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Gender disparities on overall survival rates in HPV-associated head and neck cancer: a systematic review and meta-analysis

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Evidence in Context

- No significant gender differences in survival for HPV-associated head and neck cancers.
- High heterogeneity indicates variability across studies.
- Significant publication bias detected.
- Study analyzed over 200,000 patients globally.
- Findings highlight the need to consider factors beyond gender in treatment

To view Article

Abstract

Background: The incidence of HPV-associated head and neck cancers, especially in the oropharyngeal region, is rising sharply, raising substantial clinical and public health concerns. These cancers are distinct from those caused by other etiologies such as tobacco and alcohol due to the unique prognosis of HPV-positive cases. Despite their generally better prognosis, there is significant uncertainty regarding the variation in survival outcomes between genders. This study aims to closely examine and understand gender differences in survival rates among patients with HPV-associated head and neck cancers, exploring potential disparities to inform treatment strategies and improve patient outcomes.

Methods: A systematic review and meta-analysis were conducted using data from 13 studies involving 203,346 HNC patients. The studies were sourced from PubMed, Embase, and Web of Science, covering research until May 2024. The analysis involved calculating pooled hazard ratios (HRs) for survival, assessing heterogeneity and publication bias using the I^2 statistic, funnel plots, and Egger's test.

Results: The findings showed a slight, non-significant survival advantage for females in HPV-positive HNCs (HR 0.952). In HPV-negative HNCs, there was also no significant gender difference in survival (HR 1.053). The study noted high heterogeneity and significant publication bias.

Conclusions: No significant gender disparities in survival for HPV-positive or HPV-negative HNCs, suggesting the need for personalized care strategies beyond gender considerations.

Keywords: *Systematic review, gender disparities, HPV, survival rates, head and neck cancer, meta-analysis*

Introduction

Human papillomavirus (HPV) infection is largely to blame for the rising incidence rates of head and neck cancers (HNC), which represent a serious worldwide health concern. About 4.5% of all cancers worldwide are caused by HPV, which accounts for 630,000 new cases each year. Women are more likely than men to be infected with HPV (8.6% vs. 0.8%). It is most commonly linked to cervical cancer, which is responsible for 83% of cases linked to HPV. But, particularly in more developed nations, HPV also has a major effect on oropharyngeal and other anogenital malignancies. The study finds that most of these malignancies are associated with HPV types 16/18, along with types 6/11/16/18/31/33/45/52/58, based on data on the prevalence of HPV in cancer tissues [1]. Because of unique biological activities that affect patient outcomes, HPV-positive malignancies typically have a better prognosis than HPV-negative ones [2].

With increasing incidence rates associated with HPV infection, HNC represent a significant worldwide health concern. HPV causes about 4.5% of all malignancies worldwide, translating to 630,000 new cases per year. The frequency is higher in women (8.6%) than in men (0.8%). Although HPV is primarily responsible for 83% of cervical cancer cases, it also significantly affects other anogenital and oropharyngeal malignancies, especially in more industrialized nations. The majority of these malignancies are associated with HPV types 16/18 and a combination of HPV types 6/11/16/18/31/33/45/52/58, according to data on the frequency of HPV in cancer tissues used to evaluate attributable fractions and HPV type contributions. Our understanding of oropharyngeal cancers has evolved due to HPV's notable association with these diseases. Approximately 70% of oropharyngeal cancers in the US are caused by HPV, distinguishing them from other HNCs linked to alcohol and tobacco use [3]. HPV-positive malignancies usually have a better prognosis than HPV-negative ones due to differing biological activities affecting patient outcomes [2].

In high-income countries, the incidence of HPV-related oropharyngeal cancers is substantial, with variations across sex, race, and age [4]. Gender disparities in survival rates for HPV-positive HNC persist, with studies showing significant differences in overall survival between males and females. Recent research indicates that the incidence of HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) is more than twice as high in men compared to women [5-10]. Understanding the impact of gender on survival rates in HPV-associated HNC is crucial for effective patient management and public health strategies to reduce cancer-related disparities. Examining these demographic factors is essential for developing tailored interventions and improving outcomes for all individuals, ensuring both men and women receive optimal, personalized care based on their specific needs and risk factors [11, 12].

