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RESEARCH ARTICLE

Late toxicity after IMRT for head and neck cancer and its predictors in routine practice: A retrospective single-center cohort study

Baş-boyun kanserinde IMRT sonrası geç toksisite ve rutin klinik uygulamadaki öngördürücüleri: Retrospektif, tek merkezli bir kohort çalışması

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Abstract

Aim: Late toxicities remain a major determinant of long-term morbidity after intensity-modulated radiotherapy (IMRT) for head and neck cancer (HNC). However, the relative contribution of patient- and treatment-related predictors in routine clinical practice remains insufficiently characterized. This study aimed to evaluate factors associated with late toxicity burden in IMRT-treated HNC patients.

Methods: We conducted a retrospective single-center cohort study including HNC patients treated with IMRT. Late toxicities occurring at least 90 days after radiotherapy were graded according to CTCAE v5.0. Dysphagia, mucositis, dermatitis, and xerostomia were evaluated, and a composite toxicity burden score was generated by summing the four toxicity domains. Clinical, treatment-related, and smoking-related variables were analyzed using univariable statistical methods and exploratory CHAID decision-tree models.

Results: A total of 220 patients were included in the final analysis. Mean age was 59.82±11.7 years, and 80.91% of patients were male. Grade 2 dysphagia and mucositis were observed in 40.45% and 40.91% of patients, respectively, while most patients experienced grade 0 dermatitis and xerostomia. Higher composite toxicity burden was significantly associated with total radiation dose, irradiation time per fraction, body mass index, smoking exposure, concurrent chemotherapy, and smoking status (all $p<0.05$). In exploratory CHAID analyses, smoking status consistently emerged as the most influential predictor of toxicity burden.

Conclusion: Smoking exposure was the strongest predictor of late toxicity burden in IMRT-treated HNC patients, with additional contributions from treatment intensity and concurrent chemotherapy. These findings emphasize the importance of incorporating detailed smoking history into late-toxicity risk stratification and survivorship planning in patients undergoing IMRT for HNC.

Keywords: Chemoradiotherapy, CTCAE, decision trees, CHAI, head and neck cancer, IMRT, late toxicity, smoking.

Özet

Amaç: Geç toksisiteler, baş-boyun kanserinde (HNC) yoğunluk ayarlı radyoterapi (IMRT) sonrası uzun dönem morbiditenin en önemli belirleyicilerinden biridir. Ancak günlük klinik uygulamada hasta ve tedaviye bağlı risk faktörlerinin göreceli katkısı halen yeterince net değildir. Bu çalışmada, IMRT uygulanan HNC hastalarında geç toksisite yükü ile ilişkili faktörlerin değerlendirilmesi amaçlandı.

Yöntemler: Bu retrospektif tek merkezli kohort çalışmasına IMRT uygulanan HNC hastaları dahil edildi. Radyoterapiden en az 90 gün sonra gelişen geç toksisiteler CTCAE v5.0 kriterlerine göre derecelendirildi. Disfaji, mukozit, dermatit ve kserostomi değerlendirildi ve dört toksisite alanının toplamı ile kompozit toksisite yükü skoru oluşturuldu. Klinik, tedaviye bağlı ve sigara kullanımına ilişkin değişkenler tek değişkenli istatistiksel yöntemler ve keşifsel CHAID karar ağacı modelleri ile analiz edildi.

Bulgular: Nihai analize toplam 220 hasta dahil edildi. Hastaların ortalama yaşı 59,82±11,7 yıl olup, %80,91'i erkekti. Grade 2 disfaji ve mukozit sırasıyla hastaların %40,45 ve %40,91'inde gözlendi; dermatit ve kserostomi olgularının çoğu grade 0 düzeyindeydi. Daha yüksek kompozit toksisite yükü; toplam radyasyon dozu, fraksiyon başına ışınlama süresi, vücut kitle indeksi, sigara maruziyeti, eş zamanlı kemoterapi ve sigara içme durumu ile anlamlı şekilde ilişkili bulundu (tüm $p<0,05$). Keşifsel CHAID analizlerinde sigara içme durumunun toksisite yükünü öngören en güçlü değişken olduğu görüldü.

