



Recent progress in the treatment of locally advanced head and neck squamous cell carcinomas

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Abstract – Purpose: Concurrent chemoradiotherapy (CRT) has become the standard of care (SOC) for locally advanced (LA) head and neck squamous cell carcinomas (HNSCC) since the French meta-analysis MACH-NC. This review synthesizes recent clinical research progress in LA-HNSCC, focusing on findings from Institut Gustave-Roussy and the French Head and Neck Oncology and Radiotherapy Group (GORTEC). *Recent findings:* Recent phase 3 trials have explored modifications to CRT protocols with mixed results. The GORTEC 99-02 phase 3 trial demonstrated no additional benefit from combining accelerated radiotherapy (RT) with CRT. Similarly, induction chemotherapy with taxane-platinum-5FU (TPF) followed by RT with cetuximab did not improve outcomes compared to CRT alone in patients with LA-HNSCC (>N2a) in the GORTEC 2007-02 trial. However, in patients with N0-N2a HNSCC, concurrent chemotherapy plus cetuximab-RT outperformed cetuximab-RT in the GORTEC 2007-01 phase 3 trial. Another targeted therapy, the IAP antagonist xevinapant, combined with cisplatin-RT, exhibited promising outcomes in the randomized phase 2 trial Debio1143-201 (GORTEC 2015-03). However, the subsequent phase 3 Trilynx trial failed to confirm xevinapant's benefit when added to CRT in LA-HNSCC. Immunotherapy integration has been extensively studied. Since 2015, several phase 2/3 trials, including GORTEC 2015-01 (PembroRad), GORTEC 2017-01 (REACH), KEYNOTE-412, and GORTEC 2018-02 (REWRITe), have evaluated immune checkpoint inhibitors (ICIs) combined with RT/CRT in cisplatin-eligible and ineligible patients with unresectable LA-HNSCC. These trials found no clear benefit from concurrent or adjuvant ICI use alongside RT/CRT. In contrast, the KEYNOTE-689 trial, which investigated perioperative pembrolizumab with standard surgery and postoperative RT/CRT for resectable LA-HNSCC, and the GORTEC 2018-01 (NIVOPOSTOP) phase 3 trial, which assessed post-operative nivolumab with cisplatin-RT in resected high-risk LA-HNSCC, have shown preliminary encouraging results with full data expected soon. *Summary:* Platinum-based CRT remains the SOC for LA-HNSCC. Emerging evidence suggests that perioperative pembrolizumab or postoperative nivolumab may redefine the SOC for resectable or resected HNSCC. Novel combinations, including molecular targeted therapies and ICIs with RT/CRT, require further investigation to establish their efficacy.

Key words: Head and neck squamous cell carcinoma, Radiotherapy, Chemotherapy, Targeted therapy, Immunotherapy.

Introduction

Head and neck cancers (HNC) are a diverse group of clinically, pathologically, and biologically complex diseases originating in various sites within the head and neck region [1]. Radiotherapy (RT) is a cornerstone of HNC management, particularly for locally advanced cases, where it is used as a definitive treatment or in combination with surgery and/or chemotherapy [2]. Concurrent chemoradiotherapy (CRT) has emerged as the standard of care (SOC) in locally advanced (LA) head and neck squamous cell carcinomas (HNSCC), following the influential French meta-analysis MACH-NC by

Institut Gustave-Roussy [3]. This review highlights recent advancements in clinical research on LA-HNSCC, with a focus on insights from the Institut Gustave-Roussy and the French head and neck oncology and radiotherapy group (GORTEC).

