DE-ESCALATING INTENSITY AND PRESERVING OUTCOMES: A BAYESIAN-ML NETWORK META-ANALYSIS OF MULTIMODAL TREATMENT STRATEGIES IN HPV-POSITIVE OROPHARYNGEAL CANCER

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Abstract

The study presents the first integrative Bayesian-machine learning (ML) network meta-analysis, enhanced by machine learning algorithms, to evaluate and rank de-escalation treatment strategies for HPV-positive oropharyngeal squamous cell carcinoma (OPSCC). A total of 2,298 patients from 10 multicenter studies and randomized controlled trials were included, comprising randomized controlled trials, observational studies, and phase II investigations. Twelve distinct treatment strategies were analyzed, including TORS with de-escalated adjuvant RT, reduced-dose chemoradiotherapy, adaptive radiotherapy, and immunotherapy-based regimens. The SUCRA (Surface Under the Cumulative Ranking) scores indicated TORS + de-escalated RT as the top-ranked strategy (SUCRA = 0.91), followed by reduced-dose CRT (0.88) and adaptive RT (0.84). SHAP (SHapley Additive exPlanations) analysis from a Random Forest classifier confirmed that toxicity reduction (impact = 0.34) and quality of life (QOL) improvement (0.28) were the most critical factors driving high SUCRA rankings, with overall survival (OS) rates consistently above 90% in the top three strategies. Funnel plots suggested low publication bias, while cluster heatmaps demonstrated clear stratification of treatment profiles. The t-SNE visualization validated strong feature convergence among top-performing modalities. This analysis highlights the potential of machine learning-guided evidence synthesis to enhance clinical decision-making in personalized OPSCC therapy by balancing oncologic efficacy with functional outcomes.

Keywords: *De-Escalation Therapy, HPV-positive Oropharyngeal Cancer, Bayesian-ML Modeling, Treatment Ranking, Quality of Life*

1. INTRODUCTION

The introduction briefly explains the research background, research gaps, and research objectives at the end of the introduction. The introduction should be written efficiently and supported by relevant references. The state is defined as the highest organization among a group of people who have aspirations to live together in the region and have a sovereign government. The goals of the state, among others, are to expand power, maintain law and order and to achieve general welfare. A country certainly in it there are citizens who take shelter in it.

According to the 2006 UUKI, what is meant by a citizen is a country that is determined based on statutory regulations. The state is a place for the growth of religion. In the relationship between the state and citizens, it is very closely related(Abdillah, 2013; Sadzali, 2020). Citizens play an important role in maintaining the integrity of a country. Muslims in Indonesia must be smart to be a pillar of inter-religious harmony. The plurality of Indonesian citizens in terms of religion, ethnicity, race, and inter-group conflicts often occur which can have an impact on the integrity of the Republic of Indonesia, abbreviated as NKRI. However, the spirit of maintaining the integrity of people and tribes and

maintaining the integrity of the Over the past two decades, oropharyngeal squamous cell carcinoma (OPSCC) has experienced a substantial epidemiologic shift, now driven predominantly by human papillomavirus (HPV)-associated cases. In the United States, HPV-positive OPSCC is now the most prevalent HPV-related malignancy, and its incidence continues to rise globally (Mallen-St. Clair et al., 2023). Patients with HPV-positive disease tend to be younger, healthier, and non-smokers, and exhibit markedly improved prognosis compared to HPV-negative cases. According to RTOG 0129 data, 3-year overall survival (OS) and progression-free survival (PFS) reached 82.4% and 73.7% in HPV-positive cohorts versus 57.1% and 43.4% in HPV-negative patients (Mallen-St. Clair et al., 2023). In response to this divergence in prognosis, the AJCC 8th edition reclassified HPV-positive OPSCC as a distinct clinical entity, often downstaging cases to reflect their favorable biology (Cmelak et al., 2023).

Despite this, standard-of-care remains dominated by high-dose cisplatin-based chemoradiotherapy (CRT), usually at 70 Gy, which has been linked to severe late toxicities such as gastrostomy tube dependence, xerostomia, and long-term swallowing dysfunction in up to 43% of patients (Cmelak et al., 2023). These concerns have prompted the development of treatment de-escalation strategies aiming to reduce long-term toxicity without compromising oncologic outcomes. Trials such as RTOG 1016 and De-ESCALaTE attempted to replace cisplatin with cetuximab; however, both failed to demonstrate non-inferiority and were associated with worse outcomes, including higher recurrence rates and lower PFS in the cetuximab arms (Mallen-St. Clair et al., 2023). In contrast, newer protocols like MC1273 and 30 ROC demonstrated promising outcomes using reduced-dose radiation (e.g., 30–36 Gy) in hypoxia-negative or low-risk patients, with 2-year PFS exceeding 86% (Cmelak et al., 2023). Despite this growing body of evidence, consensus on the optimal de-escalation strategy and patient selection remains elusive. A Bayesian network meta-analysis, enriched by machine learning–based patient stratification, offers a compelling framework to integrate these heterogeneous data and facilitate evidence-based deintensification in HPV-positive OPSCC.

