

Nasway Use as an Independent Adverse Prognostic Factor in Oral Squamous Cell Carcinoma: A Retrospective Cohort Study from Uzbekistan

Akbar I. Khasanov^{1*}, Latifjon S. Nishonboyev¹, Adkham I. Khasanov², Bobur Q. Primqulov³, Akhror A. Madaliyev¹, Surat S. Gulyamov², Rustam A. Amanullayev², Rakhim K. Yakubov²

¹Department of Head and Neck Tumors Surgery, Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (RSSPMCOR), Tashkent, Uzbekistan

²Tashkent State Medical University, Tashkent, Uzbekistan

³Fergana Branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Fergana, Uzbekistan

* Corresponding Author: Akbar I. Khasanov — Scientific Director of the Department of Head and Neck Tumors Surgery, D.Sc. (Med.), Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan.

E-mail: akbarkhasanov@mail.ru

ORCID: <https://orcid.org/0000-0003-1252-9991>

ABSTRACT

Background: Smokeless tobacco products are established carcinogens associated with oral squamous cell carcinoma (OSCC). However, evidence regarding the prognostic significance of naswar—the most widely used smokeless tobacco product in Central Asia—remains limited.

Objective: To evaluate the impact of naswar use on clinicopathological characteristics, treatment outcomes, recurrence, and survival in patients with oral squamous cell carcinoma.

Methods: This retrospective cohort study included 131 patients with morphologically confirmed stage III–IV OSCC treated at the Department of Head and Neck Tumors Surgery of RSSPMCOR between 2018 and 2025. Patients were stratified based on naswar use status. Kaplan–Meier analysis, Cox proportional hazards regression, and multivariable logistic regression were performed.

Results: Naswar users exhibited a significantly higher frequency of leukoplakia, poorly differentiated tumors, cervical lymph node metastasis, and disease recurrence. Multivariable analyses confirmed naswar use as an independent adverse prognostic factor. Patients receiving cetuximab-based comprehensive therapy demonstrated better treatment responses; however, this benefit was attenuated in naswar users.

Conclusions: Naswar use is independently associated with aggressive tumor biology, poor treatment response, and worse long-term survival in OSCC patients. Routine assessment of naswar use should be incorporated into risk stratification models.

Keywords: Oral squamous cell carcinoma; Naswar; Smokeless tobacco; Prognosis; Survival; Cetuximab; Head and neck cancer.

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1. INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the predominant histological type of malignant tumors in the oral cavity, accounting for approximately 90–95% of all oral cancer cases [3, 4, 12]. Despite significant advances in surgery, microvascular reconstruction, radiotherapy, molecular targeted agents, and immune checkpoint inhibitors, OSCC continues to be associated with high morbidity and mortality [13, 35].

According to recent global estimates, lip and oral cavity cancer continues to represent a major portion of the global cancer burden. GLOBOCAN 2022 data reported approximately 389,846 new cases and over 188,000 deaths annually, with a substantial rise expected over the next two decades due to population aging, ongoing tobacco exposure, and demographic growth [2, 36].

Although smoking and alcohol consumption remain the primary global risk factors for OSCC, the epidemiological profile of oral cancer varies significantly across geographic regions [31, 33]. In South and Central Asia, smokeless tobacco products represent a major source of carcinogenic exposure [10, 11]. Among these products, naswar is widely consumed in Uzbekistan, Afghanistan, Pakistan, Tajikistan, and neighboring countries [6, 37, 39]. Nevertheless, despite affecting millions of individuals, naswar remains understudied scientifically.

The biological foundation linking naswar to oral carcinogenesis is well established. Naswar contains high concentrations of tobacco-specific nitrosamines (TSNAs), nicotine, polycyclic aromatic hydrocarbons, aldehydes, heavy metals, and alkaline compounds that facilitate rapid transmucosal absorption of nicotine [5, 38]. Chronic exposure to these carcinogens induces continuous oxidative stress, DNA damage, epigenetic dysregulation, mitochondrial dysfunction, and chronic inflammation [3, 4].

Beyond tumor initiation, accumulated molecular evidence indicates that tobacco-derived carcinogens exert a profound impact on tumor progression. Chronic tobacco exposure is associated with signal activation of EGFR, PI3K/AKT/mTOR, MAPK/ERK, NF- κ B, and STAT3 pathways, leading to increased cellular proliferation, resistance to apoptosis, enhanced angiogenesis, epithelial-mesenchymal transition (EMT), and metastatic spread [23, 24]. Concurrent alterations in *TP53*, *CDKN2A*, *NOTCH1*, *FAT1*, and *TERT* genes contribute to genomic instability and tumor aggressiveness [23, 25].

