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ESSENTIALS FOR PRACTITIONERS IN ONCOLOGY

Human papillomavirus–associated oropharyngeal cancer: review of current evidence and management

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ABSTRACT

Oropharyngeal cancer (OPC) has become the leading site for human papillomavirus (HPV)–associated cancers in humans. It is an epidemic that remains relatively unfamiliar to most physicians, potentially delaying diagnosis and treatment. Traditionally, cancers involving the head and neck have occurred in smokers and in those with a significant alcohol history. Typically, HPV-positive OPC presents in a younger, healthier population with a different set of risk factors and good prognosis for survival. However, many head-and-neck cancer patients, including those with HPV-positive disease, develop lifelong disabilities because of the morbid nature of their treatments, and those patients have the highest level of unmet needs in studies spanning cancer sites.

Knowledge of this epidemic, a high index of suspicion, and an understanding of how the tumours present in clinical practice can help physicians to make an early diagnosis, thus sparing the patient significant morbidity from treatments associated with more advanced disease stages. Furthermore, recognizing that these patients have distinct psychosocial needs and implementing a collaborative team approach is critical to providing optimal care and improving quality of life in the survivorship period.

Key Words Human papillomavirus, oropharyngeal cancer, prognosis, survivorship, treatment, vaccines

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INTRODUCTION

Prevalence of Oropharyngeal Cancers Associated with the Human Papillomavirus

Head-and-neck squamous cell carcinomas include cancers of the oral cavity, larynx, hypopharynx, and oropharynx[1]. The oropharynx comprises the tonsils and the base of the tongue. Despite a steady decline in the incidence of head-and-neck cancers in the last few decades, the incidence of oropharyngeal cancer (OPC) has shown an overall increase that is largely attributable to the rise in infections with the human papillomavirus (HPV)[2]. Habbous *et al.*[3] estimated that the prevalence of HPV-positive OPC in 6 Canadian centres increased from approximately 47% in 2000 to about 74% in 2012. In the United States, the incidence of HPV-positive OPC was reported to have increased by 225% between 1988 and 2004[4] and to now constitute up to 90% of all new cases of OPC. The patients are often younger and healthier (median age at diagnosis: 54 years)[5], with a high socioeconomic status and minimal to no smoking history, marking a shift in cause from the traditional older patient with a long history of tobacco and alcohol abuse[2,6–8]. In the absence of those traditional risk factors, a combination of inherent genetic factors, HPV exposure, and behavioural risk factors (including an increased number of sexual partners, earlier onset of sexual activity, and in men, a history of anogenital warts) are thought to be contributory[9]. Once treated, HPV-positive OPC is also associated with a more favourable prognosis. However, this increasingly prevalent entity remains unfamiliar to many physicians, and compounded by complacency on the part of young and healthy patients without a smoking history about seeking medical attention for cancer symptoms, diagnosis and treatment are often delayed.

hpv阳性的口咽癌2012年有74%（加拿大）。1988-2004年增长了225%（美国）

预后是好的

此类病人年轻、自满、社会地位高，所以不以为然

患病人群都比较高级

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According to the World Health Organization, HPV is now the most common sexually transmitted infection worldwide[10]. Although most cases go unreported, the U.S. Centers for Disease Control and Prevention estimates that up to 75% of the U.S. reproductive-age population has been exposed to HPV[11]. At any one time, 6.9% of individuals are harbouring detectable levels of HPV in the oral cavity or oropharynx[2]. Transmission of HPV occurs primarily through sexual contact, and orogenital contact can lead to oral or oropharyngeal HPV infection[8]. Although most infections are asymptomatic and spontaneously cleared within the first 2 years, at least 15 of more than 100 viral types are characterized by high oncogenicity[12]. The greatest proportion of HPV-related cancer cases are HPV 16–positive and are therefore amenable to preventive methods such as vaccination[8,13].

