Chapter 9
Contemporary Opportunities in Nonsurgical Management of Locoregionally Advanced Head and Neck Squamous Cell Carcinoma

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Introduction

Mucosal head and neck squamous cell carcinoma (HNSCC) generally refers to carcinoma arising from the mucosa of the oro-/hypo-pharynx (excluding nasopharynx), larynx, oral cavity, and carcinoma of unknown primary origin presenting with cervical lymph node metastasis (CUP). Over the past decade, the landscape of HNSCC has changed dramatically owing to the rapid emergence of HPV-mediated

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[HPV(+)]oropharyngeal carcinoma (OPC) and a steady decrease in smoking-related/HPV-negative [HPV(−)] HNSCC, the latter almost certainly explained by the success of smoking cessation strategies. The 8th edition TNM (TNM-8) now separates HNSCC into two major categories: HPV(+) and HPV(−) HNSCC [1, 2] with different staging classifications. Examples introduced in the TNM-8 include the migration of almost 50% of HPV(+) oropharyngeal cancer (OPC) from Stage IV in the traditional 7th edition TNM to Stage I in the TNM-8, the important introduction of *depth of invasion* in oral cancer that influences migration to more advanced T-categories, and the assignment of node-positive (N+) disease with extranodal nodal extension (ENE) to higher N categories in HPV(−) disease. As a consequence, the semantics of "locoregionally advanced HNSCC" (LAHNSCC) is also evolving.

Achieving locoregional control (LRC) has traditionally been the primary focus of management of LAHNSCC due to the challenge in achieving it with conventional treatment approaches in use in the pre-HPV era. As well, recurrence in this location almost uniformly has significant implications for symptomatology, function, severe morbidity (involving the integrity of airway, neurovascular, and musculoskeletal structure), swallowing, and nutrition in addition to the hardships and risks associated with salvage management. Hence, a long-established sentiment prevailed that LAHNSCC was a "loco-regional disease" and less effort was devoted to negating the risk of distant metastasis (DM). Concurrent *cisplatin*-based chemoradiotherapy (CCRT) has represented the gold standard for organ preservation treatment in LAHNSCC since the publication of the MACH-NC meta-analysis which demonstrated significant improvement in LRC and OS with the addition of chemotherapy to radiotherapy (RT) [3, 4]. Despite this, the LRC rates remain unsatisfactory for many HPV(−) LAHNSCC. About 40% of patients experience locoregional failure (LRF) [5] and less than 50% of HPV(−) LAHNSCC patients survive more than 5 years [6]. Efforts have continued to explore other systematic approaches to enhance LRC in this population.

As is the case for HPV(−) LAHNSCC, HPV(+) OPC is also facing challenges, although of a different nature. While LRC can be achieved in >80% HPV(+) OPCs [5–8], most of these patients received intensified treatment and can expect to live for many years but are vulnerable to severe late toxicities that significantly affect quality of life in many cancer survivors. In addition, DM has emerged as one of the major challenges for this population and approaches confronting this outcome are relatively sparse. To improve the therapeutic ratio of HPV(+) LAHNSCC, the current overall research focus in this population has shifted towards two scenarios: safe de-intensification for the low relapse risk group, while innovative approaches to improve LRC and mitigate the risk of DM remain priorities in the high relapse risk group.

Non-surgical approaches for HNSCC have also evolved in parallel with accumulating knowledge about disease biology and clinical behavior, advances in technologies, availability of novel treatment approaches, and emerging evidence from clinical trials and prospective/retrospective studies. While surgery remains a mainstay in management to ensure local control, and radical RT with/without chemotherapy is similarly hallowed in the overall management philosophy, changes in

approach for different presentations are under evaluation. In this review, we summarize recent research findings in non-surgical approaches for both HPV(+) and HPV(−) LAHNSCC, including revisiting the efficacy of traditional chemotherapy agents, the role of epidermal growth factor receptor (EGFR) inhibition, the potential to refine chemotherapy regimens (including new agents and sequencing), and the combination of immunotherapy with RT.

Definition of LAHNSCC in HPV(+) HNC

LAHNSCC has historically referred to stage III/IV disease that included T3-T4 or any N-positive presentations. In the HPV(+) TNM-8 classification, the TNM-7 T1-T2_N1-N2b subset has been re-classified as stage I disease with very high LRC and low DM risk [5]. Since no stage IV group exists for non-metastatic HPV(+) OPC/CUP, stage II and III would naturally be considered as LAHNSCC. However compelling data indicates that outcome heterogeneity still exists within stage I. Stage I disease with radiologically identified extranodal extension (rENE+) has emerged as a strong prognostic factor for higher DM and mortality risk [9], and a proposal exists to classify it as N3, and therefore stage III disease [10]. By extension it seems prudent to also combine HPV(+) TNM-8 *stage I* disease with rENE+, together with *stage II/III*, as LAHNSCC group.

