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Review Article

Non-cisplatin concurrent agents plus definitive radiotherapy for locally advanced head and neck cancer: A network *meta*-analysis of randomized studies

Fausto Petrelli [a,*], Francesca Trevisan [b], Massimiliano Nardone [c], Daniela Carioli [c], Angela Gasparini [c], Chiara Bramati [e], Lorenza Bruschieri [b], Valentina Riboldi [b], Vincenzo Capriotti [d], Agostina De Stefani [b], Luigi Lorini [e], Daniele Spada [c], Veronica Lonati [a], Paolo Bossi [e]

[a] *Oncology Unit, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047 Treviglio, BG, Italy*
[b] *Radiotherapy Unit, ASST Bergamo Ovest, Treviglio, BG, Italy*
[c] *Otorhinolaringology Unit, Department of Neuroscience, ASST Bergamo Ovest, Treviglio, BG, Italy*
[d] *Otorhinolaryngology Unit, Surgery Department, Portogruaro Hospital, ULSS4 Veneto Orientale, Portugruaro, Italy*
[e] *Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy*

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ABSTRACT

Introduction: Head and neck squamous cell carcinoma (HNSCC) poses a significant clinical challenge, particularly in its locally advanced stages. Cisplatin-based, definitive, chemoradiotherapy (CRT) is recognized as the preferred treatment strategy, providing substantial survival benefits and currently achieving the best locoregional control (LRC). However, the toxicity profile of cisplatin, which includes nephrotoxicity, neurotoxicity, and ototoxicity, restricts its application in patients with comorbidities or those of advanced age. Emerging alternatives such as carboplatin, taxanes, cetuximab, and immune checkpoint inhibitors (ICIs) are gaining attention. This study undertakes a network *meta*-analysis (NMA) to assess the effectiveness and safety of these agents in conjunction with definitive RT.

Methods: The inclusion criteria targeted definitive RT in conjunction with non-cisplatin systemic therapies, compared to RT with or without cisplatin in adult HNSCC patients. The outcomes evaluated included overall survival (OS), progression-free survival (PFS), and locoregional control (LRC). Statistical methodologies, including the Surface Under the Cumulative Ranking Curve (SUCRA), were employed to rank the treatment protocols.

Results: The analysis incorporated 29 randomized controlled trials assessing 18 treatment modalities. Three cisplatin-based regimens combined with RT consistently demonstrated superior efficacy in OS, ranking as the 3 most effective option for OS, followed by weekly docetaxel combined with RT. Non-cisplatin alternatives such as mitomycin C-based regimens + RT, and methotrexate + RT, demonstrated promising efficacy. For PFS, they ranked first and second, with SUCRA scores of 83 % and 79 %, respectively. Regarding LRC, mitomycin C-based regimens + RT and weekly docetaxel + RT emerged as the top two options, achieving SUCRA scores of 97 % and 93 %, respectively. Cetuximab and ICIs combined with RT ranked lowest across all assessed outcomes.

Conclusion: While cisplatin remains the standard of care, carboplatin, mitomycin C-based, and weekly docetaxel + RT regimens present viable alternatives as concurrent agents during RT for patients with stage III-IV HNSCC who are not eligible for cisplatin. It is imperative to develop tailored treatment strategies to enhance clinical outcomes.

* Corresponding author.
E-mail address: faupe@libero.it (F. Petrelli).

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Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is the 7th most common cancer worldwide, and 60 % of cases are classified as locally advanced (LA) at diagnosis [1]. Cisplatin (CDDP), in combination with radiotherapy (RT), serves as the standard systemic treatment for locally advanced (LA) head and neck squamous cell carcinoma (HNSCC) in definitive contexts. The treatment regimen typically involves three 100 mg/m^2 infusions of CDDP administered every three weeks or a weekly infusion of 40 mg/m^2 alongside conventionally fractionated external beam RT [2]. Although this approach yields favorable clinical outcomes, chemoradiotherapy (CRT) is associated with both acute and late toxicities. Numerous clinical trials have been conducted to identify an optimal balance between curative intent and minimizing adverse effects. Despite its demonstrated efficacy, CDDP is subject to several contraindications, including but not limited to performance status, age, renal dysfunction, hearing impairment, neuropathy, bone marrow, hepatic, respiratory, and cardiovascular dysfunctions, as well as pregnancy and hypersensitivity to platinum-based agents [3]. Various options could be taken into account when relative or absolute contraindications to CDDP stand out, considering that up to one third of LA HNSCC patients are considered platinum ineligible [4]. According to the multidisciplinary evaluation and expertise, a practitioner could opt for patients with a relative contraindication to high-dose CDDP. Various treatment options may be considered when faced with relative or absolute contraindications to CDDP.

In the case of patients with relative contraindications to high-dose CDDP, a feasible strategy involves reducing the peak concentration of CDDP by either extending the infusion duration, decreasing the single dose, or opting for a weekly regimen, which demonstrated non-inferiority in terms of survival and higher tolerability in the post-operative setting. Alternatively, various non-CDDP agents have been employed as monotherapy or combined. The efficacy of different regimens, including carboplatin (CARBO), taxanes, 5-fluorouracil (5-FU), and cetuximab, has been investigated in several clinical trials in definitive setting [2]. Immune checkpoint inhibitors (ICIs) have also been explored in combination with radiotherapy for patients deemed ineligible for CDDP, demonstrating heterogeneous outcomes. Despite ongoing research efforts, international guidelines do not endorse specific treatment regimens for CDDP-unfit HNSCC patients [5–7]. This systematic review seeks to synthesize the existing literature through a rigorous network *meta*-analysis (NMA), assessing the comparative efficacy and safety of non-CDDP agents for patients undergoing definitive RT in conjunction with systemic therapy for HNSCC, thereby optimizing therapeutic strategies within this complex clinical landscape.

Materials and methods

This study was conducted in accordance with the PRISMA-NMA extended statement of preferred reporting items for systematic reviews included in NMA.

Inclusion and exclusion criteria

Inclusion criteria: (1) The subjects were adult cancer patients with HNSCC treated with definitive RT (with or without neoadjuvant CT); (2) the study involved at least one arm of concurrent non-CDDP agents as systemic therapy interventions associated with RT; (3) the study type was a phase II-III randomized controlled trial (RCT); (4) the comparator arm was RT alone, RT plus (triweekly or less than triweekly) CDDP or RT plus non-CDDP agents.

Exclusion criteria: (1) studies with toxicity data only; (2) documents whose full text is not available or not publicly available; (3) nasopharyngeal, non-squamous cell histology, or skin cancers; (4) documents in languages other than English; (5) studies with fewer than 50 patients; (6) studies with CDDP included in both arms, and (7) studies in the adjuvant setting or with non-concurrent schedules of CT and RT (e.g., alternating or sequential CRT).

Search strategy

We used a combination of subject terms and free words to conduct systematic searches in the Cochrane Library, Embase, and PubMed. The search timeframe was from the database's construction to November 2024. We searched using the following Boolean logical operators: ("head and neck" OR "pharynx" OR "oral" OR "larynx" OR "laryngeal") AND "randomized" AND ("cisplatin" OR "carboplatin" OR "chemotherapy" OR "anti-EGFR" OR "PD-1" OR "PD-L1") AND radiotherapy AND (cancer OR carcinoma). In the literature selection process, relevant synonyms were flexibly used to ensure the comprehensiveness of literature retrieval.

