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ORIGINAL ARTICLE

Validation of a prognostic nomogram for locally advanced oropharyngeal carcinoma treated with intensity-modulated radiotherapy with/without systemic therapy

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Background: Head and neck squamous-cell carcinoma (HNSCC), particularly oropharyngeal cancer (OPC), exhibits diverse prognostic factors influenced by demographic and lifestyle variables. Prognostic nomograms, such as the one developed by Fakhry et al., incorporate clinical and biological markers to predict overall survival (OS) and progression-free survival (PFS) in OPC patients. However, their applicability to European populations remains unverified. This study aimed to externally validate Fakhry's prognostic nomogram in a large European cohort of locally advanced OPC patients treated with definitive intensity-modulated radiotherapy (IMRT) with or without systemic therapy.

Methods: This is a retrospective external validation study conducted on 805 OPC patients from 14 Southern European oncology centers, with a median follow-up of 6 years. Variables including age, smoking status, p16 expression, anemia, performance status, T and N stage, education, marital status, alcohol consumption, comorbidities (ACE-27), and caregiver presence were collected. Cox proportional hazards models and Harrell's C-index assessed discrimination and calibration of the nomogram for 2- and 5-year OS and PFS predictions. Analyses were carried out on 781 records with complete survival information.

Results: The validation confirmed the robust prognostic value of Fakhry's nomogram, with a C-index of 0.75 for OS. Smoking history and p16 status were the strongest predictors, while age was less influential than previously reported. Incorporating additional variables—particularly alcohol consumption and the interaction between smoking and p16 status—significantly improved predictive accuracy (C-index up to 0.79 for OS). These findings highlight the relevance of lifestyle factors and molecular status to European OPC prognosis and support nomogram adaptation for population-specific risk stratification.

Conclusion: Fakhry's model is valid for European OPC patients, and its refinement by including alcohol consumption and smoking—p16 interaction enhances prognostic precision. This improved model may facilitate personalized treatment strategies and clinical trial stratification in this population.

Key words: head and neck, squamous cell carcinoma, oropharynx, nomogram, validation

INTRODUCTION

Head and neck squamous-cell carcinoma (HNSCC) comprises a heterogeneous group of malignancies originating from various anatomical subsites within the head and neck region, including the oral cavity, oropharynx, hypopharynx,

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and larynx. HNSCC represents the sixth most frequently diagnosed cancer worldwide, with ∼800 000 new cases and 400 000 associated deaths reported annually.[1,2] The highest incidence is observed among males aged 50-70 years; however, the geographic distribution of specific subsites exhibits considerable variability.[3]

A noteworthy trend in recent years is the increasing prevalence of oropharyngeal cancer (OPC), largely attributable to the rising incidence of oral human papillomavirus (HPV) infection due to high-risk sexual behavior.[4] It is estimated that globally HPV infection accounts for 20%-40% of OPC cases, with HPV16 responsible for ∼80% of these infections.[5] HPV status is well established as an independent predictor of survival in OPC patients, but for OPC and more broadly for HNSCC, prognostic markers are few and often inconsistent across different studies, frequently leading to bias, reproducibility issues, and study failure. In response, the development of standardized nomograms and risk models could help to unify patient evaluation and stratification.

The NRG Oncology Radiation Therapy Oncology Group (RTOG) developed a risk model that incorporates key survival factors to guide therapeutic de-intensification or intensification for low-risk and intermediate/high-risk OPC, respectively.[5] However, this model does not encompass several known prognostic factors, such as age and performance status.

In an effort to enhance prognostic accuracy, Rios Velazquez et al.[6] published an externally validated HPV-based prognostic nomogram for OPC patients, incorporating variables such as anemia, smoking, T stage, N stage, and HPV status. Despite its methodological rigor, the study's retrospective design and limited follow-up period restrict its clinical applicability.

Furthermore, Fakhry et al.[7] developed and validated nomograms for predicting overall survival (OS) and progression-free survival (PFS) at 2 years and 5 years, respectively. These models included a comprehensive set of variables, including age, anemia, smoking history, education level, p16 status, T and N stage, and Zubrod performance status. While Fakhry's nomogram is notably thorough and supported by external validation, its clinical utility is limited by the homogeneity of the patient cohort, as all subjects were from the United States. The lack of evidence supporting the applicability of prognostic nomograms to diverse ethnic populations is of particular concern, given the potential interactions between risk factors and sociodemographic, geographic, epidemiological, and genetic variables.

