



Pulmonary papillary squamous cell carcinoma: a population-based analysis of incidence, treatment, and prognosis

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Background: Pulmonary papillary squamous cell carcinoma (PSCC) is a rare variant of pulmonary squamous cell carcinoma (SCC). This study aims to improve relevant understanding and demonstrate the incidence, treatment, and prognosis of pulmonary PSCC using a population-based database.

Methods: The Surveillance, Epidemiology and End Results (SEER) database was used to extract data of cases diagnosed with PSCC from 1973 to 2015 and analyze the incidence, treatment, and prognosis.

Results: A total of 151 pulmonary PSCC cases were identified. The incidence of pulmonary PSCC cases in 2015 was 0.009 per 100,000 persons. The tumor grade of pulmonary PSCC cases was significantly lower than that of SCC cases ($P<0.001$). Both cancer-specific (CSS) and overall survival (OS) of pulmonary PSCC were significantly higher than those of other pulmonary SCCs ($P<0.001$). The outcomes of pulmonary PSCC cases receiving surgery were significantly better than cases without surgery ($P<0.001$). On the contrary, patients with radiotherapy had a worsened prognosis compared with those without radiotherapy ($P<0.05$). As expected, the prognosis of pulmonary PSCC cases receiving surgery was significantly better than that of pulmonary PSCC cases receiving chemotherapy and radiotherapy (both $P<0.05$).

Conclusions: Our population-based evidence shows that pulmonary PSCC, as a rare cancer, has a better prognosis compared with other pulmonary SCCs. Surgery was the only effective treatment to improve CSS and OS, while chemotherapy was ineffective and radiotherapy worsened prognosis.

Keywords: Pulmonary cancer; papillary squamous cell carcinoma (PSCC); survival analysis

Submitted Jul 06, 2019. Accepted for publication Sep 12, 2019.

doi: 10.21037/jtd.2019.09.71

View this article at: <http://dx.doi.org/10.21037/jtd.2019.09.71>

Introduction

Pulmonary malignancies have put large social and economic burdens on human society. Currently, pulmonary squamous cell carcinoma (SCC) is the second most prevalent pulmonary malignancy (1). However, as a subtype of pulmonary SCC, pulmonary papillary SCC (PSCC) has a low incidence rate (2,3). Principal symptoms of pulmonary

PSCC include cough, hemoptysis, and pulmonary infection, but asymptomatic patients also exist (4). Apart from radioactive examination such as computed tomography (CT) scanning, bronchoscopy biopsy allows for precise diagnosis of pulmonary PSCC (5). In addition, magnetic resonance imaging and positron emission tomography-CT (PET-CT) are also able to detect clinically invisible PSCC at an early

stage (6).

Compared with other subtypes of pulmonary SCC, pulmonary PSCC possesses distinctively different morphological properties: a well differentiated SCC featuring a papillary/exophytic growth pattern (7). Grossly, the sessile lesion can be either single or multiple well-encompassed masses enlarging and obstructing the airways. Microscopically, the fingerlike structure with neoplastic epithelium and a fibrovascular core is remarkable. However, while pulmonary PSCC *in situ* has an intact basal membrane under epithelial proliferation, its invasive type manifests epithelial infiltration to the stromal core or beyond. Therefore, such uncertain (benign/malignant) properties of pulmonary PSCC may influence treatment efficacy and patient survival.

Despite sporadic reports on pulmonary PSCC (5,8), there have been no population-based analyses of pulmonary PSCC. Hence, this study examines the Surveillance, Epidemiology and End Results (SEER) registry to evaluate the incidence, treatment, and prognosis of pulmonary PSCC. We analyzed clinical and pathological features of pulmonary PSCC and compared the prognosis of various treatments, including surgery, chemotherapy, and radiotherapy. By evaluating such population-based evidence, we hope to improve the relevant understandings of the underexplored pulmonary PSCC.

Methods

Patient and tumor characteristics

Data extraction of pulmonary PSCC and other pulmonary SCC cases from 1973 to 2015, including frequency, incidence, and survival data, was executed in the SEER 18 database. Because of the omitted patient identifiers, it was unnecessary to obtain the approval of the Institutional Review Board in this study.

