Head and Neck Squamous-Cell-Carcinoma

Subjects: Others

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Head and neck squamous cell carcinoma (HNSCC) is the most common cancer arising in the head and neck region. The most common risk factors are smoking, excessive drinking, and human papillomavirus (HPV) infection.

head and neck squamous cell carcinoma

1. Introduction

Head and neck cancer is the seventh most common cancer worldwide, accounting for 3% of all cancers, with approximately 900,000 new cases and half a million deaths annually [1]. Among all cancers occurring in the head and neck region including oral cavity, oropharynx, hypopharynx, and larynx, the squamous cell carcinoma histology accounts for approximately 90% [2][3]. The major risk factors of head and neck squamous cell carcinoma (HNSCC) are tobacco and heavy alcohol use and human papillomavirus infection [4][5][6][7]. There has been a significant decline in smoking in high-income countries during the last few decades, which has led to a sharp decline in smoking related HNSCC [8][9]. In contrast, there has been a significant increase in global incidence of human papillomavirus (HPV)-associated or positive (+) HNSCC [4,10–16]. In addition to the shift in the common risk factors, we also have observed the shift in the management of HNSCC from indiscriminate intensification with a sole focus on improving survival to more personalized approaches based on understanding of the biology and leveraging advancements in biomarkers and immunotherapy.

2. Epidemiology and Pathophysiology of HNSCC

2.1. HPV Positive (+) HNSCC

Human papillomavirus infection is now recognized as the major causative agent for HNSCC, especially in the oropharynx (OPSCC), accounting for approximately 60–70% of OPSCC in the United States, while the prevalence varies more within Western Europe ranging between 6.1 and 75% [16–18]. In third world countries, HPV(+) HNSCC is relatively rare with a <10% prevalence [10]. These variabilities are thought to be, at least in part, due to the different sensitivity and specificity of the HPV detection assays and differences in the study cohorts as well as different sexual practices and their associated risk factors in the study population [11]. HPV(+) HNSCC shows marked differences in epidemiology and pathophysiology as compared to HPV unrelated or negative (−) HNSCC [12][13]. Demographically, HPV(+) OPSCC patients tend to be younger males with a mean age of diagnosis in the 40–50's and non-smokers or oligo-smokers [14][15]. HPV infection has a 10–30-year latency period between

infection and clinical presentation with HPV(+) OPSCC [15]. Because HPV(+) OPSCC arises in the deep crypts in the tonsillar tissues without any associated pre-malignant clinical lesion within the oropharynx, early detection through screening is not possible [16]. In 2018, the FDA extended the approved age range of candidates for the preventive vaccine against HPV, GARDASIL 9, to include men and women <45 years of age. Epidemiological data suggest that prophylactic HPV vaccination reduces the prevalence of oral HPV infection by 88–93%. Considering the slow uptake and long latency period, vaccination is expected to reduce the incidence of oropharyngeal cancer by 2060, and we do not expect immediate changes in the current HPV(+) OPSCC incidence [17][18].

Regarding HPV-related pathophysiology, it is clearly established that HPV viral oncoproteins, E6 and E7, degrade two major tumor suppressors, p53 and pRb, upon infection, resulting in tumorigenesis in the reticular epithelium covering the tonsillar tissues, and persistent expression of E6 and E7 is required for tumor maintenance [19][20]. Disruption of the pRb function leads to a compensatory increase in expression of $p16^{INK4A}$, which has been adapted as a surrogate marker of HPV infection in OPSCC [21]. The expression of p16 is now routinely tested using an immunohistochemistry staining as a standard of care in all OPSCC [22].

2.2. HPV Negative (−) HNSCC

The HPV(−) HNSCC is typically seen in patients with history of heavy tobacco and alcohol use [23]. There has been a significant decline in smoking in high-income countries during the last few decades, which has led to a sharp decline in smoking related HNSCC [8][9]. However, smoking-related cancers are still a significant problem in developing and third world countries[9]. In addition, HPV(−) HNSCC can occur in relatively young patients with no history of tobacco use, and the incidence has been rising with unclear etiology [24][25]. The most common genomic abnormalities in HPV(−) HNSCC from smokers are seen in *TP53* encoding p53 and *CDKN2A* encoding p16 with a distinct smoking signature, while the tumors from non-smokers have *TP53* mutations with aging and ultraviolet light exposure signatures [25][26][27].

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