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ORIGINAL RESEARCH

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Demographic and pathologic factor regression to a growth rate model of p16-negative oral cavity squamous cell carcinoma

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Abstract

Objectives: The current study aims to quantify the growth rate of p16-negative oral cavity squamous cell carcinoma, characterize causative relationships between demographic risk factors and tumor growth, and examine pathologic findings associated with the tumor growth rate at a tertiary care institution. It is hypothesized that causative relationships will be drawn between the individual sociodemographic and pathologic factors and oral cavity p16-negative squamous cell carcinoma growth rate.

Methods: Prospectively recruited participants, receiving surgical intervention only, were followed from initial staging CT scan to surgical resection. Interval growth was calculated in cm^3/week. Demographic information including age, sex, smoking history, alcohol consumption history, previous all-type malignancy, previous chemotherapy treatment, previous head or neck radiation exposure, and time interval elapsed between diagnosis and surgery was collected from each participant, and regression analysis was applied to determine causality.

Results: Summary statistics revealed a mean growth rate for the study sample of 1.385cm^3/week. Statistically significant regression correlations were detected between tumor growth and alcohol consumption, origination at the retromolar trigone, and clinical nodal stage.

Conclusions: Through a small prospective cohort sample, the current study suggests clinical associations between alcohol consumption, origination at the retromolar trigone, and clinical nodal stage with rate of tumor growth. Future work will validate these relationships in a larger patient cohort, and against stronger modeling techniques.

Level of Evidence: Prospective non-random cohort design.

KEYWORDS

computed tomography, growth rate, oral cavity squamous cell carcinoma, risk factors, tumor growth modeling

1 | INTRODUCTION

Squamous cell carcinoma (SCC) represents a unique clinical entity in head and neck oncology, accounting for approximately 95% of malignancies arising throughout the oropharyngeal tract.[1] Specifically, oral cavity squamous cell carcinoma (OSCC) may arise from the mucosal lining of the lip, anterior tongue, floor of mouth, buccal mucosa, retromolar trigone, or hard palate. Complex anatomical interfaces in the oral cavity often result in OSCC exhibiting unpredictable growth patterns between initial clinical assessment and surgical excision, requiring more radical intervention than anticipated.[2] Consequently, a thorough understanding of demographic and pathologic factors associated with OSCC growth patterns will yield important clinical insight, critically informing treatment prioritization in an era of unpredictable surgical delays precipitated by the CoVID-19 pandemic.[3,4]

In head and neck cancer, delays between diagnosis and surgical treatment lead to disease progression, poorer outcomes, and increased risk of death.[3,5] Population-based data from the Netherlands has showed treatment delays of 30 days past baseline result in 20% increases in death hazard, and are associated with low socioeconomic status, male sex, and referral from a peripheral center.[5] Comparably, Southwestern Ontario data specific to OSCC has shown decreases in specialty-specific operating room access of 10% increase disease recurrence by 59%.[3] Additionally, individuals seen by a head and neck surgeon for primary malignancy workup preceding a month with below-average operating room hours were found to have a higher risk of disease recurrence and death.[3] Currently, Ontario surgical treatment guidelines recommend target wait times of 28 days from specialist consult to surgical resection for tumors of the head and neck in allcomers, leaving prioritization to individual surgeon's discretion.[6] Understanding factors associated with tumor volume growth between initial assessment and planned surgical resection will allow for improvement in evidence-based treatment prioritization, resulting in improved outcomes.

The role of growth rate in outcome prediction for biopsy-proven carcinoma has been previously examined skin, pancreatic, and breast cancer.[7–10] Cutaneous squamous cell carcinoma with a linear measured growth rate of greater than 4 mm per month in any orientation has been shown to exhibit higher risk of nodal progression and increased rates of nodal metastasis.[7] In literature pertaining to ductal pancreatic carcinoma, Furukawa et al. found a strong correlation between tumor volume doubling time and patient survival.[9] When examining tumors of the oral cavity, anatomical intricacy invites complexity to the analysis of cancers easily measured on superficial dermatologic structures or high resolution abdominal CT: dental amalgam can cause artifact and distortion, limiting the clinical utility of cross sectional imaging. Limited previous work has examined the role of growth rate in anatomically complex OSCC: Diffusion-weighted MRI models have shown strong predictive value for assessing the tumor growth rate in head and neck SCC patients; however, no extractable data specific to the oral cavity were presented.[11] In the current study, we employ a cursory model of oral cavity growth for the purpose of examining oral cavity tumor growth rate.