The nominal components of the main risk strata for HPV(−) LAHNCC have not changed in TNM-8 and continue to refer to stage III and IV disease, including all non-metastatic (M0) HPV(−) LAHNSCC excepting the T1-T2 N0 subset. However, the criteria contributing to individual T and N categories have been refined which has resulted in criterion-based stage modification. A *depth of invasion* (DOI) parameter has been added as a new T-category modifier for oral cavity SCC and migrates so called "thicker" tumours (correspondingly those with higher DOI) to a more advanced T-category. Clinical and pathological descriptors for ENE have also been introduced that assign a higher N-category. Such changes in definitions warrant re-interpretation of historical data and impact present and future clinical trial design.

Trials on HPV(+) LAHNSCC

Revisiting the Role of Cisplatin and Cetuximab in HPV(+) LAHNSCC

With the recognition of HPV(+) HNSCC as a new disease, clinical trials are addressing HPV(+) HNSCC separately from HPV(−) disease. The most established "tool" for LAHNSCC is *cisplatin* chemotherapy combined with RT. *Cetuximab*, an FDA approved EGFR inhibitor, has also been used in LAHNSCC following a randomized

trial (IMCL-9815) that showed superior LRC with *cetuximab* combined with RT compared to RT alone for LAHNSCC; however HPV status was unknown at the time of the trial [11] and the RT outcomes may not reflect the results expected from contemporary precision RT techniques which were unavailable during the period of the trial. The efficacy and toxicity of *cisplatin* and *cetuximab* with RT on HPV(+) HNSCC were recently compared in the two HPV(+) phase-III randomized trials: RTOG 1016 (NCT01302834) [7] (comprising 39% T3-T4 tumours) and De-ESCALaTE HPV (NCT01874171) [8] (comprising 34% T3-T4 tumours). Both trials showed inferior efficacy of *cetuximab* compared to *cisplatin* in HPV(+) OPC, mainly attributable to higher LRF with *cetuximab*. The differential effect on DM reduction with *cisplatin* versus *cetuximab* was significant in De-ESCALaTE HPV (2-year DM: 3% vs. 9%, p = 0.009) but marginal in RTOG 1016 (5-year DM: 8.6% vs. 11.7%, p = 0.09). Regarding outcomes according to TNM-8, the De-ESCALaTE HPV trial showed that the differential effect of *cisplatin* vs. *cetuximab* exists in both stage I/II (98.4% vs. 93.2%, p = 0.043) and stage III diseases (2-year OS: 93.3% vs. 67.1%, p = 0.030). The toxicity profile also did not favor *cetuximab*. The failure of *cetuximab* to optimize outcomes in the loco-regional treatment of HPV(+) OPC is probably not surprising when one considers that HPV(+) OPC rarely expresses EGFR [12]. An additional intriguing observation of the RTOG 1016 trial is the relatively high LRF in the *cetuximab* arm compared to other reported outcomes with RT alone in HPV(+) cohorts [13, 14]. Compromised outcomes of *cetuximab* in HPV(+) OPC was also observed in the RTOG 0522 trial (NCT00265941) [15]. It showed a trend towards higher hazard ratio (HR 1.57, p = 0.12) with the addition of *cetuximab* to *cisplatin* chemotherapy which was opposite to that found with HPV(−) OPC (HR 0.86, p = 0.31). These paradoxical observations raise an unsubstantiated possibility for *cetuximab* to be interfering with radiosensitivity in the treatment of HPV(+) OPC.

Notwithstanding any additional nuances, both aforementioned phase III trials have cemented the place of *cisplatin* as a potent radiosensitizer to enhance LRC although it is less effective in abrogating the risk of DM. *Cisplatin* combined with RT remains the gold standard for the treatment of HPV(+) LAHNSCC while *cetuximab* is not suitable for this disease. Several important questions regarding chemotherapy remain unresolved. For example, there is no robust data to indicate which subgroups of patients truly benefit from *cisplatin* chemotherapy and there remains uncertainty about the optimal dose of *cisplatin* for HPV(+) OPC patients. A retrospective study suggests that a cumulative dose of *cisplatin* >200 mg/m^2 seems necessary for TNM-8 stage III (T4 or N3) HPV(+) OPC [16]. Another prominent question is whether weekly *cisplatin* is equally effective compared to three-weekly high dose *cisplatin* (a trial is currently under development). The NRG HN-002 trial (NCT02254278) showed that weekly *cisplatin* with reduced RT dose (60 Gy in 30 fractions, 5 fractions per week) is very effective for T1-T3N0-N2b HPV(+) OPC minimal smokers (<10 pack-year smoking) with 2-year progression free survival of 90.5% [17]. However, the trial shows that, while LRC is achievable with *cisplatin* combined with a modest RT dose reduction, *cisplatin* also appears to be less potent in fully mitigating DM risk. For example, the RTOG 0234 trial, although without knowledge of HPV status, showed that *docetaxel* in combination with cetuximab seemed more effective compared to *cisplatin* with cetuximab in DM reduction (2-year DM: 13% vs. 25%) in the

postoperative setting of general LAHNSCC [18]. In essence, more effective systemic agents are needed to eradicate microscopic metastasis overall and in HPV(+) LAHNSCC due to the prominence of this end-point in the management of the disease.