Based on the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3), pulmonary PSCC was identified by the histology code 8052 and pulmonary SCCs by codes 8070–8076, 8078, 8083, 8084, and 8094. We used behavior code 3 to identify malignant tumors. After filtration, only cases labeled with ICD-O-3 topography codes including the primary site of the lung and bronchus: C34.0 (main bronchus), C34.1 (upper lobe, lung), C34.2 (middle lobe, lung), C34.3 (lower lobe, lung), C34.8 (overlapping lesion of lung), and C34.9 [lung, not otherwise specified (NOS)] were selected for subsequent analysis.

Patients with diagnostic confirmation (microscopically/not microscopically confirmed) were included for further analysis and those with unknown diagnostic confirmation were excluded. Classification and statistical analysis were performed based on patient profiles including sex, ethnicity, marital status, age, tumor location, and grade. Tumor characteristics were depicted by recording the Tumor-Node-Metastasis (TNM) stage, American Joint Committee on Cancer (AJCC) stage, and intervention type. Patients who survived to the deadline, lost to follow-up, or died of other reasons belong to the right-censored data for the overall survival (OS) and cancer-specific survival (CSS) analysis.

Incidence and survival

All rates were reported per 100,000 persons and age of the patients was adapted for the 2000 US Standard Population (19 age groups, census P25-1130). The annual percent change (APC) in the incidence rate was also demonstrated using 1-year endpoints to analyze survival rate. Two parameters, OS and CSS, were used to reflect survival trends and calculated in the Kaplan-Meier model.

Statistical analysis

Statistical analysis was performed using SPSS (version 20.0, SPSS Inc, Chicago, IL, USA) or SEER*Stat 8.3.5 software (National Cancer Institute, Bethesda, Maryland) following the extraction of frequency, incidence, and survival data in all cases from the SEER 18 database. Incidence data were analyzed using weighted least squares to generate the annual percentage change based on 1-year endpoints. Student's *t*-tests and χ -squared tests were used for continuous and categorical variables, respectively. All P values were two-tailed and those <0.05 were considered statistically significant.

Results

Patient characteristics

In the SEER 18 database, 151 patients with pulmonary PSCC and 197,415 patients with other pulmonary SCCs were identified from 1973 to 2015. All demographic characteristics are shown in *Table 1*. Patients with pulmonary PSCC were significantly younger than patients with other pulmonary SCCs (median: 66 *vs.* 69 years, mean: 65.77 *vs.*

Table 1 Patient characteristics for pulmonary PSCC and other types of pulmonary SCC

Parameter	Pulmonary PSCC (n=151)	Other pulmonary SCCs (n=197,415)	P value
Year, n (%)			0.280
1973–1983	22 (14.6)	29,158 (14.8)	
1984–1994	18 (11.9)	35,261 (17.9)	
1995–2004	44 (29.1)	52,247 (26.5)	
2005–2015	67 (44.4)	80,749 (40.9)	
Age (years)			0.003
Median	66	69	
Mean	65.77	68.30	
Range	33–88	14–105	
Size (cm)			0.439
Median	2.3	1.9	
Mean	2.63	3.16	
Range	0.1–11.5	0.1–99.0	
Sex, n (%)			0.043
Male	115 (76.2)	135,242 (68.5)	
Female	36 (23.8)	62,173 (31.5)	
Race/ethnicity, n (%)			0.685
White	121 (80.1)	163,200 (82.7)	
Black	20 (13.2)	24,811 (12.6)	
Other	10 (6.6)	9,257 (4.7)	
Unknown	0	147 (0.1)	
Grade, n (%)			<0.001
I	18 (11.9)	6,323 (3.2)	
II	52 (34.4)	49,489 (25.1)	
III	28 (18.5)	69,682 (35.3)	
IV	2 (1.3)	3,282 (1.7)	
Unknown	51 (33.8)	68,639 (34.8)	
Marital status, n (%)			0.023
Married	86 (57.0)	108,532 (55.0)	
Unmarried	43 (28.5)	43,556 (22.1)	
Others	22 (14.6)	45,327 (23.0)	
Incidence (2015)	0.009	11.826	
Annual percentage change (2000–2015)	–0.23 (P=0.908)	–0.762 (P=0.003)	

Rates are per 100,000 and age adjusted to the 2000 US Standard Population (19 age groups, census P25-1130) standard. PSCC, papillary squamous cell carcinoma; SCC, squamous cell carcinoma.