This systematic review and meta-analysis evaluated the existing literature on the impact of gender on survival outcomes in HPV-associated HNCs to identify significant trends and underlying mechanisms that explain observed disparities. Focusing on these factors is crucial in the era of precision medicine, enhancing our understanding of diverse patient needs and potentially leading to more effective, personalized cancer treatment strategies.

Methods

This review followed the PRISMA-2020 guidelines (Table S1) and the study protocol was registered with PROSPERO (CRD42024547847) [13].

Search strategy

We executed an extensive search of the literature using multiple databases such as PubMed, Web of Science, and Embase, starting from their inception until May 2024. Our search methodology utilized a mix of keywords and Medical Subject Headings (MeSH) related to HPV, and head and neck cancer. Details of the search terms and strategies are outlined in Supplementary Table S2. There were no language or publication date restrictions, ensuring a comprehensive inclusion of pertinent studies.

Inclusion and exclusion criteria

Studies qualified for inclusion in our analysis if they: involved patients diagnosed with HPV-associated head and neck cancer, provided data on overall survival rates categorized by gender,

And constituted original research, including cohort and case-control studies. Exclusion criteria included studies that did not stratify survival data by gender among head and neck cancers and without HPV status, review articles, case reports, conference abstracts, or unpublished data.

Screening and data extraction

Two reviewers independently evaluated the titles and abstracts of the identified papers using Nested Knowledge software. After that, full texts were obtained and their suitability was assessed. Disagreements were settled by conversation or by seeking advice from a third reviewer. The first author, publication year, study location, sample size, patient demographics, HPV status, and gender-specific survival rates, data were extracted using Nested Knowledge's tagging feature.

Quality assessment

The Newcastle-Ottawa Scale (NOS) for cohort and case-control studies was used to evaluate the quality of the included research. This scale evaluates the studies based on their selection, comparability, and outcome measures. Studies that achieved a score of six or more out of nine stars were classified as high quality.

Statistical analysis

The primary endpoint of our analysis was overall survival (OS), stratified by gender, among patients with HPV-associated head and neck cancers (HNC). For the meta-analysis, we employed a random-effects model to account for possible variation among the included studies. The hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled to assess the differences in survival between male and female patients. The I^2 statistic was used to assess study heterogeneity; values greater than 50% indicated considerable heterogeneity. Funnel plots and Egger's test were used to evaluate the publication bias. All statistical operations were performed using R software, version 4.2.3. Forest plots provided a visual summary of both individual and aggregated HRs for overall survival, and prediction intervals were derived to forecast the range of potential effects in future research contexts [14, 15].

Results

Literature search

Initially, we identified 121 records through searches in various databases: 27 from Embase, 64 from PubMed, and 30 from Web of Science. Before the screening phase, 50 duplicate records were removed, leaving 71 records for detailed review (Figure 1). Screening led to the exclusion of 43 records for reasons such as irrelevance to the study criteria, resulting in 28 full-text articles being thoroughly evaluated for eligibility. Out of these, 15 articles were excluded because they were reviews (2), lacked an HPV association (9), or did not report specific survival outcomes (4). Ultimately, 13 studies met all criteria and were included in the meta-analysis.

Characteristics of included studies

The features of the 13 retrospective studies that made up our analysis—which included 203,346 individuals with HNC in total—are shown in Table 1. Of these, 145,818 are male and 33,420 are female. The majority of studies were conducted in the USA (10 studies) [5-7, 9, 10, 16-20], with additional studies from Canada [21], Germany [8], and China [22]. The types of HNCs included were oral cavity squamous cell carcinoma (OCSCC), oropharyngeal cancer (OPC), OPSCC, and non-OPSCC carcinomas. The studies included in our review were rated as moderate to high quality according to the Newcastle-Ottawa Scale (NOS). (Table S3).

Overall Survival of HPV-Positive HNCs Based on Gender

A meta-analysis examined overall survival in HPV-positive HNC patients by gender. The pooled HR for overall survival, comparing females to males, was 0.952, with a 95% CI ranging from 0.847 to 1.057, indicating no significant difference in overall survival between genders. The prediction interval spanned from 0.604 to 1.301, suggesting variability in outcomes across different studies. The analysis also revealed high heterogeneity, as evidenced by an I^2 value of 65%. Figure 2 demonstrates these findings, which imply that although some individual studies suggest better survival rates for females, the combined effect across studies does not demonstrate a significant disparity in survival outcomes between genders among HPV-positive HNC patients.

