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Prevalence and outcome of human papilloma virus-mediated oropharyngeal squamous cell carcinoma in a low- and middle-income setting

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Background: Oropharyngeal squamous cell carcinoma (OPSCC) is divided into two distinct disease entities, distinguished by p16 status, which confers significant prognostic benefit when positive (human papilloma virus-mediated). Limited data exist in low- and middle-income countries (LMICs) to correlate whether this translates to our setting, where lifestyle risk factors are rife such as heavy alcohol, tobacco consumption and poor socioeconomic status.

Aim: This study aimed to evaluate the prevalence and compare overall survival (OS) of p16-positive and negative OPSCC within a LMIC setting.

Setting: This single-centre study was conducted at Groote Schuur Hospital, Cape Town, South Africa.

Methods: Retrospective observational study where data were collected on patients with OPSCC from January 2017 to December 2020, exploring prevalence and OS at 3-years in patients treated with curative intent. Demographic and lifestyle factors were analysed to identify statistical significance.

Results: A total of 190 patients were included. Prevalence of p16-positive OPSCC was 20.8%. A total of 111 patients were treated with curative intent: 3-year OS in patients with p16-positive was 57% (median OS 59 months, 95% confidence interval [CI]: 0.00–120.16) and p16-negative patients 33% (median OS 16 months, 95% CI: 11.85–20.15), which is statistically significant ($p = 0.03$).

Conclusion: P16-positive OPSCC has superior OS compared to p16-negative OPSCC, with lower prevalence compared to developed countries.

Contribution: P16-positive OPSCC comprises an important minority (20.8%) of OPSCC where p16 status, smoking and alcohol consumption are the most important prognostic factors.

Keywords: oropharyngeal squamous cell carcinoma; p16-positive/negative; HPV-mediated; prevalence; overall survival; low- and middle-income countries.

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) forms part of a greater collection of cancers involving the head and neck (HNC), which result in significant morbidity and mortality. A substantial proportion of HNC cases arise in developing countries, contributing to 67% of global prevalence and 82% of HNC-related deaths worldwide.[1] Traditionally, HNC is often associated with poor socioeconomic status and heavy alcohol and tobacco consumption. However, data from global studies have shown that in the last 20 years there has been a steady increase in HNCs associated with human papilloma virus (HPV) infection, with specific relevance in OPSCC.[2] Human papilloma virus's relationship with cancer has been extensively researched. It can be identified within tumour cells using in situ hybridisation (ISH) or by using p16 immunohistochemistry (IHC) as a surrogate marker. Overexpression of p16 in HPV-mediated OPSCC is because of the inactivation of the Rb protein (via the E7 oncoprotein)[2] and resultant overproduction of p16 via a feedback-loop.[3] A tumour is classified as HPV-positive if IHC staining for p16 is positive in ≥ 70% of the histological specimen.[4] P16 has been shown to be a reliable test,

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in that it is both sensitive and specific in identifying HPV-mediated oncogenesis in OPSCC; however, it does possess drawbacks as false positives can occur in the absence of HPV-coinfection. Dual testing of p16 and HPV deoxyribonucleic acid/ribonucleic acid (DNA/RNA) may be considered to improve specificity and prognostic accuracy.[5] P16 positivity is noted in all oncogenic strains of HPV-mediated OPSCC and provides no information on the specific HPV-strain that is the causative oncogenic vector. Extensive research has been done to clarify which strains are associated with OPSCC, with HPV-16 being the dominant strain,[6] both internationally and in sub-Saharan Africa,[7] including South Africa.[8]

