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Human papillomavirus associated oropharyngeal cancer now the most common mucosal head and neck cancer in Queensland

Sandro V Porceddu,[1,2] Theresa Negrello,[3] Neal Rawson,[3] Nathan Dunn,[2,3] Martin Batstone,[2,4] Michael Collins,[5,6] Sam Dowthwaite,[7,8] Brett GM Hughes,[2,9] Liz Kenny,[2,10] Rahul Ladwa,[1,2] Ben Panizza[2,11] and Danica Cossio[3]

1 Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
2 Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia
3 Queensland Cancer Control Analysis Team (QCCAT), Cancer Alliance Queensland, Brisbane, Queensland, Australia
4 Department of Surgery, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
5 Department of Radiation Oncology, Townsville Hospital, Townsville, Queensland, Australia
6 James Cook University, Townsville, Queensland, Australia
7 Gold Coast University Hospital, Gold Coast, Queensland, Australia
8 Griffith University, Gold Coast, Queensland, Australia
9 Department of Medical Oncology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
10 Department of Radiation Oncology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
11 Department of Otolaryngology, Head and Neck Surgery, Princess Alexandra Hospital, Brisbane, Queensland, Australia

SV Porceddu BSc, MBBS(Hons), FRANZCR, MD; **T Negrello** BPsycSc(Hons); **N Rawson** BBus (Fin); **N Dunn** BSc (Hons); **M Batstone** MBBS, BDSc, MPhil(Surg), FRACDS(OMFS), FRCS(OMFS); **M Collins** MBBS, FRANZCR; **S Dowthwaite** MBBS, FRACS; **B GM Hughes** MBBS, FRACP; **L Kenny** MBBS, FRANZCR, FACR(Hon), FBIR (Hon), FRCR(Hon), FCIRSE; **R Ladwa** MBChB, BSc, FRACP, MPhil; **B Panizza** MBBS, MBA, FRACS; **D Cossio** BHSc (HIM).

Correspondence
Sandro V Porceddu, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Vic. 3000, Australia.
Email: sandro.porceddu@petermac.org

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Abstract

Introduction: The profile and outcomes of head and neck cancer throughout Australia has changed over the past decade. The aim of this study was to perform a population-based analysis of incidence, demographics, stage, treatments and outcomes of patients diagnosed with oropharyngeal squamous cell carcinoma (OPSCC), with a particular focus on HPV-associated disease.
Methods: This was a retrospective analysis of prospectively collected data within the Queensland Oncology Repository (QOR) and analysed by the Queensland Cancer Control Analysis Team. The cohort included patients diagnosed in Queensland between 1 January 2015 and 31 December 2019. Outcome measures included incidence of new OPSCC cases, age-standardised rates (ASR) (3-year average), demographics, p16 status, stage (8th Edition American Joint Commission on Cancer), treatments, and 2- and 5-year overall survival.
Results: There were 1527 newly diagnosed OPSCC, representing 96% (1527/1584) of all oropharyngeal cancers. It was the most common head and neck cancer diagnosed, with oral cavity cancer being the second most common (n = 1171). Seventy-seven percent were p16 positive (1170/1527), of which 87% (1019/1170) were male. The median age was 61 years and 49% (568/1170) presented with Stage I disease. The ASR was 6.3/100,000, representing a 144% incidence increase since 1982 (2.6/100,000). Radiotherapy was utilised in 91% of p16+ cases with 2- and 5- year overall survival of 89% and 79%, respectively.
Conclusion: OPSCC is now the most common mucosal head and neck cancer diagnosed in Queensland, having surpassed oral cavity cancer. The majority are HPV-associated (p16+), presenting with early-stage disease with a favourable prognosis.

Key words: head and neck cancer; human papillomavirus; oropharyngeal; radiotherapy; squamous cell carcinoma.