Combination of chemotherapy and altered fractionated radiotherapy

Chemotherapy is an integral part of treating LA-HNSCC. Several chemotherapeutic agents have been evaluated with concurrent RT in LA-HNSCC by GORTEC, including oral cisplatin (in a phase 1 Gustave-Roussy trial) [4], oral VP-16 (in the phase 1 GORTEC 2004-02 trial) [5], docetaxel (in the phase 2 GORTEC 98-02 trial) [6], and fractionated cisplatin

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(in the phase 2 GORTEC 2015-02 CisFRad trial) [7], besides high-dose cisplatin. In the phase 3 randomized trial GORTEC 94-01, concurrent CRT with carboplatin and 5-fluorouracil significantly improved 5-year local control and overall survival (OS) compared to RT alone in advanced-stage oropharyngeal carcinoma [8]. An updated MACH-NC meta-analysis encompassing 93 randomized trials and 17,346 patients reported a 4.5% absolute survival benefit at 5 years with chemotherapy, with a more pronounced 6.5% benefit for concurrent CRT [9]. The French MARCH collaborative group's meta-analysis found that altered fractionated radiotherapy (AFRT) yielded a 3.4% absolute 5-year survival benefit, with hyperfractionated RT showing the greatest benefit (8%) [10]. In the GORTEC 94-02 phase 3 trial [11], a very accelerated regimen improved locoregional control by 24% at 6 years compared to conventional RT in LA-HNSCC patients. The potential synergy of chemotherapy and AFRT was explored in subsequent trials. In a phase 2 randomized trial, GORTEC 96-01 evaluated accelerated radiotherapy and concomitant high-dose chemotherapy in non-resectable stage IV locally advanced HNSCC [12]. The very intense CRT schedule was more efficient in controlling diseases, but was also more toxic than accelerated RT alone, showing no clear improvement in the therapeutic index. This study highlights the limits of dose-intensification, with concomitant CRT; however, this schedule could be beneficial for very advanced locoregional HNSCC, such as N3 disease [13].

The GORTEC 99-02 phase 3 trial, involving 840 patients with LA-HNSCC, compared three arms: very accelerated RT alone (64.8 Gy in 3.5 weeks), CRT with conventional RT (70 Gy in 7 weeks with 3 cycles of carboplatin-fluorouracil), and accelerated CRT (70 Gy in 6 weeks with 2 cycles of carboplatin-fluorouracil) [14]. With a median follow-up of 5.2 years, conventional CRT improved progression-free survival (PFS) compared to very accelerated RT (HR 0.82, 95% CI 0.67–0.99; $p = 0.041$), but accelerated CRT showed no PFS benefit over conventional CRT (HR 1.02, 95% CI 0.84–1.23; $p = 0.88$) or very accelerated RT (HR 0.83, 95% CI 0.69–1.01; $p = 0.060$). Three-year PFS was 37.6% (conventional CRT), 34.1% (accelerated CRT), and 32.2% (very accelerated RT). Overall, there was no significant difference in OS with concurrent CRT improving the local control rate compared to very accelerated RT alone, but no difference between conventional and accelerated CRT. This 3-arm GORTEC 99-02 trial underscores that CRT outperforms very accelerated RT alone but highlights the lack of additional benefit from RT acceleration in the presence of concurrent chemotherapy. Long-term results reinforce these findings, emphasizing the importance of optimizing treatment intensity to balance efficacy and toxicity [15].

Induction chemotherapy based on taxanes and platinum

Cisplatin-based induction chemotherapy (IC) achieves high response rates in LA-HNSCC. Adding docetaxel to cisplatin-5FU (TPF) has demonstrated a survival advantage [16, 17]. Whether TPF followed by CRT outperforms CRT alone remains under investigation. IC is not yet regarded as a standard treatment for LA-HNSCC except for larynx preservation in

laryngeal/hypopharyngeal cancer. Key questions include: (1) Is CRT necessary after taxane- and platinum-based IC? (2) Does IC followed by CRT or RT alone improve survival compared to CRT alone? (3) Are alternative IC regimens, such as TPF with cetuximab, superior? The GORTEC 2007-02 phase 3 trial randomized LA-HNSCC patients with significant nodal spread (N2b-N3) to receive either concurrent CRT (70 Gy/7 weeks plus 3 cycles of carboplatin 70 mg/m²/day and 5FU 600 mg/m²/day, days 1–4) [18] or TPF IC followed by cetuximab-RT [19]. No survival benefit was observed with TPF followed by cetuximab-RT compared to CRT. The IC arm experienced higher rates of grade 3–4 neutropenia and a 6.6% treatment-related mortality rate. However, the TPF arm showed a reduced distant metastases rate (HR 0.54; 95% CI 0.30–0.99, $p = 0.05$). No benefit was observed in oropharyngeal carcinoma (OPC) patients regardless of p16 status [20].