Sonuç: IMRT uygulanan baş-boyun kanseri hastalarında sigara maruziyeti, geç toksisite yükünün en güçlü belirleyicisi olarak saptandı. Tedavi yoğunluğu ve eş zamanlı kemoterapi de toksisite üzerinde ek etkiye sahipti. Bu bulgular, geç toksisite risk sınıflandırması ve sağkalım sonrası takip planlamasında ayrıntılı sigara öyküsünün dikkate alınmasının önemini göstermektedir.

Anahtar Kelimeler: Kemoradyoterapi, CTCAE, karar ağaçları, CHAID, baş-boyun kanseri, IMRT, geç toksisite, sigara.

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INTRODUCTION

Head and neck cancer (HNC) is commonly treated with definitive or postoperative radiotherapy, frequently with concurrent systemic therapy in patients with locally advanced disease. Over the last two decades, intensity-modulated radiotherapy (IMRT) has become standard because it improves dose conformality and allows better sparing of organs at risk, particularly the major salivary glands (1). In the PARSPORT randomized trial, parotid-sparing IMRT reduced clinically meaningful xerostomia compared with conventional radiotherapy, supporting IMRT as a standard approach in modern head and neck radiotherapy (1).

Despite these technical gains, late toxicity remains a major driver of long-term morbidity. Dysphagia and xerostomia are among the most consequential complications after head and neck irradiation, with persistent functional impairment that can extend well beyond the acute treatment phase (2,3). Late effects reflect a combination of treatment-related exposures and individual susceptibility, and they continue to shape survivorship needs as outcomes improve.

Concurrent chemotherapy is a key contributor to toxicity risk. Large-scale evidence shows that adding chemotherapy to radiotherapy improves outcomes in selected patients with non-metastatic HNC, but this benefit comes with increased treatment-related adverse effects that often necessitate intensified supportive care (4). Beyond treatment intensity, patient factors and lifestyle exposures may further modify normal-tissue tolerance. Smoking, in particular, is biologically plausible as a modifier of radiation injury and recovery through vascular and inflammatory pathways, and clinical studies have suggested associations between smoking during radiotherapy and clinically significant mucositis and dermatitis (5).

In routine-practice cohorts, the relative contribution and hierarchy of patient- and treatment-related predictors of late toxicity are not consistently established, particularly when outcomes are abstracted retrospectively from outpatient records. Therefore, we performed a retrospective, single-center analysis of IMRT-treated HNC patients, defining late toxicity as events documented ≥90 days after radiotherapy completion and graded using CTCAE v5.0. We aimed to characterize the distribution of late dysphagia, mucositis, dermatitis, and xerostomia and to evaluate their associations with smoking exposure, concurrent chemotherapy, and key treatment parameters, including irradiation time per fraction.

METHODS

Study Design and Setting

This retrospective, single-center cohort study evaluated consecutive patients with head and neck cancer treated with intensity-modulated radiotherapy (IMRT) in routine clinical practice. The source dataset initially comprised 278 patients. During prespecified data-quality procedures, records with incomplete documentation for key analytic variables (11.15%) and observations flagged as statistical outliers (10.93%) were excluded, resulting in a final analytic cohort of 220 patients. Missingness was attributed primarily to incomplete documentation inherent to retrospective real-world data capture.

Participants and Data Sources

Eligible patients were those who received IMRT for head and neck cancer and had outpatient follow-up documentation available to ascertain late toxicities. Demographic and anthropometric variables included age, sex, weight, height, and body mass index (BMI). Smoking history was categorized as never smoker, current smoker, or former smoker; among ever smokers, cumulative exposure was summarized as pack-years. Treatment-related variables included total prescribed radiotherapy dose (Gy), irradiation (beam-on) time per fraction (hours), and receipt of concurrent chemotherapy. All variables were extracted retrospectively from institutional radiotherapy records and the electronic medical record.