Recent systematic reviews on global prevalence of HPV-mediated OPSCC indicate that the prevalence varies significantly. A pooled proportional meta-analysis published in 2020 indicates that the global prevalence is 44.8%[5], with the highest prevalence in Northern Europe, United States (US), China and South Korea.[9] Multiple studies indicate a continued increase in the burden of HPV-mediated OPSCC globally. There is limited information from the developing nations; however, a recent study reviewing HPV-mediated OPSCC in sub-Saharan Africa, indicates a prevalence of 20.3%, with HPV-16 being the dominant strain.[7] P16-positive OPSCC, according to global data, tends to affect a younger population compared to p16-negative OPSCC. Patients with a history of multiple sexual-partners, engaging in oral sex and early sexual debut are at higher risk for p16-positive OPSCC. Men account for the majority of OPSCC incidence, including p16-positive OPSCC. Smoking and alcohol consumption remain significant negative prognostic factors.[6,10] Research on HPV vaccination in preventing cervix cancer[11] translates effectively in p16-positive OPSCC. Numerous systematic reviews have shown the association between p16-positive OPSCC and improved treatment outcomes.[2,12] P16 positivity is now accepted as the most significant prognostic marker in OPSCC – to the extent that the AJCC 8th edition has separate classifications for p16-positive and p16-negative OPSCC.[13] Most typically, p16-positive OPSCC manifests clinically with smaller primary tumours, and larger, often cystic, nodal metastases.[9] No statistically significant data are available to correlate poorer outcomes with specific HPV-strain(s).[14] Treatment for OPSCC is ideally carried out by multi-disciplinary teams with primary clinical assessment of the tumour and nodal status is important to accurately stage and prognosticate. Surgical approaches include transoral resection with electrocautery, CO_2 laser microsurgery or robotic surgery.[15] Primary surgery in early-stage p16-negative OPSCC may have favourable outcomes compared to definitive radiotherapy (RT).[10,16] Adjuvant RT ± concurrent chemotherapy is required in as many as two-thirds of patients,[17] with accelerated RT schedules improving outcomes.[18] Replacing cisplatin with cetuximab in concurrent chemoradiotherapy (CCRT) has led to reduced survival without reduced toxicity, and thus is not recommended in patients eligible for cisplatin.[19,20] Response to induction chemotherapy is also an important prognostic marker in locally advanced cases.[21] However, there are conflicting data as to whether induction chemotherapy may negatively affect treatment outcome compared to primary CCRT, especially in p16-positive OPSCC.[22,23] Treatment outcomes are universally improved; the Nichols et al.[14] study data demonstrate this: patients with p16-positive tumours had a 90% 3-year overall survival (OS) versus 65% in p16-negative tumours; and an 85% versus 49% 3-year disease-free survival, respectively.[24] The trend continues with long-term data. Clark et al.[10] demonstrated, in a meta-analysis of prospectively collected data, that patients with p16-positive tumours had a 60.2% 10-year OS versus 29.6% in p16-negative tumours; and a 56.5% versus 21.2% 15-year OS, respectively. Despite the higher propensity for late-onset distant metastases, long-term survival remains superior in p16-positive OPSCC. Metastatic sites most commonly seen are lung (61%), while liver, abdominal, bone and dermal metastases are also observed.[25] However, regardless of p16 status, the highest likelihood of developing disease recurrence is within the first 2 years.[26] Literature from LMICs is limited to small retrospective studies focused primarily on prevalence of HPV-mediated HNC. This study aims to identify the prevalence and treatment outcome of HPV-mediated (p16-positive) OPSCC patients compared to p16-negative OPSCC treated at Groote Schuur Hospital (GSH) in a LMIC setting between 2017 and 2020.

Methods

We conducted a retrospective observational study of patients with newly diagnosed oropharyngeal cancer at GSH between January 2017 and December 2020. All patients with a new histologically confirmed diagnosis of squamous cell carcinoma of the oropharynx, including subsites: base of tongue, tonsils, soft palate and pharyngeal wall were included. Patients diagnosed with non-OPSCC pathology, recurrent disease or treated at an institution other than GSH were excluded. Those who were offered curative treatment were included in the assessment of OS at 3 years.

Data collection methods

Clinical data were collected from patient medical records, the departmental electronic patient registry (EPR), National Health Laboratory Service (NHLS) online portal (TrakCare). Where p16 status was unknown, p16 IHC was requested to be performed on 70 archived specimens via a collaboration between the departments of Anatomical Pathology and Radiation Oncology at GSH, University of Cape Town. Funding for the material costs involved in performing these tests was obtained from Radiation Oncology departmental research funds. Data collection was completed between January 2024 and March 2024. A participant number was assigned to each patient included in the study and data de-identified before data analysis was performed.

