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Head and Neck Cancer Treatment with Concurrent Chemoradiotherapy: A Multi-Institutional Phase III Randomized Controlled Trial with Biomarker-Integrated Treatment Stratification

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Abstract

Head and neck squamous cell carcinoma (HNSCC) of the oral cavity, oropharynx, larynx, and hypopharynx represents a biologically heterogeneous malignancy with approximately 890,000 new cases and 450,000 deaths reported globally per year, with incidence rising in HPV-driven oropharyngeal cancers in Western countries while tobacco-related disease predominates in South and Southeast Asia [1, 16]. Despite the established superiority of concurrent chemoradiotherapy (CCRT) over radiotherapy (RT) alone in locally advanced HNSCC (LA-HNSCC), optimal chemotherapy selection, radiation dose-fractionation, and validated predictive biomarkers remain contested. This multi-institutional Phase III randomized controlled trial (RCT) is the first prospective evaluation of a multi-analyte Composite Biomarker Index (CBI) for treatment stratification in LA-HNSCC. From January 2020 to December 2023, 425 patients with Stage III–IVB HNSCC were enrolled at six international tertiary centres and randomised 1:1:1 to: (A) standard CCRT (cisplatin 100 mg/m² q21d, 70 Gy/35 fractions); (B) radiotherapy alone (RT); or (C) TPF induction chemotherapy followed by CCRT. The CBI integrates HPV/p16 status, tumour mutational burden (TMB), and plasma circulating tumour DNA (ctDNA) kinetics into a prospectively validated scoring system. Primary endpoints were 3-year overall survival (OS) and locoregional control (LRC). Secondary endpoints included disease-free survival (DFS), acute and late toxicity (CTCAE v5.0), and quality of life (EORTC QLQ-C30/H&N35). At a median follow-up of 38.4 months, CCRT demonstrated superior 3-year OS versus RT alone (64.2% vs 47.8%; HR 0.71, 95% CI 0.61–0.82; p<0.001) with comparable OS to induction+CCRT (67.1%; HR 0.94, 95% CI 0.80–1.10; p=0.44). CBI-High patients treated with CCRT achieved 3-year OS of 78.3% versus 51.4% in CBI-Low patients (interaction p=0.003), establishing the CBI as a clinically actionable predictive biomarker. Grade 3–4 toxicities were highest in the induction+CCRT arm. IMRT was associated with significantly lower Grade 2–3 xerostomia compared to 3D-CRT (31.2% vs 52.4%; p<0.001). These results support a precision oncology framework for LA-HNSCC treatment allocation guided by the CBI.

Keywords: Head and Neck Cancer, Chemoradiotherapy, Cisplatin, IMRT, Circulating Tumour DNA, Composite Biomarker Index, Locoregional Control, HPV, Tumour Mutational Burden

Introduction

Head and neck squamous cell carcinoma (HNSCC), which includes oral cavity, oropharynx, larynx, hypopharynx, and nasopharynx represents the sixth most prevalent cancer in the world. It is a significant oncológico burden in the world with an estimated 890.000 new cases each year and 450.000 deaths (GLOBOCAN 2022). The geographical epidemiological pattern is complex: OPC

in North America and Northern Europe is linked to HPV infection, with more than 70 percent of new diagnoses being linked to HPV, whereas in South Asia, Southeast Asia and sub-Saharan Africa, OPC is associated with tobacco and alcohol use. This trial excluded special cases such as nasopharyngeal carcinoma, which is endemic in Southeast Asia and North Africa, and has different biology and treatment approaches. Most patients will have locally advanced disease (stage III–IVB) and surgery will not be the initial treatment strategy.

In LA-HNSCC, the landmark MACH-NC meta-analysis showed an absolute improvement of 6.5% in 5-year overall survival in favour of CCRT (HR 0.81; $p<0.0001$) [2, 12]. The most commonly used radiosensitiser is cisplatin which acts cooperatively with ionising radiation by formation of platinum-DNA adducts and interstrand cross-links which prevent repair of DNA double-strand breaks, or by the generation of reactive oxygen species (ROS), G2/M arrest of cell cycle, and suppression of sublethal damage repair. Although these improvements have been made, locoregional failure is still the most common cause of treatment failure, affecting 30–50% of cases within 3 years of completion of treatment [17].

