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ORIGINAL SCIENTIFIC REPORT

Primary Squamous Cell Carcinoma in the Thyroid Gland: A Population-Based Analysis Using the SEER Database

Shuwen Yang[1,2,3] · Cunfu Li[4] · Xiao Shi[1,2] · Ben Ma[1,2,3] · Weibo Xu[1,2,3] · Hongyi Jiang[1,2,3] · Wanlin Liu[1,2] · Qinghai Ji[1,2,3] · Yu Wang[1,2,3]

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Abstract

Objects To evaluate prognostic factors and treatment outcomes of primary squamous cell carcinoma in thyroid (PSCCTh) over the past decades using a large national database.

Methods All patients diagnosed with PSCCTh between 1973 and 2015 were identified with the Surveillance, Epidemiology, and End Results Program (SEER) 18-registry database. Relevant clinical data were collected, and prognostic factors of overall survival (OS) and disease-specific survival (DSS) were analyzed.

Results This cohort study included 242 patients, accounting for 0.12% of all primary thyroid carcinomas from 1973 to 2015 nationwide. Of the patients with PSCCTh, 75% were older than 60 years at diagnosis. Patient age older than 60 years (HR 2.242, 95% CI 1.367–3.676, $P = 0.001$) and a tumor size larger than or equal to 50 mm (HR 1.479, 95% CI 1.011–2.165, $P = 0.044$) were independent negative prognostic factors. The univariate analysis suggested that the morphological subtype (OS, $P = 0.033$; DSS, $P = 0.048$), clinical treatment modality (OS, $P < 0.0001$; DSS, $P < 0.0001$), and T stage (OS, $P = 0.004$; DSS, $P = 0.001$) were important predictive factors for OS and DSS. In contrast, gender, race, year of diagnosis, geographic location, N stage, and M stage were not prognostic factors.

Conclusions PSCCTh is a rare malignancy with an aggressive nature and poor prognosis. Survival is predicted by the treatment modality, patient age, T stage, tumor size, and morphological subtypes. This study showed that early diagnosis and complete surgical resection plus adjuvant radiation therapy were associated with a better outcome.

Introduction

Primary squamous cell carcinoma in thyroid (PSCCTh) is a highly aggressive malignant tumor associated with a poor prognosis [1], which was first reported by Vonkarst in 1858 [2]. It is a rare malignancy constituting less than 1% of all primary carcinomas of the thyroid gland. Due to the limited number of reported cases and difficulty associated with performing prospective studies at a single institution, consensus management of PSCCTh remains inconclusive [3]. To gain a better understanding of various factors affecting prognosis and treatment outcomes, we performed a retrospective analysis based on the Surveillance, Epidemiology, and End Results Program (SEER) 18-registry database.

Shuwen Yang and Cunfu Li are co-first authors.

✉ Yu Wang
neck130@126.com

1 Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China

2 Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

3 Cancer Research Institute, Fudan University Shanghai Cancer Center, Shanghai 200032, China

4 Department of Thyroid Surgery, Weihai Central Hospital, Weihai 264400, China

Methods

Data collection

The data were collected from the SEER 18-registry database, which provided detailed cancer outcomes representing 28% of the US population. All the tumor cases studied in this article were from patients aged 35 years or older who were diagnosed with PSCCTh between 1973 and 2015. We identified squamous cell carcinoma per the International Classification of Diseases for Oncology third edition (ICD-O-3)/World Health Organization (WHO) 2008 histology code and behavior from 8070/3 to 8076/3 and thyroid primary site code C73.9. Primary data were extracted from the Individual Cancer Cases database. Demographic variables collected included patient record number, age at diagnosis, years of diagnosis, gender, geographic location, and race. Clinical factors of interest included survival months, cause of death (COD) according to the site record, cause-specific death classification, ICD-O-3 histologic type, tumor grade (well/moderately/poorly differentiated and undifferentiated), tumor size NAACCR (North American Association of Central Cancer Registries) #2800 (information on tumor size, available for 2004+), #780 (available for 1988–2003), #860 (available for 1983–1987), surgery performed, surgery primary site NAACCR #1290 (available for 1998+), #1640 (available for 1973–1997), T stage, N stage, and M stage based on the derived AJCCT(American Joint Committee on Cancer Staging) 6th (2004+).

