Evaluation of Neoadjuvant Immunotherapy Regimens for Head and Neck Squamous Cell Carcinoma: A Systematic Review and Single-arm and Network Meta-analysis

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Abstract

Background: Although multiple neoadjuvant immunotherapy (NIT) regimens have been explored in head and neck squamous cell carcinoma (HNSCC) recently, the optimal selection remains largely debatable. The present study aimed to comparatively evaluate clinical outcomes across various NIT regimens in resectable HNSCC.

Methods: We systematically searched studies published from 2000 to June 2025. Data encompassing treatment efficacy (objective response rate [ORR], pathological complete response [pCR], major pathological response [MPR], tumor downstaging), survival outcomes (e.g. overall survival [OS], disease-free survival [DFS]), and safety profiles (grade ≥3 immune-related adverse events [irAEs]) were pooled and analyzed from eligible studies. Subsequently, network meta-analysis (NMA) with surface under the cumulative ranking curve (SUCRA) was implemented to comparatively evaluate therapeutic regimens across studies.

Results: A total of 44 studies (7 randomized controlled trials and 39 single-armed trials) involving 1,688 patients were included. Pooled analysis revealed superior treatment response with immunochemotherapy (IC) versus alternative regimens: ORR=80% (0.70-0.88), pCR=40% (0.35-0.44), MPR=64% (0.59-0.69), and pathological downstaging=79% (0.71-0.86), complemented by favorable survival (2-year OS=91% [0.86-0.94]; 2-year DFS=90% [0.83-0.94]). NMA of 7 RCTs demonstrated that IC conferred significant improvements in pCR and downstaging rates compared to mono-immunotherapy, immune-targeted therapy, and dual-immunotherapy. Additionally, IC trended towards better ORR, MPR, and 2-year DFS, though the differences failed to attain statistical significance. SUCRA analysis consistently ranked IC highest across all evaluated efficacy endpoints.

Notably, while SUCRA analysis ranked IC highest for irAE risk, NMA revealed no significant differences in the incidence rates across regimens.

Conclusions: Our findings establish neoadjuvant IC as the optimal regimen for achieving pCR and tumor downstaging in HNSCC patients, thereby providing robust evidence to support its clinical prioritization and assist in treatment decision-making. Nevertheless, further high-quality trial validation is warranted.

Keywords: Neoadjuvant immunotherapy; Neoadjuvant immunochemotherapy; Head and Neck squamous Cell Carcinoma; Meta-analysis; Network-meta analysis.

Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) represents a significant global health burden, ranking as the seventh most common cancer worldwide and the eighth leading cause of cancer-related mortality(1). A substantial proportion of patients present with locally advanced disease at diagnosis, often accompanied by lymph node metastasis(2). The standard treatment paradigm for locally advanced HNSCC involves multimodal strategies—surgery, radiotherapy, and chemotherapy—administered either sequentially or concurrently. Nevertheless, despite these intensive therapeutic approaches, long-term outcomes remain unsatisfactory(3).

The emergence of immune checkpoint inhibitors (ICIs) has revolutionized therapeutic paradigms in HNSCC, particularly for advanced-stage disease(4), attracting growing clinical interest. Most recently, the application of neoadjuvant immunotherapy (NIT) in HNSCC has drawn considerable attention owing to its profound potential in functional preservation and survival improvement(5). Although early trials have investigated in various treatment regimens, including mono-immunotherapy (I)(6, 7), dual immunotherapy (DI)(8, 9), and immunochemotherapy (IC)(10, 11), immunoradiotherapy (IR)(12, 13), and immuno-target therapy (IT)(14, 15), most of them were constrained by single-armed design with limited sample sizes. Previou systematic reviews predominantly synthesized outcomes from these single-arm trials, thereby precluding direct comparison of therapeutic efficacy and safety across different regimens. Consequently, a critical knowledge gap persists regarding the comparative evaluation of the efficacy and safety profile among existing NIT strategies, leaving the optimal NIT regimen in HNSCC largely debatable.

The present systematic review and meta-analysis incorporated clinical trials investigation various NIT regimens in resectable HNSCC and performed a comprehensive pooled analysis. Furthermore, network meta-analysis (NMA) with surface under the cumulative ranking curve (SUCRA) was implemented to comparatively evaluat the efficacy and safety of different NIT regimens in this setting. By synthesizing these available evidence, we seek to provide critical insights to inform clinical decision-making in HNSCC.

Methods

This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. The present study was registered in the website https://www.crd.york.ac.uk/PROSPERO (identifier: CRD420251065614).

Search Strategy and Eligibility Criteria

We searched PubMed, Web of Science, Embase, and Cochrane Central databases, Web of Science, Clinical Trials, Scopus, as well as international conference abstracts from American Society of Clinical Oncology, European Society for Medical Oncology and American Association for Cancer Research, along with various other resources, until June, 2025 (Supplementary Table 1). Eligible studies included patients with histologically confirmed, resectable HNSCC receiving NIT (alone or combined with chemotherapy, radiotherapy, targeted therapy, etc.) followed by surgery. Retrospective studies not meeting Methodological Index for Non-randomized Studies (MINORS) high/intermediate criteria were excluded. Population, Intervention, Comparison, Outcome, and Study Design (PICOS) principles (Supplementary Table 2) guided selection; detailed inclusion/exclusion criteria are in Supplementary Table 3.

Study Selection and Data Extraction

Two authors (YZW, FWJ) independently screened studies and extracted data, with a third (ZB) resolving discrepancies. Extracted data included study characteristics (author, year, design, registration), patient demographics, treatment details, and outcome data.

Outcomes

Outcomes included efficacy (Objective Response Rate [ORR], pathological Complete Response [pCR], Major Pathologic Response [MPR]), survival (Progression-Free Survival [PFS], Overall Survival [OS], Disease-Free Survival [DFS], Relapse-Free Survival [RFS]), and safety (grade ≥3 immune-related adverse events [irAEs]). The primary objective was to assess the efficacy and safety of NIT and compare different regimens.

Risk of Bias Assessment

Two authors (YZW, FWJ) independently assessed study quality, with a third (ZB) resolving discrepancies. Single-arm and dual-arm studies were assessed using MINORS, classifying quality as high, intermediate, or low. Randomized controlled trials (RCTs) used the Cochrane Risk of Bias tool (RoB 2, 2020), categorizing bias as low, some concerns, or high in supplementary table 4 and 6. Overall review quality was evaluated using PRISMA 2020 and AMSTAR-2 checklists.

