955]	0.016
	other	0.705[0.545-0.912]	0.008	0.742[0.572-0.963]	0.025
Age	<55	1	-	1	-
	≥55	4.727[4.172-5.355]	<0.001	4.499(3.967-5.102)	<0.001
Median Income	<\$55,000	1	-	1	-
	≥\$55,000	0.662[0.581-0.755]	<0.001	0.785(0.687-0.897)	<0.001
Surgery Performed	No	1	-	1	-
	Yes	0.103[0.083-0.128]	<0.001	0.192(0.152-0.242)	<0.001
Histology Recode /Pathological Type	Medullary	1	-	1	-
	HCC ^a	0.794[0.585-1.079]	0.141	1.017[0.737-1.403]	0.918
	Fillicular	0.541[0.409-0.717]	<0.001	0.814[0.606-1.094]	0.173
	Pap with Fv ^b	0.423[0.333-0.536]	<0.001	0.719[0.558-0.928]	0.011
	Papillary	0.422[0.338-0.527]	<0.001	0.750[0.592-0.951]	0.028
T Stage	Tx	1.851[0.871-3.933]	0.11	0.677[0.314-1.463]	0.321
	T0	1.264[0.760-2.103]	0.367	0.783[0.462-1.326]	0.363
	T1	0.219[0.187-0.257]	<0.001	0.391[0.316-0.484]	<0.001
	T2	0.229[0.189-0.276]	<0.001	0.441[0.351-0.554]	<0.001
	T3	0.303[0.257-0.359]	<0.001	0.498[0.413-0.601]	<0.001
	T4	1	-	1	-
N Stage	Nx	1.444[1.039-2.008]	0.029	1.214[0.864-1.707]	0.263
	N0	0.741[0.665-0.825]	<0.001	0.965[0.822-1.133]	0.664
	N1	1	-	1	-
M Stage	Mx	0.186[0.114-0.304]	<0.001	0.432[0.260-0.718]	0.001
	M0	0.132[0.111-0.156]	<0.001	0.364[0.291-0.457]	<0.001
	M1	1	-	1	-
Combined Summary Stage	Localized	1	-	1	-
	Regional	1.163[1.037-1.304]	0.01	1.135[0.998-1.291]	0.054
	Distant	6.217[5.356-7.217]	<0.001	2.153[1.639-2.829]	<0.001

a. HCC: Hurthle cell carcinoma;

Table 6. Univariate and Multivariate Cox Regression Analyses of Cancer-specific Survival in Female Thyroid Cancer.					
Characteristics	Variable	Univariate Analysis		Multivariate Analysis	
		HR[95%CI]	P	HR[95%CI]	P
Tumor Size	≤1cm	1	-	1	-
	>1cm	4.004[3.094-5.181]	<0.001	1.578(1.199-2.077)	<0.001
Race	black	1	-	1	-
	white	0.760[0.543-1.063]	0.109	0.761[0.541-1.070]	0.116
	other	1.339[0.915-1.960]	0.133	0.770[0.520-1.140]	0.192
Age	<55	1	-	1	-
	≥55	8.766[6.952-11.055]	<0.001	7.054(5.562-8.946)	<0.001
Median Income	<\$55,000	1	-	1	-
	≥\$55,000	0.875[0.682-1.123]	0.293	0.949[0.736-1.224]	0.686
Surgery Performed	No	1	-	1	-
	Yes	0.031[0.023-0.042]	<0.001	0.153(0.109-0.217)	<0.001
Histology Recode /Pathological Type	Medullary	1	-	1	-
	HCC ^a	0.589[0.372-0.933]	0.024	1.468[0.902-2.390]	0.123
	Fillicular	0.379[0.248-0.579]	<0.001	0.968[0.613-1.529]	0.889
	Pap with Fv ^b	0.108[0.073-0.160]	<0.001	0.500[0.327-0.764]	0.001
	Papillary	0.123[0.086-0.175]	<0.001	0.426[0.291-0.624]	<0.001
T Stage	Tx	0.456[0.113-1.839]	0.27	0.136[0.033-0.560]	0.006
	T0	0.633[0.260-1.544]	0.315	0.326[0.125-0.850]	0.022
	T1	0.023[0.018-0.030]	<0.001	0.178[0.122-0.260]	<0.001
	T2	0.046[0.034-0.063]	<0.001	0.251[0.170-0.368]	<0.001
	T3	0.136[0.109-0.171]	<0.001	0.428[0.329-0.557]	<0.001
	T4	1	-	1	-
N Stage	Nx	0.757[0.431-1.328]	0.332	0.753[0.424-1.337]	0.333
	N0	0.297[0.246-0.358]	<0.001	0.700[0.565-0.868]	0.001
	N1	1	-	1	-
M Stage	Mx	0.042[0.020-0.091]	<0.001	0.210[0.096-0.460]	<0.001
	M0	0.020[0.016-0.025]	<0.001	0.243[0.178-0.333]	<0.001
	M1	1	-	1	-
Combined Summary Stage	Localized	1	-	1	-
	Regional	3.413[2.679-4.326]	<0.001	1.594[1.180-2.152]	<0.001
	Distant	59.119[47.079-74.238]	<0.001	4.986[3.247-7.658]	<0.001
a. HCC: Hurthle cell carcinoma;					

