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SURVIVAL AND RADIATION-RELATED OUTCOMES IN LIFELONG NEVER-SMOKERS AND EVER-SMOKERS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA: A PROSPECTIVE MATCHED-PAIR COHORT STUDY FROM A TERTIARY CANCER CARE CENTRE

Radiation Oncology

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ABSTRACT

Background: Although smoking is a well-established prognostic factor in head and neck squamous cell carcinoma (HNSCC), evidence from prospectively matched cohorts evaluating both oncologic outcomes and radiation-related toxicities remains limited, particularly in tertiary cancer care settings. This study aimed to evaluate the independent impact of smoking history on treatment outcomes following curative-intent radiotherapy. **Objective:** To compare survival outcomes, disease control, and radiation-related toxicities between lifelong never-smokers and ever-smokers with HNSCC using a prospective matched-pair cohort design. **Materials and Methods:** This prospective matched-pair cohort study included 70 patients with histologically confirmed HNSCC treated with curative-intent radiotherapy at a tertiary cancer care centre. Thirty-five lifelong never-smokers were matched 1:1 with 35 ever-smokers (>10 pack-years) for age, sex, Karnofsky Performance Status, primary tumour site, AJCC stage, treatment modality, radiation dose, and treatment period. Patients received definitive or postoperative radiotherapy with or without concurrent chemotherapy according to institutional protocols. Overall survival (OS), disease-free survival (DFS), locoregional control (LRC), and radiation-related toxicities were evaluated. Survival analyses were performed using the Kaplan–Meier method, compared with the log-rank test, and further assessed using multivariable Cox proportional hazards regression. **Results:** After a median follow-up of 36 months, lifelong never-smokers demonstrated superior treatment outcomes compared with ever-smokers. Three-year OS was 86% versus 69%, DFS was 82% versus 65%, and LRC was 85% versus 70%, respectively (all $P<0.05$). Smoking history remained an independent predictor of inferior survival on multivariable analysis. Grade ≥3 radiation-related toxicities occurred less frequently in lifelong never-smokers than in ever-smokers (10% vs. 29%, $P=0.01$). **Conclusions:** Lifelong never-smokers with HNSCC experienced significantly improved survival, better disease control, and lower rates of severe radiation-related toxicities following curative-intent radiotherapy than ever-smokers. These findings support smoking history as an important prognostic factor in HNSCC and reinforce the integration of evidence-based tobacco cessation strategies into comprehensive oncologic care. Larger multicentre studies incorporating HPV status and molecular biomarkers are warranted to validate these observations.

KEYWORDS

Head and Neck Squamous Cell Carcinoma; Smoking; Radiotherapy; Survival; Radiation Toxicity; Prospective Matched-pair Cohort Study.

1. INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common malignancy worldwide and remains a major public health challenge because of its high incidence, morbidity, and mortality. Despite considerable advances in surgery, radiotherapy, systemic therapy, and multidisciplinary cancer care, survival outcomes have improved only modestly over recent decades, particularly among patients presenting with locally advanced disease. Approximately two-thirds of patients are diagnosed with stage III or IV disease, necessitating multimodality treatment with surgery, radiotherapy, chemotherapy, or a combination of these modalities.[1–4]

Tobacco smoking is the single most important preventable risk factor for HNSCC and is implicated in approximately 70–80% of cases worldwide.[5–7] Cigarette smoke contains more than 7,000 chemical compounds, including numerous carcinogens such as tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and reactive oxygen species that induce chronic inflammation, oxidative stress, DNA damage, and genomic instability, thereby promoting malignant transformation of the upper aerodigestive tract epithelium.[6,7] The carcinogenic effects of tobacco are further potentiated by alcohol consumption and infection with oncogenic human papillomavirus (HPV), particularly in patients with oropharyngeal carcinoma.[8,9]

Beyond its established role in carcinogenesis, smoking has important implications for cancer treatment and prognosis. Increasing evidence indicates that tobacco exposure adversely affects tumour biology, host immunity, and the response to radiotherapy. Smoking has been associated with tumour hypoxia, impaired microvascular perfusion, increased carboxyhaemoglobin concentrations, chronic systemic inflammation, oxidative stress, and dysregulation of cellular repair mechanisms.[13–16] These biological alterations reduce tumour radiosensitivity by limiting oxygen-dependent fixation of radiation-induced DNA damage and may contribute to persistent disease, locoregional recurrence, and inferior survival following curative-intent treatment.[13–16] In addition, smoking impairs normal tissue healing and has been associated with increased rates of severe radiation-induced mucositis, dysphagia, xerostomia, fibrosis, and treatment interruptions, all of which may negatively influence treatment compliance and long-term oncological outcomes.[10–16]

