Squamous Cell Carcinoma of the Soft Palate in the United States: A Population-Based Study

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Abstract

Objectives. To describe the incidence and determinants of survival of patients with squamous cell carcinoma of the soft palate (SCCSP) using the Surveillance, Epidemiology, and End Results (SEER) database.

Study Design. Retrospective, population-based cohort study of patients.

Setting. SEER cancer registry.

Subjects and Methods. Patients from the SEER cancer registry from 1973 to 2015 were used to analyze demographics and survival of SCCSP.

Results. A total of 4366 cases were identified. The average overall survival (OS) and disease-specific survival (DSS) were 68.7 months and 161.3 months, respectively. Multivariate analysis revealed that male sex, stage, and treatment (hazard ratio [HR] = 0.690, \( P = .019 \); HR = 1.73, \( P < .001 \); HR = 0.64, \( P < .001 \), respectively) were independent determinants of better or worse DSS. Age, stage, and treatment (HR = 1.02, \( P < .001 \); HR = 1.49, \( P < .001 \); HR = 0.66, \( P < .001 \); HR = 0.48, \( P < .001 \), respectively) were independent determinants of better or worse OS. For stages I, II, and III, radiation alone and surgery alone have nearly equivalent OS. Patients with stage IV disease who underwent both surgery and radiation had a significantly higher median OS at 50.0 months.

Conclusion. Radiation alone and surgery alone both have nearly equivalent OS benefit for stages I to III, while surgery and radiation provide the most survival benefit for stage IV disease. The large discrepancy between OS and DSS can be due to significant comorbidities. Future studies should aim to address the determinants of quality-of-life variables that help direct treatment decisions and might indirectly affect survival.

Keywords

squamous cell carcinoma, oropharyngeal cancer, soft palate, head and neck surgery, otolaryngology

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Previous case series have reported excellent survival for early-stage SCCSP limited to the primary site. T1 and T2 lesions have a 5-year overall survival (OS) of 91% to 100% and 70% to 75%, respectively. Despite multimodality treatment, T3 and T4 lesions have much lower survival, ranging between 33% and 47%. Efforts have focused on minimizing the defect size, optimizing adjuvant therapy, and designing innovative reconstructive options to enhance quality of life and ultimately survival. The first successful soft palate reconstruction using a pedicled buccal mucosal flap was described by Cardwell. With technological advancement, laser resection, custom-made oral prostheses, and free flap reconstruction are currently being used to preserve proper function of the soft palate.

Due to the rarity of SCCSP, most studies analyze SCCSP with other oropharyngeal cancers; therefore, limited data independently examine the incidence and factors of survival for patients with SCCSP. Thus, the goal of this study was to evaluate characteristics and outcomes of SCCSP using the Surveillance, Epidemiology, and End Results (SEER) cancer registry, a population-level database maintained by the National Cancer Institute, to characterize the epidemiology and predictors of survival.

Methods
A population-based cohort analysis was performed using patient information in the case-listing session of the SEER 18 database (http://www.seer.cancer.gov), which is a widely used cancer registry that covers an estimated 27.8% of the US population. Internal review board approval of the University of California, Los Angeles was not required because the database uses publicly available information with no personal identifiers.

Patients with SCCSP from 1973 to 2015, the widest range available in the latest version of the SEER software, were identified using the histology code C05.1 (soft palate, not otherwise specified [NOS]). The following primary data were extracted from the database for analysis: age at diagnosis, sex, race/ethnicity, primary site, treatment with surgery and/or radiation therapy, tumor TNM stage, tumor grade, and OS and disease-specific survival (DSS) in months. Staging as well as T stage information was only present for patients entered into the database after 2004. The T stage was retroactively determined where possible for patients with staging information using the extent of disease and collaborative staging codes for tumor size and locations, following the classification protocol developed by the American Joint Committee on Cancer.