Treatment

All patients were reviewed at the HNC clinic by a multidisciplinary team to determine appropriate treatment

intent and management plan. Patients suitable for curative treatment received one of the following: locally advanced cancers received induction chemotherapy (either TPF: taxane, platinum and fluorouracil; or platinum and fluorouracil if unfit for TPF) followed by CCRT (3-weekly or weekly platinum: cisplatin or carboplatin) or RT alone. Surgery was used in selected early-stage cancers, with adjuvant RT if clinically indicated. Concurrent cetuximab was not available for platinum ineligible patients. All patients receiving definitive RT were treated with volumetric modulated arc therapy (VMAT) and the simultaneous integrated boost (SIB) technique. Radiotherapy prescription was typically a 3-dose level plan. Primary tumour and involved nodes received the highest dose with an equivalent dose at conventional fractionation (EQD2) of 66 Gy – 70 Gy; intermediate risk nodal stations received an EQD2 of 60 Gy – 64 Gy and uninvolved nodal stations at risk received an EQD2 of 48 Gy – 54 Gy. Radiotherapy was administered in 30–33 fractions, once daily, Monday to Friday. Patients were monitored weekly with clinical assessment and blood tests. Supportive care was provided including nutritional support and feeding tubes when indicated. Patients deemed unfit for curative intent, by consensus decision of the multidisciplinary HNC team, were offered appropriate palliative treatment, including palliative RT, chemotherapy and supportive care. Palliative RT was commonly planned with lateral-opposed fields and prescribed to 30 Gy – 36 Gy in 3 Gy fractions. P16 status was not considered in determining treatment intent. Clinical follow-up, including indirect laryngoscopy if indicated, was carried out at 6 weeks post-treatment, and thereafter, 3 monthly for 1–2 years, 6 monthly for 3 years, and annually from 5 years post-treatment. Imaging, biopsies and further investigations were carried out as clinically indicated. Patients with disease recurrence were considered for salvage, palliative treatment or supportive care.

Statistical analysis

To achieve statistical significance for the primary objective, a minimum sample size of 75 patients, at an expected p16 positivity of 20%, was estimated utilising a log-rank calculator. A 4-year study period was chosen to accrue sufficient patients. Statistical Package for the Social Sciences (SPSS version 29) software was used for descriptive and inferential statistics to analyse the data. Kaplan–Meier survival analysis was used to determine OS (defined as time from new patient consultation until the date of death or last follow-up) with p-values ≤ 0.05 considered statistically significant. Univariate log-rank pairwise comparisons and the chi-square test were used to analyse subgroups on survival distributions and Bonferroni corrections were applied to identify statistical significance.

Ethical considerations

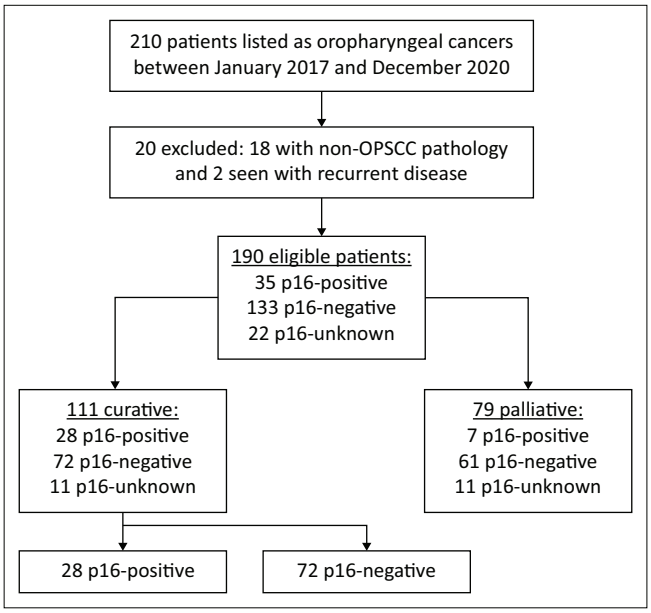
Ethical clearance to conduct this study was obtained from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (No. 022/2024). Informed consent was not required as this was a retrospective review of medical records.

Results

Patient characteristics

A total of 210 medical records were reviewed, with 20 excluded: 18 with non-OPSCC pathology and 2 seen with recurrent disease. A total of 190 patients were eligible for inclusion in the section of the study assessing prevalence; 100 patients were eligible for inclusion in the assessment of OS at 3 years. A total of 190 patients were eligible for the study (Figure 1) with 111 patients (58%) treated with curative intent and 79 (42%) treated palliatively. Prevalence of HPV-mediated OPSCC (p16-positive) in our study population with known p16 status was 20.8%. Palliative patients had a lower p16 prevalence: 10.3% compared to 28% in patients who received curative treatment.

