

Head and neck verrucous carcinoma

A population-based analysis of incidence, treatment, and prognosis

Na Wang, MD^a, Ming Huang, MD^b, Hong Lv, MD, PhD^{c,*}

Abstract

Verrucous carcinoma is a rare variant of squamous cell carcinoma. The oral cavity, genitals, larynx, esophagus, and skin are usually affected, and the head and neck regions are the most affected areas. Few studies reported about head and neck verrucous carcinoma (VC) in the literature. Therefore, we conducted an extensive population-based study about the VCs to use population-based data to further investigate the incidence, treatment, and survival of head and neck verrucous carcinoma.

Patients from Surveillance, Epidemiology, and End Results database (SEER) between 1973 and 2015 were brought into our study. The data of VCs and other head and neck malignancies (OHNMs) patients were extracted for analysis. We compared characteristics of patients with VC with those of patients with OHNMs.

Results were obtained for 2039 cases of VC and 394,739 cases of OHNM. Compared to patients with OHNM, patients with VC were more often female (36.6% vs 31.1%; $P < .001$), younger (median age 62 vs 67 years; $P < .001$), and had a smaller tumor size ($P < .001$). VC cases were of lower histological grade and SEER stage ($P < .001$). The incidence of VC was 0.075 per 100,000 and decreased over time (annual change -1.855% , $P < .001$), whereas the incidence of OHNM showed no change. The primary treatment method for VC was surgery, with other treatments showing no significant therapeutic effect.

VC is rare, with a decreasing incident trend. The outcome is better compared with OHNM patients. Surgery could significantly improve VC patients' prognosis.

Abbreviations: CSS = cancer-specific survival, OHNMs = other head and neck malignancies, OS = overall survival, SEER = surveillance, epidemiology, and end results database, VC = head and neck verrucous carcinoma.

Keywords: SEER, survival, verrucous carcinoma

1. Introduction

Verrucous carcinoma is a rare variant of squamous cell carcinoma. It was first reported as an exogenous and well-differentiated variant by Ackerman in 1948.^[1] The oral cavity, genitals, larynx, esophagus, and skin are usually involved, and

the head and neck regions are the most affected areas.^[2] It grows slowly, mainly exogenously, and can reach a considerable extent before the patients notice it. It looks like a papillary mass with a grayish-white or red color, which is different from the typical ulcer nodule characteristics of squamous cell tumors. Histologically, verrucous carcinoma shows severe keratinization, well-differentiated, and lack of atypia. It has only local invasiveness and little metastatic potential.^[3,4]

Verrucous cancer mainly affects the mouth and throat in the head and neck. It is mainly found in older men, usually around the age of sixty, and is closely related to the use of tobacco and areca.^[5,6] Surgery is still the primary treatment, radiotherapy, and chemotherapy as adjuvant therapy.^[7-9]

Although there are some studies on head and neck squamous cell carcinoma in the literature,^[10-12] there is no extensive population-based analysis of head and neck verrucous cancer. Because this type of tumor is very rare, only a few case reports describe the epidemiology and relevant factors that influence survival outcomes.^[13-15] Therefore, we decided to use population-based data to further investigate the incidence, treatment, and survival of head and neck verrucous carcinoma.

2. Materials and methods

2.1. Data extraction and management

We used VC and OHNM cases from the SEER database (1973–2015) for analysis. Since the patients' information is anonymous, and all data comes from the SEER public database, an additional

Editor: Eric Bush.

NW and MH contribute equally to this work.

The authors have no funding and conflicts of interest to disclose.

All data supporting the results of this article are from the SEER database (1973–2015).

^a Department of otolaryngology, Medical School of Facial Sciences, Hubei University of Science and technology, ^b Department of Thyroid and breast surgery, Xianning Central Hospital, the First Affiliated Hospital of Hubei University of Science and Technology, ^c School of Nursing, Hubei University of Science and Technology, Xianning, China.

* Correspondence: Hong Lv, School of Nursing, Hubei University of Science and Technology, Xianning, China (e-mail: lvhong1212@126.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Wang N, Huang M, Lv H. Head and neck verrucous carcinoma: A population-based analysis of incidence, treatment, and prognosis. *Medicine* 2020;99:2(e18660).

Received: 4 May 2019 / Received in final form: 14 November 2019 / Accepted: 4 December 2019

<http://dx.doi.org/10.1097/MD.0000000000018660>

approval from the ethics committee or institutional review board is not necessary. Using the topography codes (C00-C14; C30-C33; C41.0; C41.1; C44.0–4; C47.0; C49.0; C76.0 and C77.0), we identified the malignancies happened in head and neck. The historical type code (8051/3) of the International Classification of Diseases for Oncology, third edition (ICD-O-3), was used to retrieve the VCs' data. By combining the topography codes with the historical type code, we extracted data of head and neck VC patients. In the meantime, we extracted data from all head and neck malignancies without a historical type code of 8051/3 as the ONHMs group. We excluded patients using the following criteria:

- (1) VC was not the first tumor;
- (2) lacking histology confirmation;
- (3) missing essential information.

The patient demographics, clinical characteristics, follow-up, and vital status, were acquired using SEER*Stat software (version 8.3.4; National Cancer Institute, Bethesda, MD). We set cancer-specific survival (CSS) and overall survival (OS) as the endpoints.