Radiotherapy and Concurrent Chemotherapy

All patients were treated with IMRT according to institutional standards. Total prescribed dose was highly standardized in this cohort, with a median dose of 70 Gy. Concurrent chemotherapy was administered according to standard-of-care indications and clinician judgment, consistent with established evidence supporting

Turk J Clin Res. 2026;2(1):1-8
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chemoradiation in selected patients with non-metastatic head and neck cancer. For analyses, concurrent chemotherapy was modeled as a dichotomous exposure (administered vs not administered).

Outcome Definitions

Late toxicity was defined as toxicity documented at least 90 days after completion of radiotherapy. Late adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (6). Toxicity outcomes were ascertained retrospectively from outpatient clinic documentation and included dysphagia, mucositis, dermatitis, and xerostomia. For each toxicity domain, grade 0 indicated absence of toxicity

Composite Toxicity Burden

A pragmatic, count-based composite late-toxicity burden score was derived by summing the presence of the four toxicity domains (each coded as present vs absent), yielding a score ranging from 0 (no recorded late toxicity) to 4 (all four toxicities recorded). Because the retrospective clinical documentation did not allow uniform, severity-weighted scoring across all domains, the composite endpoint was intentionally restricted to a presence/absence framework to capture the breadth of late toxicity burden in routine practice.

Statistical Analysis

Baseline and treatment characteristics were summarized using descriptive statistics. The distribution of continuous variables was assessed using Shapiro-Wilk and Kolmogorov–Smirnov tests. Continuous variables were reported as mean (standard deviation) or median (range), as appropriate. Associations between continuous variables were evaluated using Spearman rank correlation. Associations between categorical predictors (including smoking status and concurrent chemotherapy) and toxicity outcomes were assessed using chi-square tests. Where distributional assumptions were not met, non-parametric methods were applied for group comparisons.

To explore multivariable and hierarchical predictor structure in an interpretable, clinically oriented manner, decision-tree models were developed using Chi-square Automatic Interaction Detection (CHAID) (7). Separate CHAID models were trained for the composite toxicity burden score and for each individual toxicity endpoint. Model performance was summarized using overall classification accuracy. All decision-tree analyses were considered exploratory and intended to support hypothesis generation rather than definitive prediction. Statistical significance was evaluated using a two-sided threshold of $p<0.05$.

RESULTS

Patient Cohort and Baseline Characteristics

A total of 278 consecutive patients treated with IMRT for head and neck cancer were screened. After data cleaning, 220 patients comprised the final analytic cohort following exclusion for missing key variables (11.15%) and statistical outliers (10.93%). The mean age was 59.82±11.7 years (range, 27-87), and 80.91% of patients were male. Mean weight was 73.3 kg, mean height was 168.93 cm, and mean body mass index (BMI) was 25.66 kg/m^2.

Radiotherapy dosing was relatively homogeneous. The mean total prescribed dose was 67.19 Gy (SD, 3.79), with both the median and mode at 70.0 Gy (coefficient of variation, 0.06). Concurrent chemotherapy was administered to 77.73% of patients. Regarding smoking history, 48.18% were never smokers, 30.46% were current smokers, and 21.36% were former smokers. Among ever smokers, cumulative exposure averaged 40.12±27.11 pack-years. Baseline demographic and treatment characteristics are summarized in Table 1.

Distributional Assessment and Correlations

Normality testing suggested that age and weight approximated normal distributions, whereas total dose, irradiation (beam-on) time per fraction, and smoking exposure deviated from normality. In Spearman correlation analyses, total dose was strongly correlated with irradiation time per fraction ($\rho\approx0.748$). Weight and BMI were strongly correlated as expected ($\rho\approx0.881$). Age showed a weak positive correlation with smoking exposure ($\rho\approx0.168$).