Clinical tumor-node-metastasis staging has long been standard for classifying the anatomical extent of oral cavity cancer, used in prognostication and surgical, radiotherapeutic, and chemotherapeutic planning.[12] However, despite existing correlations between tumor volume and T-stage, clinical TNM staging fails to account for intra-stage variability in tumor volume and bulk.[13] In operative planning, utility of the clinical TNM stage from the date of diagnosis is limited by morphological and volumetric changes which occur in the pre-operative interval.[14] In recent years, global efforts have been observed to incorporate tumor measurement to alongside staging information in OSCC treatment planning, as component measurements in tumor bulk estimation have been shown to be associated with depth of invasion and cervical lymph node metastasis.[15,16]

To the best of our knowledge, tumor growth rate of oral cavity squamous cell carcinoma has yet to be characterized in the context of demographic and pathologic factors. The current study aims to quantify the growth rate of p16-negative oral cavity squamous cell carcinoma, characterize causative relationships between demographic risk factors and tumor growth, and examine pathologic findings associated with the tumor growth rate at a tertiary care institution. We present a technique for tumor growth analysis via comparison of CT-measured tumor volume to post-resection pathologic measurements. Previous data have shown predictability in post-resection tissue shrinkage, allowing for comparison modeling of in vivo malignancy to post-resection tissue.[17,18] It is hypothesized that causative relationships will be drawn between individual sociodemographic and pathologic factors and oral cavity squamous cell carcinoma growth rate. In future work, results from the current study are expected to improve prediction accuracy of tumor size at operation and identify patients at high risk for rapid tumor growth, improving treatment prioritization and outcomes.

2 | MATERIALS AND METHODS

This study was undertaken with approval from the Western University Research and Ethics Board (REB ID: 116164) and Lawson Health Research Institute Research Board (ReDA ID: 11568).

2.1 | Participant recruitment

Participants were prospectively recruited from referral list of the Multidisciplinary Head and Neck Cancer Clinic at London Health Sciences Centre (LHSC), London, Ontario, Canada. Eligibility was determined based on a biopsy-proven diagnosis of squamous cell carcinoma of primary site in the anterior tongue, floor of mouth, buccal mucosa, retromolar trigone, or hard palate. Human papillomavirus strain 16-positive tumors, as determined on initial biopsy cytopathology, were excluded. Participants were included based on scheduling for surgical resection with curative intent, with no chemotherapeutic or radiotherapeutic treatment over the pre-operative interval. Participation in this study had no bearing on clinical treatment decisions.

Eligible participants were explained details of the study, questions were answered to their satisfaction, and written consent was obtained.

2.2 | Data collection

Demographic information was collected from consented participants via consultation record and supplemented with telephone interview, including age, sex, smoking history, alcohol consumption history, previous all-type malignancy, previous chemotherapy treatment, previous head or neck radiation exposure, and time interval elapsed between diagnosis and surgery.

Initial antero-posterior (A-P), craniocaudal (C-C), and depth of invasion (DOI) tumor measurements were collected by a trained head and neck radiologist (K.Y.T.) from the first captured head and neck computed tomography (CT) scan identifying the presenting malignancy. Participants' clinical course was passively observed through the pre-operative interval to ensure no indication for acute intervention, which would provide basis for exclusion. Upon surgical resection, tissues were oriented to the anterior and caudal directions, fixed in 10% formalin solution, and processed per standard pathological sample protocol. After 24 hours of tissue fixation, equivalent A-P, C-C, and DOI dimensions of the specific tumor were collected by the attending pathologist. Values were corrected by a literature-based coefficient of spatial shrinkage, to account for resection- and formalin-caused tissue deformation.[17]

Tumor volume was approximated at the date of initial imaging ($V_{imaging}$) and the date of resection ($V_{resection}$) as one-half the product of maximum dimensions in the A-P, C-C, and DOI orientations. The cumulative pre-operative interval (Δt) was defined at the elapsed time between initial CT scan and date of resection, recorded in days. Linear growth rate was determined over the pre-operative interval in cm^3/week.