2.2. Statistical analysis

For baseline characteristics, continuous variables were described by means and standard deviations and compared using the *t* test. Categorical variables were described using frequencies and percentages and compared using the Chi-square test or Fisher exact test. We used propensity score matching (1-to-1) method to mimic randomized controlled trials and reduce the selection bias. Nearest-neighbor matching was performed with a stringent caliper of 0.02, and age and sex were selected into the logistic regression model. The survival period was calculated from the

Table 1
Patient characteristics for head and neck verrucous carcinoma.

Unmatched cohort				Matched cohort			
Parameter, n (%)	Head and neck Verrucous carcinoma (n = 2039)	Other head and neck malignancies (n = 394739)	P	Parameter, n (%)	Head and neck Verrucous carcinoma (n = 888)	Other head and neck malignancies (n = 888)	P
Year (%)				Year (%)			
1973-1983	284 (13.9)	42820 (10.8)	<.001	1973-1983	0 (0.0)	0 (0.0)	<.001
1984-1994	379 (18.6)	57029 (14.4)		1984-1994	104 (11.7)	209 (23.5)	
1995-2005	652 (32.0)	124544 (31.6)		1995-2005	331 (37.3)	239 (26.9)	
2006-2015	724 (35.5)	170346 (43.2)		2006-2015	453 (51.0)	440 (49.5)	
Age (years)				Age (years)			1
Median	67	62	<.001	≤60	299 (33.7)	299 (33.7)	
Mean	66.4	61.1		>60	589 (66.3)	589 (66.3)	
Range	25-102	0-110		Size (cm)			
Size (cm)				Median	2.2	2	<.001
Median	2.2	3	<.001	Mean	4.5	9.9	
Mean	4.5	19.3		Range	0-99	0-99	
Range	0-99	0-99		Sex (%)			
Sex (%)				Male	363 (40.9)	363 (40.9)	1
Male	1292 (63.4)	272001 (68.9)	<.001	Female	525 (59.1)	525 (59.1)	
Female	747 (36.6)	122738 (31.1)		Race/ethnicity (%)			
Race/ethnicity (%)				White	745 (83.9)	706 (79.5)	.001
White	1765 (86.6)	332667 (84.3)	<.001	Black	62 (7.0)	107 (12.0)	
Black	120 (5.9)	34475 (8.7)		Other	70 (7.9)	72 (8.1)	
Other	125 (6.1)	22376 (5.7)		Unknown	11 (1.2)	3 (0.3)	
Unknown	29 (1.4)	5221 (1.3)		Grade (%)			
Grade (%)				I	379 (42.7)	82 (9.2)	<.001
I	706 (34.6)	38693 (10.0)	<.001	II	55 (6.2)	236 (26.6)	
II	113 (5.5)	92370 (23.4)		III	7 (0.8)	172 (19.4)	
III	15 (0.7)	61387 (15.6)		IV	0 (0.0)	40 (4.5)	
IV	1 (0.1)	10217 (2.6)		Unknown	447 (50.3)	358 (40.3)	
Unknown	1204 (59.0)	192072 (48.7)		Marital			
Marital				Married	445 (50.1)	308 (34.7)	<.001
Married	1036 (50.8)	207141 (52.5)	.064	Status			
Status				Unmarried	371 (41.8)	545 (61.4)	
Unmarried	781 (38.3)	150265 (38.1)		Others	72 (8.1)	35 (3.9)	
Others	222 (10.9)	37333 (9.5)		Seer stage			
Seer stage				I	571 (64.3)	265 (29.8)	<.001
I	1173 (57.5)	133863 (33.9)	<.001	II	223 (25.1)	348 (39.2)	
II	451 (22.1)	115443 (29.2)		III	15 (1.7)	84 (9.5)	
III	31 (1.5)	31194 (7.9)		IV	20 (2.3)	81 (9.1)	
IV	175 (8.6)	78866 (20.0)		Unknown	59 (6.6)	110 (12.4)	
Unknown	209 (10.3)	35373 (9.0)		Incidence (2015)			
Incidence (2015)	0.075	24.816		Annual percentage change (1973–2015)			
Annual percentage change (1973–2015)	−1.855 (P < .001)	0.033 (P = .413)					

Rates are per 100,000 and age adjusted to the 2000 US Standard Population (19 age groups, census P25-1130) standard.