Targeted therapy with EGFR inhibition and radiation

Combining cetuximab, an anti-EGFR monoclonal antibody, with RT has proven more effective than RT alone [21]. A similar approach has been observed when combining other cytotoxic agents with Erbitux in recurrent or metastatic HNSCC [22]. A 5-year update of a phase 3 trial by Bonner et al. reported improved OS with cetuximab plus RT (45.6%) compared to RT alone (36.4%), [23]. Notably, patients with $\geq$ grade 2 rash had better survival outcomes. However, radio-dermatitis is a concern with cetuximab-RT. Acting as a regenerating agent (RTTA), OTD70DERM is a structural and functional analogue of glycosaminoglycans. Preclinical studies from the Gustave-Roussy team have shown that topical RGTA can significantly reduce radiation-induced mucosal and cutaneous toxicities without tumour protection [24]. However, the GORTEC 2009-01 randomised trial found no reduction in radiodermatitis incidence or severity with topical RGTA in HNC patients receiving cetuximab-RT [25]. The GORTEC 2007-01 phase 3 trial evaluated cetuximab combined with CRT *versus* cetuximab-RT in LA-HNSCC patients with limited nodal spread (N0–N2a, non-palpable N2b) [26]. Cetuximab was given as a loading dose of 400 mg/m² followed by weekly 250 mg/m² during RT. Total RT's dose was 70 Gy (2 Gy/day, 5 days/week). Concurrent CT was 3 cycles of carboplatin 70 mg/m²/d + 5FU 600 mg/m²/d, D1–4. 406 patients were randomized to CT-cetux-RT *or* cetux-RT. With a median follow-up of 4.4 years, the HR for PFS was in favour of the CT-cetux-RT arm (HR = 0.73; 95% CI 0.57–0.94; $p = 0.015$) with 3-year PFS of 52.3% *versus* 40.5% and a median PFS of 37.9 months *versus* 22.4 months. For loco-regional control, HR was 0.54 (95% CI 0.38–0.76, $p = 0.0005$) in favour of the CT- cetux-RT arm. Benefits were consistent across p16 status in OPC. No significant differences were observed in OS (HR = 0.80, $p = 0.11$) or distant metastases (HR = 1.19, $p = 0.50$). Grade 3–4 adverse events were similar (91%), but mucositis (73% *vs.* 61%, $p = 0.014$) and hospitalizations (42% *vs.* 22%, $p < 0.0001$) were higher in the CT-cetux-RT arm. This was the first evidence of a clinical benefit for treatment intensification using cetux-RT as a mainstay in LA-HNSCC.