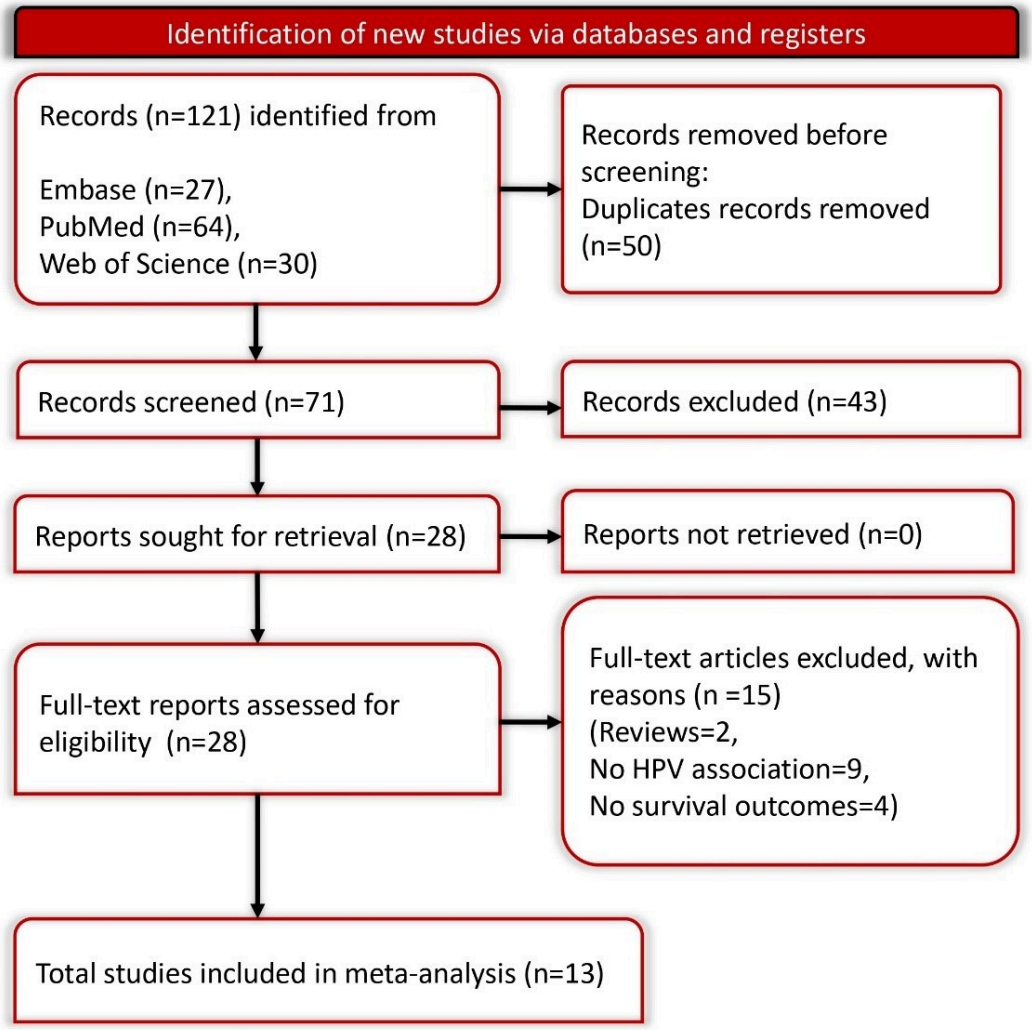

Figure 1.PRISM flow diagram

Overall Survival of HPV-Negative HNCs Based on Gender

A meta-analysis examined overall survival in HPV-negative HNC patients by gender. The HR for OS, comparing females to males, was 1.053 with a 95% CI from 0.903 to 1.203, indicating no significant difference in overall survival between the genders. The prediction interval ranged from 0.559 to 1.547, highlighting variability in outcomes across different studies. Additionally, the analysis showed significant heterogeneity, as evidenced by an I^2 value of 86%. Figure 3 illustrates these results, suggesting that although individual studies might report either better or worse survival for females, the overall pooled estimate does not demonstrate a significant gender disparity in survival outcomes for HPV-negative HNC patients.

