De-escalation in HPV-positive oropharyngeal cancer: What trials have settled

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The rising incidence of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) presents a unique clinical challenge. These patients, often younger and with better prognoses than their HPV-negative counterparts, face significant acute and long-term toxicities from standard aggressive treatments. The field has been grappling with how to maintain high cure rates while mitigating treatment burden, a question that drives the current wave of de-escalation trials. A review in Frontiers in Oncology examined the ongoing clinical trial pipeline for HPV-positive OPSCC de-escalation.1

KEY TAKEAWAYS

- The Pivot: HPV-positive OPSCC patients, with their favourable prognosis, are the focus of de-escalation efforts to reduce treatment-related morbidity.
- The Data: Ongoing trials are investigating reduced radiation doses, altered chemotherapy regimens, and immunotherapy combinations, but definitive phase III data supporting widespread de-escalation are still emerging.
- The Action: Clinicians should continue to adhere to established guidelines for HPV-positive OPSCC, reserving de-escalation for patients enrolled in clinical trials or under specific, evidence-backed protocols.

Standard treatment for HPV-positive oropharyngeal cancer often involves a combination of surgery, radiation, and chemotherapy. While these regimens achieve high cure rates, particularly in this patient population, the associated morbidities are substantial. Patients frequently experience dysphagia, xerostomia, trismus, and taste alterations, which can severely impact quality of life for decades post-treatment. These long-term sequelae drive the imperative to explore less intensive, but equally effective, therapeutic strategies.1

The review by Mensour, Alam, and Mawani focused on the current trial pipeline of clinical trials investigating de-escalation in HPV-positive OPSCC.1 These trials generally target patients with early-stage disease or those who exhibit favourable prognostic markers, such as low T-stage and N-stage, or a robust response to induction therapy. The primary endpoints for these studies typically include overall survival (OS), progression-free survival (PFS), and various quality of life (QoL) measures, aiming to demonstrate non-inferiority in oncologic outcomes while showing superiority in toxicity profiles.1

De-escalation Strategies Under Investigation

Several distinct approaches to de-escalation are under active investigation. One major avenue involves reducing the intensity or volume of radiation therapy. Standard radiation doses for OPSCC typically range from 60 to 70 Gy. Trials

are exploring reductions to doses such as 50 Gy or 30 Gy, often in combination with other modalities. For instance, some studies are evaluating reduced-dose radiation after a positive response to induction chemotherapy, hypothesising that patients who achieve a complete clinical response may require less aggressive local treatment.1

Another strategy focuses on de-escalating systemic therapy. This includes reducing the number of chemotherapy cycles, using less toxic chemotherapy agents, or even omitting chemotherapy entirely in certain low-risk groups. Cisplatin, a highly effective but toxic agent, is often the backbone of concurrent chemoradiation. Trials are investigating replacing cisplatin with less toxic alternatives like cetuximab or carboplatin, or even eliminating concurrent chemotherapy altogether for very low-risk patients.1

The role of surgery, particularly transoral robotic surgery (TORS), also features in de-escalation protocols. TORS allows for precise tumour removal with minimal morbidity, potentially enabling subsequent de-escalation of adjuvant radiation or chemotherapy. Some trials are using TORS followed by risk stratification based on pathological findings, where patients with favourable pathology (e.g., negative margins, no extranodal extension) receive reduced adjuvant therapy or observation.1

Immunotherapy has also entered the de-escalation conversation. While not strictly a de-escalation of traditional cytotoxic treatments, combining immunotherapy with reduced-intensity radiation or chemotherapy could potentially maintain efficacy with a different toxicity profile. Trials are exploring checkpoint inhibitors, such as pembrolizumab or nivolumab, in combination with de-escalated radiation or as part of induction regimens. The hope is that the immune system's sustained response could compensate for reduced conventional therapy.1

Key Trials and Their Progress

The review highlighted several important trials, each exploring a different facet of de-escalation. The role of smoking in HPV-positive OPSCC prognosis is a crucial factor in patient selection for these trials, as smokers often have a less favourable response to de-escalation.1

One notable trial, NRG-HN002, investigated reduced-dose radiation (60 Gy vs 70 Gy) with concurrent cisplatin in patients with intermediate-risk HPV-positive OPSCC. The trial aimed to show non-inferiority in PFS and improved swallowing function. Another, ECOG-ACRIN 3311, evaluated TORS followed by risk-adapted adjuvant therapy, where patients with low-risk pathological features received reduced radiation or observation. These trials represent the ongoing effort to precisely tailor treatment based on individual patient and tumour characteristics.1

The OPTIMA trial, for example, is assessing whether patients with HPV-positive OPSCC who achieve a complete response to induction chemotherapy can safely undergo reduced-dose radiation or even observation. This approach seeks to identify a subgroup of patients who might avoid radiation entirely, a significant step towards reducing long-term morbidity. The primary endpoint for OPTIMA is 2-year PFS, with secondary endpoints including quality of life and toxicity.1

Another trial, Quarterback, is exploring a novel approach using transoral surgery followed by a short course of adjuvant radiation (30 Gy) for low-risk patients. This contrasts with the standard 60-70 Gy, aiming for a substantial reduction in radiation exposure. The trial's success hinges on demonstrating that this significantly de-escalated regimen maintains oncologic control.1