Literature screening and data extraction

The literature search was carried out independently by two authors (FP and VC) according to the classification criteria, and literature screening and data extraction were conducted after reading the title, abstract, and general content. The inclusion of controversial documents was discussed by the two authors, with the assistance of a third researcher if necessary (FT). The extraction of relevant data was independently performed by five authors (FT, DC, CB, DS, and AG), focusing on the following information: study characteristics and the name of the first author, publication year and type, primary site and stage, treatments delivered for both treatment and control arms, follow-up durations, and country. Furthermore, hazard ratios (HRs) and 95 % confidence intervals (CIs) were extracted from Cox regression models for OS, PFS, and LRC. Any discrepancies in data extraction were resolved through consensus among co-authors.

Literature quality assessment

The methodological quality of the included randomized controlled trials was assessed using the Cochrane Risk of Bias tool, which evaluates six domains: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), and (6) selective reporting (reporting bias). Each domain was rated as having a low, high, or unclear risk of bias based on predefined criteria.

Two independent reviewers conducted the assessments, and discrepancies were resolved by consensus or with input from a third reviewer. Overall risk of bias for each study was categorized based on the following rules: Low risk (all key domains rated as low risk), Unclear risk (one or more domains rated as unclear risk with no high-risk domains), High risk (one or more domains rated as high risk).

Statistical analysis

The primary endpoint was overall survival (OS); secondary endpoints were progression (or event)-free survival (PFS or EFS) and locoregional control (LRC). In the process of data analysis, the outcome variables were expressed as hazard ratios (HR). The I^2 test determined the degree of heterogeneity of the included studies, and when $I^2 = 0$, it indicated that no heterogeneity was observed. The low, medium, and high degrees of heterogeneity were expressed as I^2 equal to 25 %, 50 %, and 75 %, respectively. If $P > 0.05$ and $I^2 < 50$ %, there is less heterogeneity; thus, a fixed effects model is chosen for analysis. There was obvious heterogeneity if $I^2 > 50$ %, and the random effects model was selected for combined analysis. We used the gemtc package (https://gemtc.drugis.org) software to draw the NMA network map of the included data to realize the direct or indirect comparison between the effects of different non-CDDP interventions on the outcome of HNSCC.

The nodes in the network plot represent different interventions, and the connecting lines between the nodes represent direct comparisons of different interventions in the included studies, which were weighted by the number of studies containing directly compared interventions. A larger node indicates a larger sample size receiving the intervention, and a thicker line indicates a larger number of corresponding pairwise comparisons. Multiple closed loops were formed between the therapies, and their overall inconsistency was judged by the inconsistency factor (IF) and 95 % CI. If the starting point of the 95 % CI is 0 and $p > 0.05$, the consistency between direct comparison and indirect comparison is good; or if it was about 0, there was no significant inconsistency of the closed loop, with the test level of $\alpha = 0.05$. Since different data sources of each node may have differences, we usually use the node splitting method to test their local inconsistency. If $P < 0.05$, local inconsistency is considered to exist. Ranking the effectiveness of interventions is one of the key steps in this study. We will use the surface under the cumulative ranking curve (SUCRA) to rank the effectiveness of each non-pharmacological therapy. The larger the area under the curve, the greater the likelihood that therapy is the best intervention, with a range of values from 0 % to 100 %.

The certainty of evidence for each outcome was assessed according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework. Starting from high certainty for randomized controlled trials, we considered potential downgrades for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Overall survival, PFS, and LRC were rated as moderate to high certainty, primarily due to the indirect nature of some comparisons within the network *meta*-analysis and imprecision in selected trials.

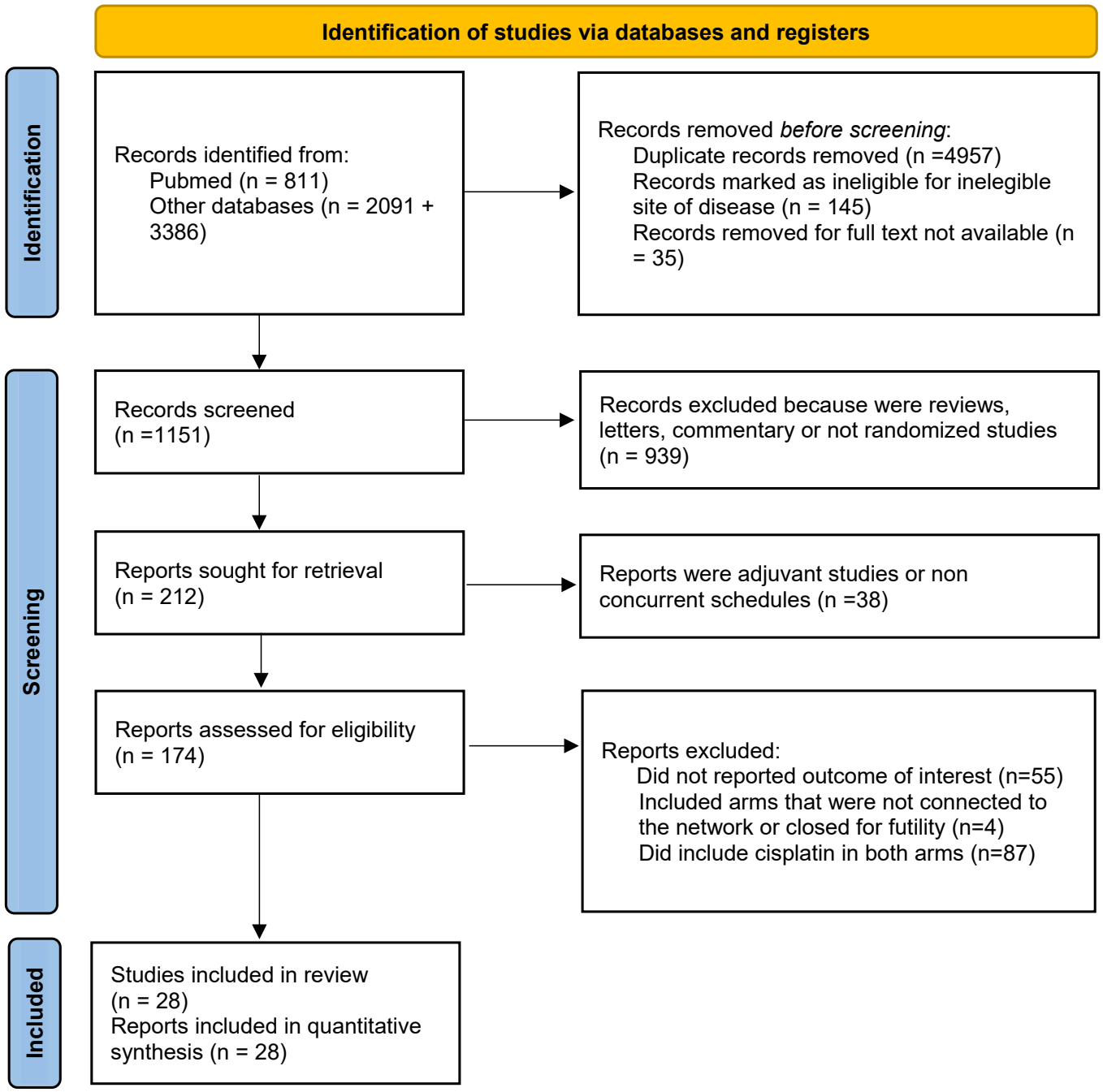

Fig. 1. Flow diagram of included studies.