Precision Oncology has revolutionized therapeutic decision making in HNSCC. Because HPV-associated OPCs have greater immunogenicity and are treated with much better results than HPV-negative disease [3], there are multiple international trials underway to treat patients with HPV-associated disease with treatment de-escalation, such as the De-ESCALaTE HPV trial [5], the NRG Oncology HN002 trial [15], ECOG-ACRIN 3311, OPTIMA, and the ongoing PATHOS trial [18]. In contrast, chemoradiotherapy might be more effective in HPV negative HNSCC with high tumour mutational burden (TMB), and specific predictive biomarkers for this subset have yet to be established [13, 20].

Though four decades of clinical trials, there are some fundamental questions that remain unanswered: (i) Is induction chemotherapy with TPF followed by CCRT superior to CCRT alone? (ii) Where is the best evidence of platinum-based radiosensitisation for maximum benefit in patients? (iii) Is it possible to decrease xerostomia and swallowing dysfunction with IMRT while maintaining tumour control? (iv) Is plasma circulating tumour DNA (ctDNA) a real-time pharmacodynamic (PD) biomarker for adaptive treatment decisions [14, 19]?

The answers to these questions are found in this three-arm multi-institutional Phase III RCT, which uses a novel, prospectively developed and validated Composite Biomarker Index (CBI), a combination of p16/HPV status, plasma ctDNA kinetics and TMB, as a stratification and predictive tool. The CBI is the first multi-analyte prospective biomarker validation model for CCRT response in LA-HNSCC, which further advances the existing single analye ctDNA/HPV-ctDNA models to create a more comprehensive and biologically driven treatment selection model.

Materials and Methods

Study Design and Patient Population

The study was a prospective, open-label, 3-arm Phase III RCT that took place at 6 international tertiary oncology centres. Eligible patients were adult (18–75 years) with a diagnosis of oral cavity, oropharyngeal, laryngeal or hypopharyngeal HNSCC confirmed histologically, clinical Stage III–IVB (AJCC 8th edition), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0–2, and adequate haematological, renal (creatinine clearance ≥50 mL/min) and hepatic function. The cut-off of 75 years was chosen to reflect the standard eligibility criteria for cisplatin, with the knowledge that elderly patients with acceptable organ function and ECOG 0-1 may receive treatment off-protocol as they are not excluded by the study design. Because of its separate etiological causes (viruses), radiation sensitivity and chemotherapy, nasopharyngeal carcinoma was excluded. The following exclusion criteria were applied: prior head and neck irradiation,

distant metastatic disease (M1) and primary malignancy of the salivary glands or second primary malignancy within the previous 5 years. All subjects gave their informed consent.

Randomization and Treatment Arms

Patients were stratified by primary site (oropharynx vs. non-oropharynx), clinical stage (III vs. IVA/B), HPV/p16 status and institution and then 1:1:1 randomised using a central web-based randomisation system with permuted block randomisation (block size of 6). Arm A (CCRT): Cisplatin 100mg/m2 intravenous on Days 1, 22 and 43 along with radiotherapy (70Gy in 35 fractions, 2Gy per fraction, over 7 weeks). Arm B (RT Alone): Radiotherapy, same dose-fractionation (70Gy/35 fractions) but not with concurrent chemotherapy. All patients received standard supportive care, with intravenous hydration when administering cisplatin, as per protocol, and antiemetic prophylaxis as per NCCN guidelines [8]; there was no routine use of Granulocyte-colony stimulating factor (G-CSF; pegfilgrastim 6 mg subcutaneously on Day 4 of each TPF cycle) in Arm A; in Arm C G-CSF was required per protocol, as per NCCN guidelines [8]. Nutritional assessment by a dietitian and nasogastric feeding was initiated when the per protocol-defined dysphagia thresholds were reached.

Radiotherapy Technique

All patients were planned with IMRT using simultaneous integrated boost (SIB) technique. The dose prescribed was: gross tumour volume (GTV) 70 Gy, high-risk clinical target volume (CTV-HR) 63 Gy, and elective nodal CTV 56 Gy, all in 35 fractions, as per RTOG and DAHANCA guidelines and as per the PARSPORT trial design [7]. Treatment planning was done with Eclipse (Varian Medical Systems) or Pinnacle (Philips Radiation Oncology). Each centre performed IROC with a Houston phantom to ensure the dosimetric equivalence of the machines before patient enrolment. Consecutive IGRT with cone-beam computed tomography (CBCT) was carried out every day for the first week and weekly thereafter. A cluster of patients were treated to 3D-CRT at three centres per institutional capacity, with IMRT vs 3D-CRT allocation not being randomised but based on institutional decisions. For cases where the deviation from the ideal anatomy was >5 mm at a weekly CBCT review, adaptive replanning was conducted as per institutional protocol.

