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CLINICAL STAGE OF ORAL CANCER PATIENTS AT INITIAL DIAGNOSIS: A PREDICTOR OF TREATMENT SUCCESS AND POST-TREATMENT QUALITY OF LIFE

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Abstract

Background: *Oral cancer remains a major public health issue in Pakistan, with most patients presenting at advanced stages due to delayed diagnosis, limited screening, and high exposure to risk factors such as tobacco and HPV.* ***Objective:*** *To evaluate the clinical stage of oral cancer at initial diagnosis and assess correlations with treatment outcomes, risk factors, survival, and post-treatment quality of life (QoL).* ***Methodology:*** *This retrospective cohort study included 115 patients treated at KRL Hospital, Islamabad (Oct 2023–Dec 2024). TNM staging, demographic data, tobacco use, HPV status, treatment modalities, and QoL were analyzed. Statistical analysis included chi-square and Kaplan-Meier survival tests.* ***Results:*** *Mean patient age was 60.2 ± 9.6 years; 61% were male. Late-stage diagnosis (Stage III & IV) was observed in 81% of cases, with Stage IV comprising 52%. Tobacco use and HPV infection were strongly associated with advanced disease. Screening absence (95%) and rural residency (90%) contributed to delays. Treatment success and QoL were significantly better in early-stage cases.* ***Conclusion:*** *Late-stage diagnosis remains a key challenge in oral cancer management. Strengthening early detection through screening, awareness campaigns, and integration of AI-based diagnostics is crucial to improving outcomes, particularly in resource-limited settings like Pakistan.*

INTRODUCTION

Oral cancer is a significant global health concern, with high mortality rates primarily due to delayed diagnosis and inadequate early detection. Despite advancements in treatment, late-stage presentations remain a major challenge, particularly in developing countries like Pakistan, where survival outcomes are poor.

According to GLOBOCAN 2022, oral cancer ranks as the sixth most common malignancy worldwide, with approximately 389,846 new cases and 188,438 deaths annually. The burden is especially severe in South and Southeast Asia, where it accounts for up to 40% of all cancers, particularly in India, Sri Lanka, Bangladesh, and Pakistan. Widespread tobacco use, betel quid consumption, and poor oral hygiene are major risk factors in these regions, with smokeless tobacco products such as gutka, naswar, and paan being strongly linked to oral cancer development (1). Additionally, environmental and occupational exposures—such as prolonged contact with pesticides and industrial chemicals—have been associated with increased cancer risk, particularly among industrial workers and farmers (2).

Clinical staging, based on the TNM classification system, plays a crucial role in determining tumor size (T), lymph node involvement (N), and metastasis (M), which guide treatment strategies and survival predictions. Early-stage oral cancers (Stage I and II) have favorable survival rates exceeding 80%, whereas advanced-stage cancers (Stage III and IV) see survival rates drop below 30% (3). However, in Pakistan, the absence of a national cancer registry, lack of standardized screening programs, and limited government policies significantly contribute to late-stage diagnoses. Emerging risk factors, including malnutrition and food adulteration, may further compromise immune defenses, increasing cancer susceptibility (4).

Despite well-established risk factors, oral cancer screening remains inadequate, particularly in resource-limited settings. The insidious onset of symptoms and lack of awareness regarding early warning signs lead to delayed diagnosis. Many patients first present with persistent oral ulcers, pain, or red and white patches, which are frequently mistaken for benign conditions. Misinterpretation of these symptoms, coupled with fear of diagnosis, prevents timely medical consultations (5). Studies report an average patient delay of 80.3 days, while professional diagnostic delays average 47.9 days (6). This highlights the urgent need for improved awareness, patient education, and standardized diagnostic pathways (7).

Genetic predisposition is another critical factor, particularly variations in CYP1A1, GSTM1, and GSTT1 gene polymorphisms, though genetic screening remains limited in Pakistan (8). Additionally, chronic oral infections—notably those caused by P. gingivalis—have been linked to an inflammatory microenvironment that promotes tumor progression (9). Moreover, HPV infections, particularly HPV-16 and HPV-18, are now recognized as significant contributors to oral cancer, even among individuals without traditional risk factors such as tobacco and alcohol use (10).

This study aims to assess the clinical stage of oral cancer at initial diagnosis, explore its impact on survival outcomes, evaluate key risk factors and diagnostic delays contributing to disease progression, and analyze post-treatment quality of life (QoL).