Table 2 TNM stage for pulmonary PSCC (AJCC Stage 7th, year 2010+, n=44)

Stage	Number	Percent
T stage		
T1	9	20.5
T2	17	38.6
T3	11	25.0
T4	5	11.4
TX	2	4.5
N stage		
N0	22	50.0
N1	8	18.2
N2	11	25.0
NX	3	6.8
M stage		
M0	33	75.0
M1	11	25.0
AJCC stage		
I	11	25.0
II	10	22.7
III	10	22.7
IV	11	25.0
Unknown	2	4.5

TNM, Tumor-Node-Metastasis; PSCC, papillary squamous cell carcinoma; AJCC, American Joint Committee on Cancer.

68.30 years; $P=0.003$). Compared with other pulmonary SCCs, pulmonary PSCC was comprised of a significantly larger proportion of males (76.2% *vs.* 68.5%; $P=0.043$) and married patients (57.0% *vs.* 55.0%; $P=0.023$). Patients with pulmonary PSCC had lower grade lesions than those of other pulmonary SCCs ($P<0.001$). No difference existed regarding the tumor size and race/ethnicity ($P=0.439$ and 0.685, respectively).

Tumor characteristics

For pulmonary PSCC, the TNM and AJCC stages are

presented in *Table 2*. In pulmonary PSCC, the T2 stage was the most identified (38.6%), followed by T3 (25.0%), T1 (20.5%), and T4 (11.4%). Lymph node involvement was moderate with 50% N0. For distant metastasis, metastasis (M1) appeared in 25.0% of cases and 75.0% had no distant metastasis. For AJCC stage, the proportion of stage I was equal to that of stage IV accounting for 25.0%, while both stage II and III reached 22.7%.

Incidence analysis

The incidence of pulmonary PSCC was verified to be 0.009 per 100,000 persons between 2000 and 2015, after age adjustment to the 2000 US Standard Population (19 age groups, census P25-1130; *Table 1*). Although annual percentage change (2000–2015) was -0.23% , this change was not significant ($P=0.908$; *Table 1*, *Figure 1*). In contrast, the incidence of other pulmonary SCCs was 11.826 per 100,000 persons, which exhibited a significant annual percentage change (2000–2015) of -0.762% ($P=0.003$; *Table 1*, *Figure 1*).

Treatment and survival analysis

The profiles of treatment type are summarized in *Table 3*. Specifically, surgery was executed in 69.5% and 54.8% of patients with pulmonary PSCC and other pulmonary SCCs, respectively ($P<0.001$). Among different surgical options, partial pneumonectomy was the most common clarified surgery type in pulmonary PSCC (21.2%) and other pulmonary SCCs (11.6%). Radiotherapy was significantly less used in pulmonary PSCC (35.8%) compared with other SCCs (49.2%; $P=0.001$). Chemotherapy was used in 21.9% and 69.8% of patients with pulmonary PSCC and other pulmonary SCCs, respectively ($P=0.025$). Furthermore, in 44 pulmonary PSCC patients with TNM stage, those receiving radiotherapy or chemotherapy had a higher AJCC stage ($P=0.009$ and 0.036, respectively). Additionally, pulmonary PSCC patients receiving chemotherapy had a significantly higher N stage ($P=0.033$).

For both CSS and OS, pulmonary PSCC demonstrated a significantly better prognosis than other pulmonary SCC (*Figure 2*). We used survival rate to evaluate the effectiveness of surgery, chemotherapy, and radiotherapy for pulmonary PSCC treatment. Kaplan-Meier analysis on OS and CSS showed significant improvement after surgery (*Figure 3A,B*). Meanwhile, as chemotherapy had no beneficial effect