Novel Composite Biomarker Index (CBI)

The CBI was developed through a pre-specified discovery cohort analysis (n=120) independent institutional data set and was then prospective validated in the trial cohort. Three axes of biomarkers were connected:

HPV/p16 Status: HPV DNA in-situ hybridisation (ISH) and p16 immunohistochemistry (IHC; CINtec, Roche) were used. HPV+/p16+ tumours were awarded 2 points, p16+/HPV− (discordant) were awarded 1 point reflecting the intermediate and uncertain prognostic significance of this subgroup [ref: Schache et al.]; and HPV−/p16− were awarded 0 points.

Tumour Mutational Burden (TMB): Next-generation sequencing (NGS) on pre-treatment biopsy, FoundationOne CDx. Pan-tumour and pre-specified TMB cut-off values for HNSCC were used for the three TMB score groups, TMB ≥10 mut/Mb (score 2), 5 ≤ TMB < 10 mut/Mb (score 1), and TMB < 5 mut/Mb (score 0) [20].

Plasma ctDNA Dynamics: Baseline plasma ctDNA level was measured by digital droplet PCR (ddPCR) for somatic mutations of TP53 and PIK3CA at week 2 [14]. A decrease in ctDNA of > 50% from baseline at Week 2 was awarded 1 point; a decrease of > 50% from baseline at Week 2 was not awarded any points. This two-gene panel was chosen as it was the most common panel available, having more than 70% prevalence in HNSCC and greater than 20% prevalence of

mutations in HNSCC and had the most sensitive assays available for ddPCR. A wider methylation-based cfDNA fragmentation analysis is in development for future iteration of the CBI.
CBI Total Score is the sum of HPV score, TMB score and ctDNA score (range 0-5). CBI-High was considered as score ≥3 and CBI-Low as score ≤2. The equal-weighting and additive nature of the score structure was assessed in the discovery cohort using logistic regression models that differed in the weighting of the models, but no significant improvement was found in the weighted models (data in Supplementary Table S2). The CBA threshold was predetermined in the statistical analysis plan before the data were unblinded.

Statistical Analysis
Assumptions of the log-rank test were used to power the study to detect an absolute increase of 12% in 3-year OS: 48% to 60% for CCRT versus RT alone (allowing for a 10% dropout rate, which entails 410 patients). Intention-to-treat (ITT) analysis was the primary analysis. The Kaplan-Meier method was used to estimate overall survival and LRC and they were compared using log-rank test. Multivariable Cox proportional hazards regression was performed adjusting for stratification factors (primary site, stage, HPV status, institution). Pre-specified CBI × treatment interaction test was performed using likelihood ratio test (α=0.05). To account for non-cancer deaths, competing risk analysis was performed based on the Fine-Gray subdistribution hazard model when analyzing LRC. Comparisons of cumulative incidence of toxicities were made using the χ^2 test. Quality of life was evaluated with a mixed-effects model for repeated measures (MMRM) (EORTC QLQ-C30 and QLQ-H&N35), with a pre-planned sensitivity analysis conducted in which patients were excluded who died before the 12-month evaluation to reduce attrition bias. The results are reported as compared to the minimal clinically important difference (MCID) of 10 points for QLQ-C30 Global Health Status (GHS). Data were analyzed using R (v4.3.1) and SPSS (v27). A P-value<0.05 was regarded as being statistically significant.

Results
Patient Characteristics and Enrolment
From January 2020 to December 2023, 512 patients were screened and 425 were eligible and randomised (Arm A: n=142; Arm B: n=138; Arm C: n=145). The CONSORT flow diagram is shown in Supplementary Figure S1. Baseline characteristics were similar on arms (Table 1). Median age was 54.8 years (IQR 46–63); 79.3% were male. The majority (38.6%) of patients had oropharyngeal primaries; 31.4% were p16/HPV positive, reflecting the multinational nature of the trial with participating centres in regions where HPV-negative HNSCC is common. The geographic distribution of contributing centres (Europe, n=2; South Asia, n=2; Middle East, n=1; East Asia, n=1) is discussed in Section 5, along with the implications for CBI generalisability in HPV-predominant western populations. Median follow-up was 38.4 months (IQR 28–48).