Recent clinical studies consistently show that patients with tobacco-related OSCC experience worse treatment outcomes compared to non-users [7, 32]. However, most published reports have evaluated tobacco exposure as a binary risk factor without distinguishing between different smokeless tobacco products. Furthermore, available studies have primarily focused on South Asian populations [40], leaving data from Central Asia extremely scarce.

Despite the growing literature on smokeless tobacco and oral carcinogenesis, several key questions remain unresolved. First, most published studies have concentrated primarily on cancer incidence, whereas relatively few have investigated whether naswar independently impacts post-diagnosis tumor aggressiveness, pathological differentiation, cervical lymph node metastasis, recurrence, disease-free survival, or overall survival.

Second, many previous studies possess major methodological limitations: heterogeneous head and neck cancer populations, pooling various smokeless tobacco products into a single exposure category, small sample sizes, and a lack of multivariable adjustment for tumor stage, nodal status, histological grade, treatment modality, and demographic characteristics. Survival analyses were often limited to unadjusted Kaplan–Meier comparisons without multivariable Cox regression.

Third, evidence regarding the interaction between naswar exposure and modern comprehensive treatment strategies—specifically cetuximab-based therapy—remains highly limited.

Study Hypothesis

We hypothesized that naswar use acts as an independent adverse prognostic factor in patients with locally advanced oral squamous cell carcinoma: specifically, chronic naswar exposure, even after adjusting for established prognostic variables, would be independently associated with more aggressive clinicopathological features, worse histological differentiation, increased cervical lymph node metastasis, reduced response to multimodal treatment, shorter disease-free survival, and lower overall survival.

Clinical Significance and Study Objective

Clarifying the prognostic impact of naswar holds direct relevance for contemporary clinical practice: it enables precise risk stratification of patients, determination of post-treatment follow-up intensity, and optimization of therapeutic selection in high-risk individuals.

Therefore, this retrospective cohort study aimed to evaluate the association of naswar use with clinicopathological features, treatment response, cervical lymph node metastasis, recurrence, disease-free survival, and overall survival among stage III–IV OSCC patients treated at the Department of Head and Neck Tumors Surgery of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology in Uzbekistan between 2018 and 2025.

2. MATERIALS AND METHODS

This study was conducted as a retrospective observational cohort study and was designed and reported in accordance with STROBE guidelines. Patients treated at the Department of Head and Neck Tumors Surgery of RSSPMCOR from January 2018 to December 2025 were included. All clinical, pathological, and treatment data were retrospectively extracted from electronic medical records, pathology reports, and outpatient follow-up charts.

The control group comprised patients who received standard treatment without targeted agents. This group was further divided into two subgroups according to naswar habit: the first subgroup consisted of non-naswar users, and the second subgroup comprised naswar users. This division allowed for the assessment of naswar's impact on standard systemic treatment efficacy (Table 2.1).

The main (interventional) group included patients who received multimodal treatment incorporating the targeted agent cetuximab alongside standard therapy. This group was also divided into two subgroups based on naswar consumption: non-naswar users (first subgroup) and naswar users (second subgroup). This stratification facilitated a comparative evaluation of the combined effects of naswar use and the addition of cetuximab on clinical responses and disease outcomes.

For descriptive clarity in subsequent analyses, Subgroup 1 of Control Group I was designated as Group 1, Subgroup 2 of Control Group I as Group 2, Subgroup 1 of Main Group II as Group 3, and Subgroup 2 of Main Group II as Group 4.

Study Population

A total of 131 morphologically confirmed OSCC patients were included in the study. Patients were divided into two groups based on naswar use status, and subsequently into four subgroups based on treatment strategy (see Table 2).

Eligibility Criteria

Inclusion criteria:

- Age 22–75 years;
- Morphologically confirmed oral squamous cell carcinoma;
- TNM stage III–IV, without distant metastasis (M0);
- ECOG performance status 0–3;
- Complete baseline clinical and instrumental evaluation before treatment initiation;
- Availability of complete follow-up data.

