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Changing Prevalence and Treatment Outcomes of Patients with p16 Human Papillomavirus Related Oropharyngeal Squamous Cell Carcinoma in New Zealand

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Abstract

There has, to our knowledge, been no previous report of changes in the prevalence and outcomes of treatment of HPV-positive (+) oropharyngeal squamous cell carcinoma (SCC) in New Zealand. We identified all affected patients in the greater Wellington region between 1 January 1994 and 30 November 2014 from the New Zealand Cancer Registry. Their personal details, characteristics of their tumours, treatment, complications, and outcomes were collected retrospectively from their casenotes and the New Zealand Death Registry, followed by p16 immunohistochemical staining. Of the 161 patients included, 131 (81%) were men. p16 immunohistochemical staining was done routinely in 13 patients during investigations, and retrospectively for 135 patients. The proportion of p16+ oropharyngeal SCC increased from 24% during 1994-1999, to 76% during 2009-2014 ($p < 0.001$). Oropharyngeal SCC among Europeans was more likely to be p16+ than in non-Europeans (67% compared with 44%, $p = 0.036$). Patients with p16+ disease were younger (mean (SD) 56 (±10) compared with 66 (±9) years, $p < 0.01$) with fewer coexisting conditions (mean (SD) Charlson Comorbidity Index: 2.45 (±0.82) compared with 2.92 (±1.16), $p = 0.01$), and less likely to have smoked (57/81(70%) compared with 38/42 (91%) $p = 0.035$), or misused alcohol (12/81 (15%) compared with 14/42 (31%), $p = 0.042$), or both. They were also more likely to have poorly differentiated tumours (30/52 (58%) compared with 9/34 (26%), $p = 0.019$) with nodal metastases (74/85 (87%) compared with 17/30 (57%), $p = 0.001$). Overall 5-year all-cause survival was more favourable for patients with p16+ disease (65/86 (76%) compared with 15/49 (31%), $p = 0.000$). Interestingly, all-cause age at death was younger in p16+ patients (62 (±11.1) compared with 71 (±11.2) years, $p = 0.001$). The prevalence of p16+ oropharyngeal SCC had tripled in this population between 1994 and 2014, and affected patients have distinct characteristics and outcomes of treatment.

Keywords: Oropharyngeal; squamous cell carcinoma; alpha-papillomavirus; human papillomavirus; New Zealand

Introduction

Many countries have reported a dramatic increase in the incidence of oropharyngeal squamous cell carcinoma (SCC) over the past 10-30 years,[1–3] coinciding with a stable or

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decreasing rate of smoking and alcohol misuse.[4,5] This has been attributed to a greater proportion of these tumours being associated with the human papillomavirus (HPV), which also implicated in cervical and anal malignancies.[6]

Clinically and epidemiologically, HPV positive (+) oropharyngeal SCC is distinct from HPV negative (-) oropharyngeal SCC, as it presents in younger patients and is associated with better survival.[6]

In New Zealand, the rapid rise in the incidence of oropharyngeal SCC began around 2005, increasing by 11.9% annually until 2010.[7] It is not certain if this increase is attributable to HPV infection and whether overseas data can be applied to New Zealand, which has a unique multi-ethnic population, particularly Māori and Pacific Islanders.

We have quantified changes in the prevalence of HPV+ oropharyngeal SCC in the greater Wellington region over a 20-year period, and compared characteristics of both tumours and patients and the outcomes of treatment in patients with HPV+ disease with their HPV- counterparts.

Patients and Methods

Identification of patients

All patients who lived in the greater Wellington region of New Zealand and were treated for SCC of the oropharynx (tongue base, palatine tonsil, soft palate, and lateral and posterior pharyngeal walls) between 1 January 1994 and 30 November 2014, were identified from the New Zealand Cancer Registry using ICD-10 codes: C01 (malignant neoplasm of base of tongue), C02 (malignant neoplasm of other and unspecified parts of tongue), C05 (malignant neoplasm of palate), C09 (malignant neoplasm of tonsil), C10 (malignant neoplasm of oropharynx), C14 (malignant neoplasm of other and ill-defined sites). All patients with tumours that were not oropharyngeal SCC were excluded.

Patients' clinical records were reviewed and their demographic data (age, sex, ethnicity, New Zealand Deprivation Index (NZDI - an estimate of socioeconomic status), smoking status (ever smoked or never smoked), alcohol misuse (if alcoholism or alcohol misuse was documented), coexisting conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcers, diabetes mellitus, chronic renal disease, hemiplegia, leukaemia, lymphoma, solid tumour, metastatic tumour, liver disease, or HIV/AIDS); the characteristics of the tumour (anatomical site, stage, histological grade, status of prospective HPV testing); treatment (surgery, radiotherapy, or chemotherapy) and complications (unable to complete treatment, percutaneous gastrostomy tube or nasogastric tube feeding, severe mucositis or skin reaction, or both, trismus, tube feeding for longer than six months after treatment, or death during treatment); and the presence and date of recurrence, were collected. Mortality data were obtained from the New Zealand Death Registry.

Archived formalin-fixed, paraffin-embedded, tissue blocks of oropharyngeal SCC were retrieved from the laboratories at Wellington Regional Hospital, Hutt Hospital, and Aotea Pathology and, where adequate tissue was available, used for testing.

Histological and immunohistochemical staining

The diagnosis of oropharyngeal SCC in the tissues being studied was confirmed by reviewing the slides stained with haematoxylin and eosin. In two cases only metastatic regional nodes were available.

After the slides had been reviewed (by pathologist HDB), formalin-fixed, paraffin-embedded sections, 4 μm-thick, of oropharyngeal SCC were stained immunohistochemically with a monoclonal antibody to p16 (CINtec Histology kit, Clone E6H4) with a Bond™ RX autostainer (Leica, Nussloch, Germany) according to the manufacturer's instructions, using a published protocol.[8] A known p16+ oropharyngeal SCC was used as positive control.

All immunohistochemically-stained slides were examined independently by two pathologists (HDB and SB). Tumours showing ≥ 70% p16 staining of cells were deemed positive for HPV[1] and the results were classified (0, negative; 1+, equivocal (focal positive staining involving < 70% of the tumour); 2+, > 70%) and compared.

Statistical analysis

Fisher's exact test (FET) for categorical variables and Student's *t* test after Levene's test for variances was performed with the aid of IBM SPSS Statistics for Windows (version 22, IBM Corp, Armonk, NY, USA). FET results were confirmed with χ^2. The level of statistical significance was $p < 0.05$. The reason for checking on Fishers exact test by also using χ^2 is that Fishers test is now known to have an asymmetrical bias. Interestingly so does χ^2 but in the opposite direction so if used together they allow the biases to cancel each other, by selecting an appropriate value between the two results.

Results

Details of patients (Table 1)

Of the 251 patients reviewed, 161 patients (131 men) with a mean (range) age 60 (28-88) years, were included in the study (Fig. 1A). Ninety cases were excluded as the tumours were outside the oropharynx. The most common ethnicity was European (n = 137, 85%), followed by Māori (n = 15, 9%), Asian (n = 7, 4%), and Pacific Islander (n = 3, 2%).

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