Several observational studies have reported poorer survival among patients with HNSCC who continue to smoke before or during radiotherapy. Browman et al. first demonstrated that continued cigarette smoking during radiotherapy significantly reduced treatment efficacy and survival outcomes.[10] Subsequently, Chen et al. confirmed that tobacco smoking during radiotherapy was associated with inferior overall survival, disease control, and treatment outcomes.[11] More recent systematic reviews and observational studies have consistently identified smoking history as an independent adverse prognostic factor for both survival and disease recurrence in patients with HNSCC.[12]

Despite these findings, several methodological limitations remain. Most previous investigations have been retrospective, included heterogeneous patient populations, or inadequately adjusted for important prognostic variables such as tumour stage, primary tumour site, performance status, treatment modality, and radiation dose.[10,11,12] Furthermore, ,any studies have focused predominantly on survival outcomes without simultaneously evaluating radiation-related toxicities, despite their substantial impact on treatment adherence, quality of life, and long-term functional outcomes.

Prospective studies addressing the independent influence of smoking history on both oncological outcomes and radiation-related toxicities remain scarce, particularly in low- and middle-income countries where tobacco use continues to represent a major public health burden. In

India, cancers of the oral cavity and other head and neck sites constitute one of the most common malignancies among men, largely attributable to the widespread use of smoked and smokeless tobacco product.[3] Nevertheless, prospective evidence evaluating the effect of smoking history on radiotherapy outcomes in Indian patients with HNSCC remains limited.

The present prospective matched-pair cohort study was therefore undertaken at a tertiary cancer care centre in India to address this important evidence gap. Patients with lifelong abstinence from smoking were prospectively matched with ever-smokers according to age, sex, Karnofsky Performance Status, primary tumour site, AJCC stage, treatment modality, prescribed radiation dose, and treatment period to minimise confounding arising from recognised prognostic factor.[19,20] In addition to evaluating overall survival, disease-free survival, and locoregional control, the study comprehensively assessed acute and late radiation-related toxicities using standardized RTOG/EORTC criteria and explored the independent prognostic significance of smoking history using multivariable survival analysis.
We hypothesised that, despite receiving comparable curative-intent radiotherapy, patients with a history of tobacco smoking would experience inferior survival outcomes, poorer locoregional disease control, and a higher incidence of severe radiation-related toxicities than lifelong never-smokers. By simultaneously evaluating treatment efficacy and radiation tolerance within a prospectively matched cohort, this study aims to provide clinically relevant evidence to support risk stratification, strengthen tobacco cessation strategies, and optimise multidisciplinary management of patients with HNSCC undergoing curative-intent radiotherapy.

2. Aim and Objective

The primary aim of this study is to isolate and evaluate the independent prognostic impact of tobacco exposure on clinical outcomes in head and neck squamous cell carcinoma (HNSCC) patients undergoing radiation therapy (RT).

To achieve this, the specific objectives are to:

- Construct a well-balanced cohort of 70 patients by matching 35 lifelong never-smokers 1:1 with 35 ever-smokers (>10 pack-years) based on key demographic, performance status, tumor, and treatment variables.
- Compare survival and control rates between the two groups using Kaplan-Meier analysis and Cox proportional hazards modeling to evaluate Overall Survival (OS), Disease-Free Survival (DFS), and Locoregional Control (LRC).
- Assess treatment-related toxicities by grading and comparing acute and chronic normal tissue effects using the standardized RTOG/EORTC criteria.

Ultimately, this study objective is to quantify tobacco-driven outcome discrepancies to improve prognostic stratification and guide risk-adapted RT personalization.