Table 7. Univariate and Multivariate Cox Regression Analyses of Cancer-specific Survival in Male Thyroid Cancer.					
Characteristics	Variable	Univariate Analysis		Multivariate Analysis	
		HR[95%CI]	P	HR[95%CI]	P
Tumor Size	≤1cm	1	-	1	-
	>1cm	3.354[2.457-4.579]	<0.001	1.705[1.380-2.106]	<0.001
Race	black	1	-	1	-
	white	0.947[0.596-1.505]	0.819	0.916[0.697-1.205]	0.531
	other	0.933[0.535-1.626]	0.807	0.814[0.591-1.122]	0.209
Age	<55	1	-	1	-
	≥55	4.003[3.161-5.070]	<0.001	3.392(2.661-4.325)	<0.001
Median Income	<\$55,000	1	-	1	-
	≥\$55,000	0.635[0.493-0.816]	<0.001	0.739(0.574-0.953)	0.02
Surgery Performed	No	1	-	1	-
	Yes	0.063[0.045-0.088]	<0.001	0.272(0.188-0.395)	<0.001
Histology Recode /Pathological Type	Medullary	1	-	1	-
	HCCv ^a	0.539[0.348-0.836]	0.006	1.263[0.901-1.770]	0.175
	Fillicular	0.247[0.159-0.385]	<0.001	0.831[0.601-1.150]	0.264
	Pap with Fv ^b	0.107[0.073-0.157]	<0.001	0.437[0.325-0.588]	<0.001
	Papillary	0.171[0.126-0.231]	<0.001	0.459[0.355-0.593]	<0.001
T Stage	Tx	1.912[0.782-4.677]	0.156	0.315[0.146-0.680]	0.003
	T0	0.479[0.177-1.296]	0.147	0.475[0.232-0.973]	0.042
	T1	0.036[0.027-0.050]	<0.001	0.188[0.141-0.251]	<0.001
	T2	0.068[0.048-0.095]	<0.001	0.274[0.207-0.363]	<0.001
	T3	0.154[0.121-0.196]	<0.001	0.439[0.363-0.531]	<0.001
	T4	1	-	1	-
N Stage	Nx	0.642[0.414-0.996]	0.048	0.721[0.458-1.134]	0.157
	N0	0.258[0.225-0.296]	<0.001	0.753[0.638-0.889]	0.001
	N1	1	-	1	-
M Stage	Mx	0.044[0.024-0.081]	<0.001	0.240[0.129-0.446]	<0.001
	M0	0.024[0.020-0.028]	<0.001	0.256[0.204-0.320]	<0.001
	M1	1	-	1	-
Combined Summary Stage	Localized	1	-	1	-
	Regional	3.688[3.084-4.411]	<0.001	1.826[1.456-2.291]	<0.001
	Distant	56.280[47.287-66.984]	<0.001	5.129[3.700-7.110]	<0.001
a. HCC: Hurthle cell carcinoma;					

Figures

Figure 1

Flowchart of the SEER Cohort.

Figure 2

Epidemiological differences between male and female patients with thyroid cancer from SEER database. (a) Overall, female and male age adjusted incidence rates of thyroid cancer shown for 1 year peroids between 2004 and 2018. Data was obtained from SEER*stat 8.3.9. (b) Proportion of death in overall, female and male patients diagnosed with thyroid cancer from 2004 to 2018, proportion of death defined as the contribution of thyroid-cancer-specific deaths in incident cases. (c) Proportion of patients died of thyroid cancer for overall, female and male all-cause deaths, defined as the ratio of thyroid-cancer-specific deaths to dead population of the year.

Figure 3

Kaplan–Meier function of the SEER cohort. Overall survival (a) and cancer-specific survival (b) functions for overall, female and male patients with thyroid cancer in the SEER cohort, log-rank test, $P < 0.001$, respectively.

Figure 4

Overall and cancer-specific survival functions after propensity score matching including different factors, one-to-one match. (a) and (b) Only race and age of diagnosis were included in matching. (c) and (d) race, age of diagnosis and combined summary stage included. (e) and (f) race, age of diagnosis, combined summary stage and histology recode included. (g) and (h) race, age of diagnosis, combined summary stage, histology recode and tumor size included. (i) and (j) race, age of diagnosis, combined summary stage, histology recode, tumor size, and surgery performed or not included. K-M functions were compared using log-rank test, $P < 0.001$, respectively.

Figure 5

Kaplan-Meier function of the post-PSM cohort. All the factors (except for laterality in Table 1) with an impact on the survival prognosis were included in matching. Baseline characteristics were shown in supplement material. Overall survival (a) and cancer-specific survival (b) functions for female and male patients with thyroid cancer in the post-PSM cohort, log-rank test, $P < 0.001$, respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1UnivariateandMultivariateCoxRegressionAnalysesofSurvivalintheSEERCohort.xlsx](#)
- [Additionalfile2SexDifferencesinNodalRatio.xlsx](#)
- [Additionalfile3BaselineCharacteristicsofthePostPSMCohort.xlsx](#)