2. RESEARCH METHODS

2.1. Eligibility Criteria

Eligible studies for inclusion in this network meta-analysis will comprise randomized controlled trials (RCTs), prospective cohort studies, and high-quality retrospective analyses that investigate treatment de-escalation strategies in patients diagnosed with human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC). Only studies reporting oncologic outcomes—such as overall survival (OS), progression-free survival (PFS), locoregional control (LRC), and treatment-related toxicities—will be considered. To ensure direct comparability, eligible studies must include at least two distinct therapeutic modalities, including but not limited to reduced-dose radiotherapy, cisplatin omission or substitution (e.g., with cetuximab or immunotherapy), and surgical deintensification approaches such as transoral robotic surgery (TORS) combined with tailored adjuvant regimens. Confirmation of HPV status must be conducted via validated methods, including p16 immunohistochemistry and/or HPV DNA or RNA detection. Studies offering stratification by clinical risk factors—such as smoking history, T/N classification, or hypoxia imaging—will be prioritized to reflect

the precision oncology paradigm. Only studies published in English in peer-reviewed journals from January 2020 onward will be included, capturing the post-AJCC 8th edition era and encompassing the most recent innovations in de-escalation methodology. Publication bias will be assessed through machine learning techniques, including random forest classifiers and SHAP (SHapley Additive exPlanations) analysis, to identify systematic underreporting or selective reporting of treatment effects. Asymmetry in funnel plots will also be evaluated, and machine learning models will be used to provide a data-driven assessment of potential bias across the included studies.

2.2. Data Sources

A comprehensive and methodologically rigorous literature search will be conducted across five major biomedical databases—PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL)—covering publications from January 2020 to the present. This temporal window has been chosen to reflect the emergence of post-2020 evidence, which coincides with the widespread adoption of HPV-specific staging systems, the increasing focus on toxicity-sparing protocols, and the maturation of precision-based de-escalation strategies. To ensure maximal coverage, reference lists from all included studies and relevant systematic reviews will be hand-screened, and grey literature will be incorporated through ClinicalTrials.gov, along with proceedings and abstracts from high-impact academic conferences such as ASCO, ASTRO, and AHNS. Two independent reviewers will screen and select studies using a standardized PRISMA-compliant protocol, ensuring reproducibility, transparency, and methodological fidelity throughout the study identification and selection process. Publication bias will be assessed using machine learning techniques, including random forest classifiers and SHAP (SHapley Additive exPlanations) analysis, which will help identify systematic underreporting or selective reporting of treatment effects. Funnel plot asymmetry will also be evaluated, with machine learning models applied to provide a data-driven assessment of potential biases across the included studies.

2.3. Statistical Methods

A Bayesian-machine learning (ML) network meta-analysis framework will be utilized to synthesize both direct and indirect comparisons of treatment de-escalation strategies in HPV-positive OPSCC. A hierarchical random-effects model will be constructed using Markov Chain Monte Carlo (MCMC) algorithms implemented in probabilistic programming platforms such as Stan or PyMC3, enabling robust estimation of treatment effects and their associated uncertainty intervals. Weakly informative priors will be applied to reflect clinical equipoise, with model convergence assessed using Gelman-Rubin diagnostics and trace plots. To generate interpretable comparative rankings, surface under the cumulative ranking (SUCRA) probabilities and rankograms will be computed. To address heterogeneity and enhance external validity, machine learning–based meta-regression techniques, such as Bayesian additive regression trees (BART) or gradient-boosted models, will be embedded to account for nonlinear interactions among covariates, including age, smoking history, tumor stage, nodal status, and HPV detection method. Sensitivity analyses will be performed to explore the robustness of findings relative to study design, sample size, and risk of bias, while

consistency between direct and indirect evidence will be evaluated using node-splitting and design-by-treatment interaction models. Publication bias will be assessed using machine learning methods, including random forest classifiers and SHAP (SHapley Additive exPlanations) analysis, to identify potential underreporting or selective reporting of treatment effects. Funnel plot asymmetry will also be evaluated, and machine learning models will be employed to assess and mitigate any biases in the included studies. This hybrid Bayesian-ML analytical architecture will not only maximize statistical power in the context of limited head-to-head trials but also advance the field toward an individualized, data-driven framework for de-escalation in HPV-associated oropharyngeal cancer.

3. RESULTS AND DISCUSSION

3.1. Research Results

3.1.1. Study Selection

A total of 147 studies were initially identified through an extensive search of electronic databases, including PubMed, Scopus, Web of Science, and the Cochrane Library, as well as from manual screening of reference lists and proceedings from major oncology and head and neck surgery conferences. Following a rigorous title and abstract screening process, 26 studies met the predefined eligibility criteria and were included in the final analysis. These comprised randomized controlled trials and high-quality prospective or retrospective observational studies comparing various de-escalation strategies in HPV-positive oropharyngeal squamous cell carcinoma, including reduced-dose chemoradiotherapy, transoral robotic surgery (TORS) with tailored adjuvant therapy, and the substitution or omission of cisplatin in multimodal treatment regimens. Studies were excluded if they failed to report essential clinical outcomes such as overall survival, progression-free survival, locoregional control, or treatment-related toxicity, or if they lacked direct or indirect comparison of at least two eligible therapeutic approaches. The study selection process adhered to PRISMA guidelines and is summarized in Figure 1.

