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Prognosis of a rare subtype of thyroid cancer

Spindle cell thyroid carcinoma

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Abstract

Systemic illustrations of spindle cell thyroid cancer (SCTC), based on a large cohort, are few. We investigated the prognosis of SCTC compared to the most common subtypes, papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC).

Information of patients with a diagnosis of SCTC, PTC, or FTC, between 2004 and 2013, was obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Patient survival curves were investigated using Kaplan–Meier analyses, log-rank tests, and Cox proportional hazards regression analyses.

In a Kaplan–Meier analysis of the entire cohort of thyroid cancer patients, cancer specific survival declined sharply for patients with SCTC, but declined more modestly for patients with PTC and FTC. Unadjusted Cox regression analysis and Kaplan–Meier curve analysis showed that SCTC had a poorer cancer-specific mortality and all-cause mortality compared to PTC and FTC. Similar results were obtained after adjustment for different confounding factors.

Our study assessed the prognosis of SCTC, based on a large cohort, compared to PTC and FTC, and found relatively accurate hazard ratios of death rate in SCTC as compared to PTC and FTC. Thus, our findings would provide beneficial insights on patients with SCTC, and aid in treatment decision making, more radical treatment like total-thyoridectomy and/or plus central lymph node dissection should be performed for patients with SCTC.

Abbreviations: FTC = follicular thyroid cancer, PTC = papillary thyroid cancer, SCTC = spindle cell thyroid cancer, SEER = Surveillance, Epidemiology, and End Results.

Keywords: hazard ratios, prognosis, SEER, spindle cell thyroid cancer

1. Introduction

Thyroid cancer is the most common endocrine malignancy, and the incidence rate of thyroid cancer has been continuing to rise rapidly in recent decades.[1–5] Thyroid cancer consists of several histological variants, and the common subtypes consist of papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), medullary thyroid cancer, and anaplastic thyroid cancer. Thyroid cancer also consists of many other rare subtypes, including Hürthle cell thyroid cancer, insular thyroid cancer, and spindle cell thyroid cancer.[6–10]

Spindle cell thyroid carcinoma (SCTC) is a rare type of squamous cell carcinoma; it originates in poorly differentiated elongated epithelial cells that features as a sarcoma-like proliferation.[10,11] Spindle cell carcinoma is found in the head and neck region including the larynx, tongue, nasal cavity, and thyroid.[10–16]

Most previous publications focus on cases reports that represent individual features of SCTC patients.[17–20] Systemic illustration based on a large cohort is few. Therefore, to find out the accurate hazard ratio (HR) for cancer specific mortality and all-cause mortality of this rare subtype, we analyzed the prognosis of SCTC in comparison to the most common subtypes, PTC and FTC, based on the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.

2. Materials and methods

2.1. Ethics statement and database

This investigation has been conducted in accordance with the ethical standards, according to the Declaration of Helsinki, and according to national and international guidelines. It has been approved by the review board of our Hospital. We investigated SCTC, PTC, and FTC in a large cohort of patients from SEER. The SEER project is supported by the National Cancer Institute and the Centers for Disease Control and Prevention and it is a United States population-based cancer registry that began in 1973. It covers approximately 30% of the population of the United States with containing data of incidence, prevalence, mortality across multiple geographic regions.

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2.2. Data collection and analysis

Patients were examined from SEER database for 2004 to 2013 with a diagnosis of STC (n=98), PTC (n=143439) and FTC (n=12054) as defined by a combination of ICD-O site code of C73.9 (i.e., thyroid) from the International Classification of Diseases for Oncology (3rd edition). The following diagnostic codes were included in the study: "papillary carcinoma," "papillary adenocarcinoma," "spindle cell carcinoma", "follicular adenocarcinoma," "papillary carcinoma, follicular variant," and "papillary and follicular adenocarcinoma," Demographic information, age, sex, tumor size, extrathyroidal extension, multifocality, nodal metastasis, distant metastasis, surgical treatment, and radiation treatment were compiled from the SEER dataset, and a survival analysis was performed to evaluate the associations between different subtypes and prognosis.