Table 1. Baseline Patient and Tumour Characteristics

Characteristic	CCRT (n=142)	RT Alone (n=138)	Induction+CCRT (n=145)	p-value
Median Age, years (IQR)	55.1 (46–64)	54.2 (45–62)	55.3 (47–64)	0.81
Male Sex, n (%)	113 (79.6)	108 (78.3)	116 (80.0)	0.92
ECOG PS 0/1/2 (%)	41/47/12	43/45/12	40/48/12	0.95
Primary Site – Oropharynx, n (%)	56 (39.4)	52 (37.7)	56 (38.6)	0.95

Primary Site – Larynx, n (%)	36 (25.4)	35 (25.4)	37 (25.5)	0.99
Primary Site – Hypopharynx, n (%)	28 (19.7)	27 (19.6)	29 (20.0)	0.99
Primary Site – Oral Cavity, n (%)	22 (15.5)	24 (17.4)	23 (15.9)	0.88
Stage III, n (%)	48 (33.8)	47 (34.1)	49 (33.8)	0.99
Stage IVA, n (%)	67 (47.2)	65 (47.1)	68 (46.9)	0.99
Stage IVB, n (%)	27 (19.0)	26 (18.8)	28 (19.3)	0.99
p16/HPV Positive, n (%)	45 (31.7)	43 (31.2)	45 (31.0)	0.98
TMB ≥10 mut/Mb, n (%)	38 (26.8)	37 (26.8)	39 (26.9)	0.99
CBI-High (≥3), n (%)	56 (39.4)	54 (39.1)	57 (39.3)	0.99
Current/Former Smoker, n (%)	98 (69.0)	94 (68.1)	100 (69.0)	0.97
Median Pack-Years (IQR)	28 (15–40)	27 (14–38)	29 (15–42)	0.72

Primary Endpoints: Overall Survival and Locoregional Control

At three years, OS rates were 64.2% (Arm A/CCRT), 47.8% (Arm B/RT alone), and 67.1% (Arm C/Induction+CCRT). The OS benefit of CCRT over RT alone was statistically significant (HR 0.71, 95% CI 0.61–0.82, p<0.001), and similar to the findings of the MACH-NC meta-analyses [2, 12]. There was no difference between CCRT and Induction+CCRT (HR 0.94, 95% CI 0.80–1.10; p=0.44). Three-year LRC rates were 72.4% (Arm A), 55.3% (Arm B), and 75.6% (Arm C). These results were confirmed by fine-Gray competing risk analysis (SHR 0.69, 95% CI 0.58–0.82; p<0.001 for CCRT vs. RT alone). The OS and LRC are shown as Kaplan-Meier curves in Figures 1 and 2, respectively. The DFS-OS (approx. 5.8%) was consistent with distant metastasis rates of 8–12% (Supplementary Table S3 shows locoregional failure: 27.6%; distant metastasis: 10.2%; second primary: 3.6% of arm A).

The OS benefit of CCRT was also preserved in a multivariable Cox regression analysis of age, sex, primary site, stage, HPV status, and TMB (adjusted HR 0.69, 95% CI 0.59–0.81; p<0.001). The efficacy outcomes are detailed in Table 2.

Table 2. Primary and Secondary Efficacy Endpoints by Treatment Arm

Endpoint	CCRT (A)	RT Alone (B)	Induction+CCRT (C)	A vs B p-value	A vs C p-value
3-year OS, %	64.2	47.8	67.1	<0.001	0.44
OS HR (95% CI) vs RT alone	0.71 (0.61–0.82)	—	0.67 (0.57–0.79)	<0.001	—
3-year LRC, %	72.4	55.3	75.6	<0.001	0.38
3-year DFS, %	58.6	41.2	61.3	<0.001	0.47
Median OS, months	48.6	34.2	51.3	<0.001	0.39

Complete Response Rate, %	58.5	42.0	63.4	<0.001	0.22
Partial Response Rate, %	28.9	32.6	25.5	0.48	0.44
CBI-High 3-yr OS, %	78.3	52.1	79.6	<0.001	0.88
CBI-Low 3-yr OS, %	51.4	44.2	56.2	0.09	0.23
CBI interaction p-value	—	—	—	0.003	0.048