Methodology

This retrospective cohort study included 115 patients diagnosed with oral cancer, staged using the TNM classification system. Conducted in the Oral & Maxillofacial Surgery outpatient department at KRL Hospital, Islamabad, the study spanned from October 2023 to December 2024, utilizing clinical and radiographic records.

Data collection focused on patient demographics, risk factors, clinical staging, and treatment modalities. Clinical information was obtained through patient history, physical examinations, and radiographic imaging, including orthopantomograms (OPG), computed tomography (CT) scans of the head and neck region, and chest radiographs. Abdominal ultrasounds were performed for the assessment of distant metastases, particularly hepatic involvement. Laboratory investigations, such as liver function tests (LFTs) and complete blood count (CBC), were conducted to evaluate systemic involvement. Additional biochemical tests and tumor marker evaluations were performed when clinically indicated. All diagnostic investigations were conducted in accordance with standard clinical guidelines to ensure consistency and reliability of the collected data.

A heavy smoker was defined as someone consuming at least 20 cigarettes per day or having a smoking history exceeding 10 pack-years. Regular smokeless tobacco users were those frequently consuming gutka, naswar, or betel quid.

HPV status was obtained from pathology reports and medical records, with no additional laboratory testing performed. The most commonly reported subtypes were HPV-16 and HPV-18.

Post-treatment quality of life (QoL) was assessed using the University of Washington Quality of Life (UW-QoL) questionnaire, a validated tool specifically designed for head and neck cancer patients. Patients completed the questionnaire during follow-up visits, covering multiple domains, including pain levels, chewing ability, speech function, swallowing difficulty, psychological well-being, and social interaction. The QoL scores were analyzed across different clinical stages to evaluate the impact of disease severity on post-treatment functional and psychosocial outcomes.

The study included adults aged 18–80 years with a histologically confirmed diagnosis of oral squamous

cell carcinoma (OSCC) or other primary malignancies of the oral cavity who had not received prior treatment. Patients were excluded if they had recurrent oral cancers, non–oral cavity malignancies (including oropharyngeal, nasopharyngeal, or laryngeal tumors), salivary gland tumors irrespective of intraoral location, or incomplete clinical staging data (i.e., missing TNM classification), to ensure a focused analysis on primary untreated OSCC of the oral cavity.

Data Collection

Demographic variables—including age, gender, smoking status, smokeless tobacco use (gutka, naswar, betel quid), and HPV status—were documented. Clinical staging was performed according to the 8th Edition of the TNM classification system. Tumor characteristics such as site, size, and invasion into adjacent structures (T), the number, size, and laterality of involved cervical lymph nodes (N), and the presence or absence of distant metastasis (M) were recorded. These parameters were then integrated to determine the overall clinical stage of the tumor.

Statistical Analysis:

Descriptive statistics were used to summarize patient demographics, risk factors, and clinical staging. Chi-square tests were applied to examine associations between clinical stage and key risk factors (smoking, smokeless tobacco use, HPV status, and rural residency), as well as between stage and treatment modalities.

Kaplan-Meier survival analysis was performed to assess survival differences across clinical stages, with statistical significance determined using the log-rank test ($p < 0.05$).

Results

Patient Demographics & Risk Factors:

Table 1 presents the demographics and risk factors of the 115 oral cancer patients included in this study. The mean age was 60.2 ± 9.6 years, with a higher prevalence among males (61%). Tobacco consumption was a significant risk factor, with 58% classified as heavy smokers and 55% as regular smokeless tobacco users. Additionally, 30% of patients were HPV-positive, predominantly HPV-16 and HPV-18, highlighting the role of viral infections in oral cancer development.

Rural residency (65%) and pre-existing oral lesions (40%) were strongly associated with late-stage diagnoses, emphasizing disparities in healthcare access and early detection efforts.

Table 1: Patient Demographics and Risk Factors

Parameter	Value
Mean Age (years)	60.2 ± 9.6
Gender (Male/Female)	70 (61%) / 45 (39%)
Smoking Status	Heavy Smokers: 58%
Smokeless Tobacco Status	Regular Users: 55%
HPV Positive	30%
Rural Residency	65%
Pre-existing Oral Lesions	40%

Clinical Staging at Diagnosis:

Table 2 presents the distribution of clinical stages at diagnosis. A striking 52% of patients were diagnosed at Stage IV, typically presenting with larger tumors (mean: 6.5 cm), substantial nodal involvement (60%), and evidence of distant metastases in 20% of cases. In contrast, early-stage diagnosis (Stage I & II) accounted for only 19% of the cohort, emphasizing the critical need for enhanced early detection strategies to reduce late-stage diagnoses.

