Small Cell Carcinoma: a Rare Subtype of Thyroid Cancer with Unanticipated Prognosis

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Summary: The prognosis of small cell thyroid carcinoma (SCTC) in a large cohort has not been well reported in the literature. In this study, we analyzed the mortality of SCTC, in comparison to medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC), based on the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, to determine the prognosis of SCTC. Information regarding patients with a diagnosis of MTC, ATC, or SCTC, between 2004 and 2013, was acquired from the SEER database. Patient survival curves were assessed by Cox proportional hazards regression analyses, Kaplan-Meier analyses, and log-rank tests. In a Kaplan-Meier analysis of the entire cohort of thyroid cancer patients, cancer-specific survival declined sharply for patients with SCTC, but it declined more modestly for patients with MTC. The cancer-specific survival was not significantly different between SCTC and ATC. Unadjusted Cox regression analysis showed that SCTC had a higher cancer-specific mortality than MTC but a similar prognosis as ATC. SCTC showed a higher cancer-specific mortality than MTC and ATC after adjustments for various confounding factors. SCTC was found to have a more highly lethal clinical course than MTC and had a similar death rate to ATC. Therefore, we recommend that aggressive, radical treatment like surgery or radiation should be performed for these patients.
Key words: small cell carcinoma; medullary thyroid cancer; anaplastic thyroid cancer

The incidence of thyroid cancer has been increasing, as reported by a number of researchers[1–4]. Regardless of whether this increase in cancer incidence has resulted from a real increase in occurrence or increased diagnostic scrutiny, thyroid cancer is attracting more and more attention from surgeons and endocrine clinicians.

Beyond the four common subtypes of thyroid cancer, i.e., papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC), there are still some rare histological types with specific biological features, including tall cell thyroid cancer, oxyphilic cell thyroid cancer, and large cell thyroid cancer[5–14].

A unique presentation of the prognosis of small cell thyroid carcinoma (SCTC), in a large cohort, has not been well reported in the literature. Small cell tumors of thyroid have been claimed to be lymphomas and anaplastic small cell carcinomas just once[15]. For now, only a few case reports attempt to demonstrate the biological behavior of SCTC[15–21]. To address this issue, this study compared the mortality of SCTC to that of MTC and ATC, based on the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, to determine the prognosis of SCTC.

1 MATERIALS AND METHODS

1.1 Ethics Statement and Database

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

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that began in 1973.

1.2 Data Collection and Analysis

Patients were identified from the SEER database for 2004–2013 with a diagnosis of SCTC, MTC, or ATC, as defined by a combination of the ICD-O site code C73.9 (i.e., thyroid) from the International Classification of Diseases for Oncology (3rd edition). The following diagnostic codes were included in the study: "8002/3: Malignant tumor, small cell type", "8041/3: Small cell carcinoma", "8510/3: Medullary carcinoma", "8021/3: Carcinoma, anaplastic", and "8020/3: Carcinoma, undifferentiated". 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.

1.3 Statistical Analysis

The quantitative variables were expressed as the mean±standard deviation (SD), and the categorical ones were presented as percentages. The outcome 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. Hazard ratios (HRs) were used to show the magnitude of the effect of different histological subtypes (SCTC, MTC, and ATC) on cancer-specific mortality and all-cause mortality. Ninety-five percent confidence intervals (CIs) were used to indicate the significance of the risks. All *P* values were two-sided, and *P* value less than 0.05 was regarded as statistical significance. Analyses were performed using SPSS version 23.0 (IBM Corp, USA), Stata/SE version 12 (Stata Corp, College Station, USA), and GraphPad Prism version 6 (GraphPad Software Inc., USA).

2 RESULTS

2.1 Demographic and Clinical Features

All included patients were followed up until December 2013. The baseline characteristics (demographic data, clinicopathological features, and treatment) were compared among SCTC, MTC, and ATC (table 1). The mean survival durations during the study period were 16.91, 46.80, and 20.70 months for SCTC, MTC, and ATC, respectively. The mean age of patients with SCTC was similar to that of patients with PTC (66.79±14.20 *vs.* 55.35±17.23 years, *P*=0.601) and that of patients with ATC (66.79±14.20 *vs.* 64.83±17.18 years, *P*=0.981, table 1).

