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Review

Treatment de-intensification strategies for head and neck cancer

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Abstract Increasingly, squamous cell carcinoma of the oropharynx (OPSCC) is attributable to transformation resulting from high-risk human papillomavirus (HPV) infection. Such cancers are significantly more responsive to treatment than traditional tobacco- and alcohol-associated squamous cell cancers of the head and neck. Conventional management with definitive chemoradiation, surgery and adjuvant radiation, or radiation given with altered fractionation schemes, while effective, incurs long-term morbidity that escalates with treatment intensity and significantly impairs quality of life. Recent trials have suggested that less intensive treatment regimens may achieve similar efficacy with decreased toxicity. In this article, we review the primary strategies used for de-escalation of treatment, which include the reduction of radiation dose, substitution and/or elimination of concurrent radiosensitising chemotherapy, and the use of minimally invasive surgery. We discuss the rationale behind these approaches and the preliminary data demonstrating the success of de-escalation, as well as potential considerations raised by treatment de-intensification in HPV-associated OPSCC.

1. Introduction

Epidemiologic trends from the 1980s onward have demonstrated a decline in the incidence of squamous cell cancers in the larynx, hypopharynx, and oral cavity [1], related to the parallel decline in tobacco use. However, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) over this same period has increased,

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attributable to the rise of high-risk human papillomavirus (HPV) infection leading to HPV-associated OPSCC [2,3]. The incidence of HPV-associated OPSSC now accounts for over 70% of newly diagnosed OPSCC in the United States [3]. The virus is thought to be transmitted sexually, and a high lifetime number of sexual partners is associated with an increased risk of oropharyngeal cancer, regardless of the presence of established risk factors including tobacco and alcohol use [4,5]. Clinical and demographic factors differ between patients with HPV-positive and HPV-negative disease; patients with HPV-positive OPSCC are typically younger and more likely to have nodal involvement than their HPV-negative counterparts [6].

HPV is a DNA virus that is implicated in the carcinogenesis of neoplasms in the cervix, oropharynx, and anus [7,8]. HPV DNA integrates with the host DNA, allowing for the production of viral proteins E6 and E7. These proteins interfere with the activation of host tumour suppressor proteins p53 and Rb, respectively [9]. While HPV-negative tumours commonly harbour mutated p53, HPV-associated OPSCC is typically p53 wild type [10,11]. Inactivation of Rb by E7 results in the overexpression of p16, a marker commonly used to identify HPV-associated cases [12]. Data from The Cancer Genome Atlas observed complex mutational patterns including loss of TRAF3, activating mutations of PIK3CA, and amplification of E2F1 in HPV-associated oropharyngeal cancers, pointing to aberrant activation of NF-κB, other oncogenic pathways, and cell cycle dysregulation as critical in the pathogenesis of these tumours [11]. Non-HPV-associated cancers have also been shown to have higher expression of the epidermal growth factor receptor (EGFR) than their HPV-associated counterparts [13]. Additionally, HPV-associated tumours may be less hypoxic [14], another factor predicted to enhance response to radiotherapy.

As both EGFR expression and p53 status are correlated with treatment responsiveness and survival, these biologic differences would be expected to contribute to differential outcomes in OPSCC based on HPV status. In fact, in multiple prospective trials published over the past decade, HPV positivity has conferred improved prognosis for patients with OPSCC compared with patients with similar stage HPV-negative tumours [14–23]. Eastern Cooperative Oncology Group (ECOG) 2399 was the first prospective study to demonstrate improved outcomes in patients with HPV-associated disease. In this trial, patients with HPV-positive tumours had a superior response to induction chemotherapy (82% versus 55%, $p = 0.01$), chemoradiotherapy (84% versus 57%, $p = 0.007$) and improved 2-year overall survival (OS) (95% versus 62%, $p = 0.005$) [16].

The effect of HPV status on clinical outcomes was validated by Ang et al. in their retrospective analysis of the Radiation Therapy Oncology Group (RTOG) 0129 study cohort, in which 63.8% of patients with stage III–IV OPSCC were found to have HPV-associated cancers [15]. OS at 3 years was 82.4% in patients with HPV-associated disease and 57.1% in patients with non-HPV-associated cancer ($p < 0.001$). The risk of death increased significantly with each additional pack-year of smoking. Patients were thus grouped by risk: those with HPV-associated disease and ≤10 pack-year smoking history as well as those with HPV-associated disease, >10 pack-year smoking history, and N0–N2a disease were deemed low-risk, with a 3-year OS of 93%; those with HPV-associated disease, >10 pack-year smoking history, and N2b-N3 disease were intermediate-risk, with a 3-year OS of 70.8%. Of note, no patients with HPV-associated disease were classified as high-risk, with a 3-year OS of 46.2%.

However, the current standard of care for OPSCC is derived from older trials of head and neck cancer patients with predominately HPV-negative disease, potentially representing overtreatment of favourable-risk, HPV-positive patients. Given the different aetiology, natural history [24–26], biomolecular signature [11,27], and treatment responsiveness, it is now accepted that HPV-positive and HPV-negative OPSCCs are distinct diseases to be studied separately in trials. Consequently, a number of clinical trials are underway to investigate strategies for the de-intensification of treatment in patients with HPV-associated OPSCC in order to minimise morbidity while maintaining excellent outcomes.

2. Rationale for treatment de-intensification

In medically fit patients with locally advanced head and neck cancer, the non-surgical standard of care is radiotherapy to a dose of 70 Gy with concurrent cisplatin, determined by prospective randomised trials as well as a meta-analysis of over 17,000 patients [28–30]. While these publications demonstrated improved OS in patients treated with concurrent chemoradiation (5-year OS 33.7% versus 27.2% without chemotherapy) [28], this regimen incurs notable acute and long-term morbidity. For the treatment-responsive HPV-associated cancers, current therapies may be more intensive than necessary to achieve cure. Increasing the intensity of therapy with some combination of surgery, chemotherapy and/or radiation therapy has been shown to increase treatment-induced toxicity [31] as well as cost [32]. Published rates of gastrostomy tube placement, for example, range from 5% [33] to as high as 85% [34], depending on the patient population and the therapeutic modalities used.

Large portions of the pharyngeal axis and soft tissues in the neck receive high doses of radiation in patients undergoing definitive management for OPSCC; the toxic effects are augmented by radiosensitising chemotherapy. The rates of acute and late grade ≥3 toxicity are