2.3. Statistical analysis

All included patients were followed up until December 2013. The quantitative variables were expressed as mean ± standard deviation (SD), while the categorical ones were presented as percentages. The outcomes measures were thyroid carcinoma-specific mortality and all-cause mortality. Patient survival curves were investigated using Kaplan–Meier analyses, log-rank tests, and Cox proportional hazards regression analyses. HRs were used to show the magnitude of the effect of different histological subtypes on cancer-specific mortality, all-cause mortality. Around 95% CIs were used to indicate the significance of the risks. All *P* values were 2-sided and *P* <.05 was regarded as indicating statistical significance. Analyses were performed using SPSS version 23.0 (IBM Corp, Armonk, NY), Stata/SE version 12 (Stata Corp, College Station, TX), and GraphPad Prism version 6 (GraphPad Software Inc, La Jolla, CA).

3. Results

3.1. Demographic and clinical features

The baseline characteristics (demographic data, clinicopathological features, and treatment) were compared between SCTC, and PTC, FTC (Table 1). The mean durations of survival during the study period were 19.39, 97.1, 2 and 123.79 months for SCTC, PTC, and FTC, respectively. Mean age was higher in patients with SCTC than with PTC (69.09 ± 14.09 vs 48.14 ± 15.66 years, *P* < .001) and FTC (69.09 ± 14.09 vs 50.64 ± 17.61 years, *P* < .001, Table 1).

3.2. Cancer-specific and all-cause mortality rates for different histological subtypes

In the study cohort, the cancer-specific mortality rate, per 1000 person-years, for SCTC, PTC, and FTC were 410.526 [95% confidence interval (CI), 321.931–523.504], 2.336 (95% CI, 2.249–2.425), and 6.031 (95% CI, 5.612–6.481), respectively (Table 2). The all-cause mortality, per 1000 person-years, in patients with SCTC, PTC, and FTC were 486.315 (95% CI, 388.969–608.025), 12.374 (95% CI, 12.173–12.579) and 22.347 (95% CI, 21.528–23.198), respectively (Table 2).

On comparing PTC and FTC versus SCTC patients, the HRs for cancer-specific deaths were 0.008 (95% CI, 0.007–0.011) and 0.024 (95% CI, 0.019–0.031), respectively. After adjustment for demographic data: age at diagnosis, race, gender, the HRs for cancer-specific deaths of PTC and FTC were 0.007 (95% CI,

Table 1

Characteristics for patients with different histological types.

Covariate	Level	Histological types				
		SCTC (n=98)	PTC (n=143439)	*P* value	FTC (n=12054)	P value
Age, years		69.09 ± 14.09	48.14 ± 15.66	<.001	50.64 ± 17.61	<0.001
Sex	Female	56(57.1%)	110167(76.8%)	<.001	8610(71.4%)	0.002
	Male	42(42.9%)	33272(23.2%)		3444(28.6%)	
Race	White	81(83.5%)	117863(83.1%)	.067	9423(79.0%)	0.429
	Black	10(10.3%)	8299(5.8%)		1316(11.0%)	
	Other	6(6.2%)	15731(11.1%)		1192(10.0%)	
T stage	T1	0(0.0%)	55793(62.4%)	<.001	1288(23.8%)	<0.001
	T2	0(0.0%)	13823(15.4%)		2174(40.2%)	
	T3	0(0.0%)	16412(18.3%)		1753(32.4%)	
	T4	37(100.0%)	3467(3.9%)		194(3.6%)	
N-stage	N0	19(67.9%)	69704(79.1%)	.145	5380(97.0%)	<0.001
	N1	9(32.1%)	18466(20.9%)		169(3.0%)	
M-stage	M0	19(52.8%)	89903(98.8%)	<.001	5387(94.2%)	<0.001
	M1	17(47.2%)	1138(1.2%)		331(5.8%)	
Multifocality	No	19(65.5%)	52542(58.4%)	.439	4745(85.6%)	0.002
	Yes	10(34.5%)	37379(41.6%)		799(14.4%)	
Extension	No	8(21.6%)	76237(83.7%)	<.001	5124(90.5%)	<0.001
	Yes	29(78.4%)	14853(16.3%)		541(9.5%)	
Radiation	None or refused	33(34.4%)	74802(54.0%)	<.001	6142(54.0%)	<0.001
	Radiation Beam or Rdioactive implants	61(63.5%)	3495(2.5%)		502(4.4%)	
	Radioisotopes or Radiation beam plus isotopes or implants	2(2.1%)	60191(43.5%)		4735(41.6%)	
Surgery	Lobectomy	15(48.4%)	17295(15.2%)	<.001	1903(25.3%)	0.012
	Subtotal or near-total thyroidectomy	2(6.4%)	5456(4.8%)		472(6.3%)	
	Total thyroidectomy	14(45.2%)	90881(80.0%)		5133(68.4%)	
Survival months, month		19.39 ± 57.08	97.12 ± 92.28	<.001	123.79 ± 112.35	<0.001

FTC=follicular thyroid carcinoma, PTC=papillary thyroid cancer, SCTC=Spindle cell thyroid carcinoma.