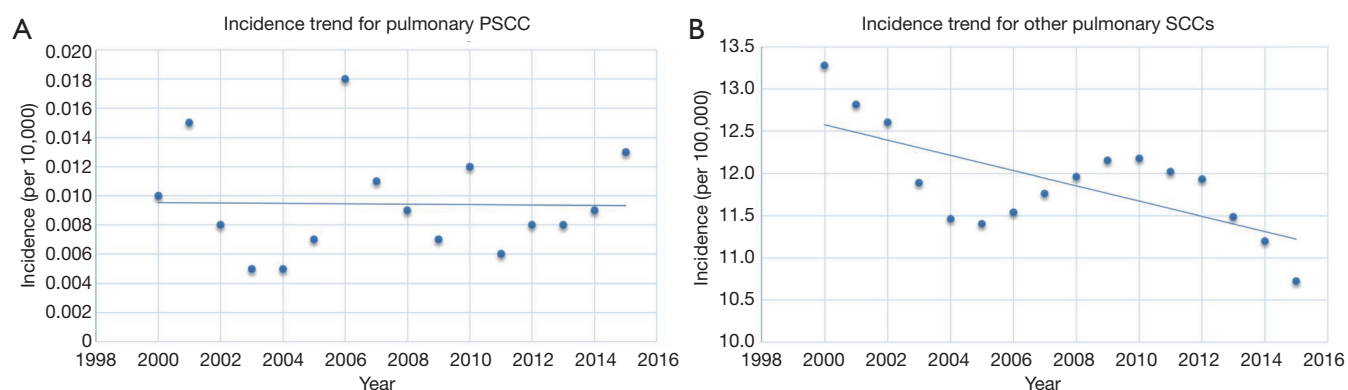


Figure 1 Incidence trends for (A) pulmonary papillary squamous cell carcinoma (PSCC) and (B) other types of pulmonary squamous cell carcinoma (SCC).

Table 3 Treatments for pulmonary PSCC and other types of pulmonary SCC

Treatment type	Pulmonary PSCC (n=151), n (%)	Other pulmonary SCCs (n=197,415), n (%)	P value
Surgery type			<0.001
No surgery	46 (30.5)	89,343 (45.2)	
Excision or resection of less than one lobe (including local tumor destruction or excision)	12 (7.9)	5,571 (2.8)	
Partial pneumonectomy	32 (21.2)	22,805 (11.6)	
Pneumonectomy and extended pneumonectomy	10 (6.6)	3,951 (2.0)	
Uncertain surgical procedure	0 (0)	215 (0.1)	
Unknown	51 (33.8)	75,530 (38.3)	
Radiotherapy			0.001
No radiotherapy	97 (64.2)	100,313 (50.8)	
Radiotherapy	54 (35.8)	97,102 (49.2)	
Chemotherapy			0.025
No chemotherapy	118 (78.1)	59,699 (30.2)	
Chemotherapy	33 (21.9)	137,716 (69.8)	

PSCC, papillary squamous cell carcinoma; SCC, squamous cell carcinoma.

(Figure 3C,D), radiotherapy-treated patients had a worsened prognosis (Figure 3E,F). Moreover, we made a comparison of different treatment modalities, including surgery alone, chemotherapy alone, radiotherapy alone, and combined therapy (surgery + chemotherapy; surgery + radiotherapy) and the results revealed that surgery is the most effective factor to improve the prognosis of pulmonary PSCC, compared with chemotherapy and radiotherapy (Figure 4).

Discussion

Pulmonary malignancies have been well studied (9,10) and conventional SCC is a common cancer type (1,11-14). However, our understanding of common SCC types cannot be completely applied to rare variants of SCC, such as PSCC (7,15-19). Pulmonary PSCC is very rare and consequently, there is a lack of research. As no population-based studies on pulmonary PSCC have been conducted,

