Improvement of patient stratification in human papilloma virus-associated oropharyngeal squamous cell carcinoma by defining a multivariable risk score

Maximilian Oberste MD1 | Armands Riders MD1 | Bektasch Abbaspour MD1 | Laura Kerschke MSc2 | Achim G. Beule MD1 | Claudia Rudack MD1

1Department of Otorhinolaryngology – Head and Neck Surgery, University of Münster, Münster, Germany
2Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany

Correspondence
Maximilian Oberste, Department of Otorhinolaryngology – Head and Neck Surgery, University Hospital of Münster, Kardinal-von-Galen-Ring 10, D-48149 Münster, Germany.
Email: maximilian.oberste@ukmuenster.de

Abstract

Background: Precise risk stratification models are necessary to determine patient selection for deintensifying treatment trials in human papilloma virus (HPV)-associated oropharyngeal squamous cell cancer (HPV+ OPSCC).

Methods: We examined 526 cases with OPSCC treated at our department between 2002 and 2017. Every patient was classified after the 7th and 8th edition UICC staging manual. For HPV+ OPSCC, we calculated a simple risk score with four risk groups based on multivariable Cox regression analysis of clinical and lifestyle parameters (UICC 8th edition stage, tobacco/alcohol abuse, age, gender).

Results: Two hundred and thirty-nine patients with OPSCC (45.4%) showed a positive histological HPV status. In comparison to UICC 8th edition stages, our proposed risk model showed a tendency for better stratification between risk strata I/III, I/IV, and II/IV (each \( p < 0.002 \)) and I/II, II/III, and III/IV (each \( p < 0.09 \)).

Conclusion: Age, gender, tobacco, and alcohol abuse should be added to the current UICC staging system in order to improve risk stratification in HPV+ OPSCC.

KEYWORDS

8th edition UICC TNM staging system, deintensifying trials, human papilloma virus, oropharyngeal cancer, risk stratification

1 | INTRODUCTION

Oropharyngeal squamous cell cancer (OPSCC) comprises two entities with different clinical and pathologic characteristics: OPSCC, which is driven by cancerogenic alcohol and nicotine abuse (following named HPV− OPSCC), and human papilloma virus-related OPSCC (following named HPV+ OPSCC), which is mainly affected through orogenital intercourse. HPV+ OPSCC has substantially increased over the last decades in the United States and Western Europe and accounts for up to nearly 50% of all oropharyngeal cancers.1−3 This led to a general increase of OPSCC incidence despite general decreasing tobacco consumption.4 HPV+ OPSCC is more often seen in young, white people and shows better therapeutical response resulting in higher overall survival (OS) rates than HPV−...
OPSCC.\textsuperscript{5,6} The risk stratification of OPSCC according to UICC/AJCC staging manual (UICC) in its 7th edition did not account for HPV status; therefore it disregarded an important prognostic criterion for a long time. HPV+ OPSCC often presents with small tumor size but advanced nodal metastatic status at first diagnosis. These tumors were classified in higher classification stages in the 7th edition UICC despite good survival rates. This circumstance led to revision of UICC classification in 2017. On basis of the ICON-S study in which the impact of HPV+ OPSCC was assessed in an OPSCC cohort with primary radiation therapy (RT), the TNM classification differentiates since 2017 between p16+ and p16− OPSCC as a surrogate marker for HPV status.\textsuperscript{7} Since then, discrimination between stages has significantly improved.\textsuperscript{8−10} Nevertheless the 8th edition UICC remains imperfect in certain subgroups concerning their prognosis. Various authors showed that the 8th edition UICC does not discriminate well between Stage II and III in patients with HPV+ OPSCC.\textsuperscript{1,11} Therefore other prognostic factors are needed to improve risk stratification in OPSCC. Especially for deintensifying the therapy of HPV+ OPSCC, a more precise risk stratification is necessary. Some authors point out that the stratification of p16-positive OPSCC into UICC stages with the current 8th edition classification without considering further markers is not sufficient to justify possible de-escalation strategies of HPV+ OPSCC in future.\textsuperscript{11,12}

The aim of this study was (1) to investigate the prognostic value of the widely used 8th edition UICC/AJCC TNM staging system in a Western Europe single center cohort with mainly performed primary surgery, (2) to develop a simple risk score (RS) system for the HPV+ OPSCC by taking into account additional prognostic factors besides UICC 8th edition staging namely intense tobacco (>10 pack years [py]) and alcohol abuse (>3 days a week), gender and age (<65 years or ≥65 years), and (3) to explore if this risk model can stratify better than the current UICC 8th edition in this cohort.