Tumor case cohort

The initial cohort included 243 tumor cases. Due to death certificate only or autopsy only, one case with unknown survival months was eliminated from the analysis. Ten different morphological subtypes of squamous cell carcinoma were defined in the SEER database. They were coded from 8070/2 to 8078/3 based on ICD-O-3 histology. Four of these 10 subtypes were diagnosed as PSCCTh and were included in our analysis: 8070/3: squamous cell carcinoma, NOS (not otherwise specified); 8071/3: keratinizing; 8072/3: large cell, nonkeratinizing; 8074/3: spindle cell; 8076/3: microinvasive.

Given that we did not have a large number of cases and the values of the factors did not show a normal distribution, we converted several continuous variables into dichotomous variables. For tumor stage, all cases were divided into two groups based on the AJCCT 6th edition T classification. The lower-stage group included T1, T2, and T3, while the higher-stage group included T4a, T4b, and T4NOS. In this study, tumor sizes ranged from 10 to 150 mm, the mean size was 53 mm, and the median size was 50 mm. For an improved analysis, we divided the tumors into two groups, with the large size group consisting of a tumor size that was larger than or equal to 50 mm, while all other tumors were included in the small tumor size group. Four groups were defined based on the different treatment modalities: extensive surgical treatment with adjuvant radiation therapy, surgery alone, radiation alone, and no treatment. Complete demographic and histologic details across all collected cases are presented in Table 1.

Comparative tests were utilized to check the correlation between treatments and other variables, the Chi-square test was used for discrete variables, and the Kruskal–Wallis test was used for continuous variables. Kaplan–Meier survival analysis (log-rank test) and multivariable Cox proportional hazards analyses were performed to evaluate OS (overall survival) and DDS (disease-specific survival) based on potential prognostic factors such as age at diagnosis, tumor grade, tumor size, surgery performed, surgery primary site, and TNM stage. Covariates in all models included year of diagnosis, gender, geographic location, and race. $P < 0.05$ was considered statistically significant for tests. All analyses were conducted using SPSS software version 22.0 (IBM Corp, New York).

Results

There were 140 men and 102 women diagnosed with PSCCTh from 1973 to 2015 in the SEER 18 registries database. The number of registered cases of thyroid malignancy has increased annually, and in contrast, the annual incidence of PSCCTh has decreased from 0.4% in 1973 to 0.1% in 2015.

Clinical characteristics

The data showed that PSCCTh was a more common disease (75%) in elderly people (age > 60 years). The median survival of the elderly group was 4 months, while it was 14 months in the younger group. Among the collected cases, 58% were female patients and 42% were male. The median survival in the female group was 5 months, while it was 7 months in the male group. OS and DSS showed a statistically significant difference by age at diagnosis (OS, $P < 0.0001$; DSS, $P < 0.0001$). However, there were no statistically significant difference in survival based on sex (OS, $P = 0.444$; DSS, $P = 0.317$). Additional univariate log-rank testing of other prognostic factors is presented in Table 2.

The majority of the morphological subtypes were squamous cell carcinoma NOS (85%), for which the 6-month median survival was predicted. The best predictor

Table 1 Demographic, clinical, and pathologic characteristics in 242 patients with primary squamous cell carcinoma in thyroid, 1973–2015