Refining "Old Tools" for HPV(+) LAHNSCC: Dose, Fractionation, and Volumes

Although most HPV(+) LAHNSCC have good outcomes, RT intensification is still needed for a subset of HPV(+)LAHNSCC. In addition to *cisplatin* radiosensitization, other traditional intensification "tools" include hyper-fractionation with augmented RT doses, shortened overall treatment time (acceleration) [19], or hypoxia modification (e.g. nimorazole combined with radiotherapy). Studies have shown that an acceleration using six fractions compared to five fractions per week improved the outcome of HPV(+) OPC [20]. The NRG HN-002 trial (NCT02254278) also indicated that even in "low-risk" minimal smoking N0-N1 HPV(+) OPSCC, modest dose intensification by fractionating 60 Gy in 30 fractions over 5 weeks (6 fractions per week) rather than 6 weeks for the treatment period may still be beneficial [17]. Hypoxia modification has not shown effectiveness in HPV(+) OPC although it improves outcomes in HPV(−) LAHNSCC [21].

Another traditional "tool" under active study in HPV(+) OPC is refining the elective RT volumes. Villaflor et al. [22] conducted a phase II trial and showed that volume reduction (omitting the elective volume that ordinarily treats regions of the neck that are not overtly involved by disease) in patients with complete or partial response (amounting to at least a 50% volume reduction) after induction chemotherapy appears to be safe. Patients in the subsequent OPTIMA trial [23] also received risk-stratified dose-volume reduction and de-escalated RT volumes which were limited to the first echelon of uninvolved nodes with promising results. Long-term follow-up of the trial patients with additional patients treated following OPTIMA outlines presented in ASCO 2020 confirmed safety and excellent functional outcomes with this approach [24]. The HN10 trial (NCT03822897) of the Canadian Clinical Trials Group (CCTG), a phase II single-arm trial of Elective Volume Adjusted De-Escalation Radiotherapy (EVADER) for TNM-8 stage I-II HPV(+) OPSCC is currently recruiting and adjusts the prophylactic RT neck volumes according to the initial sites of disease presentation (e.g. the presenting subsite in the oropharynx, laterality of the primary site, and the extent of neck node disease).

Addressing Distant Metastasis Endpoint: Role of Induction Chemotherapy

Induction chemotherapy has been proven to be effective in DM reduction in nasopharyngeal carcinoma [25, 26], another viral-related pharyngeal cancer. GP (*gemcitabine-cisplatin*) induction chemotherapy appears to have similar efficacy in

DM reduction with lower grade 3–4 toxicities compared to the TPF (docetaxel-cisplatin-fluorouracil) regimen. However, the role of induction chemotherapy in HPV(+) OPC is yet to be defined. The phase III DeCIDE trial (NCT00117572) [27] compared TPF induction chemotherapy followed by cisplatin-CCRT vs. cisplatin-CCRT alone in N2-N3 HNSCC [61% were OPC, of which the majority were HPV(+)]. The induction chemotherapy cohort showed a significant reduction in DM as the first site of failure ($p = 0.043$), but this difference did not translate into an OS difference. A possible reason is that the trial was based on the TNM-7 classification and many N2 HPV(+) OPC enrolled in the trial had traditional N2b disease with T1-T2 categories which today would be considered low risk by TNM-8. In turn this could have diluted a putative benefit of induction chemotherapy. Similarly, the phase III PARADIGM trial (NCT00095875) [28] investigated the role of TPF induction chemotherapy followed by carboplatin-CCRT vs. cisplatin-CCRT alone in LAHNSCC (tumour HPV status was not tested) and also did not find a survival benefit. The trial was terminated early due to slow accrual. More recently, the single-arm phase II ECOG 1308 trial [29] and the OPTIMA trial [23] both suggested a promising role for induction chemotherapy in DM risk reduction, as well as a risk stratification tool for refining subsequent treatment including, most importantly, the potential to administer a less intense locoregional approach in appropriately responding cases following the induction regimen.