Publication Bias

The unequal distribution of research in the funnel plot (Figure 4) raises the possibility of publication bias. Smaller studies with negative or null results may be underrepresented in the analysis, as seen by this imbalance. Because of these missing studies, the observed effects may be overstated, which emphasizes the need for careful interpretation of the meta-analysis results. Further statistical tests, such as Egger's test, with a p-value of 0.004, confirm the presence of significant publication bias.

Table 1. Characteristics of included studies.

Study	Country	Study design	Males	Females	Type of HNCs	Total no. of HNC patients	Overall score of NOS
Abdel-Rahman 2020 [21]	Canada	Retrospective study	12,976	2548	OPC	15,524	6
Amini 2016 [5]	USA	Retrospective study	3262	690	OPC	3952	5
Baliga 2023 [6]	USA	Retrospective study	1349	249	OPSCC	1727	7
Berger 2021 [16]	USA	Retrospective study	9232	1374	OPC	10606	6
Faraji 2019 [7]	USA	Retrospective study	34,806	7218	OPC	42024	6
Goodman 2015 [17]	USA	Retrospective study	394	135	OPSCC	529	8
Kao 2022 [18]	USA	Retrospective study	11880	2303	OPSCC	14183	7
Li 2018 [10]	USA	Retrospective study	23448	7259	OCSCC, OPSCC	30707	6
Preissner 2022 [8]	Germany	Retrospective study	NA	NA	OPC	62775	7
Sheth 2021 [19]	USA	Retrospective study	129	28	OPSCC	157	8
Wookey 2019 [20]	USA	Retrospective study	9005	4903	Non-OPSCC Carcinoma	13908	6
Wu 2021 [22]	China	Retrospective study	8,308	1,635	HNC	9,943	5
Yin 2018 [9]	USA	Retrospective study	160	79	OPSCC	239	6

HNC: Head and Neck Cancers;NOS: Newcastle-Ottawa Scale; NA: Not Available; OCSCC: Oral Cavity Squamous Cell Carcinoma; OPC: Oropharyngeal Cancer; OPSCC: Oropharyngeal Squamous Cell Carcinoma

Discussion

The results from this review offer important insights into gender disparities in overall survival rates among patients with HPV-associated HNC. While HPV-positive HNCs generally exhibit a more favorable prognosis than HPV-negative ones, our analysis revealed that gender does not significantly affect survival outcomes in HPV-positive cases.

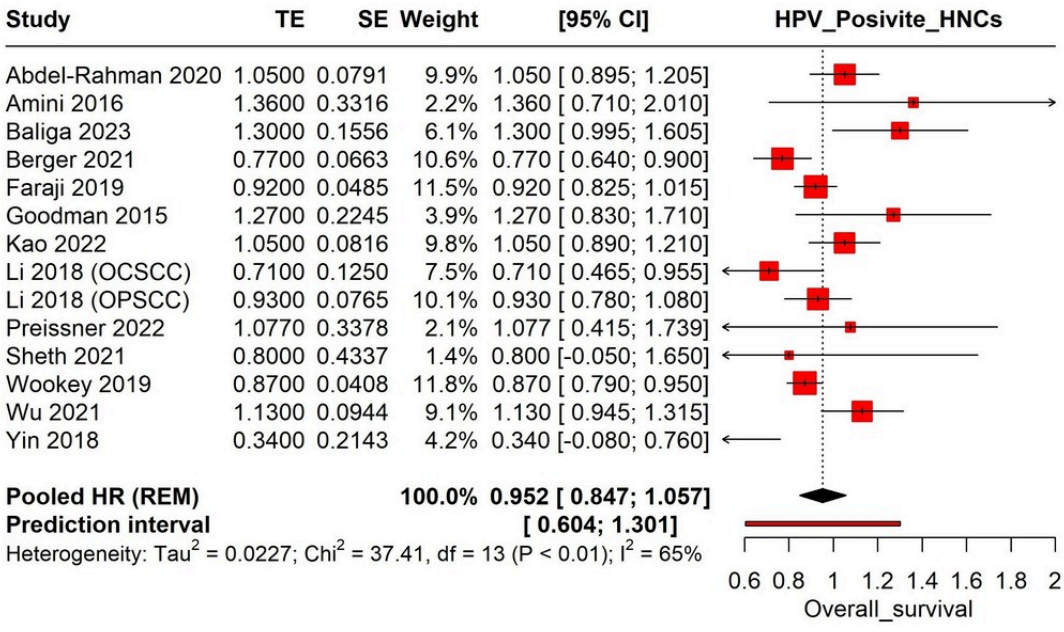

Figure 2. Forest plot showing the overall survival of HPV-positive HNCs female patients compared to males