The primary outcome was defined as the time in months from diagnosis to death from any cause for OS and as the time from diagnosis to death specific to the cancer-related diagnosis for DSS. Descriptive statistics were calculated for all variables. The OS and DSS absolute difference in mean survival and 95% confidence interval around the difference were formally tested using the log-rank test. Complete data were available for 454 patients, and covariates were assessed for predictive performance with univariate and multivariate analyses. The comparisons between the groups were deemed statistically significant at the $P < .05$ level. Covariates were chosen for multivariate analysis based on the factors identified as clinically significant or with log-rank $P < .25$ on univariate analysis. This method was selected to minimize the total number of covariates, thus improving the generalizability of the findings and minimizing instability within the model. As a default, age and sex were included in all multivariate models. Using this method, there were no fewer than 10 events per covariate for each model. The statistical analyses were performed with SPSS, version 23 (SPSS, Inc, an IBM Company, Chicago, Illinois).

Results
From January 1, 1973, to December 31, 2015, the SEER database yielded 4366 patients with a diagnosis of SCCSP. Demographics, treatment modality, stage, and grade characteristics of patients with SCCSP are listed in Table 1. Data available for tumor stage comprised 1173 patients, which showed a bimodal distribution for tumor stage with 26.7% (n = 313) presenting with stage I disease and 44.2% (n = 518) with stage IV disease. The majority had localized tumors, with 60.5% (n = 817) without lymph node involvement and 96.5% (n = 1303) without distant metastasis. Of the choices, most patients underwent radiation (48.5%).

Table 2 shows the OS and DSS analysis at 2, 5, and 10 years after treatment for 3281 patients. The 2-year, 5-year, and 10-year OS rates were 56%, 31%, and 13%, respectively, with a median of 68.7 months. DSS was similar to OS with 57%, 34%, and 14% at 2, 5, and 10 years, respectively. However, survival at least doubled for DSS, with a median of 161.3 months.

The Kaplan-Meier survival curve in Figure 1 demonstrates that stage I tumors (median OS 76.2 months) had the best prognosis while stage IV disease (median OS 19.0 months) had the worst. For the entire cohort, the median survival was 40.0 months.

Table 3 shows the multivariate analysis of OS and DSS. Increasing age (hazard ratio [HR] = 1.02, $P < .001$) and higher stage (HR = 1.49, $P < .001$) were independent significant predictors of a worse OS. Treatment (radiation only, surgery only, or surgery and radiation) was an independent significant predictor of a better OS (HR = 0.66, $P < .001$). Male sex (HR = 0.690, $P = .019$), stage (HR = 1.73, $P < .001$), and treatment (HR = 0.64, $P < .001$) were independent significant predictors of a better DSS. Higher stage was an independent significant predictor of a worse DSS. Age was not found to be a significant predictor for DSS.

The Kaplan-Meier survival curve demonstrates OS in Figure 2A-D and DSS in Figure 3A-D by treatment modality for stages I to IV. Patients who received neither surgery nor radiation fared the worst OS and DSS for all stages. For stage I SCCSP, monotherapy (surgery median OS 93.0 months and radiation median OS 86.0 months) resulted in better outcomes than multimodal therapy.
In contrast, patients with SCCSP who underwent surgery fared the best DSS for stage I tumors. For stage II and stage III SCCSP, all 3 types of treatment modalities had comparable median OS. Similar to OS for stage III, all 3 types of treatments resulted in similar DSS with no statistical difference in DSS among the 3. On the other hand, for stage II, surgery alone and radiation alone had comparable DSS ($P = .252$), but surgery alone had a higher DSS compared to multimodal therapy ($P = .038$). Patients who received both surgery and radiation therapy for stage IV tumors had the highest median OS at 50.0 months. For stage IV cancers, surgery only (median OS 18.0 months) and radiation only (median OS 24.0 months) treatments had similar survival. Interestingly, surgery and radiation therapy did not statistically significantly improve DSS compared to single-modality treatments ($P = .183$ and $P = .080$ for surgery only and radiation only, respectively) as seen in OS for stage IV disease.