Results

A total of 6,288 articles were obtained through a preliminary search of databases and related information channels, and 1,151 articles remained after removing duplicates and non-conforming articles. After reading the abstract and/or full text to remove articles, 939 were excluded due to a lack of relevant data, inconsistent intervention measures, relevant outcome indicators, or inconsistent patient types. Finally, 29 randomized controlled trials were included among the 212 studies analyzed (Fig. 1) [8–36].

Among these, n = 11 compared RT alone with CRT, n = 3 compared RT alone with RT + anti-EGFR agents (cetuximab and nimotuzumab), and n = 15 compared RT + concurrent agents in both arms (n = 10 with an anti-EGFR drug and CT, n = 2 with anti-EGFR agents and immune checkpoint inhibitors [ICIs], and n = 3 with different cytotoxic agents). Only n = 1 study included a neoadjuvant arm. See Table 1 for characteristics of included studies.

Overall, n = 19 studies had a low risk of bias, n = 1 had an uncertain risk, and n = 3 had a high risk of bias. In the Jeremic et al. study, only the RT + CARBO arm was compared to RT alone as part of the inclusion criteria. In all analyses, a random effects model was used [25]. In Garden et al. 3-arms study, only the CDDP/5FU arm 1 was compared to non-CDDP arm (5FU + hydroxyurea; arm 2) [10].

A total of 16 treatment modalities were compared for OS (Figs. 2a, 2b, and 2c). No treatment resulted in better OS than triweekly-CDDP plus or minus cetuximab. Cisplatin combinations resulted in the three best options, followed by weekly CDDP + RT. Radiotherapy + CDDP/5FU, RT alone, and RT + durvalumab were the worst combinations (SUCRA 34, 32 and 26 %).

A total of 15 treatment modalities were compared for PFS (Fig. 3b). No treatment resulted in better PFS than triweekly-CDDP. Mitomycin (MMC) + 5FU + RT, MTX + RT, and weekly docetaxel + RT resulted in the three best options (SUCRA 83 %, 79 %, and 78 %; Fig. 3a). Radiotherapy + cetuximab and RT + durvalumab were the worst combinations (SUCRA 8 % and 6 %). Among the non-CDDP schedules, MMC + 5FU + RT and methotrexate (MTX) + RT resulted in non-significantly better PFS than triweekly-CDDP + RT (HR = 0.6, 95 % CI 0.11–3.6 and 0.64, 95 % CI 0.11–3.7, respectively; Fig. 3c).

A total of 14 treatment modalities were compared for LRC (Fig. 4b). No treatment resulted in better LRC than triweekly-CDDP-CRT. Mitomycin + 5FU + RT and weekly docetaxel resulted in the two best options (SUCRA 97 % and 93 %; Figs. 4a and 4c). Radiotherapy + cetuximab and RT + durvalumab were the worst combinations (SUCRA 2 % and 1.6 %).

After the exclusion of n = 3 studies that enrolled only HPV+ HNSCC and one with planned neoadjuvant CT, the final results did not change significantly.

According to the GRADE framework, the overall certainty of evidence was rated as moderate to high for OS and moderate for both PFS and LRC. These ratings reflect the generally low risk of bias across the included randomized controlled trials, low inconsistency, and clinically relevant outcomes. Downgrading was applied primarily due to indirect comparisons inherent to the network *meta*-analysis methodology and imprecision in some hazard ratios with wide confidence intervals. Despite these limitations, the consistency of ranking across treatments supports the robustness of the findings.

Inconsistency assessment

OS: The overall fit of the Bayesian network *meta*-analysis model was satisfactory. The mean residual deviance was 32.0, closely matching the number of data points (n = 28), indicating good agreement between the model and observed data. The leverage value (pp = 21.6) fell within acceptable limits, suggesting that no individual study exerted disproportionate influence on the model estimates. The DIC was 53.7, consistent with an adequate model complexity relative to fit. The leverage versus residual deviance plot did not reveal any studies with simultaneously high leverage and high residual deviance, supporting the absence of influential outliers or local inconsistency within the network.

PFS: The model demonstrated a good overall fit. The mean residual deviance was 20.0, closely approximating the number of data points (n = 19), indicating that the model adequately captured the observed data. The effective number of parameters was 17.8, suggesting an appropriate level of model complexity. The DIC was 37.8, supporting the relative adequacy of the model. The leverage versus residual deviance plot showed no studies with high leverage and large residuals, confirming the absence of influential outliers or notable inconsistency.

LRC: The Bayesian network *meta*-analysis model showed an overall satisfactory fit. The mean residual deviance was 19.2, which aligns closely with the number of data points (n = 19), indicating adequate concordance between the observed and predicted data. The estimated model complexity, as reflected by the leverage, was within expected bounds. The DIC was 35.9, favoring this model in terms of parsimony and fit. The leverage versus residual deviance plot confirmed model adequacy, as all studies fell within acceptable boundaries. No studies showed both high leverage and large residual deviance, suggesting no influential outliers and supporting the consistency and robustness of the model.

Discussion

Concurrent CRT with CDDP remains the standard treatment for patients with LA-HNSCC, based on consistent evidence of improved OS (6 % at 5 years) and LRC [37]. However, due to age, frailty, or organ dysfunction, a substantial proportion of patients are ineligible for cisplatin. This NMA systematically compared alternative systemic agents combined with RT, synthesizing evidence from 29 randomized trials and 18 treatment strategies. While CDDP-based regimens maintained the highest efficacy across all endpoints—particularly OS—several non-CDDP options demonstrated comparable performance in select secondary outcomes such as PFS and LRC [4,38–42]. Although our analysis was not specifically designed to evaluate outcomes in CDDP-ineligible patients (this was not an inclusion criteria of trials in all except 1 study), the results provide clinically useful insights into the relative efficacy of non-platinum agents when cisplatin is not a viable option. We sought, infact, to systematically compare and rank non-CDDP systemic therapies, which may inform treatment choices in patients for whom platinum agents are not feasible.