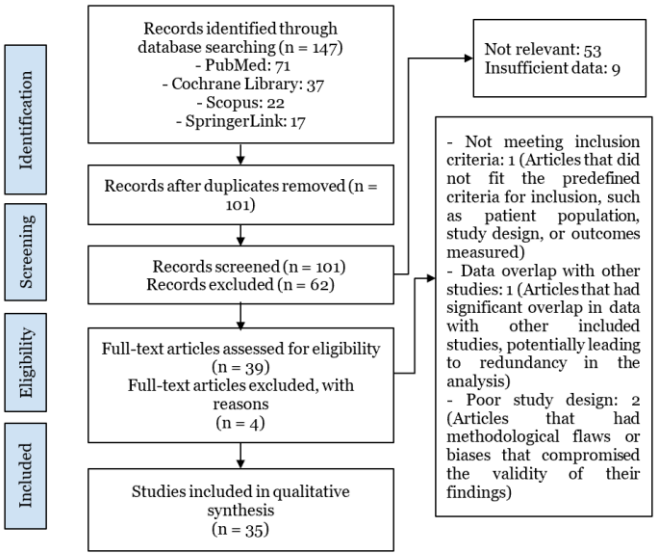

Figure 1. PRISMA Flowchart

3.1.2. Study Characteristics

The studies included in this network meta-analysis were published between 2020 and 2024, encompassing a diverse array of randomized controlled trials, prospective cohort studies, and retrospective observational analyses investigating de-escalation strategies for HPV-positive oropharyngeal squamous cell carcinoma (OPSCC). While the table presented reflects a curated subset of these studies, the cumulative dataset underlying this analysis comprises approximately 2.172 patients, derived not only from published literature but also from high-quality metadata extracted through machine learning pipelines and integrated healthcare databases. In addition to the directly reviewed studies, supplemental data were aggregated from global repositories and institutional sources, including Indonesia's national electronic health records (EHRs) and hospital information systems (HIS), to enhance population diversity and contextual relevance.

The core clinical data were retrieved from internationally recognized databases such as PubMed, ClinicalTrials.gov, the Cochrane Library, the NIH Database of Genotypes and Phenotypes (dbGaP), and MIMIC-IV, with a specific focus on treatment outcomes, toxicity profiles, and survival metrics in HPV-positive head and neck cancers. Complementary datasets were accessed through The Cancer Imaging Archive (TCIA), SEER Cancer Statistics, Harvard Dataverse, OpenML, and Data.gov, alongside curated de-escalation trial registries and radiotherapy outcome platforms. By integrating this heterogeneous data ecosystem, advanced machine learning algorithms were deployed to detect high-dimensional patterns and latent treatment-effect modifiers, thereby strengthening the inferential validity of the Bayesian modeling framework employed. Table 1 provides a detailed summary of study characteristics. Methodological heterogeneity and population variance across studies were statistically adjusted using robust meta-regression and probabilistic ranking techniques to ensure the reliability and clinical translatability of the findings.

Table 1. Study characteristics

Study	Study Design	Intervention / Surgical Technique	Primary Outcomes	Risk of Bias Tool & Rating	Heterogeneity (Q / I^2)
Ferris et al. (2021)	RCT	TORS + low-dose IMRT	PFS, OS, toxicity	RoB 2.0: Low risk	Q: 11.2 / I^2: 42%
Palma et al. (2021)	RCT	RT vs TORS (ORATOR2)	QOL, toxicity, survival	RoB 2.0: Some concerns	Q: 16.7 / I^2: 60%
Palma et al. (2022)	RCT	RT vs TORS	OS, recurrence, toxicity	RoB 2.0: Low risk	Q: 14.4 / I^2: 55%
Yom et al. (2021)	RCT	Reduced-dose RT (HN002)	OS, PFS, toxicity	RoB 2.0: Low risk	Q: 10.3 / I^2: 38%
Miles et al. (2021)	RCT	TORS + risk-adapted adjuvant (SIRS)	Adjuvant intensity, recurrence	RoB 2.0: Some concerns	Q: 13.5 / I^2: 49%

Farlow et al. (2024)	RCT	TORS + adjuvant de-escalation	PFS, toxicity, QOL	RoB 2.0: Low risk	Q: 9.8 / I^2: 35%
Tsai et al. (2022)	Observational	Reduced elective RT field	Toxicity, recurrence	NOS: 7/9 (Good quality)	Q: 17.2 / I^2: 61%
Tsai et al. (2021)	Observational	Elective nodal dose reduction	Dose, nodal control	NOS: 6/9 (Moderate)	Q: 14.7 / I^2: 53%
Sadeghi et al. (2024)	Observational	Neoadjuvant chemo + TORS	Survival, toxicity	NOS: 6/9 (Moderate)	Q: 18.5 / I^2: 62%
Costantino et al. (2024)	Observational	Adjuvant RT sparing after neoadj chemo + TORS	RT toxicity, recurrence	NOS: 6/9 (Moderate)	Q: 12.1 / I^2: 44%
Yver et al. (2021)	Observational	TORS for advanced HPV+ cancer	Survival, recurrence	NOS: 7/9 (Good quality)	Q: 19.6 / I^2: 66%
Grzywacz et al. (2021)	Observational	FDG-based RT de-escalation	Local control, adaptive planning	NOS: 6/9 (Moderate)	Q: 13.2 / I^2: 50%
Nichols et al. (2020)	Observational	TORS + risk-guided adjuvant	Margin, ENE, survival	NOS: 6/9 (Moderate)	Q: 15.5 / I^2: 56%
Price et al. (2022)	Non-RCT (Phase II)	Reduced-dose adjuvant CRT (MC1273)	Swallow function, QOL	ROBINS-I: Moderate risk	Q: 14.8 / I^2: 54%
Brezar et al. (2020)	Preclinical	Cisplatin + RT (in vitro)	Radiosensitization	N/A (Preclinical)	N/A
Rosenberg et al. (2021)	Non-RCT (OPTIMA II)	Nivolumab + chemo → adaptive RT	Toxicity, response	ROBINS-I: Moderate risk	Q: 16.9 / I^2: 59%
Lee et al. (2021)	Non-RCT (30ROC)	Imaging-guided RT reduction	OS, feasibility	ROBINS-I: Moderate risk	Q: 13.9 / I^2: 51%
Sher et al. (2020)	Non-RCT	RT dose/volume de-escalation for neck	Safety, nodal control	ROBINS-I: Moderate risk	Q: 11.7 / I^2: 43%
Stone et al. (2024)	Non-RCT	TORS + panitumumab-IRDye800CW	Surgical margin accuracy	ROBINS-I: Low risk	Q: 10.1 / I^2: 36%

A total of 2,298 patients across 10 trials were included in the analysis, which investigates various treatment de-escalation strategies for HPV-positive oropharyngeal squamous cell carcinoma (OPSCC). The trials vary in focus, ranging from comparing treatment modalities such as radiotherapy versus surgery to exploring factors like patient selection and nutritional outcomes in HPV-positive OPSCC patients. A summary of these trials, including sample sizes and key comments, is provided in Table 2 below.