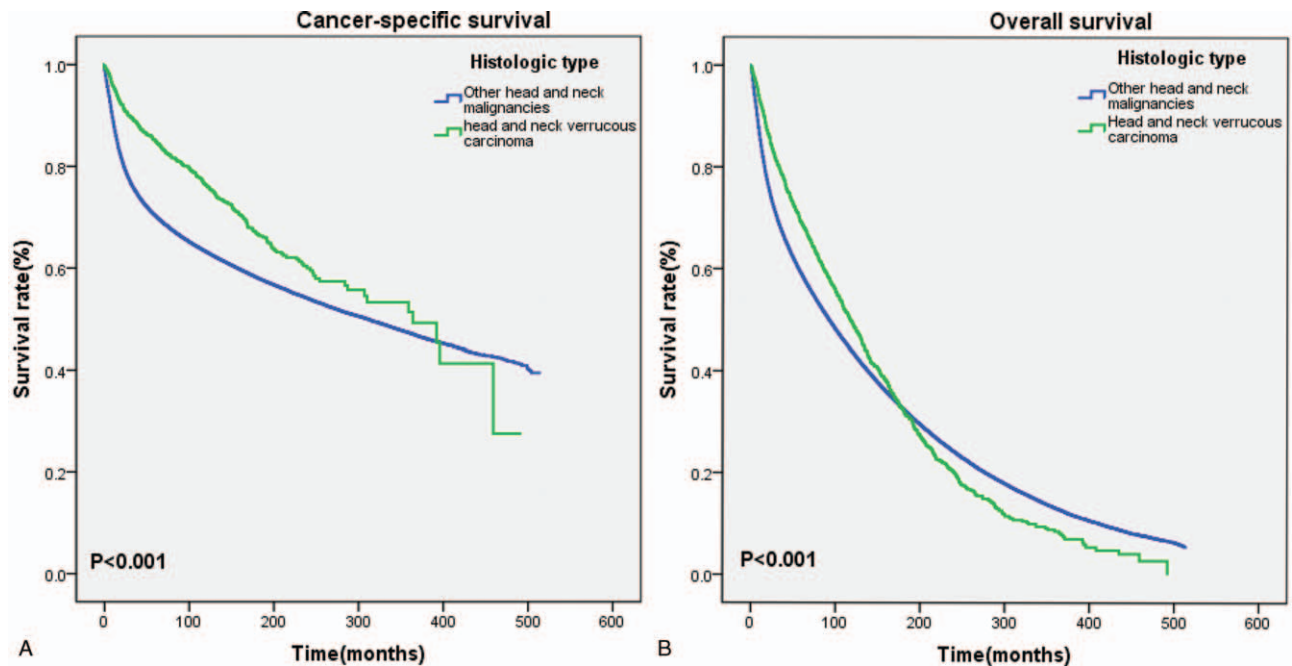


Figure 1. The Kaplan–Meier curves for VC and OHNM patients. In Figure 1A, VC patients had better cancer-specific survival compared with the OHNM patients ($P < .001$). For overall survival in 1B, VC patients have better short-time survival while a worse long-time survival ($P < .001$).

date of the VC diagnosis until the time of death or the last follow-up. The survival analysis was conducted using the Kaplan–Meier method with the log-rank test. We conducted all the analysis using SPSS, version 24.0 (SPSS Inc., Chicago, IL). A Two-sided $P < .05$ was considered statistically significant.

3. Results

3.1. Demographics

In our study, 2039 VC patients and 394,739 patients with other head and neck malignancies (OHNMs) between 1973 and 2015 from the SEER database were extracted. The demographic characteristics are shown in Table 1. Patients with VC were older than patients with OHNMs (median age: 67 vs 62 years, $P < .001$). Compared with OHNMs, more VC cases were found in females (36.6% vs 31.1%; $P < .001$) and had a smaller tumor size ($P < .001$). The tumors of VC patients had a lower histological grade and SEER stage than OHNMs’ (both $P < .001$). Besides, there was no significant difference in gender between both groups. As shown in Figure 1, VC patients (green line) had a better cancer-specific survival rate compared with the OHNM patients (Fig. 1A, $P < .001$). For the overall survival, survival for VC seems to be better, up to about 200 months, and gets worse subsequently (Fig. 1B, $P < .001$).

3.2. Tumor characteristics of VCs

As shown in Table 2, we summarized the TNM and American Joint Committee on Cancer (AJCC) seventh stages of VCs (year 2010+, $n = 445$). For these patients, T1 was the most common stage (39.8%), followed by T2 (22.9%), T3 (6.7%), and T4 (5.6%). The 84.9% of VC patients had no lymph node involvement, and no patients had distant metastasis. About

AJCC staging, the fractions were decreased corresponding to the stages from high to low: I (37.5%), II (21.1%), III (8.3%) and IV (6.5%).

Table 2

Tumor characteristics for head and neck verrucous carcinoma and other head and neck malignancies.

AJCC Stage 7th, year 2010+

Tumor characteristics	AJCC Stage 7th, year 2010+		P
	VCs	OHNMs	
	Number (%)	Number (%)	
T stage	0 (0.0)	187 (0.2)	<.001
T1	177 (39.8)	31875 (30.3)	
T2	102 (22.9)	19429 (18.5)	
T3	30 (6.7)	12084 (11.5)	
T4	25 (5.6)	12900 (12.3)	
TX	111 (24.9)	28657 (27.3)	
N stage			<.001
N0	378 (84.9)	49630 (47.2)	
N1	14 (3.1)	10169 (9.7)	
N2	7 (1.6)	20457 (19.5)	
N3	0 (0.0)	2317 (2.2)	
NX	46 (10.3)	22559 (21.5)	
M stage			<.001
M0	442 (99.3)	84098 (80.0)	
M1	0 (0)	3252 (3.1)	
MX	3 (0.7)	17782 (16.9)	
AJCC stage			<.001
I	167 (37.5)	33520 (31.9)	
II	94 (21.1)	13523 (12.9)	
III	37 (8.3)	12001 (11.4)	
IV	29 (6.5)	30304 (28.8)	
Unknown	118 (26.5)	15784 (15.0)	

AJCC = American Joint Committee on Cancer, OHNM = other head and neck malignancies, VC = head and neck verrucous carcinoma.