Specimen measurements were collected from the final pathology report of the resected tumor, including: pathological 'T' stage, pathological 'N' stage, grade, site of origin, focality, presence of lymphovascular or perineural invasion, number of nodes examined operatively, and minimum attained surgical margin.

2.3 | Data analysis

Descriptive statistics were used to characterize the study population by age, sex, smoking history, alcohol consumption history, previous all-type malignancy, previous chemotherapy treatment, previous head or neck radiation exposure, and elapsed interval between diagnosis and surgical resection. Regression analysis was used to assess causal relationships between demographic and pathologic factors—as collected from patient interview and pathologic analysis—and squamous cell carcinoma tumor growth. Preliminary analyses were performed to ensure no violation of assumptions of normality, linearity, and multicollinearity. Multifactorial regression was applied to assess the influence of independent demographic factors of age, sex, smoking history, alcohol consumption history, previous all-type malignancy, previous chemotherapy treatment, previous head or neck radiation exposure, and elapsed interval between diagnosis and surgical resection on variability of tumor growth rate. Unilinear regression was used to assess the impact of tumor growth rate on pathological 'T' stage, pathological 'N' stage, grade, site of origin, focality, presence of lymphovascular or perineural invasion, number of nodes examined operatively, and minimum attained surgical margin.

3 | RESULTS

Of nineteen participants prospectively recruited, four were excluded from analysis as oral artifact deemed preoperative CT scan ineligible for measurement review. Of the remaining fifteen participants, eight (53%) were male and seven (47%) were female. For complete demographic summary, see Table 1. Individual patient growth rates were graphically summarized using literature-derived exponential growth models of squamous cell carcinoma (Figure 1).[4,19] Summary statistics revealed a mean growth rate for the study sample of 1.385cm^3/week [95% CI: 1.303; 1.467] (Table 2).

The examined demographic factors accounted for 69.3% of variability in tumor growth data [$R^2 = 0.693$]. Post-hoc analysis revealed daily alcohol consumption was positively correlated with increased tumor growth rate of OSCC [$\beta = 85.72$; $p = .014$; 95% CI: 23.51, 147.94]. No significant causative relationship was detected between tumor growth rate and age, sex, smoking history, previous all-type malignancy, previous chemotherapy treatment, previous head and neck radiation exposure, or elapsed interval between diagnosis and surgical resection (Table 3).

No significant causative relationship was detected between the tumor growth rate and pathological 'T' stage, grade, focality, presence of lymphovascular or perineural invasion, number of nodes examined operatively, and minimum attained surgical margin. However, in examining the tumor site of origin, a significant causative relationship was detected between tumor growth and origination at the retromolar trigone [$\beta = .001$; $p = .020$; 95% CI: −0.18, 0.21]. Otherwise, no

TABLE 1 Demographic information of recruited patients

Demographic factor	Count (%)
Sex	
Male	8 (53%)
Female	7 (47%)
Previous malignancy	4 (27%)
Previous chemotherapy	1 (7%)
Previous H&N radiotherapy	2 (14%)
Demographic factor (unit)	**Mean (SD)**
Age (years)	61.4 (19.0)
Smoking (pack – years)	21.15 (6.00)
Alcohol (standard drinks per day)	1.6 (0.91)

significant relationship was noted between the tumor growth rate and origin at the lateral tongue, buccal mucosa, oral floor, or central tongue. Finally, tumor growth rate was found to be significantly causative in predicting pathological 'N' stage [$\beta = .291$; $p = .038$; 95% CI: −0.48, 0.74] (Table 4).

4 | DISCUSSION

The current study presents the first known prospective examination of causal variance between pathological and clinical correlates and growth rate of p16-negative oral cavity squamous cell carcinoma. In a small pilot study sample, we have observed significantly causative relationships between tumor growth rate and regular alcohol consumption [$R^2 = 0.693$, $p < .05$], pathological "N" stage [$R^2 = 0.291$, $p < .05$], and origin at the retromolar trigone [$R^2 = 0.351$, $p < .05$]. Tumor growth rate was observed to be 1.385cm^3/week [95% CI: 1.303; 1.467] among our participant sample ($n = 15$). No causative relationships were observed between the tumor growth rate and other pathologic or demographic factors. No significant causative relationship was observed between the tumor growth rate and elapsed interval between diagnosis and resection.