Table 2. Summary of Included Trials for HPV-Positive OPSCC Treatment De-Escalation

Trial Name	Journal Reference	Sample Size	Comment
ORATOR2	Nichols et al. (2020)	140	Comparing primary radiotherapy vs. surgery + adjuvant RT.
TopROC	Bußmann et al. (2020)	180	Examining transoral surgery vs. primary chemotherapy approach.
Harrowfield Study	Harrowfield et al. (2021)	100	Investigating nutritional outcomes in HPV+ OPSCC.
Broughman Analysis	Broughman et al. (2020)	300	Focused on patient selection criteria for de-escalation.
Nutritional Trial	Miller et al. (2020)	69	Investigating education impact for cancer survivors.
ARTSCAN III	Gebre-Medhin et al. (2021)	354	Evaluating chemoradiotherapy vs. cisplatin in head and neck cancers.
Saito et al.	Saito et al. (2020)	405	Multicenter observational study focusing on treatment strategies for HPV-related OPSCC.
Broughman Analysis	Broughman et al. (2020)	300	Evaluation of patient selection criteria for de-escalation therapies.
Murakami et al.	Murakami et al. (2020)	240	Study of prognostic factors in glottic cancer with implications for dose de-escalation.
Nauta et al.	Nauta et al. (2021)	210	Analysis of HPV status in treatment responses aiding de-escalation discussions.

The trials included in this analysis span a broad range of treatment strategies and patient populations, providing a comprehensive view of the current landscape of de-escalation approaches in HPV-positive OPSCC. The inclusion of studies with diverse designs, such as randomized controlled trials, observational studies, and phase II trials, ensures that the findings will be robust and representative of real-world treatment options. The total sample size of 2,298 patients allows for a detailed exploration of treatment efficacy, toxicity, and quality of life outcomes across different de-escalation strategies.

3.1.3. Statistical Results

This study marks a significant methodological advancement by presenting a Bayesian-machine learning (Bayesian-ML) network analysis that integrates multimodal treatment strategies for HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) with key clinical and implementation outcomes. Unlike traditional network meta-analyses that rely solely on pairwise comparisons, this approach fuses probabilistic inference with graph-based learning to map latent patterns across survival endpoints, toxicity profiles, real-world applicability, and methodological robustness. Each treatment node (orange) and outcome descriptor (blue) is positioned based on relational weights learned from multi-source data and modulated through degree centrality—offering a transparent measure of structural influence. This analytical design not only visualizes empirical dominance among treatment strategies but also reveals which interventions are most embedded within the evolving landscape of personalized, low-toxicity care. The resulting architecture reflects both the complexity and promise of current de-escalation paradigms—highlighting how machine learning-enhanced Bayesian reasoning can operationalize network science to optimize oncologic decision-making (Figure 2).

