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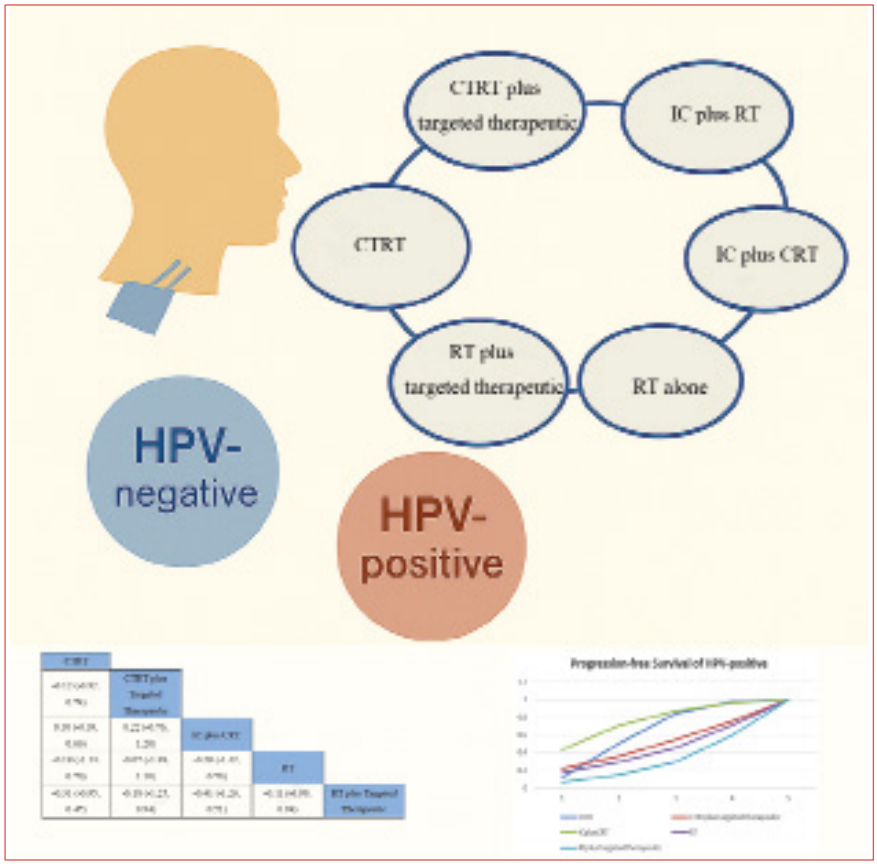
REVIEW

A systematic review and network meta-analysis of therapies for locally advanced head and neck squamous cell carcinoma with different HPV status



Cover figure. A systematic review and network meta-analysis of therapies for locally advanced head and neck squamous cell carcinoma with different HPV status.

Meixin Chen, Cheng Rao, Chang Lu, Shiyun Li, Dan Tian, Chunlin Zhang

Department of Otorhinolaryngology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China

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Correspondence
Chunlin Zhang
E-mail: echo_zcl1314@qq.com

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Summary

Infection with high-risk human papillomavirus (HPV) is considered a major cause of head and neck squamous cell carcinoma (HNSCC). However, the optimal treatment choice remains uncertain for both HPV-positive and HPV-negative locally advanced HNSCC (LA-HNSCC) in patients who are unable to tolerate surgery. To assess the effectiveness of various treatment strategies for HPV-positive and HPV-negative LA-HNSCC, this systematic review and network meta-analysis evaluated 4 databases and identified 31 relevant studies. The selected outcomes included overall survival, progression-free survival, locoregional control, distant metastasis, and disease-free survival. Hazard ratios with 95% confidence intervals were pooled for each outcome, and treatment modality rankings were calculated using the surface under the cumulative ranking curve. We found that induction chemotherapy combined with radiotherapy and chemoradiotherapy were optimal for HPV-positive

patients, while concurrent chemoradiotherapy and concurrent chemoradiotherapy combined with targeted therapy were most effective for HPV-negative patients. These findings highlight the importance of individualised treatment protocols and lay the groundwork for future clinical trials to optimise outcomes in LA-HNSCC.

Key words: human papillomavirus, head and neck, squamous cell carcinoma, cancer, treatment

Introduction

Head and neck squamous cell carcinomas (HNSCC) represents a major global health burden due to its high rates of morbidity and mortality, and is the sixth most common cancer worldwide [1], with the majority of cases being diagnosed at a locally advanced stage. Locally advanced HNSCC (LA-HNSCC) is defined by categories T3/4 and N1-3, with a clinical stage of III/IV [2,3]. LA-HNSCC is associated with poor prognosis, high recurrence rates, and low 5-year survival. Functional outcomes, such as speech and swallowing abilities, are often significantly impaired following long-term treatment, frequently necessitating multidisciplinary care [4-6]. Treatment for LA-HNSCC typically includes chemotherapy, surgery, and systemic therapy. However, certain cases of LA-HNSCC are unsuitable for surgical intervention due to the tumour's location, extent, or associated comorbidities. Compared with radiotherapy (RT) alone, concurrent chemoradiotherapy (CTRT) significantly improves survival rates and quality of life for patients with LA-HNSCC, and is generally considered as standard treatment [7-9]. However, chemotherapy, particularly platinum-based agents, often causes severe adverse events in the early stages of treatment [10,11]. Consequently, induction chemotherapy (IC) has been proposed for patients with LA-HNSCC although its benefits remain controversial [12,13]. Additionally, the epidermal growth factor receptor (EGFR) had been identified as a therapeutic target for HNSCC, and targeted therapies had been used in patients with LA-HNSCC, showing associations with improved prognosis [14,15]. Despite these promising findings, randomised trials indicate that cetuximab does not significantly improve overall survival (OS) in patients with LA-HNSCC. Importantly, the addition of cetuximab has been associated with poorer prognostic outcomes [16]. Currently, advances in understanding the tumour immune microenvironment have propelled immunotherapy to the forefront of research. Immunotherapy has achieved certain advancements in the treatment of recurrent or metastatic HNSCC [17]. However, it has not yet been incorporated as a first-line treatment for LA-HNSCC. Although current multimodal treatments have provided more therapeutic options for LA-HNSCC, concerns persist regarding the increased toxicity associated with these regimens. The optimal treatment approach for LA-HNSCC remains controversial.

Traditionally, tobacco and alcohol use have been regarded as key risk factors in the development and progression of HNSCC [18]. However, recent studies indicate that the incidence of HNSCC without abuse of tobacco and alcohol has been increasing over the years [19,20]. Infection with high-risk human papillomavirus (HPV) has become a major cause of HNSCC, alongside smoking and alcohol consumption [21]. Notably, HPV is predominantly associated with a subset of oropharyngeal squamous cell carcinoma (OPSCC). Globally, approximately 33% of OPSCC cases are HPV-positive [22]. Importantly, HPV-positive and HPV-negative HNSCC differ in clinical presentation, prognosis, and response to treatment [23,24]. HPV-positive HNSCC primarily occurrs in the oropharynx and is characterised by lower recurrence rates and better prognosis, prompting active exploration of treatment strategies for HPV-positive HNSCC [22,25]. In contrast, HPV-negative HNSCC is linked to traditional risk factors, such as tobacco and alcohol use, and typically follows a more aggressive course with poorer outcomes [4,25]. Globally, especially in developing countries, HPV-negative HNSCC remains the predominant form, driving continuous efforts to develop more aggressive combination therapies [26,27].

Despite advances in multimodal therapy, including surgery, RT, chemotherapy, and targeted agents, the optimal treatment approach for both HPV-positive and HPV-negative LA-HNSCC remains controversial. The lack of a standardised regimen tailored to the biological differences of these two subtypes poses significant clinical challenges [28,29]. Given these complexities, understanding how each therapeutic strategy performs in HPV-positive and HPV-negative LA-HNSCC is critical for advancing personalised treatments.

This systematic review and network meta-analysis aims to fill this gap by evaluating the following six treatment strategies: IC followed by RT, RT combined with targeted therapy, IC followed by chemoradiotherapy, CTRT, CTRT combined with targeted therapy, and RT alone. By comparing the relative efficacy of different treatment strategies for HPV-positive and HPV-negative LA-HNSCC, this analysis provides evidence-based insights to guide clinical decision-making.