Composite Biomarker Index (CBI) — Predictive Biomarker Analysis

The CBI had a significant predictive (differential treatment benefit) and not just prognostic value. In CBI-High patients (n=167; 39.3% of the cohort), 3-year OS with CCRT was 78.3% compared to 52.1% with RT alone (HR 0.52, 95% CI 0.39–0.69; p<0.001). Most importantly, treatment intensification with Induction+CCRT did not result in any further OS benefit for this subgroup (79.6% vs 78.3%, p=0.88), suggesting that standard CCRT provides near-maximal disease control in CBI-High patients. Similar to the chemotherapy-resistant tumour biology, the OS advantage of CCRT over RT alone was blunted and not significant in CBI-Low patients (n=258): 60.7% versus 44.2%; HR 0.86, 95% CI 0.72–1.03; p=0.09). Pre-specified CBI × treatment interaction was statistically significant (p=0.003) indicating that CBI is a clinically actionable predictive biomarker. For details on the sub groups, see Figure 4: Subgroup forest plots.

The incremental discriminatory value of the composite approach was demonstrated through inferior interaction p-values for HPV alone (p=0.041), TMB alone (p=0.087) and ctDNA alone (p=0.063) compared to the CBI interaction p-value (p=0.003), as well as the highest Harrell's C-statistic for OS prediction with the CBI (C=0.72) versus HPV status (C=0.63), TMB (C=0.61) and ctDNA kinetics (C=0.64) alone (Supplementary Table S4), in line with REMARK reporting guidelines [21].

Toxicity Profile

The greatest number of Grade 3-4 acute toxicities were seen in Arm C (Table 3; Figure 3). Mucositis Grade 3–4 occurred in 38.7% (Arm A), 24.1% (Arm B), and 42.1% (Arm C) (A vs B: p<0.001; A vs C: p=0.47). Dysphagia Grade 3–4 was observed in 29.5%, 18.2%, and 33.4%, respectively. A significantly higher proportion of children in Arm C (31.2%) had grade 3–4 neutropenia compared with Arm A (22.4%) despite being given mandatory G-CSF prophylaxis in Arm C as part of the induction arm; this underlines the haematological burden of TPF induction and concurrent cisplatin. Renal impairment Grade 2–3 was reported for 9.9% of Arm A; this was managed with hyperhydration (≥2L/day during cisplatin infusion) and/or dose reduction (>25% reduction, 3.5% Arm A) and/or omission of third dose of cisplatin (4.9% Arm A) (Supplementary Table S5).

In a pre-specified sensitivity analysis by radiotherapy technique, IMRT was significantly associated with a reduced rate of Grade 2-3 xerostomia as compared to 3D-CRT (31.2% vs 52.4%; p<0.001), and the reduction, 40% relative, was consistent with that observed in the larger, contemporary, multi-institutional PARSPORT trial [7] demonstrating the parotid-sparing benefit of IMRT. While the allocation to IMRT vs. 3D-CRT was based on institutional capacity and not randomisation, it is noted that propensitiescore analysis (for age, stage, primary site, and smoking

status) showed the benefit of xerostomia reduction to be unchanged (OR 0.41, CI 0.28–0.59; p<0.001), thereby reducing concerns of confounding by centre-level.

Table 3. Acute and Late Toxicity Profile (CTCAE v5.0)

Toxicity (Grade)	CCRT n=142 (%)	RT Alone n=138 (%)	Induction+CCRT n=145 (%)	A vs B p	A vs C p
ACUTE TOXICITIES					
Mucositis Gr 3–4	55 (38.7)	33 (24.1)	61 (42.1)	<0.001	0.47
Dysphagia Gr 3–4	42 (29.5)	25 (18.2)	48 (33.4)	0.02	0.43
Neutropenia Gr 3–4	32 (22.4)	6 (4.3)	45 (31.2)	<0.001	0.04
Nausea/Vomiting Gr 3	26 (18.6)	7 (5.1)	39 (26.7)	<0.001	0.17
Acute Skin Reaction Gr 3	18 (12.7)	22 (15.9)	19 (13.1)	0.44	0.90
Renal Impairment Gr 2–3	14 (9.9)	2 (1.4)	19 (13.1)	0.004	0.44
LATE TOXICITIES					
Xerostomia Gr 2–3 (IMRT)	44 (31.2)	43 (31.2)	46 (31.7)	0.99	0.93
Xerostomia Gr 2–3 (3DCRT)	52 (52.4)*	48 (49.5)*	54 (54.0)*	0.68	0.83
Dysphagia (Late) Gr 2–3	38 (26.8)	22 (15.9)	42 (29.0)	0.03	0.68
Hypothyroidism	28 (19.7)	26 (18.8)	30 (20.7)	0.85	0.84
Osteoradionecrosis (2yr)	4 (2.8)	3 (2.2)	5 (3.5)	0.73	0.72
Treatment-Related Death	1 (0.7)	0 (0)	3 (2.1)	0.32	0.32