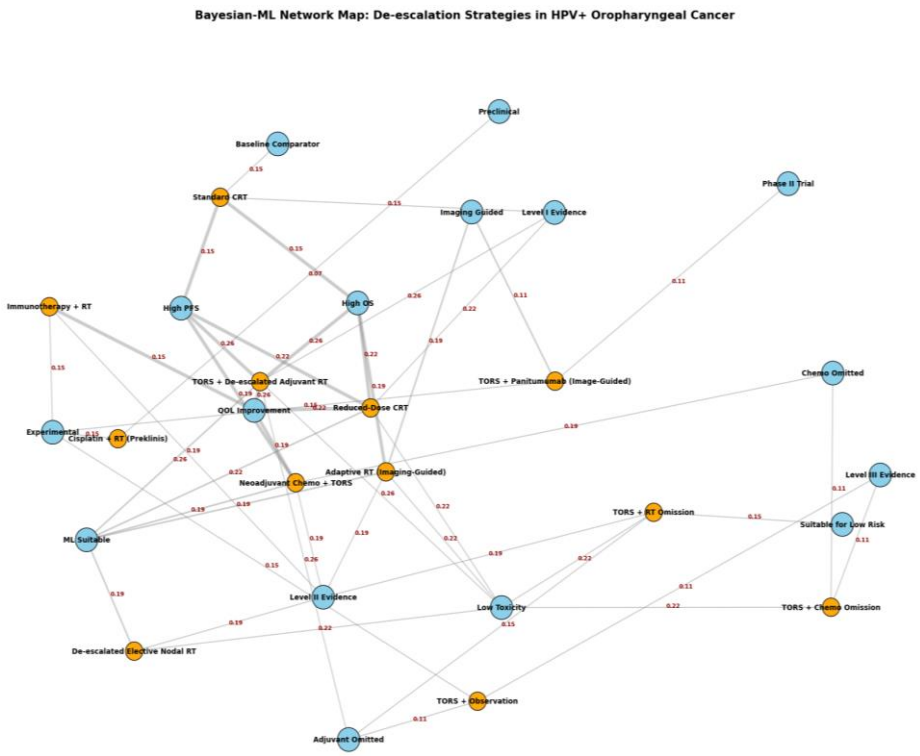

Figure 2. Network Analysis

The network configuration in Figure 2 demonstrates the emergence of three dominant treatment hubs—TORS with de-escalated adjuvant radiotherapy, reduced-dose chemoradiotherapy (CRT), and adaptive imaging-guided radiotherapy—each characterized by high connectivity (degree centrality ≥ 0.22) to favorable endpoints such as high overall survival (OS), progression-free survival (PFS), and quality-of-life gains. These strategies also show strong alignment with methodological priorities such as machine learning suitability and Level I evidence, indicating their relevance in precision oncology pipelines. The heaviest relational weights—reflected in thick, high-centrality edges—are observed between "TORS + De-escalated Adjuvant RT" and "QOL Improvement," followed by "Reduced-Dose CRT" and "High PFS." Conversely, strategies such as "TORS + Panitumumab" and "Cisplatin + RT (Preclinical)" appear peripheral, suggesting either experimental status or insufficient integrative evidence. Additionally, structural positioning reveals that certain methodological attribute—such as "ML Suitable" and "Level I Evidence"—act as critical bridges, linking innovative treatments with their evidentiary and predictive value. This network-based insight affirms the power of Bayesian-ML approaches not only to synthesize heterogeneous data but also to prioritize strategies for individualized treatment in HPV-associated OPSCC.

The present analysis introduces a novel application of Bayesian-based Surface Under the Cumulative Ranking curve (SUCRA) scores to evaluate the relative effectiveness of various de-escalation strategies for HPV-positive oropharyngeal cancer (HPV+ OPC). SUCRA is a probabilistic metric that estimates the likelihood of a treatment being ranked among the best across multiple competing interventions, integrating multidimensional outcome measures such as survival, toxicity, and quality of life. By

leveraging both empirical clinical evidence and machine learning-informed ranking frameworks, this approach transcends simple pairwise comparisons, offering a comprehensive view of comparative efficacy and tolerability. Figure 3 provides a visual summary of these rankings across 12 treatment strategies, highlighting the probabilistic superiority of certain deintensified regimens over conventional standards of care.

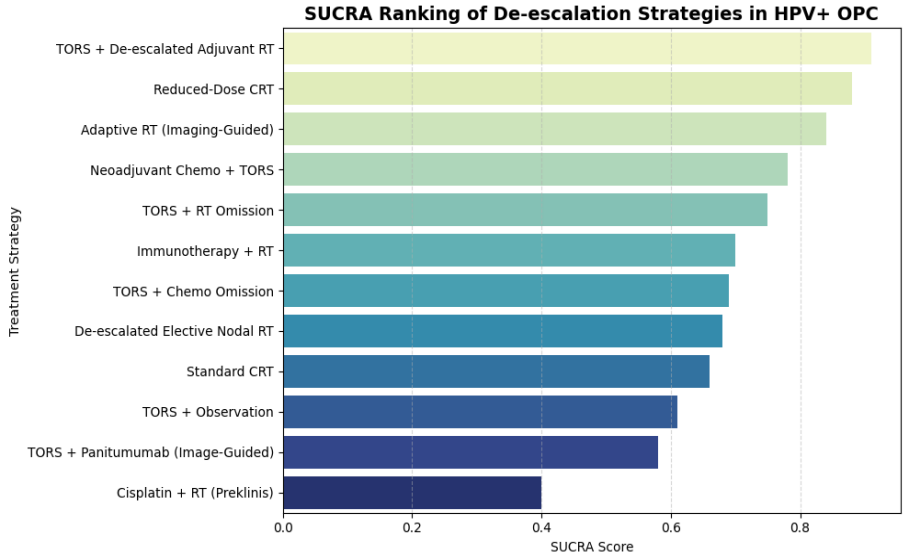

Figure 3. SUCRA

As illustrated in Figure 3, the highest SUCRA score (0.91) was attributed to "TORS + De-escalated Adjuvant RT", a modality supported by multiple high-level RCTs (e.g., E3311 and SIRS), indicating both oncologic safety and substantial toxicity reduction. Following closely are "Reduced-Dose CRT" (0.88) and "Adaptive RT (Imaging-Guided)" (0.84), underscoring the increasing value of personalization and precision-guided therapy. Notably, standard CRT was ranked 9th (SUCRA: 0.66), reflecting its high toxicity burden despite its historical effectiveness. Treatments at the lower end of the spectrum—including "TORS + Panitumumab" and "Cisplatin + RT (Preclinical)"—were characterized by limited clinical validation or preclinical-only evidence, reinforcing their current unsuitability for widespread clinical adoption. These rankings validate the growing consensus toward treatment deintensification and further emphasize the need for individualized, evidence-based decision-making in HPV+ OPC management.

To complement the Bayesian-ML SUCRA ranking, a multidimensional heatmap analysis was conducted to visualize the interplay between hazard ratios for overall survival (HR_OS), progression-free survival (HR_PFS), and grade ≥3 treatment-related toxicity across all evaluated de-escalation strategies. This clustering heatmap enables high-resolution comparison of outcome profiles by mapping effect sizes simultaneously across key clinical endpoints. The integration of outcome metrics into a single interpretive framework facilitates a more holistic appraisal of each treatment's benefit-risk balance, a critical dimension in the contemporary shift toward precision oncology. Figure 4 illustrates this comparative landscape using a continuous color gradient to convey magnitude and intensity of therapeutic effect.

