Analysis on The CSS Difference and Its Influence Factors Between ATC and PSCCT

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Abstract

Background:The clinical manifestations and treatments of ATC and PSCCT are similar .Their prognosis is worse than other types of thyroid cancer. This study aims to analyze on the CSS Difference and Its prognosis Factors Between ATC and PSCCT.

Methods:We reviewed the data of patients who were diagnosed as ATC and PSCCT between 2004 and 2015 in the Surveillance, Epidemiology, and End Results (SEER) database. Statistical analysis included Kaplan-Mier survival analysis, Cox regression models and the log-rank test. The predictive accuracy ability of the model were determined by concordance index (C-index)

Result:1164 patients with ATC and 124 patients with PSCCT were included. The clinical treatment rate and distant metastasis rate of ATC is higher than that of PSCCT($p<0.05$). PSCCT CSS is better than ATC CSS($p=0.0074$). Multivariable analyses showed that Age,Sex, Radiation,Chemotherapy,Sequencenumber,Marital,SurgPrimSite or M stage were independent prognostic factors,the C-index of this model is 0.803 (95%CI: 0.787-0.819). Age, Radiation, Sequencenumber, SurgPrimSite are independent prognostic factors of PSCCT CSS, C-index of the model is 0.829, (95%CI: 0.786-0.872)

Conclusions:Although the overall CSS prognosis of PSCCT patients is better than that of ATC patients, the prognostic factors of ATC and PSCCT are not exactly the same. It is necessary to formulate clinical treatment and management plans based on the type of disease.

Introduction

Anaplastic thyroid carcinoma (hereinafter referred to as ATC) is the most aggressive thyroid tumor among primary thyroid cancers, which accounts for about 1-2% of the total and occurs mostly in the elderly. There is no clear differentiation in anaplastic, while giant, spindle and squamous cells show obvious pleomorphism^{1,2}. Primary squamous cell carcinoma of the thyroid(hereinafter referred to as PSCCT) is an extremely rare and highly aggressive malignant tumor, accounting for less than 1% of all primary thyroid cancers and resulting in unfavourable prognosis. In terms of cytology, it is only composed of large and pleomorphic epithelial cells with keratinization, and necrotic components are common-seen^{3,4}. The most common symptom of PSCCT is an enlarged anterior neck mass, followed by difficulty breathing or swallowing and changing voice. ATC and PSCCT both show abundant squamous cell-like cells. Therefore, they are easily confused in clinical diagnosis. Related studies showed that they are identical in clinical manifestations for the similar treatment is adopted.

In fact, the research on the difference and correlation between ATC and PSCCT has drawn an increasing attention. However, it is difficult to carry out prospective studies based on large samples due to the rarity. With poor prognosis, these two carcinomas are highly aggressive for human body. Nowadays, though combined treatments including surgery, radiotherapy and chemotherapy are often adopted in clinical

treatment⁶, different studies have figured out that adjuvant therapies exert unclear impact on them^{7,8}. However, the difference of CSS between ATC and PSCCT has not been extensively studied, and it is highly necessary to study the prognostic factors of CSS between ATC and PSCCT.

In order to better understand the demographic and clinical treatment-related indicators of ATC and PSCCT so as to have a difference analysis and explore the prognosis of CSS and its influencing factors, we conducted a retrospective study based on the Surveillance, Epidemiology, and End Results Program (SEER) 18-registry database⁹.

Materials And Methods

Data Source

The study conducted an in-depth analysis on the registered data of The Surveillance, Epidemiology, and End Results Program database and extract data from 18 Regs Custom Data (with additional treatment fields). Nov 2018 Sub (1975-2016 varying) with SEER*Stat 8.3.6. The patient information in this data set has been removed, so this procedure does not involve patient's consent.

Study Population

The carcinoma samples adopted in the study are ATC or PSCCT diagnosed between 2004-2015. We selected samples based on the organizational behavior code in the International Classification of Diseases for Oncology third edition (ICD-O-3) issued by the World Health Organization (WHO) in 2008, in which the histology code of ATC is 8012, 8020, 8021, 8030 -8032, the histological code of PSCCT is 8070-8076, and the primary thyroid location code is C73.9 for all samples. The study included demographic and clinical data related variables, such as the year of diagnosis, patient's age, race, gender, and marital status at diagnosis, whether or not multiple primary carcinoma, surgical status, N stage, M stage, radiotherapy, chemotherapy, survival time, and SEER cause-specific death classification and excluded data where the race survival time was unknown, the surgical status and N stage are Blanks.

