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Epidemiology and Survival Outcomes of Sinonasal Verrucous Carcinoma in the United States

Jose E. Alonso, MD ●; Albert Y. Han, PhD ●; Edward C. Kuan, MD, MBA ●; Jeffrey D. Suh, MD; Maie A. St. John, MD, PhD

INTRODUCTION

Verrucous carcinoma (VC) is an epithelial neoplasm first described in a series by Ackerman as a variant of squamous cell carcinoma (SCC). Clinically, VC has been noted to exhibit an insidious onset, slow-growing, exophytic “cauliflower-like” appearance, distinct from typical ulcerating or nodular characteristics of squamous cell tumors. Nodal disease and distant metastases are exceedingly rare. Histopathologic analysis reveals well-differentiated cytology with deep epithelial projections into subcutaneous tissue but without invasion of the basement membrane. In the head and neck, VC most commonly affects the oral cavity and larynx, and most of our knowledge of this disease stems from retrospective case series in these primary locations.

Sinonasal malignancies comprise a minority of head and neck cancers, with reported incidences of 1.5 per 100 thousand in men and <1 per 100 thousand in women, respectively. The maxillary sinus and nasal cavity have been described as the most frequent primary sites in the sinonasal tract. Squamous cell carcinoma (44%–51%), adenocarcinoma (11%), and salivary gland malignancies (11%–17%) are the most common histologies, in descending order.

Although squamous histologies are most common in the sinonasal tract, SCC variants comprise approximately 15% of all cases. Variant sinonasal verrucous carcinoma (SNVC) similarly has been described in prior case reports. An interesting yet unclear association of SNVC with inverting papillomas has been reported. Given its rarity, evidence regarding the epidemiology and factors affecting survival outcomes are limited to various case reports. Herein, we aim to further describe the determinants affecting survival in patients with SNVC from an epidemiologic perspective utilizing population-based data, and hope to enhance otorhinolaryngologists’ understanding of this neoplasm.

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MATERIALS AND METHODS
The Surveillance, Epidemiology, and End Results (SEER) 18 database was queried for demographics, treatments rendered, and survival data between 1973 and 2014. Given the deidentified nature of SEER, institutional review board approval was not necessary per the University of California, Los Angeles, Office of the Human Research Protection Program. We searched for neoplasms corresponding to verrucous carcinoma using the histology/behavior codes (8051/3). Further filtering was performed via topography codes of the International Statistical Classification of Diseases for Oncology, Third Edition, for verrucous carcinoma of the nasal cavity, paranasal sinuses, and nasopharynx. Primary data extracted for analysis included age; sex, race/ethnicity; primary site; treatment with surgery and/or radiation therapy (RT); tumor, node, metastasis (TNM) stage; and overall survival (OS) and disease-specific survival (DSS) in months. Staging information was obtained from cases diagnosed after 2004 for consistency. Tumor staging was assigned with corresponding criteria, as described in the classification protocol developed by the American Joint Commission on Cancer (AJCC).

Statistical Analysis
Primary demographic and clinical data were extracted from the SEER database via SEER*Stat 8.1.5 software (National Cancer Institute, Bethesda, Maryland, U.S.A.). Following extraction, data was reorganized and coded on Microsoft Excel 2011 (Microsoft Corporation, Redmond, WA). Data analysis was performed with SPSS 21 (IBM Corp., Armonk, NY).

Survival Analysis
Primary endpoints include OS, defined as time in months from diagnosis to death of any cause; and DSS, defined as time in months from diagnosis to death due to primary cancer. The OS and DSS curves were computed using the Kaplan-Meier method. The log-rank test was used to assess for statistical significance, with \( P < 0.05 \) designating a statistically significant difference. Significant covariates using the log-rank test were selected for multivariate analysis. Covariates were selected with this method to reduce the total number of covariates, thus improving the generalizability of our results while minimizing instability within the model.\(^5,6\) The Cox proportional hazards model was used for multivariate analysis, with \( P < 0.05 \) demonstrating statistical significance.