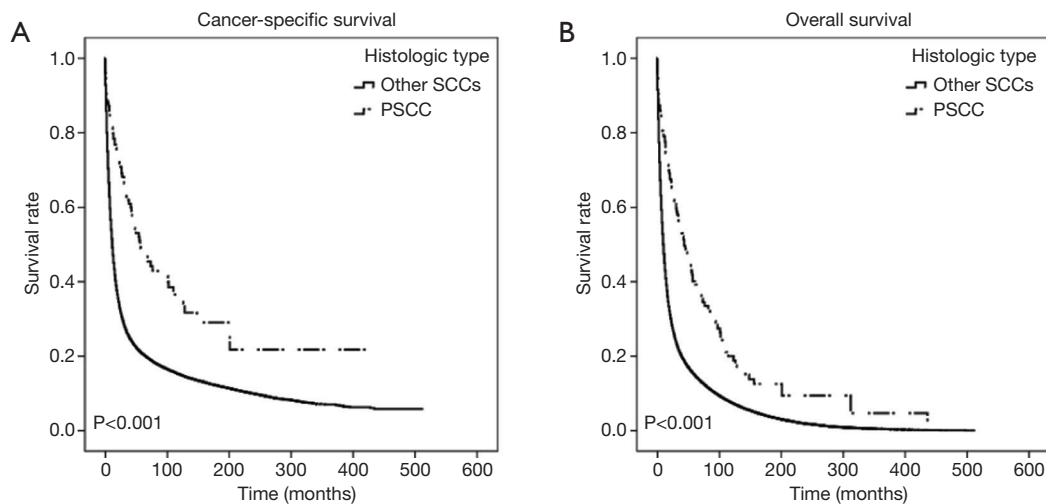


Figure 2 Survival analysis between pulmonary papillary squamous cell carcinoma (PSCC) and other types of pulmonary squamous cell carcinoma (SCC). (A) Cancer-specific survival; (B) overall survival.

this study aimed to improve the understanding of pulmonary PSCC with respect to the incidence, treatment, and prognosis by providing population-based evidence.

Pulmonary PSCC is a special variant of SCC, characterized by its histologic papillary/exophytic growth pattern consisting of a fibrovascular core covered by malignant squamous epithelium. Pulmonary PSCC differs from most common pulmonary SCCs marked by abundant intracellular and/or extracellular keratin material. Another important differential diagnosis of PSCC is squamous papilloma, a common benign tumor. Both PSCC and squamous papilloma can have exophytic growth patterns. Thus, microscopic and cytological examination is essential for differential diagnosis. PSCC contains papillae completely covered by immature basaloid cells, which are cytologically malignant. The overlying squamous epithelium is malignant and surface keratinization is usually limited or absent. However, squamous papilloma has benign squamous epithelium encompassing delicate fibrovascular cores without downward pushing growth into the lamina propria. Focal cytologic abnormalities, such as individual cell keratinization and abnormal mitosis, may also be seen but do not reach the level of dysplasia in PSCC. Therefore, it is mainly the presence of malignant epithelium that separates PSCC from squamous papilloma.

Though not investigated in this study, as the SEER database does not contain relevant data, the potential role of human papillomavirus (HPV) in the development of pulmonary PSCCs should be considered. HPV has been

proven to act in wide-range cancers (20-22). In addition, among studies of PSCC on other sites, especially head and neck, HPV participates in the development of PSCC (19,23-25). Paradoxically, for certain types of SCCs, HPV-positive tumors tend to have both overall and disease-specific survival benefits compared with HPV-negative tumors (26,27). Unfortunately, to date, no adequate evidence allows us to depict a clear picture of HPV in pulmonary PSCC.

In our study, for tumor grade, most pulmonary PSCCs were initially recognized at grade II which is significantly lower than other SCCs, in which grade III accounts for the largest proportion (*Table 1*). Meanwhile, the proportion of patients without surgery significantly differed between pulmonary PSCC (30.5%) and other pulmonary SCCs (45.2%; *Table 3*). Such differences can be attributed to the timely detection of most pulmonary PSCCs; in this way, the opportunity for surgical intervention is still possible. In addition, the papillary/exophytic growth pattern of pulmonary PSCC to the airway may discomfort patients at an early stage and thus, be another factor contributing to timely treatment. However, TNM stage was only available in more than a quarter ($n=44$) of cases. Although only some cases reported TNM stage, there was enough evidence indicating the low invasiveness of PSCC (28,29). To our surprise, in this study, situations based on the TNM stage were not comparatively optimistic. The number of early staged pulmonary PSCCs was equal to late staged lesions: stage I and stage IV are the most commonly described, both