**Discussion**

Consistent with previous retrospective case series, our results demonstrate that SCCSP most commonly affects white men in their mid-60s.\textsuperscript{10,11,13} Most patients with SCCSP presented with T1 or T2 tumors, likely due to timely diagnosis through visualization of an early lesion.\textsuperscript{7} This is similar to what has been reported previously.\textsuperscript{14,15} Over 44% of patients presented with stage IV SCCSP, higher than what has been shown in previous studies.\textsuperscript{15} However, median DSS of the current series is lower than what has been reported, which ranges from 54% to 73%.\textsuperscript{10,16-19} This could be attributed to a greater proportion

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (n = 4366), y</td>
<td>Mean 63.28</td>
</tr>
<tr>
<td>Sex (n = 4366), % (No.)</td>
<td>Female 33.7 (1470)</td>
</tr>
<tr>
<td>Race (n = 4366), % (No.)</td>
<td>White 78.8 (3439)</td>
</tr>
<tr>
<td>Treatment modality (n = 2243), % (No.)</td>
<td>No treatment 11.3 (254)</td>
</tr>
<tr>
<td>Stage (n = 1173), % (No.)</td>
<td>I 26.7 (313)</td>
</tr>
<tr>
<td>Grade (n = 3349), % (No.)</td>
<td>Undifferentiated 0.8 (28)</td>
</tr>
<tr>
<td>T stage (n = 1120), % (No.)</td>
<td>T0 0.2 (3)</td>
</tr>
<tr>
<td>N stage (n = 1350), % (No.)</td>
<td>N0 60.5 (817)</td>
</tr>
<tr>
<td>M stage (n = 1350), % (No.)</td>
<td>M0 96.5 (1303)</td>
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Table 1. Characteristics of Patients with Squamous Cell Carcinoma of the Soft Palate.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Survival</th>
<th>Disease-Specific Survival</th>
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<tbody>
<tr>
<td>Overall median survival, mo</td>
<td>68.7</td>
<td>161.3</td>
</tr>
<tr>
<td>Percent survival</td>
<td>At 2 years 56</td>
<td>57</td>
</tr>
<tr>
<td>At 5 years 31</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>At 10 years 13</td>
<td>14</td>
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</tbody>
</table>

Table 2. Survival Analysis of Patients with Squamous Cell Carcinoma of the Soft Palate.
presenting with a more advanced stage compared to previous studies. We believe this proportion is a more accurate representation of patients with SCCSP, as this is the largest scale study investigating the epidemiology of SCCSP.

Our data highlight that single-modality treatments result in comparable OS for stage I tumors. There has been much debate about the preferred modality of therapy for T1 and T2 staged SCCSP. For early-stage tumors, retrospective studies have demonstrated surgery and radiation monotherapy to be of comparable efficacy for locoregional control and survival.10,11 Consistent with previous studies, the use of either surgery or radiation alone had better survival than using dual-
modality treatment for stage I. Interestingly, the type of treatment did not affect OS for stage II and stage III cancer.

Surgery followed by adjuvant radiation was the superior treatment for stage IV cancer in this study. Indeed, previous studies argue that radiation therapy is superior because it preserves the velopharyngeal apparatus critical for swallowing, and treatment can be extended to the retro/parapharyngeal nodal basin, which can be difficult to access surgically.\textsuperscript{20,21} However, radiation therapy comes at a cost. Following adjuvant therapy, deterioration in swallowing and speech generally occurs.\textsuperscript{3,22} The primary mechanism of this process is due to radiation-induced palatal retraction and fibrosis.\textsuperscript{23} In addition, spillover of the radiation may cause collateral scarring of the neighboring structures (eg, tonsillar pillars, pharyngeal constrictors) beyond the targeted location.\textsuperscript{24}

Age was a significant prognosticator of OS, but the degree of its effect was smaller compared to other independent factors. Age has been shown to be a prognosticator of OS in certain head and neck cancers likely due to the increasing comorbidities associated with advanced age.\textsuperscript{25} Mirroring the findings of Iyer et al,\textsuperscript{10} our results demonstrate that age was a significant predictor for OS but not for patients with SCCSP. On the other hand, male sex was an independent predictor of improved DSS but not OS. Others have yet to show sex to have an effect on survival for SCCSP but was reported to be associated with decreased DSS in other oropharyngeal carcinomas, specifically tonsillar cancer.\textsuperscript{26-28} Quality of life following treatment and concurrent morbidities could perhaps elucidate such differences between OS and DSS.

