The role of biomarkers in the management of HPV-related oropharyngeal cancer

Benjamin D. Hopkins and James E. Bates

Purpose of review
Patients with HPV-related oropharyngeal cancer have very good survival outcomes but a high burden of toxicity. This has led to significant efforts to attempt to use a variety of biomarkers to select patients who are candidates for de-escalated treatment.

Recent findings
Initially, the field used HPV status alone as a biomarker to select patients with oropharyngeal cancer for de-escalation, however, the recently presented results of NRG Oncology HN005 showed that this is an insufficient strategy to select patients for potential de-escalation as patients in that study who received 60 Gy rather than the standard 70 Gy of radiation had diminished progression-free survival. This has led to a myriad of other strategies to potentially identify patients who may be able to receive less intense treatment but maintain a high rate of cure.

Summary
Many biomarker options exist to try and select patients for potential treatment de-escalation. We anxiously await the results of multiple ongoing phase II studies regarding many of these biomarkers and believe that the future of treatment for oropharyngeal cancer will be significantly more personalized.

Keywords
biomarker, ctDNA, ctHPVDNA, HPV, oropharynx cancer

INTRODUCTION

We have witnessed an increasing incidence of HPV-related oropharyngeal squamous cell (HPV-OPSSC) in the last 20 years with HPV-OPSSC now accounting for the most common cancer of the head and neck. Patients with HPV-OPSSC have very good survival outcomes but a high burden of toxicity. This has led to significant efforts to attempt to use a variety of biomarkers to select patients who are candidates for de-escalated treatment. Initially, the field unsuccessfully used HPV status alone as a biomarker to select patients with oropharyngeal cancer for de-escalation. Many other strategies with more sophisticated treatment personalization have since developed which we describe in this review.

INCIDENCE, TRENDS, EPIDEMIOLOGY OF HPV-RELATED OROPHARYNGEAL CANCER

In the recent decades, the incidence of human papilloma virus related oropharyngeal cancer (HPV-OPSCC) has dramatically increased and now accounts for the majority of oropharyngeal cancers in the United States and 30% of cases globally [1,2]. In the United States, the incidence of HPV-OPSCC is now 4.62 per 100 000 persons [3]. Initially, males under the age of 60 were the predominant population affected by this epidemic of HPV-OPSCC [4]. However, in more recent years the prevalence of HPV infection has increased in older adults and the mean age of patients with HPV-OPSCC has increased beyond than 60 years [5]. This trend of diagnosis in older patients will likely continue, as HPV vaccination in younger populations has led epidemiologists to project a lower incidence of HPV related cancers in younger patients [6]. The Center for Disease Control in 2022 estimated that 58% of females and 34.8% of males ages 18–26 had received HPV vaccination [7]. These CDC data also describe lower utilization of HPV vaccination among Black and Hispanic populations, contributing to a more rapid increased prevalence of HPV-OPSCC amongst these minority populations [8].

Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, Georgia, USA

Correspondence to James E. Bates, MD, Department of Radiation Oncology, Emory University, Atlanta, GA 30308, USA.
Tel: +1 404 778 3473; e-mail: james.edward.bates@emory.edu

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KEY POINTS

- Patients with HPV-related oropharyngeal squamous cell have very good survival outcomes, but a high burden of toxicity has led to significant efforts to attempt to use biomarkers to select patients who are candidates for de-escalated treatment.
- HPV status alone has not proven to be a reliable biomarker with recent evidence cautioning against the use of broad, nonpersonalized biomarkers for treatment de-escalation.
- In recent years, we have seen various personalized strategies using pathology, imaging, and genomic based biomarkers to successfully individualize treatment de-escalation, leading to many ongoing trials further validating these approaches.