The demographic data of the study population is detailed in Table 1. The mean age of patients at presentation was 58.5 years old. The study population consisted predominantly of males (71%), alcohol consumers (74%), smokers (96%) and patients with comorbidities (66%). Locally advanced disease (Stage III–IVB) predominated (83%) with only one patient presenting with Stage IVC de novo metastatic disease (1%). The p16-positive group consisted of more never-smokers (23%) and non-alcohol users (46%); in comparison to the p16-negative group who had greater associations with alcohol (77%) and > 20 pack-year history tobacco usage (68%). The majority of p16-positive patients presented with early-stage disease I–II (60%) and were offered curative treatment (80%). There was no significant disparity in age, gender, subsite, human immunodeficiency virus (HIV) status and comorbidities between the two groups.



OPSCC, oropharyngeal squamous cell carcinoma; OS, overall survival.

FIGURE 1: Flowchart of study profile.

TABLE 1: Demographic data of study population – Included patients (N =190).

Parameter	*n*	%	± s.d.	p16-positive (*n* = 35)			p16-negative (*n* = 133)			p16-unknown (*n* = 22)		
				n	%	± s.d.	*n*	%	± s.d.	*n*	%	± s.d.
Age (years)	58.5	-	± 9.66	57.3	-	±12.02	57.6	-	± 7.92	65.3	-	± 8.77
Gender												
Male	135	71	-	21	60	-	97	73	-	17	77	-
Female	55	29	-	14	40	-	36	27	-	5	23	-
Subsite												
Tonsil	83	44	-	16	46	-	57	43	-	10	46	-
Soft palate	41	21	-	8	23	-	27	20	-	6	27	-
Base of tongue	57	30	-	10	29	-	43	32	-	4	18	-
Pharyngeal wall	9	5	-	1	2	-	6	5	-	2	9	-
HIV												
Positive	12	6	-	2	6	-	9	7	-	1	5	-
Negative	141	74	-	23	66	-	100	75	-	18	82	-
Unknown	37	20	-	10	28	-	24	18	-	3	14	-
Comorbidities												
Yes	126	66	-	24	69	-	93	70	-	9	41	-
No	64	34	-	11	31	-	40	30	-	13	59	-
Smoking history												
Never	8	4	-	8	23	-	0	0	-	0	0	-
< 10 pyh	26	14	-	8	23	-	17	12	-	1	4	-
10–20 pyh	37	20	-	8	23	-	26	20	-	3	14	-
21–40 pyh	66	34	-	8	23	-	49	37	-	9	41	-
> 40 pyh	53	28	-	3	8	-	41	31	-	9	41	-
Alcohol												
No	49	26	-	16	46	-	30	23	-	3	14	-
Yes	141	74	-	19	54	-	103	77	-	19	86	-
TNM (AJCC 8th)												
I	4	2	-	3	9	-	1	1	-	0	0	-
II	27	14	-	18	51	-	6	4	-	3	14	-
III	40	21	-	14	40	-	23	17	-	3	14	-
IV (p16+) / IVA	92	48	-	0	0	-	77	58	-	15	68	-
IVB	26	14	-	0	0	-	25	19	-	1	4	-
IVC	1	1	-	0	0	-	1	1	-	0	0	-
Treatment												
Curative	111	58	-	28	80	-	72	54	-	11	50	-
Palliative	79	42	-	7	20	-	61	46	-	11	50	-

s.d., standard deviation; HIV, human immunodeficiency virus; pyh, pack-year history.

TABLE 2: Curative-intent treatment (N = 111).

Treatment	*N*	%	Radiotherapy	*n*	%
Induction chemo	76	81.1	-	-	-
	-	-	CCRT	58	76.3
	-	-	RT alone	10	13.2
	-	-	No RT / Complications	8	10.5
Definitive RT	8	7.2	-	-	-
	-	-	CCRT	4	50.0
	-	-	RT alone	1	12.5
	-	-	No RT / Complications	3	37.5
Surgery	27	24.3	-	-	-
	-	-	Adjuvant CCRT	2	7.4
	-	-	Adjuvant RT alone	20	74.1
	-	-	No adjuvant RT needed	3	11.1
	-	-	Complications	2	7.4

CCRT, concurrent chemoradiotherapy; RT, radiotherapy.