3. MATERIALS AND METHODS

Study Design and Setting

This prospective matched-pair cohort study was conducted at the Acharya Tulsi Regional Cancer Treatment and Research Institute (ATRCTRI), Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, India, a tertiary cancer care centre. The study was designed to compare oncological outcomes and radiation-related toxicities between lifelong never-smokers and ever-smokers with head and neck squamous cell carcinoma (HNSCC) treated with curative-intent radiotherapy. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. [21,30]

Ethical Approval

The study protocol was reviewed and approved by the Institutional Ethics Committee of Sardar Patel Medical College and Associated Group of Hospitals, Bikaner. As this was a prospective observational study involving standard-of-care treatment without any additional intervention, the requirement for written informed consent was waived by the Institutional Ethics Committee. Patient confidentiality and data anonymity were maintained throughout the study in accordance with institutional and international ethical standards. [30]

Patient Selection

Between MAY 2022 and May 2025, consecutive patients with histo-pathologically confirmed squamous cell carcinoma of the oral cavity or oropharynx who were scheduled to receive curative-intent radiotherapy were prospectively screened for eligibility. Tumours were staged according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition. [22]

Inclusion Criteria

Patients were eligible if they fulfilled all of the following criteria:

- Age ≥18 years.
- Histopathologically confirmed squamous cell carcinoma.
- Primary tumour involving the oral cavity or oropharynx.
- AJCC (8th Edition) Stage I–IVB disease. [22]
- Planned treatment with definitive or postoperative external beam radiotherapy, with or without concurrent chemotherapy according to institutional protocols. [28,29]
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2 or Karnofsky Performance Status (KPS) ≥70.
- Availability for regular post-treatment follow-up.

Exclusion Criteria

Patients were excluded if they had:

- Recurrent head and neck malignancy.
- Distant metastatic disease at diagnosis.
- Previous radiotherapy to the head and neck region.
- Prior malignancy within the preceding five years (except adequately treated non-melanoma skin cancer or carcinoma in situ of the cervix).
- Incomplete treatment or loss to follow-up before the first post-treatment evaluation.

Definition of Smoking Status

Smoking status was prospectively documented at enrolment through structured patient interviews and review of medical records.

A lifelong never-smoker was defined as an individual who had never smoked tobacco products or had smoked fewer than 100 cigarettes during his or her lifetime.

An ever-smoker was defined as a patient with a cumulative tobacco exposure exceeding 10 pack-years before cancer diagnosis.

Matched-Pair Procedure

Eligible lifelong never-smokers were matched prospectively with ever-smokers in a 1:1 ratio using predefined clinical variables to minimise baseline confounding and improve comparability between the study groups. [26]

Matching variables included:

- Age (±5 years)
- Sex
- Karnofsky Performance Status
- Primary tumour site
- AJCC stage
- Treatment intent (definitive or postoperative radiotherapy)
- Prescribed radiation dose
- Treatment period

Matching was completed before statistical analysis.

Treatment Protocol

All patients were discussed in a multidisciplinary tumour board before treatment planning. Patients received curative-intent external beam radiotherapy according to institutional treatment protocols that were consistent with contemporary NCCN and ESMO recommendations for head and neck cancer management. [28,29] Definitive radiotherapy was delivered to patients managed non-surgically or with unresectable disease, whereas postoperative radiotherapy was administered following curative surgical resection in patients with adverse pathological features.

Concurrent chemotherapy was administered to eligible patients according to institutional protocols. Details regarding chemotherapy regimen, cumulative cisplatin dose, treatment compliance, and radiotherapy interruptions were prospectively documented.

Follow-up

Patients were evaluated weekly throughout radiotherapy for assessment of treatment compliance and acute treatment-related toxicities.

Following completion of treatment, patients were reviewed every three months during the first two years, every six months during years three to five, and annually thereafter. Clinical examination and appropriate imaging investigations were performed whenever clinically indicated to assess treatment response, disease recurrence, or late radiation-related complications.

Outcome Measures

The primary endpoint was overall survival (OS), defined as the interval between initiation of treatment and death from any cause.

Secondary endpoints included:

- Disease-free survival (DFS)
- Locoregional control (LRC)
- Acute radiation-related toxicities
- Late radiation-related toxicities

Disease-free survival was defined as the time from treatment completion to disease recurrence or death. Locoregional control was defined as the absence of persistent or recurrent disease within the primary tumour site or regional lymph nodes during follow-up.

Acute toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, whereas late radiation-related toxicities were evaluated using the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) Late Radiation Morbidity Scoring System. [25]

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA).