Introduction

Head and neck cancer arising from the upper aerodigestive tract are commonly squamous cell carcinomas (SCC) related to tobacco and/or alcohol abuse.[1] In many parts of the world, including North America and Europe, there has been a rise in the incidence of oropharyngeal SCC (OPSCC) compared with those from other head and neck sites. This has been primarily driven by the oncogenic variants of the human papillomavirus (HPV).[2]

Compared with traditional non-HPV-associated OPSCC and those arising from non-oropharyngeal sites, patients tend to be younger with fewer co-morbidities, do not necessarily have a smoking history and respond favourably to treatment.[3–5] Where a non-surgical approach is employed in the curative management of head and neck cancer the standard of care has been concurrent chemoradiotherapy with high-dose cisplatin.[4]

The presence of p16 immunostaining of greater than 70% of tumour cells in OPSCC is considered to be a reliable surrogate for HPV-associated disease.[6]

Queensland Cancer Control Analysis Team (QCCAT) compiles and analyses information about cancer incidence, mortality, treatment, and survival housed in the Queensland Oncology Repository (QOR). The QOR contains approximately 50 million records between 1982 and 2019.

Between 2011 and 2015 the oropharynx became the most common newly diagnosed head and neck cancer in Queensland, surpassing oral cavity cancer.[7] This change in incidence has resource and treatment implications, as the majority are more likely to be treated with chemoradiotherapy rather than surgery and are likely to be long-term survivors.[8,9] The primary aim of this study was to analyse incidence trends of OPSCC relative to other head and neck cancers, patient demographics, p16 status, treatments utilised, and survival outcomes, between 1 January 2015 and 31 December 2019, based on QOR. The analysis predominantly focuses on the OPSCC p16+ cohort.

Previously published outcomes for this disease are mainly based on selected patients enrolled in clinical trials. This data provides real-world outcomes for unselected patients presenting with newly diagnosed OPSCC in Queensland, and is likely to reflect what is happening throughout Australia. This study received Metro South Health Human Research & Ethics Committee approval (HREC/2022/QMS/81561).

Methods

The primary aim is to analyse OPCSCC and, in particular, OPCSCC p16+, using the Queensland Oncology Repository (QOR) to benchmark incidence trends relative to other cancers.

This retrospective population-based study used linked QOR data, which collates and matches data from the Queensland Cancer Register together with public and private hospital admissions, surgery, radiation therapy, multidisciplinary team records (primarily in the public sector), and mortality data.

Staging classification and p16 status

Staging data was primarily obtained from Multidisciplinary Team meeting systems, chemotherapy systems, or radiation therapy systems across Queensland during patient episodes of care. The Cancer Alliance Queensland reviewed all staging information from these data sources to confirm accuracy.

Due to the emerging survival data based on p16/HPV status, the staging classification for this disease changed from the 7th Edition American Joint Commission on Cancer (AJCC) classification to the 8th edition in 2017. As such, the entire cohort was retrospectively re-staged according to the new staging classification for the purposes of this analysis.[10,11]

Where p16 status was unknown, patients were staged according to the p16/HPV-negative classification (as per the TNM staging classification rules).[12] Cancer stage and p16 status were recorded in multidisciplinary QOOL meeting software. This data was then linked to the individual patient record in QOR.

Treatment modalities utilised

As this is a population-based database, accordingly the cohort is composed of patients receiving a range of treatment modalities and/or in differing sequences along individual institutional policies. The use of surgery, chemotherapy, radiotherapy and concurrent chemoradiotherapy treatments will be described, providing an insight into the resources utilised for this disease in a population-based setting.

Head and neck cancer surgeries were identified from hospital admissions using the Australian Classification of Health Interventions (ACHI) 11th edition.[13] Radiation therapy and intravenous systemic therapy records were linked to the earliest records created from treatment systems. Surgery and treatment records were then linked to the head and neck cancer diagnosis record if the start date was 30 days before diagnosis and up to 365 days after histological diagnosis to capture adjuvant therapy.

Comorbidities

The individual list of comorbidities considered are those contained within the Charlson Comorbidity Index (1987). No weighting was applied to the individual comorbidities, but a simple count of comorbidities present was used.[14] The capturing of comorbidity data is limited to conditions coded in any hospital admission between 12 months before and 12 months after the date of cancer diagnosis. For any given cancer diagnosis, comorbidity is restricted

to conditions other than the primary cancer. Smoking data is not captured at a population level.