Materials and methods

This systematic review has been prospectively registered in the International Prospective Register of Systematic Reviews (registration number: CRD42024590601) and was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [30].

Search strategy

We conducted the systematic review using four electronic databases: PubMed, EMBASE, Web of Science, and the Cochrane Library. The results were reported following the PRISMA guidelines, with the final search completed on July 20, 2024. The search employed key terms such as "head and neck squamous cell carcinoma," and "human papillomavirus." The complete search strategy is provided in the supplementary section (Tab. SI). There were no restrictions on language or publication type, and only full-text articles were considered. Additionally, we manually reviewed the reference lists of primary studies and review papers to identify other relevant studies.

Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were: (1) studies comparing different treatment strategies for HPV-positive and HPV-negative LA-HNSCC in pairwise comparisons; (2) phase II/III randomised controlled trials (RCTs); (3) patients diagnosed with LA-HNSCC (Stage III/IV); (4) no surgical treatment options; (5) HPV status determined through immunohistochemical detection of p16, in situ hybridisation, or real-time quantitative PCR targeting HPV nucleic acids.

Exclusion criteria were: (1) duplicate publications, abstract-only papers, editorial commentaries, letters, case reports, reviews, meta-analyses, and irrelevant titles or abstracts; (2) studies with incomplete or unclear data; (3) when patient populations overlapped between studies, only the most recent publication was included.

Quality assessment

We assessed the risk of bias using the Cochrane Collaboration's tool [31], covering domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases. Each study was classified as having a high, low, or unclear risk of bias. Two authors independently evaluated each domain, with a third author resolving any disagreements.

Data extraction

All data were independently collected by two reviewers. The following study characteristics were recorded for each trial: (1) study and patient characteristics, including staging, histology, and methods of HPV group classification; (2) number of patients per group and treatment regimens; and (3) reported outcome measures, including OS, progression-free survival (PFS), locoregional control (LRC), distant metastasis (DM), and disease-free survival (DFS).

Statistical analysis

The primary endpoint of our network meta-analysis was OS, with additional endpoints including PFS, LRC, DM, and DFS. For survival analysis, the preferred outcome measure was the unadjusted hazard ratio (HR) with the corresponding 95% confidence interval (CI). HR and 95% CI were extracted and transformed into log HR and corresponding standard error to obtain the Summary HR (SHR). When necessary HR were also derived from published survival curves by accurately extracting curve coordinates using digitisation software (DigitizeIt) [32]. These coordinates were then used to generate summary statistics according to Parmar's method [33]. Furthermore, the rankings of different treatment strategies were calculated by the surface under the cumulative ranking curve (SUCRA), which ranges from 0 to 1, with higher values indicating more favourable treatment outcomes.

The I^2 statistic was used to assess heterogeneity across studies, with values above 50% indicating high heterogeneity. Random effects were employed, using an identity link function and non-informative priors (uniform and normal distributions) to fit the model. Posterior distributions of the model parameters were obtained through 25,000 iterations, with a burn-in of 5,000 iterations and a thinning interval of 20. Convergence was assessed using the Brooks-Gelman-Rubin method. Posterior distributions were used to estimate the probabilities of each treatment being the best, second-best, and so on. Effect sizes in the Bayesian network meta-analysis were described using 95% credible regions (CR). The probability of each strategy being the best was calculated by ranking the relative efficacy of all interventions across iterations and determining the proportion of iterations in which each strategy ranked first. All analyses were conducted using the R packages "Metaphor" and "Gemtc" (https://www.r-project.org/). In addition, this study employed a meta-regression approach, using the proportion of smokers as the independent variable and the log-transformed HR (log HR) as the dependent variable. Separate meta-regression models were fitted for two clinical endpoints: OS and PFS. A random-effects linear meta-regression model was used to

evaluate the association between the proportion of smokers and survival outcomes by estimating the regression coefficients, standard errors, t values, p values, and 95% CI.

Results

Study selection

We searched four databases, retrieving a total of 21,903 initial records. After removing duplicates, 14,320 records remained. After screening titles and abstracts, 142 articles were identified for further evaluation. Following detailed assessment, 111 articles were excluded: 36 lacked extractable survival data, 29 involved non-locally advanced cancer, 35 did not perform HPV subgroup comparisons, 5 were systematic reviews, meta-analyses, commentaries, or letters, 2 were duplicates, and 4 had unavailable full texts. Ultimately, 31 studies were included [34-64]. Figure 1 presents the PRISMA flow diagram illustrating the study selection process.

Summary of included studies and quality assessment

A total of 31 studies were included, comprising 5779 cases with HPV-positive and 2921 cases with HPV-negative cancer. HPV diagnostic tests included immunohistochemical p16, PCR, and in situ hybridisation for detecting HPV nucleic acids. Three studies did not specify the methods used for HPV differentiation. Of the 31 studies, 3 involved three comparison groups, while the rest compared two groups. The interventions included CTRT, CTRT plus targeted therapy, RT alone, RT plus targeted therapy, IC plus CRT and IC plus RT. Table I outlines the study details and the interventions used for both control and experimental groups.

The overall quality of the included trials ranged from moderate to high, as depicted in Supplementary Figure 1 and Supplementary Figure 2, we identified a high risk of performance bias in 10 RCTs, while the remaining RCTs exhibited a low risk of bias. Most studies did not explicitly indicate whether allocation concealment was implemented, and some studies did not provide sufficient information to assess the presence of random sequence generation and selective reporting biases. In addition, smoking status data specific to HPV-positive patients were extracted, with 12 studies reporting smoking behaviour among individuals with HPV-positive HNSCC (Tab. II).

Outcomes

Overall survival

A total of 21 studies were included in this research, with 19 reporting HPV-positive HNSCC. Among these, two studies involved comparisons between three intervention groups, with a combined sample size of 4137 cases and overall heterogeneity was $I^2 = 18\%$ (Fig. 2A). Ten studies reported on HPV-negative cases, including one study comparing three intervention groups, with a total sample size of 1000 cases, and the overall heterogeneity was $I^2 = 15\%$ (Fig. 2B). In HPV-positive HNSCC, according to the forest plots and the league table, the results were not statistically significant (Figs. 3A, 4A). The ranking based on Surface Under the Cumulative Ranking curve (SUCRA) was as follows: IC plus RT (SUCRA = 83.3%) was the most effective in improving OS among HPV-positive patients, followed by RT plus Targeted Therapeutic (SUCRA = 78.7%), CTRT (SUCRA = 58.9%), IC plus CRT (SUCRA = 58%), RT alone (SUCRA = 42.6%), and CTRT plus Targeted Therapeutic (SUCRA = 30.3%) (Fig. 5A).

In HPV-negative HNSCC, as shown in the forest plots and league tables, the results did not indicate statistically significant differences (Figs. 3B, 4B). According to the ranking plot (Fig. 5B), among HPV-negative patients, CTRT (SUCRA = 82.7%) was the most effective, followed by CTRT plus Targeted Therapeutic (SUCRA = 71.9%), IC plus CRT (SUCRA = 58.1%), RT plus Targeted Therapeutic (SUCRA = 44.1%), and RT alone (SUCRA = 43%).

Progression-free survival

A total of 14 studies were included in the analysis, with 12 reporting on HPV-positive HNSCC, involving a total of 2183 cases. The overall heterogeneity was $I^2 = 20\%$ (Fig. 2C). Seven studies reported on HPV-negative cases, with a total of 1229 cases. The overall heterogeneity was $I^2 = 21\%$ (Fig. 2D). In HPV-positive HNSCC, according to the forest plots and the league table, the results were not statistically significant (Figs. 3C, 4C). According to the ranking plot (Fig. 5C), for HPV-positive HNSCC, IC plus CRT (SUCRA = 81.2%) and CTRT (SUCRA = 71.8%) were the most effective treatments, followed by CTRT plus Targeted Therapeutic (SUCRA = 56.7%), RT alone (SUCRA = 51.2%), and RT plus Targeted Therapeutic (SUCRA = 39.1%).

In HPV-negative HNSCC, according to the forest plots and the league table, the results were not statistically significant (Figs. 3D, 4D). According to the ranking plot (Fig. 5D), for HPV-negative HNSCC, the treatments were ranked as follows: CTRT (SUCRA = 84.4%), CTRT plus Targeted Therapeutic (SUCRA = 70.9%), and IC plus CRT (SUCRA = 44.5%).