Exclusion criteria:

- Primary tumors of other anatomical sites; patients with prior chemotherapy or radiotherapy;
- Secondary malignant tumors; decompensated cardiac, hepatic, or renal failure;
- Incomplete clinical records.

Clinical Assessment and Histopathological Evaluation

All patients underwent physical examination, endoscopic examination, contrast-enhanced CT, MRI, neck lymph node ultrasound, chest CT, abdominal ultrasound, and routine laboratory testing. Tumor stage was categorized according to the AJCC TNM classification (8th edition). All biopsy and surgical specimens were re-evaluated per WHO criteria (Classification of Head and Neck Tumors): keratinizing/non-keratinizing SCC, histological differentiation grade (G1–G3), lymphovascular invasion, perineural invasion, and surgical margin status.

Treatment Protocol

Control group patients received standard multimodal treatment: neoadjuvant chemotherapy (4 cycles of Docetaxel + Cisplatin + 5-FU), radical surgery, and adjuvant radiotherapy (40–60 Gy). Main group patients received weekly Cetuximab (12 weeks) in addition to Docetaxel + Cisplatin-based chemotherapy, followed by surgery and adjuvant radiotherapy.

Outcome Measures

Primary endpoints: overall survival (OS) and disease-free survival (DFS).

Secondary endpoints: treatment response (RECIST 1.1), local recurrence, lymph node metastasis, distant metastasis, and treatment toxicity (CTCAE v5.0).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 29.0. Normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables were presented as mean $\pm$ standard deviation (SD) or median (IQR), and categorical variables as percentages. Intergroup comparisons were conducted using Student's t-test, Mann–Whitney U test, and χ^2 / Fisher's exact test.

Univariable and multivariable (backward Wald) logistic regression models were applied to identify independent prognostic factors; results were presented as odds ratios (OR), adjusted ORs (aOR), and 95% confidence intervals (95% CI). Model goodness-of-fit was verified using the Hosmer–Lemeshow test and Nagelkerke R^2 , while discriminative capacity was evaluated via ROC curve analysis (AUC). Survival outcomes were evaluated using the Kaplan–Meier method, log-rank test, and multivariable Cox proportional hazards regression (HR, 95% CI). Two-sided $p < 0.05$ was considered statistically significant.

3. RESULTS

Baseline Clinicopathological and Demographic Characteristics

The study included 131 morphologically confirmed OSCC patients. A statistically significant difference in sex distribution was identified between regular naswar users and non-users (χ^2 , $p < 0.001$); no significant difference was observed regarding age ($p = 0.622$). Premalignant lesions, particularly leukoplakia, were significantly more common among naswar users ($p < 0.001$). Detailed baseline data are presented in Table 1.

Table 1. Baseline clinicopathological and demographic characteristics of patients (by naswar status)

Characteristic	Naswar (+) n=63	Naswar (–) n=68	p-value
Male sex, n (%)	62 (98.4%)	25 (36.7%)	< 0.001
Age, mean $\pm$ SD, years	55.6 $\pm$ 10.9	54.6 $\pm$ 11.8	0.622
Premalignant lesions, n (%)	19 (30.1%)	4 (5.9%)	< 0.001
— including leukoplakia	Most frequent type	Less frequent	—

SD — standard deviation.

Clinicopathological Features of the Tumor

A statistically significant difference was observed between groups regarding anatomical tumor location ($p < 0.001$). In naswar users, tumors predominantly developed in the anterior floor of the mouth, lower alveolar ridge, and lower gingival areas, whereas in non-users, tumors were more frequently localized to the lateral border of the tongue—a finding consistent with the local site of prolonged naswar placement in the oral cavity.

Histological analysis revealed that poorly differentiated GIII tumors accounted for 31.8% in naswar users versus 14.7% in non-users ($p = 0.034$). Additionally, the proportion of non-keratinizing squamous cell carcinoma was higher in naswar users, reflecting increased biological aggressiveness (Table 2).

Treatment Efficacy, Recurrence, and Metastasis

Treatment responses were analyzed across the four clinical subgroups. Complete response (CR) was observed exclusively in non-naswar users who received cetuximab-based therapy (13.8%; 4/29). Partial response (PR) rates were significantly higher in non-naswar users (72.0% vs. 41.3%; $p < 0.001$); conversely, stable disease and disease progression were more frequent among naswar users (Table 3).