The review also touched upon trials incorporating molecular markers beyond HPV status. For instance, p16 expression is a surrogate for HPV infection and is routinely used for patient selection. But other biomarkers, such as tumour mutational

burden or specific gene amplifications, could further refine risk stratification and guide de-escalation decisions. The advances in targeted therapy for lung cancer offer a parallel for how molecular insights can drive treatment refinement in other solid tumours.1

Challenges and Unanswered Questions

The primary challenge in de-escalation trials is ensuring oncologic non-inferiority. Reducing treatment intensity carries the inherent risk of compromising cure rates, which are already high for HPV-positive OPSCC. Demonstrating that reduced therapy is as effective as standard care, particularly in terms of long-term survival, requires large, well-designed phase III trials with extended follow-up periods. The statistical power needed to prove non-inferiority can be substantial, especially when the event rate (recurrence) is low in the control arm.1

Patient selection remains a critical hurdle. While HPV-positive OPSCC generally has a better prognosis, heterogeneity exists within this group. Factors such as smoking history, tumour volume, nodal burden, and extranodal extension can influence treatment response and recurrence risk. Accurately identifying the ideal candidates for de-escalation is paramount. The current review highlighted that many ongoing trials are still in phase II, meaning definitive answers on broad applicability are not yet available.1

Measuring quality of life endpoints also presents complexities. While objective measures of toxicity (e.g., dysphagia scores, xerostomia scales) are used, patient-reported outcomes (PROs) are equally important. Capturing the subjective experience of living with treatment side effects requires robust PRO instruments and careful analysis. The long-term nature of these toxicities means that QoL assessments must extend for many years post-treatment.1

The integration of novel agents, such as immunotherapy, into de-escalation protocols also introduces new considerations. While these agents may reduce the need for conventional cytotoxic therapy, they come with their own unique toxicity profiles, including immune-related adverse events. Balancing the benefits of de-escalation with the potential for new types of side effects is an ongoing area of research. Clinicians managing these complex cases often consult comprehensive resources like the Oxford Handbook of Oncology for up-to-date guidance on treatment protocols and adverse event management.1

But the field still lacks a universally accepted, validated biomarker that can definitively predict which HPV-positive OPSCC patients will benefit most from de-escalation. While p16 status is standard, it is not a perfect predictor of treatment response or long-term outcomes in the context of reduced therapy. The search for more precise predictive biomarkers continues, with genomic and proteomic analyses offering potential avenues.1

The open-label design of many de-escalation trials is an obvious caveat. While blinding is often impractical in surgical or radiation oncology trials, the lack of blinding can introduce bias in patient-reported outcomes and clinician assessments of toxicity. This is a common limitation in oncology research, but one that must be considered when interpreting results.1

The review also points out that many trials are still in their early phases, meaning the long-term oncologic outcomes, which are crucial for maintaining cure rates in cancer treatment, are not yet mature. Cancer recurrence can occur many years after initial treatment, and de-escalation strategies must prove their durability over extended follow-up periods. This gap matters for clinicians making long-term treatment decisions.1

What the Future Holds

The future of de-escalation in HPV-positive OPSCC will likely involve increasingly personalised approaches. This means moving beyond a one-size-fits-all strategy to one that integrates clinical, pathological, and molecular factors to guide treatment intensity. The goal is to identify the minimal effective treatment for each patient, thereby maximising quality of life without compromising survival.1

The ongoing trials, once mature, will provide critical data to inform future guidelines. Until then, standard of care remains the benchmark. The enthusiasm for de-escalation is palpable, but it must be tempered by rigorous evidence. The field awaits definitive phase III results that robustly demonstrate non-inferiority in survival outcomes alongside significant reductions in toxicity.1

CLINICAL IMPLICATIONS

For European GPs and specialists, the current market of de-escalation in HPV-positive oropharyngeal cancer remains one of cautious optimism. While the rationale for reducing treatment intensity is compelling, particularly given the excellent prognosis and young age of many patients, definitive evidence to widely implement de-escalated regimens outside of clinical trials is not yet available. Clinicians must continue to adhere to established guidelines, which currently favour standard, aggressive approaches for most patients. The ongoing trials are crucial for establishing new standards of care, but their results will take time to mature. It is tempting to de-escalate based on early phase data or anecdotal success, but the risk of compromising oncologic control in a curable disease is too high. Patient selection for these trials is highly specific, often excluding those with significant smoking histories or advanced disease, factors that complicate prognosis in HPV-positive OPSCC.

The industry's focus on developing less toxic alternatives or combination therapies that allow for de-escalation is a positive step. But the onus is on pharmaceutical companies and academic institutions to deliver robust phase III data demonstrating non-inferiority in survival endpoints. Without this, the promise of reduced toxicity remains just that: a promise, not a clinical reality for the majority of patients.

Patients, understandably, are eager for less debilitating treatments. It is our role to manage these expectations, explaining that while research is progressing rapidly, the current standard of care offers the best chance of cure. Participation in well-designed clinical trials remains the most responsible path for those seeking de-escalated therapy.

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REFERENCES

1. 1. Mensour EA, Alam S, Mawani S. What is the future of treatment de-escalation for HPV-positive oropharyngeal cancer? A review of ongoing clinical trials. Front Oncol. 2022;12:1072935. doi:10.3389/fonc.2022.1072935

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