2.2 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, MTC, and ATC was 354.740 (95% CI, 246.516–510.474), 45.474 (95% CI, 41.486–49.846), and 270.124 (95% CI, 254.195–287.050), respectively (table 2). The all-cause mortality, per 1000 person-years, in patients with SCTC, MTC, and ATC was 599.388 (95% CI, 453.010–793.064), 80.378 (95% CI, 75.017–86.124) and 329.862 (95% CI, 312.211–348.512), respectively (table 2).

For the comparisons of MTC *vs.* SCTC and ATC *vs.* SCTC, the HRs for cancer-specific deaths were 0.173 (95% CI, 0.123–0.241) and 0.900 (95% CI, 0.649–1.248), respectively (table 3). After adjusting for demographic data (age at diagnosis, race, and gender), the HRs for cancer-specific death of MTC and ATC, compared to SCTC, were 0.237 (95% CI, 0.169–0.331) and 1.108 (95% CI, 0.798–1.536), respectively. Furthermore, after adjusting for demographic data and clinicopathological risk factors [tumor, node, metastasis (TNM) stage; multifocality; extension], compared to SCTC, the HRs for cancer-specific death of MTC and ATC were 0.087 (95% CI, 0.027–0.284) and 0.210 (95% CI, 0.065–0.681), respectively. After adjusting for demographic data, clinicopathological risk factors, and treatment (radiation and surgical approaches), the HRs for cancer-specific death of MTC and ATC, compared to SCTC, were 0.067 (95% CI, 0.020–0.228) and 0.209 (95% CI, 0.0.062–0.710), respectively (table 3).

For the comparisons of MTC *vs.* SCTC and ATC *vs.* SCTC patients, the HRs for all-cause death were 0.179 (95% CI, 0.137–0.234) and 0.673 (95% CI, 0.518–0.875), respectively (table 4). After adjusting for demographic data (age at diagnosis, race, and gender), the HRs for all-cause death of MTC and ATC, compared to SCTC, were 0.257 (95% CI, 0.196–0.336) and 0.880 (95% CI, 0.675–1.147), respectively. Furthermore, after adjusting for demographic data and clinicopathological risk factors (TNM stage, multifocality, and extension), the HRs for all-cause death of MTC and ATC, compared to SCTC, were 0.088 (95% CI, 0.027–0.282) and 0.168 (95% CI, 0.052–0.536), respectively. In addition, after adjusting for demographic data, clinicopathological risk factors, and treatment (radiation and surgical approaches), the HRs for all-cause death of MTC and ATC, compared to SCTC, were 0.059 (95% CI, 0.018–0.195) and 0.140 (95% CI, 0.042–0.460), respectively (table 4).

2.3 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 MTC (Log-rank test, *P*<0.001) (fig. 1). Cancer-specific survival was not significantly different between SCTC and ATC (Log-rank test, *P*=0.767) (fig. 1). For all-cause survival data,

Table 1 Characteristics for patients with different histological types

Characteristics	Histological types				
	SCTC (*n*=58)	MTC (*n*=2571)	*P* value	ATC (*n*=2231)	*P* value
Age (year)	66.79±14.20	55.35±17.23	0.601	64.83±17.18	0.981
Sex					
Female	32 (55.2%)	1440 (56.0%)	0.899	1466 (65.7%)	0.096
Male	26 (44.8%)	1131 (44.0%)		765 (34.3%)	
Race					
White	48 (84.2%)	2189 (86.1%)		1820 (82.1%)	
Black	4 (7.0%)	208 (8.2%)	0.599	146 (6.6%)	0.828
Other	5 (8.8%)	145 (5.7%)		252 (11.4%)	
T stage					
T1	0 (0.0%)	844 (45.4%)		220 (16.4%)	
T2	0 (0.0%)	443 (23.8%)	<0.001	62 (4.6%)	0.722
T3	1 (20.0%)	404 (21.7%)		215 (16.1%)	
T4	4 (80.0%)	169 (9.1%)		844 (62.9%)	
N-stage					
N0	2 (50.0%)	1160 (62.4%)	0.608	697 (57.0%)	0.778
N1	2 (50.0%)	698 (37.6%)		526 (43.0%)	
M-stage					
M0	3 (42.9%)	1777 (90.9%)	<0.001	974 (70.0%)	0.118
M1	4 (57.1%)	177 (9.1%)		417 (30.0%)	
Multifocality					
No	1 (20.0%)	1307 (70.1%)	0.015	915 (71.9%)	0.010
Yes	4 (80.0%)	558 (29.9%)		358 (28.1%)	
Extension					
No	2 (40.0%)	1547 (81.9%)	0.015	512 (37.9%)	0.924
Yes	3 (60.0%)	342 (18.1%)		838 (62.1%)	
Radiation					
None or refused	25 (45.5%)	2031 (81.1%)		915 (42.1%)	
Radiation beam or radioactive implants	30 (54.5%)	345 (13.8%)	<0.001	894 (41.2%)	0.003
Radioisotopes or radiation beam plus isotopes or implants	0 (0.0%)	127 (5.1%)		362 (16.7%)	
Surgery					
Lobectomy	0 (0.0%)	164 (8.1%)		276 (23.9%)	
Subtotal or near-total thyroidectomy	1 (20.0%)	49 (2.4%)	0.035	93 (8.1%)	0.337
Total thyroidectomy	4 (80.0%)	1808 (89.5%)		785 (68.0%)	
Survival time (month)	16.91±23.94	46.80±34.37	0.081	20.70±31.14	0.219