Table 2

Hazard Ratios of different histological types for the cancer specific deaths and all cause deaths of thyroid cancer.

Histological types	Cancer-specific deaths, No.	%	Cancer-specific deaths per 1000 person-years	95% CI	All cause deaths, No.	%	All cause deaths per 1000 person-years	95% CI
SCTC	77	78.57	410.526	321.931–523.504	90	91.83	486.315	388.969–608.025
PTC	2798	1.95	2.336	2.249–2.425	15842	11.04	12.374	12.173–12.579
FTC	787	6.53	6.031	5.612–6.481	2957	24.53	22.347	21.528–23.198

FTC = follicular thyroid carcinoma, PTC = papillary thyroid cancer, SCTC = Spindle cell thyroid carcinoma.

0.001–0.054), 0.085 (95% CI, 0.046–0.159), respectively compared to SCTC patients. Furthermore, after adjustments for demographic data and clinicopathological risk factors (Tumor, Node, Metastasis (TNM) stage, multifocality, extension), compared to SCTC, the HRs for cancer-specific deaths of PTC and FTC were 0.009 (95% CI, 0.000–0.866) and 0.143 (95% CI, 0.040–0.517), respectively. After adjustment for demographic data, clinicopathological risk factors and treatments (radiation, surgical approaches), the HRs for cancer-specific deaths of PTC and FTC were 0.097 (95% CI, 0.012–0.808) and 0.010 (95% CI, 0.000–5.225), respectively, compared to SCTC patients (Table 3).

Comparing PTC and FTC vs. SCTC patients, the HR for all-cause deaths were 0.029 (95% CI, 0.023–0.035) and 0.056 (95% CI, 0.045–0.069), respectively. After adjustments for demographic data, age at diagnosis, race, and gender, the HRs for cancer-specific deaths of PTC and FTC were 0.065 (95% CI, 0.035–0.124), 0.149 (95% CI, 0.095–0.235), respectively compared to SCTC patients. Furthermore, after adjustments for demographic data and clinicopathological risk factors (TNM stage, multifocality, extension), the HRs for cancer-specific deaths of PTC and FTC were 0.037 (95% CI, 0.005–0.288) and 0.145 (95% CI, 0.047–0.448), respectively, compared to SCTC patients. In addition, after adjustment for demographic data, clinicopathological risk factors, and treatments (radiation, surgical approaches), the HRs for cancer-specific deaths of PTC and FTC were 0.087 (95% CI, 0.011–0.710) and 0.081 (95% CI, 0.010–0.660), respectively, compared to SCTC patients (Table 4).

3.3. Kaplan–Meier survival analysis of patients with different subtypes of thyroid cancer

In a Kaplan–Meier analysis of the entire cohort of thyroid cancer patients, cancer specific survival declined sharply for patients with SCTC, but declined more modestly for patients with PTC and FTC (Log-rank test, $P < .001$) (Fig. 1). Similar results were observed for all-cause survival data; patients with SCTC showed a sharp decline while patients with PTC and FTC showed a more modest decline in all-cause survival (log-rank test, $P = .005$) (Fig. 2).

4. Discussion

Histologically, spindle cells have a fusiform appearance and are always arranged with the intersecting fascicles.[15] Spindle cell tumors of the thyroid gland are rare. Due to the rarity of the tumors, the cell biology and prognosis of spindle cells in thyroid gland tumors are not fully understood. In previous case reports, most scholars support the fact that the spindle cells of the thyroid glands may represent a metaplastic transformation of the follicular cells because of to the expression of thyroglobulin.[15,20,21]

Table 3

Risk factors for survival: outcome of thyroid cancer specific mortality.