Statistical Analysis

The primary efficacy endpoints were objective response rate (ORR), pathological complete response (pCR), major pathological response (MPR), overall survival (OS), and disease-free survival (DFS), while the primary safety endpoint was the incidence of immune-related adverse events (irAEs). For time-to-event outcomes (OS and DFS), hazard ratios (HRs) and their 95% confidence intervals (CIs) were pooled using pairwise meta-analyses. For dichotomous outcomes (ORR, pCR, MPR, survival rates at predefined timepoints, and irAE incidence), a frequentist network meta-analysis (NMA) was conducted to estimate pooled odds ratios (ORs) and corresponding 95% CIs for all pairwise comparisons. Heterogeneity across studies in the NMA was assessed using the I^2 statistic and Cochran's Q test. A fixed-effects model was applied when heterogeneity was low ($I^2 < 50\%$ and Q-test $P > 0.1$); otherwise, a random-effects model was used.

The relative ranking of treatments for each outcome in the NMA was assessed using P-scores or Surface Under the Cumulative Ranking (SUCRA) probabilities, where higher values indicate a greater likelihood of a treatment being more effective (or safer, depending on the outcome's directionality). The consistency between direct and indirect evidence was assessed globally using a design-by-treatment interaction model, and locally via node-splitting analysis. Potential publication bias and small-study effects were evaluated using comparison-adjusted funnel plots.

In this frequentist framework, a $P < 0.05$ was considered statistically significant. It is important to note that this reliance on *P* for significance testing is characteristic of frequentist statistics. Alternative NMA approaches, such as Bayesian methods (BUGSnet), do not typically generate *P* in the same manner. Instead, Bayesian inference focuses on posterior probability distributions, and the significance of differences is often assessed by examining whether the 95% credible interval (CrI) for an effect estimate (e.g., an OR or HR) excludes the null value (e.g., 1 for ratios, 0 for differences).

Analyses were performed using R software (version 4.4.1) and the 'netmeta' package (version X.Y.Z; G. Rücker et al.), which facilitates frequentist NMA. This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for NMA.

Results

Basic Characteristics and Quality Assessment

From 1,655 initially considered records, 44 studies (1,688 patients) published between 2000 and June 2025 were included (Figure 1). These comprised 7 dual-arm RCTs and 37 single-arm studies (non-RCTs), all meeting MINORS quality criteria. By regimen, there were 14 mono-immunotherapy (I; n=773 patients) (6, 7, 9, 16-25), 21 immuno-chemotherapy (IC; n=670) (10, 11, 23, 26-43), 3 immuno-radiotherapy (IR; n=48) (12, 13, 44), 7 immuno-target-therapy (IT; n=117) (14, 15, 45-48), and 6 dual immunotherapy (DI; n=80; including anti-PD-1 + anti-CTLA-4 or anti-LAG-3) studies(8, 9, 21, 22, 25).

The median patient age ranged from 55-63 years (overall range 19-87). HNSCC subtypes included oral cavity, oropharynx, hypopharynx, and larynx. Detailed study characteristics are in Table 1, methodological quality assessment in Supplementary Table 4, and neoadjuvant regimen metadata in Supplementary Table 5. All studies

reported complete outcomes; seven RCTs used random allocation.

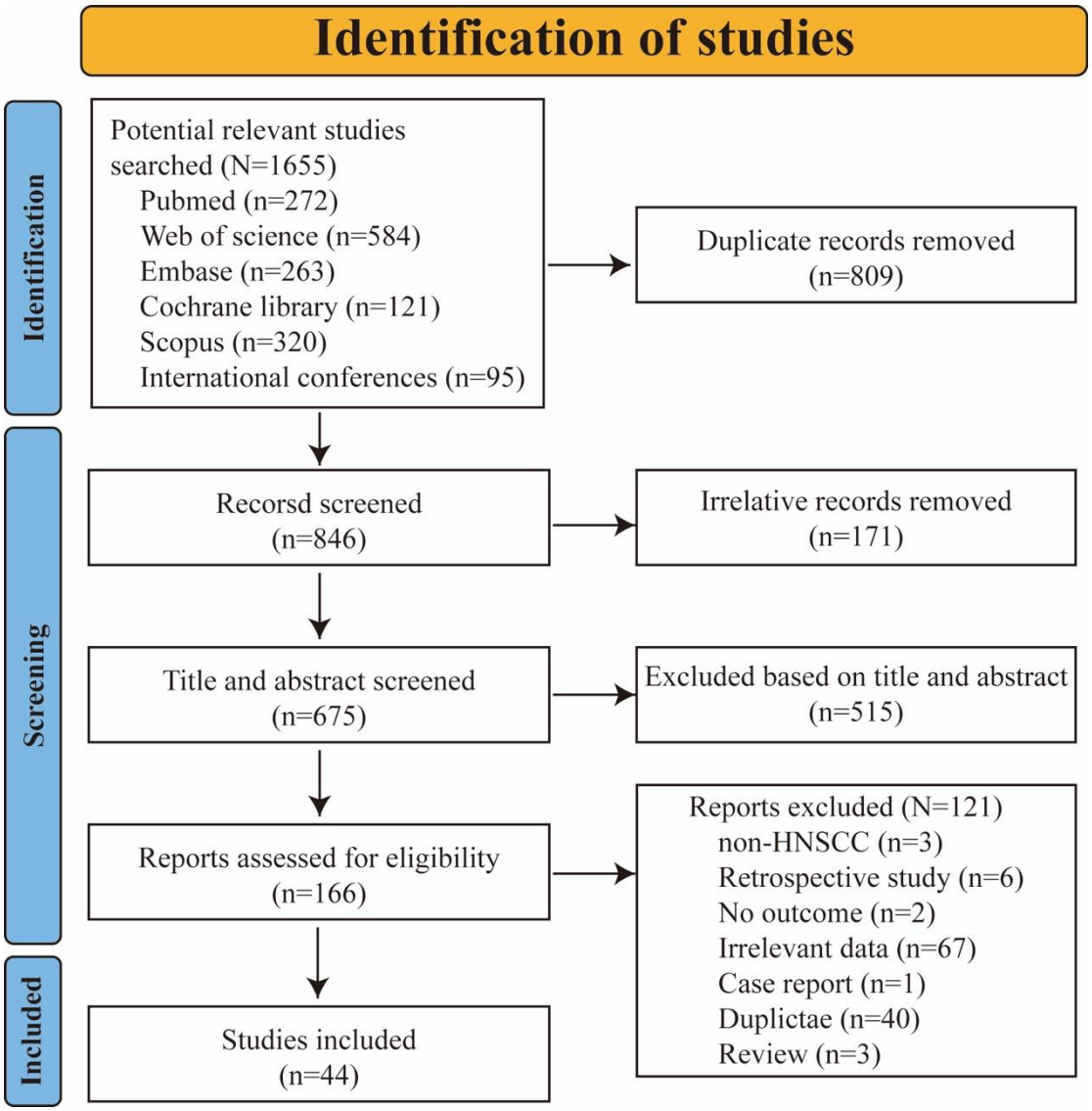

Figure 1. PRISMA flow diagram.