IAP antagonist Xevinapant and radiotherapy

Inhibitors of apoptosis proteins (IAPs), including X chromosome-linked IAP (XIAP), cellular IAP1 (cIAP1; also known as BIRC2), and cIAP2, are a class of proteins negatively regulating apoptosis, modulating immune and inflammatory responses, and affecting multiple other cellular processes that are frequently deregulated in human cancers [27]. IAPs are highly expressed in several human tumours, including HNSCC [28]. Xevinapant (Debio 1143, also known as AT-406 and SM-406) is an orally available antagonist of IAPs, also called SMAC (second mitochondria-derived activator of caspase) mimetic, with the potential to enhance the antitumour activity of cisplatin and RT [29, 30]. The radiosensitizing effect of xevinapant is mediated through caspase activation and TNF, IFN γ , and CD8 T cell-dependent pathways [30, 31]. A Phase 1/2 trial evaluated xevinapant with CRT in patients with high-risk, unresected LA-HNSCC [32]. In the phase 1, open-label, dose-escalation part of the trial, xevinapant (100–300 mg/day, days 1–14, 3-week cycles) was combined with cisplatin (100 mg/m², day 2, every 3 weeks) and RT (70 Gy, 2 Gy/day, 5 days/week). The maximum tolerated dose was 200 mg/day, with an 85% objective response rate [33]. In the double-blind, phase 2 part of the trial, 96 patients received xevinapant (200 mg/day) or placebo with CRT [34]. At 1.5 years from the end of CRT, a significantly larger proportion of patients achieved primary endpoint of locoregional control with xevinapant + CRT (54%; 95% CI, 39–69) *versus* placebo + CRT (33%; 95% CI, 20–48; odds ratio, 2.74; 95% CI, 1.15–6.53; $p = 0.0232$). Over 3 years of follow-up, xevinapant + CRT prolonged PFS and duration of response *versus* placebo + CRT: median PFS was not reached *versus* 16.9 months (HR = 0.33; 95% CI, 0.17–0.67; $p = 0.0019$), the risk of death or disease progression after initial response was reduced by 79% (HR = 0.21; 95% CI, 0.08–0.54; $p = 0.0011$) [35]. The mortality risk over 5 years of follow-up was more than halved with xevinapant + CRT *versus* placebo + CRT (HR = 0.47; 95% CI, 0.27–0.84; $p = 0.0101$) [36]. In summary, results from the phase 1/2 trial of xevinapant + CRT in patients with unresected LA-HNSCC suggest that the addition of xevinapant to standard-of-care CRT is well tolerated [37].

The phase 3 TrilynX trial, evaluating xevinapant with CRT in >700 patients, was discontinued after an interim analysis indicated it was unlikely to meet its event-free survival (EFS) endpoint. The X-ray Vision phase 3 trial, assessing xevinapant with RT in cisplatin-ineligible patients post-resection, was also terminated. The GORTEC 2022-01 XXL phase 3 trial, comparing xevinapant plus cetuximab-RT to placebo plus cetuximab-RT in cisplatin-ineligible LA-HNSCC, is ongoing, with PFS as the primary endpoint.

Combination of radiotherapy and immune checkpoint inhibitors

Anti-PD-1 inhibition with pembrolizumab, one of the ICIs, was shown to be active in recurrent/metastatic (R/M) SCCHN [38], confirmed by later large-scale randomized trials, which subsequently showed both nivolumab (CHECKMATE-141) [39] and pembrolizumab (KEYNOTE-040 [40] and

KEYNOTE-048 [41]) PD-1 inhibition yielded new standards of care in first- and second-line R/M SCCHN. There is also a strong pre-clinical rationale for combining PD-1 targeting with RT [42, 43] and clinical data regarding safety and efficacy already support such a combination in various cancer types [44].

The phase 2 trial GORTEC 2015-01 PembroRad is the first randomized trial to combine RT and concurrent immunotherapy alone, compared to cetuximab-RT in cisplatin-ineligible patients with LA-HNSCC [45]. Patients with non-operated stage III–IV HNSCC and unfit for receiving high-dose cisplatin were enrolled. Patients received once-daily radiotherapy up to 70 Gy in 33 fractions with weekly cetuximab (Cetuximab-RT arm) or 200 mg Q3W pembrolizumab during RT (pembrolizumab-RT arm). Among 133 patients, with a median follow-up of 25 months, 15-month LRC (“primary endpoint”) was similar (59% *vs.* 60%, odds ratio 1.05, 95% CI 0.43–2.59, $p = 0.91$), with no differences in PFS (HR 0.85, 95% CI 0.55–1.32, $p = 0.47$) or OS (HR 0.83, 95% CI 0.49–1.40, $p = 0.49$). Pembrolizumab-RT had lower toxicity (74% *vs.* 92% grade ≥ 3 adverse events, $p = 0.006$), particularly for mucositis and radiodermatitis [46]. More follow-up is still needed to understand the long-term benefit of the combination of pembrolizumab and RT in LA-HNSCC.

The KEYNOTE-412 phase 3 trial evaluated pembrolizumab before, during, and after CRT *versus* placebo in unresected LA-HNSCC. Preliminary results at ESMO 2022 showed a non-significant EFS (primary endpoint) improvement at 36 months (57.4% *vs.* 52.1%, $p = 0.042$). In patients with PD-L1 CPS ≥ 20 , EFS was 66.7% *versus* 57.2% (HR 0.73) [47]. The long-term results with two more years of follow-up will be presented in ASCO 2025 because EFS events were not attained (nearly 10% less than expected) when the preliminary results were presented in ESMO 2022 [48].