The NMA highlights CARBO plus RT and weekly docetaxel plus RT as high-ranking alternatives across survival endpoints, after CDDP schedules, with SUCRA scores of 73 % and 70 %, respectively. These regimens offer a balance of efficacy and tolerability, making them viable options for patients ineligible for CDDP. For PFS, MMC + 5FU + RT and weekly docetaxel + RT emerge as the most effective regimens (SUCRA 83 %, 79 %), with MMC + 5FU + RT and weekly docetaxel + RT also leading for LRC (SUCRA 97 %, 93 %), surpassing traditional CDDP-based concurrent agents. However, variability in responses to non-CDDP regimens complicates their broader clinical application. This NMA provides moderate to high certainty evidence supporting the efficacy of selected non-cisplatin systemic regimens in combination with radiotherapy for HNSCC. According to the GRADE framework, OS was supported by moderate-to-high certainty evidence, while PFS and LRC outcomes were rated as moderate, owing to the presence of some imprecision and indirectness. Despite these limitations, the overall robustness and consistency of the included randomized trials lend strong support to the clinical relevance of non-cisplatin alternatives in cisplatin-ineligible patients.

The selection of alternatives must balance efficacy against toxicity. For example, CARBO offers a safety advantage over CDDP but may be less potent in certain cases. Randomized trials—such as those by Gasparini et al. and Homma et al. [8,9,17]—have shown comparable OS and response rates between CARBO-RT and CDDP-RT, with CARBO demonstrating reduced nephrotoxicity but increased stomatitis and

Table 1
Characteristics of included studies.

Author/ Year	Study Type	Country	N° Patients	Median Follow-up (months)	NMA comparison	Experimental Arm	Control Arm	RT Dose (Gy)	Stage % (I/II vs III/ IV)	HPV+ %	Primary Site	Primary Endpoint	Bias
Gasparini/ 1993	Randomised trial	Italy	53	12	**RT + CARBO**	RT + 3wCARBO (375 mg/m2)	RT + 3wCDDP (80 mg/m2)	64	III/IV (100)	NA	Oral cavity (28 %), Oropharynx (40 %), Hypopharynx (23 %), Larynx (9 %)	Side effects and response rates	Uncertain
Dobrowsky/ 2000	Randomised trial	Europe	239	48	**RT + MMC**	Hyperfractionated RT + MMC (20 mg/m2 day 5)	RT	70	III/IV (100)	NA	Oral cavity (30 %), Oropharynx (41 %), Hypopharynx (17 %), Larynx (12 %)	OS	Low
Staar/2001	Randomised trial	Europe (Germany)	240	22.3	**RT + nonCDDP/ 5FU**	RT + 5FU (600 mg/m2 days 1–5) + CARBO (70 mg/m2 days 1–5) weeks 1 & 5	RT alone	69.9	III/IV (100)	NA	Oropharynx (74 %), Hypopharynx (26 %)	OS, LC	Moderate
Gupta and Swindell/ 2001	Randomised trial	UK	313	60	**RT + MTX**	RT + MTX (100 mg/m2 days 1,14)	RT alone	55	III/IV (100)	NA	Oral cavity (22 %), Oropharynx (34 %), Hypopharynx (16 %), Larynx (18 %)	LC	Low
Grau/2003	Phase 3	Europe, Asia	478	10	**RT + MMC**	RT + MMC (15 mg/m2 first week)	RT alone	66	III/IV (100)	NA	Oral cavity (48 %), Oropharynx (29 %), Hypopharynx (14 %), Larynx (9 %)	OS	Low
Garden/ 2004	Phase II	US	241	32	**RT + 5FUic**	RT + daily 5FU (800 mg/m2) + HU (2000 mg)	RT + daily CDDP (10 mg/m2)/ 5FU (400 mg/m2) x 10 days	70	III/IV (100)	NA	Oropharynx (67 %), Hypopharynx (17 %)	DFS and OS	Moderate
Jeremic/ 2004	Phase 3	Serbia	289	12.5 and 34	**RT + CARBO**	wCARBO (100 mg/m2) + RT	Hfx RT	70 vs 50.6	III/IV (100)	/	Oral cavity (18 %), Oropharynx (37 %), Hypopharynx (18 %), Larynx (17 %), Nasopharynx (10 %)	5y OS	Moderate
Homma/ 2004	Phase 2	Japan	119	63	**RT + CARBO**	wCARBO (100 mg/m2) + RT (60)	Daily CDDP (4 mg/m2) + RT (59)	65	II 44, III/IV 56	/	Oral cavity (2 %), Oropharynx (26 %), Hypopharynx (19 %), Larynx (53 %)	5y OS	Moderate
Denis/2004	Phase 3 randomised trial	Europe (France)	226	66	**RT + CARBO**	RT + CARBO (70 mg/ m2 x 4 days) + FU (600 mg/m2 x 4 days) q3w	RT alone	70	III/IV (100)	NA	Oropharynx (100 %)	OS	Low
Budach/ 2005	Phase 3	Europe (Germany)	384	23	**RT + MMC**	RT hyperfractionated (77.6 Gy) alone	RT + FU (600 mg/m2 days 1–5) e MMC (10 mg/m2 days 5 and 36)	70.6/77.6	III/IV (100)	NA	Oropharynx (59 %), Hypopharynx (32 %)	LRC	Low

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Table 1 (*continued*)

Author/ Year	Study Type	Country	N° Patients	Median Follow-up (months)	NMA comparison	Experimental Arm	Control Arm	RT Dose (Gy)	Stage % (I/II vs III/ IV)	HPV+ %	Primary Site	Primary Endpoint	Bias
Semrau/ 2006	Phase 3	Germany	240	57	**RT + nonCDDP/ 5FU**	RT + CARBO (70 mg/ m2 days 1–5) + 5FU (600 mg/m2 days 1–5) q3w	RT	69.9	III/IV (100)	/	Oropharynx (74 %), Hypopharynx (26 %)	OS	Low
Bonner/ 2010	Phase 3 randomised trial	US	424	49	**RT + CET**	RT + CET (400/250 mg/m2)	RT	70	III/IV (100)	NA	Oropharynx (60 %), Hypopharynx (15 %), Larynx (25 %)	LRC	Low
Rodriguez/ 2010	**Randomized trial**	**Cuba**	**106**	**NR**	**RT + NIMOITUZUMAB**	**RT + wNIMOTUZUMAB (200 mg)**	**RT**	**60–66**	**III-IV (100)**	**NR**	**Orapharynx (70 %)**	**OS**	**High**
Reddy/2014	Phase 2b	India	92	30	**RT + NIMOTUZUMAB**	RT + wNIMOTUZUMAB (200 mg)	RT	60–66	III/IV (100)	/	Oropharynx (43 %), Oral cavity (21 %), Hypopharynx (21 %)	ORR	Moderate
Giralt/2015	Phase 2	International	151	26 vs 30	**RT + PANI**	PANI (9 mg/kg q3w) + RT (61)	3wCDDP (100 mg/ m2) + RT (90)	70–72	III/IV (100)	15 vs 17	Oropharynx (48 %), Oral cavity (11 %), Hypopharynx (16 %), Larynx (24 %)	2y LRC	High
Seiwert/ 2016	Phase 2	US	110	72	**Rt + nonCDDP + 5FU + CET**	Hfx RT + HU (1000 mg days 1–5) + 5FU (600 mg/m2 days 1–5) q4w + CET (400/250 MG/ M2)	acc RT + CET (400/ 250 mg/m2)	cetu-fhx 75, cetu-px 72	III/IV (100)	44	Hypopharynx (10 %), Larynx (11 %), Oral cavity (13 %), Oropharynx (61 %)	ORR	Moderate
Siu/2017	Phase 3	Canada	320	56	**RT + PANI**	3wCDDP (100 mg/m2) + RT	acc RT + PANI	70	NR	68	Oropharynx (81 %), Larynx (11 %)	2y OS	Low
Tao/2018	Phase 3	France	405	48	**RT + nonCDDP/ 5FU + CET**	CARBO (70 mg/m2 days 1–4) + 5FU (600 mg/m2 days 1–4) q3w + CET (400/250 mg/ m2) + RT	CET (400/ 250 mg/ m2) + RT	70	II/IV (100)	89	Oropharynx (65 %), Oral cavity (12 %), Hypopharynx (14 %)	3y PFS	Low
Ruo Redda/ 2018	Phase 3	Italy	157	26.2	**RT + CARBO**	RT + daily CARBO (45 mg/m2) days 1–5 q2w	RT	70	III/IV (100)	/	Oral cavity (14 %), Oropharynx (40 %), Larynx (10 %)	LRFS	Low
Gillison/ 2019	Randomised trial	US and Canada	849	54	**RT + CET**	RT + CET (400/250 MG/M2)	RT + 3wCDDP (100 mg/ m2)	70	III/IV (100)	100	Oropharynx (100 %)	OS	Low
Mehanna/ 2019	Phase 3	Ireland, Netherlands, UK	334	25.9	**RT + CET**	RT + 3wCDDP (100 mg/m2)	RT + CET (400/250 MG/M2)	65–70	NR	90 %	Oropharynx (100 %)	Overall severe toxicity (grades 3–5)	Low
Gebre-Medhin/ 2020	Phase 3 randomised trial	US	298	38	**RT + CET**	RT + CET (400/250 MG/M2)	RT + wCDDP (40 mg/m2)	68–73.1	III/IV (100)	74	Oral cavity (6 %), Oropharynx (84 %), Hypopharynx (5 %), Larynx (5 %)	OS	Low