Turk J Clin Res. 2026;2(1):1-8
https://doi.org/10.63909/1453037

Table 1. Baseline demographic and treatment characteristics (n=220)

Characteristic	Value
Age, years, mean±SD (range)	59.82±11.7 (27–87)
Sex, male, n (%)	178 (80.91)
Sex, female, n (%)	42 (19.09)
Weight, kg, mean	73.3
Height, cm, mean	168.93
Body mass index, kg/m², mean	25.66
Total radiotherapy dose, Gy, mean±SD	67.19±3.79
Total radiotherapy dose, Gy, median (mode)	70.0 (70.0)
Concurrent chemotherapy, administered, n (%)	171 (77.73)
Smoking status, n (%)	
Never smoker	106 (48.18)
Current smoker	67 (30.46)
Former smoker	47 (21.36)
Pack-years among ever smokers, mean ± SD	40.12±27.11

Footnote: Values are mean±SD or n (%), unless otherwise indicated. Pack-years are reported among ever smokers (current or former). Concurrent chemotherapy was analyzed as administered vs not administered.

Late Toxicity Profile

Late dysphagia and mucositis represented the most frequent grade 2 toxicities, occurring in 40.45% and 40.91% of patients, respectively. In contrast, dermatitis and xerostomia were most commonly absent, with grade 0 reported in 55.45% and 59.09% of patients, respectively.

For the count-based composite toxicity burden score (0–4), 25% of patients had no recorded late toxicity (score 0), whereas 29.09% experienced all four assessed toxicities (score 4), indicating substantial inter-patient heterogeneity in late-effect burden.

Predictors of Composite Toxicity Burden

In univariable analyses, higher composite toxicity burden was significantly associated with total radiotherapy dose (p=0.001), irradiation time per fraction (p=0.022), BMI (p=0.041), and smoking exposure expressed as pack-years (p<0.001). A dose–toxicity gradient was observed across burden categories; for example, mean total dose was higher among patients with the maximum composite burden (score 4: 68.16 Gy) compared with those with no recorded toxicity (score 0: 65.65 Gy).

In categorical analyses, concurrent chemotherapy (p=0.001) and smoking status (p<0.001) showed strong associations with overall composite burden, whereas sex was not associated (p=0.29). Univariable associations for the composite toxicity burden and selected endpoints are presented in Table 2.

Smoking Exposure and Persistence of Risk

In post-hoc comparisons, never smokers demonstrated significantly lower toxicity than both current and former smokers (p<0.01). By contrast, no statistically significant differences were observed between former and current smokers for any endpoint except xerostomia (all other comparisons p>0.05), suggesting that prior smoking exposure may be associated with a persistent elevation in late-toxicity risk in this cohort.

Table 2. Univariable associations between candidate predictors and late toxicity outcomes

Predictor	Composite toxicity burden (p value)	Selected endpoint associations (p value)
Total radiotherapy dose	0.001	Mucositis: 0.002; Dermatitis: 0.001
Irradiation (beam-on) time per fraction	0.022	Mucositis: 0.017; Dermatitis: 0.024
Body mass index	0.041	Mucositis: 0.032
Smoking exposure (pack-years)	<0.001	—
Smoking status (never/current/former)	<0.001	Dysphagia: <0.001
Concurrent chemotherapy (administered vs not)	0.001	Dysphagia: 0.030
Sex	0.290	—

Footnote: P values are from univariable association testing (two-sided). Endpoint-specific p values are shown only where available from the current analytic output.

Turk J Clin Res. 2026;2(1):1-8
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Exploratory Multivariable Modeling Using Chaid

CHAID decision-tree models were developed to explore hierarchical predictor structures for the composite burden and each individual toxicity endpoint. Overall classification accuracy ranged from 38.2% to 60.9%. In the composite toxicity model, smoking status emerged as the dominant root-node predictor (relative contribution 78.3%). Smoking status also served as the root node for dysphagia (relative contribution 91.8%), with total radiotherapy dose contributing as a secondary splitter (8.2%). For mucositis and dermatitis, smoking status remained the leading predictor (71.6% and 75.8%, respectively), with irradiation time per fraction and total dose acting as secondary modifiers. For xerostomia, irradiation time per fraction was the root-node predictor, indicating a closer relationship with treatment delivery dynamics than with other covariates within this dataset.