Statistical analysis

We adopted chi-square test to analyze count data rate or percentage difference. The destination of this study is the cancer-specific survival (hereinafter referred to as CSS) of ATC and PSCCT. We evaluated the CSS of the two types of thyroid cancer with Kaplan-meier method and evaluated the difference of the CSS with Log-rank method. Single-factor and multi-factor COX regression were used to evaluate the impact of demographic and clinical indicators on the CSS of ATC and PSCCT. Harrel's concordance index (C-index) was used to evaluate research model. We adopted the level of two-sided 0.05 for all p-values. The drawing and statistical calculations in this study were all carried out by R language 3.6.0 (<http://www.r-project.org/>).

Results

Analysis on the difference between demographic and clinical indicators

By selecting, this study included 1288 patients with primary thyroid cancer in SEER database from 2004 to 2015, in which there are 1164 patients with ATC and 124 patients with PSCCT. The difference analysis of demographic and clinical data of ATC and PSCCT is shown in Table 1. The study figured that the prevalence of ATC and PSCCT is mostly concentrated in the elderly, in which the prevalence of females is higher than that of males. However, there is no difference in the distribution of age, gender, race, marital status, and proximal metastasis between the two diseases. Compared with PSCCT patients, ATC patients have a higher proportion of chemotherapy, radiotherapy, surgical conditions, distant metastasis, and multiple primary conditions, thus the difference was statistically significant ($p<0.05$).

Table 1 Analysis on the different demographic and clinical indicators between ATC and PSCCT

Characteristics	ATC	PSCCTh	χ ²	p
Age			0.387	0.534
<65	375	36		
≥65	789	88		
Race			1.261	0.532
Black	97	7		
Other	142	14		
White	925	103		
Sex			0.748	0.387
Female	718	71		
Male	446	53		
Radiation			5.728	0.017
No/Unknown	530	71		
Yes	634	53		
Chemotherapy			4.876	0.027
No/Unknown	683	86		
Yes	481	38		
Sequencenumber			4.792	0.029
One	276	41		
More one	888	83		
Marital			0.018	0.895
Married	632	66		
Other	532	58		
SurgPrimSite			7.771	0.005
No/Unknown	631	84		
Yes	533	40		
N			4.466	0.107
N0	425	48		
N1	566	50		

NX	173	26		
M			19.019	<0.001
M0	557	77		
M1	512	30		
MX	95	17		

Analysis on the CSS difference between ATC and PSCCT

In order to study the CSS prognosis of ATC and PSCCT, we visually presented it and analyzed the difference. After drawing the Kaplan-Meier curve of the study samples, the median survival time of CSS of ATC patients was 4 months, and PSCCT patients was about 10 months. After Log-rank test, it is shown that CSS of PSCCT patients was higher than that of ATC patients. Therefore, the difference is statistically significant ($p < 0.01$) (Figure 1).

Analysis on the influencing factors of CSS of ATC patients

We incorporated relevant variables into the single-factor COX regression model to study the influence of different factors on the prognosis of CSS in patients with ATC. After the single-factor COX model test, compared with the black race, the white race is a protective factor for the CSS of ATC patients ($p < 0.05$). Radiotherapy, chemotherapy, surgery, and married are also its the protective factors. Single primary and unmarried status at the time of diagnosis, distant metastasis, proximal metastasis, and unclear whether there is proximal metastasis to distant metastasis are risk factors. The stepwise multivariate COX model test found that age, gender, radiotherapy, whether chemotherapy is surgery, whether multiple primary, marital status, and distant metastasis are independent prognostic factors for CSS of ATC patients (Table 2). The C-index of the model is 0.803 (95%CI: 0.787-0.819), which shows that the model has a favourable fitting degree.