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Table 1 (*continued*)

Author/ Year	Study Type	Country	N° Patients	Median Follow-up (months)	NMA comparison	Experimental Arm	Control Arm	RT Dose (Gy)	Stage % (I/II vs III/ IV)	HPV+ %	Primary Site	Primary Endpoint	Bias
Maddalo/ 2020	Phase 2	Italy	70	17 and 41	**RT + CET**	RT + CET (400/250 MG/M2)	RT + wCDDP (40 mg/m2)	70 (T e N +), 50 (N-)	III/IV (100)	26 % VS 29 %	Oral cavity (14 %), Oropharynx (47 %), Hypopharynx (20 %), Larynx (19 %)	OS and tox	High
Rischin/ 2021	Phase 3	Australia, New Zealand	189	49.2	**RT + CET**	RT + wCDDP (40 mg/ m2)	RT + CET (400/250 mg/m2)	70	III/IV (100)	100	Oropharynx (100 %)	3y FFS	Low
Hitt/2022	Phase 3	Spain	407	41.1 vs 43.9	**RT + CET**	ICT (TCF regimen x3 cycles) CET (400/250 MG/M2) + RT (202)	ICT (TCF regimens x3 cycles) 3wCDDP (100 mg/ m2) + RT (205)	70	III/IV (100)	/	Oropharynx (43 %), Oral cavity (17 %), Hypopharynx (18 %), Larynx (21 %)	OS	Low
Patil/2023	Phase 3	India	356	/	**RT + wDOCE**	wDocetaxel (15 mg/ m2) + RT	RT	70 Gy (definitive), 60 (adjuvant), 46-50G (N-neck)	III/IV (100)	3.8 % vs 4.2 %	Oral cavity (37 %), Oropharynx (28 %), Hypopharynx (17 %), Larynx (15 %), CUP (3 %)	2y DFS	Low
Tao/2023	Phase 3	France	131	25.8	**RT + PEMBRO**	PEMBRO (200 mg q3w) + RT	CET (400/ 250 mg/ m2) + RT	69.96	III/IV (100)	100	Oropharynx (60 %), Hypopharynx (22 %), Larynx (11 %)	PFS	Low
Mell/2024	Phase 2–3	US	186	6.4	**RT + DURVA**	RT + DURVA (1500 mg q4 weeks)	RT + CET (400/250 MG/M2)	70	III/IV (100)	59 % VS 56 %	Oropharynx (52 %), Hypopharynx (12 %), Larynx (26 %)	OS	Low
Browman/ 1994	Phase 3	Canada	175	42	**RT + 5FUic**	RT + 5FUic (1200 mg/ m2 x 3 days)	RT + PLAC	66	III/IV (100)	–	Oropharynx (42 %), Larynx (27 %)	OS	Low

Panitumumab (PANI); Cetuximab (CET); Carboplatin (CARBO); hyperfractionated RT (HfxRT); accelerated RT (acc RT); pembrolizumab (PEMBRO); 5-Fluorouracil (5FU); mitomycin (MMC), paclitaxel (PLAC), methotrexate (MTX), CUP (carcinoma of unknown primary; weekly (w); Hydroxiurea (HU); durvalumab (DURVA); Docetaxel + Cisplatin + 5Fluorouracil (TCF).

	Treatment	SUCRA (Rank 17 Bes
1	CET + CDDP + RT	0.86
2	<3wCDDP + RT	0.75
3	3wCDDP + RT	0.71
4	wDOCE + RT	0.7
5	nonCDDP/5FU + CET + RT	0.67
6	CBDCA + RT	0.67
7	nonCDDP/5FU + RT	0.64
8	PEMBRO + RT	0.62
9	Nimotuzumab + RT	0.59
10	5FUic + RT	0.57
11	MMC + RT	0.54
12	PANI + RT	0.52
13	CET + RT	0.4
14	MTX + RT	0.4
15	CDDP/5FU + RT	0.34
16	RT	0.32
17	DURVA + RT	0.26

Fig. 2a. SUCRA ranking of various treatments for overall survival outcome (SUCRA scores estimate the probability that a treatment is among the most effective options, ranging from 0% (least effective) to 100% (most effective). Higher SUCRA values suggest better ranking in terms of efficacy for the specified endpoint). CET: cetuximab; 3wCDDP: 3-weekly cisplatin; CBDCA; carboplatin; nonCDDP/5FU: carboplatin/5Fluorouracil; MTX: methotrexate; DURVA: durvalumab; PANI: panitumumab; MMC: mitomycin C; PEMBRO: pembrolizumab; wDOCE: weekly docetaxel; <3wCDDP: weekly or daily cisplatin; RT: radiotherapy; 5FUic: 5Fluorouracil continuos infusion.

hematologic toxicity. These findings confirm CARBO's relevance for patients unable to tolerate CDDP, though further research is needed to optimize its integration with modern RT techniques (weekly vs triweekly schedules).