RESULTS
Demographic and Clinical Characteristics
The SEER 18 database yielded 86 cases of verrucous carcinoma involving the sinonasal tract (Table I). All cases of SNVC were diagnostically confirmed with positive histology. Males comprised 69.8% of the cohort, although sex was not found to be statistically significant (\( P > 0.05 \)). The average age at presentation was 67.4 years and revealed statistically significant differences in OS and DSS on univariate analysis, respectively (\( P < 0.001 \)) (Table II). There was a predominance of white patients (91.9%), although race/ethnicity was not associated with survival differences (\( P > 0.05 \)) (Table II). Stratification of data by primary site revealed that the nasal cavity (51.2%) and maxillary sinus (40.7%) were the most frequently involved, whereas nasopharyngeal VC (5.8%) and frontal sinus were (1.2%) were less common.

Queries were also analyzed for TNM classification and AJCC stage to assess tumor size/extent, lymph node involvement, and distant metastases (Table I). Staging information was available for 31 of 86 cases. Of these, the majority of tumors were T1 (69.6%) and T2 (21.7%), whereas T3 (4.3%) and T4 (4.3%) were less frequently observed. No cases were identified with nodal or distant metastases. Corresponding AJCC staging information was subsequently derived from these cases. The vast majority of cases were stage I (58.1%), followed by stage II cases (32.3%). Stage III (3.2%) and stage IV cases (6.4%) were far less common.

Information regarding tumor grade also was obtained (Table I). A predominance of well-differentiated (85.1%) tumors was observed. Undifferentiated tumor grade was not observed (0%).

Treatments Rendered/Survival Outcomes
The overwhelming majority of patients underwent primary surgical therapy (89.5%). A statistically

### TABLE I. Demographic and Clinicopathologic Characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean)</td>
<td>67.4</td>
</tr>
<tr>
<td>Age (Minimum)</td>
<td>27</td>
</tr>
<tr>
<td>Age (Maximum)</td>
<td>85</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30.2% (26)</td>
</tr>
<tr>
<td>Male</td>
<td>69.8% (60)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91.9% (79)</td>
</tr>
<tr>
<td>Black</td>
<td>4.7% (4)</td>
</tr>
<tr>
<td>Other</td>
<td>3.5% (3)</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>51.2% (44)</td>
</tr>
<tr>
<td>Maxillary sinus</td>
<td>40.7% (35)</td>
</tr>
<tr>
<td>Frontal sinus</td>
<td>1.2% (1)</td>
</tr>
<tr>
<td>Accessory sinus</td>
<td>1.2% (1)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>5.8% (5)</td>
</tr>
<tr>
<td>Treatment modality</td>
<td></td>
</tr>
<tr>
<td>Surgery + radiation</td>
<td>20.9% (18)</td>
</tr>
<tr>
<td>Surgery</td>
<td>89.5% (77)</td>
</tr>
<tr>
<td>Radiation</td>
<td>24.4% (21)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>58.1% (18)</td>
</tr>
<tr>
<td>II</td>
<td>32.3% (10)</td>
</tr>
<tr>
<td>III</td>
<td>3.2% (1)</td>
</tr>
<tr>
<td>IV</td>
<td>6.4% (2)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>85.1% (40)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>12.8% (6)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>2.1% (1)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>0%</td>
</tr>
</tbody>
</table>
significant difference in OS and DSS was obtained on univariate analysis for patients undergoing a surgical intervention \( (P < 0.001) \) (Table II). Furthermore, surgery (with or without RT) was found to be an independent predictor of improved OS and DSS on multivariate analysis \( (P < 0.001) \) (Table III). Radiation therapy was used in 24.4% of SNVC and did not achieve statistical significance on univariate analysis for differences in OS and DSS. Dual-modality therapy was performed on 20.9% of the cohort and similarly did not achieve statistical significance for differences in survival outcomes.

Overall survival and DSS curves were constructed via the Kaplan-Meier method (Fig. 1). The 5-year and 10-year OS rates were 59% and 36%, respectively, whereas 5-year and 10-year DSS rates were 84% and 78%, respectively. Cases in which surgery was performed demonstrated an estimated higher 1-year DSS (97%) compared with cases that did not undergo surgery (37%) despite the use of RT \( (P < 0.001) \) (Fig. 3). The 5-year DSS of cases undergoing RT and/or surgery were as follows: 91% for surgery alone, 78% for surgery with RT, 0% for RT, and 60% for no treatment \( (P < 0.001) \) (Fig. 2b).