This comprehensive review synthesizes data from multiple studies, offering a nuanced understanding of these malignancies in the context of gender differences. Our meta-analysis indicated a pooled hazard ratio (HR) of 0.952 for overall survival when comparing female to male patients with HPV-positive HNC. This finding suggests no significant gender difference in survival outcomes, despite some individual studies reporting better survival rates for women. The substantial heterogeneity (I^2 = 65%) highlights the variability across studies. The observed non-significant gender disparity in survival rates for HPV-positive HNC might be attributable to several factors. Biological differences, including immune response to HPV infection, hormonal influences, and genetic variations, differences in socioeconomic status and access to care could play roles but are not fully elucidated. Additionally, lifestyle factors such as alcohol consumption and smoking, which are more prevalent among men and adversely affect cancer prognosis, might contribute to these differences. However, the favorable prognosis generally associated with HPV-positive status might mitigate these adverse effects, leading to similar survival outcomes across genders.

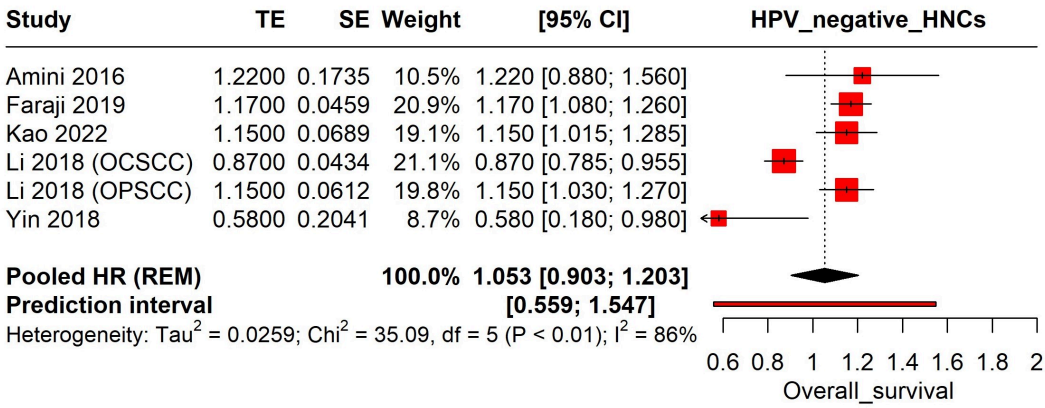

Figure 3. Forest plot showing the overall survival of HPV-negative HNCs female patients compared to males

In contrast, our analysis of HPV-negative HNCs also showed no significant gender difference in survival outcomes, with a pooled HR of 1.053. The heterogeneity was higher (I^2 = 86%), indicating greater variability among the included studies. The lack of a significant gender disparity in HPV-negative HNC could be explained by the dominant influence of environmental risk factors, such as tobacco, betel nut chewing and alcohol, which overshadow potential biological differences between genders. In the United States, current tobacco usage rates are lower among women than men. Consequently, women's lower overall lifetime exposure to tobacco may partially account for their survival advantage slightly with HNCs.

Understanding the impact of gender on survival rates in HPV-associated HNC is vital for improving patient management and tailoring treatment strategies. The lack of significant gender differences in our analysis underscores the importance of considering other demographic and clinical factors in treatment planning [10]. Clinicians should continue to focus on individual patient characteristics, including HPV status, tumor location, stage at diagnosis, and comorbidities, to optimize treatment outcomes.

Moreover, public health strategies should prioritize HPV vaccination and screening programs, particularly targeting populations at higher risk, such as men who have lower vaccination rates and higher incidence of HPV-positive HNC. Efforts to reduce smoking and alcohol consumption across both genders are also crucial, given their significant impact on HNC prognosis [23].