2 | MATERIALS AND METHODS

All patients with histological confirmed OPSCC treated between January 1, 2002 and January 1, 2017 at the Department of Otorhinolaryngology, Head and Neck Surgery of the University Hospital of Münster, Germany were included in the study. Patients with age lower than 18 years, prior treatment, recurrent disease at first consultation, and follow-up <6 months were excluded. Five hundred and twenty-six patients met inclusion criteria. Demographic factors, histopathology reports with TNM/UICC stage, surgical reports, and information on follow-up (recurrent disease, second primary malignoma, survival) were analyzed retrospectively via digital patient files. All patients had been discussed in our certified interdisciplinary tumor board, where primary therapy was determined. In this cohort, OPSCC was treated with surgery alone, surgery combined with adjuvant RT, surgery combined with radiochemotherapy (RCT), RT alone, or definitive RCT. Patients were followed up after primary therapy in regular oncologic aftercare at our hospital with clinical examination, ultrasound of the neck, computed tomography (CT) and magnetic resonance imaging (MRI) in regular intervals for restaging. Patient age was assessed in categories <65 years or ≥65 years. Smoking status was grouped into nonsmokers/le10 py and heavy smokers with >10 py.\textsuperscript{13,14} Alcohol consumption was defined as none/moderate (weekend drinkers, ≤3 days per week) or as intense (>3 days per week) referring to the survey of Hartz et al.\textsuperscript{15} Pathologic staging was classified after the 7th and 8th edition UICC (clinical staging for nonsurgery group, pathological staging for surgery group).\textsuperscript{16,17}

Furthermore, the HPV status was assessed. Therefore, formalin-fixed paraffin-embedded tumor tissues from pathological archives of the Department of Pathology Munster, Germany were investigated for HPV16 E6/E7 DNA with real-time polymerase chain reaction (PCR).

DNA was isolated with a commercial KIT (QIamp DNA Mini Kit, QUIAGEN) and PCR were performed with ABI Prism 79900HT sequence targeting system, TaqMan Genotyping PCR Master Mix (Applied Biosystems, Thermo Fisher Scientific) as indicated by the manufacturer. The study protocol was reviewed and approved by the ethics committee of the Westphalia-Lippe Medical Association and the Münster University of Applied Sciences.

2.1 | Statistics

Statistical analysis was conducted with SPSS Version 26 and 27 of IBM SPSS software (IBM) and R version 4.0.2. Categorical parameters were shown as absolute and relative frequencies and continuous parameters as mean ± SD. The chi-square test was used to compare patient characteristics between HPV+ and HPV− OPSCC. OS was defined as the time from OPSCC diagnosis until death from any cause or last contact in oncologic aftercare. Univariable Kaplan-Meier analyses were performed to assess the impact of prognostic parameters on OS. Five-year OS (5yOS) and corresponding 95% confidence intervals (95% CIs) were calculated. Kaplan-Meier estimates were compared using the log-rank test. Pairwise comparisons between >2 groups were based on a Bonferroni-Holm correction for multiple testing. Patients with HPV+ OPSCC were included for
developing a new RS system. A multivariable Cox regression for the HPV+ OPSCC was used to estimate the impact of clinical and lifestyle parameters on OS, adjusted for the individual treatment the patients have received. The following variables were included in the model: gender (male vs. female), age ($\geq 65$ years vs. $<65$ years), therapy (surgery, surgery + RT, surgery + RCT, definite RT, definite RCT vs. none), UICC 8th edition (UICC Stage I vs. II, I vs. III, and I vs. IV), smoking status ($\leq 10$ py vs. $>10$ py), and alcohol consumption (none/moderate vs. intense). The parameter estimates of the nontherapy variables were used to derive a RS.