SCTC: small cell thyroid cancer; MTC: medullary thyroid cancer; ATC: anaplastic thyroid cancer

Table 2 Hazard ratios of different histological types for the cancer-specific mortality and all-cause mortality of thyroid cancer

Histological types	Cancer-specific deaths, *n*	%	Cancer-specific deaths, per 1000 person-years	95% CI	All-cause deaths, *n*	%	All-cause deaths, per 1000 person-years	95% CI
SCTC	37	63.79	354.740	246.516–510.474	58	100.00	599.388	453.010–793.064
MTC	477	18.55	45.474	41.486–49.846	844	32.82	80.378	75.017–86.124
ATC	1298	58.18	270.124	254.195–287.050	1587	71.13	329.862	312.211–348.512

SCTC: small cell thyroid cancer; MTC: medullary thyroid cancer; ATC: anaplastic thyroid cancer

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	
MTC	0.173 (0.123–0.241)	<0.001	0.237 (0.169–0.331)	<0.001	0.087 (0.027–0.284)	<0.001	0.067 (0.020–0.228)	<0.001
ATC	0.900 (0.649–1.248)	0.528	1.108 (0.798–1.536)	0.541	0.210 (0.065–0.681)	0.009	0.209 (0.0.062–0.710)	0.012

SCTC: small cell thyroid cancer; MTC: medullary thyroid cancer; ATC: anaplastic thyroid cancer.
Adjusted 1 Cox regression: cox regression for age, sex and race matched subtype pairs; Adjusted 2 Cox regression: cox regression for age, sex, race, T/N/M stage, multifocality and extension matched subtype pairs; Adjusted 3 Cox regression: cox regression for age, sex, race, T/N/M stage, multifocality, extension, surgery and radiation treatment matched subtype pairs

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	
MTC	0.179 (0.137–0.234)	<0.001	0.257 (0.196–0.336)	<0.001	0.088 (0.027–0.282)	<0.001	0.059 (0.018–0.195)	<0.001
ATC	0.673 (0.518–0.875)	0.003	0.880 (0.675–1.147)	<0.344	0.168 (0.052–0.536)	0.003	0.140 (0.042–0.460)	0.001

SCTC: small cell thyroid cancer; MTC: medullary thyroid cancer; ATC: anaplastic thyroid cancer.
Adjusted 1 Cox regression: cox regression for age, sex and race matched subtype pairs; Adjusted 2 Cox regression: cox regression for age, sex, race, T/N/M stage, multifocality and extension matched subtype pairs; Adjusted 3 Cox regression: cox regression for age, sex, race, T/N/M stage, multifocality, extension, surgery and radiation treatment matched subtype pairs

patients with SCTC showed a sharp decline, while patients with MTC and ATC showed more modest declines in all-cause survival (Log-rank test, $P<0.001$, $P=0.012$, respectively) (fig. 2).

3 DISCUSSION

The existence of "true" small cell carcinomas of the thyroid has been a major issue of debate for years[15]. The small cell phenotype can manifest as poorly differentiated carcinoma and lymphoma. Squamous cell carcinomas, primary small cell neuroendocrine carcinomas, neuroblastomas, and basaloid neoplasms with solid cell nest features may also present a small cell phenotype[22, 23]. Therefore, for problems in differential diagnosis, Eloy *et al* suggested that when facing a small cell tumor of the thyroid, lymphoma should be first distinguished from carcinoma and other nonlymphoid/nonepithelial tumors, and then neuroendocrine features should be checked for; lastly, primary tumors should be separated from metastatic tumors[15].