Table 2 Univariate and multivariate COX analysis of ATC CSS

Characteristics	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Age						
<65	Reference			Reference		
≥65	1.157	0.999-1.339	0.051	1.291	1.109-1.503	<0.001
Race						
Black	Reference					
Other	0.957	0.710-1.290	0.773			
White	0.765	0.601-0.973	0.029			
Sex						
Female	Reference			Reference		
Male	0.891	0.772-1.029	0.118	0.581	0.341-0.992	0.047
Radiation						
No/Unknown	Reference			Reference		
Yes	0.46	0.399-0.531	<0.001	0.55	0.470-0.644	<0.001
Chemotherapy						
No/Unknown	Reference			Reference		
Yes	0.534	0.463-0.617	<0.001	0.655	0.557-0.771	<0.001
Sequencenumber						
More one	Reference			Reference		
One	12.95	8.476-19.790	<0.001	13.937	9.108-21.326	<0.001
Marital						
Married	Reference			Reference		
Other	1.262	1.097-1.451	0.001	1.272	1.102-1.469	0.001
SurgPrimSite						
No/Unknown	Reference			Reference		
Yes	0.434	0.375-0.502	<0.001	0.516	0.443-0.600	<0.001
N stage						
N0	Reference					

N1	1.318	1.128-1.539	<0.001			
NX	1.58	1.275-1.958	<0.001			
M stage						
M0	Reference			Reference		
M1	2.428	2.089-2.823	<0.001	1.991	1.698-2.334	<0.001
MX	1.546	1.176-2.032	0.002	1.202	0.910-1.589	0.195

Analysis on the influencing factors of CSS of PSCCT patients

In order to study the influence of various variables on the CSS of PSCCT patients, we established single-factor and multi-factor COX models for analysis. The single-factor COX test results showed that age, gender, and whether multiple primary or not are the influencing factors of CSS of PSCCT patients, and PSCCT elderly patients, women, and single primary have an unfavourable CSS. The stepwise multi-factor COX model showed that age, radiation therapy, multiple primary conditions, and surgery are independent prognostic factors for CSS of PSCCT patients, and surgery, radiation therapy, and multiple primary conditions are protective factors for CSS of PSCCT patients. Distant metastasis is no longer meaningful in the model, but its test value is close to the test standard (Table 3). The C-index of the model is 0.829, (95%CI: 0.786-0.872), which also shows that the CSS model of PSCCT patients in this study has a favourable fitting degree.

Table3 Univariate and multivariate COX analysis of PSCCT CSS

Characteristics	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Age						
<65	Reference			Reference		
≥65	1.93	1.134-3.286	0.015	2.033	1.141-3.621	0.016
Race						
Black	Reference					
Other	1.021	0.313-3.324	0.973			
White	0.958	0.367-2.644	0.933			
Sex						
Female	Reference					
Male	0.546	0.329-0.905	0.019			
Radiation						
No/Unknown	Reference			Reference		
Yes	0.962	0.607-1.569	0.921	0.529	0.314-0.889	0.016
Chemotherapy						
No/Unknown	Reference					
Yes	1.036	0.638-1.682	0.887			
Sequencenumber						
More one	Reference			Reference		
One	33.64	4.669-242.400	<0.001	48.055	6.593-350.287	<0.001
Marital						
Married	Reference					
Other	1.427	0.890-2.286	0.14			
SurgPrimSite						
No/Unknown	Reference			Reference		
Yes	0.741	0.450-1.218	0.237	0.534	0.318-0.897	0.018
N stage						
N0	Reference					

N1	1.305	0.763-2.234	0.331			
NX	1.276	0.679-2.401	0.449			
M stage						
M0	Reference			Reference		
M1	1.342	0.796-2.265	0.270	1.544	0.883-2.697	0.127
MX	0.977	0.218-1.228	0.135	0.412	0.168-1.007	0.052

Discussion

Both ATC and PSCCT are rare malignant thyroid tumors. The data of this study including 1164 ATC patients and 124 PSCCT patients during 2004-2015 are all adopted from the SEER database. The study showed that compared with PSCCT patients, the median survival time of CSS is better than that of ATC patients, matching highly with existing studies¹⁰. It also confirmed that ATC has a higher proportion of distant metastases, which is in line with the study conducted by scholars like Glaser.

Consistent with previous research results, the proportion of women with ATC and PSCCT is higher than that of men, which may be related to the biological characteristics of the cancer itself^{12, 13}. Because PSCCT is a rare histological type of thyroid cancer and the clinical treatment experience is limited, its treatment is controversial. At present, the treatment methods of PSCCT and ATC are similar, and most of them are chemotherapy, radiotherapy, and surgery. However, the treatment rate of ATC is higher than that of PSCCT. The reason is that compared with PSCCT, ATC has clear histology and positioning¹⁰.