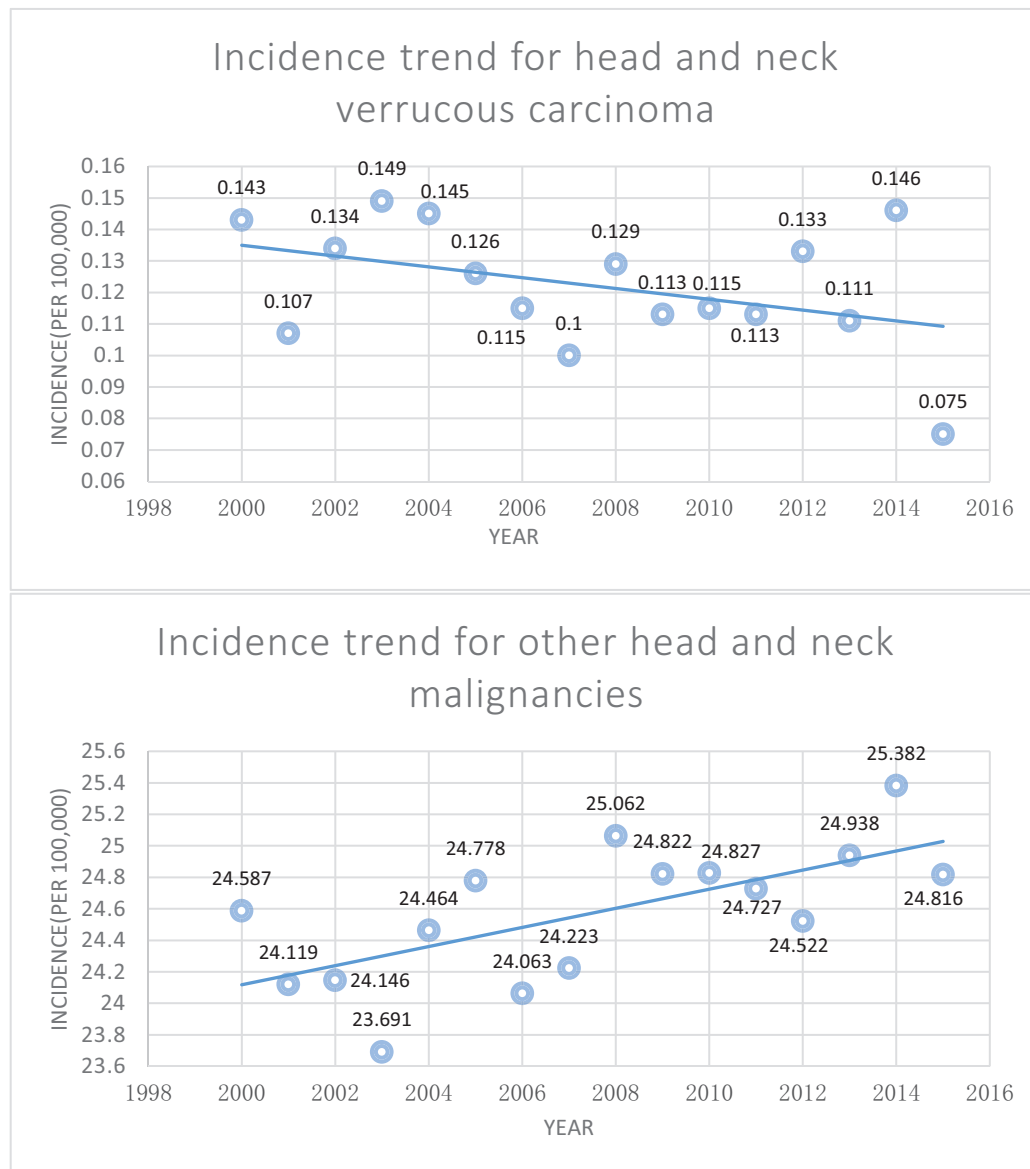


Figure 2. The incidence trend for VCs and OHNMs. The incidence of OHNM has increased, in contrast, which of VC has decreased.

3.3. Incidence exploration

After age adjustment to the 2000 US Standard Population, the incident rate of VC was 0.075 per 100,000 between 2000 and 2015 (Table 1). It is different from the relatively stable incidence of OHNMs (0.033 per 100,000, $P = .413$), where the incidence rate of VC was decreasing (Fig. 2). The annual percentage change of the incidence was -1.855 ($P < .001$).

3.4. The relationship between different therapies and VC patients' survival

The treatments for VCs and OHNMs were shown in Table 3. Most VC patients had conducted surgical treatments (51.3%), a statistical difference compared with the OHNM cohort (41.0%, $P < .001$). Patients with OHNMs had undergone more frequent

chemotherapy, radiotherapy, and a combination of multiple treatments compared to the VC patients (27.2% vs 4.1%; 48.3% vs 21.0%; 5.8% vs 1.4%, all $P < .001$).

The Kaplan–Meier analysis was used to evaluate the effectiveness of different therapies in VC patients. As Figure 3 showed, both for OS and CSS, surgical treatment exhibited an excellent therapeutic effect ($P < .001$). However, the prognosis for VC patients given chemotherapy and radiotherapy was worse than the ones who did not.

What is more, we made a comparison among three treatment modalities, including surgery alone, chemotherapy alone, radiotherapy alone, combined surgery with chemotherapy, and combined surgery with radiotherapy (Fig. 4). The overall survival and cancer-specific survival exhibit the same trend. The result showed that surgical treatment could effectively prolong the patients' prognosis. A combination of a variety of treatments

Table 3

Treatment for head and neck verrucous carcinoma and other malignancies. OR: odds ratio; 95%CI: 95% confidence intervals; ORs were obtained through (without treatment group) / (treatment group).