Histological types	Unadjusted Cox regression		Adjusted 1* Cox regression		Adjusted 2# Cox regression		Adjusted 3† Cox regression	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
SCTC	Ref		Ref		Ref		Ref	
PTC	0.008 (0.007–0.011)	<.001	0.007 (0.001–0.054)	<.001	0.009 (0.000–0.866)	.043	0.097 (0.012–0.808)	.031
FTC	0.024 (0.019–0.031)	<.001	0.085 (0.046–0.159)	<.001	0.143 (0.040–0.517)	.003	0.010 (0.000–5.225)	.150

FTC = follicular thyroid carcinoma, PTC = papillary thyroid cancer, SCTC = spindle cell thyroid carcinoma.
* Adjustment 1 was made for patient age at diagnosis, race, gender.
# Adjustment 2 was made for patient age at diagnosis, race, gender, T/N/M stage, multifocality, extension.
† Adjustment 3 was made for patient age at diagnosis, race, gender, T/N/M stage, multifocality, extension, radiation and surgery treatment.

Table 4

Risk factors for survival: outcome of all-cause mortality.

Histological types	Unadjusted Cox regression		Adjusted 1* Cox regression		Adjusted 2† Cox regression		Adjusted 3‡ Cox regression	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
SCTC	Ref		ref		Ref		Ref	
PTC	0.029 (0.023–0.035)	<.001	0.065(0.035–0.124)	<.001	0.037 (0.005–0.288)	.002	0.087 (0.011–0.710)	.023
FTC	0.056 (0.045–0.069)	<.001	0.149 (0.095–0.235)	<.001	0.145 (0.047–0.448)	.001	0.081 (0.010–0.660)	.019

FTC = follicular thyroid carcinoma, PTC = papillary thyroid cancer, SCTC = spindle cell thyroid carcinoma.
* Adjustment 1 was made for patient age at diagnosis, race, and gender.
† Adjustment 2 was made for patient age at diagnosis, race, gender, T/N/M stage, multifocality, extension.
‡ Adjustment 3 was made for patient age at diagnosis, race, gender, T/N/M stage, multifocality, extension, radiation, and surgery treatment.

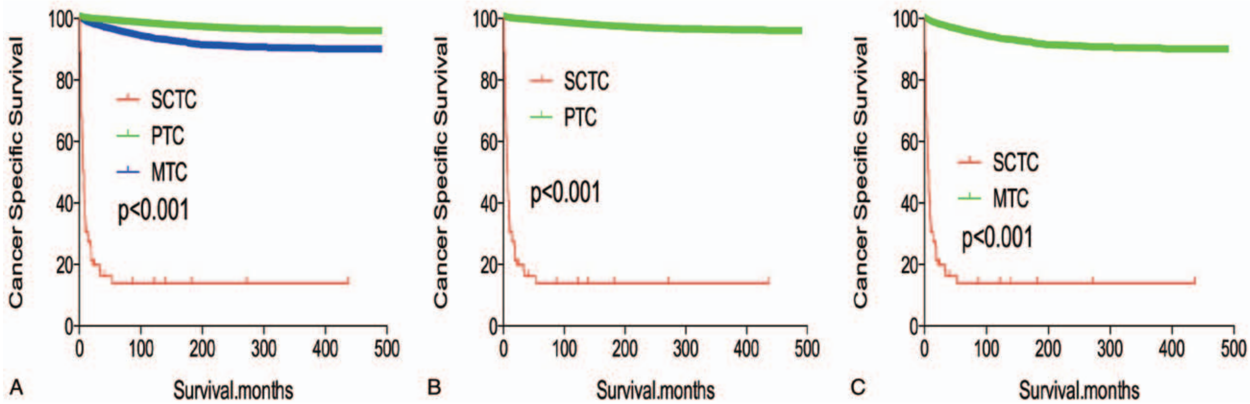

Figure 1. Kaplan–Meier curves among patients stratified by subtype for cancer-specific survival (A–C).

Sophie et al. have reported a spindle cell follicular carcinoma of the thyroid gland and suggested that more clinical, histopathological, molecular, and prognostic studies of spindle cell thyroid cancer are needed for a better comparison with the more conventional thyroid tumors.[15] However, until now, there are no systematic descriptions of SCTC due to the small number cases from single institutions.

In this study, however, we collected and included a large cohort of patients with SCTC from the SEER database. This made up for the deficiency of small sample size. In our study, SCTC presents with aggressive clinicopathological characteristics compared to PTC and FTC. TNM system for stage and extension, Cox regression analysis, and Kaplan Meier curve analysis showed that SCTC had a poorer cancer-specific mortality and all-cause mortality compared to PTC and FTC.