Characteristic	No. of patients (%)
Gender	
Male	102 (41.2)
Female	140 (57.8)
Age (year)	
≤ 60	61 (25.2)
> 60	181 (74.8)
Treatment modality	
Surgery and radiation	64 (26.4)
Surgery alone	42 (17.4)
Radiation alone	63 (26)
No surgery and no radiation	67 (27.7)
Unknown	6 (2.5)
Grade	
Well differentiated; grade I	12 (5)
Moderately differentiated; grade II	36 (14.9)
Poorly differentiated; grade III	84 (34.7)
Undifferentiated; anaplastic; grade IV	34 (14)
Unknown	76 (31.4)
Tumor size (mm)	
< 50	65 (26.9)
≥ 50	72 (29.8)
Unknown	105 (43.4)
Subtype	
8070/3: squamous cell carcinoma, NOS	206 (85.1)
8071/3: squamous cell carcinoma, keratinizing, NOS	20 (8.3)
8072/3: squamous cell carcinoma, large cell, nonkeratinizing	3 (1.2)
8074/3: squamous cell carcinoma, spindle cell	12 (5)
8076/3: squamous cell carcinoma, microinvasive	1 (0.4)
T stage	
T1 T2 T3	23 (9.5)
T4a T4b T4NOS	71 (29.3)
TX unknown	148 (61.2)
N stage	
N0	49 (20.2)
N1a N1b N1NOS	50 (20.7)
NX unknown	143 (59.1)
M stage	
MO	78 (32.2)
M1	30 (12.4)
MX unknown	134 (55.4)
Chemotherapy	
Yes	67 (27.7)
No/unknown	175 (72.3)
Race	
White	195 (80.6)
Black	18 (7.4)
Other (American Indian/AK Native, Asian/ Pacific Islander)	27 (11.2)
Unknown	2 (0.8)

NOS: not otherwise specified

Table 2 Univariate analysis of prognostic factors for primary squamous cell carcinoma in thyroid per the Kaplan–Meier method

	Univariate log-rank *P* value	
	OS	DSS
Gender	0.444	0.317
Age	**0**	**0**
Treatment Modality	**0**	**0**
Grade	**0.001**	**0.001**
Tumor size	**0**	**0.001**
Subtype	**0.033**	**0.048**
T stage	**0.004**	**0.001**
N stage	0.134	0.379
M stage	0.529	0.424
Race	0.313	0.311
Year	0.237	0.525

Bold values are statistically significant ($P < 0.05$)

OS: overall survival, DSS: disease-specific survival

was squamous cell carcinoma of large cell, nonkeratinizing with a median survival of 30 months. For both OS and DSS prediction, the subtypes showed significant differences (OS, $P = 0.033$; DSS, $P = 0.048$). For tumor stage, the majority of cases were T4 stage (76%), which showed a significantly shorter median survival than T1–T3 stage (T4: 3 months; T1–T3: 18 months). This predictor revealed significant differences for both OS and DSS (OS 0.004; DSS 0.001).

The tumor grade of PSCCTh was the mostly poorly differentiated. The percentages of all graded tumors were 7%, 21%, 51% and 21% for well, moderately, and poorly differentiated and undifferentiated, and the median survival was 24, 9, 4, and 4 months, respectively. As a predictor, the tumor grade showed a significant influence on both OS and DSS (OS 0.001; DSS 0.001). The overall survival plot is presented in Fig. 1a.

We found that 47% of the cases in this cohort belonged to the small tumor size group with a 9-month median survival, while 53% of the cases belonged to the large tumor size group with a 4-month median survival. Both OS