The present study aims to validate the Fakhry's prognostic nomogram for predicting OS and PFS in European patients with locally advanced OPC who received primary radiotherapy (RT), with or without concurrent systemic treatments (ST).

METHODS

A large retrospective review from 805 consecutive series of locally advanced American Joint Committee on Cancer (AJCC) 7th edition stage III-IVa/b OPC from 14 Southern European oncology units (Italy, Greece, Spain) treated with definitive intensity-modulated radiotherapy (IMRT), with or without ST, was carried out. We collected a consecutive series of AJCC 7th edition locally advanced OPC treated with definitive IMRT with/without ST, having at least 2 years of follow-up.

History of cigarette smoking in pack-years (p/y) and alcohol consumption were obtained at enrollment. According to smoking status, patients were divided into never smokers, light smokers ($<$10 p/y), or heavy smokers ($\geq$10 p/y), while for alcohol consumption patients were clustered as never or light drinkers ($\leq$1 alcohol unit per day), moderate drinkers (2-3 alcohol units per day), and heavy drinkers ($>$3 alcohol units per day).

Other data collected were patient age, disease stage, HPV and p16 status (evaluated by immunohistochemistry, with positivity defined as strong and diffuse nuclear and cytoplasmic staining in $\geq$70% of tumor cells), presence/absence of a caregiver, anemia (if hemoglobin value was $<$13.5 g/dl and $<$12.5 g/dl for male and female, respectively), weight loss from baseline ($<$5% or $>$5% relative to normal body weight), marital status, Adult Comorbidity Evaluation-27 (ACE-27), and educational status (high school or less versus college or more).

Patients with missing survival data were excluded, as well as cases with more than two clinical data items not available. Of the total, 24 patients were not included in the analyses that were conducted on the remaining 781 patients.

Statistical analysis

Following Fakhry et al.,[7] Cox proportional hazard models were fit to the proposed set of covariates, both for OS and PFS. Results are reported as estimated hazard ratio (HR) and corresponding 95% confidence intervals (CIs).

Clinical prediction model validation can be carried out in terms of how well the model separates subjects who experienced the event from those who did not ('discrimination'), and in terms of how accurate the event probability predicted by the model on new data is ('calibration'). The baseline cumulative hazards were estimated from a Cox model fitted on our data, predicting the survival for a hypothetical subject with all risk factors set at the reference level.

The clinical prediction model proposed by Fakhry et al.,[7] at either time points, was validated in terms of discrimination using Harrell's C-index, and in terms of calibration using both the ratio of observed versus expected events (i.e. mean calibration or calibration-in-the-large) and the calibration slope (weak calibration). For a perfectly calibrated model we would expect both calibration measures to be equal to 1. A graphical description of model calibration is provided modeling observed events as function of predicted survival probabilities using a spline function. This allows a graphical inspection of the pattern of over/underestimation across the survival probabilities range.

Table 1. Patient characteristics

Characteristic, *n* (%)	Category	*n* (%)
Total number of patients, $N = 781$		
Age, 781 (100)	<50 years	67 (8.6)
	≥50 years	714 (91.4)
Sex, 781 (100)	Male	601 (76.9)
	Female	180 (23.1)
Smoker, 779 (99.7)	Never	200 (25.6)
	<10 pack-year	98 (12.5)
	≥10 pack-year	481 (61.6)
Zubrod, 777 (99.6)	0	501 (64.2)
	1	240 (30.8)
	2	34 (4.4)
	3	2 (0.2)
p16, 671 (85.9)	Negative	249 (31.9)
	Positive	422 (54.0)
Stage T, 778 (99.7)	Low (1-2)	314 (40.2)
	High (3-4)	464 (59.5)
Stage N, 779 (99.7)	Low (0-1)	174 (22.3)
	High (2-3)	605 (77.4)
Comorbidity, 652 (83.4)	0-1	502 (64.2)
	≥2	150 (19.2)
Alcohol, 748 (95.7)	Never or light	473 (60.5)
	Moderate or heavy	275 (35.2)
Caregiver, 710 (90.9)	Not present	88 (11.3)
	Present	622 (79.6)
Hemoglobin, 521 (66.7)	Low	172 (22.0)
	Normal	349 (44.7)

All the analyses were carried out using R (version 4.5.1, R Core Team, 2025). All numerical and graphical estimates are reported with the associated 95% CIs.