	Unmatched cohort			Matched cohort			
	Head and neck verrucous carcinoma (n=2039, OR (95%CI))	All other head and neck malignancies (n=394739, OR (95%CI))	P	Head and neck verrucous carcinoma (n=888, OR (95%CI))	All other head and neck malignancies (n=888, OR (95%CI))	P	
	No. (%)	No. (%)		No. (%)	No. (%)		
Surgery	OR: 0.4 (0.4–0.5)	OR: 1.0 (1.0–1.0)	<.001	Surgery	OR: 0.3 (0.27–0.34)	OR: 3.6 (3.2–4.2)	<.001
No surgery	994 (48.7)	233075 (59.0)		No surgery	234 (26.4)	717 (80.7)	
Surgery	1045 (51.3)	161664 (41.0)		Surgery	654 (73.6)	171 (19.3)	
Radiotherapy	OR: 4.4 (3.7–5.2)	OR: 1.0 (1.0–1.0)	<.001	Radiotherapy	OR: 2.5 (2.0–2.5)	OR: 0.5 (0.5–0.6)	<.001
No radiotherapy	1611 (79.0)	204239 (51.7)		No radiotherapy	728 (82.0)	424 (47.7)	
Radiotherapy	428 (21.0)	190500 (48.3)		Radiotherapy	160 (18.0)	464 (52.3)	
Chemotherapy	OR: 8.8 (6.5–11.8)	OR: 1.0 (1.0–1.0)	<.001	Chemotherapy	OR: 6.3 (4.8–8.4)	OR: 0.4 (0.38–0.44)	<.001
No chemotherapy	1955 (95.9)	287450 (72.8)		No chemotherapy	843 (94.9)	484 (54.5)	
Chemotherapy	84 (4.1)	107289 (27.2)		Chemotherapy	45 (5.1)	404 (45.5)	
Surgery+Radiotherapy+Chemotherapy	OR: 4.2 (2.6–6.5)	OR: 1.0 (1.0–1.0)	<.001	Surgery+Radiotherapy+Chemotherapy	OR: 1.1 (0.8–1.5)	OR: 0.9 (0.7–1.2)	.541
None	2011 (98.6)	371829 (94.2)		None	868 (97.7)	864 (97.3)	
Surgery+Radiotherapy+Chemotherapy	28 (1.4)	22910 (5.8)		Surgery+Radiotherapy+Chemotherapy	20 (2.3)	24 (2.7)	