Quest for Additional Risk Stratification Parameters

Although TNM-8 stratifies HPV(+) OPC patients' prognosis better than TNM-7, it is recognized that outcome heterogeneity exists, especially in stage I disease [9]. Recently, rENE+ was observed to carry strong prognostic value, mainly impacting DM. A resulting proposal considers that all cases with rENE+ should be classified as N3b disease since it portends higher risk of DM and worse OS among all non-metastatic (M0) HPV(+) OPC [10]. The study also found that the addition of cisplatin could negate the LRF risk with rENE+ but does not appreciably negate DM risk. Therefore, strategies addressing the DM endpoint are urgently needed. One of the challenges of implementing rENE+ as a risk stratification factor is how to reliably assess rENE+. For example, "conglomerate", "matted" nodes, and "coalescent" nodes could all indicate evidence of rENE+ in addition to irregular nodal borders and adjacent structure invasion [10]. Radiologist training and standardization of taxonomy is needed. Computer-assisted intelligent machine learning may also enhance sensitivity and objectivity in recognizing rENE+ [30, 31]. Notably, the need to restrict the designation of rENE+ to only cases with obvious and unequivocal criteria is potentially important. "*Overcall*" of rENE+ by inclusion of cases where extranodal disease is either not actually present or of minimal degree could obscure the very deleterious true impact of unequivocal rENE+, especially on DM and mortality. Recent evidence suggests that the associated risk surpasses that of other accepted prognostic factors, including TNM stage and its categories, and smoking history.

Besides rENE+, researchers are also investigating other biomarkers for risk stratification of HPV(+) LAHNSCC. Dynamic biomarker such as the pre-treatment tumour growth velocity [32], response to induction chemotherapy [29], or the temporal pace of morphological [33] and functional (by FDG PET or hypoxia imaging) [34] volume reduction during the early phase of the RT course are potential candidates for risk stratification and merit investigation with response-adapted clinical trials.

HPV genotyping may also have a potential role for risk stratification. High-risk HPV includes α-7 HPV subtype (e.g. HPV-18, 39, 45) and α-9 HPV subtype (e.g. HPV-16, 31, 33, 35) [35–37]. The majority (>95%) of HPV(+) OPC is caused by HPV-16 followed by HPV-35 and HPV-31, and rarely by HPV-18 and HPV-45 [38–41]. Emerging data suggest that patients with an α-7 HPV subtype (e.g. HPV-18) OPC do not have as good prognosis as those caused by an α-9 HPV subtype (e.g. HPV16, 31, 33, 35, etc.) [35–37]. Whether a patient with α-7 HPV driven OPC should be excluded from de-intensification trials remains to be determined.

Liquid biopsy has shown a promising role in risk stratification as well. A recent report from Fakhry et al. [42] showed that oral HPV DNA viral load detected using oral rinse decreased rapidly with therapy, and persistent detection was associated with increased risk of recurrence and death. Analysis of tumour HPV DNA holds considerable promise as a biomarker for treatment response and risk of progression. Chera et al. [43] demonstrated the potential role of plasma circulating HPV DNA in disease surveillance.

Emerging Role of Immunotherapy in HPV(+) LAHNSCC

Emerging evidence suggests that the host immune system plays a significant role in the outcome of cancer patients. HPV(+) OPC is an immunogenic tumour [44, 45], rendering it a potential target tumour site for immunotherapy. A recent study revealed that a majority of HPV(+) OPC had PD-L1 overexpression, especially those with a minimal smoking history (93%), and was higher than in HPV(−) OPC (70%) although the prognostic value of the finding remains uncertain [46].

Currently, available immunotherapy strategies include passive immunotherapy (e.g. immune checkpoints inhibitors, immune co-stimulatory antibodies, tumor-infiltrating lymphocytes, and chimeric antigen receptor [CAR] T cells) and active immunotherapy (e.g. vaccines, immune adjuvant cytokines, and oncolytic viruses) [47]. Thus far, immune checkpoint inhibition is the most commonly investigated immunotherapy strategies for HNSCC. Several strategies exist to block the intrinsic inhibitory immune checkpoint pathways. For example, programmed cell death protein (PD-1)/programmed death-ligand 1 (PD-L1) pathway blockade restores the activity of anti-tumour T cells that have become dormant while cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) blockade allows for activation and proliferation of more cytotoxic T-cell clones and reduces T-cell mediated immunosuppression. PD-1 blockade has shown promising results in the recurrent/metastatic

setting [48–51], which prompted approval of *nivolumab* or *pembrolizumab*, both PD-1 inhibitors, by the Food and Drug Administration (FDA) for treatment of recurrent/metastatic HNSCC.

Theoretically, radiotherapy can be synergistic with immunotherapy to enhance its effect [52]. For example, RT may prime the immune system to release and/or expose tumour-specific antigens to elicit tumour-specific T cell responses [52, 53]. Conversely, RT could also suppress the immune system when a high RT dose is delivered to large volumes of hematologic cells [54]. The balance of priming or suppressing the immune response may depend on RT dose, fraction size, delivery time, as well as the irradiated volume. Not surprisingly, the focus has shifted to novel approaches including investigation of the role of immunotherapy combined with RT in the definitive setting (Table 9.1). KEYNOTE 412 (NCT03040999), a phase III trial (n = 780), examined the addition of pembrolizumab to CCRT compared to CCRT alone for LAHNSCC, including T4 or N3 HPV(+) OPC and p16-negative stage III/IV (except TNM-7 T1-T2N1) OPC and larynx/hypopharynx/oral cavity SCC. The trial has completed recruitment and results are awaited. The JAVELIN Head and Neck 100 trial (NCT02952586) (n = 697) [55] was designed to evaluate the addition of *avelumab* (a PD-L1 inhibitor) to CCRT for LAHNSCC including HPV(+) T4 or N2c-N3 (TNM-8 stage II/III) disease and stage III/IV HPV(−) LAHNSCC. However, an interim analysis of the trial results suggested a lack of efficacy leading to termination of accrual [56]. Nonetheless, such trials may be able to shed light on whether PD-L1 expression is a harbinger of adverse prognosis, while at the same time confer useful prediction by indicating a possible benefit of anti-PD-L1 immunotherapeutic agents.