DISCUSSION

In this retrospective single-center cohort of IMRT-treated head and neck cancer patients, clinically relevant late toxicity remained common despite contemporary planning approaches and relatively homogeneous prescription dosing. Dysphagia and mucosal symptoms were frequent at clinically meaningful grades, and the composite count-based burden captured substantial heterogeneity across patients. This pattern is consistent with the broader IMRT-era literature showing that swallowing dysfunction and salivary complications continue to shape long-term morbidity and survivorship needs after head and neck radiotherapy (2,8,9).

The most robust finding was the strong and persistent association between smoking exposure and late-toxicity burden. Smoking status and cumulative exposure (pack-years) were both associated with higher composite burden, and smoking emerged as the dominant splitting variable in the exploratory CHAID models. Although the present design does not permit causal inference, the direction and consistency of the association support a clinically meaningful relationship. Tobacco exposure plausibly contributes to chronic microvascular injury, impaired tissue repair, and pro-inflammatory signaling, all of which may amplify susceptibility to radiation-related late effects. Importantly, former smokers showed a toxicity profile broadly similar to current smokers for most endpoints in this dataset, suggesting that cumulative exposure may leave a lasting vulnerability that does not normalize quickly after cessation. Recent clinical evidence also supports an adverse association between smoking and chemoradiation tolerance and outcomes, including higher toxicity risk in some series (5). Taken together, these data argue for routine capture of smoking history with adequate resolution, including current status and pack-years, when counseling patients and planning follow-up.

Treatment intensity and delivery characteristics also carried a signal. The total radiotherapy dose was associated with composite burden and specific endpoints, such as mucositis and dermatitis. Even within a cohort with relatively standardized prescriptions, modest dose variation may reflect differences in disease extent, target volumes, or clinical decision-making that translate into toxicity gradients. Concurrent chemotherapy was associated with higher overall burden and dysphagia, aligning with the established trade-off that chemoradiation improves outcomes in selected non-metastatic head and neck cancer at the cost of increased morbidity and supportive care needs (4,10,11). These observations reinforce that late effects arise from the combined impact of host factors and treatment intensity rather than from a single determinant.

A distinctive component of this analysis was the inclusion of irradiation (beam-on) time per fraction as a treatment delivery parameter. A longer irradiation time per fraction was associated with composite burden and mucositis and dermatitis, and it was selected as the root predictor for xerostomia in the decision-tree models. This signal should be interpreted cautiously. Beam-on time may serve as a surrogate for plan complexity or delivery characteristics that correlate with unmeasured factors, such as dose distribution to organs at risk, patient anatomy, or treatment course variability. The xerostomia finding is nevertheless clinically plausible in the context of the well-established dose–volume dependence of salivary dysfunction. QUANTEC-based work has consistently linked parotid mean dose constraints with xerostomia risk and recovery trajectories, highlighting the importance of detailed organ-at-risk dosing when interpreting salivary outcomes (12,13). Future analyses integrating dose–volume metrics for salivary glands, the oral cavity, the pharyngeal constrictors, and laryngeal

Turk J Clin Res. 2026;2(1):1-8
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structures are expected to refine these associations and improve model discrimination.

Decision-tree analyses (CHAID) were used to explore hierarchical predictor structures and potential interactions with an emphasis on interpretability. The modest classification accuracy is unsurprising given the limited covariate set and retrospective outcome ascertainment. In this setting, tree-based models are best interpreted as exploratory complements to conventional analyses, helping identify candidate high-yield stratifiers for future prospective modeling. The recurrent selection of smoking status as the primary splitter across models was consistent with the univariable results and supports prioritizing detailed smoking history in subsequent risk-stratification frameworks (7,14).