We identify tumor stage to be predictors of both OS and DSS. Supporting this finding, published studies have shown T and N classification to be determinants of OS and DSS.\textsuperscript{11,29,30} Some have even shown that distant metastasis is one of the most important prognostic factors for survival.\textsuperscript{22,31} Thus, accurate T, N, and M classification is important in predicting prognosis.

One salient observation in this study was the large discrepancy between OS and DSS in SCCSP. This finding could be attributed to other major associated comorbidities, particularly those related to smoking and regular alcohol use. Furthermore, the quality-of-life factors associated with head and neck surgery could also account for such difference. Lv et al\textsuperscript{32} reported that the defect of the soft palate created

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Disease-specific survival analysis of patients with squamous cell carcinoma of the soft palate by stage (A) I, (B) II, (C) III, and (D) IV. Cum, cumulative.}
\end{figure}
by resection is the most important factor in determining postoperative function. Patients with a larger defect who require flap reconstruction have poorer function than those with primary closure. Following surgery, speech and swallowing dysfunction may significantly diminish patients’ quality of life. Palatal obturators and surgical reconstruction methods, including radial forearm free flap, may improve the functional status of the soft palate, but studies show that the results are still inferior to patients treated with radiation. Other complications of surgery range from mucositis and dysphagia to osteoradionecrosis and ischemic stroke. These physical, functional, and psychosocial comorbidities following treatment of SCCSP can greatly affect overall survival.

A population-level study using the SEER database allows for capturing epidemiology and predictors of outcome with greater statistical power and minimal sampling error. However, this study design has inherent limitations, as there are incomplete detailed pathologic data, including depth of invasion and margin status, comorbid conditions, extent of surgery, and chemotherapy. Thus, the role of chemotherapy on survival is not clearly delineated. Nonetheless, analysis of this database provides an important contribution to our limited knowledge of SCCSP due to its rare occurrence. Furthermore, this is one of the few studies that independently examines SCCSP from the other oropharyngeal subsites.

Conclusion
To our knowledge, this is the first large-scale national database describing the incidence and determinants of survival of SCCSP. Although SCCSP accounts for a small proportion of oropharyngeal carcinomas, quality of life is significantly affected. Our results show that a significant difference between OS and DSS exists. Independent determinants of OS include age, tumor stage and treatment. For stages I, II, and III, radiation alone and surgery alone have nearly equivalent OS benefit. Patients with stage IV disease who underwent both surgery and radiation had the most benefit compared to single-modality therapy. These results enhance our knowledge of SCCSP and would help those responsible for developing further treatment guidelines. Future studies should aim to determine the variables that affect quality of life in patients with SCCSP that might indirectly affect survival.

Author Contributions
Carmen K. Chan, interpretation of data, data analysis, drafting of the manuscript; Albert Y. Han, interpretation of data, data analysis, conception and design, critical revision of the manuscript; Jose E. Alonso, acquisition of data, critical revision of the manuscript; Mary J. Xu, conception and design, data analysis, critical revision of the manuscript; Jon Mallen-St Clair, conception and design, data analysis, critical revision of the manuscript, supervision; Chase M. Heaton, conception and design, data analysis, critical revision of the manuscript, supervision; Edward C. Kuan, interpretation of data, data analysis, conception and design, critical revision of the manuscript, supervision; Maie A. St John, conception and design, data analysis, critical revision of the manuscript, supervision.

Disclosures
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