HPV Vaccination

Two HPV vaccines are currently available: the quadrivalent HPV vaccine Gardasil (Merck Sharp and Dohme, Kenilworth, NJ, U.S.A.), which protects against HPV 6, 11, 16, and 18, and the bivalent Cervarix (GlaxoSmithKline, Brentford, U.K.), which protects against HPV types 16 and 18[14]. While awaiting data evaluating the long-term effects of those vaccines on cervical cancer outcomes, accumulated data has ascertained their role in preventing precancerous lesions. A recent Cochrane review of twenty-six trials including 73,428 participants demonstrated high-certainty evidence that the vaccines reduce rates of cervical intraepithelial neoplasia grade 2 to 2/10,000 from 164/10,000, grade 3 to 0/10,000 from 70/10,000, and adenocarcinoma *in situ,* to 0/10,000 from 9/10,000 in women 15–26 years of age[15]. No increased risk of adverse effects associated with vaccination have been identified. Furthermore, recent studies showed that vaccination is also effective in preventing cancer recurrence after loop electrosurgical excision procedures, with decreases in grades 2–3 cervical intraepithelial neoplasia of up to 86.5% in one prospective trial[16,17].

In Canada, the National Advisory Committee on Immunization has recommended routine HPV vaccination for all girls, women, boys, and men between 9 and 26 years of age, and "permissive" vaccination in individuals more than 26 years of age if previously unvaccinated[18]. However, coverage or conditions for boys and men to receive the vaccines continues to vary with the province, because such vaccination is believed to be less cost-effective. In the United States, new guidelines advise routine vaccination for all children at 11 or 12 years of age, or for all girls and women up to 26 years of age and for boys and men 13–21 years of age if previously unvaccinated. Only a "permissive" recommendation was issued for men who are between the ages of 22 and 26 and who have sex with men or who are at high-risk for anogenital cancers[19]. Patients and their partners will often ask about vaccination. We feel that vaccinating both is reasonable. The efficacy, immunogenicity, and safety of HPV vaccination have been validated in older patients[20,21].

Historically, the main focus of vaccination was to prevent cervical cancer, but evidence is also emerging that the HPV vaccines have a clear role in preventing many non-cervical cancers. In a cohort study of 202 patients with a previously treated high-grade anal intraepithelial neoplasia, the quadrivalent HPV vaccine was associated with a decreased risk of recurrence at 2 years after study entry (hazard ratio: 0.47; $p = 0.05$)[22]. Furthermore, by 2020, the number of HPV-positive OPCs is expected to exceed the number of cervical cancers[4]. Men are at an especially elevated risk of contracting an HPV-positive OPC (between 2.9 and 4.5 times the risk for their female counterparts)[23]. Those numbers highlight the need to further quantify the burden of disease and possibly re-emphasize male vaccination, given the likelihood that an even greater benefit from the vaccines will be realized[14].

HPV-Positive Compared with HPV-Negative Prognosis

In addition to the differences already outlined in terms of risk factors, prognosis is distinctly better for HPV-positive OPCs than for HPV-negative disease. Several studies have helped establish that significant difference, and HPV status is now routinely used as a stratification variable in medical trials and has to be considered by clinicians during patient consultations. Ang *et al.*[24] retrospectively analyzed the 0129 Radiation Therapy Oncology Group trial and found that 3-year overall survival (OS) was 82.4% for patients with HPV-positive disease and 57.1% for those with HPV-negative disease. In HPV-positive patients with no smoking history and a low nodal status (N0, N1, N2a), the 3-year OS could reach up to 93%. A smoking history of more than 10 pack–years and advanced T and N stage (N3, N4) were negative prognostic factors and were associated with an intermediate prognosis in HPV-positive patients (3-year OS: 71%)[24]. Similarly, O'Sullivan *et al.*[25] retrospectively studied 800 patients treated in Toronto and found a locoregional control rate of 95% for early-stage and 78% for late-stage HPV-positive disease at 3 years. However, for HPV-negative disease, the locoregional control rate was only 76% for early-stage disease and 62% for late-stage disease[25]. Longer-term outcomes were also comparable, the 5-year OS being 82% for patients with HPV-positive disease and 35% for those with HPV-negative disease[26].