Mitomycin C and MTX have also been studied in concurrent regimens for squamous cell cancers. Budach et al. demonstrated that MMC with hyperfractionated RT improves local response rates and reduces acute toxicities like mucositis compared to RT alone. However, Gupta et al. reported that MTX, while improving local control and survival, was associated with more severe mucosal reactions and higher intercurrent deaths. These findings highlight the need for careful patient selection when incorporating these agents [30,34]. Given their limited use in contemporary practice and lack of head-to-head comparisons with current regimens, MMC-based strategies should not be interpreted as preferred alternatives in today's clinical setting.

Weekly docetaxel combined with RT stands out as a promising alternative for patients ineligible for CDDP, offering notable efficacy in controlling disease progression with manageable safety profiles. The NMA ranks weekly docetaxel + RT among the top treatments for PFS and LRC, reinforcing its capacity to delay disease recurrence. A Phase III trial by Patil et al. demonstrated significant improvements in disease-free survival (DFS) and median OS compared to RT alone, though adverse events like grade 3 mucositis necessitate vigilant monitoring [23]. Weekly docetaxel's dosing schedule reduces cumulative toxicity, making it suitable for patients with poor performance status or high disease burden.

In order to increase treatment activity while maintaining tolerability, other treatment combinations are under evaluation. Retrospective and prospective phase 2, non-randomized clinical trials showed promising results in terms of safety and survival with CARBO and paclitaxel combined with RT in the LA HNSCC setting; [43–46] on the other hand, combinations of CARBO + 5FU did not guarantee good tolerability. Thus, it is necessary to offer differing options to physicians and patients in order to maintain adequate tumor control even in platinum-ineligible

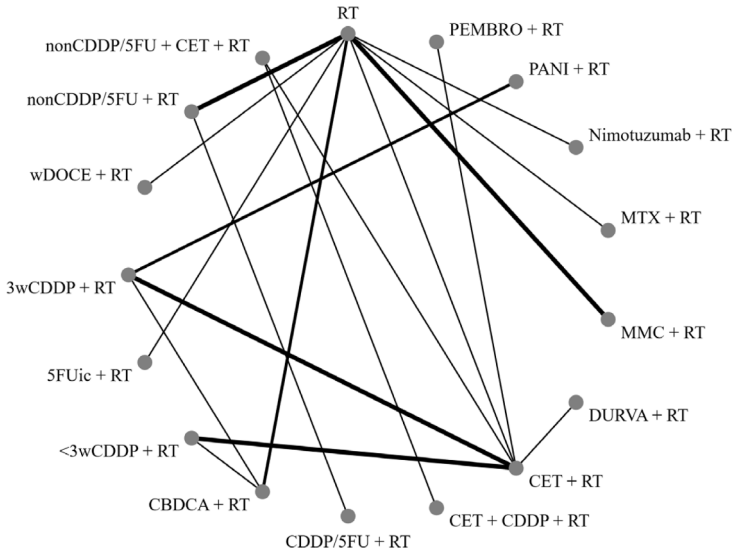

Fig. 2b. Different treatment compared for overall survival outcome.

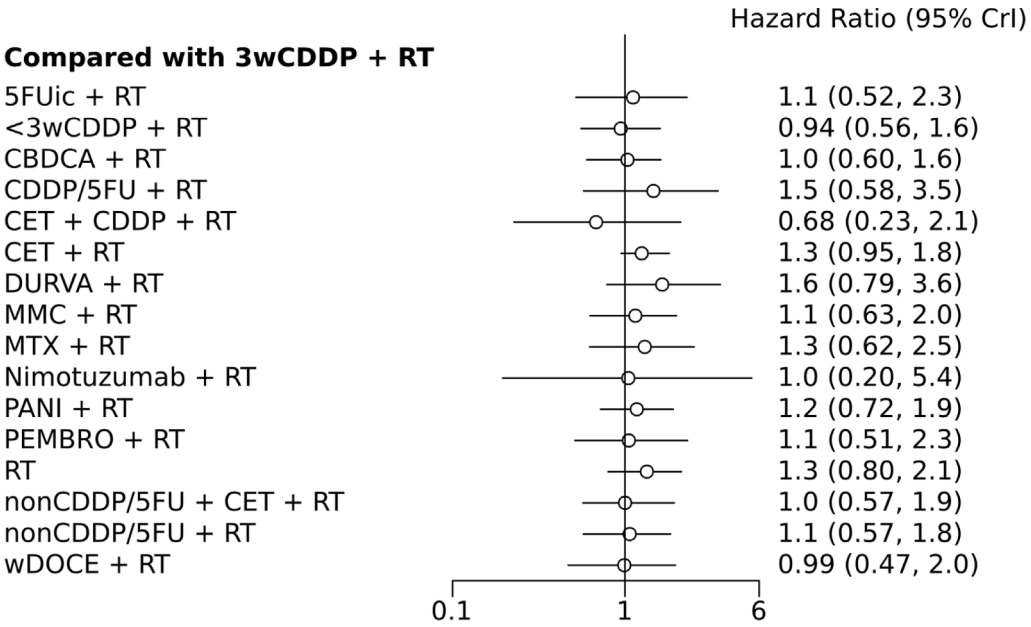

Fig. 2c. Forest plot for comparison of triweekly-cisplatin + RT with other RT + systemic agents. CET: cetuximab; 3wCDDP: 3-weekly cisplatin; CBDCA; carboplatin; nonCDDP/5FU: carboplatin/5Fluorouracil; MTX: methotrexate; DURVA: durvalumab; PANI: panitumumab; MMC: mitomycin C; PEMBRO: pembrolizumab; wDOCE: weekly docetaxel; <3wCDDP: weekly or daily cisplatin; RT: radiotherapy; 5FUic: 5Fluorouracil continuous infusion.

patients [47].

The subset of HPV-positive HNSCC represents a distinct clinical entity, typically associated with better prognoses due to favorable treatment responses. Strategies for HPV + HNSCC emphasize de-escalation to minimize toxicity while preserving efficacy, without encouraging results with other drugs than cisplatin so far [48]. This NMA confirms cetuximab's overall poor performance in OS, PFS, and LRC metrics, indicating its limited utility. Future research should explore biomarkers to refine patient selection for de-escalation strategie [49].

Additionally, modern adaptive RT techniques, such as intensity-modulated radiotherapy (IMRT) and proton therapy, or the selection of different treatment intensities incorporating novel functional imaging modalities offer new opportunities to reduce toxicities associated with combined regimens. These advancements may enhance the therapeutic index of both CDDP and non-CDDP regimens, especially in anatomically complex or high-risk cases. While these techniques represent current standards of care, their integration with systemic agents holds promise for refining multimodal approaches to HNSCC management. The integration of novel treatment strategies extends beyond RT and systemic agents [50,51].

Emerging research into the tumor microenvironment highlights potential targets for improving therapeutic efficacy. For instance, combining ICIs with agents targeting hypoxia pathways or angiogenesis could amplify the antitumor response initiated by RT. Such combinations may also mitigate resistance mechanisms often encountered with monotherapy. Furthermore, adaptive immune modulation through personalized vaccination strategies or tumor-infiltrating lymphocyte (TIL) therapies is under active investigation, potentially redefining the treatment landscape for advanced HNSCC [52,53].