Ethical approval and informed consent

Each center received ethical approval from its own committee, and all included patients signed informed consent.

RESULTS

A total of 805 patients were analyzed with a median follow-up of 6 years (95% CI 5.69-6.26 years)

To validate Fakhry's prognostic nomogram,[7] all the included variables were collected (age, smoking status, Zubrod score, p16, T and N stage, anemia, education, marital status, weight loss), to which alcohol consumption, presence/absence of caregiver(s), and the interaction between p16 status and smoking history were added.

The patient characteristics are presented in Table 1.

Overall survival

Considering all the 781 records that have nonmissing survival information, the estimated 2-year and 5-year OS were 84.0% (95% CI 81.5% to 86.7%) (versus 83.6% observed by Fakhry), and 76.3% (95% CI 73.2% to 79.4%) (versus 72.0% observed by Fakhry), respectively.

Considering the 478 records that had nonmissing information for all the variables in the model, the estimated 2-year OS was 86.5% (95% CI 83.5% to 89.7%) (versus 83.6% observed by Fakhry), while the 5-year survival was 80.1% (76.5% to 83.9%) (versus 72.0% observed by Fakhry).

In multivariable analysis, all the factors found to be significantly associated with OS in Fakhry's nomogram were confirmed, and smoking history and p16 status were the most significant. Differing from the original study, we did not observe a strong correlation from the association between age and smoking status, while the interaction between smoking status (<10 p/y or ≥10 p/y) and p16 status (positive or negative) proved a significative prognostic role, especially for p16-positive patients (HR 6.48, 95% CI 2.50-16.81, $P < 0.01$).

The model for OS is listed in Table 2. Validation was carried out on complete cases. The prediction model showed good discrimination for OS both at 2 and 5 years, and was not dissimilar from the original external validation, with a C-index of 0.75 (95% CI 0.70-0.79).

Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.esmoop.2025.105859 show the calibration plots for the 2- and 5-year OS models, respectively, in which the model-predicted probability of 2- and 5-year OS is plotted against the observed probabilities computed on the new data.

Progression-free survival

Considering all 774 records that had nonmissing survival information, the estimated 2-year PFS was 75.7% (95% CI 72.6% to 78.8%), while the 5-year survival was 70.3% (95% CI 67.0% to 73.7%).

Considering 528 records that had nonmissing information for all the variables in the model, the estimated 2-year PFS was 77.4% (95% CI 73.8% to 81.1%) (versus 69.7%, 95% CI 65.4% to 73.6% observed by Fakhry), while the 5-year PFS was 71.5% (95% CI 67.6% to 75.6%) (versus 61.1% observed by Fakhry).

In multivariable analysis, all the factors found to be significantly associated with PFS in the reference nomogram were confirmed, except for age, which did not prove to be as relevant as in Fakhry's study. The model for PFS is listed in Table 3, and Supplementary Figures 3 and 4, available at https://doi.org/10.1016/j.esmoop.2025.105859 show the calibration plots for the PFS model.

Additional data

In consideration of the available data, patient characteristics, and lifestyle, to attempt to improve the Fakhry's nomogram efficacy both for PFS and OS we evaluated additional parameters to the data previously used, such as alcohol consumption, ACE27, presence/absence of caregiver(s), and the interaction between smoking history and p16 status.

At first, only ACE27, alcohol consumption, and caregiver status were included. When compared with the previously obtained results, this first extended model proved to have an increased accuracy in predicting 2- and 5-year OS (Harrell's C-index 0.78, 95% CI 0.74-0.83) (Table 4) and PFS (Harrell's C-index 0.71, 95% CI 0.66-0.76) (Table 5), but not enough to deviate significantly from Fakhry's model.