Age is an influencing factor of the CSS of ATC patients, for example the CSS of patients older than 65 years old is less than that of patients younger than 65 years old, which has been confirmed by the study conducted by researchers like Gui. Studies conducted by Smallridge and other scholars have proven that for early patients diagnosed with ATC, surgical treatment, chemotherapy, radiotherapy and systemic treatment can achieve the optimal survival goals for patients, and active palliative care and clinical care for patients with terminal ATC are also important components for achieving the optimal survival goals¹⁶. Relevant studies^{17, 18} have confirmed that gender, surgical treatment, radiotherapy and chemotherapy are all prognostic factors of the CSS of ATC patients, which are consistent with the results of this study. This study showed that marital status is an influencing factor for the CSS of ATC patients. Many studies have suggested that various family care and psychological care in different marital status cause different survival conditions of patients^{19, 20}.

Our study confirms that PSCCT is more likely to occur in elderly female patients since age is an independent factor, but gender and race are not. Radiotherapy is a protective factor for the CSS of PSCCT patients, which is echoed by related studies²¹. Shimaoka's²¹ case study suggested that chemotherapy plays an active role in the treatment of PSCCT, but in this study chemotherapy is not an influencing factor for the CSS of PSCCT patients. Surgical treatment is also an independent factor for the CSS of PSCCT

patients. Studies figured that the best treatment for PSCCT is early diagnosis and then aggressive surgery to prevent bleeding or suffocation caused by obstruction²³. Different from the CSS of ATC patients, marital status is not an influencing factor for the CSS of PSCCT patients. Studies conducted by scholars like AU⁷ found that surgery, radiotherapy, and combined surgery and radiotherapy are not influencing factors for the CSS of PSCCT patients. This is different from the results of this study, which may have something to do with the surgical and radiation method. This study shows that surgical treatment is a protective factor for the CSS of PSCCT patients. In this study, the distant metastasis variables in the model were statistically tested to close the limits. The HR value of multiple primary cases is larger, which may be caused by limited amount of samples in addition to the actual effect of the variables.

By the comparison between the survival rates of patients with single primary and multiple primary cancers, Amer²⁴ found that the overall survival rate of patients with multiple primary cancers is higher than that of single primary cancers. This may be related to the characteristics of thyroid cancer for the survival time of many types of cancer patients is not long enough to develop to the second origin. Studies conducted by researchers like Lin¹⁷ showed that although the OS of patients with multiple primary thyroid cancer is much lower than that of single primary thyroid cancer, there is no difference between their CSS. This study figured that multiple primary cancers are a protective factor for the CSS of patients with ATC and PSCCT, which does not mean that the mortality rate of single primary thyroid cancer is lower. This may be because the mortality rate of other cancers in multiple primary patients is higher than that caused by thyroid cancer.

This is the first study on CSS of ATC and PSCCT patients based on a large population cohort. Both ATC and PSCCT are aggressive thyroid malignancies, and the CSS prognosis of PSCCT patients is favourable than that of ATC patients. We have established prognostic models of CSS for patients with ATC and PSCCT respectively. The prognostic factors of the two are not exactly the same, which means although the histological manifestations of ATC and PSCCT are similar to the current treatment plan, the clinical treatment and management plans need to be targeted for different type of diseases.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

SJ and YNY contributed to the conception and design of the study. SJ collected and analyzed data. DHL and DDP wrote the manuscript; All authors reviewed and approved the final version of the manuscript.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Study data was publicly available in the SEER database.

Competing interests

The authors declare that they have no competing interest.

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Figures

Cancer-Specific Survival

Type — ATC — PSCCT

Figure 1

In order to study the CSS prognosis of ATC and PSCCT, we visually presented it and analyzed the difference. After drawing the Kaplan-Meier curve of the study samples, the median survival time of CSS of ATC patients was 4 months, and PSCCT patients was about 10 months. After Log-rank test, it is shown that CSS of PSCCT patients was higher than that of ATC patients. Therefore, the difference is statistically significant ($p < 0.01$) (Figure 1).