Loco-regional control

A total of 5 studies were included, all of which reported on HPV-positive HNSCC with a total of 506 cases. The overall heterogeneity was $I^2 = 26\%$ (Fig. 2E). Five studies reported on HPV-negative cases, with a total of 497 cases. The over-

all heterogeneity was I^2 = 0% (Fig. 2F). In HPV-positive HNSCC, as shown in the forest plots and league tables, the results did not indicate statistically significant differences (Fig. 3E, 4E). According to the ranking plot for HPV-positive HNSCC (Fig. 5E), the treatments were ranked as follows: CTRT (SUCRA = 91.3%) was the most effective, followed by RT plus Targeted Therapeutic (SUCRA = 73.4%) and RT alone (SUCRA = 35.1%).

In HPV-negative HNSCC, as shown in the forest plots and league tables, the results did not indicate statistically significant differences (Figs. 3F, 4F). According to the ranking plot for HPV-negative HNSCC (Fig. 5F), the order is as follows: RT plus Targeted Therapeutic (SUCRA = 85.9%), CTRT (SUCRA = 85%), RT alone (SUCRA = 51.7%) and CTRT plus Targeted Therapeutic (SUCRA = 27.3%).

Distant metastases

A total of 7 studies were included in this research, with 4 reporting on HPV-positive HNSCC, involving a total of 1841 cases. The overall heterogeneity was I^2 = 30% (Fig. 2G). Three studies reported on HPV-negative cases, including one study comparing three intervention groups, with a total sample size of 616 cases and an overall heterogeneity of I^2 = 16% (Fig. 2H). In HPV-positive HNSCC, according to the forest plots and the league table, the results were not statistically significant (Figs. 3G, 4G). According to the ranking plot for HPV-positive HNSCC: IC plus CRT (SUCRA = 90.4%), RT alone (SUCRA = 78.2%), CTRT (SUCRA = 56.9%) and RT plus Targeted Therapeutic (SUCRA = 24.4%) (Fig. 5G).

In HPV-related HNSCC, according to the forest plots and the league table, the results were not statistically significant (Figs. 3H, 4H). According to the ranking plot for HPV-negative cases (Fig. 5H), CTRT plus targeted therapy (SUCRA = 84.3%) ranks highest, followed by RT plus targeted therapy (SUCRA = 77.2%), RT alone (SUCRA = 53.7%), and CTRT (SUCRA = 34.7%).

Disease-free survival

A total of 6 studies were included in the research, with four reporting HPV-positive HNSCC, comprising 397 cases in total. The overall heterogeneity was I^2 = 35% (Fig. 2I). Three studies focused on HPV-negative cases, with a total of 410 cases and an overall heterogeneity of I^2 = 28% (Fig. 2J). In HPV-positive HNSCC, according to the forest plots and the league table, the results were not statistically significant (Figs. 3I, 4I). For HPV-positive HNSCC, the ranking based on SUCRA was as follows (Fig. 5I): RT alone (SUCRA = 65.5%) and CTRT (SUCRA = 65.5%) were the most effective treatments, followed by RT plus targeted therapy (SUCRA = 62.4%) and CTRT plus targeted therapy (SUCRA = 56.5%).

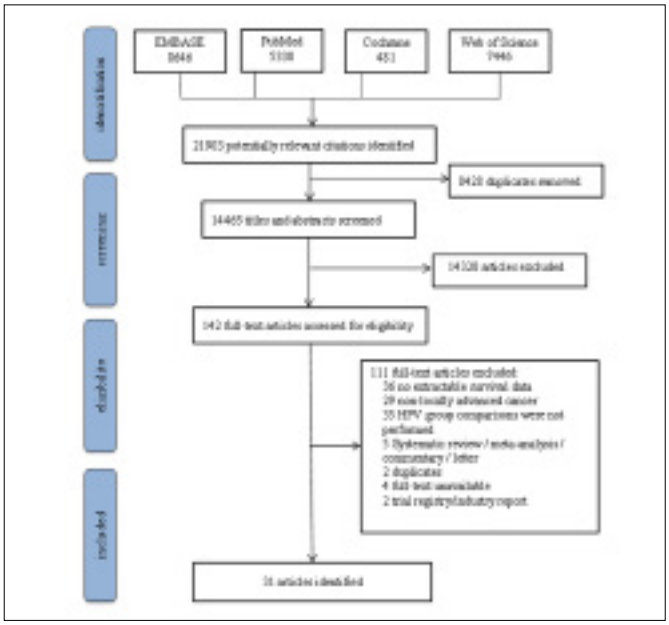

Figure 1. PRISMA flow diagram illustrating the study selection process.

In HPV-negative HNSCC, according to the forest plots and the league table, the results were not statistically significant (Figs. 3J, 4J). According to the ranking chart for HPV-negative HNSCC (Fig. 5J), the treatment hierarchy was as follows: CTRT plus targeted therapy (SUCRA = 85.7%), IC plus CRT (SUCRA = 81.7%) and CTRT (SUCRA = 32.4%). The meta-regression analysis yielded positive coefficients for both PFS and OS (0.34 and 0.45, respectively), indicating a possible association between higher smoking prevalence and increased hazard (Fig. 6). However, in the meta-regression analysis, both PFS and OS were associated with large standard errors and wide 95% CIs (PFS: −5.09 to 5.78; OS: −7.72 to 8.61), resulting in no statistically significant associations ($p > 0.05$) (Tab. III).

Discussion

Currently, LA-HNSCC continues to show high recurrence and metastasis rates, with poor prognosis, leading to ongoing debate regarding the optimal treatment strategy [6]. As a primary aetiological factor, HPV infection is correlated with prognosis of HNSCC [23,24]. HPV is predominantly associated with a subset of OPSCC. To date, no treatment regimen has been tailored to address the biological differences between HPV-positive and HPV-negative LA-HNSCC. This study systematically compared the outcomes of various therapeutic strategies for HPV-positive

Table I. Characteristics of included trials.

Author	Year	Experimental arm	Control arm	Control arm	
Harrington [34]	2012	CTRT plus targeted therapeutic	CTRT	/	
Mesía [35]	2015	CTRT	CTRT plus targeted therapeutic	/	
Strom [36]	2015	CTRT	RT plus targeted therapeutic	/	
Tang [37]	2015	RT plus targeted therapeutic	CTRT plus targeted therapeutic	CTRT	
Nien [38]	2016	CTRT	RT plus targeted therapeutic	/	
Ou [39]	2016	CTRT	RT plus targeted therapeutic	/	
Rosenthal [30]	2016	RT	RT plus targeted therapeutic	/	
Adkins [41]	2017	CTRT plus targeted therapeutic	CTRT	/	
Buglione [42]	2016	CTRT	RT plus targeted therapeutic	/	
Barney [43]	2018	CTRT	RT plus targeted therapeutic	/	
Onita [44]	2018	RT plus targeted therapeutic	CTRT	/	
Gillison [45]	2019	RT plus targeted therapeutic	CTRT	/	
Mehanna [46]	2019	CTRT	RT plus targeted therapeutic	/	
Patil [47]	2019	CTRT	CTRT plus targeted therapeutic	/	
Beckham [48]	2020	CTRT	RT plus targeted therapeutic	/	
Jeong [49]	2020	CTRT	RT plus targeted therapeutic	/	
Lee [50]	2021	CTRT plus targeted therapeutic	CTRT	/	
Rischin [51]	2021	RT plus targeted therapeutic	CTRT	/	
Yom [52]	2021	RT	CTRT	/	
Wong [53]	2023	CTRT	CTRT plus targeted therapeutic	/	
Sher [54]	2016	CTRT	IC plus RT	/	
Bhattasali [55]	2018	IC plus RT	CTRT	/	
Lorch [56]	2016	CTRT	IC plus RT	/	
Dobrosotskaya [57]	2013	IC plus RT	CTRT	/	
Mercke [58]	2023	IC plus RT	CTRT	/	
Geoffrois [59]	2018	IC plus RT	CTRT	/	
Golubev [60]	2023	IC plus RT	CTRT	/	
Hall [61]	2018	CTRT	RT	/	
Burtness [62]	2019	CTRT plus targeted therapeutic	CTRT	/	
De Felice [63]	2016	IC plus RT	CTRT	/	
Riaz [64]	2016	RT plus targeted therapeutic	CTRT	/	

RT radiotherapy; CTRT: concurrent chemoradiation therapy; IC plus CRT: induction chemotherapy plus chemoradiotherapy; IHC-p16: p16 immunohistochemistry; ISH: in situ hybridisation; PCR: polymerase chain reaction; OS: overall survival; PFS: progression-free survival; LRC: locoregional control; DM: distant metastasis; DFS: disease-free survival.

and HPV-negative LA-HNSCC across 5 key endpoints: OS, PFS, LRC, DM and DFS. These outcomes underscore the clinical importance of tailoring treatment strategies based on HPV status, as different patterns emerged between the two subtypes.