Adding the interaction between p16 status and smoking history to the extended model, the accuracy in predicting 2- and 5-year OS further improved (Harrell's C-index 0.79, 95%

Table 2. The 2- and 5-year overall survival multivariate model using the same variable of Fakhry's nomogram

Overall survival multivariate model						
2-year Characteristics	HR	95% CI	*P* value	5-year HR	95% CI	*P* value
Age						
<50 years	—	—	—	—	—	—
>50 years	am	0.61-3.25	0.4	1.51	0.65-3.49	0.3
Smoking						
<10 pack-years	—	—	—	—	—	—
>10 pack-years	3.46	1.72-6.97	<0.001	6.48	2.50-16.8	<0.001
Zubrod	1.03	0.66-1.62	0.9	1.06	0.68-1.66	0.8
p16						
Positive	—	—	—	—	—	—
Negative	1.43	0.88-2.34	0.15	7.24	2.00-26.3	0.003
Stage N						
Low	—	—	—	—	—	—
High	2.51	1.68-3.76	<0.001	2.51	1.68-3.76	<0.001
Stage T						
Low	—	—	—	—	—	—
High	2.33	1.54-3.51	<0.001	2.25	1.49-3.40	<0.001
Comorbidity						
2	—	—	—	—	—	—
0 + 1	0.85	0.53-1.35	0.5	0.88	0.55-1.41	0.6
Alcohol						
No	—	—	—	—	—	—
Yes	1.63	1.01-2.63	0.047	1.55	0.97-2.50	0.069
Caregiver						
Not present	—	—	—	—	—	—
Present	0.70	0.38-1.29	0.3	0.68	0.37-1.24	0.2
Hemoglobin						
No	—	—	—	—	—	—
Yes	1.42	0.95-2.12	0.090	1.41	0.94-2.11	0.093

CI, confidence interval; HR, hazard ratio.

CI 0.75-0.83) (Table 4), with substantial stability in the obtained data if only alcohol consumption and the interaction between p16 and smoking history are considered (Table 4).

DISCUSSION

The development of standardized nomograms and risk models is of considerable importance in HNSCC, and particularly in OPC, to unify patient evaluation and stratification both for improving patient assessment in clinical practice and for patient inclusion and stratification in clinical trials.

Although most patients in Fakhry's cohort were of Caucasian ethnicity, notable differences exist between the United States and European populations concerning sociodemographic, behavior, epidemiological, and genetic characteristics. In addition to the predictors used by Fakhry for PFS and OS, in view of the different patients characteristics and habits, further parameters (ACE-27, alcohol consumption, presence/absence of caregiver(s), and the interaction between p16 status and smoking history) were collected to implement the reference model.

Firstly, the efficacy of Fakhry's nomograms was confirmed both for 2- and 5-year OS and PFS, demonstrating that these predictive models are applicable to European patients.

In the European population, smoking history (quantified as p/y) and p16 status were the most significant predictors, whereas the correlation between smoking and age was not particularly significant, in contrast to Fakhry's findings.

We also added further predictors to the model such as alcohol consumption, ACE27, and presence/absence of caregiver(s), but these did not significantly improve the model for either 2-year or 5-year OS and PFS. The ACE 27, already used in the Rios Velasquez trial,[6] is a validated, relevant, scoring system for patients being operated on for SCC of the head and neck, used to identify important medical comorbidities and grade severity.[8] The lack of statistical significance is likely attributable to the fact that the patients' performance status had already been evaluated using the Zubrod score, and these two predictors may exhibit considerable overlap. The same statement applies to the presence/absence of caregiver(s), which often overlaps with marital status, since the main caregiver is often the wife/husband, particularly for male patients.

The interaction between smoking and p16 status was incorporated into the extended model, resulting in a significant increase in the Harrell C-index, compared with the previous model (Tables 4 and 5). Subsequently, we excluded both ACE-27 and caregiver presence/absence from the extended model, considering only alcohol consumption and p16 status × smoking history, showed no change in values previously observed: the statistical significance was maintained, indicating that the interaction between smoking and p16 expression and alcohol consumption were the most relevant added predictors.