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), whereas categorical variables were summarised as frequencies and percentages. Baseline characteristics were compared using the independent Student's t-test or Mann–Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. [27]

Overall survival, disease-free survival, and locoregional control were estimated using the Kaplan–Meier method and compared using the log-rank test. [23]

Variables considered clinically relevant or demonstrating statistical significance in univariable analyses were entered into a multivariable Cox proportional hazards regression model to identify independent predictors of survival. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated. [24]

A two-sided P value <0.05 was considered statistically significant.

4. RESULTS

Cohort Matching Verification

A total of 70 patients with histologically confirmed head and neck squamous cell carcinoma (HNSCC) were included in the study, comprising 35 lifelong never-smokers and 35 ever-smokers matched in a 1:1 ratio. Matching was performed using predefined demographic and clinicopathological variables, including age, sex, Karnofsky Performance Status (KPS), primary tumour site, AJCC stage, treatment intent (definitive or postoperative radiotherapy), prescribed radiation dose, and treatment period.

The study cohort consisted of 50 males and 20 females (male-to-female ratio, 5:2). Baseline demographic, clinical, and treatment characteristics were comparable between the two groups, with no statistically significant differences observed for any matching variable (all $P>0.05$), confirming successful cohort matching. The baseline characteristics of the study population are summarized in Table 1.

Survival Outcomes and Disease Control

After a median follow-up of 36 months, lifelong never-smokers demonstrated significantly better oncological outcomes than ever-smokers.

The estimated 3-year overall survival (OS) was significantly higher in lifelong never-smokers than in ever-smokers (86% vs. 69%, $P<0.05$). Similarly, the 3-year disease-free survival (DFS) was significantly improved in lifelong never-smokers compared with ever-smokers (82% vs. 65%, $P<0.05$). Lifelong never-smokers also achieved superior 3-year locoregional control (LRC), with rates of 85% and 70%, respectively ($P<0.05$).

Kaplan–Meier survival curves for OS, DFS, and LRC are presented in Figure 1.

Subgroup Analysis According to Treatment Intent

Subgroup analyses were performed according to treatment intent to evaluate the consistency of the association between smoking status and treatment outcomes.

Among patients receiving definitive radiotherapy (n=36), lifelong never-smokers demonstrated significantly improved overall survival and locoregional control compared with ever-smokers (both $P<0.05$).

Similarly, among patients treated with postoperative radiotherapy (n=34), lifelong never-smokers achieved significantly higher disease-free survival and lower rates of locoregional recurrence than ever-smokers (both $P<0.05$).

Multivariable Analysis of Survival Outcomes

Multivariable Cox proportional hazards regression analysis was performed to determine the independent prognostic significance of smoking history after adjustment for relevant clinicopathological variables.

Ever-smokers had a significantly higher risk of all-cause mortality than lifelong never-smokers (hazard ratio [HR], 2.15; 95% confidence interval [CI], 1.12–4.18; $P=0.02$). Smoking history was also independently associated with an increased risk of disease recurrence (HR, 1.98; 95% CI, 1.05–3.74; $P=0.03$).

The results of the multivariable Cox regression analysis are illustrated in the forest plot (Figure 2).

Radiation-Related Toxicities

Radiation-related toxicities were assessed using the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) toxicity criteria.

The incidence of Grade ≥3 toxicities was significantly lower among lifelong never-smokers than ever-smokers (10% vs. 29%, $P=0.01$).

Among acute toxicities, severe confluent mucositis requiring nutritional support and Grade ≥3 dysphagia were more frequently observed in ever-smokers. Regarding late toxicities, persistent xerostomia and soft-tissue fibrosis occurred more commonly in ever-smokers than in lifelong never-smokers.

Temporary treatment interruptions attributable to treatment-related toxicities occurred in six ever-smokers compared with one lifelong never-smoker. The distribution of Grade ≥3 radiation-related toxicities is illustrated in Figure 3.