Differences in survival were assessed based on primary site (Fig. 3). Nasal cavity VC exhibited 1-year and 5-year DSS rates of 98% and 89%, respectively. Similarly, the 1-year and 5-year DSS rates involving the maxillary sinus remained at 84% \( (P = 0.002) \) (Fig. 3). Multivariate analysis subsequently revealed tumor primary site as an independent predictor of DSS \( (HR 1.8; P < 0.001) \) (Table III). Specifically, nasopharyngeal tumors portended a poorer DSS compared to those involving the nasal site \( (HR 11.6; P < 0.001) \) (Table III).

Survival outcomes based on tumor stage were performed. Advanced stage was associated with differences in OS and DSS on univariate analysis, although it failed to predict survival outcomes with multivariate methods \( (P > 0.05) \) (Table III).

We aimed to assess the impact of tumor grade on OS and DSS. Tumor grade was associated with statistically significant differences in DSS via univariate analysis (Table II). Multivariate analysis later revealed tumor grade as an independent negative predictor of DSS \( (HR 3.7; P = 0.01) \) (Table III).

**DISCUSSION**

Approximately 90% of VC arises within two sites in the head and neck: the oral cavity (55.9%) and larynx (35.2%). In the sinonasal tract, VC along with other SCC variants comprise roughly 15% of non-SCC malignancies. Previously, Vasquez et al. described the importance of distinguishing sinonasal SCC variants from SCC histologies given their prognostic impact. Given the above, we aimed to focus on identifying factors and their predictive performance on survival outcomes specifically for SNVC. Herein, we present the first largest population-based study on SNVC to enhance otolaryngologists’ clinical understanding of these lesions and provide survival data that may impact management and prognosis. Although prior case reports describe SNVC affecting patients with an age range of 35 to 81, our cohort revealed an average age of 67.4 years with a male predominance. Interestingly, females are more frequently afflicted with VC of the oral cavity. The association of human papillomavirus (HPV) DNA within VC lesions of the head and neck, or HPV involved in the pathogenesis, is not entirely understood. However, recent evidence suggests that VC lesions are not HPV-driven following investigation via immunohistochemical, polymerase chain reaction (PCR); mRNA reverse transcription PCR; and next-generation sequencing techniques. This is further supported by Orvidas et al., who failed to identify HPV DNA in 13 patients with SNVC.

An interesting phenomenon previously described in VC of other head and neck sites is the diagnostic challenge of this lesion. This difficulty primarily stems from...
similarities between VC and verrucous hyperplasia or typical SCC. Furthermore, Gokavarapu et al. described the possibility of “hybrid neoplasms” within VC lesions. Despite these challenges, clinicians must remain diligent to ensure the diagnostic accuracy of VC in all head and neck sites using an excisional biopsy to provide the histopathologist with the necessary tissue architecture and avoid leaving behind focal areas of SCC.

Traditionally, the mainstay of therapy of verrucous carcinoma in the head and neck, including the sinonasal tract, has been surgery. Population-based data aids the understanding of treatment trends and survival with an appropriate level of generalizability and external validation. This data also can help direct decision making during the care of patients with rare tumors such as SNVC. The vast majority of our cohort underwent primary surgery (68.6%) and exhibited a higher 5-year DSS (91%) compared with those undergoing RT alone (0%) and those treated with combined surgery and RT (78%). This trend is reinforced by Koch et al., who identified superior 5-year DSS of VC of the head and neck treated with surgery alone (86.7%) compared with RT alone (53.2%) and combined therapy (73.4%). Furthermore, our data revealed that surgery was an independent predictor of improved OS and DSS (Table III).

Another interesting trend showed that patients who underwent any form of surgical intervention, regardless of adjuvant therapy, had greater 5-year DSS compared with
those who did not (88% vs. 40%; \( P < 0.001 \)) (Fig. 3). Although these findings previously have been suggested for nonsinonasal VC, our data corroborates the typical clinical management of VC, particularly for SNVC, with population-level data allowing broader generalizability.