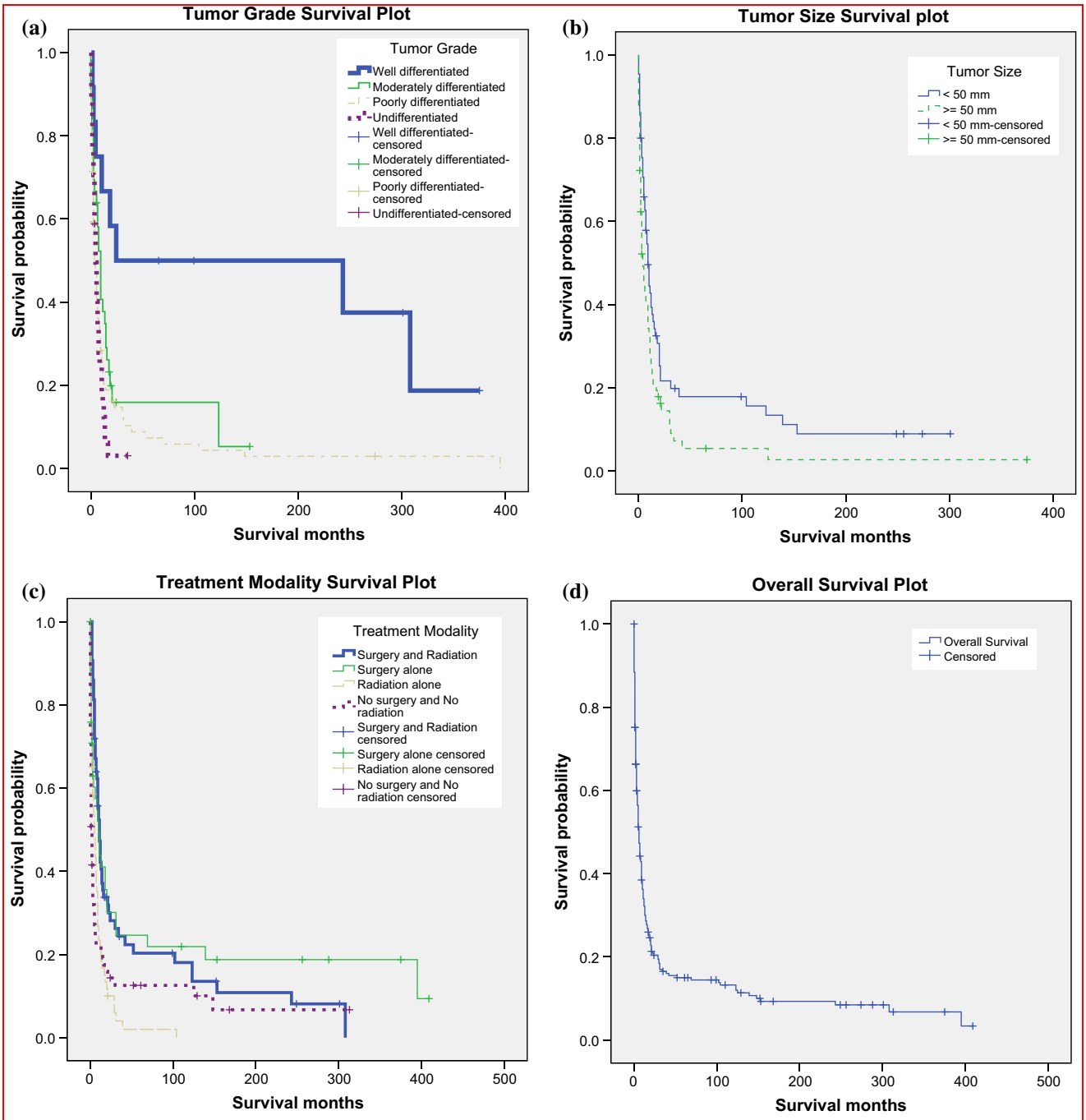

Fig. 1 **a** Survival plot for different tumor grades of primary squamous cell carcinoma in thyroid by Kaplan–Meier method. **b** Survival plot for different tumor sizes of primary squamous cell carcinoma in thyroid by Kaplan–Meier method. **c** Survival plot for different treatment modalities of primary squamous cell carcinoma in thyroid by Kaplan–Meier method. **d** Survival plot for primary squamous cell carcinoma in thyroid by Kaplan–Meier method

and DSS showed a statistically significant difference in survival based on the tumor size (OS, $P < 0.0001$; DSS, $P = 0.001$). Figure 1b shows the overall survival plot.

For treatment modality, extensive surgical treatment with adjuvant radiation therapy showed the best prognosis, with a median survival of 11 months. While surgery alone, radiation alone and no treatment provided predicted results of 10, 5 and 2 months, respectively (Fig. 1c). Significant differences were found in both OS and DSS (OS, $P < 0.0001$; DSS, $P < 0.0001$).