For OS, IC plus RT was the most effective therapeutic approach for HPV-positive HNSCC, while CTRT proved to be the best for HPV-negative HNSCC. For PFS, HPV-positive HNSCC demonstrated longer PFS compared to HPV-negative patients, with IC plus CRT being the most effective for

	Cancer site	Stage	Determination of HPV status	HPV-positive	HPV-negative	Evaluated endpoints		
	Oral cav	III/IVA	IHC-p16	7	30	PFS	/	/
	Oral cav	III/IVA	IHC-p16	42	57	PFS	OS	/
	Oral cav	III/IVA	IHC-p16	99	49	LRC	OS	/
	Oral cav	III/IV	IHC-p16	103	74	OS	/	/
	Oropharynx	III/IV	IHC-p16	339	0	OS	/	/
	Oral cav	III/IV (97%)	IHC-p16	88	177	PFS	LRC	/
	Oropharynx	III/IV	IHC-p16	107	63	PFS	OS	LRC
	Oropharynx	III/IV	IHC-p16	34	26	OS	/	/
	Oropharynx	III/IVA	IHC-p16	7	21	/	LRC	OS
	Oropharynx	III/IV	IHC-p16	205	0	OS	LRC	DFS
	Oropharynx	III	IHC-p16	291	0	DM	/	/
	Oropharynx	III/IV	IHC-p16	805	0	OS	PFS	DM
	Oropharynx	III/IV	IHC-p16	334	0	OS	/	/
	Oropharynx	III/IV	IHC-p16	24	187	/	PFS OS LRC DFS	
	Oropharynx	III/IV	IHC-p16	0	316	OS	DM	/
	Oropharynx	III/IV	IHC-p16	55	16	OS	/	/
	Oropharynx	III/IV	IHC-p16	338	459	PFS	/	/
	Oropharynx	III/IV	IHC-p16	182	0	OS	/	/
	Oropharynx	III/IV	IHC-p16	306	0	PFS	OS	DM
	Oropharynx	III/IV	IHC-p16	0	127	OS	PFS	DM
	Oropharynx	III/IV	PCR	984	815	OS	/	/
	Oropharynx	III/IV	IHC-p16	87	0	OS	PFS	DM
	Oropharynx	III/IV	IHC-p16 PCR	164	138	OS	PFS	/
	Oropharynx	III/IV	PCR	54	16	OS	/	/
	Oropharynx tonsil base of tongue	III/IV	IHC-p16 PCR	150	0	OS	PFS	/
	Oropharynx	III/IV	IHC-p16	45	127	PFS	/	/
	Oropharynx	III/IV	IHC-p16	27	0	PFS	/	/
	Oropharynx	III/IV (82%)	IHC-p16 ISH	352	173	DM	/	/
	Oropharynx hypopharynx larynx oral cavity	III/IV	IHC-p16	94	196	DFS	/	/
	Oropharynx	III/IV	/	0	27	DFS	/	/
	Oropharynx	III/IV	IHC-p16	182	0	OS	/	/

HPV-positive HNSCC and CTRT leading to the best results for HPV-negative HNSCC. In terms of LRC, HPV-positive HNSCC also fared better in loco-regional control, particularly with CTRT, which was the most effective in controlling local tumour growth. Conversely, in HPV-negative HNSCC, RT plus targeted therapies provided better loco-regional control, reflecting the need to address the more aggressive and widespread nature of HPV-negative HNSCC. In terms of DM, the patterns further differentiate the two subtypes. HPV-positive HNSCC experienced lower rates of distant

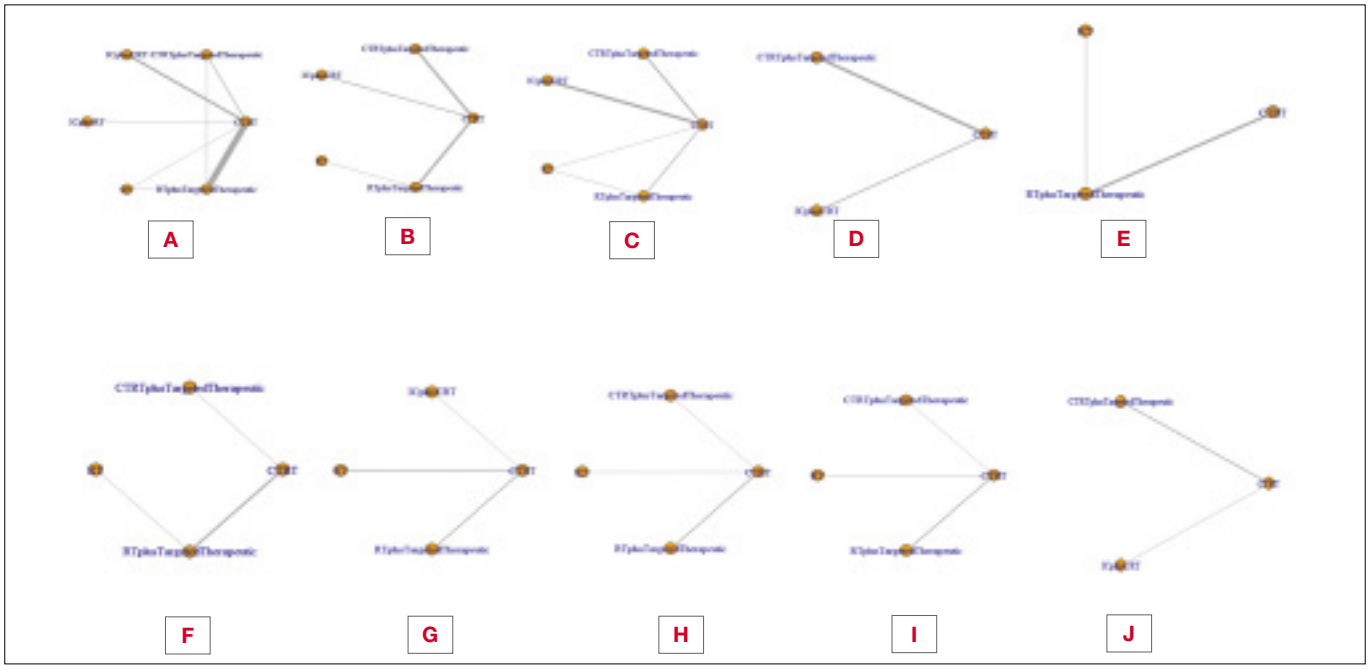

Figure 2. Network diagrams: (**A**) comparing overall survival of HPV-positive HNSCC patients with different treatment options; (**B**) network diagram comparing overall survival of HPV-negative HNSCC patients; (**C**) progression-free survival of HPV-positive HNSCC patients; (**D**) progression-free survival of HPV-negative HNSCC patients; (**E**) loco-regional control of HPV-positive HNSCC patients; (**F**) loco-regional control of HPV-negative HNSCC patients; (**G**) distant metastases of HPV-positive HNSCC patients; (**H**) distant metastases of HPV-negative HNSCC patients; (**I**) disease-free survival of HPV-positive HNSCC patients; (**J**) disease-free survival of HPV-negative HNSCC patients.

Table II. Distribution of smoking status among HPV-positive HNSCC.