THE CURRENT STANDARD OF CARE

Standard treatments for HPV-OPSCC vary by anatomic subsite and stage at presentation. In early-stage presentations (T1–2 N0–1) treatment options include radiation with or without chemotherapy and transoral surgery (TOS). In more advanced disease, the standard treatment is typically concurrent chemotherapy and radiation; specifically, a radiation course of 70 Gy in 35 fractions with concurrent cisplatin. Secondary analysis of RTOG 0129 established the role of HPV status in creating low, intermediate, and high risk patient groups prognostic for outcomes [9]. This analysis found a marked absolute difference of 25.3% in 3-year overall survival (82.4% HPV+ vs. 57.1% HPV–) in patients with HPV associated cancers vs. patients with HPV negative cancer, with a similar difference in three-year progression free survival (73.7% HPV+ vs. 43.4% HPV−). The analysis further found that the risk of death or cancer relapse significantly increased by 1% for each additional pack-year of tobacco smoking. These factors (HPV status and smoking pack years) along with tumor and nodal staging form the three risk groups that we continue to rely upon for prognostication and treatment algorithms.

The first attempts at de-escalation in HPV-OPSCC were attempts to reduce the impact of platinum-based concurrent chemotherapy. In 2006, the Bonner trial demonstrated a significant survival benefit of the addition of cetuximab to radiation alone in the setting of locally advanced HN cancers (roughly 60% of which were oropharyngeal cancers) [10]. This trial set the stage for significant investment in cooperative group trials motivated by the potential for systemic therapy deintensification from the typical cytotoxic chemotherapy. Unfortunately, RTOG 1016, RTOG 0522, and De-ESCALaTE HPV all proved the futility of replacing cisplatin or adding cetuximab to cisplatin [11–13]. Fortunately, RTOG 1016 provided strong benchmark toxicity data that can be the comparator for future regimens and deintensification efforts. It must be noted that this benchmark toxicity data from RTOG 1016 portends to a burdensome toxicity profile with 81.7% of patients experiencing acute grade 3–4 adverse effects and 20.4% of patients having late grade 3–4 adverse effects. Notably, this includes 61.5% of patients utilizing a feeding tube by the end of treatment and 9.2% continuing to use a feeding tube at 1 year. These data represent the challenging toxicity of current standard of care chemoradiation regimens and underscore the importance of using biomarkers to identify a patient population who may be able to safely receive de-escalated treatment.

EARLY BIOMARKER FOR DE-ESCALATION: HPV STATUS

Given the extremely high burden of cure seen in RTOG 1016 of 70 Gy and concurrent cisplatin, efforts moved to attempting to reducing the total radiation dose in this patient population. These efforts have been further fueled by significant progress in the understanding of the biologic basis for increased radiosensitivity in HPV-related head and neck cancers [14]. This has led to the development of multiple trials in the past decade using HPV status as an early biomarker to attempt to select patients for treatment de-escalation.

A multiinstitutional single arm phase II trial performed and University of North Carolina and University of Florida investigated the use of a 60 Gy dose with concurrent cisplatin (30 mg/m^2) in the treatment of T0–T3, N0–N2c HPV-OPSCC [15]. This trial met its endpoint of pathologic complete response (pCR) with a pCR of 86% with decreased toxicity relative to historic standards. This study, while limited by single arm nature and limited sample size, served as motivation for future studies and was followed by a subsequent phase II single arm trial which used PET to assess complete response (CR) rates rather than biopsy or TOS [16]. They found that the same regimen led to a 93% post treatment radiologic CR rate, 86% two year progression-free survival (PFS), and 95% overall survival (OS). These results solidified this de-escalation regimen without the use of adjuvant surgery.

The momentum of these trials led to NRG-HN002. NRG-HN002 was a randomized, phase II trial and included patients with HPV+, T1–T2 N1–N2, or T3 N0–N2b oropharyngeal cancer. Randomization was between 60 Gy in 6 weeks with concurrent weekly cisplatin vs. 60 Gy in 5 weeks without

chemotherapy. To progress to the phase III NRG-HN005 an arm had to achieve a 2-year PFS superior to historical control of 85%. The trial found that 60 Gy in 6 weeks with concurrent cisplatin achieved significantly improved 2-year PFS of 90.5%, the radiation alone arm did not achieve a significantly improved PFS. As a result, the 60 Gy chemoradiation arm met criteria to advance to the phase III NRG-HN005.