This study has several limitations. The inclusion of trials with varying disease stages and subsites reduces generalizability. Furthermore, older RT techniques used in earlier studies may have been surpassed by

Rank	Treatment	Total
1	MMC/5FU + RT	0.83
2	MTX + RT	0.80
3	wDOCE + RT	0.79
4	nonCDDP/5FU + RT	0.74
5	<3wCDDP + RT	0.73
6	5FUic + RT	0.67
7	CET + CDDP + RT	0.59
8	CBDCA + RT	0.47
9	3wCDDP + RT	0.47
10	RT	0.45
11	nonCDDP/5FU + CET + RT	0.32
12	PANI + RT	0.24
13	PEMBRO + RT	0.24
14	CET + RT	0.08
15	DURVA + RT	0.06

Fig. 3a. SUCRA ranking of various treatments for progression-free survival outcome (SUCRA scores estimate the probability that a treatment is among the most effective options, ranging from 0% (least effective) to 100% (most effective). Higher SUCRA values suggest better ranking in terms of efficacy for the specified endpoint). CET: cetuximab; 3wCDDP: 3-weekly cisplatin; CBDCA; carboplatin; nonCDDP/5FU: carboplatin/5Fluorouracil; MTX: methotrexate; DURVA: durvalumab; PANI: panitumumab; MMC: mitomycin C; PEMBRO: pembrolizumab; wDOCE: weekly docetaxel; <3wCDDP: weekly or daily cisplatin; RT: radiotherapy; 5FUic: 5Fluorouracil continuous infusion.

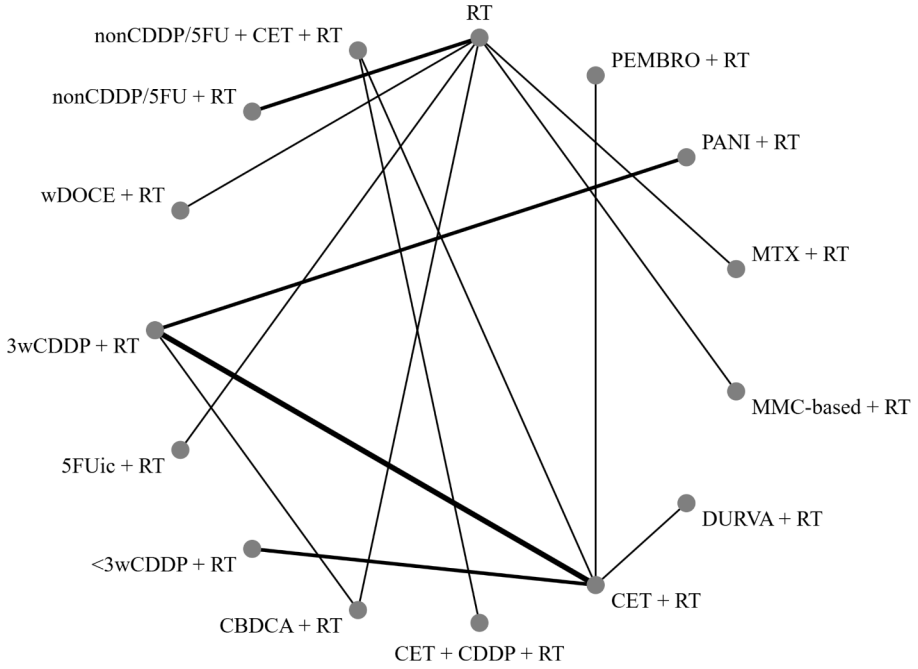

Fig. 3b. Different treatment compared for for progression-free survival outcome.

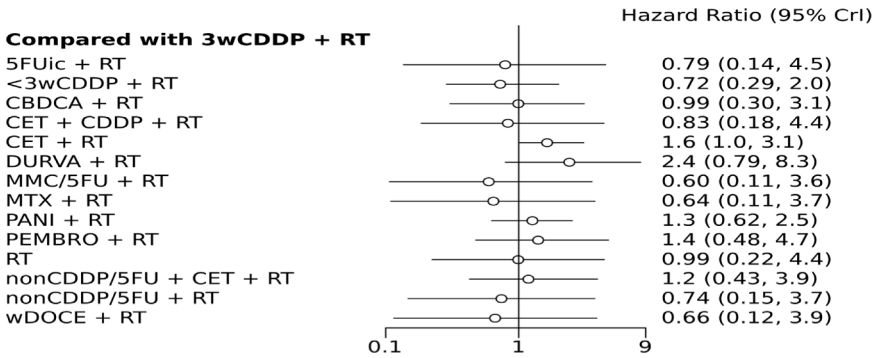

Fig. 3c. Forest plot for comparison of triweekly-cisplatin + RT with other RT + systemic agents. CET: cetuximab; 3wCDDP: 3-weekly cisplatin; CBDCA; carboplatin; nonCDDP/5FU: carboplatin/5Fluorouracil; MTX: methotrexate; DURVA: durvalumab; PANI: panitumumab; MMC: mitomycin C; PEMBRO: pembrolizumab; wDOCE: weekly docetaxel; <3wCDDP: weekly or daily cisplatin; RT: radiotherapy; 5FUic: 5Fluorouracil continuous infusion.

Rank	Treatment	Total Probability
1	MMC/5FU + RT	0.97
2	wDOCE + RT	0.93
3	CBDCA + RT	0.92
4	nonCDDP/SFU + RT	0.89
5	MTX + RT	0.90
6	CDDP/5FU + RT	0.81
7	RT	0.69
8	<3wCDDP + RT	0.34
9	nonCDDP/SFU + CET + RT	0.33
10	3wCDDP + RT	0.09
11	PEMBRO + RT	0.05
12	PAN + RT	0.03
13	CET + RT	0.02
14	DURVA + RT	0.02

Fig. 4a. SUCRA ranking of various treatment for locoregional control outcome (SUCRA scores estimate the probability that a treatment is among the most effective options, ranging from 0% (least effective) to 100% (most effective). Higher SUCRA values suggest better ranking in terms of efficacy for the specified endpoint). CET: cetuximab; 3wCDDP: 3-weekly cisplatin; CBDCA; carboplatin; nonCDDP/5FU: carboplatin/5Fluorouracil; MTX: methotrexate; DURVA: durvalumab; PANI: panitumumab; MMC: mitomycin C; PEMBRO: pembrolizumab; wDOCE: weekly docetaxel; <3wCDDP: weekly or daily cisplatin; RT: radiotherapy; 5FUic: 5Fluorouracil continuous infusion.

current methods, potentially affecting the observed efficacy of systemic agents combined with RT. Heterogeneity in follow-up duration and patient subsites also complicates the interpretation of results. Despite these challenges, alternatives like CARBO and docetaxel offer viable options for patients ineligible for CDDP, mainly when disease burden necessitates effective control. The inherent complexity of NMAs introduces additional challenges. Indirect comparisons rely heavily on the consistency of underlying data, and any disparities in trial designs or endpoints may affect the robustness of conclusions. Also, while most studies reported OS, a subset lacked sufficient data on PFS or LRC, which led to their exclusion from those specific analyses. As a result, each network was constructed using only those trials and treatment nodes with available and analyzable outcome data, in accordance with NMA methodology. Additionally, the lack of individual patient data limits the ability to perform subgroup analyses that could refine treatment recommendations for specific populations (e.g subsites, HPV status). Future studies should strive to address these gaps by incorporating harmonized protocols and leveraging real-world evidence. Finally, while SUCRA rankings provide a probabilistic hierarchy of treatment efficacy, they do not reflect statistical uncertainty and lack associated confidence or credible intervals. This is particularly relevant in our network, where many treatment nodes are weakly connected through a single comparator, limiting the reliability of indirect comparisons and undermining robust inconsistency testing. The apparent absence of inconsistency should therefore be interpreted with caution, as sparsely connected networks may lack the statistical power to detect true inconsistency across nodes.