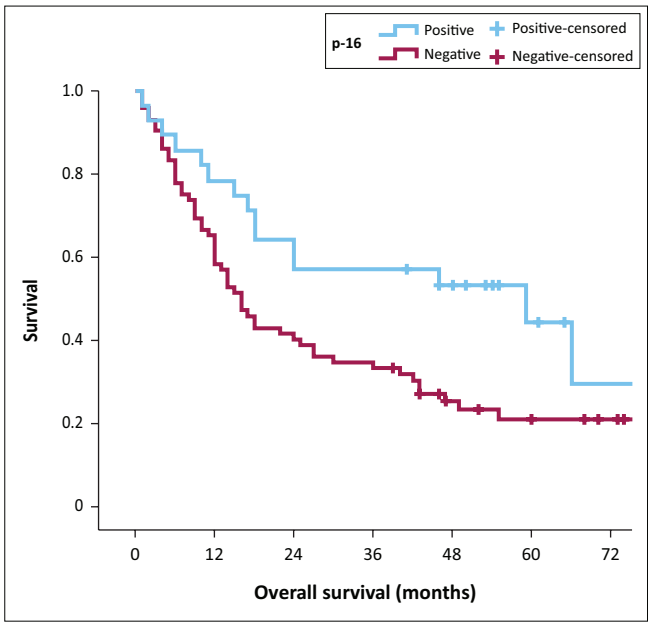
A total of 111 patients (Table 2) were treated with curative intent, and 90 patients (81.1%) completed the prescribed treatment course. Treatment was abandoned in 21 patients (18.9%) for one of the following reasons: complications related to induction chemotherapy in eight (7.2%), deemed unfit post-operatively for adjuvant RT in two (1.8%), complications during RT in eight (7.2%) and patient demised before definitive treatment could commence in three cases (2.7%).

Treatment outcomes

The primary endpoint, the 3-year OS in p16-positive and negative patients treated with curative intent (Figure 2) was 57% (median OS 59 months, 95% confidence interval [CI]: 0.00–120.16) and 33% (median OS 16 months, 95% CI: 11.85–20.15), respectively. This is statistically significant ($\chi^2[1] = 4.58$, $p = 0.03$).

Predictive factors for overall survival

A univariate analysis identified p16 status, smoking history, alcohol consumption and treatment completion as significant predictors of OS. In contrast, sex, anatomical subsite, HIV status and comorbidity burden were not significantly associated with OS (Table 3). Tumour, Node, Metastasis (TNM) staging was found to be statistically significant ($p = 0.001$) when analysed within the entire patient



Note: The survival benefit was also statistically significant ($\chi^2(1) = 10.957$, $p = 0.001$) in all patients regardless of treatment intent: in p16-positive and p16-negative patients, the 3-year OS was 46% (median OS 24 months, 95% CI: 0.00–51.61) and 18% (median OS 7 months, 95% CI: 5.12–8.88), respectively.

OS, overall survival; CI, confidence interval.

FIGURE 2: Kaplan–Meier survival curve for overall survival in patients with curative-intent treatment according to p16 status ($p = 0.03$).

population, but not within the curative-intent subset ($p = 0.19$). Treatment intent was a notable factor in determining OS with 40% OS at 3 years for patients offered curative treatment as compared to 0% in the palliative intent subset ($p < 0.001$). Pairwise log-rank comparisons demonstrated that both surgery and induction chemotherapy were associated with statistically superior survival compared with no induction chemotherapy ($p < 0.001$). No significant difference in survival was observed between surgery and induction chemotherapy after Bonferroni correction ($p = 0.025$; adjusted significance threshold $p < 0.02$). Concurrent chemoradiotherapy was statistically superior to both RT and no RT ($p < 0.001$), and RT was superior to no RT ($p < 0.001$).

Discussion

The prevalence of HPV-mediated OPSCC defined by p16 positivity was identified in 20.8% of the tested study population, which correlates with a recent systematic review in sub-Saharan Africa which showed a prevalence of 20.3% (78 of 384 patients).[7] This differs significantly from the global prevalence (44.8%),[5] with several developed countries seeing prevalence above 70%.[5,9] Global systematic reviews have a paucity of data from African countries, and so this study is researching an important knowledge gap. Patients with p16-positive OPSCC treated with curative intent have an OS at 3-years of 57% ($p = 0.03$) and lived a median of 43 months longer compared with patients with p16-negative OPSCC. A survival advantage for p16-positive OPSCC is in concordance with international data; however, the OS is notably lower than described in international studies.[14] Possible explanations for this include discordance of p16 IHC status, where p16

TABLE 3: Overall survival (curative intent) log-rank pairwise comparisons.