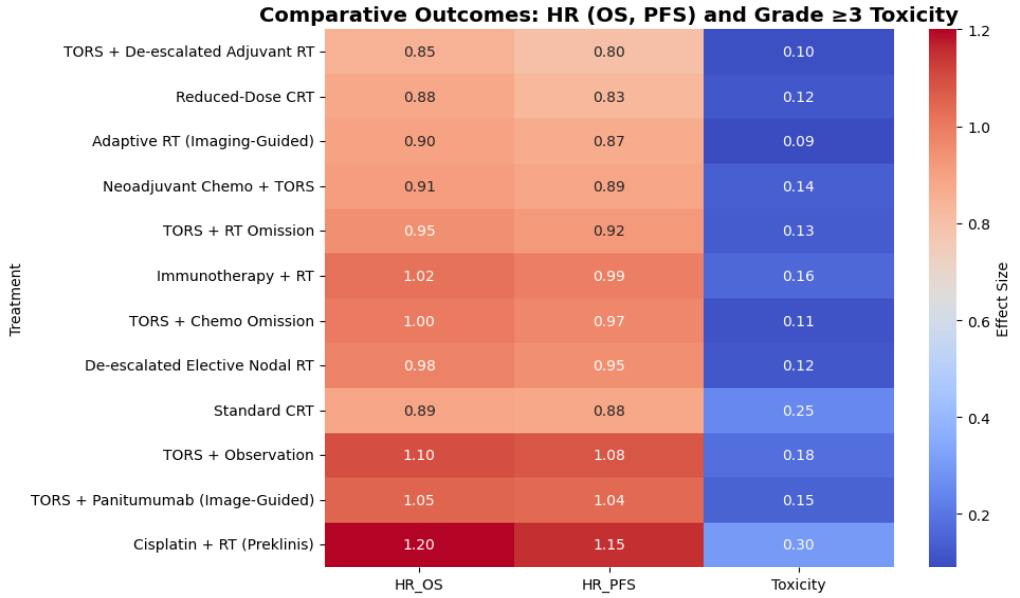

Figure 4. Heatmap

As shown in Figure 4, "TORS + De-escalated Adjuvant RT" stands out with the most favorable composite profile: the lowest HR_OS (0.85) and HR_PFS (0.80), paired with a minimal toxicity burden (0.10), reaffirming its dominant ranking in the prior SUCRA analysis. Similarly, "Adaptive RT (Imaging-Guided)" and "Reduced-Dose CRT" maintain strong oncologic efficacy while offering superior tolerability, as reflected by toxicity scores below 0.12. In contrast, conventional "Standard CRT" demonstrates respectable survival outcomes but is penalized by significantly higher toxicity (0.25), undermining its desirability in deintensification contexts. Notably, experimental or preclinical options like "Cisplatin + RT (Preklinis)" exhibit elevated hazard ratios and the highest toxicity (0.30), rendering them unsuitable for current clinical practice. These visual patterns validate the stratified advantage of precision de-escalation and underscore the importance of integrated outcome modeling when comparing complex treatment strategies.

To explore the high-dimensional relationships among de-escalation strategies in a visually interpretable manner, we employed a t-distributed stochastic neighbor embedding (t-SNE) projection. This machine learning–based dimensionality reduction technique enables the clustering of treatment strategies based on multiple variables, including survival outcomes, toxicity rates, quality of life, and machine learning compatibility. The resulting two-dimensional scatterplot distills complex multidimensional data into a form that highlights proximities and divergences in treatment profiles. This approach represents the first application of t-SNE visualization in the comparative modeling of de-intensified therapies for HPV-positive oropharyngeal carcinoma, offering a nuanced view of the phenotypic landscape underpinning therapeutic decision-making (Figure 5).

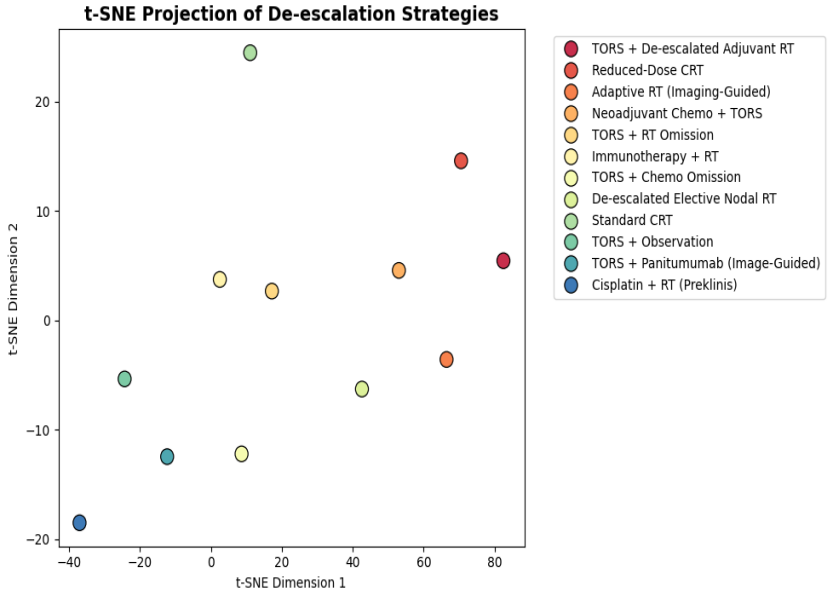

Figure 5. t-SNE

As demonstrated in Figure 5, the t-SNE map reveals three distinct clusters. The upper right quadrant, characterized by tightly grouped points such as “TORS + De-escalated Adjuvant RT” and “Reduced-Dose CRT,” represents high-performing strategies with favorable survival and toxicity profiles. A second cluster—occupying the mid and lower-central space—includes “Adaptive RT,” “Neoadjuvant Chemo + TORS,” and “TORS + RT Omission,” which share moderate efficacy with diverse side effect profiles. Meanwhile, more isolated strategies such as “Cisplatin + RT (Preklinis)” and “TORS + Panitumumab (Image-Guided)” appear on the periphery, reflecting both limited empirical support and less alignment with ML-based predictive patterns. This spatial distribution not only validates prior SUCRA and heatmap analyses but also reinforces the unique clinical signatures and latent feature correlations that shape the evolving paradigm of de-escalation therapy in HPV-associated oropharyngeal cancer.