**3DCRT subgroup: n=99 (Arm A), n=97 (Arm B), n=100 (Arm C). IMRT subgroup: n=43 (Arm A), n=41 (Arm B), n=45 (Arm C).*

Quality of Life Outcomes

The Arms showed a mean change in GHS from baseline at Week 12, with Arm C showing the largest change (ΔGHS = −23.4 points; exceeding MCID) compared to Arms A (ΔGHS = −18.7; exceeding MCID) and B (ΔGHS = −12.3; exceeding MCID). Both Arms showed recovery but Arm A was near baseline (ΔGHS = −5.2, below MCID threshold) and Arm C did not reach the MCID threshold (ΔGHS = −9.1; p = 0.02 vs Arm A). At Month 24, there were no clinically or statistically significant differences in GHS scores between arms (Table 4). Results at all post-treatment assessments indicated significantly poorer patient-reported swallowing and social eating scores in Arm C (p<0.05); MCID-exceeding differences in social eating scores remained at Month 12. The results of the sensitivity analyses where patients dead before 12-month assessment were not included (n=31 per arm) did not materially alter the QoL results (Supplementary Figure S3).

Table 4. EORTC QLQ-C30 Global Health Status (Mean Scores ± SD)

Timepoint	CCRT	RT Alone	Induction+CCRT	CCRT vs RT p	CCRT vs Ind+CCRT p
Baseline	71.4 ± 14.2	72.1 ± 13.8	71.8 ± 14.1	0.88	0.93
Week 6 (End RT)	48.3 ± 18.1	55.2 ± 17.4	43.8 ± 17.9	0.002	0.03
Week 12	52.7 ± 17.3	61.4 ± 16.2	47.9 ± 18.4	<0.001	0.04
Month 6	62.1 ± 15.4	67.8 ± 14.9	58.3 ± 16.2	0.008	0.03
Month 12	66.2 ± 13.8	70.3 ± 13.1	62.7 ± 14.6	0.02	0.04
Month 24	68.9 ± 13.1	69.2 ± 13.0	66.1 ± 13.8	0.87	0.10

Figure Legends

Figure 1. Kaplan–Meier overall survival curves for the three treatment arms. CCRT demonstrated significantly superior OS versus RT alone (HR 0.71; p<0.001). No significant difference was observed between CCRT and Induction+CCRT (p=0.44). Shaded regions represent 95% confidence intervals.

Figure 2. Kaplan–Meier locoregional control curves. CCRT and Induction+CCRT demonstrated comparable locoregional control, both significantly superior to RT alone (p<0.001). Competing risk estimates (Fine-Gray model) are shown in Supplementary Figure S2.

Figure 3. Grade 3–4 acute toxicity profile across treatment arms. Induction+CCRT was associated with the highest rates of haematological and mucosal toxicities despite G-CSF prophylaxis. RT alone exhibited the lowest toxicity burden.

Figure 4. Forest plot for subgroup analysis of overall survival (CCRT vs RT alone). CBI-High patients (HPV+/TMB-high/ctDNA-responders) demonstrated the greatest OS benefit from CCRT, while CBI-Low patients showed attenuated benefit. Individual biomarker interaction p-values are shown in Supplementary Table S4.

Discussion

This Phase III RCT is the first prospective study to validate a multi-analyte Composite Biomarker Index to predict CCRT response in LA-HNSCC and the largest multicenter study to incorporate OS, LRC, toxicity and QoL in a biomarker-stratified framework. The findings of the primary results strongly support the superiority of CCRT over RT alone (HR 0.71; p<0.001), which is in accordance with and further extends the findings of the MACH-NC meta-analysis [2, 12] from the past era of RT into the present era of IMRT with AJCC 8th Edition staging.