Table 3. The 2- and 5-year progression-free survival multivariate model using the same variable of Fakhry's nomogram

Progression-free survival multivariate model						
2-year Characteristics	HR	95% CI	*P* value	5-year HR	95% CI	*P* value
Age						
<50 years	—	—	—	—	—	—
>50 years	0.82	0.43-1.54	0.5	0.82	0.44-1.55	0.5
Smoking						
>10 pack-years	—	—	—	—	—	—
>10 pack-years	2.00	1.16-3.45	0.013	2.21	1.19-4.13	0.013
Zubrod	0.90	0.59-1.38	0.6	0.90	0.59-1.38	0.6
p16						
Positive	—	—	—	—	—	—
Negative	1.77	1.10-2.83	0.018	2.60	0.82-8.20	0.10
Stage N						
Low	—	—	—	—	—	—
High	1.85	1.27-2.68	0.001	1.85	1.27-2.68	0.001
Stage T						
Low	—	—	—	—	—	—
High	1.41	0.97-2.05	0.069	1.39	0.96-2.03	0.081
Comorbidity						
2	—	—	—	—	—	—
0 + 1	0.76	0.50-1.16	0.2	0.77	0.50-1.17	0.2
Alcohol						
No	—	—	—	—	—	—
Yes	1.37	0.88-2.15	0.2	1.37	0.87-2.13	0.2
Caregiver						
Not present	—	—	—	—	—	—
Present	1.10	0.57-2.12	0.8	1.10	0.57-2.11	0.8
Hemoglobin						
No	—	—	—	—	—	—
Yes	1.08	0.73-1.59	0.7	1.08	0.73-1.59	0.7

CI, confidence interval; HR, hazard ratio.

Alcohol consumption is known to be an important risk factor in the carcinogenesis and prognosis of HNSCCs. Considering the very high average consumption among the European population, its inclusion in the model was of importance and its role as a predictor could not be ignored.[9]

Table 4. Overall survival: comparing Harrell C and Uno C values obtained in different models

Comparing 2- and 5-year overall survival in different models						
Same variables as Fakhry's						
Characteristics	Apparent			Internal (bootstrap)		
	Estimate	Lower 0.95	Upper 0.95	Estimate	Lower 0.95	Upper 0.95
Harrell C	0.78	0.73	0.82	0.76	0.72	0.79
Uno C	0.69	0.54	0.84	0.68	0.56	0.8
Extended model						
Characteristics	**Apparent**			**Internal (bootstrap)**		
	Estimate	**Lower 0.95**	**Upper 0.95**	**Estimate**	**Lower 0.95**	**Upper 0.95**
Harrell C	0.78	0.74	0.83	0.76	0.71	0.8
Uno C	0.73	0.63	0.84	0.7	0.62	0.79
Extended model plus p16/smoking history						
Characteristics	**Apparent**			**Internal (bootstrap)**		
	Estimate	**Lower 0.95**	**Upper 0.95**	**Estimate**	**Lower 0.95**	**Upper 0.95**
Harrell C	0.79	0.75	0.83	0.76	0.72	0.8
Uno C	0.74	0.64	0.85	0.71	0.62	0.8
p16/smoking status plus alcohol consumption						
Characteristics	**Apparent**			**Internal (bootstrap)**		
	Estimate	**Lower 0.95**	**Upper 0.95**	**Estimate**	**Lower 0.95**	**Upper 0.95**
Harrell C	0.79	0.75	0.83	0.77	0.74	0.81
Uno C	0.75	0.64	0.85	0.72	0.64	0.8

Table 5. Progression-free survival: comparing Harrell C and Uno C values obtained in different models