Clinical Outcomes of Neoadjuvant Immunotherapy Regimens

Regarding direct therapeutic effects, ORR were reported in 31 trials. The pooled ORR (95% CI) were: I - 19% [10%-32%]; IC - 80% [70%-88%]; DI - 29% [17%-44%]; IR - 46% [31%-62%]; and IT - 30% [0%-100%] (Figure 2A). pCR rates were reported in 44 trials, with pooled pCRs (95% CI) as follows: I - 18% [14%-23%]; IC - 40% [35%-44%]; DI - 4% [1%-11%]; IR - 63% [44%-79%] and IT - 11% [7%-18%] (Figure 2B). Furthermore, MPR rates were available from 39 trials, with pooled MPRs (95% CI) of: I - 15% [6%-32%]; IC - 64% [59%-69%]; DI

- 14% [8%-23%]; IR - 81% [65%-91%] and IT - 31% [23%-41%] (Figure 2C). In addition, downstaging rates were reported in 14 trails, and pooled downstaging (95% CI)) included: I - 18% [3%-61%]; IC - 79% [71%-86%]; DI - 53% [27%-79%]; IR - 93% [75%-98%] and IT - 58% [0%-100%] (Figure 2D). Collectively, IC demonstrated the highest ORR, pCR and downstaging rates, underscoring its efficacy in maximizing tumor response. Conversely, IR achieved the highest MPR rate, potentially reflecting enhanced radio-sensitization. These findings emphasize the general superiority of combination strategies over immunotherapy monotherapy. In terms of safety, the highest rates of irAEs were observed in DI - 19%, although the wide confidence interval indicates considerable inter-trial variabilityI. IC - 14% [11%-17%] and I - 11% [4%-26%] exhibited comparable irAEs rates (Supplementary Figure 1), suggesting that the addition of chemotherapy to immunotherapy did not substantially increase immune-related toxicity within this cohort. In addition, IR that included only one trial also showed relative high irAEs rate, 19% [5%-42%].

In terms of survival outcomes, IC consistently demonstrated superiority, achieving high 1-year OS - 97% [92%-99%], 2-year OS - 91% [86%-94%], 1-year DFS - 89% [80%-95%] and 2-year DFS - 90% [83%-94%] highlighting a more pronounced survival benefit (Figure 3A–D). These results support IC can provide patients with better survival benefits. IR showed a comparatively lower 1-year OS - 90% [77%-96%] (Figure 3A), warranting further investigation, particularly in advanced HNSCC. DI yielded a promising 1-year OS - 97% [84%-100%], and its 1-year DFS was 75% [53%-90%] (Figure 3A, B).

Consequently, future studies should continue to prioritize IC as a first-line neoadjuvant option, given its favorable profile across both direct therapeutic efficacy (Figure 2) and survival-related endpoints (Figure 3). Detailed long-term survival outcomes, including 3-year OS, 3-year DFS, and 1-year/2-year PFS and RFS rates, are provided in Supplementary Figure 2.