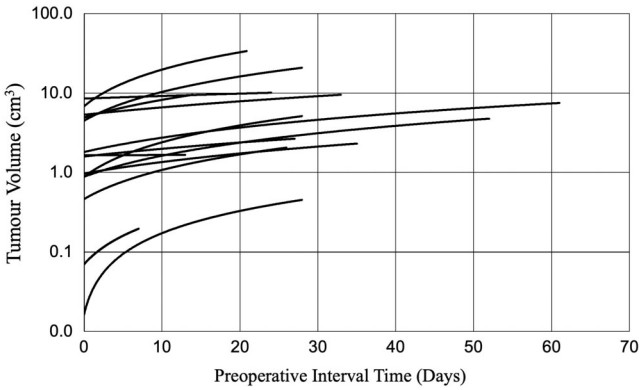

FIGURE 1 Oral cavity squamous cell carcinoma tumor volume as modeled. Plotted logarithmically as a function of time. Normalized to day 0 of initial CT scan

TABLE 2 Summary statistics for tumor growth in

	Mean (cm^3/week)	95% CI	
		Lower	Upper
Tumor growth rate	1.385	1.303	1.467

Alcohol consumption history (patient reported in standard drinks/week) was found to explain a significant proportion of variance in the tumor growth rate. Alcohol use has long been associated, in synergistic effect with tobacco consumption, as a primary risk factor for OSCC pathogenesis.[2] While no specific mechanism is viewed as solely responsible, the most widely accepted explanation is a combination of systemic immunosuppression, checkpoint inhibitor downregulation, and DNA hypomethylation altering oncogene expression and allowing uncontrolled cell division.[20,21] Previous systematic reviews have shown the relative risk OSCC development in heavy alcohol drinkers to be 5.13, as compared to light or non-alcohol drinkers.[22] However, these patients are also at an increased risk of carcinoma development in the oropharynx and hypopharynx, due to prolonged carcinogenic exposure time.[23] Alcohol abstinence has been shown to have profound effects in risk reduction: previous heavy-drinkers return to baseline risk after twenty years of abstinence, and cohort data has also shown alcohol cessation after OSCC diagnosis to decrease disease-specific mortality.[24]

The relationship between alcohol use and tumor growth has been studied in other human carcinomas. Alcohol intake has been shown to be a strong predictor of tumor doubling and two-year survival in hepatocellular carcinoma.[25,26] Additionally, a positive association has been observed between moderate to high alcohol consumption (defined as >5 drinks per week) and aggressive basal cell carcinoma.[27] We conclude that our current causative finding is consistent with previous literature published in the field of human carcinoma, and mechanisms responsible are likely multifactorial. Future work in this field will continue to examine potential mechanism for this relationship, and its interplay with increase pathogenic risk of OSCC development.

TABLE 3 Multifactor regression analysis of demographic factors' causative role in tumor growth rate of OSCC

Factor	Coefficient	R^2	p Value	95% CI	
				Lower	Upper
Age	5.715	0.693	.235	−4.68	16.11
Sex	−158		.460	321.13	638.54
Smoking	−5.675		.629	−14.85	3.50
Alcohol use*	**85.720**		**.014**	**23.51**	**147.94**
Previous cancer	−146.196		.662	−904.42	612.03
Previous chemotherapy	−82.723		.852	−1095.25	929.81
Previous radiotherapy	−161.610		.686	−1066.72	743.50
Elapsed surgical interval	29.38		.606	20.11	38.65

*Significance denoted at $p < .05$.

TABLE 4 Unifactor regression analysis of tumor growth's causative role in pathologic outcomes in OSCC

Factor	Coefficient	R^2	*p* Value	95% CI	
				Lower	Upper
Tumor stage	0.001	0.182	.112	1.84	3.30
Nodal stage*	**0.002**	**0.291**	**.038**	**−0.48**	**0.74**
Lateral tongue	0.000	0.053	.411	0.03	0.63
Buccal mucosa	0.001	0.248	.059	−0.05	0.55
Oral floor	0.000	0.025	.576	−0.07	0.40
Central tongue	0.000	0.012	.699	−0.09	0.26
Retromolar trigone*	**0.001**	**0.351**	**.020**	**−0.18**	**0.21**
Tumor grade	0.000	0.006	.792	1.81	2.51
Lymphovascular invasion	0.000	0.017	.647	−0.08	0.40
Perineural invasion	0.000	0.016	.657	0.16	0.85
Nodes examined	0.010	0.023	.590	14.24	44.53
Surgical margin	0.000	0.008	.758	1.20	4.21

*Significance denoted at $p < .05$.