HN-005 was a phase II/phase III designed clinical trial that compared three treatment regimens in the setting of T1–2N1 or T3N0-N1 oropharyngeal squamous cell carcinoma: 70 Gy over 6 weeks with cisplatin vs. 60 Gy over 6 weeks with cisplatin vs. 60 Gy over 5 weeks with nivolumab [17]. It was recently reported that the two experimental 60 Gy arms were closed at time of futility analysis due to significantly worse two year PFS (98.1%, 88.6%, and 90.3% in the three arms, respectively) [18▪▪]. As a result, the trial will not progress to phase III. This trial reinforces that the regimen of 70 Gy with concurrent cisplatin is an exceptionally strong regimen in the HPV+ oropharyngeal carcinoma setting and remains an especially high bar to improve on. Further, it suggests that HPV status alone is not a sufficient biomarker to select patients with HPV-OPSCC for de-escalation of therapy and emphasizes the importance of identifying alternative biomarkers in the definitive chemoRT setting to select patients for de-escalation.

PREDICTING TREATMENT RESPONSE WITH ADDITION BIOMARKER AND IMAGING STRATEGIES

As we have learned from prior data, de-escalation applied too broadly leads to unacceptable failure rates. Conversely, in select groups of patients, de-escalation strategies have equivalent control rates with favorable toxicity. This necessitates approaches that utilize novel precision techniques in identifying the correct subsets of patients that would benefit from de-escalation. Fortunately, we have seen considerable efforts in this space that may come to eventually define the standard of care.

In a study performed at the Universities of North Carolina and Florida investigating the use of a 60 Gy dose with concurrent cisplatin (30 mg/m^2) in the treatment of T0–T3, N0–N2c HPV-OPSCC, 67 patients had weekly ctHPVDNA drawn [19▪▪]. Analysis of these patients found that in the 28% of patients with favorable (>95%) clearance of ctHPVDNA, none had disease recurrences. This has motivated at least five institutional trials de-escalating or terminating radiation mid-course based on ctHPVDNA clearance (NCT05307939, NCT05541016, NCT03215719, NCT06323460, NCT05268614). We eagerly await the results of these efforts utilizing ctHPVDNA as a biomarker to de-intensify treatment.

Other trials have sought to utilize advanced imaging as a biomarker to de-escalate radiation courses. Investigators from Memorial Sloan Kettering have utilized F-MISO PET imaging to guide post-TOS adjuvant radiation dosing based on tumor hypoxia in patients with HPV+ T0–2/N1–N2c oropharyngeal cancer [20▪]. Patients underwent resection of their primary tumor but not neck dissection. After surgery F-MISO PET was obtained and in patients with tumor hypoxia, standard chemoradiation with a dose of 70 Gy was utilized. Patients with nonhypoxic tumors received 30 Gy in three weeks with concurrent radiation. Investigators found excellent tumor control and overall survival in both arms of the trial and toxicity was significantly improved for patients who received the de-escalated regimen. Although there are significant hurdles to widespread use of F-MISO PET imaging, this novel approach represents the value of advanced imaging in personalized biomarker driven de-escalation efforts.

Another recent phase II Trial investigated the use of FDG-PET imaging in the de-escalation of definitive chemoradiation for stage I-II HPV+ oropharyngeal squamous cell carcinoma [21▪]. All patients were planned for standard of care chemoradiation to a dose of 70 Gy in 7 weeks. After fraction 10, FDG-PET imaging was obtained and if metabolic tumor volume was reduced by greater than 50% at this time point, CRT was completed after a dose of 54 Gy in 24 fractions. The authors found similar disease control rates in patients treated to both treatment doses with a favorable toxicity profile in patients who were able to receive the de-escalated regimen. With the widespread availability of FDG-PET imaging, this trial represents a practical and promising approach to biomarker driven treatment de-escalation.