While this study offers valuable insights, it has a few limitations. High heterogeneity among studies, indicated by high I^2 values, reflects variability in populations, methodologies, and treatment protocols, affecting generalizability. The presence of publication bias, confirmed by Egger's test, suggests underrepresentation of smaller studies with null results, potentially skewing estimates. The retrospective nature of most studies also limits causal inference and increases selection bias risk. Despite these limitations, the study's strengths include a comprehensive literature search, robust statistical methods, adherence to PRISMA guidelines, and a large, diverse sample size.

These strengths enhance the reliability and applicability of the findings, providing critical insights into gender disparities in HPV-associated head and neck cancer and informing future research and clinical practice.

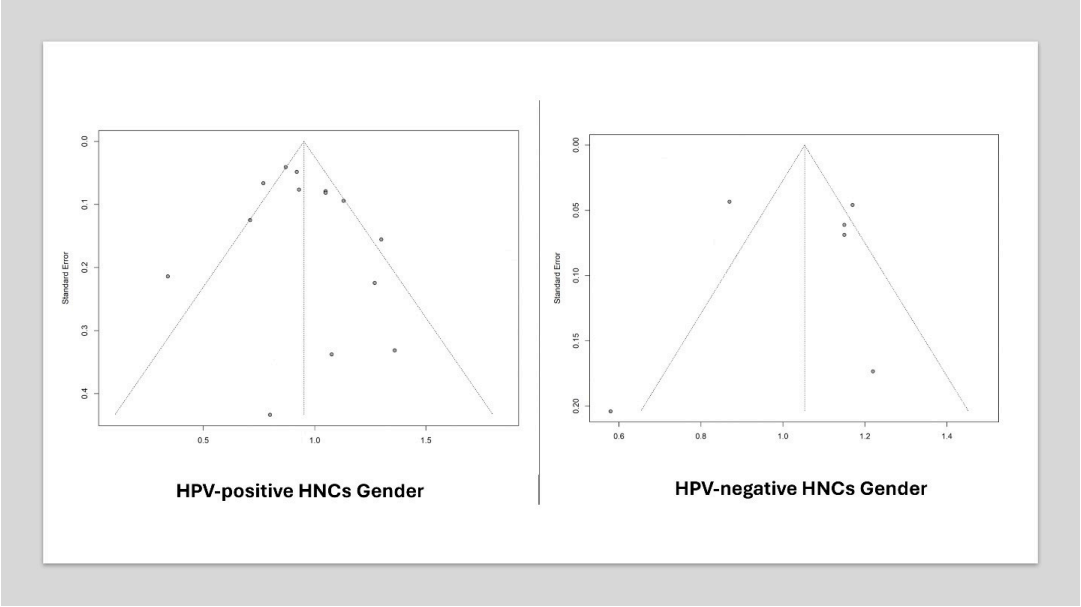

Figure 4.The funnel plot represents the publication of the studies included

This review highlights the need for more detailed investigations into the biological mechanisms underlying HPV-associated HNC and how they might differ between genders. Prospective cohort studies with larger, more diverse populations and standardized methodologies are necessary to validate our findings and explore the potential influences of hormonal, genetic, and immunological factors on survival outcomes.

Additionally, research should examine the interplay between gender, HPV status, race, age and treatment modalities. Understanding how these variables interact can lead to more personalized and effective treatment approaches, aligning with the goals of precision medicine.

Conclusion

This review found no significant gender differences in overall survival rates for patients with HPV-associated HNC, despite some individual studies suggesting better outcomes for women. The analysis highlights substantial heterogeneity and potential publication bias, underscoring the complexity of interpreting survival outcomes across genders. These findings emphasize the importance of individualized patient care that considers various demographic and clinical factors beyond gender alone. Moving forward, future research should focus on detailed, prospective studies to better understand the biological and environmental interactions influencing survival in HPV-associated HNC. Enhanced public health strategies, including targeted HPV vaccination and lifestyle modifications, remain crucial for improving outcomes across all patient populations.

Abbreviations

CI: Confidence interval

HR: Hazard ratios

HNC: Head and neck cancers

HPV: Human Papillomavirus

OCSSC: Oral cavity squamous cell carcinoma

OR: Oropharyngeal cancer

OPSCC: Oropharyngeal squamous cell carcinoma

OS: Overall survival

Supporting information: None

Ethical Considerations: Not applicable

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Clinical Trial: Not applicable

Consent for publication: Note applicable

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