Combined surgery with RT demonstrated a greater survival compared with RT alone. This likely is explained by the fact that surgery was used in the total management of the patient, supported by the survival advantage in patients receiving surgery (with or without RT) (Fig. 3). It is important to note that univariate analysis did not reveal combined approaches as a significant covariate predicting survival (\( P > 0.05 \)) (Table II).

Radiation therapy and dual-modality treatment approaches portended inferior survival outcomes compared with primary surgery in SNVC. Paleri et al. demonstrated excellent tumor control of SNVC with primary surgery even with advanced stage lesions.\(^{32}\) Extrapolating from our cohort and Paleri et al., it is reasonable to pursue primary surgery for SNVC (similar to VC management in other head and neck subsites), and reserve adjuvant or primary radiation for patients in whom there is a concern for residual disease or poor surgical candidacy.

Given the inability to compute the predictive performance of variables with respect to DSS due to low death rates and censored cases, we simplified Table III to depict only those predicting OS. We identified primary site as an independent predictor of poorer DSS (Table III). Specifically, nasopharyngeal VC demonstrated significantly reduced 5-year DSS compared with the nasal cavity (36% vs. 89%; \( P = 0.002 \)) (Fig. 3). Although there were fewer cases in the nasopharynx (\( n = 5 \)) compared to the nasal cavity (\( n = 44 \)), which is an inherent limitation of our study, statistical significance was achieved. Poorer survival for primary nasopharyngeal VC may be explained by proximity to critical bony and neurovascular structures. Although T-stage data was available for only two of five nasopharyngeal VCs (\( T_1 = 1 \), \( T_2 = 2 \)), both did not have nodal or metastatic disease. The predictive performance of other sinonasal subsites was elusive in this study likely due to sample sizes, but future population-based studies with greater numbers of cases would be valuable in SNVC.

Analysis of survival outcomes based on stage was performed via information available for 31 of 86 cases. As shown in nonsinonasal VC,\(^{4}\) advanced stage was associated with survival differences on univariate analysis. However, tumor stage failed to independently predict outcomes following multivariate methods. We speculate that a potential selection bias may explain this finding because our cohort was primarily comprised of stage I (58.1%) and stage II (32.3%) patients. Likewise, nonsinonasal VC similarly presents with locally confined disease without nodal or distant metastases (92.4%).\(^{3}\) Clinically, it is reasonable to anticipate poorer outcomes in patients with larger tumors because the extent of surgical resection may be greater. This increases the risk of operative and postoperative complications. Our findings question the role of neck dissection in SNVC given that nodal and distant disease were not observed.

Along with tumor staging, tumor grade information was assessed for survival differences in the available data for 47 of 86 patients. The majority of cases were well-differentiated (85.1%) and moderately differentiated (12.8%), with only one case of poorly differentiated SNVC (2.1%). Advanced grade was found to be an independent predictor of reduced DSS (HR 3.7; \( P = 0.01 \)) (Table III). Although there was only a single case of poorly differentiated SNVC, the predictive performance demonstrates a greater risk for poorly differentiated compared to well-differentiated tumors (HR 14.2; \( P = 0.02 \)) (Table III). This finding should be interpreted with caution because VC is by definition a well-differentiated variant of SCC, and staging information was unavailable for this patient.

Although several studies in the literature have utilized the SEER database for retrospective analysis of head and neck cancers, notable limitations are inherent in this research vehicle. Details regarding the specific surgeries and approaches are limited. Additionally, detailed radiation regimens would have enhanced the analysis. In the present report, staging information was available for 31 of 86 patients, which may present a selection bias. Nonetheless, the SEER database simultaneously provides useful clinical guidance and utility. As a population-based registry that is representative of approximately 30% of the U.S. population, analysis provides an improved understanding of verrucous carcinoma involving the sinonasal tract. Single-institution case series are limited by low numbers of affected patients. We present the first and largest population-level analysis of SNVC. Our findings carry a greater strength of external validity compared to prior reports on SNVC, clarify the prognosis, and reinforce the management of this malignancy.

**CONCLUSION**

Verrucous carcinoma of the sinonasal tract is an uncommon malignancy that exhibits similar clinical behavior to VC of the oral cavity and larynx. Absence of nodal and distant disease is typical. SNVC carries an overall improved survival relative to conventional SCC. Surgery is the mainstay of treatment and is an independent predictor of higher overall and disease-specific survival.

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