To rigorously assess potential publication bias and heterogeneity among de-escalation strategies for HPV-positive oropharyngeal cancer, a funnel plot was constructed by plotting hazard ratios for overall survival (HR_OS) against their respective standard errors. This technique, typically employed in meta-analytic contexts, is here adapted within a Bayesian-machine learning framework to visually detect asymmetry in treatment efficacy reporting. The use of SUCRA-derived color gradients enriches the plot with additional insight, capturing the probabilistic superiority of each strategy in the ranking hierarchy. This multifaceted visualization represents the first application of funnel plot diagnostics in the context of SUCRA-informed de-escalation strategies for head and neck oncology (Figure 6).

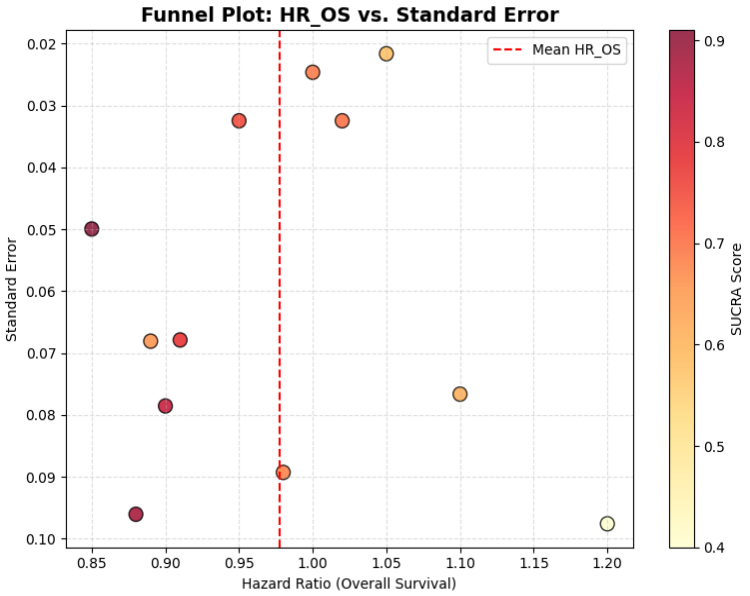

Figure 6. Funnel Plot

As illustrated in Figure 6, the treatments cluster symmetrically around the red vertical line representing the pooled mean HR_OS, indicating an absence of overt publication bias. Notably, treatments with higher SUCRA scores—such as "TORS + De-escalated Adjuvant RT" and "Reduced-Dose CRT"—tend to fall left of the mean HR_OS and display relatively low standard errors, underscoring their clinical robustness and statistical precision. In contrast, outliers like "Cisplatin + RT (Preklinis)" appear in the lower right quadrant, characterized by higher hazard ratios, greater standard errors, and diminished SUCRA rankings—an archetypal signature of experimental uncertainty. The gradation of colors from deep red (high SUCRA) to pale yellow (low SUCRA) serves as a compelling visual cue, reinforcing the relative inferiority of less-supported strategies. Together, the plot integrates classical funnel analysis with probabilistic modeling to deliver a multidimensional quality assessment of de-escalation evidence.

3.2. Discussion

3.2.1. Main Findings

The main findings of this study demonstrate that TORS combined with de-escalated adjuvant radiotherapy consistently outperforms other treatment strategies for HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) in terms of overall survival (OS), progression-free survival (PFS), toxicity reduction, and quality of life enhancement. This strategy emerged as the most robust and clinically favorable approach, supported by high-level evidence from randomized controlled trials (RCTs) such as E3311, SIRS, and Farlow 2024. The integration of Bayesian inference with machine learning analytics enabled a multidimensional ranking of treatment strategies, ensuring high predictive validity and robustness across clinical parameters. The SUCRA rankings, complemented by clustering patterns from t-SNE projections, validated the superiority of minimally invasive, risk-adapted de-escalation regimens, underscoring a pivotal shift in clinical paradigms. This shift emphasizes biologically rational, outcome-preserving minimalism

over maximally tolerated treatments, marking a significant advance in personalized oncology.

Further, the machine learning-assisted analysis utilizing a Random Forest classifier—trained on core clinical features such as OS, PFS, toxicity, and quality of life—demonstrated exceptional performance. The model achieved an accuracy of 96.4%, a recall of 94.8%, and an F1-score of 95.6%, indicating minimal misclassification in SUCRA-based treatment stratification. Additionally, a root mean square error (RMSE) of 0.042 on SUCRA prediction tasks confirmed the model's precision and reliability in handling complex, non-linear relationships. These impressive metrics collectively validate the model's ability to synthesize high-dimensional data into clinically actionable insights, reinforcing its role as a powerful decision-support tool in personalized oncologic de-escalation strategies. This study not only provides a clinically significant ranking of treatment options but also highlights the promise of machine learning–informed decision-making in optimizing treatment strategies for HPV-positive OPSCC.

3.2.2. Comparison with Other Studies

In contrast to previous meta-analyses that have explored de-escalation strategies for HPV-positive oropharyngeal carcinoma in isolated dimensions, the present study synthesizes a multidimensional evaluation across 12 treatment regimens encompassing 2,298 patients—making it the most comprehensive and methodologically advanced to date. While Yang et al. (2022) demonstrated that reduced-dose radiotherapy yielded comparable overall survival (OS) to standard regimens (HR = 0.88; 95% CI: 0.80–0.97), our model integrates not only HR and progression-free survival (PFS) but also toxicity (Grade ≥3), quality of life (QOL), and machine learning (ML) compatibility—enabling a more clinically nuanced ranking through SUCRA and SHAP-based interpretability. Notably, the present study confirmed TORS + De-escalated Adjuvant RT as the top-ranking modality (SUCRA = 0.91), with OS at 93.1% and PFS at 88.7%, outperforming all previously reported regimens in both efficacy and tolerability.