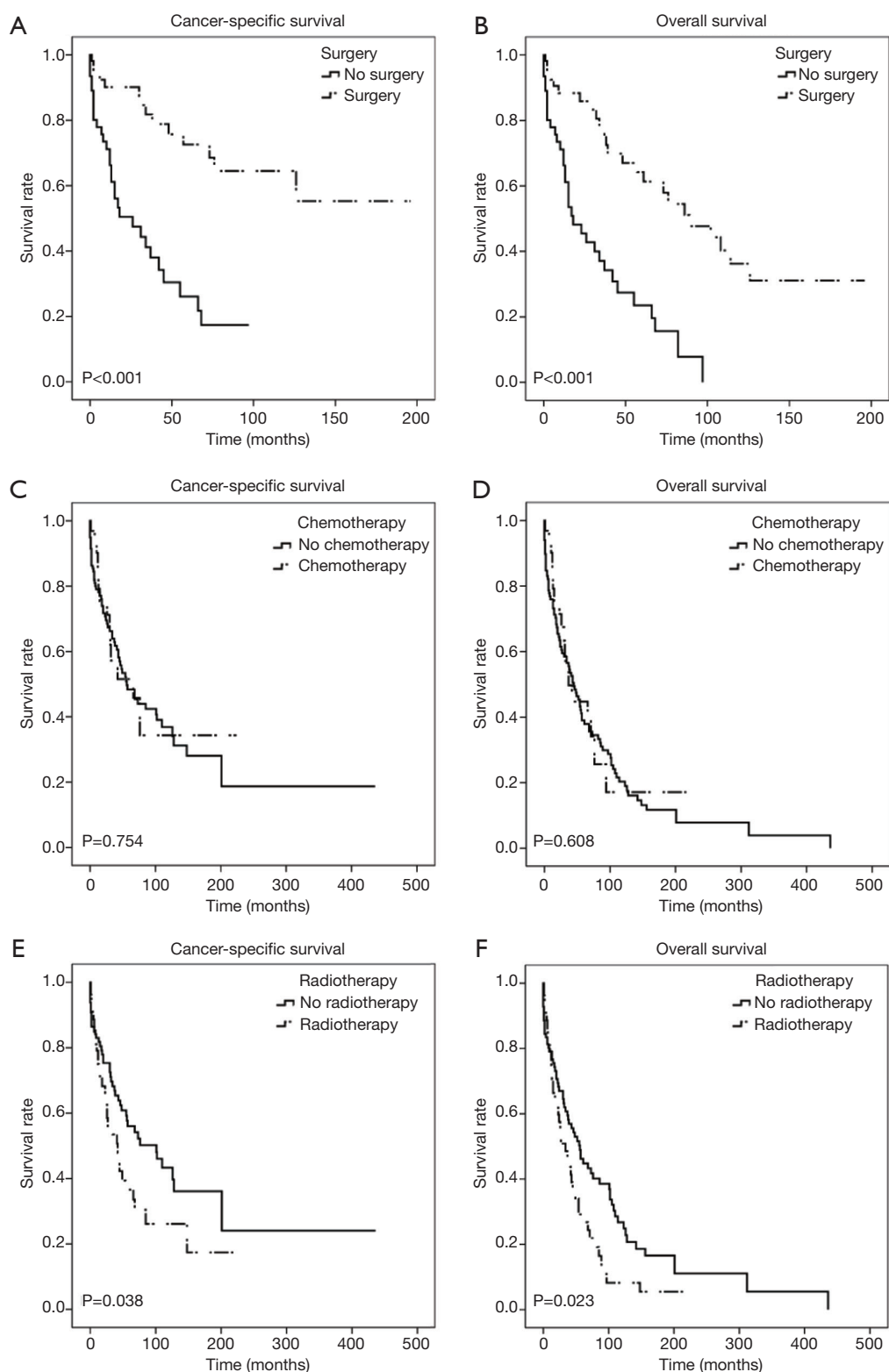


Figure 3 The effect of different treatments on the prognosis of patients with pulmonary papillary squamous cell carcinoma (PSCC). Cancer-specific survival: (A) no surgery vs. surgery; (C) no chemotherapy vs. chemotherapy; and (E) no radiotherapy vs. radiotherapy. Overall survival: (B) no surgery vs. surgery; (D) no chemotherapy vs. chemotherapy; and (F) no radiotherapy vs. radiotherapy.