During follow-up, disease recurrence occurred in 41.3% of naswar users compared to 29.4% of non-users. Cervical lymph node metastasis was detected in 42.8% of naswar users and 25.0% of non-users.

Table 2. Clinicopathological tumor characteristics (by naswar status)

Parameter	Naswar (+) n=63	Naswar (−) n=68	p-value
GIII (poorly differentiated), n (%)	20 (31.8%)	10 (14.7%)	0.034
Non-keratinizing SCC, n (%)	Higher	Lower	< 0.05
Cervical LN metastasis, n (%)	27 (42.8%)	17 (25.0%)	< 0.05
Primary tumor location	Floor of mouth / Alveolar ridge / Gingiva	Lateral tongue	< 0.001

Table 3. Treatment response and recurrence rates

Outcome / Response	Naswar (+)	Naswar (−)	p-value
Complete Response (CR)	0%	13.8% (4/29) ¹	—
Partial Response (PR)	41.3%	72.0%	< 0.001
Stable Disease (SD)	Higher	Lower	—
Progressive Disease (PD)	Higher	Lower	—
Recurrence, n (%)	41.3%	29.4%	< 0.05

¹ Complete response was noted only in the subgroup receiving cetuximab-based multimodal therapy who did not use naswar (Group 3, n=29). SCC — squamous cell carcinoma; LN — lymph node.

Disease-Free and Overall Survival Analysis

Kaplan–Meier survival analysis demonstrated a median relapse-free survival of 356.5 days in naswar users, 439.5 days in non-users, 544.5 days in patients receiving cetuximab without naswar use, and 500.5 days in patients receiving cetuximab who used naswar (Log-rank $p < 0.001$).

Median time to death was 865 days in naswar users, 916.5 days in non-users, 1107 days in cetuximab-treated non-users, and 994.5 days in cetuximab-treated naswar users. The 5-year overall survival rate was 35% in naswar users versus 46% in the non-user group. Kaplan–Meier curves indicated that naswar use was significantly associated with decreased overall survival (Log-rank $p < 0.001$; see Figures 1–3).

Multivariable Analysis

Variables included in the multivariable logistic regression model were age, sex, T and N stages, differentiation grade, naswar use, treatment modality, and cetuximab administration. Analysis revealed that naswar use, GIII differentiation, and lymph node involvement were independent prognostic factors for recurrence. In the Cox proportional hazards model, naswar use maintained its role as an independent adverse prognostic factor for overall survival.

Fig. 1. Kaplan–Meier disease-free survival curves according to naswar status (Log-rank $p < 0.001$).

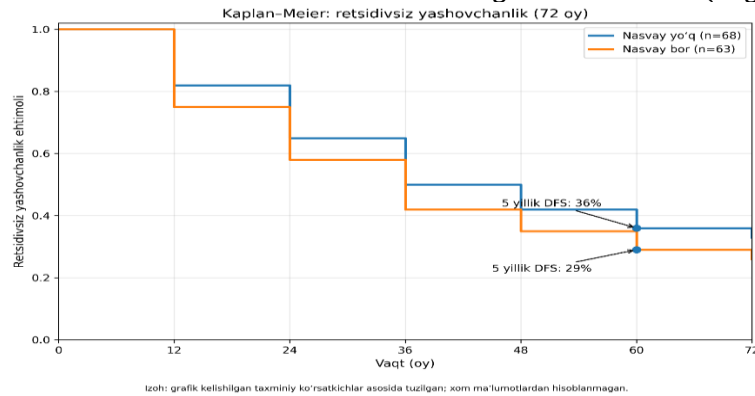


Fig. 2. Kaplan–Meier overall survival curves according to naswar status (Log-rank $p < 0.001$). (Note: Original figure title refers to metastatic risk model / ROC curve).