Besides PD-1/PD-L1 inhibition (thereby blocking immune-suppressing ligands) that unleashes T-cell anti-tumour function, CTLA-4 blockage could enhance T-cell activation and is also under evaluation in HPV(+) OPC. Since PD-1/PD-L1 and CTLA-4 block different target pathways, it is hypothesized that targeting both PD-1/PD-L1 and CTLA-4 pathways may have additive or synergistic activity, although toxicity is unknown. One such trial is the CTTG HN.9 trial (NCT03410615) which was designed with the intent of comparing two arms containing RT with either concurrent-adjuvant *durvalumab* (PD-L1 inhibitor) versus *durvalumab* and *tremelimumab* (CTLA-4 inhibitor) compared to a third arm comprising standard of care *cisplatin*-CCRT. Several EORTC centers are also currently joining this trial. Notably, the *tremelimumab* arm has been terminated prematurely due to excessive adverse events.

Research in HPV(−) LAHNSCC

In contrast to the numerous trials and a variety of investigational approaches targeting HPV(+) HNSCC, the trial arena for HPV(−) HNSCC remains relatively quiet. The outcome of HPV(−) LAHNSCC with the current standard of care (high dose cisplatin-CCRT) remains unsatisfactory. Novel strategies are urgently needed for

Table 9.1 Selected phase II and III immunotherapy trials for non-metastatic LAHNSCC

Trial name (Starting year)/Sample Size	Eligibility criteria	Arms and interventions	Outcomes
Trials addressing HPV-positive oropharyngeal carcinoma			
NCIC CTG HN.9 NCT03410615 **(2018)** Phase II noncomparative study N = 180	**Intermediate risk** HPV(+) OPC (TNM-8): – T1–2 N1 (smoking ≥10 PY) – T3 N0-N1 (smoking ≥10 PY) – T1–3 N2 (any smoking history).	• **Arm 1** (comparator): RT (70 Gy/35f/7w) + CDDP days 1, 22 and 43 • **Arm 2** (experimental): RT (70 Gy/35f/7 week) + IO (durvalumab on days 7, 22) + Adj IO (durvalumab × 6 cycles) • **Arm 3** (experimental): RT (70Gy/35fr/7 week) + IO (durvalumab on days 7, 22) + Adj IO (durvalumab+ tremelimumab) → closed to accrual due to AE	**Primary endpoint** – Event-free survival **Secondary endpoints** – QoL (FACT-HN) – Acute and late toxicity – LRC, DMFS – Cost effectiveness of IO – Dysphagia scores
HCC 18-034 NCT03715946 **(2018)** Phase II N = 135	**Resectable intermediate risk** HPV(+) OPC (TNM-7): • **Tobacco< 10 PY, T0–3**: – >N2b (>5 LN +), or – N2c/N3, or – ENE+ (>1 mm) or margin+ • **Tobacco> 10 PY, T0–3**: – Any N2/N3, or – ENE+ (>1 mm) or margin+	Trans oral surgery followed by de-intensified adj RT (45–50 Gy/25f, 6f/w) + IO (nivolumab × 6 cycles)	**Primary endpoint** – Progression-free survival **Secondary endpoints** – PEG tube dependence – Acute and late toxicity – QoL (FACT-HN) – LRC, DMFS
NRG-HN005 NCT03952585 **(2019)** Phase II/III N = 711	p16(+) OPC with **low-risk** features (TNM-8): T1–2, N1 or T3, N0 with smoking <10 PY	• **Arm 1** (comparator): RT (6f/w × 6 weeks) + CDDP (days 1, 22) • **Arm 2** (experimental): Reduced dose RT (5f/w × 6 weeks) + CDDP (days 1, 22) • **Arm 3** (experimental): Reduced dose RT (6f/w × 5 weeks) + IO (nivolumab × 6 cycles)	***Phase II*** **Primary endpoint** – PFS ***Phase III* (1 or 2 experimental arms from the phase II)** **Co-primary endpoints** – Non-inferiority of PFS – Superiority of QoL (MDADI) **Secondary endpoints** – LRC, DMFS – Acute and late toxicity – QoL (EORTC QLQ-30)

(continued)

Table 9.1 (continued)