Remoteness of residence and socioeconomic status (SES)

In this report, relative remoteness of residence is classified into three groups: Major city, Inner regional, and Other which combines Outer regional, Remote, and Very remote categories. This is based on the Australian Standard Geographical Classification (ASGC) Remoteness Structure.[15]

Socioeconomic status (SES) was assigned according to the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA), a census-based measure of social and economic well-being and was categorised as affluent (deciles 1–2), middle (deciles 3–8), and disadvantaged (deciles 9–10).[16]

Statistical analysis

Time period and incidence

QCCAT performed an analysis on incidence counts and incidence rate trends, demographics, treatment modalities utilised, and outcomes of patients with newly diagnosed OPSCC between 1 January 2015 and 31 December 2019 in Queensland. Incidence relates to newly diagnosed Queensland residents only. Age-standardised rates (ASR) were calculated using the 2001 Australian population as a reference. A 3-year rolling average of the most recent 3 years of incidence is used.

Overall survival

The 2- and 5- year overall survival (all causes of mortality) was calculated from the date of histological diagnosis to the data cut-off date, 31 December 2020. Patients still alive at this date were censored. These rates were calculated in STATA 17 using the Kaplan–Meier method.[17] Survival was plotted based on p16 status and 8th Edition AJCC Staging Classification. Only survival curves where the p16 status was known are shown.

Multivariable analysis

A Cox proportional hazards model was used to assess the impact of the following covariates on survival among patients with p16+ disease: stage, sex, age groups, SES, comorbidities, and residence at diagnosis.

The test of equality of survivor function was used to determine whether there were significant differences in survival across stage groups. We tested for any violation of the proportional hazards assumptions and found no evidence of violation. Post-estimation testing was done using the command *estat phtest* in Stata17 (StataCorp LLC, College Station, TX, USA).

Results

Incidence trends for head and neck cancer

Between 1 January 2015 and 31 December 2019 there were 135,576 new cancer diagnoses in Queensland of which 3% (4192/135,576) were of the head and neck. A total of 38% (1584/4192) arose from the oropharynx, of which the majority, 96% (1527/1584), were OPSCC (the focus of this analysis).

Cancer arising from the oropharynx was the most common newly diagnosed head and neck cancer, followed by oral cavity (n = 1171), larynx (n = 621), major salivary glands (n = 254), hypopharynx (n = 230), nasal cavity and paranasal sinuses (n = 182), nasopharynx (n = 111) and other mucosal pharyngeal sites (n = 39). Head and neck cancer of cutaneous (or presumed cutaneous) origin was excluded from this analysis.

Oral cavity cancer was more common than OPC (N = 485, N = 253) in females, while in males OPC was more common than oral cavity cancer (N = 1331, N = 686) (Fig. 1a).

Age-standardised incidence rate

When comparing the change in age-standardised incidence rate (ASR, 3-year rolling average) from 1982 to 2019 based on the available data from the QOR, cancer of the oropharynx rose from 2.6 to 6.3 per 100,000 persons, an increase of 144%, predominantly due to OPSCC. Age-standardised incidence rates (3-year rolling average) for selected head and neck cancers from 1982 to 2019 in Queensland are shown in Figure 1b. Among males, there was an increase from 3.8 to 11.0 per 100,000, and in females, there was an increase from 1.3 to 1.8 per 100,000. During the same time period, there was a decrease in the ASR for oral cavity cancer from 5.6 to 4.7 per 100,000 persons. This decrease was driven by a decrease in incidence among males (8.1 to 6.1 per 100,000), while in females incidence remained steady at 3.0 per 100,000.

Demographics for OPSCC diagnosis based on p16 status

Patient demographics and tumour stage (AJCC 8th Edition) for OPSCC diagnoses by p16 status are summarised in Table 1.

Of the 1527 OPSCC diagnoses, 77% (1170/1527) were p16 positive (+), 19% (285/1527) p16 negative (−) and 5% (72/1527) p16 unknown (u).

The median age (IQR) at diagnosis for p16+, p16− and p16u was 60 (54–66), 65 (58–71), 67 (60–77) years, respectively. Median follow-up time for these groups was 34 (21–53), 23 (10–39) and 9 (2–32) months respectively.