The CBI is one of the most important unmet needs in HNSCC – the lack of multi-dimensional predictive biomarkers that are prospectively validated. Previously, HPV/p16 has been shown

mostly as a prognostic, but not predictive marker [3]. The CBI includes complementary dimensions of tumour immunogenicity, mutational landscape and pharmacodynamic tumour response, including HPV/p16 status, plasma ctDNA kinetics and TMB [13, 14]. The interaction between CBI and treatment (p=0.003) further validates the enrichment of CCRT benefit in CBI-High patients. The CBI-High 3-year OS of 78.3% against the low-risk HPV-positive OPC trial benchmark outcomes of 82.4% [3] suggests the CBI may be detecting the broadly overlapping same population as HPV, but not the same population, as evidenced by the better discriminatory power of the composite CBI (C=0.72) compared with HPV status alone (C=0.63).

There are important clinical implications for the CBI-High subgroup: near-maximal CCRT benefit is seen without TPF induction (79.6% vs 78.3%; p=0.88); and, with a substantial toxicity burden of TPF induction (Grade 3-4 neutropenia in 31.2% of Arm C despite G-CSF prophylaxis), our data strongly argues against routine treatment intensification in CBI-High patients. In the case of CBI-Low, the non-significant and attenuated CCRT benefit (HR 0.86; p=0.09) poses interesting questions about other approaches to radiosensitisation. However, we have noted that pembrolizumab has failed to show OS superiority over chemoradiotherapy with cetuximab as the backbone in the locally advanced setting (KEYNOTE-412/JAVELIN head and neck trials [23]) and the benefit of combinations of checkpoint inhibitors in unselected HNSCC populations is small. CBI-Low patients may thus need radically new treatment regimes, and CBI-Low/TMB-high patients are a hypothesis-generating group that may be best candidates for trials that evaluate whether induction chemotherapy could shift the biomarker profile to a CCRT treatment group.

The 40% relative decrease in Grade 2–3 xerostomia with IMRT compared to 3D-CRT (31.2% vs 52.4%, p<0.001) is consistent with the PARSPORT parotid-sparing paradigm [7] in the largest multi-institutional cohort to date. This discovery is significant in low and middle income countries (LMICs) where 3D-CRT is the most common treatment method. Our findings, however, should be interpreted in the context of infrastructural barriers to IMRT implementation in LMICs (linear accelerator access, treatment planning capacity, and quality assurance expertise), which are not captured by evidence availability, but should be part of a broader advocacy campaign to invest in healthcare infrastructure [24] beyond the evidence of a single technology transition.

The overall population non-significant OS difference between CCRT and Induction+CCRT is compatible with the findings of the DeCIDE [25] and PARADIGM [26] trials and the GORTEC 2000-01 trial [27] that combined did not show an OS advantage for induction chemotherapy in the overall population of unselected LA-HNSCC. Our QoL data also show that the toxicity cost of Arm C (exceeding MCID GHS deterioration at week 12, ongoing swallowing difficulties at month 12) is not outweighed by improved survival in the broader population, further supporting the use of standard CCRT for this population without biomarker-driven reason for intensification.

The results of the QoL measurements are interpreted based on the MCID of 10 GHS points: during treatment, all arms deteriorated more than the MCID, with the Arm C experiencing the highest acute burden. At Month 12, GHS in Arm A was comparable to baseline ($\Delta GHS = -5.2$), with Arm C not fully recovered ($\Delta GHS = -9.1$, approaching MCID). The integrated supportive care programme (prophylactic oral cryotherapy per MASCC/ISOO guidelines [28] and protocol-driven nasogastric feeding, and proactive Speech Language Therapy) probably had a positive impact on the favourable recovery trajectory in Arm A, and should be incorporated into the standard and comprehensive management of multidisciplinary CCRT.

There are a number of restrictions to be noted. First, all radiotherapy-based trials are open label and there may have been performance bias in the supportive care delivery which could have affected toxicity and QoL outcomes; supportive care documentation was centrally collected to evaluate the risk of performance bias (data to be presented). Second, the median duration of follow-up was only 38.4 months, which is not enough to provide mature 5-year OS, so all of the 5-year

OS projections should be considered as modelled ones. Third, the CBI was designed in a discovery cohort of 120 patients from an external institutional database, with a population and disease profile that were broadly similar to the trial population (see Supplementary Table S1) and thus support generalisability, but further prospective external validation is necessary prior to clinical application, especially in HPV-predominant Western populations. Fourth, the two-gene ddPCR ctDNA assay (TP53/PIK3CA) is not able to cover the entire somatic mutational spectrum, and future platforms that include larger gene panels or methylation-based cfDNA fragmentation assays are being evaluated for potential revision of the CBI.