Author	Year	Experimental arm	Control arm	Control arm	HPV-positive		
					Smoker	Nonsmoker	Evaluated endpoints
Tang [37]	2015	RT plus targeted therapeutic	CTRT plus targeted therapeutic	CTRT	103	74	/
Nien [38]	2016	CTRT	RT plus targeted therapeutic	/	177	162	/
Barney [43]	2018	CTRT	RT plus targeted therapeutic	/	205	0	DFS
Gillison [45]	2019	RT plus targeted therapeutic	CTRT	/	430	375	DM
Mehanna [46]	2019	CTRT	RT plus targeted therapeutic	/	154	180	/
Rischin [51]	2021	RT plus targeted therapeutic	CTRT	/	71	111	/
Yom [52]	2021	RT	CTRT	/	93	213	DM
Bhattasali [55]	2018	IC plus CRT	CTRT	/	18	69	DM
Mercke [58]	2023	IC plus CRT	CTRT	/	53	97	/
Geoffrois [59]	2018	IC plus CRT	CTRT	/	37	8	/
Ou [39]	2016	CTRT	RT plus targeted therapeutic	/	63	25	/
Golubev [60]	2023	IC plus CRT	CTRT	/	12	15	/

RT: radiotherapy; CTRT: concurrent chemoradiation therapy; IC plus CRT: induction chemotherapy plus chemoradiotherapy; DM: distant metastasis; DFS: disease-free survival.

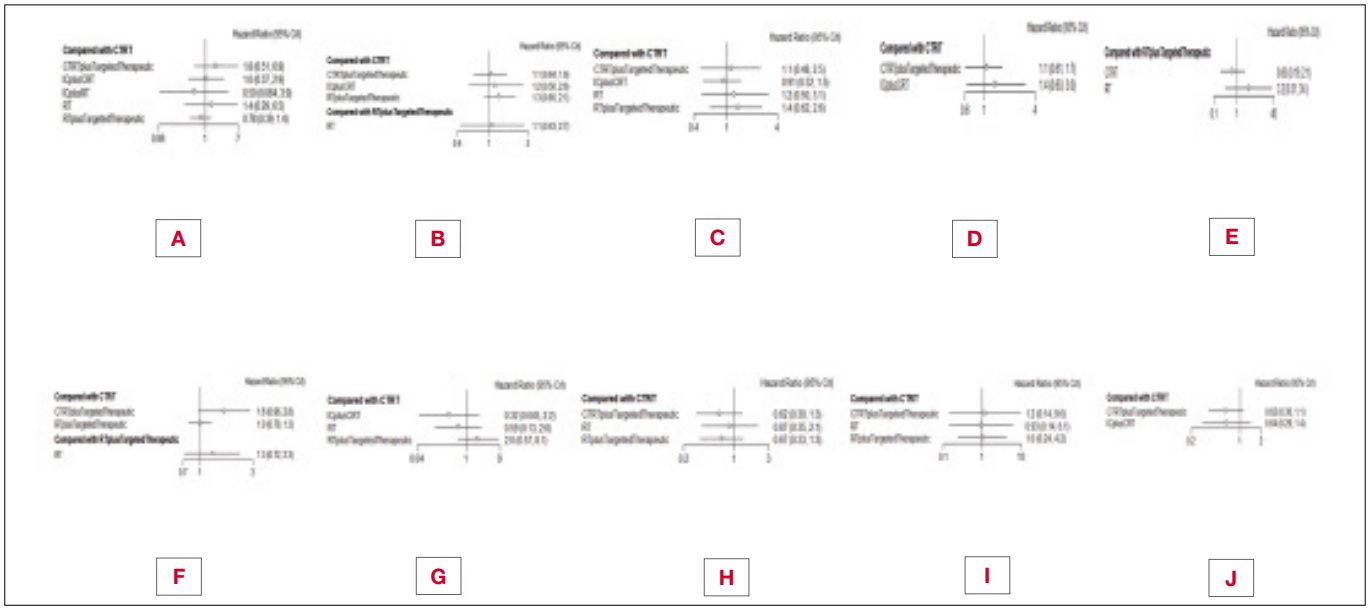

Figure 3. Forest plots: **(A)** showing overall survival for different treatments in HPV-positive head and neck squamous cell carcinoma (hazard ratios and 95% CI); **(B)** overall survival for different treatments in HPV-negative head and neck squamous cell carcinoma (hazard ratios and 95% CI); **(C)** progression-free survival for different treatments in HPV-positive head and neck squamous cell carcinoma (hazard ratios and 95% CI); **(D)** progression-free survival for different treatments in HPV-negative head and neck squamous cell carcinoma (hazard ratios and 95% CI); **(E)** loco-regional control for different treatments in HPV-positive head and neck squamous cell carcinoma (hazard ratios and 95%CI); **(F)** loco-regional control for different treatments in HPV-negative head and neck squamous cell carcinoma (hazard ratios and 95% CI); **(G)** distant metastases for different treatments in HPV-positive head and neck squamous cell carcinoma (hazard ratios and 95% CI); **(H)** distant metastases for different treatments in HPV-negative head and neck squamous cell carcinoma (hazard ratios and 95%CI); **(I)** disease-free survival for different treatments in HPV-positive head and neck squamous cell carcinoma (hazard ratios and 95% CI); **(J)** disease-free survival for different treatments in HPV-negative head and neck squamous cell carcinoma (hazard ratios and 95% CI).

metastasis, with IC plus CRT being the most effective in reducing DM. In contrast, HPV-negative HNSCC exhibited higher rates of distant metastasis, necessitating the use of CTRT plus targeted therapy to achieve better control. DFS outcomes also varied between HPV-positive and HPV-negative HNSCC. For HPV-positive HNSCC, RT alone or CTRT provided the most effective control, resulting in longer DFS. For HPV-negative HNSCC, CTRT plus targeted therapy was the most effective in improving DFS.

CTRT is considered the standard treatment regimen for LA-HNSCC [7], combining chemotherapy with radiotherapy to improve clinical prognosis. According to this study, CTRT showed the highest effectiveness in HPV-negative HNSCC compared with other treatment approaches. The addition of targeted therapy did not improve OS or PFS for HPV-negative LA-HNSCC, which may be attributed to the relative rarity of EGFR pathway alterations in HPV-negative LA-HNSCC [66-69]. However, given the more aggressive nature and broader spread of HPV-negative HNSCC, adding targeted therapy could potentially achieve better LRC and reduce DM, leading to improved survival and progression control. For HPV-positive LA-HNSCC, IC plus RT was more effective in improving OS than other treatment strategies. This enhanced outcome may be stemmed from HPV infection's impact on cell cycle and apoptosis pathways, as well as its effect on DNA damage response and repair mechanisms, which increases the tumour's responsiveness to DNA-damaging treatments like radiotherapy [70,71]. The addition of IC prior to RT or CTRT improved OS and PFS in HPV-positive HNSCC. IC enhanced the efficacy of subsequent RT and CTRT [12], the systemic control achieved through induction chemotherapy, followed by aggressive radiotherapy, played a critical role in reducing DM in HPV-negative HNSCC. HPV-positive LA-HNSCC, driven by viral oncogenesis, exhibits heightened radiosensitivity and immunogenicity, making these tumours more responsive to radiotherapy [70-72]. Consequently, unlike HPV-negative HNSCC, adding targeted therapy failed to significantly improve LRC, reduce DM, or maintain DFS in HPV-positive LA-HNSCC.

Elhalawani et al. identified that OS in HPV-positive HNSCC patients is significantly affected by tobacco exposure, particularly in those with a smoking history of more than 30