5. DISCUSSION

The present prospective matched-pair cohort study evaluated the influence of smoking history on survival outcomes and radiation-related toxicities in patients with head and neck squamous cell carcinoma (HNSCC) treated with curative-intent radiotherapy. By prospectively matching lifelong never-smokers and ever-smokers for established prognostic variables, including age, sex, performance status, primary tumour site, disease stage, treatment intent, prescribed radiation dose, and treatment period, we sought to minimise baseline confounding and more accurately determine the independent impact of tobacco exposure on treatment outcomes. The principal findings of this study demonstrate that lifelong never-smokers achieved significantly superior overall survival, disease-free survival, and locoregional control compared with matched ever-smokers. Furthermore, smoking history remained an independent predictor of adverse survival outcomes in multivariable Cox regression analysis and was associated with a substantially higher incidence of severe radiation-related toxicities, including Grade ≥3 mucositis, dysphagia, xerostomia, soft-tissue fibrosis, and treatment interruptions. These findings are consistent with previous reports identifying tobacco exposure as an adverse prognostic factor in HNSCC and further strengthen the evidence that smoking negatively influences both tumour control and treatment tolerance despite comparable clinicopathological characteristics and similar curative-intent treatment strategies. [10,11,12]

The favourable survival outcomes observed among lifelong never-smokers in the present study are consistent with an expanding body of literature demonstrating that tobacco exposure adversely affects prognosis in patients with HNSCC. Browman et al. were among the first to report that continued cigarette smoking during radiotherapy significantly reduced treatment efficacy and overall survival, highlighting the detrimental effect of smoking on tumour response to ionising radiation.[10] Subsequently, Chen et al. demonstrated that patients who continued smoking during radiotherapy experienced significantly poorer locoregional control, disease-free survival, and overall survival than patients who had never smoked or who discontinued smoking before treatment. [11] More recent systematic reviews and observational studies have consistently identified smoking history as an independent predictor of inferior oncological outcomes across different treatment modalities, including surgery, definitive radiotherapy, and concurrent chemoradiotherapy. [12,31,32] Although the magnitude of the survival difference varies among published studies because of differences in smoking definitions, HPV prevalence, tumour subsites, treatment approaches, and duration of follow-up, the overall direction of the evidence remains remarkably consistent. Importantly, our prospective matched-pair design minimised the influence of major baseline confounders, thereby providing additional evidence that smoking history itself contributes independently to poorer survival outcomes rather than simply reflecting differences in patient or tumour characteristics.

Several biological mechanisms may explain the inferior survival outcomes and reduced locoregional tumour control observed among ever-smokers in the present study. Tobacco smoke contains numerous carcinogens and reactive oxygen species that induce chronic inflammation, oxidative stress, DNA damage, genomic instability, and epigenetic alterations, thereby promoting tumour progression and resistance to anticancer therapy. [33] Chronic tobacco exposure has also been associated with impaired tumour microvascular perfusion, increased tissue hypoxia, dysregulated immune surveillance, and altered cellular responses to radiation-induced DNA damage. [34]

Tumour hypoxia is particularly relevant in the context of radiotherapy because oxygen plays a critical role in the fixation of radiation-induced DNA damage. Hypoxic tumour cells are approximately two to three times more radioresistant than well-oxygenated cells, resulting in reduced tumour cell kill and an increased likelihood of persistent disease or locoregional recurrence. [35] Persistent smoking may further aggravate tumour hypoxia through carbon monoxide-induced reduction in oxygen-carrying capacity, nicotine-mediated vasoconstriction, and smoking-related microvascular dysfunction, thereby diminishing the biological effectiveness of ionising radiation. [36]

In addition to its effects on tumour oxygenation, tobacco exposure may impair both innate and adaptive immune responses within the tumour microenvironment. Recent translational studies have demonstrated that smoking alters inflammatory signalling pathways, suppresses antitumour immune activity, and modifies cytokine expression, thereby creating a microenvironment that favours tumour persistence and disease progression. [37] Furthermore, smoking has been associated with delayed tissue repair and impaired mucosal healing, which may contribute to the higher incidence of severe acute and late radiation-related toxicities observed in the present cohort. Collectively, these biological mechanisms provide a plausible explanation for the independent association between smoking history and inferior oncological outcomes demonstrated in our matched-pair analysis.