When advising patients, it is reasonable to recall that, although pack–years and T and N stage both continue to be pertinent, HPV status clearly has an enormous effect on patient prognosis. This increasing recognition of HPV-positive cancer as a disease entity distinct from HPV-negative cancer has resulted in the inclusion of a novel OPC staging schema in the newly published 8th edition of the TNM staging manual from the American Joint Committee on Cancer and the Union for International Cancer Control, which is expected to improve predictive ability[27–29].

TREATMENT-RELATED CONCERNS AND MANAGEMENT

Head-and-neck cancer remains a relatively rare disease, accounting for only 5% of cancers worldwide. As a result, knowledge of the disease, the consequences of treatment, and patient needs after treatment are less widespread. The epidemic of HPV-positive disease requires clinicians to understand not only new risk factors and clinical presentations, but also a new set of treatment-related concerns for a younger population of patients with a better prognosis.

General Treatment Considerations

Currently, traditional standard-of-care treatment for all patients except for those with early-stage OPC is combined cisplatin-based chemoradiotherapy. That treatment has been shown to be very effective, with a long-term OS of up to 95% in HPV-positive patients, as outlined earlier. However, that success incurs a high cost in overall quality of life for the patients. A dry mouth and loss of taste are almost universal. More significant is dysphagia, which is quite severe—to the point that approximately 20%–30% of patients never go back to eating entirely by mouth and require a permanent percutaneous gastrostomy tube[30].

Given the new understanding of HPV-positive OPC, the quality-of-life implications of the side effects of treatment for affected younger patients with an excellent prognosis has resulted in several studies that aimed to de-intensify treatment while preserving antitumour efficacy. Two approaches have been taken to reduce the morbidity of chemoradiation, which has been the mainstay of treatment for more than 25 years. One approach involves lowering the dose or minimizing the field of radiation, or both. The other approach has re-introduced surgery into the treatment of this disease. Surgery was routinely used before the 1990s, after which time, the invasive transcervical approaches ("commando") were largely abandoned in favour of chemoradiation. However, newer techniques that rely on robotic surgery have come into vogue. In contrast to approaches through the neck, the new transoral procedures are nowhere near as invasive, with recent systematic reviews indicating fewer postsurgical swallowing impairments[31,32]. In many cases, patients can have the surgery and, within a few days, return home eating by mouth.

The treatment of HPV-positive disease is in flux, and ongoing, but guarded, interest in safe de-escalation continues. The recently published phase III Radiation Therapy Oncology Group 1016[33] and DE-ESCALATE HPV[34] trials both rejected cetuximab as a treatment equivalent to cisplatin, showing similar rates of toxicity, but inferior survival outcomes with cetuximab. Given those findings, de-escalation should be undertaken only within a clinical trial. A list of current de-escalation trials can be found at http://ClinicaLtrials.gov/, including the phase III Trans Tasman Radiation Oncology Group 12.01 trial, which is set to conclude in 2019.

Treatment Considerations in Metastatic Disease

Despite advances in systematic therapy, prognosis in recurrent or metastatic disease remains poor. Standard chemotherapeutic agents continue to play a role. For a single metastasis, surgery can occasionally be considered, and immunotherapy within the context of clinical trials can also be considered. It is also appropriate to consider early referral to palliative care and to ensure that patient and family fully understand the implications and side effects of proposed treatments, given the poor prognosis in metastatic disease[35].

Decreased Quality of Life and Psychosocial Distress in the Survivorship Period

In the post-treatment phase, all head-and-neck cancer patients require surveillance for cancer recurrence and second primaries, and they experience problems related to voice and swallowing. Dysphagia in particular is a highly significant ongoing concern for patients who have received chemoradiation. In addition to complex interdisciplinary care to control their cancer, patients must have their psychosocial needs addressed during treatment and in the survivorship period. According to a recent meta-analysis of 1366 patients, survivors of OPC, compared with head-and-neck cancer patients overall, face clinically significant deteriorations in xerostomia, dysphagia, and chewing at 1 year after treatment[36]. Those dysfunctions require significant readjustment: on the one hand, to maximize functional recovery (for example, through speech and eating rehabilitation) and to address the burden of physical symptoms; and on the other, to help patients reconfigure their lives and accommodate to visible changes in appearance and function[37,38].