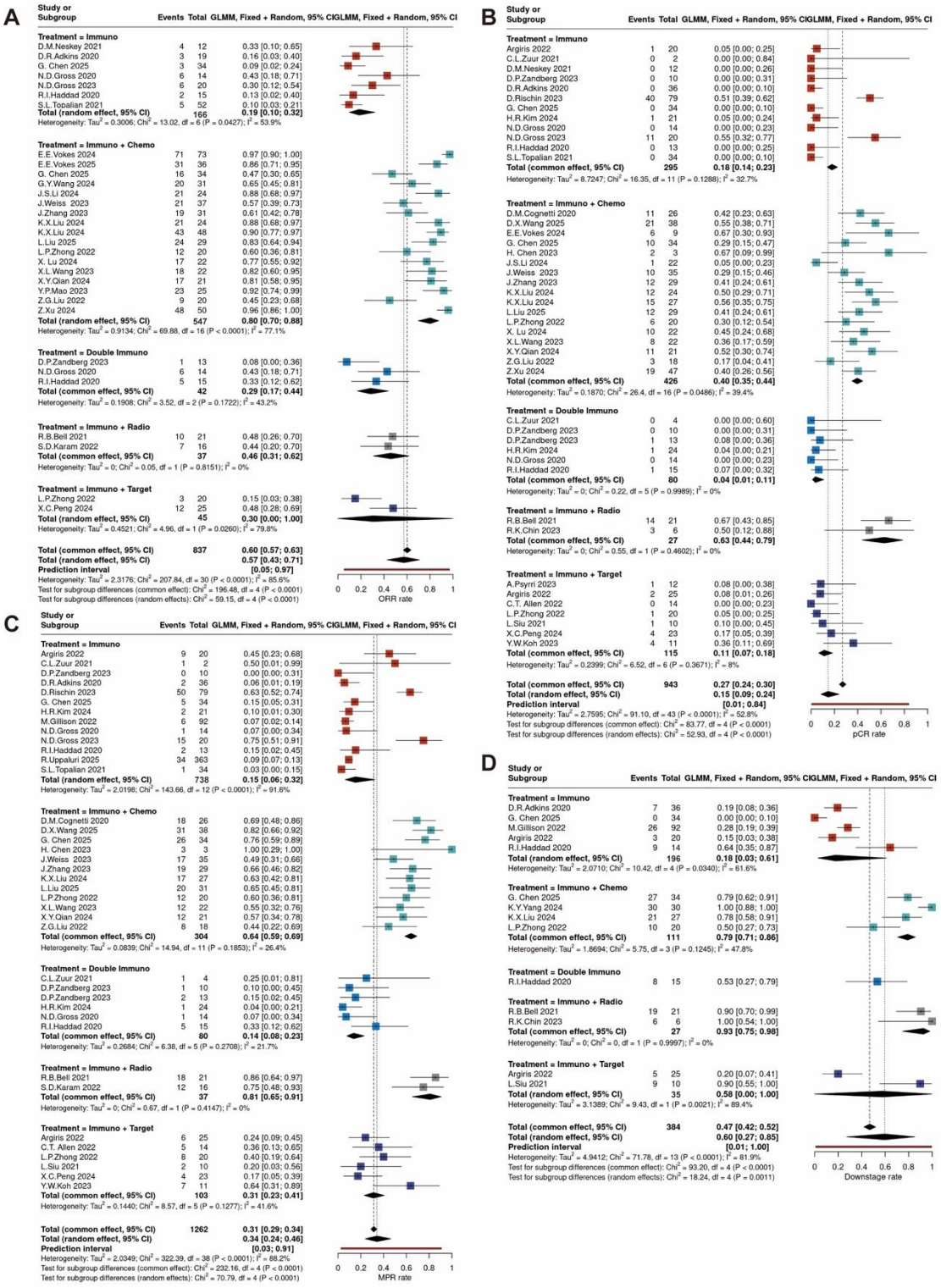

Figure 2. Forest Plot of direct therapeutic effects: (A) ORR, (B) pCR, (C) MPR and (D) Downstaging rate*. * Downstaging rate indicates clinical downstaging rate.

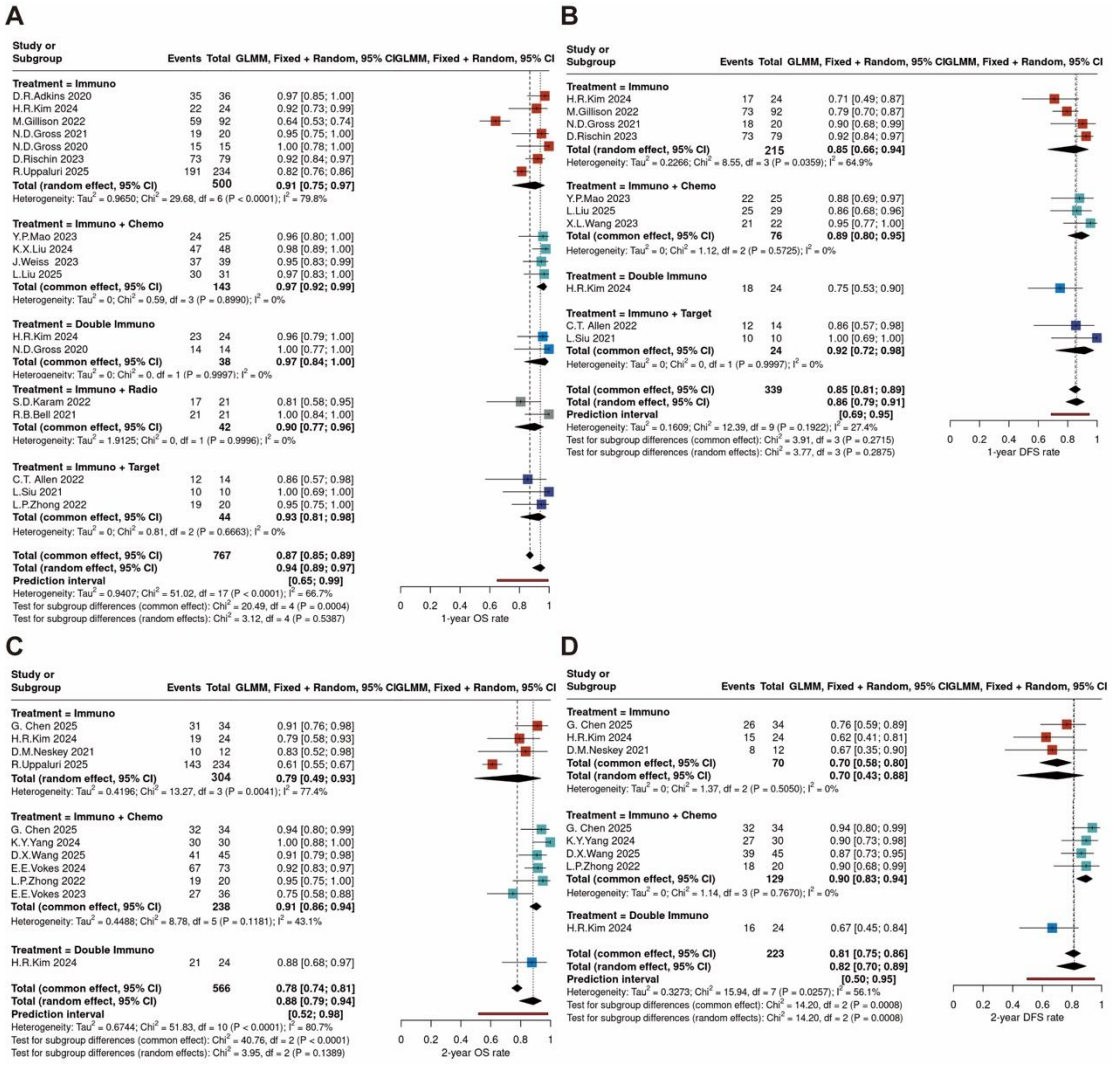

Figure 3. Forest Plot of survival outcomes: (A) 1 year-Overall Survival (OS), (B) 1 year-Disease-Free Survival (DFS), (C) 2 year-Overall Survival (OS) and (D) 2 year-Disease-Free Survival (DFS).

Quality Evaluation and Publication Bias Test

In analysis of the efficacy and safety of NIT treatments, possible publication bias in clinical studies was examined by funnel plots (Supplementary Figure 3), indicates publication bias may exist but were not apparent. The Cochrane Risk of Bias tool was used to assess 7 RCTs in our network meta in Supplementary Table 6, which includes 5 bias items(49). The quality evaluation of the present study using the PRISMA 2020 Checklist(50) and AMSTAR-2 Checklist(51) were shown in Supplementary Table 7, 8.

Sensitivity Analysis

Initial sensitivity analyses, performed by systematically omitting each study, confirmed the stability of the overall pooled results (Supplementary Figure 4, 5). However, given the notable heterogeneity observed within specific treatment subgroups for key clinical endpoints—namely ORR, pCR, Major MPR, and 1-/2-year OS—further sensitivity analyses were conducted by sequentially omitting individual trials.