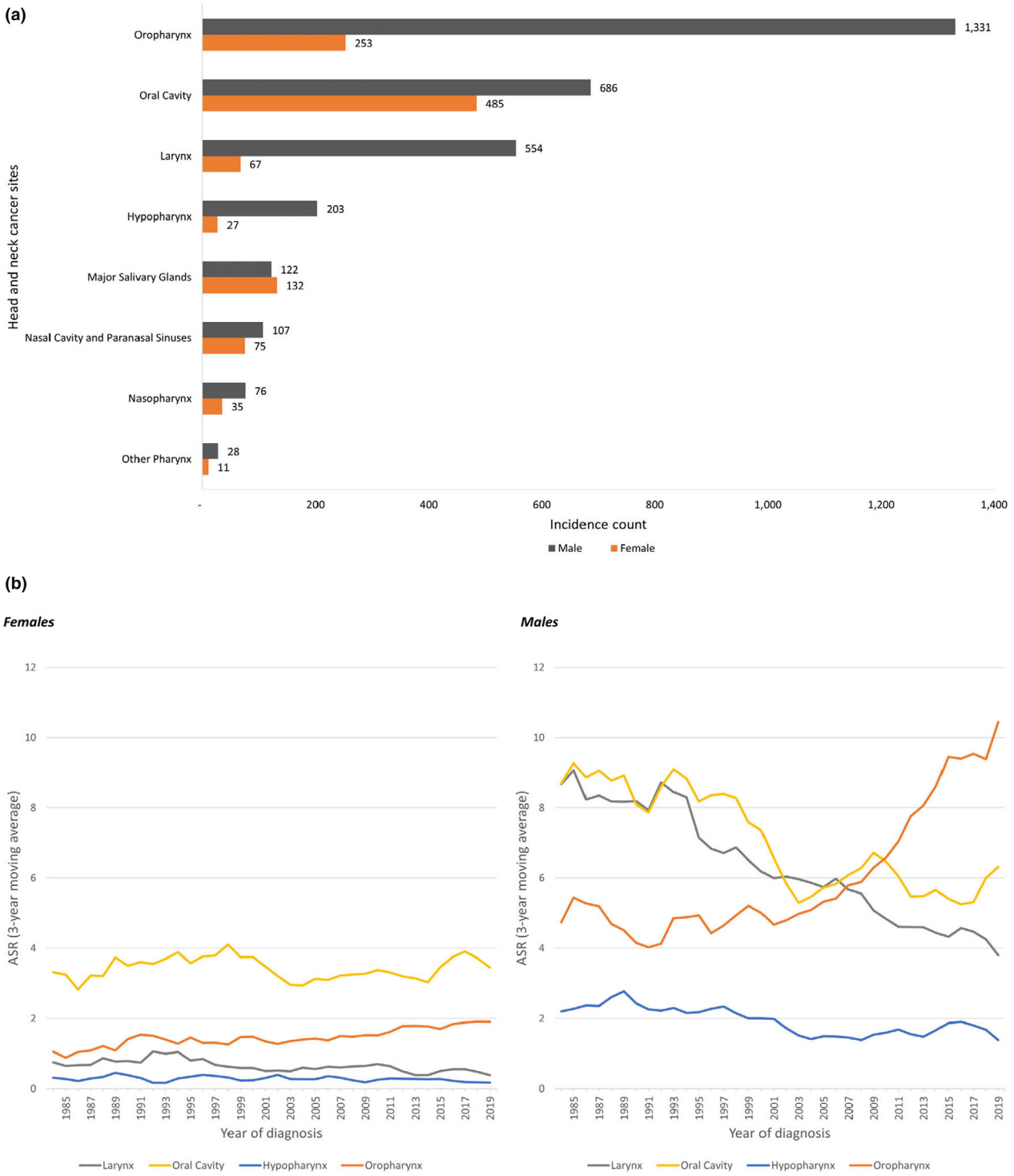

Fig. 1. (a) Incidence count of head and neck cancer sites, by sex, 2015–2019, Queensland, Australia. (b) Age-standardised incidence rate (ASR) (3-year rolling average) for selected head and neck cancer sites, by sex, 1982–2019, Queensland, Australia.