Parameter	3-year OS rate (%)	Univariate: Log-rank	
		χ^2-value	*p*-value
Gender	-	2.67	0.100
Male	35	-	-
Female	50	-	-
Subsite	-	2.58	0.460
Tonsil	44	-	-
Soft palate	41	-	-
Base of tongue	30	-	-
Pharyngeal wall	43	-	-
HIV (unknown excluded)	-	0.86	0.350
Positive	17	-	-
Negative	41	-	-
p16 (unknown excluded)	-	4.58	0.030*
Positive	57	-	-
Negative	33	-	-
Comorbidities	-	0.29	0.590
Yes	43	-	-
No	38	-	-
Smoking history	-	14.61	0.010*
Never	75	-	-
< 10 pyh	45	-	-
10–20 pyh	50	-	-
21–40 pyh	41	-	-
> 40 pyh	17	-	-
Alcohol	-	5.58	0.020*
No	58	-	-
Yes	32	-	-
TNM		6.16	0.190
I	50	-	-
II	58	-	-
III	30	-	-
IVA	35	-	-
IVB	38	-	-
Induction chemotherapy or surgery	-	9.07	0.010*
No	13	-	-
Yes	36	-	-
Surgery	59	-	-
RT	-	31.63	< 0.001*
No RT	7	-	-
RT	52	-	-
CCRT	42	-	-
Treatment completed		37.35	< 0.001*
Yes	47	-	-
No	10	-	-

OS, overall survival; HIV, human immunodeficiency virus; pyh, pack-year history; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

*, Indicate statistical significance.

positivity exists without HPV-coinfection, which may be because of genomic alterations in the retinoblastoma protein pathway by other molecular causes. A global meta-analysis showed that this discordant group has survival outcomes similar to p16-negative OPSCC.[27] This clinical scenario could be speculated to exist in at least some of the p16-positive patients in this study that have high rates of alcohol (54%) and > 20 pack-year history (pyh) tobacco (31%) usage. Further analysis of this p16-positive subset showed that patients with a significant smoking history of > 40 pyh had a 0% 3-year OS compared to 75% 3-year OS in patients who are either never-smokers or < 10 pyh smokers, which is statistically significant ($p = 0.005$). Additional testing to detect