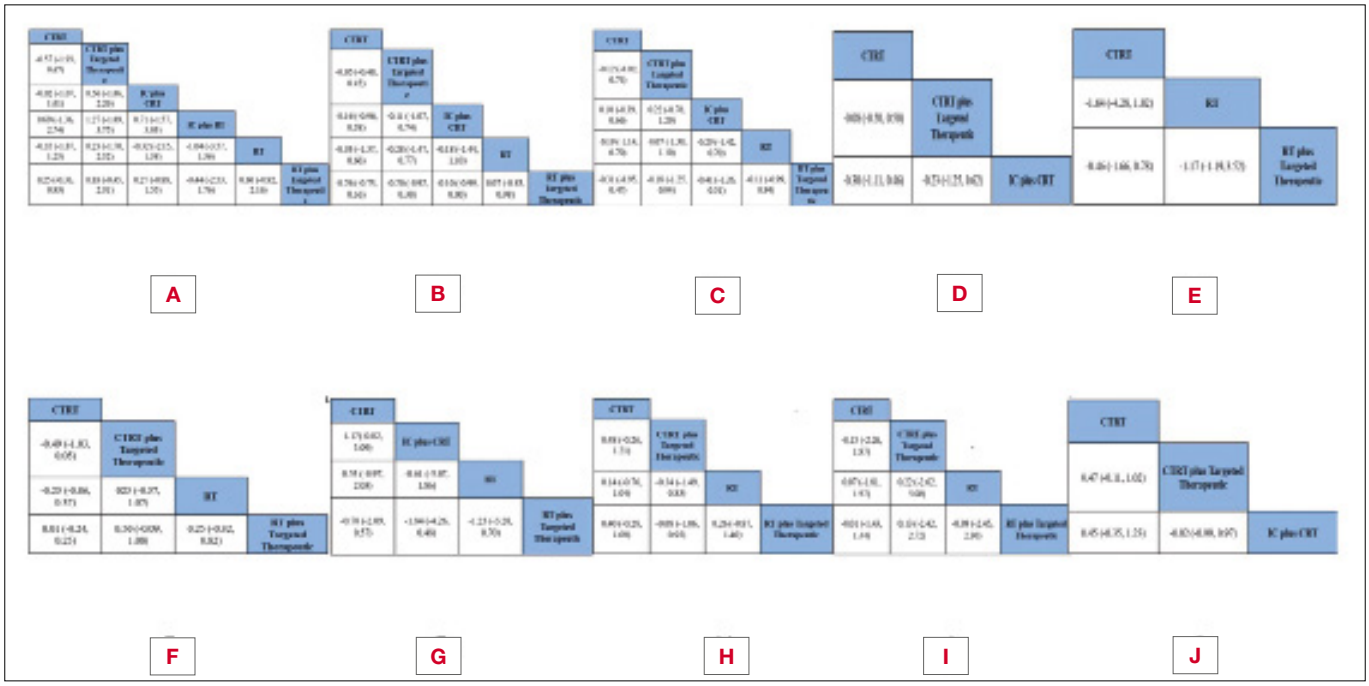

Figure 4. The league table: **(A)** showing overall survival for different treatments in HPV-positive head and neck squamous cell carcinoma (summary hazard ratios and 95% CI); **(B)** overall survival for different treatments in HPV-negative head and neck squamous cell carcinoma (summary hazard ratios and 95% CI); **(C)** progression-free survival for different treatments in HPV-positive head and neck squamous cell carcinoma (summary hazard ratios and 95% CI); **(D)** progression-free survival for different treatments in HPV-negative head and neck squamous cell carcinoma (summary hazard ratios and 95% CI); **(E)** loco-regional control for different treatments in HPV-positive head and neck squamous cell carcinoma (summary hazard ratios and 95% CI); **(F)** loco-regional control for different treatments in HPV-negative head and neck squamous cell carcinoma (summary hazard ratios and 95% CI); **(G)** distant metastases for different treatments in HPV-positive head and neck squamous cell carcinoma (summary hazard ratios and 95% CI); **(H)** distant metastases for different treatments in HPV-negative head and neck squamous cell carcinoma (summary hazard ratios and 95% CI); **(I)** the league table showing disease-free survival for different treatments in HPV-positive head and neck squamous cell carcinoma(summary hazard ratios and 95% CI); **(J)** disease-free survival for different treatments in HPV-negative head and neck squamous cell carcinoma (summary hazard ratios and 95% CI).

Table III. Meta-regression analysis.

Outcomes	Variable	Coefficient	Standard error	t	p > ltl	95% confidence interval lower	95% confidence interval upper
PFS	smoking	0.34	1.26	0.27	0.81	-5.09	5.78
OS	smoking	0.45	2.94	0.15	0.89	-7.72	8.61

pack-years [73]. However, among the studies included in this research, only 12 stratified HPV-positive patients by smoking status, and none conducted subgroup analyses specifically for HPV-positive smokers. Thus, the meta-regression was performed to assess the association between smoking prevalence and survival outcomes. Although the regression coefficients for PFS and OS were both positive (0.34 and 0.45, respectively), this analysis did not identify a statistically significant relationship between smoking prevalence and survival outcomes in HPV-positive HNSCC. The lack of statistical significance is likely due to the limited number of studies included in the regression analysis. Future studies that include high-quality research clearly reporting smoking stratification could help to further validate these findings.

Compared with previous meta-analyses, which often grouped all HNSCC cases together, this study's strengths lay in its stratification by HPV status, providing more specific insights into treatment efficacy. Earlier meta-analyses failed to account for the

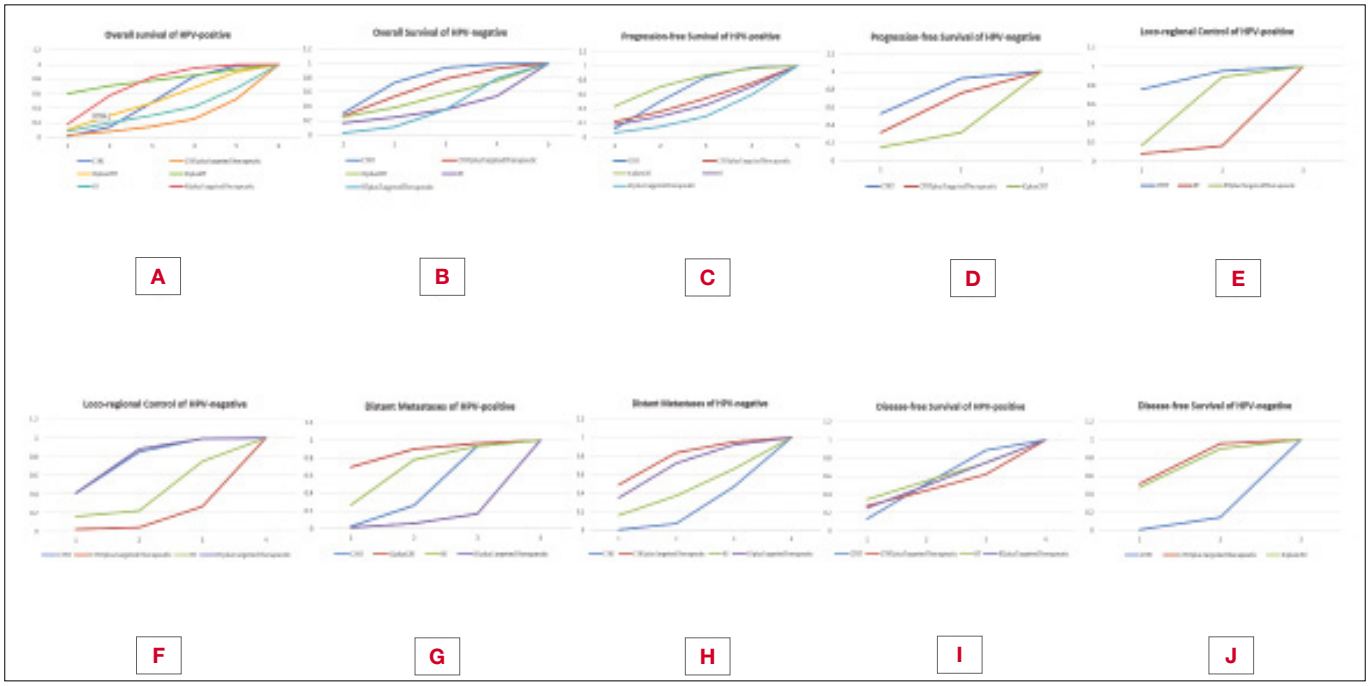

Figure 5. The rank plot: (**A**) showing overall survival for different treatments in HPV-positive head and neck squamous cell carcinoma; (**B**) overall survival for different treatments in HPV-negative head and neck squamous cell carcinoma; (C) progression-free survival for different treatments in HPV-positive head and neck squamous cell carcinoma; (**D**) progression-free survival for different treatments in HPV-negative head and neck squamous cell carcinoma; (**E**) loco-regional control for different treatments in HPV-positive head and neck squamous cell carcinoma; (**F**) loco-regional control for different treatments in HPV-negative head and neck squamous cell carcinoma; (**G**) distant metastases for different treatments in HPV-positive head and neck squamous cell carcinoma; (**H**) distant metastases for different treatments in HPV-negative head and neck squamous cell carcinoma; (**I**) disease-free survival for different treatments in HPV-positive head and neck squamous cell carcinoma; (**J**) disease-free survival for different treatments in HPV-negative head and neck squamous cell carcinoma.