CT based radiomics has been explored as a potential strategy to predict HPV status and prognosticate outcomes. A large retrospective analysis out of Cleveland Clinic utilized 582 CT scans of patients with OPSCC and found that radiomic features of peritumoral and intratumoral areas were able to strongly prognosticate DFS and HPV status [22]. Radiomic based interpretation of widely used CT imaging may lead to a further biomarker driven tool in the risk stratification of OPSCC.

A novel pathomics driven biomarker strategy has emerged in recent years investigating whether tumor infiltrating lymphocites (TILs) can prognosticate outcomes in HPV-OPSCC. Two studies have investigated this and found that TILs are prognostic

for OS and DFS even after adjusting for age, stage, and smoking status [23,24]. These studies may pave the way for the utilization of pathomics as a biomarker driven strategy for risk stratification and de-escalation in future studies.

An alternative approach to pathology driven guidance of risk stratification and treatment has emerged with genomic adjusted radiation dose (GARD) testing. This gene expression based radiation sensitivity index has been found to be predictive of therapeutic effect of radiation doses in various cancer types, including OPSCC. This testing was more recently investigated to predict overall survival in patients receiving radiation for HPV-OPSCC. This study found that GARD strongly predicts OS and outperforms AJCC8 in prognostication [25▪]. The authors suggested the use of GARD testing for personalized de-escalation of radiation dose. We look forward to results of future studies investigating this innovative approach.

TRANSORAL SURGERY AS POTENTIAL DE-ESCALATION

In the last 15 years, we have seen the increased utilization of transoral surgery in an alternative approach to treatment de-escalation in oropharyngeal cancer. The ORATOR trial conducted in Canada compared definitive radiation (70 Gy) to TOS + neck dissection (with pathology guided adjuvant radiation) and established subtly different but similar overall toxicity burden [26]. Building on the success of the trial, the investigators followed up with ORATOR 2 trial which compared 60 Gy (with cisplatin if N2) to TOS with neck dissection and pathology guided adjuvant radiation [27]. This larger trial was looking to compare survival outcomes specifically in the setting of HPV+ disease and in the setting of comparison to radiation de-escalation. Unfortunately, the trial was ended early due to deaths in the surgical arm after enrollment of only 61 patients. Although critiques of this trial include criticism of surgical technique lending to patient deaths and the use of 60 Gy with only the support of phase II data, we did learn from this study that 1 year swallowing scores were similar between the groups and these trials ultimately inspired further investigation in approaches utilizing TOS.

These trials were followed by the more recent ECOG 3311 which served to establish the standard of care in post TOS adjuvant therapy. In this phase II trial, patients were classified into low, intermediate, or high risk groups based on surgical pathology [28]. Adjuvant radiation doses (low risk – observation, intermediate risk – 50 Gy vs. 60 Gy, high risk – 66 Gy w/cisplatin) were prescribed based on these pathology driven risk groups. In the only randomization component of the trial, intermediate risk patients (any of: close margin (<3 mm), minimal ENE (<1 mm), N2a/b disease, PNI/LVSI) were randomized between 60 Gy and 50 Gy radiation doses. Notably, all risk groups and treatment regimens achieved favorable outcomes. It must be noted that although this trial sought de-escalation, approximately 90% of patients on this trial received adjuvant radiation. Finally, due to favorable results in both intermediate risk arms, this trial was able to conclude that in the setting of intermediate risk patients TOS with adjuvant de-escalated radiation (50 Gy) is worth further exploration.

It must be noted, while TOS without adjuvant radiation is a valuable approach in low risk patients, intermediate and high risk patients (based off ECOG 3311 defined risk groups) have unacceptably high rates of failure if adjuvant radiation is omitted. A retrospective analysis done at Penn and Mayo found that in intermediate and high risk patients that underwent TOS without adjuvant radiation, cumulative incidence of relapse was an unacceptable 26% (11.8% in intermediate risk, 52.4% in high risk) [29]. Approximately three quarters of these patients were able to undergo successful salvage therapy. Penn followed this series up with a retrospective analysis of 364 patients who were recommended adjuvant radiation after TOS for HPV+ oropharyngeal cancer. They found that 86% of patients underwent recommended adjuvant radiation. They compared the patients who received adjuvant radiation to those who did not and found that radiation was associated with a dramatic 28% reduction in absolute risk of locoregional failure at three years (4% with radiation vs. 32% without) [30] These data reinforce that overly aggressive de-escalation harms patients.