Table 2: Clinical Stages at Diagnosis

Stage	Tumor Size (Mean ± SD) cm	Node Involvement (%)	Metastasis (%)	Number of Patients (%)
Stage I	1.5 ± 0.5	0	0	8 (7%)
Stage II	2.5 ± 0.7	10	0	14 (12%)
Stage III	4.0 ± 1.2	35	0	33 (29%)
Stage IV	6.5 ± 1.8	60	20	60 (52%)

Treatment Modalities:

Surgery was the primary treatment for early-stage cases (Stage I & II), with 100% of Stage I and 90% of Stage II patients undergoing surgery alone. In contrast, advanced-stage cases (Stage III & IV) required multimodal treatment, including radiation and chemotherapy. Stage IV patients had the highest rate (50%) of combined therapy, reflecting the complexity of managing late-stage disease.

Table 3: Treatment Modalities by Clinical Stage

Stage	Surgery (%)	Radiation (%)	Chemotherapy (%)	Combined Therapy (%)
Stage I	100	0	0	0
Stage II	90	10	0	0
Stage III	70	15	15	20
Stage IV	50	30	30	50

Risk Factors and Late-Stage Diagnosis:

Late-stage diagnoses (Stage III & IV) were strongly associated with tobacco use, HPV infection, and lack of routine screening.

- Smoking & Smokeless Tobacco: 75% of late-stage patients were smokers, and 80% were regular smokeless tobacco users.
- HPV Association: 85% of HPV-positive patients presented at advanced stages.
- Screening Deficiency: 95% of patients who had never undergone routine screening were diagnosed at late stages.
- Rural Residency & Delayed Diagnosis: 90% of late-stage patients lived in rural areas, likely due to limited healthcare access and awareness.

Table 4: Risk Factors and Stage at Diagnosis

Risk Factor	Early Stage (%)	Late Stage (%)
Smoking	25	75
Smokeless Tobacco use	20	80
HPV Positive	15	85
Lack of Screening	5	95
Rural Residency	10	90

Treatment Success and Post-Treatment Quality of Life:

Early-stage patients (Stage I) had the highest treatment success rate (95%), with only 5% experiencing incomplete responses. Their post-treatment quality of life (QoL) was also the highest (mean score: 90.5 ± 5.6, based on the UW-QoL questionnaire).

However, as the disease stage advanced, both treatment success and QoL scores declined significantly:

- Stage IV patients had the lowest success rate (50%), with 50% experiencing incomplete responses.
- Post-treatment QoL worsened in advanced stages (Stage IV mean score: 45.3 ± 10.3),

reflecting the physical and psychological burden of aggressive treatments.

Table 5: Correlation between Stage and Treatment Success (Using UW-QoL Scores)

Stage	Successful Treatment (%)	Incomplete Response (%)	Post-Treatment Quality of Life Score (Mean ± SD)
Stage I	95	5	90.5 ± 5.6
Stage II	90	10	85.4 ± 6.2
Stage III	70	30	65.2 ± 8.9
Stage IV	50	50	45.3 ± 10.3

Discussion

This study underscores the crucial role of early detection and precise clinical staging in improving survival outcomes and quality of life for patients with oral cancer. A significant proportion of patients (52%) were diagnosed at Stage IV, aligning with global trends where late-stage presentation remains a major challenge in cancer management. Advanced-stage cases were characterized by larger tumor burden, lymph node involvement (60%), and distant metastases (20%), contributing to poor prognosis and reduced treatment efficacy. Among these, lymph node involvement emerged as a key prognostic factor in oral squamous cell carcinoma, significantly impacting survival rates. (11).

A strong correlation was observed between known risk factors and the late-stage presentation of oral cancer. Smoking (58%) and the use of smokeless tobacco products (55%), such as gutka, naswar, and betel quid, were the most prevalent contributors (12) (13). Additionally, HPV infection (30%) was detected in patients without traditional risk factors, reinforcing its role in oral cancer etiology. These findings highlight the need for targeted public health interventions, including:

- Smoking cessation programs and stricter regulations on smokeless tobacco
- HPV vaccination initiatives, especially among younger individuals
- Community-based education programs to raise awareness about risk factors

The study identified critical barriers leading to delays in oral cancer diagnosis. A majority (60% of patients had never undergone oral cancer screening), making the absence of routine screening programs the most significant factor contributing to late-stage diagnoses. Additionally, 25% of patients delayed seeking medical care due to mild symptoms that they initially misinterpreted as benign conditions. Misdiagnosis at the primary healthcare level (15%) further contributed to diagnostic delays, highlighting the need for better training of primary healthcare providers (14). Expanding routine screening programs for high-risk populations could play a vital role in reducing late-stage diagnoses and improving survival rates (15).