Several limitations should be emphasized. Toxicities were abstracted retrospectively from outpatient documentation and graded using CTCAE v5.0, which may lead to under-ascertainment and variable granularity across clinicians (6). Exclusion of missing records and outliers improved internal consistency but may introduce selection bias and limit generalizability. The dataset did not include several established determinants of late toxicity, including primary subsite, stage, HPV status, surgical treatment, detailed systemic therapy regimens, and organ-at-risk dose–volume parameters. Prior multicenter trial analyses have shown that late dysphagia and laryngopharyngeal dysfunction can be substantial and are influenced by multiple treatment and patient-related factors, underscoring the importance of richer covariate capture for robust prediction (8, 10). Finally, the composite burden score was intentionally count-based and reflects the breadth of documented late toxicities rather than severity-weighted intensity, which should be considered when interpreting effect sizes.

One of the most important innovations of this study is that it assesses the burden of late toxicity in head and neck cancer patients undergoing IMRT not only through a single side effect, but also through a composite toxicity burden score encompassing dysphagia, mucositis, dermatitis, and xerostomia. Furthermore, the examination of both patient-related and treatment-related factors in a retrospective cohort based on real-world data is important for better reflecting clinical practice. Our findings have shown that smoking exposure (pack-years and smoking status) may be a more dominant predictor of late toxicity than treatment dose and concomitant chemotherapy. This suggests that smoking history should be considered not only in prognostic analysis but also in post-treatment toxicity risk stratification. Clinically, closer follow-up, early rehabilitation strategies, and protective support approaches in patients with high smoking exposure can reduce long-term morbidity. Moreover, the emergence of smoking status as the strongest discriminant in CHAID analyses can be considered an important finding that may contribute to the development of patient-based personalized toxicity prediction models.

In summary, within a real-world IMRT-treated head and neck cancer cohort, smoking exposure emerged as the most influential predictor of late toxicity burden, with total dose, concurrent chemotherapy, BMI, and irradiation time per fraction contributing additional associations. These findings support integrating detailed smoking history into risk stratification and survivorship planning, and they motivate future work incorporating dose–volume metrics and standardized prospective toxicity capture to validate and extend these observations.

This study has several limitations. First, although the study included a relatively large patient cohort, the reliance on univariate methods in the analyses may have limited the identification of independent determinants associated with late toxicity. Even though exploratory CHAID models were used, the lack of multivariate regression analyses prevented full control of the influence of potential confounding factors. Second, the exclusion of important clinical and treatment-related variables such as tumor stage, primary tumor localization, HPV status, and dose-volume parameters for at-risk organs reduces the mechanistic interpretability of the findings. Third, while the composite toxicity burden score used in the study provides a practical approach in terms of clinical application, it may not adequately reflect some clinical differences due to its equal assessment of the clinical significance and severity of different toxicity domains. Therefore, the use of degree-based or weighted toxicity analyses in future studies may provide more comprehensive results. Finally, the retrospective study design, with the exclusion of a certain number of patients due to missing data and outliers, may have increased the risk of potential selection bias. Therefore,

Turk J Clin Res. 2026;2(1):1-8
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these results need to be validated with prospective and multicenter studies.

CONCLUSION

In this retrospective single-center cohort of patients with head and neck cancer treated with IMRT, late toxicity remained common in routine clinical practice despite contemporary radiotherapy delivery. Smoking exposure emerged as the most influential predictor of composite late-toxicity burden, with both smoking status and cumulative exposure showing consistent associations across analyses. Treatment-related factors, including total radiotherapy dose, concurrent chemotherapy, and irradiation time per fraction, also contributed to toxicity risk, underscoring the multifactorial nature of late effects after head and neck radiotherapy. These findings support the routine incorporation of detailed smoking history into late-toxicity risk stratification and survivorship planning. Prospective studies with standardized toxicity assessment and comprehensive dose–volume data are warranted to validate these observations and to refine prediction models for individualized follow-up and supportive care.

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