The RS is a measure of the risk of an event independent of the received therapy. Based on an optimal stratification of the RS, four risk groups were defined.

This was based on investigating all possible triples of cutoff values C1, C2, C3 from the set ranging from 0 to 4 by 0.1. Each cutoff triple defined four risk groups and was evaluated in a Cox regression model including the risk group plus the therapy variable.

To ensure proper model fit, only cutoff triples resulting in a minimum sample size of seven patients per stratum were considered.

Finally, the cutoff triple with the smallest $p$ value in the likelihood ratio test was chosen (unadjusted for the multiple tests of all possible cutoff triples) to define the risk strata. Median follow-up was calculated by reverse censoring. Inferential statistics were intended to be exploratory. $p$ values $<0.05$ were considered statistically noticeable.

3 | RESULTS

3.1 | General data

In this study, we examined 526 patients with primary diagnosis of OPSCC at our Department of Otorhinolaryngology, Head and Neck Surgery of the University Hospital of Münster, Germany treated between 2002 and 2017. Two hundred and thirty-four HPV+ OPSCC patients, 49.5% HPV+ OPSCC (3316 patients, 44.5%) were reclassified and down staged using the 7th edition UICC, more than half of the cases were HPV positive (30.5% vs. 18.4%). T2 carcinoma were most frequent T-stage in both groups (38.1% vs. 35.7%) whereas T3 and T4 were less common but prevailing in HPV− OPSCC carcinoma (T3: 19.9% vs. 25.8%, T4: 11.4% vs. 20.1%, $p = 0.001$, Table 1).

N0 status was observed more frequently in HPV− OPSCC than in HPV+ OPSCC (31.7% vs. 18.2%) while N1 was more frequent in HPV+ OPSCC (34.8% vs. 20.1%, $p < 0.001$, Table 1).

In general, primary surgery was performed in 328 patients (66.1%) of which primary surgery with adjuvant RCT was preferably employed (146 patients of 328 patients, 44.5%).

Primary surgery with adjuvant RT or RCT was more often in the HPV+ cohort, which was statistically noticeable (149 of 221 HPV+ patients, 67.2% vs. 136 of 275 patients, 49.5% HPV−; $p < 0.001$). On the other hand, primary RCT was more frequent in the HPV− cohort (33 of 221 HPV+ patients, 13.8% vs. 60 of 275 patients, 20.9%).

In general, 380 patients (74.7%) were heavy smokers ($>10$ py) and 227 patients (45.2%) had an intensive alcohol consume. Two hundred and thirty-four HPV− patients (84.5%) had a smoking status with $>10$ py and 157 HPV− patients (56.7%) had an intensive consumption of alcohol, which differed markedly from the HPV+ cohort with 146 patients (62.9%, heavy tobacco abuse) and 70 patients (31.1%, intensive alcohol abuse), respectively (each $p < 0.001$).

3.2 | Univariable analysis of prognostic markers for OS

In the univariable Kaplan-Meier analyses, HPV+ status ($p < 0.001$), age $< 65$ years ($p = 0.05$), less tobacco use ($\leq 10$ py ($p = 0.010$), less consumption of alcohol ($p = 0.004$), T1/T2 ($p < 0.001$), N0/N1 ($p = 0.001$), M0 ($p < 0.001$), up-front surgery ($p < 0.001$), and a low 7th/8th edition UICC stage ($p = 0.002/p < 0.001$) showed improved OS (Table 2). Gender did not play a prognostic role in our cohort. OS showed no notable difference between males and females ($p = 0.068$). Five-year OS (5yOS) of HPV+ OPSCC was 88.3% (95% CI = 83.4%–93.4%) compared to 70.0% (95% CI = 63.1%–77.6%) in HPV− OPSCC.

3.3 | Overall survival and risk stratification in the 7th and 8th edition UICC/AJCC staging manual

Calculated with the 7th edition UICC, more than half of the patients were set in Stage IV (HPV+: 59.7%, HPV−: 55.3%). 88.3% of HPV+ OPSCC (40.5% of whole study population) were reclassified and down staged using the
According to the 8th edition UICC, 83.6% of HPV+ OPSCC were classified in Stage I or II. The distribution of UICC stages based on the 8th edition UICC differed notably between the two HPV groups ($p < 0.001$).