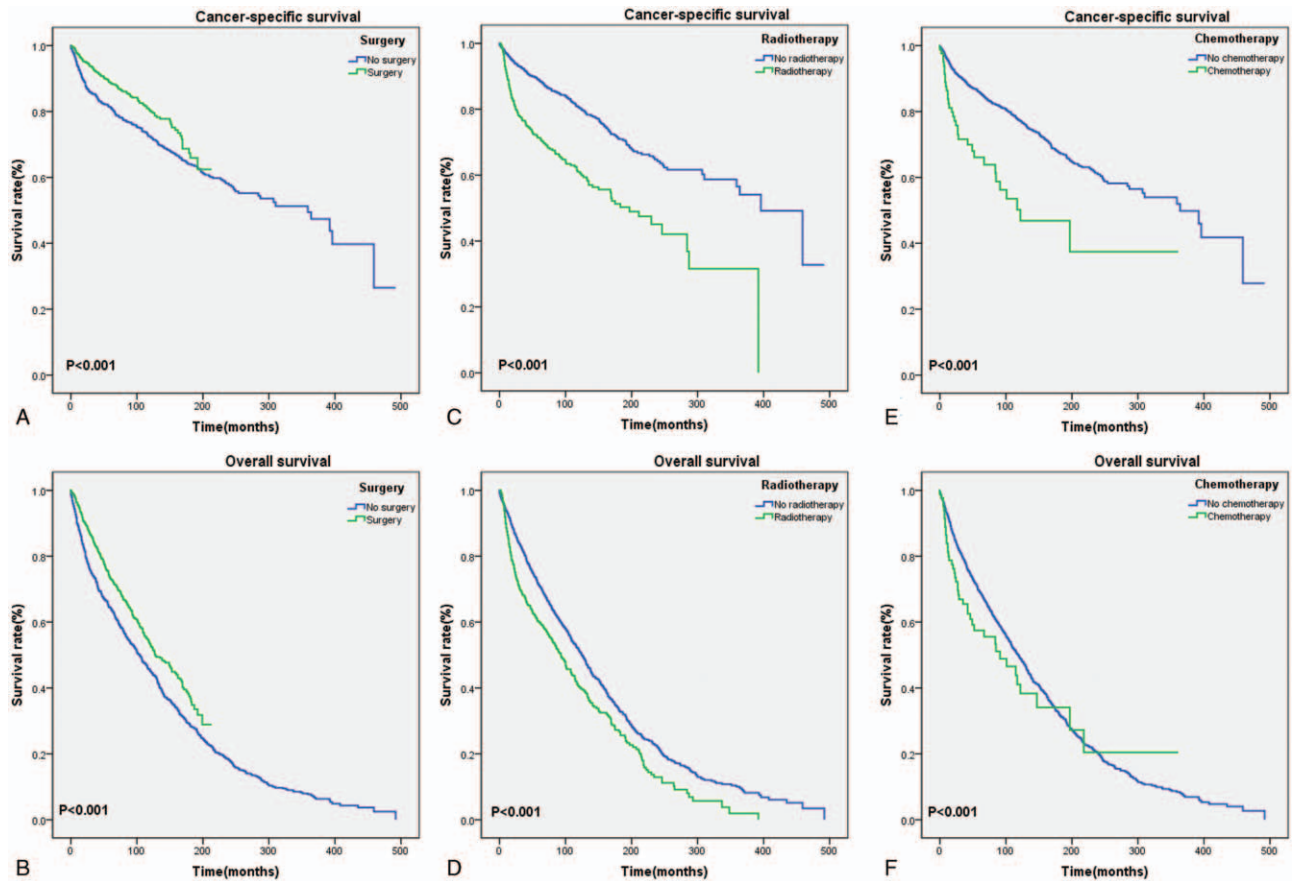


Figure 3. Survival analysis of VCs between different monotherapy groups (blue: patients without corresponding treatment; green: patients with corresponding treatment. A, B: surgery; C, D: radiotherapy; E, F: chemotherapy). Both OS and CSS, surgical treatment exhibited an excellent therapeutic effect ($P < .001$). The prognosis for VC patients who applied chemotherapy and radiotherapy were worse than without ones.

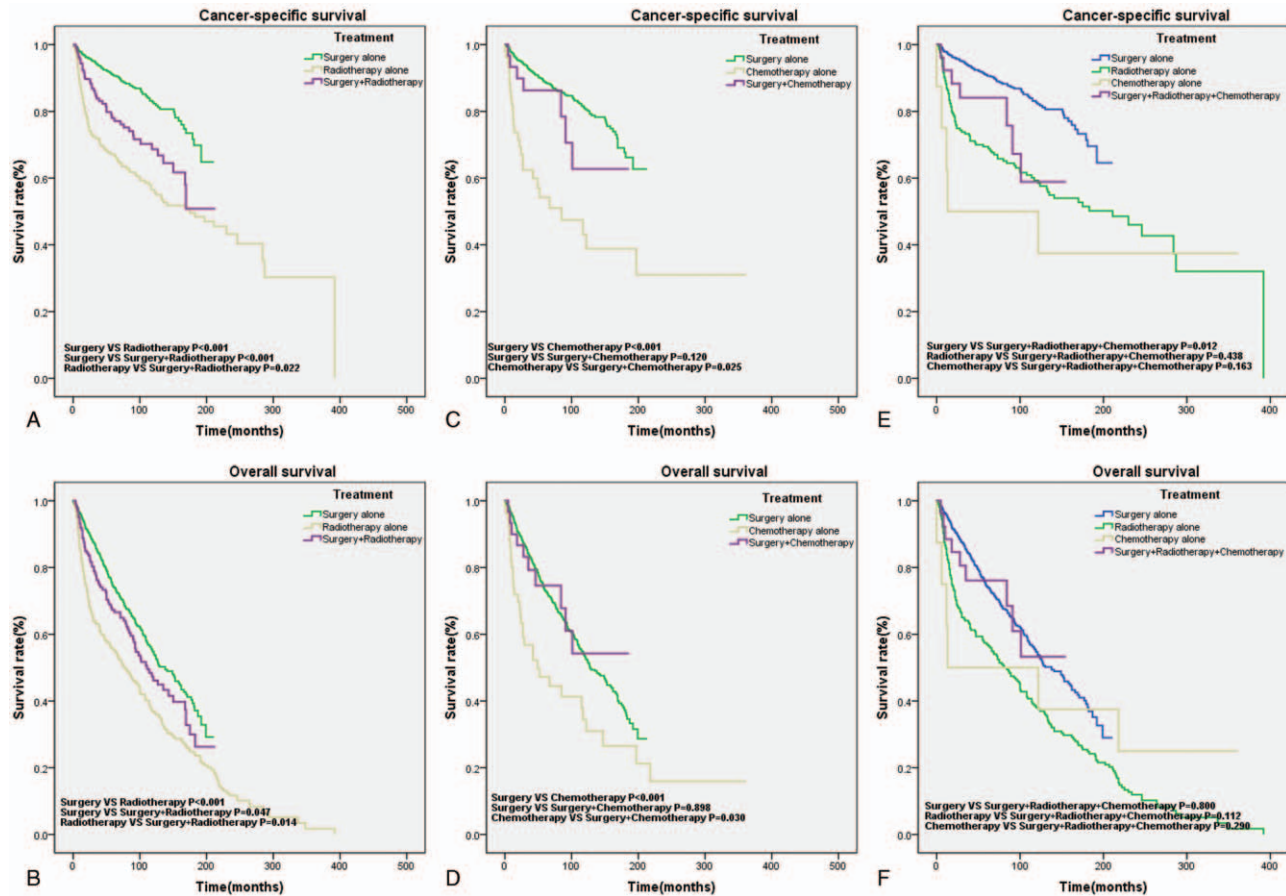


Figure 4. Survival analysis of VCs between the monotherapy group and the combined therapy group (Fig. A, B: green: surgery alone; yellow: radiotherapy alone; purple: surgery combined with radiotherapy. Fig. C, D: green: surgery alone; yellow: chemotherapy alone; purple: surgery combined with chemotherapy. Fig. E, F: blue: surgery alone; yellow: chemotherapy alone; green: radiotherapy alone; purple: surgery combined with chemotherapy and radiotherapy.). Surgical treatment could effectively prolong patients' prognosis. Combined with a variety of treatments based on surgical treatment, may improve the prognosis of patients.

based on surgical treatments may improve the patient's prognosis.