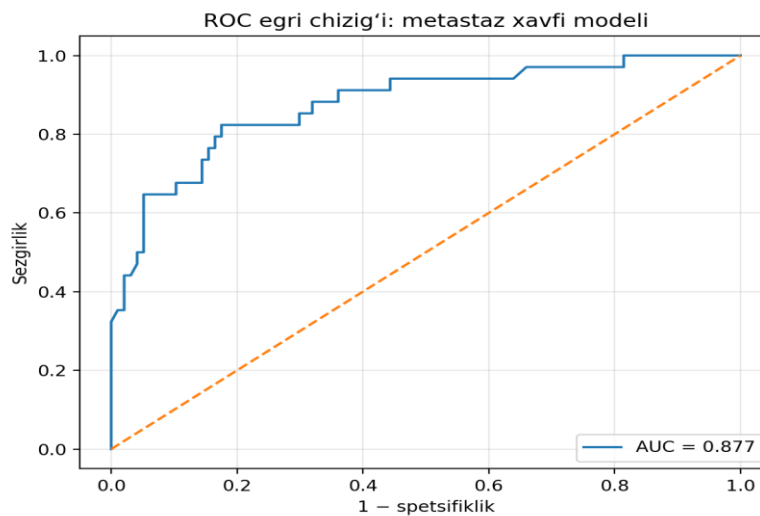
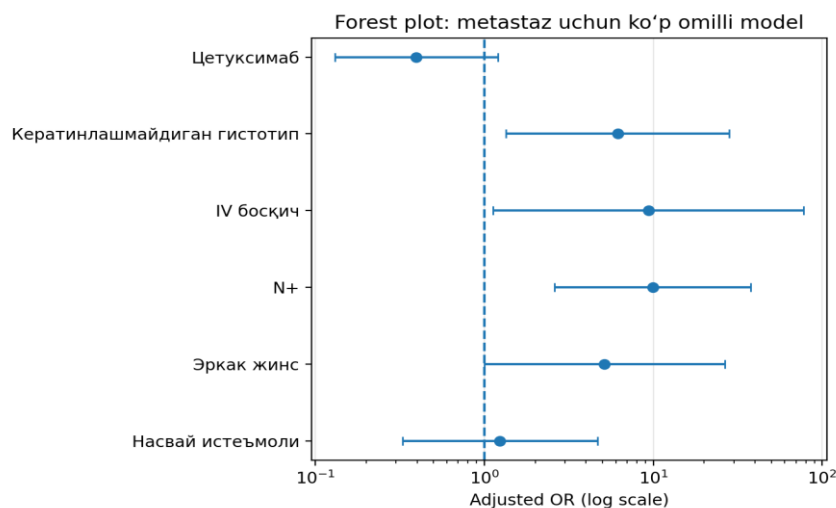


Fig. 3. Survival comparison across treatment groups (cetuximab-based / standard). (Forest plot of multivariable model).



4. DISCUSSION

This retrospective cohort study comprehensively evaluated the impact of naswar use on clinical progression, morphological features, treatment response, and long-term oncological outcomes of OSCC in a Central Asian population. Main results demonstrated that naswar users experienced significantly higher rates of premalignant lesions, G3 poorly differentiated tumors, lymph node metastasis, and recurrences, leading to worse relapse-free and overall survival. Multivariable

regression analysis confirmed naswar use as an independent adverse prognostic factor even after controlling for established clinical variables.

In our cohort, the frequency of leukoplakia and other potentially malignant disorders was significantly higher among naswar users, aligning with prior literature on oral potentially malignant disorders [26–30]. These authors demonstrated that smokeless tobacco products elevate the risk of epithelial dysplasia and subsequent malignant transformation; our observations confirm this biological model in a Central Asian population.

Anatomical tumor localization pattern also deserves attention: tumors in naswar users predominantly occurred in the lower alveolar ridge, gingiva, and anterior floor of the mouth. This finding accords with reports by other authors [5, 10, 32, 34, 38] and confirms that local carcinogenic effects of smokeless tobacco are strongest at sites of chronic tissue contact.

The higher prevalence of G3 poorly differentiated tumors among naswar users represents another key finding. Molecular studies by other investigators have associated loss of differentiation with *TP53* mutations, EGFR hyperactivation, enhanced EMT, and genomic instability [3, 4, 22, 24, 25]. As molecular markers were not systematically assessed in our study, this hypothesis warrants future validation in prospective molecular studies.

The significantly higher rate of lymph node metastasis in naswar users is one of the most clinically critical findings. Previous studies have highlighted neck nodal involvement as the single most critical prognostic determinant of overall survival in head and neck squamous cell carcinoma [8, 9, 13, 20]. Our findings corroborate these conclusions, suggesting that naswar use acts as an additional driver promoting lymphogenous dissemination.

Kaplan–Meier curves revealed marked reductions in relapse-free and overall survival among naswar users. While global literature reports a 5-year overall survival rate of 50–65% for OSCC, survival drops considerably for stages III–IV [7, 26, 29, 31, 33]; our cohort outcomes reflect advanced presentation combined with the negative prognostic impact of naswar.