The GORTEC 2017-01 REACH phase 3 trial compared the combination of avelumab with cetuximab-RT, followed by 12 months of avelumab maintenance, to standard CRT or cetuximab-RT in patients with locally advanced HNSCC [49]. This phase 3 trial comprises two cohorts of patients deemed fit to receive cisplatin (100 mg/m² Q3 W) (Cohort 1) or unfit to receive cisplatin (Cohort 2). The SOC was intensity-modulated radiation therapy (IMRT) with cisplatin in Cohort 1 (arm A) and with weekly cetuximab in Cohort 2 (arm D). In both cohorts, experimental arms (arms B and C) were IMRT with cetuximab and avelumab (10 mg/kg Day-7), followed by avelumab every two weeks for 12 months [50]. The preliminary efficacy results were presented at ESMO 2021, an increase in 2-year PFS had been shown in unfit patients (Cohort 2), which increased from 31% in the cetuximab arm to 44% in the cetuximab/avelumab arm but this was not statistically significant (HR = 0.84, $p = 0.14$). However, a significant reduction in distant metastases (14.3% for cetuximab alone *vs.* 5.4% for cetuximab/avelumab, HR = 0.31 and $p = 0.007$) [51]. The final analysis results of the two cohorts, presented at ESMO 2024, confirm a favourable effect of adding avelumab to cetuximab-RT on PFS and distant metastases, but not on OS, in cisplatin-unfit patients (Cohort 2). [52]. In cisplatin-unfit patients, 4-year PFS was 33.7% with avelumab- cetuximab-RT *versus* 18.4% with SOC cetuximab-RT (HR 0.80, 95% CI 0.60–1.06), with reduced distant metastases (subHR 0.24,

95% CI 0.11–0.49). No OS benefit was observed. In cisplatin-fit patients, SOC CRT outperformed avelumab- cetuximab-RT (4-year PFS 54.7% vs. 42.3%, HR 1.40, $p = 0.012$).

The place of nivolumab as an induction/neoadjuvant treatment has been the subject of several phase 2 studies. The French phase 2 trial IMMUNEBOOST-HPV evaluated the feasibility of nivolumab before CRT with cisplatin in high-risk HPV + OPC (SOC vs. 2 cycles of nivolumab followed by SOC). Only 88% of patients in the experimental arm met full treatment criteria, missing the feasibility target due to cisplatin dose reductions [53]. No significant response differences were observed, though distant control trends require further study.

Given the high risk of lymph node metastases in LA-HNSCC, the cervical lymph node chains generally receive prophylactic irradiation. These lymph node chains are precisely where antigen-presenting cells migrate for T-cell priming after irradiation of the primary tumour. Given the radiosensitivity of lymphocytes, prophylactic irradiation of lymph node areas during ICI treatment might impair T-cell priming and reduce the immune response and the effect of immunotherapy as a consequence. To answer this question, the GORTEC 2018-02 REWRITE study assessed durvalumab with RT limited to the primary tumour and immediately adjacent lymph nodes in N0 HNSCC patients, avoiding prophylactic neck irradiation (PNI). Among 56 evaluable patients, the 1-year neck control rate was 96.4%, with only 3.6% nodal progression, supporting reduced lymphatic irradiation with ICIs [54]. This study showed that very limited N0 neck irradiation was associated with a very low probability of nodal relapse in the non-irradiated neck in the patients with T1–T4 HNSCC. The regional control rate compared favourably to that observed in the case of large PNI. Further randomized trials will be needed to confirm the concept of reduction of neck lymphatic irradiation when combining ICI in HNSCC.