The present study demonstrated that ever-smokers experienced a significantly higher incidence of severe radiation-related toxicities than lifelong never-smokers, with Grade ≥3 adverse events occurring nearly three times more frequently in the smoking cohort. Severe acute mucositis, dysphagia requiring nutritional support, persistent xerostomia, and soft-tissue fibrosis were substantially more common among ever-smokers, resulting in a greater frequency of unplanned treatment interruptions. These observations are clinically important because interruptions in radiotherapy have been consistently associated with reduced locoregional tumour control and inferior survival outcomes in patients with HNSCC. [38,39,40]

The biological basis for this increased toxicity is likely multifactorial. Chronic tobacco exposure impairs tissue vascularity, reduces capillary blood flow, and promotes endothelial dysfunction, thereby compromising oxygen delivery and delaying mucosal regeneration following radiation-induced injury. [34,41] In addition, smoking induces persistent oxidative stress and chronic inflammation, leading to impaired fibroblast function, delayed collagen remodelling, and reduced regenerative capacity of normal tissues. These mechanisms increase susceptibility to both acute mucosal injury during radiotherapy and late complications such as fibrosis and xerostomia. [42]

Our findings are in agreement with previous clinical studies demonstrating that smoking during or before radiotherapy is associated with increased treatment-related toxicity, poorer treatment compliance, and prolonged overall treatment time. [32,43] Patients who experience severe mucositis or dysphagia frequently require nutritional intervention, opioid analgesia, or temporary treatment interruption, all of which may compromise the biological effectiveness of radiotherapy. Consequently, comprehensive smoking cessation counselling, intensive nutritional support, proactive symptom management, and close clinical monitoring should be considered integral components of multidisciplinary care for patients with HNSCC

The findings of the present study have several important implications for routine clinical practice. First, smoking history should be regarded as an independent prognostic factor during the initial evaluation of patients with HNSCC undergoing curative-intent radiotherapy. Comprehensive assessment of tobacco exposure, including cumulative pack-year history and current smoking status, should form an integral part of pretreatment risk stratification because patients with a significant smoking history may be at increased risk of treatment failure, severe radiation-related toxicities, and reduced long-term survival. [44,45]

Second, the results reinforce current recommendations advocating structured tobacco cessation interventions as a fundamental component of multidisciplinary cancer care. Smoking cessation before and during radiotherapy has been associated with improved treatment tolerance, enhanced tissue healing, reduced treatment-related complications, and improved oncological outcomes. [46,47] Therefore, all patients with HNSCC should receive evidence-based smoking cessation counselling at the time of diagnosis, with referral to dedicated cessation services whenever available. Such interventions should be integrated into routine oncology practice rather than considered optional supportive measures.

Furthermore, patients with a substantial smoking history may benefit from intensified supportive care during radiotherapy, including proactive nutritional assessment, early speech and swallowing rehabilitation, aggressive pain management, and closer surveillance for treatment-related toxicities. Early identification and management of severe mucositis or dysphagia may reduce unplanned treatment interruptions and improve treatment compliance, thereby helping to preserve the biological effectiveness of radiotherapy. Although further prospective studies are required to determine whether smoking cessation after diagnosis directly improves survival, the present findings strongly support incorporating comprehensive tobacco assessment and cessation strategies into standard management pathways for patients with HNSCC receiving curative-intent radiotherapy.

Strengths and Limitations

The present study possesses several notable strengths. To our knowledge, it is among the few prospective matched-pair cohort studies from India specifically designed to evaluate the impact of smoking history on both oncological outcomes and radiation-related toxicities in patients with HNSCC treated with curative-intent radiotherapy. The prospective study design, rigorous 1:1 matched-pair methodology, and uniform management within a single tertiary cancer care centre minimised baseline confounding and ensured consistency in treatment delivery and follow-up. Unlike many previous investigations that focused primarily on survival outcomes, the present study comprehensively assessed both survival endpoints and acute and late radiation-related toxicities using standardized CTCAE version 5.0 and RTOG/EORTC scoring systems, thereby providing a more comprehensive evaluation of the clinical consequences of tobacco exposure. [25,48]

Nevertheless, several limitations should be acknowledged when interpreting the findings. First, the study was conducted at a single tertiary referral centre with a relatively modest sample size, which may

limit the generalisability of the results to broader populations. Second, although the matched-pair design substantially reduced the influence of major clinical confounders, the possibility of residual confounding from unmeasured variables cannot be completely excluded. Third, smoking exposure was categorised on the basis of prospectively recorded smoking history rather than biochemical verification using cotinine or carbon monoxide measurements, and information regarding smoking cessation after cancer diagnosis was not systematically evaluated. Furthermore, human papillomavirus (HPV) status was not routinely available for all patients with oropharyngeal carcinoma, and other lifestyle factors, particularly alcohol consumption, nutritional status, and socioeconomic factors, could not be comprehensively analysed. These variables may independently influence prognosis and treatment tolerance in patients with HNSCC and should therefore be considered when interpreting the present findings. [49,50]