HPV itself (via ISH or polymerase chain reaction (PCR) was not available for this study, which in conjunction with p16 IHC, would increase the specificity and sensitivity in the diagnosis of HPV-mediated OPSCC.[5] Other potential contributing factors include delayed presentation, leading to locally advanced cancer (40%) with a large burden of disease. Patients are predominantly from lower socioeconomic social settings without access to high quality food and often have suboptimal physiological reserve at presentation. Over the period of this study, there was limited availability of gastrostomy feeding tubes at our institution if severe dysphagia developed. Meeting nutritional and caloric requirements was instead, dependent on attempting to preserve adequate swallowing function with basic nutritional outpatient support and supplementation via nasogastric tube feeding. At times, because of the overburdened public hospital services, there is limited access to inpatient hospital beds, and so admitting patients to support them through treatment is not always possible. TNM staging was updated in 2017 with the American Joint Committee on Cancer (AJCC) 8th edition, where HPV-mediated OPSCC was separated into a distinct disease entity. These cancers are down-staged relative to the p16-negative group with only T4 and N3 (lymph node(s) larger than 6 cm) disease classified as locally advanced, that is, stage III disease. Stage IV refers only to metastatic disease in the new staging classification. This modification reflects the improved OS outcomes with N1 and N2 disease and highlights the prognostic importance of p16 positivity.[13] P16-positive OPSCC patients in our study presented primarily with stage II (51%) and stage III (40%), and only 9% with stage I disease. This is in stark comparison to the developed world, in which a large multicentre study showed the majority (56%) of patients with p16-positive OPSCC were stage I and minority stage III (14%) at presentation.[18] In our setting, staging is performed clinically by the HNC multidisciplinary team. Advanced imaging, such as fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), magnetic resonance imaging (MRI) and/or CT of the head, neck and chest is rarely performed because of limited availability, which could also explain the under-representation of distant metastasis. Radiotherapy planning is carried out using information from clinical diagrams of the primary, flexible nasal endoscopy (if available), and the contrast-enhanced planning CT scan. Treatment with Intensity-Modulated Radiotherapy (IMRT)/Volumetric Modulated Arc Therapy (VMAT) RT techniques was the standard of care for all patients in this study. The effect of smoking was investigated and proved to be a significant poor prognostic factor (p = 0.01), with OS at 3-years as follows: never-smokers (75%), < 10 pyh (45%), 10 pyh – 20 pyh (50%), 21 pyh – 40 pyh (41%) and > 40 pyh (17%). Alcohol consumption was also shown to be a negative prognostic factor (p = 0.01), but not within the p16-positive subset treated with curative intent (p = 1.74). Sparse clinical data detailing alcohol consumption limited further interpretation of this parameter. Early-stage cancers, patients eligible for curative treatment and those who completed the full course of treatment had improved outcomes. Our study indicates that p16 status and smoking are the most important prognostic factors for OPSCC. There was no correlation with outcome and the following factors: gender, patient comorbidities and anatomical subsite. Our patients were predominantly male (71%), had ≥ 1 comorbidity (66%) and were HIV-negative (74%). Human immunodeficiency virus prevalence (6%) in this study is congruent with regional HIV prevalence in men (7.3%).[28] The tonsil (44%) was the most common anatomical subsite, with pharyngeal wall (4%) being the least common. There was no correlation with younger age distribution with p16-positive OPSCC as was expected from information gleaned from global data. The mean age was 57.3 years in the p16-positive group, compared to 58.5 years in the p16-negative subset. This study data does not correlate with the typical p16-positive OPSCC patient described in data from younger males, of good general health and non-smokers. Clinical data capture at this institution rarely includes a history of sexual behaviour, such as number of sexual partners and participation in oral sex, and so this potential association cannot be commented in this study. The validity of the data gathered by this study is limited by the single institution retrospective design and with the incomplete p16 IHC testing (88.4%). The small sample size (n = 28) of p16-positive OPSCC treated with curative intent resulted in a large CI, with the lower limit at zero; this is an inherent limitation of a small study although statistical significance was achieved it does reduce precision. Paucity of clinical data in the medical records, including standardised consultation templates and record keeping, limit the data that can be comprehensively collected. Certain details, such as type of chemotherapy used, specific RT details, treatment-related morbidity and disease-free survival were not included in this study. Including these data points may have provided more comprehensive insight into the treatment of p16-negative versus p16-positive OPSCC. P16-negative OPSCC (79.2%) remains more common than p16-positive OPSCC at our institution, thus the importance of continued public health campaigns to encourage smoking cessation and moderating alcohol usage is clear. However, as was seen in the developed world, South Africa and low- and middle-income countries are likely to see a continual rise in p16-positive OPSCC and thus gender-neutral HPV vaccination programmes and routine testing of p16 on OPSCC specimens should become the standard where feasible. P16 status provides important prognostic information to the clinician and patient. An ethical dilemma exists in resource-limited settings given the proven OS benefit conferred with p16-positive OPSCC: one could argue that prioritising limited resources to provide optimised treatment for this group, who stand to benefit the most, can be justified.

Conclusion

Oropharyngeal squamous cell carcinoma is the most common HNC, consisting of two distinct cancers distinguished by the presence or absence of HPV co-infection. This study shows that HPV-mediated OPSCC

comprises an important minority (20.8%) of OPSCC. In our local setting, p16 status, smoking and alcohol consumption are the most important prognostic factors. The treatment approach to OPSCC is unchanged, regardless of p16 status, but it is a readily available and affordable test that alters the staging and can provide valuable prognostic information to patients and clinicians. Further collaborative multicentre research in South Africa, sub-Saharan Africa and other LMICs should be conducted, to further quantify the prevalence and prognostic information relayed by p16 status in OPSCC.

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Competing interests

The authors, Travis T.S. van der Riet; Mmaphuti J. Chokoe Maluleke; Komala Pillay and Julie A. Wetter, declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

CRediT authorship contribution

Travis T.S. van der Riet: Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. Mmaphuti J. Chokoe Maluleke: Formal analysis, Investigation, Resources, Visualisation. Komala Pillay: Formal analysis, Methodology, Project administration. Julie A. Wetter: Conceptualisation, Supervision, Writing – review & editing. All authors reviewed the article, contributed to the discussion of results, approved the final version for submission and publication, and take responsibility for the integrity of its findings.

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Data availability

The data that support the findings of this study are available on request from the corresponding author, Travis T.S. van der Riet.

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