In this study, we focused on the prognosis of SCTC from the SEER database and found an unexpected finding: SCTC presents a similar cancer-specific mortality to ATC and a higher all-cause mortality than ATC, and SCTC has a poorer prognosis (both cancer-specific mortality and all-cause mortality) than MTC, based on Kaplan-Meier analysis.

Clinicopathological features such as TNM stage, multifocality, and extension play important roles in the prognosis of thyroid cancer[12]. In comparison of the prognosis for different phenotypes of thyroid cancer, after adjusting for clinicopathological factors, ATC showed a lower HR than SCTC. Therefore, SCTC may

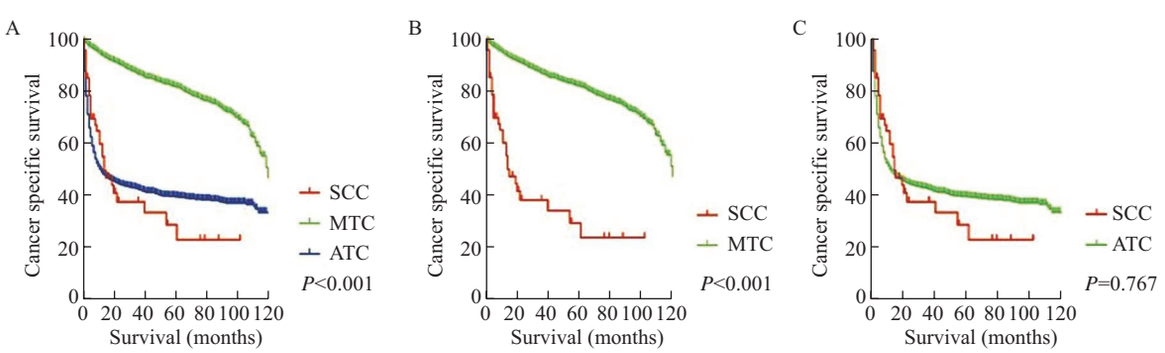

Fig. 1 Kaplan Meier curves among patients stratified by subtype for cancer-specific mortality (A, B, C)

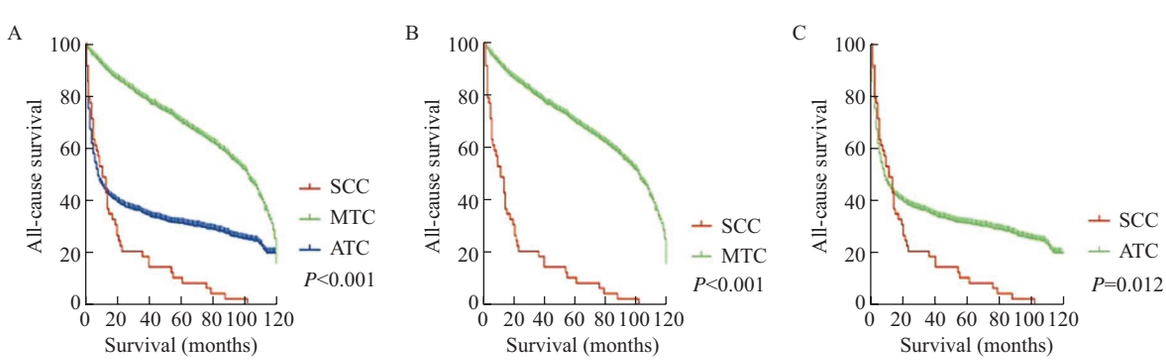

Fig. 2 Kaplan Meier curves among patients stratified by subtype for all-cause mortality (A, B, C)

be one of the poorest histological types among thyroid cancers[24].

The diagnosis of neuroendocrine tumors is made based on distinct morphological features along with characteristic cell markers. Beach *et al* reported a case of small cell carcinoma that was similar to medullary thyroid cancer, because it positively expressed CD56, synaptophysin and chromogranin[21]. In this study, however, such information was lacking because all data were from the SEER database.

There are some limitations worth mentioning in our research, even though multivariate analysis was performed to account for confounding factors. First, overestimation bias may have been introduced by the designation of only mortality rates, because the SEER database used in our study lacks data on recurrence. Furthermore, molecular markers, which play an important role in the diagnosis and prognosis of thyroid cancers, 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 regarding later events.

In summary, SCTC was found to have a more highly lethal clinical course than MTC and had a similar rate of death events as ATC. Therefore, we recommend that aggressive and radical treatment, like surgery or radiation, should be performed for these patients. Thus, our findings provide beneficial insights for patients with SCTC and can aid in making treatment decisions.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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