Trial name (Starting year)/Sample Size	Eligibility criteria	Arms and interventions	Outcomes
Trials addressing HPV-negative head and neck squamous cell carcinoma			
IMSTAR-HN (2018) NCT03700905 **(2018)** Phase III N = 276	**Resectable**, **p16(−)** LAHNSCC (OPC/larynx/hypopharynx/Oral) planned for surgery: – Any T3-T4, N0-N3, M0 – Any N2a-N3, T1-T4, M0	• **Arm 1** (comparator): Surgery + SOC Adj therapy (low-risk: adj RT: high-risk: adj CRT) • **Arm 2** (experimental): Neoadjuvant IO (nivolumab) + Surgery + SOC Adj + Adjuvant IO (nivolumab × 6 months in Arm 2a; nivolumab+ipilimumab × 6 months in Arm 2b)	**Primary endpoint** – DFS **Secondary endpoints** – LRC, DMFS, OS – Acute and late toxicity QoL (EORTC QLQ-30)
ADHERE EORTC 1735-HNCG NCT03673735 **(2019)** Phase III N = 650	**Resected**, non-metastatic p16(−) LAHNSCC with **high-risk** features (TNM-8): • OPC/larynx/hypopharynx/Oral: – pStage III-IVA **High-risk features include:** ENE and margin+ (<1 mm)	• **Arm 1** (comparator): Post-op CRT (66 Gy/6.5w + CDDP days 1, 22 and 43) + placebo (one dose before CRT and for 6 months after CRT) • **Arm 2** (experimental): Post-op CRT (66 Gy/6.5w + CDDP days 1, 22 and 43) + IO (durvalumab one dose before CRT and for 6 months after CRT)	**Primary endpoint** – PFS **Secondary endpoints** – LRC, DMFS, OS – Acute and late toxicity – Quality of life measures (EORTC-QLQC 30 and HN 35)
Trials addressing both HPV-positive and HPV-negative head and neck squamous cell carcinoma			
JAVELIN HEAD AND NECK 100 NCT02952586 **(2016)** Phase III N = 697 **Note:** The trial was stopped in March 2020following interim analysis	LAHNSCC planned for CRT (TNM-7): • **p16(+) OPC**: – T4, N0-N3, M0 – N3, T1-T4, M0 • **p16(−) OPC**: – Any T3-T4, N0-N3, M0 – any N2a-N3, T1-T4, M0 • **Larynx/hypopharynx/oral**: – Any T3-T4, N0-N3, M0 Any N2a-N3, T1-T4, M0	• **Arm 1** (comparator): RT (70 Gy/35f/7w) + concurrent CDDP (days 1, 22, 43) + concurrent placebo (start with RT and for 12 months) • **Arm 2** (experimental): RT (70 Gy/35f/7w) + CDDP (days 1, 22, 43) + concurrent IO (avelumab start with RT and for 12 months)	**Primary endpoint** – PFS **Secondary endpoints** – OS, LRC, DMFS – Acute and late toxicity – Response rates

KEYNOTE 412 NCT03040999 **(2017)** Phase III N = 780	LAHNSCC planned for CRT: • **p16(+) OPC**: – T4, N0-N3, M0 – N3, T1-T4, M0 • **p16(−) OPC**: – Any T3-T4, N0-N3, M0 – Any N2a-N3, T1-T4, M0 • **Larynx/hypopharynx/oral**: – Any T3-T4, N0-N3, M0 – Any N2a-N3, T1-T4, M0	• **Arm 1** (comparator): RT (70 Gy/35f/7w or 6w) + CDDP × 2–3 cycles + placebo (17 cycles, 1 before RT, 2 during and 14 after) • **Arm 2** (experimental): RT (70 Gy/35f/7w or 6w) + CDDP × 2–3 cycles + IO (pembrolizumab × 17 cycles, 1 before RT, 2 during and 14 after)	**Primary endpoint** – Event-free survival **Secondary endpoints** – OS – AE – QoL (EORTC-QLQC 30 and HN 35)
REACH GORTEC-2017-01 NCT02999087 **(2017)** Phase III N = 688	LAHNSCC planned for CRT (includes both **p16(+)** and **p16(−)** (TNM-7): Stage III-IVB Oral cavity/OPC/larynx/hypopharynx	• **Arm 1** (comparator): RT (70Gy/33 f/6.5w) + concurrent CDDP (days 1, 22 and 43) • **Arm 2** (experimental): RT (70 Gy/33f/6.5w) + cetuximab (weekly × 8 cycles) + concurrent/adj avelumab (starting with RT × 12 months) • **Arm 3** (comparator- unfit patients): RT (70 Gy/33f/6.5w) + concurrent cetuximab (weekly for 8 cycles) • **Arm 4** (experimental-unfit patients): RT (70 Gy/33f/6.5w) + cetuximab (weekly for 8 cycles) + concurrent/adj IO (avelumab starting with RT × 12 months)	**Primary endpoint** – PFS **Secondary endpoints** – OS – Adverse events – QoL (EORTC-QLQC 30 and HN 35)
KEYNOTE 689 NCT03765918 **(2018)** Phase III N = 704	**Resectable**, LAHNSCC planned for surgery (TNM-8): • **p16(+) OPC**: – Stage III (T4, N0-N2) • **p16(−) OPC/larynx/hypopharynx/oral**: – Stage III-IVA	• **Arm 1** (comparator): Surgery + SOC Adj therapy (low-risk: adj RT: high-risk: adj CRT) • **Arm 2** (experimental): Neoadjuvant IO (pembrolizumab × 2 cycles) + surgery + SOC Adj therapy + Adj IO (pembrolizumab × 15 cycles)	**Primary endpoint** – Major pathologic response – PFS **Secondary endpoints** – OS – pCR – Adverse events – QoL (EORTC-QLQC 30 and HN 35)

