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Original Research

Human papillomavirus–associated oropharyngeal cancer among patients aged 70 and older: Dramatically increased prevalence and clinical implications

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Abstract ***Background:*** Oropharyngeal squamous cell carcinoma (OPSCC) is increasing in incidence among older adults. However, the role of human papillomavirus (HPV) in driving this trend and its prognostic significance in this population have not been established.
Methods: The National Cancer Database was queried for patients with OPSCC diagnosed from 2010 to 2015 undergoing either surgery or radiotherapy (RT) with known HPV status. Older adults were defined as those aged 70 years or older.
Results: Among 43,427 OPSCC patients, the proportion of HPV-positive OPSCC increased from 45.1% to 63.3% in older adults ($P < 0.001$). In 19,358 patients meeting the inclusion criteria for survival analyses, HPV positivity was associated with improved survival for older adults undergoing either definitive RT (hazard ratio [HR] = 0.63, 95% confidence interval [CI] 0.55–0.72, $P < 0.001$) or surgery (HR = 0.37, 95% CI 0.25–0.53, $P < 0.001$) in multivariable analysis. In propensity score–matched cohorts, 3-year overall survival was 69.1% versus 55.5% ($P < 0.001$) in older adults with HPV-positive and HPV-negative OPSCC undergoing definitive RT, respectively, and 88.5% versus 69.1% ($P = 0.001$) for older adults undergoing surgery. Although HPV positivity was associated with improved survival among all age groups receiving RT, the magnitude of the effect diminished with increasing age (interaction

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P < 0.001). No interaction between age and the impact of HPV status on survival was seen for surgical patients (interaction P = 0.72).
Conclusions: The epidemiologic landscape of HPV-positive OPSCC is evolving, with a dramatic increase in the proportion of HPV-associated OPSCC among patients 70 years or older. HPV remains a powerful predictor of improved survival in elderly patients, but with less pronounced effect on older adults undergoing definitive RT.

1. Introduction

The epidemiologic landscape of oropharyngeal squamous cell carcinoma (OPSCC) has undergone a dramatic evolution [1–3]. Increased rates of oral HPV infection, in combination with declining rates of tobacco use [4], have transformed OPSCC from a tobacco- and alcohol-related malignancy into a disease, predominantly driven by HPV infection in developed countries [2,4,5]. Given the unique biology and clinical behaviour of HPV-associated OPSCC, this shift in epidemiology has led to markedly higher cure rates with standard treatment.

Concomitant with this change in aetiology, the overall incidence of OPSCC has steadily increased for the last two decades in the United States and other developed countries, suggesting, *en balance*, that the rise in HPV-related cancers was occurring much faster than the decline in HPV-negative tumours. Initial epidemiologic studies demonstrated that the increased incidence of OPSCC was driven exclusively by patients younger than 60 years [1,6]. Thus, HPV-positive OPSCC has been considered a disease predominantly affecting young, healthy patients. However, a recent study using more contemporary registry data demonstrated that since 2000, there has been a substantial increase in OPSCC among older adults as well, paralleling what was observed in younger patients over the previous decade [7]. Although it has been hypothesised that this trend was a result of HPV-associated tumours percolating into older age groups, HPV status is not available in most population-based registries. Therefore, an increasing prevalence of HPV-associated tumours among older adults remains speculative.

Older adults with OPSCC represent a population that is uniquely challenging to treat [8]. Older adults often have increased comorbidities, increasing their risk of death from non-cancer causes, and have difficulty tolerating standard multimodality therapy [9–12]. Moreover, patients aged 70 years or older have historically been underrepresented, or excluded entirely, from head and neck cancer clinical trials [10], limiting the available high-level evidence to guide treatment decisions for these patients. Given that older adults have competing causes of death and often cannot receive similar treatment paradigms as younger patients, it is unclear if HPV status conveys the same impact on survival in older adults as in younger patients. In this study, we explore the recent trends in the prevalence of HPV among patients 70 years and older and compare the prognostic impact of HPV status on younger and older patients with OPSCC.

2. Materials and methods

2.1. Database information

The National Cancer Database (NCDB) is a database sponsored by the American College of Surgeons and the American Cancer Society which compiles data from more than 1500 facilities. The NCDB contains data for approximately 70% of new cancer diagnoses in the United States. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the deidentified data used herein; they have not been verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by us. This study was deemed to be exempt from the full institutional review board review by Cedars-Sinai Medical Center.

2.2. Patient selection

The NCDB was queried for patients with oropharyngeal cancers (International Classification of Diseases for Oncology [ICD-O]-3 codes: C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.2) with squamous cell carcinoma histology (ICD-O-3 codes: 8050–8084) diagnosed from 2010 to 2015. Patients with ambiguous anatomic site codes (C02.8, C02.9, C05.8, C05.9, C14.0, C14.8) were excluded. HPV status is coded in NCDB based on any type of HPV testing performed, including p16 immunohistochemistry, HPV *in situ* hybridisation, or other methodologies. All OPSCC patients with known HPV status during this time period were included to assess changes in the proportion of HPV-positive OPSCC over time (Supplementary Fig. 1). This cohort was used for analysing trends in HPV positivity among OPSCC patients over time.