Comparing 2- and 5-year progression-free survival in different models						
2-year PFS. Same variables as Fakhry's						
Characteristics	Apparent			Internal (bootstrap)		
	Estimate	Lower 0.95	Upper 0.95	Estimate	Lower 0.95	Upper 0.95
Harrell C	0.3	0.26	0.34	0.68	0.65	0.72
Uno C	0.29	0.25	0.33	0.69	0.65	0.73
2-year PFS. Extended model						
Characteristics	**Apparent**			**Internal (bootstrap)**		
	Estimate	**Lower 0.95**	**Upper 0.95**	**Estimate**	**Lower 0.95**	**Upper 0.95**
Harrell C	0.71	0.66	0.76	0.67	0.63	0.71
Uno C	0.73	0.67	0.78	0.69	0.64	0.73
5-year PFS. Same variables as Fakhry's						
Characteristics	**Apparent**			**Internal (bootstrap)**		
	Estimate	**Lower 0.95**	**Upper 0.95**	**Estimate**	**Lower 0.95**	**Upper 0.95**
Harrell C	0.7	0.66	0.74	0.68	0.65	0.72
Uno C	0.71	0.67	0.75	0.69	0.65	0.73
5-year PFS. Extended model						
Characteristics	**Apparent**			**Internal (bootstrap)**		
	Estimate	**Lower 0.95**	**Upper 0.95**	**Estimate**	**Lower 0.95**	**Upper 0.95**
Harrell C	0.71	0.66	0.76	0.67	0.63	0.71
Uno C	0.73	0.67	0.78	0.69	0.64	0.73

PFS, progression-free survival.

The interaction between smoking history and p16 status in the model obtained significant results, especially in p16-positive patients, where the OS data worsened as the smoking history (evaluated in p/y) increased. This stratification has direct implications for patient selection and risk-group allocation in clinical trials, especially those investigating treatment de-escalation protocols (e.g. reduced radiation dose or omission of chemotherapy), which are currently limited to favorable-risk patients. The model may help avoid undertreatment in biologically distinct subgroups (e.g. HPV-positive heavy smokers) who might otherwise be inappropriately included in de-intensification trials based solely on p16 positivity.

Conversely, patients with favorable features (p16-positive, nonsmokers, low alcohol consumption) may be confidently selected for de-escalation strategies, minimizing treatment-related morbidity. The model could also be adapted as an inclusion or stratification tool in future prospective studies, enabling more personalized and biologically informed therapeutic approaches.

Future prospective trials are needed to validate the refined model proposed in our study.

These data underly the fact that HPV-positive patients and heavy smokers are a different subgroup of patients, more represented at European level; this is paralleled by a different molecular subtype.[10]

Smoking HPV-positive OPC patients expressed changes in the tumoral microenvironment, especially with lower cytolytic activity, level of immune infiltration, and interferon-γ pathway signaling.[11] In addition, among HPV-positive and smoker OPC, OPTIL separated stage I HPV-positive OPC with ≤30 p/y into low- and high-risk groups.[12] OPTIL is a biomarker that defines the spatial relationship between tumor-infiltrating lymphocytes and adjacent cells within histological images.[12]

There is conflicting evidence regarding discrepancy in the mutational profile between HPV-positive OPC smokers and nonsmokers: while Lassen et al. showed more CDKN2A, KRAS, NOTCH1, TP53 and fewer HLA-A mutations in smokers,[13] Mirghani et al. did not find any differences.[14]

Assessing prognosis before initiating treatment may enable clinicians to develop more personalized therapeutic approaches and consider alternative follow-up strategies. De-escalation treatments and escalation strategies are now heavily studied in OPC, without any available evidence until now. Whether this nomogram could help stratify patients to different treatment intensities is a matter for further research.[10]

We acknowledge several limitations. We cannot exclude the potential for bias in our model because of the exclusion of a proportion of enrolled patients as a result of missing data for key variables, both for the Fakhry's model validation and for data included in the extended model. Secondly, we included AJCC 7th edition T stage and N stage categories for OPCs, adding a possible staging bias, since in the 7th edition there was no separate classification of p16-positive and p16-negative OPCs p16-positive tumors.

The strengths of this study are its collection of data from homogeneous European centers with high expertise, and the inclusion of many patients, with a long follow-up.

Conclusion

We validated Fakhry's nomogram in a European population to predict 2- and 5-year PFS and OS in patients with OPC

undergoing (chemo)RT. Given the distinct patient characteristics and lifestyle factors in this population, we subsequently enhanced the model by incorporating additional predictors, including alcohol consumption and the interaction between p16 status and smoking history. These variables demonstrated significant prognostic value and improved the overall predictive performance of Fakhry's nomogram.

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DISCLOSURE

The authors have declared no conflicts of interest.

ETHICAL APPROVAL AND INFORMED CONSENT

Each center received ethical approval from its own committee and all the included patients signed informed consent.

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