For ORR, heterogeneity within the I subgroup was primarily driven by S.L. Topalian, 2021, as indicated by its influence range of [–0.195 to 0.968]. In the IC subgroup, E.E. Vokes, 2024 emerged as the principal contributor to heterogeneity, with an influence range of [–0.376 to 0.755]. In the pCR analysis, heterogeneity within the IC subgroup was largely attributable to J.S. Li, 2024 ([–2.346 to –1.111]), while in the IT subgroup, Argiris, 2022 had the most pronounced influence ([–2.377 to –1.124]). For MPR, heterogeneity in the I subgroup was mainly influenced by R. Uppaluri, 2025 ([–1.116 to –0.091]), whereas in the IC subgroup, the most substantial contributor was D.X. Wang, 2025 ([–1.224 to –0.211]). With respect to downstaging rate, heterogeneity in the IC subgroup was primarily explained by G. Chen, 2025 ([–1.117 to 1.585]), while within the I subgroup, M. Gillison, 2022 was the key contributor ([–0.936 to 1.774]). Regarding 1-year OS, M. Gillison, 2022 was again identified as the main source of heterogeneity in the I subgroup ([2.228 to 3.495]). Similarly, for 2-year OS, heterogeneity in the IC subgroup was predominantly attributed to R. Uppaluri, 2025 ([1.633 to 2.756]). These study-specific contributions to subgroup heterogeneity are detailed in Supplementary Table 9.

Outcomes of Network Meta-analysis

To comprehensively evaluate the relative efficacy and safety of different neoadjuvant treatment, a NMA was conducted. This analysis compared four distinct neoadjuvant strategies: I, IC, IT, and DI. The NMA assessed these regimens across six key outcomes: ORR, 2-year DFS, pCR, MPR, irAEs and Downstaging rates. The network, incorporating data from 7 RCTs, established connected treatment comparisons across all outcomes, as depicted in Figure 4. For all outcomes, random-effects models were employed for the NMA, and diagnostic plots for these models, are provided in Supplementary Figure 6.

The comparative treatment effects are summarized in league tables (Figure 5A), which present both direct and indirect comparisons as log odds ratios (log OR) with their corresponding 95% credible intervals (CrI). For ORR, 2-year DFS and MPR, IC trended towards better outcomes compared to DI and I, though these differences did not achieve statistical credibility (95% CrIs included the null value of zero). Notably, for pCR, IC demonstrated a statistically credible and substantial improvement over DI (log OR: 21.58, 95% CrI: 0.98–50.21), IT(log OR: 22.41, 95% CrI: 2.09–51.06) and I monotherapy (log OR: 23.40, 95% CrI: 3.63–51.54). The same trend exists in the downstaging rate. IC demonstrated a statistically credible and substantial improvement over IT(log OR: 29.27, 95% CrI: 3.97–60.37), I monotherapy (log OR: 29.73, 95% CrI: 5.63–60.51) and DI (log OR: 29.86, 95% CrI: 4.77–61.26). This suggests a robust enhancement in achieving a pCR and downstaging rates with the IC regimen. It is noteworthy that for outcomes such as pCR and MPR, the available data exhibited sparsity, characterized by a limited number of events in several study arms (Supplementary Figure 6). This sparsity posed challenges in robustly estimating the between-study heterogeneity for these specific endpoints, which is a common issue in NMAs with low event rates. Consequently, while the model was run with extended MCMC iterations, the interpretation of model fit statistics like DIC for these sparse-data outcomes requires caution. For irAEs, When comparing IC to DI and I, no statistically credible differences in the odds of irAEs were observed, as the 95% CrIs for these comparisons included zero.

Complementing the league tables, forest plots (Figure 5B) visually represent the posterior median log ORs and their 95% CrIs for each treatment strategy relative to the immunotherapy reference group. For ORR, 2-year DFS

and MPR outcomes, while IC often demonstrated the most favorable numerical effect compared to I, none of the pairwise comparisons against I (for IC, IT, or DI) reached statistical credibility, with all 95% CrIs encompassing zero. This indicates considerable uncertainty in the relative ranking for these endpoints when benchmarked against I monotherapy. Similarly, for irAEs, no treatment regimen showed a statistically credible difference in risk compared to I monotherapy. In stark contrast, the forest plot for pCR and downstaging clearly illustrates a statistically credible advantage for the IC regimen over I monotherapy, corroborating the league table findings.

