Cancer of the Oropharynx

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KEYWORDS

• Head and neck squamous cell carcinoma • Oropharynx • Pathogenesis
• Chemoradiation • Transoral surgery • Human papillomavirus

KEY POINTS

- The oropharynx has a crucial role in swallowing because of the surrounding constrictor musculature, need for mobility and pliability, and proximity of the base of tongue to the larynx.
- Human papilloma virus (HPV) infection as a cause of oropharyngeal squamous cell carcinoma (OPSCC) has increased dramatically in proportion and overall numbers of OPSCC cases.
- Better clinical response to therapy and younger age of the HPV+ OPSCC patients has caused functional and quality-of-life considerations to become much more important endpoints in evaluating efficacy of therapeutic options; "deintensification" to ameliorate toxicity is under investigation for this population.
- Poor survival continues to be a problem for patients with HPV− cancers, despite best current chemoradiation treatment; in the future, surgical resection may play a role in intensification of local therapy for these patients.

INTRODUCTION

There are approximately 41,000 cases of squamous cell carcinoma of the head and neck (SCCHN) diagnosed annually in the United States, of which approximately one-third will arise within the oropharynx.[1] Located posterior to the oral cavity and between the nasopharynx and larynx, the oropharynx is critical in maintaining normal speech and swallowing because of the surrounding constrictor musculature, need for mobility and pliability, and proximity of the base of tongue to the larynx. Its main components include the soft palate, posterior and lateral pharyngeal walls, faucial arches, tonsillar fossa, as well as the base of tongue. Its nonrestraining soft tissue boundaries as well as

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its rich lymphatic supply allow the escape of malignant cells, resulting in most patients presenting with advanced disease (stage III or IV).[1] With limited surgical exposure and the refinement of radiation therapy (RT) techniques or the use of combination chemoradiotherapy (CRT),[2] nonsurgical strategies have become standard practice in treating cancer of the oropharynx. Recently, however, the introduction of minimally invasive techniques has rekindled interest in surgical therapy.

This article focuses on how an increased understanding of the pathogenesis and prognosis of oropharyngeal malignancies has transformed therapeutic approaches as well as how technological advancements aim not only to improve oncologic outcomes but also maintain functional integrity of the oropharynx and patient-reported quality of life (QoL).

PATHOGENESIS AND PROGNOSIS FOR OROPHARYNGEAL MALIGNANCIES

Current evidence suggests that improvement in oncologic outcomes for SCCHN not only have coincided with refinement of treatment techniques but also reflect a shift in the cause and pathogenesis of oropharyngeal malignancies.[3] Converging clinical, molecular, and epidemiologic evidence now confirm that human papilloma virus (HPV) status is the single most important determinant of prognosis in oropharyngeal squamous cell carcinoma (SCC). HPV is an epitheliotropic, double-stranded DNA virus with greater than 100 characterized genotypes; HPV16, with its predilection for oropharyngeal mucosa, is the most common genotype isolated from the oropharynx.[4] HPV-initiation underlies the epidemiologic observation that both incidence and survival of oropharyngeal SCC are increasing, in contrast with cancers associated with tobacco and alcohol, whose incidence is decreasing, with survival essentially stable.[5]

The improved prognosis associated with HPV in oropharyngeal SCCHN is related to substantially different responsiveness to treatment. The carcinogenic process in HPV-related malignancies is primarily attributed to the viral oncoproteins, E6 and E7, which bind and inactivate tumor suppressors, p53 and pRb, respectively. Deficiency of p53 and Rb results in loss of cell cycle checkpoints and physiologic apoptosis. HPV-infected cells demonstrate unbridled progression through the cell cycle, a proproliferative state that benefits the HPV life cycle in early infection. HPV-related oropharyngeal malignancies more frequently appear in younger men with a good performance status and are associated with small primary tumors yet advanced nodal stage, often with cystic nodes. When compared with patients with HPV-negative (HPV−) disease, HPV-positive (HPV+) tumors are consistently associated with a 50% reduction in risk of death.[6] This association is exhibited in multiple secondary analyses of recent institutional as well as cooperative group prospective studies that examined RT alone or in combination with various chemotherapy regimens.[7]

In the first prospective trial designed to investigate HPV-related cancers, Eastern Cooperative Oncology Group (ECOG) investigators (in ECOG 2399) used an induction regimen of paclitaxel and carboplatin and reported a higher response rate in those that were HPV+.[7] In addition, after a median follow-up of 40 months, progression-free survival (PFS) and overall survival (OS) were superior in HPV+ patients when compared with those that were HPV−.[7] This significant response to CRT led to the first national cooperative group trial testing a deintensification strategy for HPV+ oropharynx cancer. In this recently completed trial (ECOG 1308), patients with resectable HPV+ oropharyngeal cancers were treated with 3 cycles of induction chemotherapy, including cisplatin, paclitaxel, and cetuximab. Complete clinical response at the primary site was used as a dynamic response biomarker; complete responders were treated with a radiation dose reduced by 20% (54.0 Gy vs 69.3 Gy). For those receiving reduced-dose RT, PFS at 23 months was 84%, primary site local control was