Patients were predominantly male regardless of p16 status; p16+ 87% (1019/1170), p16– 78% (222/285) and p16u 79% (57/72). Patients with p16+ disease were more likely to present with early-stage disease, Stage I, 49% (568/1170). Patients with p16– and p16u disease were more likely to present with more advanced

Table 1. Patient demographics and tumour stage at diagnosis of oropharyngeal squamous cell carcinoma by p16 status, 2015–2019, Queensland, Australia

	All OPCSCC†		p16+ OPCSCC		p16− OPCSCC		p16 unknown OPCSCC	
	N	Col%	*n*	Col%	*n*	Col%	*n*	Col%
Queensland	**1527**		**1170**		**285**		**72**	
(%)	**(100%)**		**(77%)**		**(19%)**		**(5%)**	
Age (at diagnosis)								
Median	61		60		65		67	
IQR	(55–68)		(54–66)		(58–71)		(60–77)	
Age group (at diagnosis)								
<40	13	0.9%	13	1.1%				
40–49	179	12%	159	14%	18	6.3%	2	2.8%
50–59	475	31%	398	34%	63	22%	14	19%
60–69	550	36%	414	35%	113	40%	23	32%
70–79	251	16%	161	14%	72	25%	18	25%
80+	59	3.9%	25	2.1%	19	6.7%	15	21%
ASR†	5.42		4.18		0.99		0.25	
Stage								
I	582	38%	568	49%	12	4.2%	2	2.8%
II	297	19%	276	24%	19	6.7%	2	2.8%
III	201	13%	169	14%	27	9.5%	5	6.9%
IV	263	17%	32	2.7%	188	66%	43	60%
Unknown	184	12%	125	11%	39	14%	20	28%
Sex								
Male	1298	85%	1019	87%	222	78%	57	79%
Female	229	15%	151	13%	63	22%	15	21%
Socioeconomic status								
Affluent	149	9.8%	129	11%	17	6%	3	4.2%
Middle	1019	67%	797	68%	179	63%	43	60%
Disadvantaged	359	24%	244	21%	89	31%	26	36%
Comorbidity								
0	1094	72%	881	75%	180	63%	33	46%
1	277	18%	187	16%	60	21%	30	42%
≥2	156	10%	102	8.7%	45	16%	9	13%
Evidence of MDT								
Yes	1418	93%	1107	95%	266	93%	45	63%
No	109	7.1%	63	5.4%	19	6.7%	27	38%

†OPSCC refers to oropharyngeal squamous cell carcinoma; p16+ refers to p16 positive, p16− refers to p16 negative. ‡Age-standardised rate (Australian per 100,000 persons). §8th Edition American Joint Commission on Cancer (AJCC) classification/Union for International Cancer Control (UICC) TNM staging.

disease, Stage IV, 66% (188/285) and 60% (43/72), respectively.

For the entire group, the majority 72% (1094/1527) had no recorded co-morbidities, while 18% (277/1527) had 1, and 10% (156/1527) had 2 or more. Based on p16 status, 2 or more co-morbidities were seen in 8.7% (102/1170) of p16+, 16% (45/285) in p16−, and 13% (9/72) in p16u patients.

Treatments

Ninety three percent (1418/1527) of OPSCC patients had a record of a discussion at a Queensland multidisciplinary clinic in QOOL.

p16+ cohort

Of the p16+ cohort ($n = 1710$), 97% (1136/1710) received anti-cancer therapy. The modalities utilised consisted of radiotherapy (91% (1063/1170)), and intravenous systemic therapy (IVST) (79% (924/1170), of which 76% (888/1170) was delivered concurrently). Surgery was utilised in 31% (362/1170) of cases (excluding biopsy).

p16− cohort

Of the p16− cohort ($n = 285$), 88% (250/285) received anti-cancer therapy. The modalities utilised consisted of radiotherapy (78% (221/285)), IVST (53% (151/285), of which 48% (138/285) was delivered concurrently). Surgery was utilised in 26% (74/285) of cases.