Adjuvant postoperative treatment or Peri-operative treatment

Post-operative concurrent CRT is generally proposed after surgical resection when the patient is at high risk for local and/or distant recurrence. This is mainly based on the findings of previous phase 3 studies confirming the benefit of adding cisplatin (100 mg/m² every 3 weeks) to RT in post-operative patients (EORTC 22931 [55] and RTOG 9501 [56]). The GORTEC 2010-02 phase 3 trial evaluated afatinib maintenance therapy post-CRT in 134 patients. Two-year disease-free survival (DFS) was similar (61% vs. 64%, HR 1.12, 95% CI 0.70–1.80), indicating no benefit [57].

The GORTEC 2018-01 NIVOPOSTOP trial was a randomized controlled, open-label phase 3 trial (NCT03576417) to evaluate nivolumab as adjuvant treatment in patients with resected LA-HNSCC. The main inclusion criteria were a high risk of relapse as defined by the extranodal extension, multiple nodal involvements, perineural invasions, and/or positive tumour margins after surgery. The study enrolled 680 patients who were randomized after surgery to receive either SOC: 66 Gy RT and high-dose cisplatin or nivolumab 240 mg (2 weeks before RT), followed by SOC cisplatin-RT with

nivolumab 360 mg Q3 W every 3 weeks during cisplatin-RT and followed by maintenance of 6 cycles of nivolumab 480 mg every 4 weeks. At a pre-determined number of DFS (primary endpoint) events, a statistically significant and clinically meaningful improvement in DFS for patients receiving nivolumab was observed. The safety profile of nivolumab was consistent with that reported in previous studies, with no new safety signals, and the compliance with SOC treatments was similar between the 2 arms of the study. A trend toward improvement in OS, a key secondary endpoint, was found for nivolumab. OS will be evaluated at the final analysis, once the pre-specified number of events has been reached.

Several phase 2 trials showed a good pathological response (20%–40%) after one or two cycles of ICI (pembrolizumab, nivolumab, and durvalumab, etc.) before surgery for the resectable HNSCC with the major pathological response (mPR) 6%–14% [58–60]. There could also be certain progressive diseases, about 7% after 2 cycles of ICI (pembrolizumab, durvalumab ± tremelimumab) before surgery. Neoadjuvant pembrolizumab or nivolumab plus chemotherapy, followed by resection with or without adjuvant anti-PD-1, significantly improved EFS in early-stage non-small cell lung cancer (NSCLC) [61, 62]. Similarly, in advanced melanoma, EFS was significantly longer among patients who received pembrolizumab both before and after surgery compared to those who received adjuvant pembrolizumab alone [63].

KEYNOTE-689 is a randomized, open-label Phase 3 trial (<https://ClinicalTrials.gov>, NCT03765918) evaluating pembrolizumab as neoadjuvant treatment, then followed by pembrolizumab in combination with SOC RT (with or without cisplatin) as adjuvant treatment and then as maintenance therapy in patients with stage III or IVA resectable locally advanced HNSCC. Efficacy outcomes are classified by PD-L1 CPS status. 704 patients were randomized to receive either: neoadjuvant pembrolizumab (200 mg IV Q3W for two cycles) before surgery, followed by either adjuvant pembrolizumab (15 cycles) plus post-operative SOC RT with (for high-risk patients) or without (low-risk) high-dose cisplatin following surgery; or no neoadjuvant therapy before surgery, followed by post-operative SOC (C)RT. At a pre-specified first interim analysis, there was a statistically significant and clinically meaningful improvement in EFS (primary endpoint) for patients receiving the pembrolizumab peri-operative treatment regimen. The study also showed a statistically significant improvement in mPR for patients in the pembrolizumab arm compared with SOC. A trend toward improvement in OS was observed for the pembrolizumab arm.

Larynx preservation

Both induction chemotherapy (IC) followed by RT and concurrent CRT are alternatives to total laryngectomy or partial pharyngectomy plus total laryngectomy in patients with locally advanced larynx or hypopharynx cancer (LHC). The GORTEC 2000-01 phase 3 trial compared TPF to PF IC in 213 LHC patients requiring laryngectomy. TPF improved overall response (80.0% vs. 59.2%) and 3-year larynx preservation (70.3% vs. 57.5%), despite higher toxicity (neutropenia, alopecia) [64].

Table 1. Milestones in the treatment of Locally Advanced Head and Neck Squamous Cell Carcinomas (LA-HNSCC).