Further research with sufficient power and proper control of confounders is needed to determine whether psychological distress (anxiety and depression) is increased for patients having HPV-positive oropharyngeal squamous cell carcinoma compared with patients having other head-and-neck cancers. Patients with oropharyngeal HPV-positive cancer are at risk for distress because of younger age and a greater impact on eating and speech, among other factors[39], which can be counterbalanced by a favourable prognosis, higher socioeconomic status, and a non-alcohol-related profile, obviating any differences uncovered in recent preliminary studies[40,41]. In general, patients with head-and-neck cancer present the highest levels of distress in oncology[42], with high levels of major depressive disorders and anxiety disorders[43,44] and increased risk for suicidal ideation[45] and completion[46]. In this population, special attention also has to be paid to body image, social reintegration, demoralization, and fear of cancer recurrence[47].

In a small body of studies, the experience of oropharyngeal HPV-positive squamous cell carcinoma has been described as being influenced by its sexually transmitted origins. In a retrospective survey of 48 patients treated between 1 and 6 years earlier[48], patients reported benefits associated with knowledge of the cancer's high rates of cure, survival, and treatment; however, 49% remained worried about the HPV status of their tumour, and 43% worried about infecting their partner. In 17%, persistently intense anxiety about how and why they became infected —and whether they were still infected—was reported. In 5%, marital or family tension after receipt of the news was reported, and 28% indicated decreased sexual intimacy. Another survey of 62 partnered patients with HPV-positive OPC who were, on average, 6.9 ± 9.9 weeks from their diagnosis[49] identified knowledge gaps in terms of the cause of their cancer (66% attributed it to HPV) and communicability (42% believed that their HPV status had somewhat increased their partner's risk of developing cancer; 8% thought their HPV had entirely increased the risk). Keeping their HPV status secret was reported by 14% of the patients (and 3% did not tell their partner) for fear of embarrassment (25%) or because of stigma (38%) or a need for privacy (25%), and 20% reported some effect on the couple (14% somewhat negative, 6% completely negative). Negative effects included

mistrust and reduced intimacy or sexuality for fear of HPV transmission. A need for more information from their physician about the implications of their HPV status was reported by 37% of patients.

Infertility connected with cancer treatment might be among the most troubling of all issues faced by young patients, producing significant psychological morbidity. Fewer than half of all oncologists in the United States are making referrals for patients to receive counselling about fertility preservation. Meanwhile, a survey of young cancer survivors indicated that 76% wanted children and more than 30% wanted additional children[35]. Failure to offer appropriate options for fertility can have lifelong consequences[50].

Physicians should properly educate patients and address their HPV-related concerns and should also screen for distress[51] and make appropriate referrals to psychosocial oncology and fertility preservation centres when needed[52]. Such approaches are especially important for maximizing outcomes in this vulnerable population.

CONCLUSIONS

Rates of HPV infection are continuing to rise, and the evidence that HPV-associated OPCs will become an important priority for the foreseeable future is compelling. Although vaccination has the potential to reverse the incidence trend, rates of vaccination for HPV continue to be low in Canada. Furthermore, given delays of up to 40 years after infection before the disease presents itself, physicians are now tasked with recognizing the manifestations of this slow-growing epidemic. These cancers usually present in younger, healthier individuals who might not have the typical risk factors for head-and-neck cancers and could therefore go unnoticed. The mainstay of treatment is combined chemoradiotherapy, and the prognosis for survival is good, but many patients will have long-term experience with the debilitating side effects of treatment. An interdisciplinary team approach with particular attention to psychosocial problems represents the cornerstone for achieving the best outcomes and quality of life during the treatment and survivorship periods.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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