4. Discussion

Although there are a small number of epidemiological studies on laryngeal squamous cell carcinoma, similar studies of head and neck verrucous carcinoma are still lacking. Head and neck verrucous cancer usually occurs in the mouth, but there are some cases reported that can occur in the throat and sinuses.^[16] It looks like a cauliflower in morphology. Under the microscope, it is composed of a thick, well-differentiated keratinized squamous epithelium that lacks cytological atypia.^[17] At the matrix interface, it always has a clear push boundary, so it is difficult to assess its invasiveness.^[18] It grows slowly compared to other head and neck malignancies. Although it can cause local damage, studies have shown that it is unlikely to transfer,^[19] which is the same as our result. Therefore, in order to have a better understanding of head and neck verrucous cancer, we compared the incidences and survival rates between head and neck verrucous cancer and other malignant tumors of the head and neck in this study.

We found that the cancer-related survival rate and overall survival rate of head and neck squamous cell carcinoma were

better than other malignant tumors of the head and neck, but the difference became less evident for the long-term survival. Although the head and neck verrucous cancer itself grows slowly and has rare metastasis,^[21] in the long term, it may cause harmful long-term effects to the body. According to our data, the incidence of head and neck verrucous cancer decreased in the recent years, which was different from other malignant tumors in the head and neck. This downward trend may be caused by the improved detection techniques, which makes it easier to identify head and neck verrucous cancer from other head and neck malignant tumors.^[22] In the old days, we distinguished them through the tumor morphology and pathological morphology. This process makes us misdiagnose easily because of human error. Now, we can use separate biomarkers, such as CK10 and CD68, or do deep biopsies, for example. These procedures are much more accurate than before.^[23,24] The trend might also be caused by the discovery about the harm of tobacco and areca in recent years,^[2] which reduces the incidence of verrucous cancer of the head and neck.

At present, the main treatment methods for head and neck verrucous cancer include surgery, radiotherapy, and chemotherapy.^[20,25] Surgical treatment has been the primary therapeutic method for verrucous cancer. It is no doubt that there would be a dysfunction after an oral tumor resection, and some patients

cannot afford surgical treatment because of their poor body condition. Therefore, a small number of patients choose to conduct radiotherapy or chemotherapy. There are few types of research which have been conducted to compare the effects of these treatments in head and neck verrucous cancer. We firstly compared the cancer-specific survival rate and the overall survival rate between the patients with or without these three treatments. We found that patients with surgical treatment had a better prognosis than patients without surgery. Their cancer-related survival rate and overall survival rate were higher than patients who had not been operated. However, in general, patients with radiation therapy had a worse prognosis than patients without radiotherapy. Moreover, patients with chemotherapy had a worse prognosis than patients without chemotherapy. Their survival rate was lower than those without radiotherapy or chemotherapy. These results indicated that the therapeutic effect of the operation was substantial, but the effect of chemotherapy and radiotherapy was not confirmed, which might be caused by the differences in the patients' disease status. Chemotherapy and radiotherapy also have adverse effects on the physical condition of the patients.^[26] We analyzed the results of receiving these three treatments alone and different combinations of treatments. By comparing the survival data, we found that patients who only had surgical treatment had a better prognosis than patients who had undergone both surgery and radiotherapy, and at the same time, patients with surgery and radiotherapy had a better prognosis than those who received radiotherapy alone. We speculated that this might be because patients who only received radiotherapy had a higher tumor severity or sparse staging, or because radiotherapy itself was not effective. Moreover, it was shown that patients with surgery alone had a better prognosis than patients with chemotherapy alone, but patients who received surgery alone had a little difference in prognosis with patients who had undergone both surgery and chemotherapy. Patients with surgery alone had a higher cancer-specific survival rate than patients with both surgery and radiotherapy, and chemotherapy but had a little difference in overall survival. All of these suggest that when treating head and neck verrucous cancer, surgery is the best therapeutic method while radiotherapy and chemotherapy should be carefully selected, and may be of no use.

There are several limitations to our study. First, the study was a retrospective research. Second, the treatment information provided by the SEER database is not comprehensive, and it does not contain specific information on neoadjuvant therapy, postoperative adjuvant therapy, and radiotherapy. What is more, the study period spans in a long time, from 1973 to 2015. Many changes happened in diagnosis, treatment, and surveillance of VC over this period, which would bring heterogeneity. Despite these limitations, our study provides a large cohort of VC patients and illustrates essential clinical information about VCs.

5. Conclusion

VC is rare and less aggressive than OHNM. Surgical treatments can significantly prolong VC patients' prognosis.

Author contributions

Conceptualization: Ming Huang, Hong Lv.

Data curation: Na Wang.

Formal analysis: Na Wang.

Investigation: Na Wang, Ming Huang.

Methodology: Na Wang, Ming Huang.

Project administration: Na Wang, Ming Huang.

Supervision: Ming Huang, Hong Lv.

Visualization: Ming Huang.