Overall survival

The 2- and 5-year overall survival for the p16+ cohort was 89% and 79%, respectively. The 2- and 5-year overall survival for the p16− cohort was 62% and 39%,

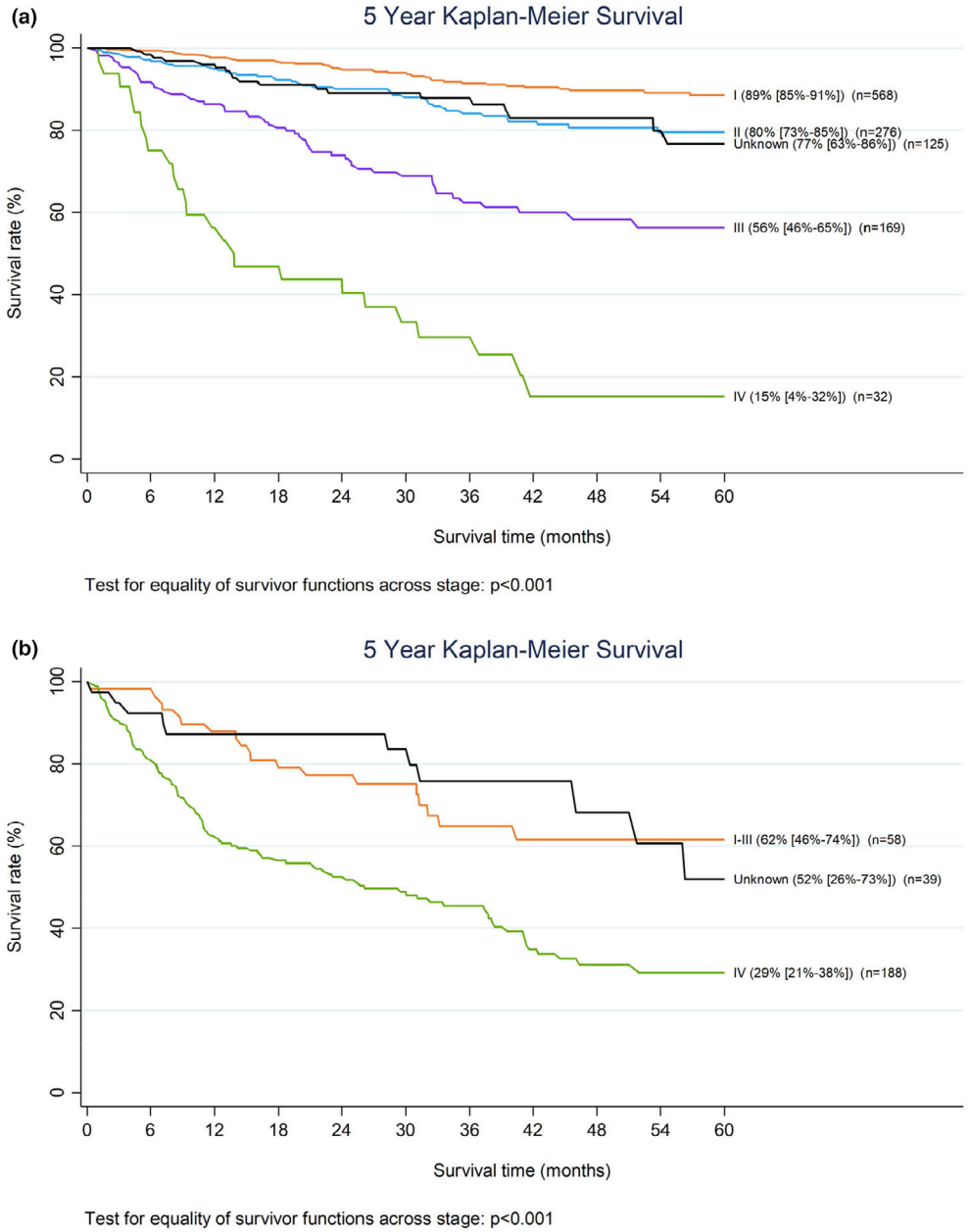

Fig. 2. (a) Kaplan–Meier survival for p16+ Oropharyngeal Squamous Cell Carcinoma, by 8th Edition AJCC/UICC TNM stage, 2015–2019, Queensland, Australia, (b) Kaplan–Meier survival for p16− Oropharyngeal Squamous Cell Carcinoma, by 8th Edition AJCC/UICC TNM stage, 2015–2019, Queensland, Australia. Test for equality of survivor functions across stage: $P < 0.01$.

respectively. Contemporaneous 2-year overall survival data was available from the database for oral cavity cancer ($n = 1166$) 77%, laryngeal cancer ($n = 622$) 72% and hypopharyngeal cancer ($n = 230$) 53%.