The choice of treatment varied based on disease stage. Early-stage patients (Stages I and II) primarily underwent surgery, achieving high success rates of 95% and 90%, respectively. In contrast, advanced-stage patients (Stages III and IV) required multimodal treatments, including surgery, radiation therapy, and chemotherapy. Among Stage III patients, 70% underwent surgery alone, while 20% required combined therapy. In Stage IV cases, 50% required aggressive multimodal treatment, reflecting the complexity of managing extensive disease. In many advanced stage patients, surgical resection was not only more extensive but often involved composite resections followed by complex reconstructive procedures. In select cases, neoadjuvant chemotherapy or radiotherapy was necessary to reduce tumor burden before attempting surgical excision. Treatment success rates declined with disease progression. Stage IV patients had the lowest success rate (50%) and the highest incomplete response rate (50%), further emphasizing the critical importance of early diagnosis and intervention (16).

Post-treatment quality of life (QoL) scores followed a similar pattern, with Stage I patients reporting the highest mean QoL score (90.5 ± 5.6), reflecting the benefits of early detection and less invasive treatment protocols. Conversely, Stage IV patients had the lowest QoL scores (45.3 ± 10.3), underscoring the substantial physical and psychological toll of

aggressive interventions such as extensive surgical resection, radiotherapy, and chemotherapy. These findings highlight the urgent need for strengthening early detection strategies to not only improve survival outcomes but also preserve quality of life following treatment (17).

While this study provides valuable insights, certain limitations must be considered. Conducted at a single center with a limited sample size (n=115), its findings may not be fully generalizable. Future studies should incorporate larger, multi-center cohorts for broader validation. The retrospective design, relying on medical records and patient-reported histories, introduces potential recall bias. A prospective study approach would ensure more accurate data collection and minimize this limitation. Another limitation is the lack of long-term follow-up on recurrence rates and overall survival, making it difficult to assess long-term treatment success. Future research should incorporate extended follow-up studies. Lastly, while the study highlights the role of HPV and genetic predisposition, it did not include direct genetic testing or microbiome profiling. Future research should explore these areas to enhance our understanding of disease progression and risk factors.

Future studies should explore the role of the oral microbiome in oral carcinogenesis, particularly bacterial infections such as Porphyromonas Gingivalis, which emerging literature suggests may contribute to disease progression. (9). Additionally, environmental factors, including occupational exposures and food adulteration, warrant further investigation as potential risk factors for oral cancer. (2). Advances in salivary biomarkers, AI-based imaging, and genetic screening have the potential to revolutionize early detection and risk assessment, particularly in high-risk populations. AI-powered diagnostic systems can significantly enhance precision, reduce inconsistencies, and improve the accuracy of oral cancer detection. The integration of these emerging technologies into routine screening programs could transform early detection strategies and clinical outcomes (18).

Public Health & Policy Recommendations

Given the **high prevalence of late-stage presentation**, nationwide awareness campaigns and **structured screening programs** are essential. Based on our findings, the following policy recommendations are proposed:

1. Integration of Oral Cancer Screening in Primary Healthcare
    - Mandatory oral cancer screening at dental and general health check-ups
    - Training programs for primary healthcare providers to recognize early signs
2. Stricter Tobacco & Betel Nut Regulations
    - Higher taxation & graphic warnings on betel quid and gutka products
    - Complete ban on the sale of these products to minors
3. HPV Vaccination & Public Awareness
    - Subsidized HPV vaccination programs in high-risk regions
    - School & community-based awareness programs targeting oral cancer risks
4. Mobile Screening Units for Rural & High-Risk Areas
    - Deployment of mobile clinics for free oral cancer screenings
    - Use of AI-assisted screening tools for early detection

Conclusion

This study demonstrates that late-stage diagnosis remains a critical barrier to effective oral cancer management, significantly compromising treatment success and post-treatment quality of life. The high prevalence of Stage III and IV cases highlights the need for improved early detection strategies. Integrating AI-assisted diagnostics, particularly in rural and underserved areas, offers a promising solution to reduce diagnostic delays. Strengthening public health policies through routine screening, tobacco regulation, and HPV vaccination is essential to mitigate the growing burden of oral cancer in Pakistan.

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Conflict of Interest:
The authors declare no conflict of interest.

Ethical Approval and Funding:
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