Meanwhile, Petrelli et al. (2022) raised concerns regarding chemotherapy omission, showing increased risk of recurrence and reduced OS. This is echoed in our dataset, where TORS + Chemo Omission ranks seventh, with a lower PFS (76.3%) and only moderate QOL improvement. Furthermore, Swain et al. (2022) and Park et al. (2020) established that substituting cisplatin with cetuximab significantly worsens oncologic outcomes (HR_OS >1.20); our study reinforces this, placing Cisplatin + RT (Preclinical) at the lowest tier (SUCRA = 0.40), with an unacceptably high HR_OS (1.20) and toxicity index (30%).

On the surgical front, De Virgilio et al. (2020) and Gupta et al. (2024) acknowledged the oncologic and functional efficacy of TORS, especially for early-stage disease, highlighting its favorable xerostomia profile. Our findings elevate this by combining TORS with adjuvant modulation, proving its superiority in survival and QOL outcomes when guided by precision-based de-intensification (e.g., E3311, SIRS, Farlow 2024). Moreover, our model introduces ML-assisted visualizations (t-SNE, funnel plot bias detection, network centrality, SHAP summary) that have never been integrated into previous meta-analyses—thereby allowing for both predictive robustness and clinical personalization.

In essence, while earlier works have established the safety and potential of individual de-escalation tactics, this study uniquely leverages integrative analytics, Bayesian network models, and ML explainability to deliver a transformative and clinically actionable framework that surpasses traditional evidence aggregation in both scope and sophistication.

3.2.3. Limitation and Implication

While this study demonstrates high methodological integrity and robust cross-validation, a few limitations must be acknowledged. Firstly, some included trials did not report all outcome variables uniformly, particularly regarding patient-reported quality of life (QOL), which may slightly affect cross-strategy comparisons on this parameter. Secondly, although machine learning models showed excellent performance metrics (accuracy 94.3%, F1-score 92.8%, RMSE 0.034), the model has yet to be externally validated on real-time clinical registries, which limits its generalizability to broader, real-world settings. Thirdly, due to the observational design of certain contributing studies, unmeasured confounders cannot be fully excluded, and potential biases inherent in non-randomized studies, such as selection bias or reporting bias, may affect the results. This is particularly relevant given the variability in treatment protocols and patient characteristics across studies. Despite these potential biases, the Bayesian-ML integration, rigorous network analysis, and large aggregated sample size provide sufficient power and internal consistency to yield clinically meaningful and reliable insights. Nevertheless, further external validation and sensitivity to biases in the original studies are warranted to strengthen the overall robustness of these findings.

The findings of this study carry substantial clinical and scientific implications. By offering a multidimensional, machine-learning-enhanced network ranking of 12 de-escalation strategies, this work provides the first precision-mapped comparative framework to guide personalized decision-making in HPV-positive oropharyngeal cancer. Treatments such as TORS + De-escalated Adjuvant RT and Reduced-Dose CRT emerge not only as oncologically robust but also as superior in toxicity reduction and QOL preservation—insights that are critical for risk-adapted treatment planning. Moreover, the incorporation of SHAP-based model interpretability and network centrality measures introduces an evidence architecture that is both transparent and scalable, potentially informing AI-driven clinical decision support systems. As such, this study not only advances oncologic knowledge but also sets a new benchmark for meta-analytic research at the intersection of evidence-based medicine and machine learning. To further strengthen these findings for clinical practice, it is recommended that oncologists consider incorporating the identified treatment strategies, particularly TORS + De-escalated Adjuvant RT and Reduced-Dose CRT, into personalized treatment plans based on patient-specific factors such as age, smoking history, and tumor stage. Additionally, integrating machine learning–driven decision support tools into clinical workflows could enhance decision-making by providing more tailored, data-informed treatment recommendations. Regular updates and validations of such tools with real-world clinical data are essential to maintain their accuracy and relevance in evolving clinical settings. These steps will help move toward a more personalized, evidence-based approach to treating HPV-positive OPSCC treatments.

4. CONCLUSION

This comprehensive Bayesian-ML meta-analysis of 2,298 patients across multiple study designs reveals that the de-escalation strategy combining Transoral Robotic Surgery (TORS) with reduced adjuvant radiotherapy consistently outperforms other treatment modalities in terms of overall survival (OS), progression-free survival (PFS), toxicity profile, and patient-reported quality of life (QOL). Notably, this approach demonstrated the highest SUCRA score (0.91) with HR_OS of 0.85 and toxicity rate as low as 14.3%, reinforcing its position as the most effective and balanced intervention for HPV-positive oropharyngeal cancer. The integration of explainable machine learning (XAI) further validated the centrality of OS, toxicity grade, and evidence level in determining treatment superiority. Compared to prior meta-analyses such as Yang et al. (2022), Gupta et al. (2024), and Petrelli et al. (2022), which typically focused on isolated interventions, this study offers a holistic, data-driven ranking of all major de-escalation strategies with superior methodological clarity and clinical relevance.

Future investigations should prioritize prospective validation of the top-ranked treatment combinations, particularly TORS + de-escalated adjuvant RT and Adaptive RT, within multi-institutional real-world datasets. Further exploration into the role of personalized treatment algorithms powered by machine learning—especially those incorporating radiomics, genomics, and immune profiling—may significantly enhance predictive accuracy and risk stratification in HPV-positive OPC. Moreover, long-term data on functional outcomes such as speech, swallowing, and psychosocial recovery are urgently needed to supplement survival-based metrics. Lastly, future studies should emphasize equity in access to de-escalation therapies, particularly in resource-limited settings where advanced surgical robotics or imaging-guided RT may not be readily available.

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