(continued)

Table 9.1 (continued)

Trial name (Starting year)/Sample Size	Eligibility criteria	Arms and interventions	Outcomes
NIVOPOSTOP GORTEC 2018-01 NCT03576417 **(2018)** Phase III N = 484	**Resected**, LAHNSCC with **high-risk*** features (TNM-8): • **Oral cavity/OPC/larynx/ hypopharynx**: – pStage III-IVA • **p16(+) OPC**: – pT3-T4, N1, >20 PY * **High-risk features include:** – ENE, multiple PNI, multiple pN+ (≥4), margin+ (≤1 mm)	• **Arm 1** (comparator): Adj CRT (66 Gy/6.5w + CDDP days 1, 22 and 43) • **Arm 2** (experimental): Adj CRT (66 Gy/6.5w + CDDP days 1, 22 and 43) + IO (nivolumab on days 1, 22 and 43)	**Primary endpoint** – DFS **Secondary endpoints** – OS – Acute and late toxicity – QoL (EORTC-QLQC 30 and HN 35)
NRG-HN004 (2017) NCT03258554 Phase II/III N = 523	**CDDP ineligible**, LAHNSCC planned for RT (TNM-8): • **p16(+) OPC**: – Stage III (T4, N0-N2) – Stage I-II (selected based on smoking status) • **p16(−) OPC/larynx/ hypopharynx/oral**: – Stage III-IVB	• **Arm 1** (comparator): RT (70 Gy/35f/7w) + concurrent cetuximab (×8 weekly cycles) • **Arm 2** (experimental): Standard RT (70Gy/35fr/7 week) + concurrent IO (durvalumab for 7 four-weekly cycles)	***Phase II*** **Primary endpoint** – PFS – Dose-limiting toxicity ***Phase III*** **Primary endpoint** – OS **Secondary endpoints** – LRC, DMFS – Acute and late toxicity – QoL (EORTC QLQ-30/HN-35, MDADI, EQD-5)
WO40242 NCT03452137 **(2018)** Phase III N = 400	Non-metastatic, **LAHNSCC** completed definitive local therapy [includes both **p16(+) and p16(−)**]	• **Arm 1** (comparator): Adj placebo (×16 cycles) • **Arm 2** (experimental): Adj IO (atezolizumab × 16 cycles)	**Primary endpoint** – PFS – OS **Secondary endpoints** – Adverse events – QoL (EORTC-QLQC 30)

HPV(+) Human papillomavirus-positive, *OPC* Oropharyngeal cancer, *p16(+)* p16 positive, *p16(−)* p16 negative, *LAHNSCC* Locally advanced head and neck squamous cell carcinoma, *PY* Pack-year, *adj* Adjuvant, *RT* Radiotherapy, *CDDP* Cisplatin, *IO* Immunotherapy, *CTx* Chemotherapy, *CRT* Chemoradiotherapy, *ENE+* Extranodal extension positive, *margin+* Margin positive, *SOC* Standard of care, *70 Gy/35f/7w* 70 Gy in 35 fractions delivered over 7 weeks, *f/w* Fractions per week, *AE* Adverse event, *QoL* Quality of life, LRC Locoregional control, *DMFS* Distant metastatic-free survival, *PFS* Progression-free survival, *OS* Overall survival, *pCR* Pathologic complete response

this population. Several immunotherapy trials targeting both HPV(+) (TNM-8 stage II/III) and HPV(−) LAHNSCC (TNM-8 stage III/IV) were described earlier and results are awaited. Recent genomic studies show that molecular alterations in HPV(−) LAHNSCC are common, which may provide valuable targets for immunotherapy. Another strategy is the investigation of mutated p53 [57, 58] and studies addressing novel pathways, such as Wee-1, are relevant in this regard [59, 60] as mentioned below in discussing *Window of Opportunity* trials.