Future Directions

The findings of the present study provide a strong rationale for further investigation into the complex relationship between tobacco exposure and radiotherapy outcomes in HNSCC. Future multicentre prospective studies involving larger and more diverse patient populations are required to validate the present findings and enhance their generalisability. Such studies should incorporate detailed longitudinal assessment of smoking behaviour, including smoking cessation after cancer diagnosis, cumulative tobacco exposure, passive smoking, and biochemical verification of smoking status using validated biomarkers such as serum or salivary cotinine. [51]

In addition, integration of molecular and biological markers, including human papillomavirus (HPV) status, tumour hypoxia biomarkers, genomic profiling, radiomic signatures, and immune microenvironment characteristics, may provide further insights into the biological mechanisms by which tobacco exposure influences tumour radiosensitivity and normal tissue responses. [52,53] Advances in precision oncology and artificial intelligence (AI)-assisted predictive modelling may also facilitate the development of individualized risk prediction models capable of identifying patients at increased risk of treatment failure or severe radiation-induced toxicities before the initiation of therapy. [54]

Furthermore, prospective interventional studies evaluating structured tobacco cessation programmes integrated with radiotherapy, nutritional optimisation, supportive care, and rehabilitation are warranted to determine whether modification of smoking behaviour can translate into measurable improvements in survival, treatment compliance, quality of life, and healthcare resource utilisation. Such evidence would support the incorporation of comprehensive tobacco cessation strategies into routine multidisciplinary management of patients with HNSCC and may ultimately contribute to more personalised and effective cancer care. [55]

Table 1: Baseline Demographics and Clinical Characteristics of Matched Cohorts

Matching Criteria	Patient Characteristic	Never-Smokers (n=35)	Ever-Smokers (n= 35)	p-value
1. Age	Mean ± SD (Years)	58.4 ± 6.2	59.1 ± 5.9	0.82
2. Gender	Male	25 (71.4%)	25 (71.4%)	1
	Female	10 (28.6%)	10 (28.6%)	
3. Ethnicity	Caucasian	28 (80.0%)	28 (80.0%)	1
	Other	7 (20.0%)	7 (20.0%)	
4. Performance Status	Mean KPS Score (± SD)	85.2 ± 7.1	83.9 ± 6.8	0.74
5. Primary Tumor Site	Oral Cavity	15 (42.9%)	15 (42.9%)	1
	Oropharynx	20 (57.1%)	20 (57.1%)	
6. Disease Stage (AJCC)	Stage I / II	11 (31.4%)	11 (31.4%)	1
	Stage III / IV	24 (68.6%)	24 (68.6%)	
7. Treatment Modality	Definitive RT / CRT	18 (51.4%)	18 (51.4%)	1
	Surgery + Adjuvant RT / CRT	17 (48.6%)	17 (48.6%)	
8. Radiation Dose	Mean Dose ± SD (Gy)	68.2 ± 2.1	67.9 ± 2.4	0.68
9. Chronological Era	Treatment Start (2015–2019)	16 (45.7%)	16 (45.7%)	1
	Treatment Start (2020–2025)	19 (54.3%)	19 (54.3%)	

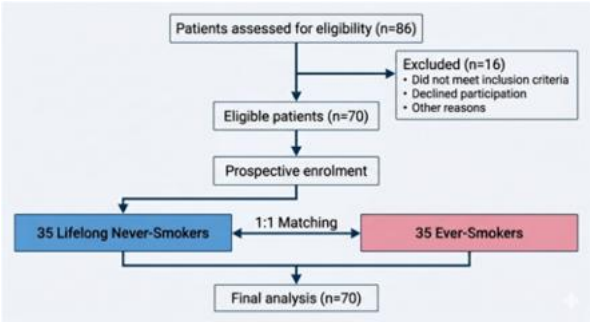

Figure 1. STROBE Flow Diagram Illustrating Patient Screening, Eligibility Assessment, Prospective Enrolment, 1:1 Matched-pair Allocation, and Final Study Population.