Table 3 Comparative tests of prognostic factors for primary squamous cell carcinoma in thyroid

	Age	Treatment modality	Grade	Tumor size	Subtype	T stage
Age	–	**0.042**	0.063	0.129	0.426	**0.023**
Treatment modality	**0.042**	–	**0.018**	0.395	0.202	0.195
Grade	0.063	**0.018**	–	0.555	**0.04**	**0.003**
Tumor size	0.129	0.395	0.555	–	0.81	**0.017**
Subtype	0.426	0.202	**0.04**	0.81	–	0.183
T stage	**0.023**	0.195	**0.003**	**0.017**	0.183	–

Result: *P* value

Bold values are statistically significant ($P < 0.05$)

Table 4 Multivariable analysis for prognostic factors among clinical variables

Characteristic	Overall survival	
	HR (95% CI)	*P* value
Age (> 60y)	2.242 (1.367–3.676)	0.001
Tumor size (≥ 50 mm)	1.479 (1.011–2.165)	0.044
Subtype	2.138 (1.079–4.238)	0.029
Radiation alone	1.692 (1.043–2.746)	0.033
No surgery and no radiation	2.179 (1.279–3.712)	0.004

HR: hazard ratio

In this study, N stage, M stage, race (black, white, other American Indian/AK native, Asian/Pacific Islander), year of diagnosis, and state (geographic of diagnosis) did not show statistically significant differences for predicting overall survival and disease-specific survival (Table 2). Thus, we eliminated these factors in the correlation comparative test, and they were also excluded from the multivariable Cox proportional hazard analyses.

In the comparative tests, we assessed the correlation between age at diagnosis, treatment modality, tumor grade, tumor size, morphological subtypes, and T stage (Table 3). We found statistically significant differences ($P < 0.05$) between T stage with age, tumor grade, and tumor size; between treatment modality with age and tumor grade; and between subtypes with tumor grade.

Clinical outcomes

The overall survival plots of PSCCTH are shown in Fig. 1d. The 1-, 3-, and 5-year overall survival rates for the whole cohort were 32.2%, 16.5% and 15%, respectively. The multivariate analysis is presented in Table 4. Elderly age (> 60 years) at diagnosis and a large tumor size (> 50 mm) portended a poor prognosis. Patient age at diagnosis ($P = 0.001$), tumor size ($P = 0.044$), morphological subtypes (squamous cell carcinoma, microinvasive: $P = 0.029$) and clinical treatments (radiation alone: $P = 0.033$; without surgical and radiation: $P = 0.004$) were independent prognostic factors.

Discussion

PSCCTh is an extremely rare thyroid malignancy, and only two patients were diagnosed with PSCCTh during the previous 5 years at the authors' cancer center. Additionally, the most published literature regarding PSCCTh consists of case reports of one or two cases. This disease only represents approximately 0.1% of primary thyroid neoplasms [4, 5], as confirmed by our cohort study. However, along with the increasing number of diagnosed thyroid neoplasms cases every year, we identified a slight decrease in the incidence of PSCCTh (from 0.4 to 0.1%) from 1973 to 2015. This phenomenon might be due to the earlier diagnosis and treatment of related thyroid diseases, because the pathological environment of thyroid diseases such as nodular goiter, thyroiditis, and papillary carcinoma may provide favorable conditions for squamous epithelialization of follicular epithelial cells, leading to PSCCTh [6].

Since the thyroid gland ordinarily does not contain squamous epithelium, the origin of PSCCTh remains inconclusive [7]. At present, three theories are controversial in terms of origin. First, in the "embryonic rest" theory described by LiVolsi and Merino in 1978 [8], the residual squamous epithelial tissue derives from the thyroglossal duct or ultimobranchial body during embryonic development. Second, squamous metaplasia is stimulated by an underlying pathology, such as the inflammatory reaction and Hashimoto's thyroiditis [6]. Third, squamous tissue differentiates from papillary, follicular, or medullary cancer [9].

Consistent with published case reports and reviews [5, 10–13], our study confirmed that PSCCT tended to occur more often in elderly patients, especially older

females. In addition, age was an independent predictor, while gender was not. Furthermore, we found that the prediction of treatment modality was not as significant in the elderly group as in the younger group, and the elderly group had a reduced median survival. Thus, extensive surgical treatment with adjuvant radiation therapy is not suggested for older patients.