Time	Treatment	Patient benefits	Key references
2000	Chemoradiotherapy (CRT) as standard	Better local control and survival (4.5% at 5 years)	Pignon et al., 2000 [3].
2004	Postoperative CRT with cisplatin	Improved local control and disease-free survival in high-risk resected HNSCC	Bernier et al., 2004 [55]; Cooper et al., 2004 [56].
2006	Altered Fractionated Radiotherapy (AFRT)	Increment of 5-year overall survival rate by 3.4%	Bourhis et al., 2006 [10].
2006	Cetuximab with RT	Improved overall survival (45.6% vs. 36.4% at 5 years)	Bonner et al., 2006 [21].
2007	TPF (docetaxel, cisplatin, fluorouracil) induction chemotherapy	Improved survival compared to cisplatin and fluorouracil alone	Posner et al., 2007 [16]; Vermorken et al., 2007 [17].
2012	Conventional CRT <i>versus</i> accelerated CRT (GORTEC 99-02)	Conventional CRT improved progression-free survival	Bourhis et al., 2012 [14].
2018	Cetuximab with CRT <i>versus</i> cetuximab-RT (GORTEC 2007-01)	Better progression-free survival and local control	Tao et al., 2018 [26].
2018	TPF induction then cetuximab-RT <i>versus</i> CRT (GORTEC 2007-02)	Reduction of metastatic rate without survival benefit	Geoffrois et al., 2018 [19].
2020	Xevinapant with CRT	Better local control (54% vs. 33%) and survival	Sun et al., 2020 [34].
2023	Pembrolizumab with RT <i>versus</i> cetuximab-RT (PembroRad GORTEC 2015-01)	Similar locoregional control (59% vs. 60%); lower toxicity with pembrolizumab-RT	Tao et al., 2023 [46].
2024	Pembrolizumab with CRT <i>versus</i> placebo (KeyNote-412)	Improved event-free survival (57.4% vs. 52.1% at 3 years, not significant); better outcomes in PD-L1 CPS ≥ 20	Machiels et al., 2024 [47].
2024	Avelumab with cetuximab-RT (REACH GORTEC 2017-01)	Better progression-free survival in cisplatin-unfit patients	Tao et al., 2024 [52].
2025	Pembrolizumab before and after surgery (KeyNote-689)	Improved event-free survival and tumor response	Uppaluri, et al. The AACR Annual Meeting 2025.
2025	Nivolumab after surgery with CRT (NIVOPOSTOP GORTEC 2018-01)	Improved disease-free survival	Bourhis, et al. The ASCO Annual Meeting 2025.

Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; CPS, combined positive score; GORTEC in English, Head and Neck Oncology and Radiotherapy Group; REACH (GORTEC 2017-01), randomized, phase III clinical trial evaluating the combination of avelumab, cetuximab, and radiotherapy *versus* standard of care in patients with locally advanced squamous cell carcinoma of the head and neck; NIVOPOSTOP (GORTEC 2018-01), nivolumab as adjuvant treatment in patients with resected head and neck squamous cell carcinoma at high risk of relapse, added to standard chemoradiotherapy; PD-L1, programmed death-ligand 1.

The GORTEC-GETTEC randomized phase 2 trial (TREMPLIN) evaluated TPF followed by concurrent cisplatin-RT *versus* cetuximab-RT in 116 LHC patients [65]. No significant differences were observed in 3-month larynx preservation (95% vs. 93%), larynx function preservation (87% vs. 82%), or 18-month OS (92% vs. 89%). Cetuximab-RT had fewer local failures and was better tolerated. The GORTEC 2014-03 SALTORL phase 3 trial has just completed enrollment with more than 250 LHC patients comparing concurrent chemoradiotherapy (SOC in the USA) with induction chemotherapy TPF followed by radiotherapy (SOC in European countries).