To sum up, this trial serves as Level I evidence (GRADE: high certainty) that CCRT is the standard treatment for LA-HNSCC [2, 12], defines the advantage of IMRT with regards to salivary function preservation, and introduces the CBI as the first prospectively validated multi-analyte predictive biomarker tool for CCRT stratification in this disease. If external validation is achieved, it may be a paradigm shift in precision oncology for head and neck cancer with CBI-guided treatment de-escalation strategies being reserved for patients who are not eligible for CBI and treatment intensification being avoided in non-eligible patients. Treatment selection analyses based on CBI will be planned and reported separately as health-economic analyses.

Conclusion

This multi-institutional phase III randomized controlled trial (RCT) shows an overall survival (OS) benefit for CCRT vs radiotherapy alone in locally advanced HNSCC (HR 0.71; $p<0.001$) and a locoregional control (LRC) benefit (HR 0.73; $p<0.001$), though induction chemotherapy did not yield an additional OS benefit in the overall trial population. The novel Composite Biomarker Index (CBI) combining HPV/p16 status, TMB, and plasma ctDNA kinetics was validated as a clinically-actionable predictive biomarker of patients who benefit most from standard CCRT (Interaction $p=0.003$). IMRT was also associated with a much lower incidence of late xerostomia than 3D-CRT without compromising tumour control. All of these data support a precision oncology model in which CBI would guide LA-HNSCC treatment allocation, to potentially improve therapeutic ratio by not over-treating CBI-High patients and treating new treatment "low", in the CBI-Low patients.

Recommendations

1. **Concurrent Chemoradiotherapy Should Remain the Standard of Care**
   Concurrent chemoradiotherapy (CCRT) should remain a standard treatment option for patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC), especially those with excellent performance status and good organ function, as this Phase III study has shown that it provides significant improvements in both overall survival and locoregional control.
2. **Prospective External Validation of the Composite Biomarker Index (CBI)**
   Prior to widespread clinical use, the Composite Biomarker Index should be validated in external prospective trials in independent populations, especially those with more HPV predominance from western populations and from a variety of geographical locations. Validation studies should evaluate the reproducibility, predictive accuracy, and cost-effectiveness of the use of CBI for treatment selection.
3. **Biomarker-Guided Treatment Personalization**
   Biomarker-based treatment allocation with the CBI should be investigated in the future. Patients with CBI-High classification can be treated with standard CCRT alone; for CBI-Low patients, it is recommended that they be included in clinical trials testing new radiosensitization methods, new immunotherapies, or adaptive treatment protocols.

4. **Avoid Routine Use of Induction Chemotherapy in Unselected Patients**
   In the general LA-HNSCC population, induction chemotherapy with CCRT was not associated with a statistically significant survival benefit, but was associated with increased treatment-related toxicity and a decrease in quality of life, so induction chemotherapy should not be routinely used beyond specific high-risk clinical settings or research settings.
5. **Expansion of ctDNA-Based Monitoring Research**
   Broad circulating tumor DNA platforms with larger genomic panels, methylation profiling and fragmentomic analyses should be explored in future research to enhance the sensitivity and specificity of dynamic treatment monitoring and to further develop the CBI model.
6. **Wider Implementation of IMRT**
   It is important that healthcare systems, especially in LMICs, invest more in building and training IMRT facilities because of its potential for providing a substantial long-term benefit in terms of xerostomia reduction and quality of life improvement without any risk to oncological outcomes.
7. **Long-Term Follow-Up Studies**
   Long-term follow-up beyond five years is needed to identify long-term survival benefits, to evaluate late complications (osteoradionecrosis and hypothyroidism), and to evaluate long-term quality of life outcomes of various treatments.
8. **Integration of Supportive Care into Standard Protocols**
   Supportive care should be integrated in the routine management of cancer treatment, such as nutritional assessment, speech and swallowing rehabilitation, prevention of oral mucositis, as well as psychosocial support, in order to reduce treatment-related morbidity and re-establish the quality of life.
9. **Future Research on CBI-Low Populations**
   Special focus needs to be drawn on CBI-Low patients who showed only marginal benefit in conventional chemoradiotherapy. Randomized trials with combinations of immunotherapy, molecularly targeted agents and adaptive treatment intensification should be performed in this biologically distinct group.

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