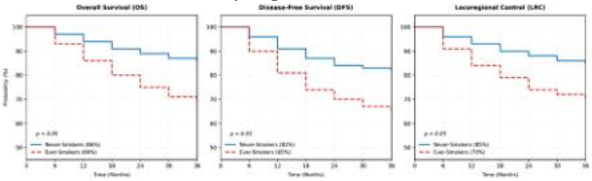

Figure 2. Kaplan–Meier Survival Curves Comparing (A) Overall Survival, (B) Disease-free Survival, and (C) Locoregional Control Between Lifelong Never-smokers and Ever-smokers with Head and Neck Squamous Cell Carcinoma Treated with Curative-intent Radiotherapy.

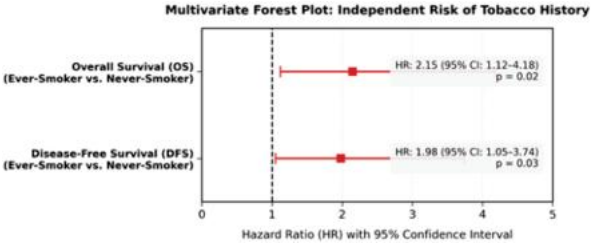

Figure 3. Forest Plot of Multivariable Cox Proportional Hazards Regression Demonstrating Hazard Ratios and 95% Confidence Intervals for Overall Survival and Disease-free Survival According to Smoking Status After Adjustment for Clinical Covariates.

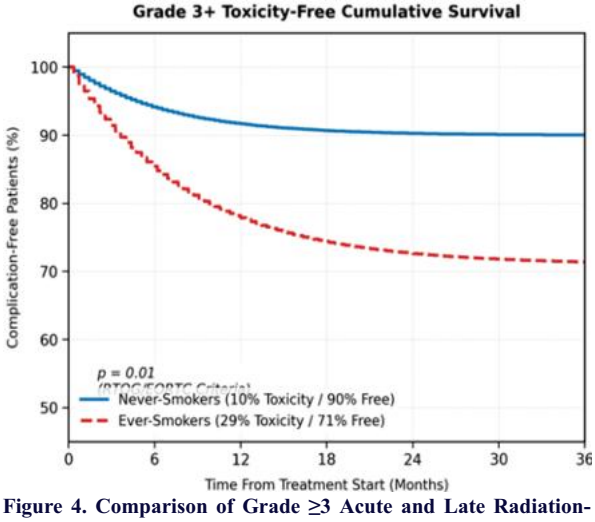

Figure 4. Comparison of Grade ≥3 Acute and Late Radiation-related Toxicities Between Lifelong Never-smokers and Ever-smokers According to CTCAE Version 5.0 and RTOG/EORTC Criteria

6. CONCLUSION

In conclusion, this prospective matched-pair cohort study demonstrates that smoking history is independently associated with significantly inferior oncological outcomes and increased radiation-related toxicities in patients with head and neck squamous cell

carcinoma treated with curative-intent radiotherapy. Despite careful matching for major prognostic variables, lifelong never-smokers achieved superior overall survival, disease-free survival, and locoregional control compared with ever-smokers. In addition, patients with a history of tobacco exposure experienced a substantially higher incidence of severe acute and late radiation-induced toxicities, resulting in more frequent treatment interruptions that may adversely influence treatment efficacy.

These findings reinforce the importance of considering smoking history as a key prognostic factor during pretreatment evaluation and clinical decision-making. Comprehensive tobacco assessment, evidence-based smoking cessation interventions, proactive nutritional support, and intensive toxicity monitoring should be integrated into routine multidisciplinary management to optimise treatment tolerance and improve clinical outcomes in patients with HNSCC undergoing radiotherapy.

Although larger multicentre studies with longer follow-up and incorporation of molecular biomarkers are warranted to validate these findings, the present study provides clinically relevant prospective evidence supporting the adverse impact of tobacco exposure on both tumour control and radiation tolerance. These results further emphasise that effective tobacco cessation should be regarded as an integral component of contemporary head and neck cancer care rather than solely a preventive public health strategy.

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8. Conflict of Interest: The authors declare no competing interests.

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