Re-irradiation and novel radiation technologies

Full-dose re-irradiation on limited RT volume with simultaneous chemotherapy is feasible after salvage surgery. The GORTEC JANORL-1 trial randomized 130 patients to re-irradiation (60 Gy with fluorouracil and hydroxyurea) or observation post-surgery. Re-irradiation improved local control but not OS, with increased grade 3–4 toxicities (28% acute, 39% late) [66]. Thus, a re-irradiation might be considered as

a potential option after salvage surgery, especially to increase local control in a few selected cases with a high risk of local relapse.

The GORTEC-GETTEC JANORL-2 randomized trial compared re-irradiation (60 Gy with fluorouracil-hydroxyurea) to hyperfractionated RT (60 Gy, 1.2 Gy twice daily) with cetuximab in 53 patients. The cetuximab arm showed a non-significant OS improvement (37.4 vs. 21.9 months, $p = 0.12$) with better tolerability [67].

The GORTEC 98-03 phase 3 trial compared re-irradiation with fluorouracil-hydroxyurea to methotrexate in 57 patients with recurrent or second primary HNSCC. No OS benefit was observed (23% vs. 22% at 1 year), and the trial was discontinued early [68]. Premature discontinuation of the trial prevented drawing firm conclusions. However, it is not conclusive that concurrent re-irradiation, fluorouracil, and hydroxyurea can improve OS compared to methotrexate alone in patients treated with palliative intent for a recurrent or second primary HNSCC.

One of the major recent advances in radiotherapy for HNSCC was IMRT [2]. One phase 3 trial (GORTEC 2004-01) has been conducted to compare 75 Gy IMRT *versus* 70 Gy

conventional RT combined with cisplatin-based chemotherapy in LA-HNSCC [69]. This trial was designed to clarify whether dose-escalated IMRT and cisplatin could improve locoregional control without increasing side-effects complications over 3D radiotherapy (3D-RT). A total of 188 patients were randomized between 70 Gy/35F in 7 weeks with 3D-RT (Arm A) *versus* 75 Gy/35F with IMRT (Arm B). Both arms received 50 Gy in 25 fractions, followed by a sequential boost of 20 Gy/10F in Arm A and 25 Gy/10F to gross tumour volume in Arm B, as well as 3 cycles of cisplatin at 100 mg/m² during RT. IMRT significantly reduced xerostomia (1-year grade ≥ 2 : 23% *vs.* 63%; 3-year: 11% *vs.* 45%, $p < 0.0001$) but did not improve LRC (HR 1.13, $p = 0.68$) or OS (HR 1.19, $p = 0.42$). Dose-escalated IMRT did not improve LRC in LA-HNSCC patients treated with concomitant CRT over standard 3D-RT. Another phase 2 GORTEC 2017-03 trial, STEREO-POSTOP, evaluated the safety and efficacy of hypofractionated stereotaxic radiotherapy (36 Gy in 6 fractions of 6 Gy, 2 weeks) for patients with resected oral cavity squamous cell carcinoma. The enrolment has been completed with 90 patients included in total, and the preliminary results have been presented at ESTRO 2025.

Conclusion

In conclusion, significant improvements have been obtained in the treatment of locally advanced HNSCC during the last decades, with AFRT, concurrent CRT, concurrent cetuximab and RT, TPF induction chemotherapy, and more recently, IAP antagonists (SMAC mimetics) and ICI (Table 1). Concurrent CRT could still be considered as a SOC in LA-HNSCC. The possibility of combining conventional therapies (RT/CRT) with molecular-targeted drugs such as IAP antagonists opens a fertile area for translational research and clinical investigations. Immunotherapy (anti-PD-1/PD-L1) has changed the standard management in R/M-HNSCC. However, in localized/LA stages, especially for patients with unresected/unresectable disease, the trials carried out aim for good tolerance but with limited benefit compared to the SOC. New trials that incorporate patient stratification/selection and the right timing (especially neoadjuvant/induction use) to introduce immunotherapy *versus* radiotherapy are necessary. Results from the two large-scale phase 3 trials KEYNOTE-689 and GORTEC 2018-01 NIVOPOSTOP are promising for respectable/resected LA-HNSCC.

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Author contribution statement

YT conceived the idea, wrote and revised the paper, and approved the manuscript.

Ethics approval

Ethical approval was not required.

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