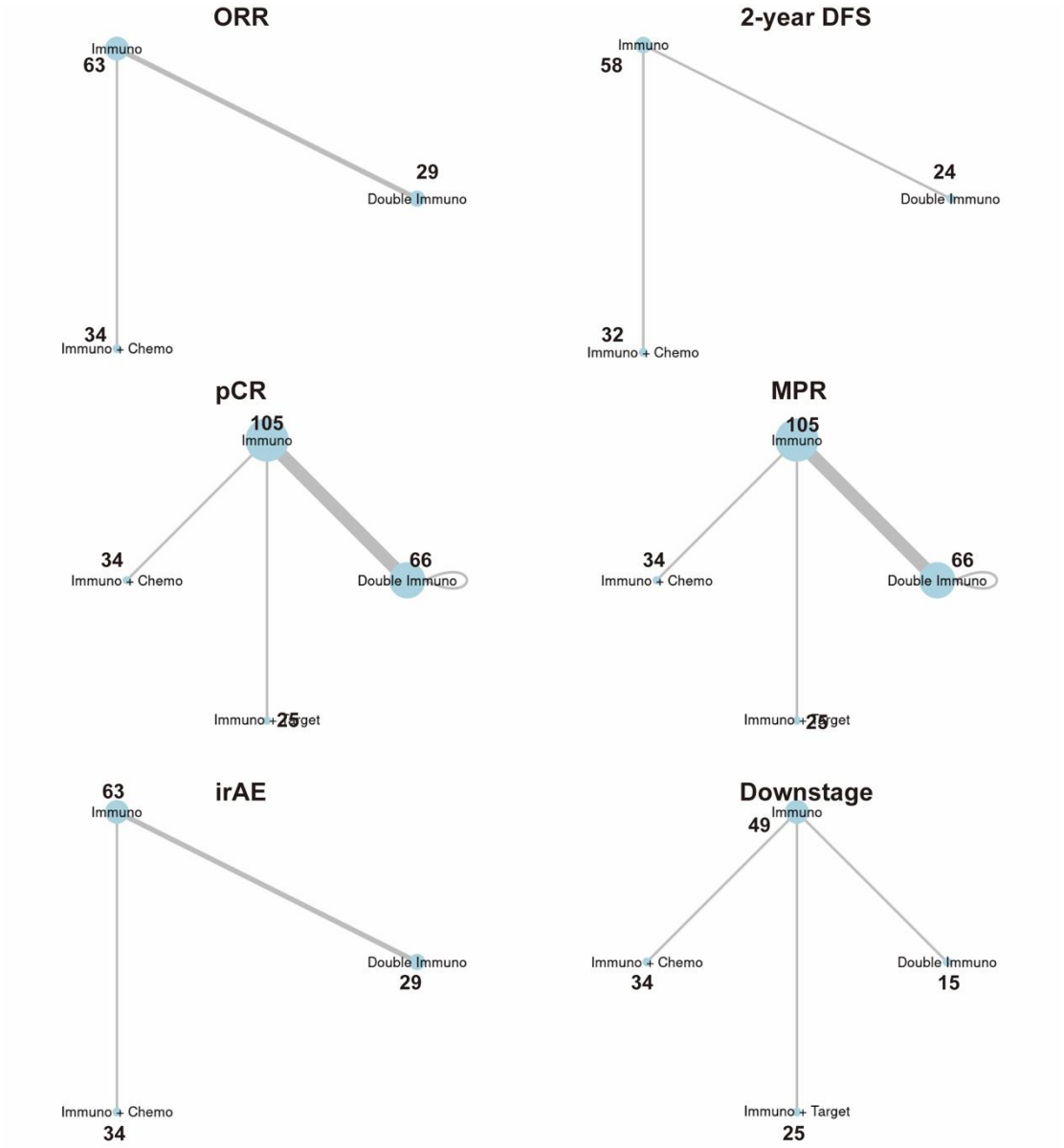

Figure 4. Network Evidence Plots of ORR, 2-year DFS, pCR, MPR, irAEs and Downstaging rates among NIT regimens.

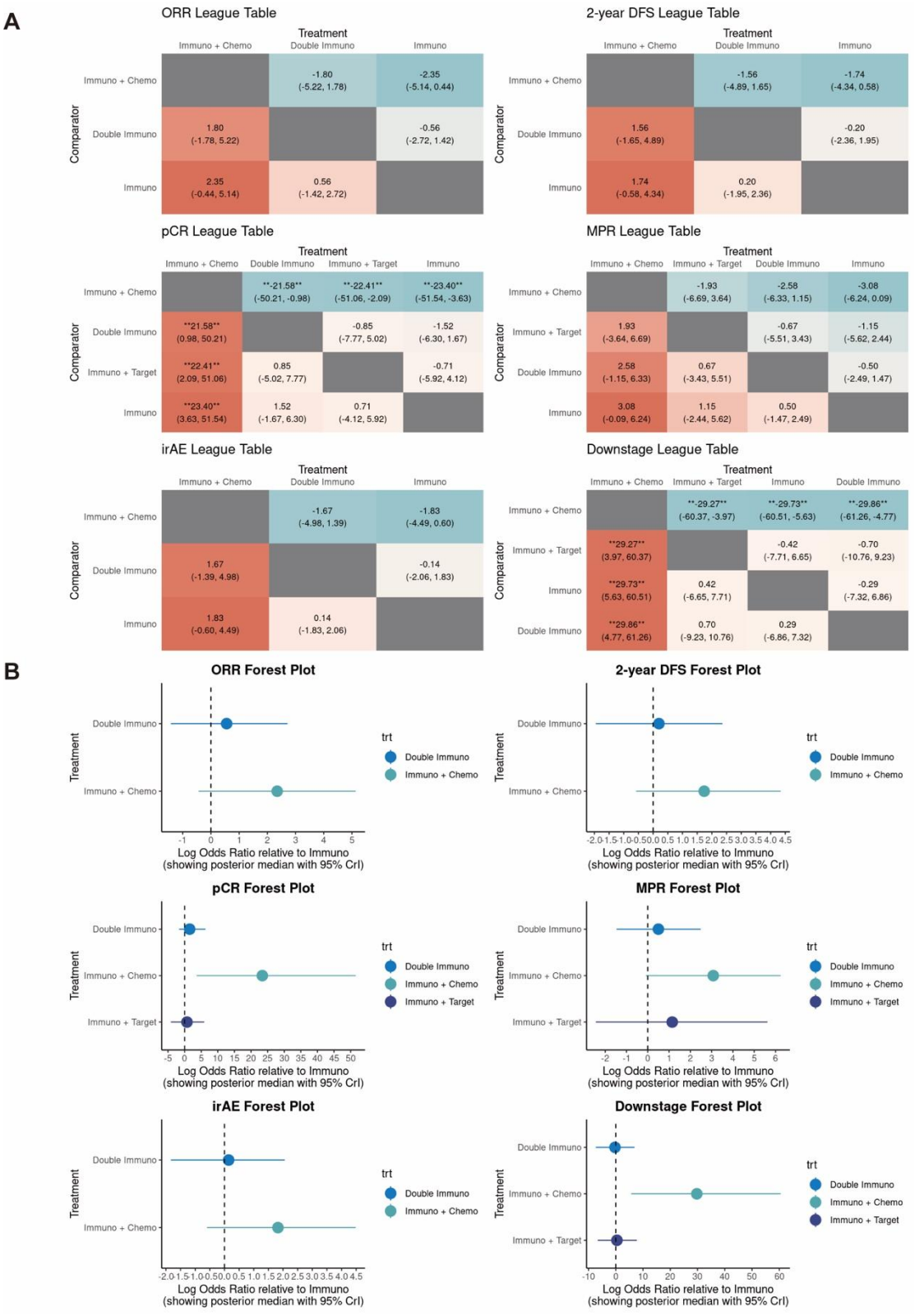

Figure 5. Outcomes of Network Meta-analysis. (A) League tables for ORR, 2-year DFS, pCR, MPR, irAEs and Downstaging rates. Values are Log Odds Ratios (LORs) with 95% CrIs. Teal cells: column treatment favored (LOR < 0); orange cells: row treatment favored (LOR > 0). ** indicates that the differences between groups were statistically significant. (B) Forest plots showing posterior median LORs (dots) and 95% CrIs (lines) for treatments relative to immunotherapy monotherapy ('Immuno'; reference line at LOR=0).