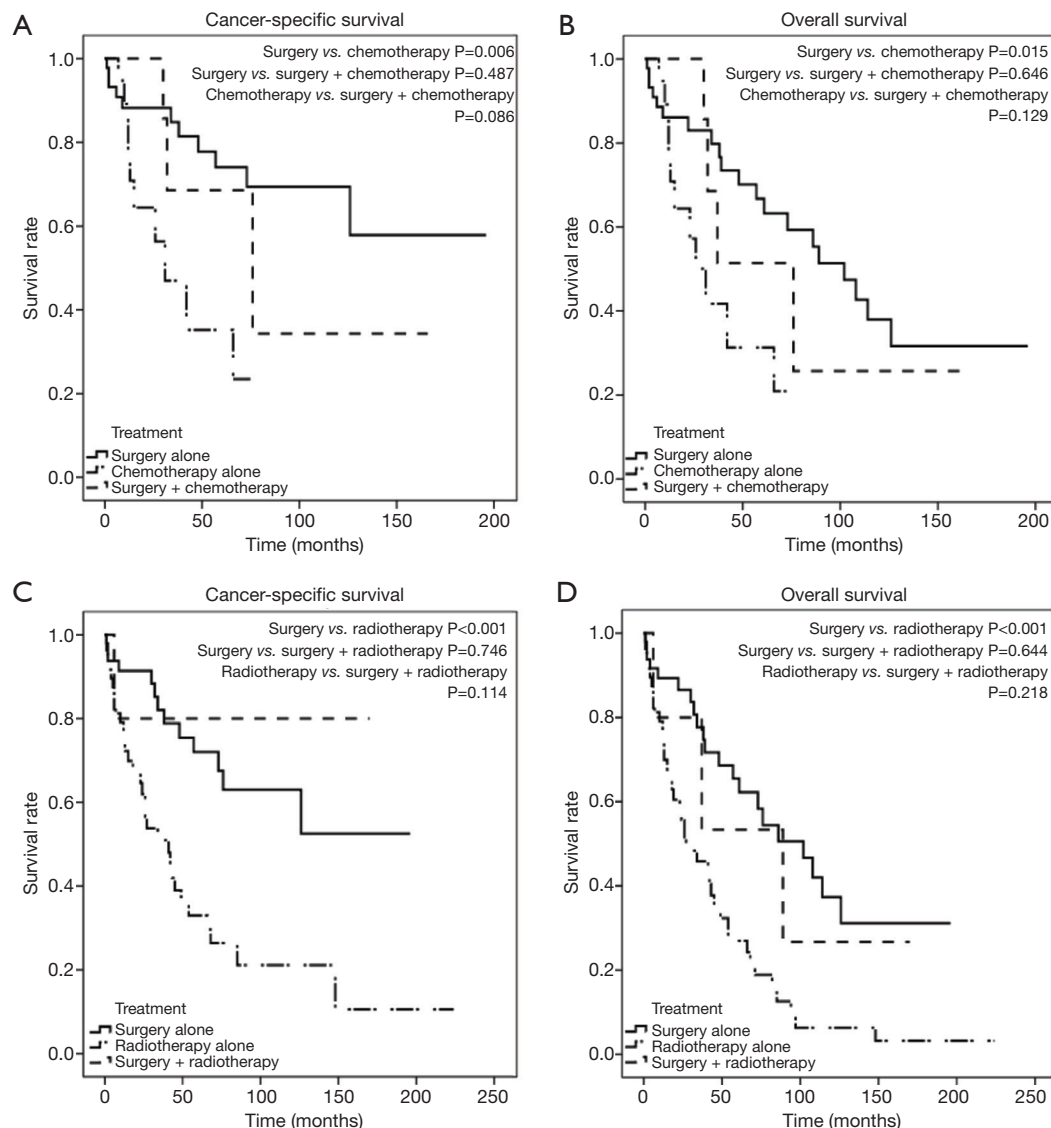


Figure 4 Kaplan-Meier analysis between different therapy modalities of patients with pulmonary papillary squamous cell carcinoma (PSCC). (A,B) Cancer-specific (A) and overall (B) survival of patients accepting surgery alone, chemotherapy alone, and surgery + chemotherapy. (C,D) Cancer-specific (C) and overall (D) survival of patients accepting surgery alone, radiotherapy alone, and surgery + radiotherapy.

occurring in 11 cases; nodal metastasis occurred in 19 cases; and distant metastases were found in 11 cases (Table 2). These data reveal the invasiveness of seemingly indolent pulmonary PSCC.