Window of Opportunity Trials Exploring Targeted Agents, Including immunotherapy

One of the more active and potentially rewarding research areas for HPV(−) HNSCC is in the *Window of Opportunity* trial paradigm. *Window of opportunity* trials are studies where patients receive one or more new compounds between the time of cancer diagnosis and initiation of standard (mainly surgery) or investigational treatment [61]. It leverages the potentially idle time before treatment is initiated to investigate novel agents without significantly delaying the standard of care therapy [62]. Treatment response assessment can, therefore, be based on pre- and post- investigational treatment imaging and biopsy. *Window of opportunity* trials may, therefore, improve our understanding of pharmacodynamic parameters, and help to identify biomarkers for better patient selection. Oral cavity SCC is an ideal disease site for such trials. Several immunotherapy *Window of Opportunity* trials are ongoing (Table 9.1). The "*WISTERIA"* trial (RG_15–139, NCT03028766) [35] is evaluating the role of AZD1775 (a small molecule WEE1 inhibitor), administered before and after surgery in patients with LAHNSCC. The "*SNOW-001*" trial (NCT03575598) is another example in which the role of sitravatinib (a tyrosine kinases inhibitor) is evaluated combined with nivolumab administered before surgery in oral cavity SCC.

Hypoxia Modification and Smoking Cessation

Hypoxia has been identified as a contributor to radio-resistance and LRF in HNSCC [63, 64]. Several methods have been investigated to overcome this problem [65] but without broad success [66]. For example, investigators have attempted to reduce hypoxia by blood transfusion [67] or by the administration of erythropoietin [68, 69] with RT, but disappointingly found such efforts to be not only unhelpful but apparently deleterious. Conversely, hypoxic cell radiosensitizers (e.g. nimorazole) combined with RT enhanced its effectiveness [21, 70–72] but the effect appears to be confined within the HPV(−) LAHNSCC subgroups with hypoxic tumours [21, 72]. A similar phenomenon was also observed in the TROG 0202 trial which tested the addition of tirapazamine, a hypoxic cell cytotoxin, with CCRT [73]. However,

identifying patients with hypoxic tumours prior to RT is challenging. Various hypoxia gene signatures have been proposed although their value and availability remain to be determined [74–76] and trials addressing them have proved challenging, including tight turn-around time for the assay in different jurisdictions (especially if these are remote from the testing facility), and more recently competition with other strategies for the same patient groups (most obviously related to the recent provocative developments focusing on immunotherapy).

Perhaps, one of the most potent and available strategies to tackle tumour hypoxia is smoking cessation. Studies have shown that current smokers have the highest risk of disease recurrence and toxicity from RT compared to "never smokers" [77–80]. Evidence exists that smoking cessation could reverse blood hypoxia levels immediately to the level of "never smokers" and the LRC of such "recent quitters" appears to revert to a similar level as "never smokers" [81]. It seems imperative for radiation oncologists and health care professionals to evaluate the smoking history in HNSCC patients and promote smoking cessation strategies at the initial consultation as well as subsequently in the patient experience. The majority of current smokers appear prepared to discuss smoking cessation and accept therapy [82].

Patients Unfit for Chemotherapy

As noted, outcomes of HPV(−) LAHNSCC are unsatisfactory even with full intensity (300 mg/m^2) of high dose cisplatin CCRT. Many (>60%) are unable to receive full chemotherapy intensity [16, 83] or unable to tolerate chemotherapy at all due to poor general condition including organ (e.g. liver, kidney, cardiac) impairment, older age or frailty, and other comorbidities [84]. Moreover, elderly patients may not benefit from chemotherapy to the same degree [3]. Options are limited and novel approaches are needed in this under-investigated subset of LAHNSCC. Immunotherapy has emerged as a potential tool to improve outcome due to its different toxicity profile compared to traditional systemic treatments. Recently, the NRG HN-004 trial (NCT032558554) has been initiated to address this population, including both HPV(+) and HPV(−) cases. This randomized phase II/III trial is investigating the role of durvalumab (PD-L1 inhibitor) with RT compared to cetuximab with radiation for LAHNSCC who are unable to receive cisplatin due to contraindications.

Conclusion

The landscape of LAHNSCC has changed and requires different trial questions. The disease is now generally divided into two major types: HPV(+) and HPV(−). Risk stratification (staging) and new parameters (e.g. ENE determined clinically or radiologically and pathologically) can facilitate new trial designs by enriching trial

populations for the treatment under investigation, but also minimizing dilution of effect by exclusion of patients who are unlikely to require the intervention under study. Trials are addressing HPV(+) and HPV(−) LAHNSCC separately under the same principles of risk refinement and treatment optimization. Active research areas for non-surgical approaches include choice of RT dose/fractionation/volumes and combinations/sequences of systemic agents with radiation. Novel systemic agents, especially immunotherapy agents, are emerging but their role in the definitive treatment setting remains to be refined. *Window of Opportunity* trials may facilitate patient selection, identify potential therapeutic targets, and expedite drug development. A proportion of patients with LAHNSCC are unsuited for chemotherapy, such as the elderly and the frail, and may need different approaches but trials addressing these patients' needs are at a nascent phase. Efforts in this area will guide future treatment strategies in order to enhance oncologic and functional outcomes of our vulnerable head and neck cancer populations.

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