Treatment Ranking

To further delineate the relative standing of the NIT strategies, SUCRA curves were generated (Figure 6). These curves provide a probabilistic summary of each treatment's likelihood of achieving a certain rank or better for efficacy outcomes, or a certain rank or worse for irAEs. For efficacy outcomes (ORR, pCR, MPR and Downstage) and survival benefit (2-year DFS), IC consistently demonstrated the most favorable ranking profile (Figure 6A-E). The SUCRA curves for IC rapidly approached 100%, indicating a very high probability of it being the best (Rank 1) or among the top-ranking treatments for achieving higher ORR, pCR, MPR and Downstage. For irAEs, when interpreting irAEs rankings, a higher rank typically indicates a higher (less desirable) rate of side effects. In this context, IC exhibited the SUCRA profile indicative of the least favorable safety. However, it is important to interpret the irAEs ranking for DI with caution (Figure 6F). While DI SUCRA profile suggested a lower probability of being ranked among treatments with frequent irAEs, this finding is based on limited data within our NMA, which included only one trial evaluating DI where just a single patient experienced an irAEs. Such sparse data can lead to unstable estimates and limit the certainty of this particular ranking.

In summary, the SUCRA analysis reinforces that IC is most likely to be the best-performing NIT for achieving superior ORR, pCR, MPR, Downstaging rate and 2-year DFS. However, this enhanced efficacy appears to be associated with IC also having the highest probability of ranking among the treatments with more frequent irAEs.

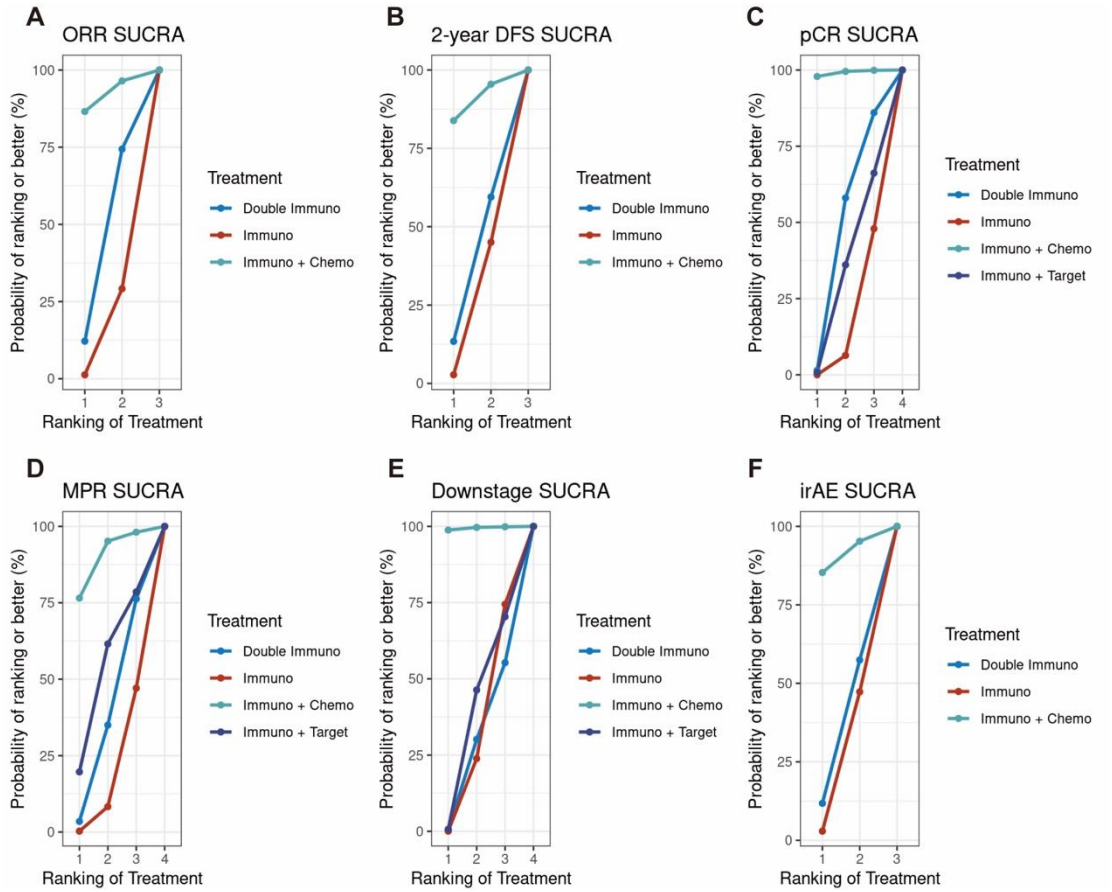

Figure 6. Treatment Ranking. SUCRA plots illustrate the probability of each treatment being ranked at a particular position or better for ORR (A), 2-year DFS (B), pCR (C), MPR (D), Downstage (E) and irAEs (F).

Higher SUCRA values indicate better efficacy (ORR, 2-year DFS, pCR, MPR, and Downstage); lower values indicate better safety (irAEs).

Discussion

The phase III KEYNOTE-689 trial, published in May 2025, investigated neoadjuvant pembrolizumab in patients with locally advanced, resectable HNSCC. Despite a modest MPR rate of only 9% in the pembrolizumab arm, the study demonstrated superior long-term survival outcomes compared to the control arm (who did not receive NIT). Specifically, the pembrolizumab arm achieved 1-, 2-, and 3-year OS rates of 81.62%, 61.11%, and 38.03%, respectively, and a 2-year EFS rate of 67.09%. These findings underscore that NIT may confer significant survival advantages over treatment regimens lacking NIT, even in the context of limited pathological responses. Building on this, we developed a meta-analysis encompassing 44 clinical trials of HNSCC. We combined anti–PD-1 and anti–PD-L1 agents in our analysis, as separate evaluations were limited by the small size of available trials. Moreover, previous studies have demonstrated no substantial difference in efficacy between these two ICIs(52). Our findings demonstrate that neoadjuvant IC offers superior clinical efficacy compared to other NIT strategies. Current aggregated evidence indicates that the IC regimen achieves superior ORR compared to other NIT strategies (Figure 2A), with a pooled ORR of 80%—significantly higher than earlier result (80% vs. 61%) (53)—attributable to several highly favorable trial outcomes reported between 2024 and 2025 (10, 28, 32, 33). Compared to I, IC exhibited consistently superior clinical efficacy across both survival and pathological outcomes—including higher 1-/2-year OS (97%, 91%) and DFS rates (89%, 90%) (Figure 3A–D), as well as improved pCR (40%), MPR (64%), and downstaging rates (79%) (Figure 2A–D). Notably, the incidence of irAEs in IC was slightly higher than I (14% vs 11%)(Supplementary Figure 1), suggesting a favorable risk–benefit profile. IR might be associated with improved pathological outcomes, including higher rates of pCR (63%), MPR (81%), as well as downstaging rates (93%) (Figure 2B, D). However, the clinical benefit of IR remains debatable due to the limited availability of clinical trial data and the absence of long-term survival endpoints such as 2-/3-year DFS or RFS (Supplementary Figure 2).