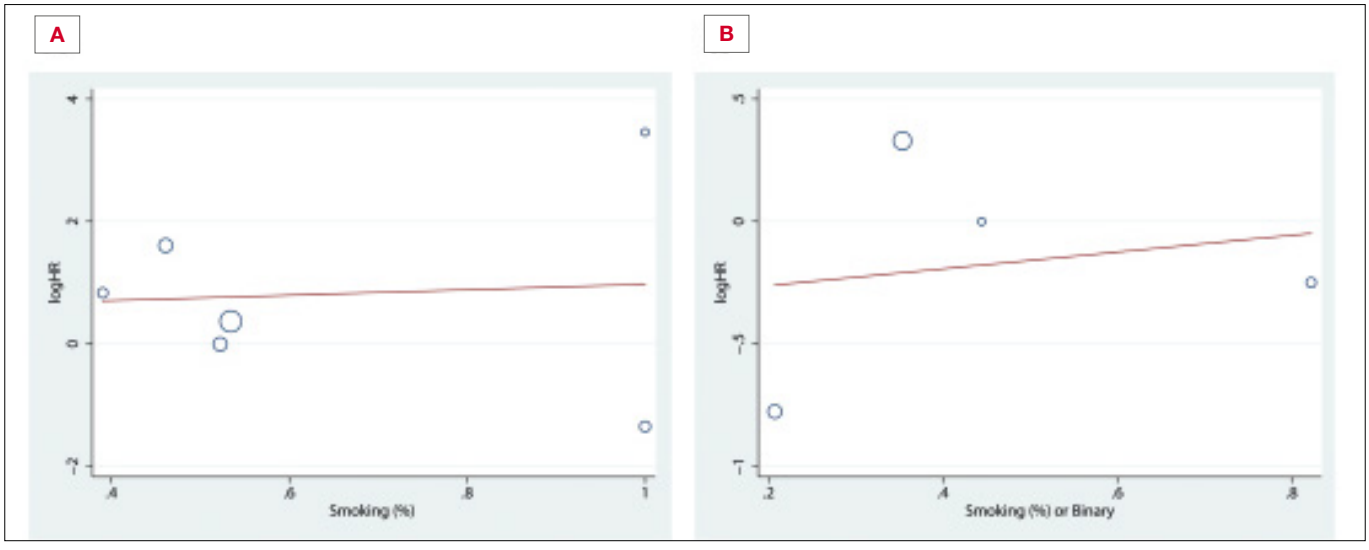

Figure 6. Meta-regression analysis of the association between smoking prevalence and survival outcomes in HPV-positive patients: (**A**) overall survival for HPV-positive HNSCC; (**B**) progression-free survival for HPV-positive HNSCC.

distinct biology of HPV-positive and HPV-negative disease, potentially leading to less informative treatment recommendations. Our use of a network meta-analysis framework also allowed for comprehensive comparisons across multiple therapeutic options, including indirect comparisons where direct head-to-head trials were unavailable. This approach enhanced the robustness of our findings and provides more nuanced guidance for clinical decision-making. Additionally, the inclusion of a broad range of outcomes, such as loco-regional control and distant metastases, offers a more complete picture of therapeutic efficacy.

Despite the strengths of this analysis, several limitations must be considered. First, although we conducted risk-of-bias assessments and included only moderate to high-quality studies, the potential for bias cannot be entirely excluded. The included studies differ in terms of patient follow-up duration, treatment methods, and other factors, which may affect the integration of results, especially regarding variations in HPV testing methods. Additionally, the lack of individual patient data was a limitation. Since this study is based on aggregated data rather than individual-level data, we failed to explore the potential relationships between patient characteristics (e.g., primary tumour site, age, gender, HPV viral load) and treatment outcomes in detail. Specifically, although HPV infection has been detected in hypopharyngeal, oral, and laryngeal squamous cell carcinoma, it is primarily associated with a subset of OPSCC [22,74]. Due to the inability of the included studies to accurately report sub-site data, subgroup analysis could not be performed. For instance, the studies by Harrington et al. and Mesía et al. did not specify the pathological subtypes of HPV-positive HNSCC [34,35]. Therefore, in future research, we will conduct further investigations by stratifying based on tumour site to explore the impact of this factor on the outcomes more effectively. Furthermore, although this study acknowledges the increasing role of immunotherapy in the management of recurrent or metastatic HNSCC, the exclusion of immunotherapy from our analysis represents a significant limitation. Consequently, future studies should investigate how immunotherapy could be effectively integrated with traditional treatments, such as CTRT. This combined approach holds promise for improving patient outcomes in HNSCC treatment.

Conclusions

In summary, this systematic review and network meta-analysis highlighted the importance of tailoring treatment strategies to the HPV status of HNSCC patients. IC plus RT and IC plus CRT emerged as leading strategies for HPV-positive patients, while CTRT and CTRT plus targeted therapeutic were most effective for HPV-negative cases. These findings underscore the need for personalised treatment protocols that account for the distinct biology of these subtypes. However, further research is required to refine these strategies, particularly in light of emerging therapies and the need to balance efficacy with toxicity.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

MC: data curation, formal analysis, methodology, software, writing – original draft; CZ: data curation, software, writing – original draft. CR: formal analysis, methodology, writing – original draft; CL: conceptualization, supervision, validation, visualization, writing – review & editing. All authors contributed to the manuscript and approved the final version for submission.

Ethical consideration

Not applicable.

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Supplementary Table I. Search strategy in PubMed, Embase, Cochrane and Web of Science.