Though pulmonary PSCC exhibited its aggressiveness, our study validated another report with respect to the increased survival of PSCC compared with other types of SCCs (30). In our study, both CSS and OS were significantly longer in pulmonary PSCC (Figure 2). The

improved prognosis of pulmonary PSCC compared with pulmonary SCC demonstrates the inherent heterogeneities in behavior that this variant displays. Furthermore, using the SEER database, we found an interesting trend in pulmonary cancer. There was a significant decrease for all other pulmonary cancers between 2000 and 2015 ($P=0.003$; Figure 1, Table 1), a finding that echoes the World Health Organization report linking such improvements to public awareness regarding smoking cessation (1). At the same

time, however, the annual percentage change in incidence for pulmonary PSCC remained stable. Does HPV in the US population contribute to maintaining the incidence of pulmonary PSCC? Current and future exploration on etiologic factors and molecular mechanisms may reveal satisfactory answers.

As expected, for patients with pulmonary PSCC, our study demonstrated that those who underwent surgery had improved CSS and OS compared with those who did not (*Figure 3*). Certainly, surgical therapy is the mainstay of treatment for pulmonary cancers. On the other hand, the roles of chemotherapy and radiotherapy are vague (31-33). Conventionally, decision-making regarding the treatment of patients with PSCCs is mainly based on clinical experience and there is no standard protocol for treating these tumors. Unfortunately, in this study, the impact of chemotherapy in our cohort seems to be unsatisfactory, even in combination with surgery. Even worse, radiotherapy plays a detrimental role for both CSS and OS (*Figures 3,4*). Such phenomenon may partially be attributed to the late TNM stage of patients with pulmonary PSCC (*Table 2*). Furthermore, unsatisfactory effects of chemotherapy/radiotherapy may indicate that the occurrence of pulmonary PSCC may not be solitary and can be complicated by other diseases, which echoes one previous report (34). In addition, metastasis (from/to other parts) is another complex reason that can hinder interpretation of pulmonary tumors (4). To date, there is still no persuasive evidence explaining the ineffectiveness of chemotherapy/radiotherapy in pulmonary PSCC and future work is required to explore the relevant mechanisms. Collectively, our results suggest that surgery is the only effective treatment for pulmonary PSCC; chemotherapy or radiotherapy can be ineffective or even detrimental for survival rate.

Despite using population-based data, this study still has some limitations. First, the lack of HPV status in the SEER database hindered relevant analysis. Second, there were insufficient details concerning surgery types, drug usage, radiotherapy doses, and comorbidities to support further analyses. Third, data input under various circumstances (such as different times, locations, recorders, etc.) may introduce considerable heterogeneities. Additionally, since the study is based on a retrospective analysis, we cannot review the slides and confirm the diagnosis ourselves.

Despite the above limitations, using the SEER database still yields great benefits. The standardized database can eliminate biases caused by geographical and institutional

heterogeneity during analysis. Moreover, the robust number can help researchers to draw powerful conclusions especially in the field of rare malignancies like pulmonary PSCC.

Conclusions

Our population-based evidence shows that pulmonary PSCC, as a rare cancer, has better prognosis compared with other types of pulmonary SCC. For both CSS and OSC of pulmonary PSCC, surgery is the only effective treatment; while chemotherapy has no effect and radiotherapy worsens prognosis.

Acknowledgments

The authors would like to thank the SEER database for providing open access.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Because of the omitted patient identifiers, it was unnecessary to obtain the approval of the Institutional Review Board in this study.

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Cite this article as: Yuan Q, Sun N, Meng Z, Chen X. Pulmonary papillary squamous cell carcinoma: a population-based analysis of incidence, treatment, and prognosis. *J Thorac Dis* 2019;11(10):4271-4281. doi: 10.21037/jtd.2019.09.71