In our study, we found similar results, even after excluding the confounding factors. For all-cause mortality, after adjustment of demographic data, clinicopathological features, and treatment approaches, patients with SCTC still had poorer prognosis than those with PTC and FTC. Regarding all-cause deaths, SCTC showed poorer prognosis than PTC after adjustment for different variants. However, the difference in values between SCTC and FTC, after adjustments for all confounding factors (including treatment), reduced. This may due to the varied sample status and the large 95% CI span.

One interesting finding was that 1000 person-years cancer-specific deaths and 1000 person-years all-cause deaths of SCTC had similar values (410.526 vs. 486.315), indicating that mortality of patients with SCTC was mostly due to cancer-specific reasons and not other causes such as nephrotic syndrome, and diseases of the heart, lung and bronchus. In other words, SCTC is an aggressive malignancy that could directly cause mortality itself without the role of other factors.

Molecular makers play an important role in diagnosis and prognosis of thyroid cancers.[21–25] Cytological examination of fine-needle aspiration biopsy is often misdiagnosed.[17] However, molecular markers help in distinguishing the histological subtypes. For example, high Mib-1 proliferation index, elevated levels of circulating serotonin and chomogranin-A, and p53 positivity favors the diagnosis of malignancies of epithelial origin,[17,26] but CD34, S-100, and calcitonin are often absent in spindle cells.[21] Unfortunately, the SEER database could not record data for these molecular markers in spindle cell thyroid cancer; therefore, systematic molecular mechanisms still need to be confirmed in future works.

This study has some limitations worth mentioning, though multivariate analysis was performed to account for confounding factors. First, overestimation bias may have been introduced by designation of only mortality rates, and a lack of data on recurrence. Furthermore, molecular markers such as thyroid

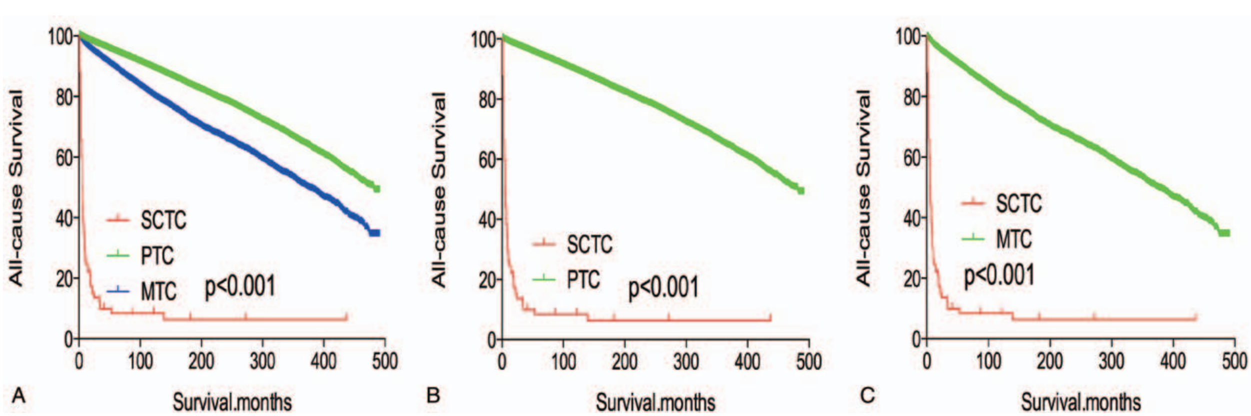

Figure 2. Kaplan–Meier curves among patients stratified by subtype for all-cause survival (A–C).

transcription factor-1, cytokeratin 19, and CD34 antigen, which may play an important role in assessment of diagnosis and prognosis of SCTC,[15,21] were not evaluated in this study. In addition, as the SEER database focuses on gathering reliable information during the diagnostic period, limited information was available on later events.

To summarize, our study, based on a large cohort, assessed the prognosis of SCTC in comparison to PTC and FTC, and found relatively accurate hazard ratios of death rate in SCTC as compared to PTC and FTC. Thus, our findings would provide beneficial insights on patients with SCTC, and aid in treatment decision-making, more radical treatment like total-thyoridectomy and/or plus central lymph node dissection should be performed for patients with SCTC.

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