The 5-year overall survival (and 95% confidence intervals (CI)) for OPSCC p16+ and p16− diagnosed based on the 8th edition AJCC/UICC TNM stage are shown in Figure 2a,b, respectively. The 5-year overall survival for p16+ disease based on stage were: I – 89% (95% CI; 85–91), II – 80% (95% CI; 73–85), III – 56% (95% CI; 46–65) and IV – 15% (95% CI; 4–32). The difference in overall survival across stage groups was considered statistically significant ($P < 0.001$) (Fig. 2a).

The 5-year overall survival for p16− disease based on stage was I–III – 62% (95% CI; 46–74) and IV – 29% (95% CI; 21–38). The difference in survival across stage groups was considered statistically significant ($P < 0.001$) (Fig. 2b).

Table 2. Factors associated with mortality for patients with p16+ disease of oropharyngeal squamous cell carcinoma, 2015–2019, Queensland, Australia

Covariate	OPCSCC p16+		Factors affecting survival from diagnosis		
	N	Deaths	Hazard ratio	[95% CI]	*P*
Queensland	**1170**	**198**			
Sex					
Female	151	22	Reference		
Male	1019	176	1.37	[0.87–2.17]	0.18
Age					
≤54	326	33	Reference		
55–64	471	72	1.32	[0.87–2]	0.19
65–74	295	63	1.79	[1.16–2.75]	0.009*
75+	78	30	3.45	[2.07–5.75]	<0.001**
Residence at diagnosis					
Major City	748	120	Reference		
Inner Regional	249	42	0.79	[0.54–1.16]	0.23
Other	173	36	1.07	[0.73–1.59]	0.72
Socioeconomic status					
Affluent	129	14	Reference		
Middle	797	125	1.18	[0.67–2.08]	0.56
Disadvantaged	244	59	2.08	[1.12–3.88]	0.021*
Comorbidity					
0	881	103	Reference		
1	187	62	2.62	[1.89–3.63]	<0.001**
2+	102	33	2.44	[1.63–3.65]	<0.001**
Stage group					
I	568	50	Reference		
II	276	46	1.97	[1.32–2.95]	<0.001**
III	169	57	3.96	[2.68–5.85]	<0.001**
IV	32	25	14.77	[8.97–24.33]	<0.001**
Unknown	125	20	1.79	[1.06–3.03]	0.03*

*<0.05, **<0.001.

Variables impacting on survival for p16+ disease

An analysis of covariables and impact on survival for OPSCC p16+ disease is shown in Table 2. On multivariable analysis, increasing stage relative to Stage I, older age (≥65 years), increasing comorbidities (≥2) and disadvantaged SES had an adverse impact on survival. Sex or residence was not shown to have an impact on survival.

Discussion

This report provides a statewide population-based analysis confirming the emergence of HPV-associated OPSCC as the most common newly diagnosed head and neck cancer in Queensland, having surpassed oral cavity cancer.

This data provides real-world outcomes for unselected patients presenting with OPSCC, within the Australian health system context. It also provides an insight into resource implications given the rising incidence of this disease and the treatments utilised. The rise in OPC has primarily been driven by the increase in OPSCC p16+ and is considered a distinct clinical entity. Human papillomavirus subtypes 16 and 18, the same ones responsible for cervical cancer, predominantly cause HPV-associated OPSCC.

The majority of our patients with OPSCC p16+ were male, had fewer comorbidities and were younger than p16− patients.

This increase throughout the Western world has been associated with an increased rate of oral sex, its commencement at a younger age, and an increase in sexual partners.[3]

The latency from infection, from when people become sexually active, to the development of cancer is generally between 20 and 30 years.[3] HPV vaccination for girls was first introduced in the Australian National Immunisation Program in 2007, and for boys in 2013. It is therefore anticipated that the incidence will continue to rise for at least another 20 years before the impact of the national vaccination program is seen. According to the current Australian Institute of Health and Welfare (AIHW) figures there has been a rise in the number of actual new cases of OPC from 1982 (n = 181) to 2017 (n = 767), with an estimated projected number of new cases of 933 in 2021. This corresponds to an increase in the ASR (per 100,000) from 1.3 in 1982 to 3.1 in 2021.[18]

A randomised phase III trial of chemoradiotherapy demonstrated superior overall survival for HPV-associated OPSCC compared with non-HPV-associated OPSCC.[4] In a single institution series from the Princess Alexandra Hospital, Brisbane, of 418 patients, Daniels *et al*.[5] reported 5-year locoregional relapse failure free survival and cancer specific survival following chemoradiotherapy of 91% (95% CI; 88–94) and 90% (95% CI; 87–93), respectively.