Metastases in the cervical lymph nodes, lung, bone, liver, heart, and kidney are common due to the aggressive course of PSCCTh [14, 15]. The present analysis showed that half of the valid reported cases had pathologically confirmed lymph node metastases, while 25% presented with distant metastasis. The patients with a lower N stage had a predicted reduced survival, while there was not much difference between a lower and higher M stage. This difference might be explained by the rapid growth of PSCCTh tumors, the results for which might not be heavily impacted by distant metastases at diagnosis, and PSCCTh is poorly responsive to chemotherapy [5, 16], which is the treatment method for distant metastases. Since no significant differences were found during univariate analysis, both N and M stages were not predictors for OS and DSS. In contrast, the T stage was found to be a significant predictor. In addition, PSCCTh was more frequently observed with a higher T stage. T1 stage represented only 5% of the proportion, while T4 stage accounted for 70%. The relatively large tumor size might be the underlying factor in the common symptoms of dyspnea, dysphagia, and dysphonia in patients with PSCCTh [5].

Our study results showed squamous carcinoma morphological subtypes were associated with survival. We found that large cell, nonkeratinizing squamous cell carcinoma had the best predicted survival with a median survival of 30 months. The spindle and microinvasive types had the worst survival with a median survival of 6 and 1 month, respectively. However, these findings might be biased by the limitations of the clinical results. Further studies may be needed to clarify the association between them. In this study, 28% of the patients were also diagnosed with PSCCTh and moderately differentiated carcinoma. In contrast, a previous series documented that 50% of patients with PSCCTh had a lower-grade carcinoma. In addition, we found that this lower-grade tumor predicted an increased OS and DSS in patients, which was consistent with the clinical experience in our cancer center and a previous study [17].

PSCCTh is even less common than undifferentiated thyroid carcinoma but behaves similarly to the aggressive course, with local invasion of vital structures and a poor prognosis. The prevailing treatment modality also resembles that for anaplastic thyroid carcinoma. Our analyses concluded that treatment modality was an independent predictor of overall survival and disease-specific survival in patients with PSCCT. Extensive surgical treatment with adjuvant radiation therapy showed the best prognosis, with a median survival of 11 months. Relative to the combined treatment modality, surgery alone (HR 1.4242, 95% CI 0.78–2.6), radiation alone (HR 1.692, 95% CI 1.043–2.746, $P = 0.033$), and no surgical and radiation treatment (HR 2.179, 95% CI 1.279–3.712 $P = 0.004$) conferred a worse overall survival. The improved survival of adjuvant radiation therapy before or after surgical treatment might be a consequence of the ability of adjuvant therapy to improve local control [11, 18]. In addition, complete thyroidectomy might be helpful to mitigate the symptom of airway obstruction, which is typically an important lethal factor [19]. The surgical resection treatment predicted a better OS than potentially predicted by radiation treatment because PSCCTh was poorly responsive to radiotherapy and relatively resistant to chemotherapy [16, 20–22]. This finding is in consistent with prior studies concluding that surgical resection is a mainstay of treatment that may reduce tumor burden and local invasion [2, 11, 13, 17, 18, 23]. As this was a retrospective study, it was possible that patients with advanced disease were not surgical candidates and why their survival was poor rather than the lack of surgery being prognostic. In addition, surgical resection would be performed even before the definite diagnosis of PSCCTh, since it would take some time to complete the histology, immunohistochemistry, and electron microscopy required to definitively identify the disease.

Limitations

Missing data are a major limitation of the SEER database. Negligence in original data entry can result in missing data, as well as revision of the requirements and specifications. For example, the data collection in this study covered 42 years, during which the criteria for tumor stage classification changed several times (this study utilized the AJCCT 6th edition T classification), resulting in data discontinuity and loss for some years. In addition, it was difficult to identify the source to request original data. Although manual screening and fixing was carried out by our team for all cases, some cases still had to be eliminated. Given the rarity of PSCCTh and insufficient clinical cases, the number of cases that could be processed for statistical analysis was even more limited.

Despite these limitations, this study is the largest integrated investigation of demographic data, treatment outcomes, and prognostic factors in PSCCTh to date. In addition, this is the first report of the association between squamous cell carcinoma morphological subtypes and OS/DSS.

Conclusions

PSCCTh is a malignancy that exhibits rapid growth and poor outcome behavior. Aggressive treatment of complete surgical resection, when possible, plus adjuvant radiation therapy was associated with a better outcome according to the results of this study. We further advocate early diagnosis, which has shown promise in extending the potential for survival.

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