NMA result further corroborated these findings, particularly for the key endpoints of pCR and downstaging rate, where the IC demonstrated statistically credible and significant superiority over other strategies (Figure 5). For other outcomes, while the NMA did not reveal statistically significant differences, the SUCRA probability analysis indicated that the IC regimen had the highest probability of yielding the greatest benefit (Figure 6). Regarding safety, our direct meta-analysis indicated that, compared to I, IC did not significantly increase the incidence of irAEs (Supplementary Figure 1). Notably, although the SUCRA ranking suggested IC might be associated with the highest risk of irAEs (Figure 6E), this conclusion warrants cautious interpretation. The irAEs data for the DI in the NMA were limited by a small sample size, which could lead to ranking bias, and pairwise comparisons in the NMA revealed no credible differences in irAEs risk between IC and other groups (Figure 5). In summary, the collective findings of this study suggest that neoadjuvant IC is a highly promising therapeutic strategy for locally advanced-, resectable- HNSCC, offering the potential to enhance efficacy while maintaining an acceptable safety profile.

The superior efficacy of neoadjuvant IC likely stems from the synergistic interplay between chemotherapy and anti-tumor immunity. Chemotherapeutic agents can induce immunogenic cell death (ICD), thereby releasing damage-associated molecular patterns (DAMPs) such as ATP, HMGB1, and ANXA1, which in turn activate

dendritic cells and enhance tumor antigen presentation(54). It may also upregulate tumor cell MHC-I, increasing susceptibility to CTL-mediated killing(55), while released tumor antigens broaden adaptive immunity via cross-presentation(56). In contrast, while radiotherapy remains a cornerstone in the multidisciplinary management of HNSCC, its integration in the neoadjuvant setting may carry limitations. Radiotherapy has been associated with impaired surgical outcomes, including increased risks of flap necrosis, fibrosis, and delayed wound healing—factors that can compromise reconstructive success and postoperative recovery(57). Moreover, clinical trials involving IR included a high proportion of HPV^+ patients, which may have contributed to favorable outcomes. Specifically, IR trials often included high proportions of HPV^+ patients (e.g., R.K.Chin 2023, 100%; R.B.Bell 2021, 76%), potentially biasing outcomes favorably. A recent clinical study on NIT combined with chemoradiotherapy reported an ORR of 64.3%, pCR of 60.9%, and MPR of 21.7%. However, grade ≥3 irAEs increased obviously, reaching 43.5%(58). The limited efficacy of IT may stem from its reliance on specific molecular targets; its target population may not fully align with immunotherapy responders in heterogeneous HNSCC(59). Likewise, DI might be limited by insufficient tumor antigen release, inadequate T-cell infiltration, or severe side effects. IC, however, may overcome these issues by fostering a more immunogenic tumor microenvironment and promoting cytotoxic T-cell responses as mentioned above.

The evolving landscape of NIT regimens for HNSCC necessitates a clear understanding of the relative merits of different therapeutic strategies. The overarching goals of NIT—downstaging unresectable disease, reducing surgical morbidity in resectable cases, and improving long-term survival—represent critical clinical objectives(60). However, current evidence is predominantly from Phase I/II trials; robust Phase III data on long-term efficacy and safety are still lacking. This paucity of high-level evidence highlights the need for systematic reviews like ours to synthesize available data, informing future research and clinical decisions. In summary, our meta-analysis provides the most up-to-date and comprehensive evidence supporting the superiority of the IC regimen as a neoadjuvant strategy for resectable HNSCC. These findings underscore the importance of integrating IC in future clinical protocols and highlight the urgent need for large sample sizes and phase III trials to confirm these promising outcomes.

Conclusion

In conclusion, this systematic review and meta-analysis, including the NMA, demonstrates that NIT combined with chemotherapy (IC) might offer superior ORR (80%), pCR (40%), MPR (64%), 1-/2-year OS (97%, 91%), 2-year DFS (90%), and downstaging rates (79%), alongside promising survival outcomes versus alternative regimens. NMA of RCTs illustrated IC conferred significant improvements in pCR and downstaging rates compared to I, IT, and DI. Meanwhile IC did not significantly increase irAEs in NME-analysis. However, more high-quality trails data are needed to support our conclusion.

Data Availability

The original contributions presented in the study are included in the Supplementary Material. Data used for the meta-analysis are available upon request from the corresponding author, Yujie Liang (liangyj35@mail.sysu.edu.cn).

Conflicts of Interest

The authors have declared no conflicts of interest.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Research Registration Unique Identifying Number (UIN)

1. Name of the registry: PROSPERO

2. Unique Identifying number or registration ID: CRD420251065614

3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/#recordDetails

Author contribution

All authors read and approved the final manuscript prior to submission. LYJ, LJY, LGQ are responsible for the conceptualization. YZW and LJY are responsible for data curation, original draft writing and formal analysis. FWJ and ZB are responsible for supervision. TRK, YS, and QJJ is responsible for methodology. YL and ZSE project administration. All authors contributed to the article and approved the submitted version.

Ethical approval

The authors Ziwu Ye, Wenjie Fan, Bin Zeng confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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Abbreviations

NIT, neoadjuvant immunotherapy; ICI, immune checkpoint inhibitor; I, mono-immunotherapy; DI, dual immunotherapy; IC, immunochemotherapy; IR, immunoradiotherapy; IT, immuno-target therapy; PICOS, Population, Intervention, Comparison, Outcome, and Study Design; ORR, Objective Response Rate; pCR, pathological complete response rate; MPR, major pathologic response; PFS, Progression-Free Survival; OS, Overall Survival; DFS, Disease-Free Survival; RFS, Relapse-Free Survival; irAEs, immune-related adverse events; MINORS, Methodological Index for Non-randomized Studies; RCTs, randomized controlled trials; NMA, network meta-analysis; ORs, Odds Ratios; SUCRA, Surface Under the Cumulative Ranking.

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