Writing – original draft: Na Wang, Hong Lv.

Writing – review & editing: Hong Lv.

References

- Ackerman LV. Verrucous carcinoma of the oral cavity. *Surgery* 1948;23:670–8.
- Alkan A, Bulut E, Gunhan O, et al. Oral verrucous carcinoma: a study of 12 cases. *Eur J Dent* 2010;4:202–7.
- Shear M, Pindborg JJ. Verrucous hyperplasia of the oral mucosa. *Cancer* 1980;46:1855–62.
- Santoro A, Pannone G, Contaldo M, et al. A troubling diagnosis of verrucous squamous cell carcinoma (“the Bad Kind” of Keratosis) and the need of clinical and pathological correlations: a review of the literature with a case report. *J Skin Cancer* 2011;2011:370605.
- Rekha KP, Angadi PV. Verrucous carcinoma of the oral cavity: a clinicopathologic appraisal of 133 cases in Indians. *Oral Maxillofac Surg* 2010;14:211–8.
- Fonts EA, Greenlaw RH, Rush BF, et al. Verrucous squamous cell carcinoma of the oral cavity. *Cancer* 1969;23:152–60.
- Koch BB, Trask DK, Hoffman HT, et al. Commission on Cancer ACoS, American Cancer S. National survey of head and neck verrucous carcinoma: patterns of presentation, care, and outcome. *Cancer* 2001;92:110–20.
- Jyothirmayi R, Sankaranarayanan R, Varghese C, et al. Radiotherapy in the treatment of verrucous carcinoma of the oral cavity. *Oral Oncol* 1997;33:124–8.
- Medina JE, Dichtel W, Luna MA. Verrucous-squamous carcinomas of the oral cavity. A clinicopathologic study of 104 cases. *Arch Otolaryngol* 1984;110:437–40.
- Challapalli SD, Simpson MC, Adjei Boakye E, et al. Head and neck squamous cell carcinoma in adolescents and young adults: survivorship patterns and disparities. *J Adolesc Young Adult Oncol* 2018;7:472–9.
- Mukdad L, Heineman TE, Alonso J, et al. Oral tongue squamous cell carcinoma survival as stratified by age and sex: a surveillance, epidemiology, and end results analysis. *Laryngoscope* 2018;129:2076–81.
- Kruse AL, Bredell M, Luebbers HT, et al. Head and neck cancer in the elderly: a retrospective study over 10 years (1999-2008). *Head Neck Oncol* 2010;2:25.
- Durden FL Jr, Moore CE, Muller S. Verrucous carcinoma of the paranasal sinuses: a case report. *Ear Nose Throat J* 2010;89:E21–23.
- Walvekar RR, Chaukar DA, Deshpande MS, et al. Verrucous carcinoma of the oral cavity: A clinical and pathological study of 101 cases. *Oral Oncol* 2009;45:47–51.
- Orvidas LJ, Olsen KD, Lewis JE, et al. Verrucous carcinoma of the larynx: a review of 53 patients. *Head Neck* 1998;20:197–203.
- Alonso JE, Han AY, Kuan EC, et al. Epidemiology and survival outcomes of sinonasal verrucous carcinoma in the United States. *Laryngoscope* 2018;128:651–6.
- Sonalika WG, Anand T. Oral verrucous carcinoma: A retrospective analysis for clinicopathologic features. *J Cancer Res Ther* 2016;12:142–5.
- Teymoortash A, Silver CE, Rinaldo A, et al. Verrucous carcinoma: a retrospective diagnosis in three historic patients. *Eur Arch Otorhinolaryngol* 2014;271:631–3.
- Odar K, Kocjan BJ, Hosnjak L, et al. Verrucous carcinoma of the head and neck - not a human papillomavirus-related tumour? *J Cell Mol Med* 2014;18:635–45.
- Chang BA, Katz S, Kompelli AR, et al. Is primary radiotherapy an acceptable treatment modality for verrucous carcinoma of the larynx? *Laryngoscope* 2019;129:1964–5.
- Sadasivan A, Thankappan K, Rajapurkar M, et al. Verrucous lesions of the oral cavity treated with surgery: analysis of clinico-pathologic features and outcome. *Contemp Clin Dent* 2012;3:60–3.
- Whitefield S, Raiser V, Shuster A, et al. The spectrum of oral lesions presenting clinically with papillary-verrucous features. *J Oral Maxillofac Surg* 2018;76:545–52.

- [23] Hosseinpour S, Mashadiabbas F, Ahsaie MG. Diagnostic biomarkers in oral verrucous carcinoma: a systematic review. *Pathol Oncol Res* 2017;23:19–32.
- [24] Thariat J, Hourseau M, Baglin AC, et al. Diagnostic and treatment pitfalls and guidelines for variants of squamous cell carcinomas of the head and neck: on behalf of the REFCOR. *Bull Cancer* 2019;106:395–403.
- [25] Devaney KO, Ferlito A, Rinaldo A, et al. Verrucous carcinoma (carcinoma cuniculatum) of the head and neck: what do we know now that we did not know a decade ago? *Eur Arch Otorhinolaryngol* 2011;268:477–80.
- [26] Edstrom S, Johansson SL, Lindstrom J, et al. Verrucous squamous cell carcinoma of the larynx: evidence for increased metastatic potential after irradiation. *Otolaryngol Head Neck Surg* 1987;97:381–4.