Chemoradiotherapy has therefore been predominantly used for this disease. This analysis confirms the high utilisation rates of chemoradiotherapy in Queensland, compared with surgery for this disease. In this series, 91% (1063/1170) of OPSCC p16+ received radiotherapy or chemoradiotherapy while only 31% (362/1170) underwent surgery. With a decline in oral cavity cancer incidence, where surgery is the preferred treatment of choice, and the increase in OPSCC, where chemoradiotherapy is the preferred treatment, there are important resource implications for the Australian health system with respect to potentially requiring greater chemotherapy and radiotherapy services.

Unlike clinical trials, this cohort is made up of patients with a wide range of co-morbidities, disease extent, stage, and fitness for treatment. As such the intent of treatment will have varied from curative, palliative, or salvage. It is therefore beyond the scope of this report to perform a detailed analysis to compare the impact of treatment modality received and outcome because of the potential bias of one treatment over another based on intent.

Nonetheless the overall utilisation rates for the various modalities provide important insights into the treatment resources used, a main goal of the analysis.

There was good concordance between stage and survival, with the increasing stage (8th Edition AJCC) resulting in lower survival. The majority of OPSCC p16+ presented with stage I disease. The 5-year overall survival for the entire OPSCC p16+ cohort of 79%, compares favourably with traditional non-HPV associated cancers, which normally have 5-year survival rates ranging between 30% and 50%.[19]

The association between tobacco abuse, the development of head and neck cancer and the adverse impact on survival outcomes has long been established.[20] The repository used for this analysis does not capture smoking history at a statewide level and so an analysis of smoking impact could not be performed. However, the Princess Alexandra Hospital in Brisbane, Queensland, analysed 404 patients with OPSCC p16+, of which a proportion of these patients also forming part of the cohort for this analysis, and found that at diagnosis 30% (121/404) were current smokers, 32% (129/404) had never smoked and 38% (154/404) were former smokers. Current smokers had an inferior survival compared with never and former smokers with a HR 2.37 (95% CI; 1.26–4.45, $P < 0.01$) and 2.58 (95% CI; 1.40–4.73, $P < 0.01$), respectively.[21]

On multivariable analysis we found that for OPSCC p16+, increasing stage, older age (≥65 years) and increasing comorbidities (≥2) had an adverse impact on survival. We also found that disadvantaged SES had a worse survival, and the reasons for this are not clear but warrant further evaluation. We did not find sex or remoteness of residence had an adverse impact on survival. Chemoradiotherapy achieves high cure rates for HPV-associated OPSCC; however, these treatments are toxic and result in both acute and long-term toxicity, such as neuropathy, hearing loss, xerostomia and swallowing difficulties. Therefore there has been great interest in de-escalating chemoradiotherapy to lessen the severity of treatment without compromising the cure.[8,22–24] Another promising option is the use of minimally invasive surgery, such as Transoral robotic surgery (TORS) or Transoral laser microsurgery (TLM) to treat the primary tumour, with or without neck surgery and then risk-adjusted post-operative radiotherapy. In a recent Phase II trial reported by Ferris *et al*., excellent oncologic and favourable functional outcomes were achieved in a group deemed as having intermediate risk OPSCC p16+, with primary TORS and post-operative radiotherapy.[25]

In conclusion, our findings confirm that OPSCC is now the most common mucosal head and neck cancer diagnosed in Queensland, having surpassed oral cavity cancer. The majority are HPV-associated (p16+), presenting with early-stage disease. Our findings confirm the favourable prognosis of this disease at a population-wide level, provide insight into the growing need for resources required to manage this disease and set the benchmark to which other jurisdictions can compare outcomes.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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