A causative relationship was found to exist between the tumor growth rate and origination at the retromolar trigone (RMT), a small triangular subsite of the oral cavity. RMT carcinoma generally requires large surgical resections as first line curative-intent therapy, due to its complex location within the head and neck. RMT carcinomas quickly infiltrate the maxilla and increase in stage; previous multivariate analysis has shown that masticator space involvement, neck recurrence, and cervical metastasis were all negative predictive factors for prognosis.[28] Previous retrospective cohort data has shown the efficacy of isolated radiation on treating early stage RMT carcinoma, as surgical treatment modalities often require extensive resections and reconstructions.[29] We conclude that OSCC originating in the retromolar trigone displays a higher incidence of fast growth compared to alternate sites of origin within the oral cavity.

Finally, a causative relationship was found to exist between tumor growth rate and nodal stage, per standard TNM staging schematic. In OSCC, this translates to an increased rate of cervical lymph node metastasis.[14] Previously, high tumor thickness has been linked to higher rates of nodal metastasis, and 'N' stage.[15] Though this has not been examined in the current paper, rapid tumor growth is likely associated with a high Ki-67 index and VEGF-A expression: indicators of increased cell turnover and worsened morbidity.[30] Presence of Ki-67 and VEGF-A have been implicated in nodal metastasis in head and neck cancer, as well as increase mortality.[30]

The current study does contain limitations which constrain extrapolation of the current data to the OSCC population. Multifactorial and unilinear regression analysis were used to determine causative relationships between pathological and clinical correlates, which examine the responsibility for variance within a dataset. Future work will clinically validate these findings within a larger dataset. Additionally, data collection was performed using a combination of radiologic and pathologic techniques, resulting in potential error at the comparison process. As we are assessing relative growth, this may impact reported growth rate; however, relationships with causative variables are unlikely to be affected. As this is a pilot study for the purpose of assessing clinical feasibility, we are also limited by a small patient population. The use of radiologic data introduces selection bias in the candidates eligible for image review. Four participants in the current study were excluded due to artifacts obscuring the region of interest; a parameter which may be associated with other potential growth rate risk factors or confounding variables, such as smoking, poor oral hygiene, and recurrent dental infections.

Complex growth patterns arising from specific anatomic locales may introduce variability to the presented analysis. Specifically, tumor origination at the RMT results in complex tumor morphology and complex patterns of spread, limiting the rigor of analysis with CT and geometric simplification as presented in the current study.[31] Gadolinium-enhanced 1.5 T MRI has been shown to identify tumor stage of RMT tumors with high accuracy, specificity, and sensitivity and may play a role in future of longitudinal growth anlysis in vivo, ahead of surgical resection.[32] Additionally, previous correlates of MR data with post-resection pathologic samples are well validated, potentially improving the extrinsic validity of this comparison based methodology.[33]

Future work in this field will continue to examine the role of alternative imaging techniques for evaluating oral cavity cancer over a defined interval, including gadolinium-enhanced MRI scanning. Recently, trans-submental three-dimensional ultrasonography has shown promise in our group for the ability to easily evaluate oral cavity SCCs of the oral floor. Similar, low cost and risk-free imaging technique will allow for more thorough temporal analysis of squamous cell carcinoma over the pre-operative interval.

5 | CONCLUSION

The current study aims to characterize the causative relationship of patient demographic and pathologic factors on p16-negative squamous cell carcinoma growth rate in the oral cavity. We have found causative associations between growth rate and alcohol consumption,

origination at the retromolar trigone, and nodal stage as defined by the TNM staging system. Future work on this topic will continue to characterize tumor growth using less restrictive modeling techniques, and the use of novel imaging modalities such as three-dimensional ultrasonography.

CONFLICT OF INTEREST

The authors of this paper have no competing interests nor conflicts of interest to disclose.

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