Search strategy			
Pubmed	1	("Squamous Cell Carcinoma of Head and Neck"[Mesh])	12146
	2	("Squamous Cell Carcinoma of Head and Neck" OR "Head And Neck Squamous Cell Carcinomas" OR "Squamous Cell Carcinoma, Head And Neck" OR "Squamous Cell Carcinoma of the Head and Neck" OR "Head and Neck Squamous Cell Carcinoma" OR "HNSCC" OR "Carcinoma, Squamous Cell of Head and Neck" OR "Squamous Cell Carcinoma of the Larynx" OR "Laryngeal Squamous Cell Carcinoma" OR "Squamous Cell Carcinoma of Larynx" OR "Squamous Cell Carcinoma of the Nasal Cavity" OR "Oral Tongue Squamous Cell Carcinoma" OR "Hypopharyngeal Squamous Cell Carcinoma" OR "Oral Squamous Cell Carcinoma" OR "Oral Cavity Squamous Cell Carcinoma" OR "Oral Squamous Cell Carcinomas" OR "Squamous Cell Carcinoma of the Mouth" OR "Oropharyngeal Squamous Cell Carcinoma")	44,470
	3	(#1) OR (#2)	44470
	4	"Human Papillomavirus Viruses"[Mesh]	7628
	5	("Human Papillomavirus Viruses" OR "Human Papillomavirus Virus" OR "Papillomavirus Virus, Human" OR "Virus, Human Papillomavirus" OR "Human Papillomavirus" OR "Human Papillomaviruses" OR "HPV, Human Papillomavirus Viruses" OR "Human Papilloma Virus" OR "Human Papilloma Viruses" OR "Papilloma Virus, Human" OR "Virus, Human Papilloma" OR "HPV Human Papillomavirus" OR "HPV Human Papillomaviruses" OR "Human Papillomavirus, HPV" OR "Human Papillomaviruses, HPV" OR "HPV" OR "Wart virus")	67038
	6	(#4) OR (#5)	67038
	7	(#3) AND (#6)	5330
Embase	1	'head and neck squamous cell carcinomas' OR 'squamous cell carcinoma, head and neck' OR 'squamous cell carcinoma of the head and neck' OR 'head and neck squamous cell carcinoma' OR 'hnscc' OR 'carcinoma, squamous cell of head and neck' OR 'squamous cell carcinoma of the larynx' OR 'laryngeal squamous cell carcinoma' OR 'squamous cell carcinoma of larynx' OR 'squamous cell carcinoma of the nasal cavity' OR 'oral tongue squamous cell carcinoma' OR 'hypopharyngeal squamous cell carcinoma' OR 'oral squamous cell carcinoma' OR 'oral cavity squamous cell carcinoma' OR 'oral squamous cell carcinomas' OR 'squamous cell carcinoma of the mouth' OR 'oropharyngeal squamous cell carcinoma'	61774
	2	'human papillomavirus viruses' OR 'human papillomavirus virus' OR 'papillomavirus virus, human' OR 'virus, human papillomavirus' OR 'human papillomavirus' OR 'human papillomaviruses' OR 'hpv' OR 'hpv, human papillomavirus viruses' OR 'human papilloma virus' OR 'human papilloma viruses' OR 'papilloma virus, human' OR 'virus, human papilloma' OR 'hpv human papillomavirus' OR 'hpv human papillomaviruses' OR 'human papillomavirus, hpv' OR 'human papillomaviruses, hpv' OR 'wart virus' OR 'HPV'	100567
	3	#1 AND #2	8646
Cochrane	1	MeSH descriptor: [Squamous Cell Carcinoma of Head and Neck] explode all trees	485
	2	(Squamous Cell Carcinoma of Head and Neck):ti,ab,kw OR (Head And Neck Squamous Cell Carcinomas):ti,ab,kw OR (Squamous Cell Carcinoma, Head And Neck):ti,ab,kw OR (Squamous Cell Carcinoma of the Head and Neck):ti,ab,kw OR (Head and Neck Squamous Cell Carcinoma):ti,ab,kw	3643
	3	(HNSCC):ti,ab,kw OR (Carcinoma, Squamous Cell of Head and Neck):ti,ab,kw OR (Squamous Cell Carcinoma of the Larynx):ti,ab,kw OR (Laryngeal Squamous Cell Carcinoma):ti,ab,kw OR (Squamous Cell Carcinoma of Larynx):ti,ab,kw	3850
	4	(Squamous Cell Carcinoma of the Nasal Cavity):ti,ab,kw OR (Oral Tongue Squamous Cell Carcinoma):ti,ab,kw OR (Hypopharyngeal Squamous Cell Carcinoma):ti,ab,kw OR (Oral Squamous Cell Carcinoma):ti,ab,kw OR (Oral Cavity Squamous Cell Carcinoma):ti,ab,kw	1862
	5	(oral squamous-cell carcinomas):ti,ab,kw OR (Squamous Cell Carcinoma of the Mouth):ti,ab,kw OR (Oropharyngeal Squamous Cell Carcinoma):ti,ab,kw	1300
	6	#1 OR #2 OR #3 OR #4 OR #5	4697
	7	MeSH descriptor: [Human Papillomavirus Viruses] explode all trees	288
	8	(Human Papillomavirus Viruses):ti,ab,kw OR (Human Papillomavirus Virus):ti,ab,kw OR (Papillomavirus Virus, Human):ti,ab,kw OR (Virus, Human Papillomavirus):ti,ab,kw OR (Human Papillomavirus):ti,ab,kw	2797
	9	(Human Papillomaviruses):ti,ab,kw OR (HPV, Human Papillomavirus Viruses):ti,ab,kw OR (Human Papilloma Virus):ti,ab,kw OR (Human Papilloma Viruses):ti,ab,kw OR (Papilloma Virus, Human):ti,ab,kw	568
	10	(Virus, Human Papilloma):ti,ab,kw OR (HPV Human Papillomavirus):ti,ab,kw OR (HPV Human Papillomaviruses):ti,ab,kw OR (Human Papillomavirus, HPV):ti,ab,kw OR (Human Papillomaviruses, HPV):ti,ab,kw	2658
	11	(HPV):ti,ab,kw OR (Wart virus):ti,ab,kw	3953
	12	#7 OR #8 OR #9 OR #10 OR #11	4367
	13	#6 AND #12	481

Web of Science	1	TS=(Squamous Cell Carcinoma of Head and Neck)	23490
	2	((((((((((ALL=(Squamous Cell Carcinoma of Head and Neck)) OR ALL=(Head And Neck Squamous Cell Carcinomas)) OR ALL=(Squamous Cell Carcinoma of the Head and Neck)) OR ALL=(Squamous Cell Carcinoma of the Larynx)) OR ALL=(Laryngeal Squamous Cell Carcinoma)) OR ALL=(Squamous Cell Carcinoma of the Nasal Cavity)) OR ALL=(Oral Tongue Squamous Cell Carcinoma)) OR ALL=(Hypopharyngeal Squamous Cell Carcinoma)) OR ALL=(Oral Squamous Cell Carcinoma)) OR ALL=(Oral Cavity Squamous Cell Carcinoma)) OR ALL=(Squamous Cell Carcinoma of the Mouth)) OR ALL=(Oropharyngeal Squamous Cell Carcinoma)	40954
	3	#2 OR #1	40954
	4	TS=(Human Papillomavirus Viruses)	6505
	5	((((((((((ALL=(Human Papillomavirus Viruses)) OR ALL=(Human Papillomavirus Virus)) OR ALL=(Papillomavirus Virus, Human)) OR ALL=(Virus, Human Papillomavirus)) OR ALL=(Human Papillomavirus)) OR ALL=(Human Papilloma Viruses)) OR ALL=(Papilloma Virus, Human)) OR ALL=(Virus, Human Papilloma)) OR ALL=(HPV Human Papillomavirus)) OR ALL=(HPV Human Papillomaviruses)) OR ALL=(Human Papillomavirus, HPV)) OR ALL=(HPV)) OR ALL=(Wart virus)	40335
	6	#4 OR #5	40189
	7	#3 AND #6	7446
Search results			21903
duplicates removed			8428
Records remained			14465

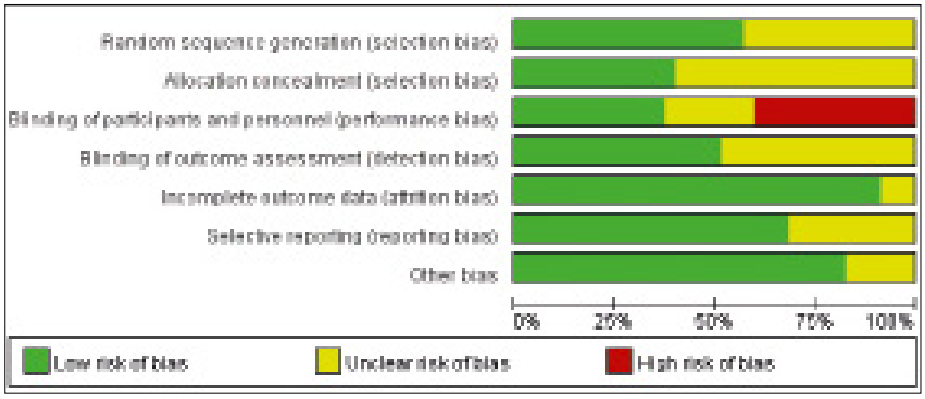

Figure S1. Risk of bias graph.

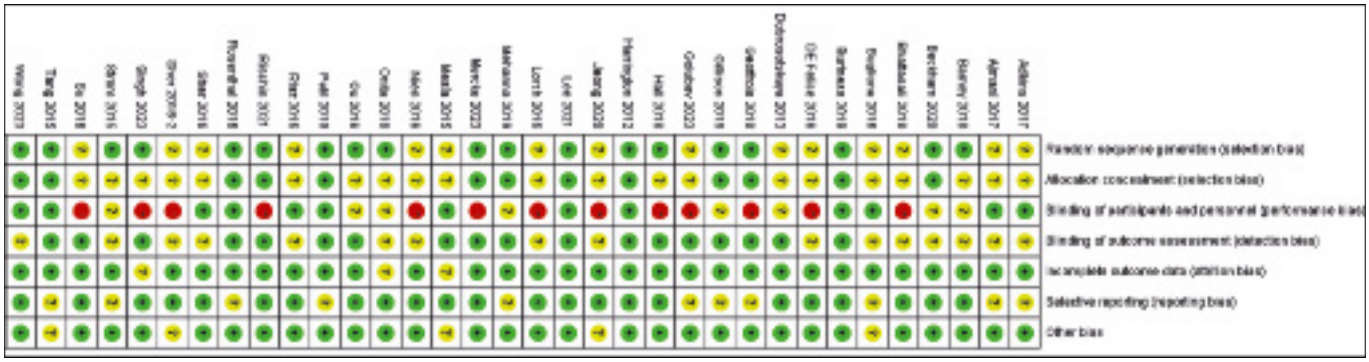

Figure S2. Risk of bias summary.