A very interesting idea was tested in a phase II trial where investigators investigated omission of radiation to the primary TOS site and prescribed radiation to the at risk nodal regions alone. This trial included 61 post TOS patients with pT1–2 p16+ oropharyngeal cancer with margins >2 mm and no perineural invasion or lymphovascular invasion [31]. Radiation was prescribed only to involved or at risk nodal areas. As a result of these target volumes, the mean dose to the primary site was a relatively low 39.6 Gy. At two years, local control was 98.3% and overall survival was 100%. This trial demonstrates that modification of treatment volumes in select patients is a viable strategy in radiation de-escalation post TOS.

Finally, investigators at Mayo led the DART trial and a follow up phase III trial which investigated dose de-escalation in 80 patients with HPV+ oropharyngeal cancer who underwent TOS. Patients

were prescribed a dose of 30 Gy in 10 fractions BID with concurrent docetaxel (with dose of 36 Gy for patients with extranodal extension) [32]. The 2-year loco-regional control was 96.2% on this trial with a favorable toxicity profile, leading to the follow up larger phase III trial comparing this BID regimen to a more standard 60 Gy in 6 weeks with concurrent cisplatin [33]. The trial accrued 194 patients and found the DART experimental arm to have less toxicity, improved swallowing function, and equivalent disease control rates. The exception in this trial was patients with extra nodal extension had worse control rates, particularly those with pN2 disease. This trial demonstrated that in select patients, alternative dose regimens can be a pathway to de-escalation after TOS.

A subset analysis of this trial introduced the idea of using circulating tumor DNA (ctDNA) to prognosticate patients after surgery. They found that in patients with detectable post op ctDNA (11% of patients), 18 months progression free survival was significantly worse (73% vs. 96%) [34] Investigators at Harvard took this concept a step further in a prospective study of 98 patients undergoing surgery for HPV-OPSCC. The study used the sensitive custom whole genome based HPV-DeepSeek assay to detect ctDNA as a biomarker for minimal residual disease (MRD) in HPV+ head and neck cancer patients. MRD detection within six weeks postsurgery predicted significantly worse 2-year PFS, and ctDNA identified recurrences earlier than clinical diagnosis [35].

These data inspired multiple phase II trials investigating de-escalation of radiation after TOS based on postoperative ctDNA levels. At Emory, we have launched one such phase II trial investigating a 36 Gy radiation regimen for patients with negative postoperative ctDNA vs. standard of care radiation for patients with positive postoperative ctDNA in intermediate risk (based on ECOG 3311) post TOS patients (NCT05387915). We hope that ctDNA can emerge as a prognostic tool to precisely identify patients who would benefit from radiation de-escalation in both the definitive radiation and adjuvant radiation settings.

CONCLUSION

The recent decades have seen much evolution in the landscape of oropharyngeal cancers. HPV-OPSCC has emerged as the predominant subtype of this disease. Fortunately, with favorable outcomes relative to HPV- disease, we have seen significant efforts to further risk stratify patients and de-escalate treatment regimens. While there needs to be continued caution before widespread adoption of regimens based on limited phase II evidence, we are confident that in the near future we will be utilizing tools such as ctDNA and advanced imaging to precisely deliver the benefits of treatment de-escalation while continuing to deliver exceptional cure rates in this disease process.

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Conflicts of interest

J.E.B. reports advisory boards for Castle Biosciences and Galera Therapeutics, not relevant to the content of this article. B.D.H. reports none.

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- ■ of special interest
- ■■ of outstanding interest

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