Emerging agents and combinations continue to expand the therapeutic landscape for HNSCC. Trials integrating immunotherapeutics with RT, such as KEYNOTE-412 and NRG-HN004 trials, substantially

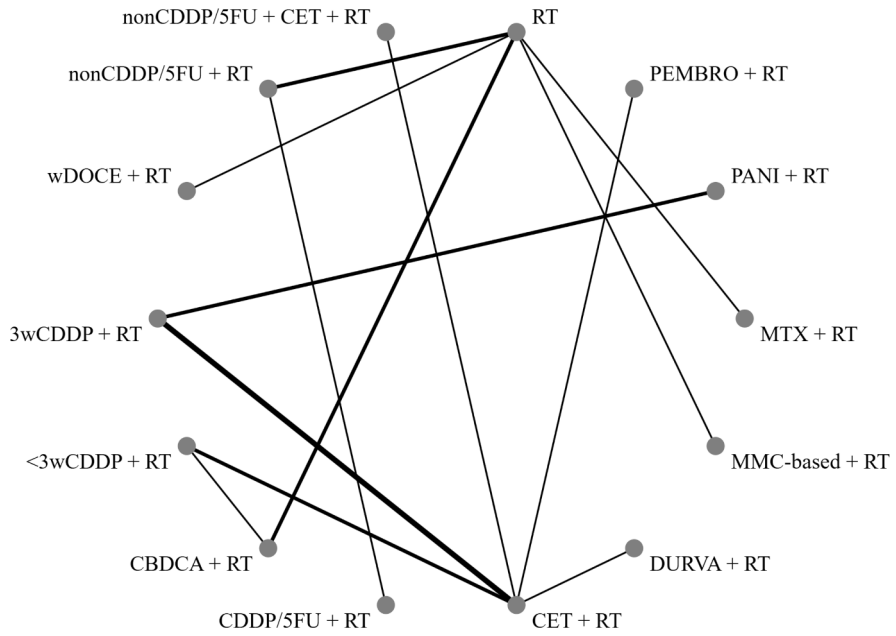

Fig. 4b. Different treatment compared for locoregional control outcome.

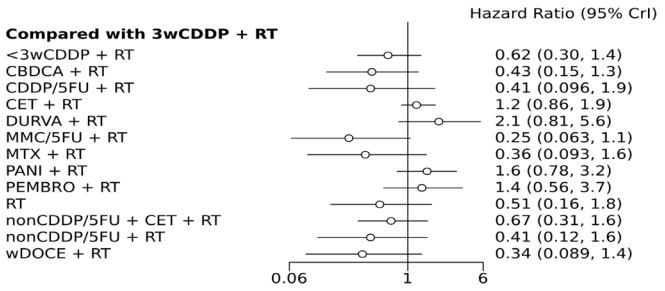

Fig. 4c. Forest plot for comparison of triweekly-cisplatin + RT with other RT + systemic agents. CET: cetuximab; 3wCDDP: 3-weekly cisplatin; CBDCA; carboplatin; nonCDDP/5FU: carboplatin/5Fluorouracil; MTX: methotrexate; DURVA: durvalumab; PANI: panitumumab; MMC: mitomycin C; PEMBRO: pembrolizumab; wDOCE: weekly docetaxel; <3wCDDP: weekly or daily cisplatin; RT: radiotherapy; 5FUic: 5Fluorouracil continuous infusion.

failed to show any advantages; however, KEYNOTE 689 showed promising preliminary data of pembrolizumab in neoadjuvant and adjuvant settings, highlighting how the use of immunotherapy in the LA setting may be a matter of timing. The trial demonstrated a significant improvement in EFS for patients receiving pembrolizumab. Specifically, the median EFS was 51.8 months in the pembrolizumab arm compared to 30.4 months in the standard-of-care arm, corresponding to a hazard ratio (HR) of 0.73 (95 % CI, 0.58–0.92; P = 0.004). The safety profile of pembrolizumab was consistent with previous studies, with no new safety signals identified [54]. Future research should prioritize dosing optimization, biomarker selection, long-term survival assessment, and novel agent combinations to maximize efficacy.

As NMAs synthesize evidence, they prove invaluable for guiding clinical decisions. By integrating novel agents and fostering biomarker-driven strategies, treatment paradigms can better meet the unique needs of HNSCC patients. Additionally, exploring the integration of systemic agents with advanced RT techniques and leveraging biomarkers for precise stratification could further optimize outcomes. Ultimately, the careful consideration of efficacy, safety, and patient-specific factors will enable the safe and effective implementation of alternative chemotherapy regimens in advanced HNSCC cases.

In summary, CDDP-based CRT remains the most effective standard for stage III-IV, LA-HNSCC. No alternative concurrent agent demonstrated superior efficacy. However, in CDDP-ineligible patients, weekly docetaxel and CARBO-based regimens appear to offer a favorable balance of disease control and tolerability. Although our analysis was not specifically designed to evaluate outcomes in CDDP-ineligible patients, the results provide clinically useful insights into the relative efficacy of non-platinum agents when CDDP is not a viable option. In such cases, regimens like weekly docetaxel or CARBO (or older agents), which ranked highly in our network, may represent relevant alternatives to be considered in clinical decision-making, especially in the absence of clear guideline recommendations for this subset of patients. Some regimens such as MMC/5-FU, however, have historical relevance but limited applicability in current practice. Further studies are needed to evaluate novel agents, optimal sequencing strategies, and individualized treatment approaches, particularly incorporating biomarkers and toxicity risk profiles to refine systemic therapy selection in this complex patient population.

CRediT authorship contribution statement

Fausto Petrelli: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Formal analysis, Data curation, Conceptualization. **Francesca Trevisan:** Validation, Supervision, Data curation. **Massimiliano Nardone:** Validation, Supervision. **Daniela Carioli:** Validation, Data curation. **Angela Gasparini:** Validation, Data curation. **Chiara Bramati:** Validation, Data curation. **Lorenza Bruschieri:** Validation. **Valentina Riboldi:** Validation. **Vincenzo Capriotti:** Validation. **Agostina De Stefani:** Validation, Supervision. **Luigi Lorini:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Daniele Spada:** Validation, Data curation. **Veronica Lonati:** Validation. **Paolo Bossi:** Writing – review & editing, Writing – original draft, Visualization, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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