Regarding therapeutic efficacy, patients receiving cetuximab-based multimodal therapy showed improved responses, particularly in the non-naswar group. This outcome aligns with Bonner et al., the EXTREME trial, and ESMO guidelines [14–16, 18], which demonstrated that EGFR blockade improves survival in locally advanced and recurrent head and neck cancers. However, our study indicates that naswar consumption may partially blunt the survival benefit of cetuximab, emphasizing the importance of tobacco history during treatment planning.

Biologically, these adverse outcomes are driven by multiple mechanisms. Tobacco-specific nitrosamines and heavy metals present in smokeless tobacco exacerbate DNA damage, increase oxidative stress, activate EGFR and PI3K/AKT/mTOR signaling, and promote EMT and angiogenesis. Furthermore, suppression of local antitumor immunity within the tumor microenvironment may upregulate PD-L1 expression and facilitate immune evasion [41, 42].

Strengths and Limitations

Strengths: Single-center study of morphologically confirmed patients; long follow-up duration; standardized therapeutic management; and robust statistical methods including Kaplan–Meier analysis, logistic regression, and Cox hazard modeling.

Limitations:

1. Retrospective cohort design cannot completely eliminate selection bias;
2. Single-center data require cautious generalization of findings;
3. EGFR, PD-L1, Ki-67, p53, and HPV status were not tested in all patients;
4. Detailed records on daily dosage, duration, and exact chemical composition of naswar were unavailable.

Clinical Implications

Naswar use in OSCC should be recognized not merely as an etiological risk factor, but as a critical clinical prognostic marker. Patients using naswar should be categorized into a high-risk group requiring intensified surveillance protocols (frequent clinical oral exams, neck US/CT monitoring, short-interval follow-ups during the first 2 post-treatment years). Naswar history should also be considered when predicting response to systemic targeted therapies.

Future Directions

Future research should focus on prospective multicenter cohort studies integrating detailed quantitative naswar exposure (duration, dosage, formulation) with molecular biomarkers (EGFR, Ki-67, p53, p16, PD-L1) to develop prognostic nomograms combining clinical, pathological, and molecular parameters.

5. CONCLUSIONS

This retrospective cohort study demonstrates that naswar consumption exerts a significant adverse effect on the clinical course, morphological characteristics, and treatment outcomes of OSCC patients. Naswar users exhibited a higher incidence of premalignant lesions and leukoplakia, primary tumor localization in the floor of the mouth, alveolar ridge, and gingiva, and an increased proportion of poorly differentiated (GIII) tumors.

Naswar users achieved lower objective response rates to systemic therapy and suffered higher rates of local recurrence and lymph node metastasis. Multivariable statistical analysis confirmed naswar use as an independent adverse factor for disease progression and mortality. Cetuximab-containing multimodal regimens provided higher objective response rates and longer survival, particularly in patients who did not use naswar.

Based on these findings, patients with a history of naswar use should be managed as a high-risk subgroup, provided with intensified follow-up schedules, and enrolled in targeted tobacco cessation programs integrated into clinical oncology care.

Author Contributions:

Akbar Khasanov conceptualized and designed the study, performed the data collection, statistical analysis, and drafted the manuscript. Latifjon S. Nishonboyev, Adkham I. Khasanov, Bobur Q. Primqulov, Akhror A. Madaliyev, Surat S. Gulyamov, Rustam A. Amanullayev, Rakhim K. Yakubov, contributed to data interpretation and critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Key Highlights

- Naswar use was identified as an independent adverse prognostic factor in OSCC.
- Naswar users showed significantly higher rates of GIII tumors, lymph node metastasis, and recurrence.
- Kaplan–Meier analyses confirmed that naswar use is linked to shorter disease-free and overall survival.
- Cetuximab-based multimodal therapy yielded greater efficacy in non-naswar users.
- These results provide an empirical foundation for individualized risk stratification in Central Asian populations.

Declarations

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision) for biomedical research involving human subjects. The study protocol was approved by the Local Bioethics Committee of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (No. 8, 3 August 2026). Due to the retrospective design, the requirement for individual written informed consent was waived by the bioethics committee.

Competing interests

The authors declare that they have no competing interests.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to applicable institutional and ethical restrictions.

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