We detected a better risk stratification in the HPV+ cohort for the 8th edition UICC than for the 7th edition UICC regarding OS (except for Stage I and II, and III and IV; each $p = 0.481$, Table 2, Figure 1).

The corresponding Kaplan-Meier curves showed a better separation as under the UICC 7th edition (Figure 1).

### Development of a RS system for HPV+ OPSCC

A new risk stratification system for patients with HPV+ OPSCC was developed based on UICC 8th edition staging, demographic, and lifestyle parameters taking into account the individual treatment the patients may have received.

The Cox regression model was fitted using data of 224/239 complete cases available to estimate the effect of each considered predictor on OS. The model fit is shown in Table 3. All nontherapeutic parameters are

### TABLE 1 Characteristics of OPSCC study population in relation to HPV status

| Group | HPV+ | HPV- | $p$ value* |
|-------|------|------|------------|
|       | N    | %    | N          | %   |
| All   | 239  | 45.4 | 287        | 54.6|
| Age < 65 years | 165  | 69.0 | 187        | 65.2 | 0.224|
| Age ≥ 65 years | 74   | 31.0 | 100        | 34.8|
| Female | 66   | 27.6 | 66         | 23.0 | 0.346|
| Male   | 173  | 72.4 | 221        | 77.0|
| Smoking ≤10 py | 86   | 37.1 | 43         | 15.5 | <0.001|
| Smoking >10 py | 146  | 62.9 | 234        | 84.5|
| Alcohol consumption (none/moderate) | 155  | 68.9 | 120        | 43.3 | <0.001|
| Alcohol consumption (intense) | 70   | 31.1 | 157        | 56.7|
| T1     | 72   | 30.5 | 52         | 18.4 | 0.001|
| T2     | 90   | 38.1 | 101        | 35.7|
| T3     | 47   | 19.9 | 73         | 25.8|
| T4     | 27   | 11.4 | 57         | 20.1|
| N0b    | 42   | 18.2 | 88         | 31.7 | <0.001|
| N1     | 80   | 34.8 | 56         | 20.1|
| N2     | 108  | 47.0 | 125        | 45.0|
| N3     | 0    | 0    | 9          | 3.2|
| M0     | 201  | 95.3 | 244        | 93.1 | 0.329|
| M1     | 10   | 4.7  | 18         | 6.9|
| UICC 7 I | 16   | 6.7  | 24         | 8.5 | 0.029|
| UICC 7 II | 15   | 6.3  | 39         | 13.7|
| UICC 7 III | 65   | 27.3 | 64         | 22.5|
| UICC 7 any IV | 142  | 59.7 | 157        | 55.3|
| UICC 8 Ib | 106  | 44.5 | 24         | 8.5 | <0.001|
| UICC 8 II | 93   | 39.1 | 40         | 14.1|
| UICC 8 III | 29   | 12.2 | 64         | 22.5|
| UICC 8 any IV | 10   | 4.2  | 156        | 54.9|
| No primary surgery | 55   | 24.9 | 113        | 41.1 | <0.001|
| Primary surgery | 166  | 75.1 | 162        | 58.9|

Abbreviations: HPV, human papilloma virus; OPSCC, oropharyngeal squamous cell cancer; py, pack years.

*Pearson's chi-square test, <0.05 denoted in bold.

bN stage classified according to the 8th edition UICC (for surgery treatment pathological staging, for nonsurgery treatment clinical staging).
generally available at the time of diagnosis and were therefore chosen to build a RS. The RS allows the individual risk of each patient to be calculated according to a formula (coefficients rounded, Table 4). An example of one patient as possible clinical case at the time point of therapy planning after initial staging is shown in Table 4. Ranging from $/C_0$ 0.084 to 6.276, with a median of 1.07 (Q1: 0.36, Q3: 1.3), the optimal cutoffs were $C_1 = 0.9$, $C_2 = 1.8$, and $C_3 = 2.9$. Consequently, the resulting four risk groups were given by: risk group 1: RS $\leq 0.9$; risk group 2: $0.9 < RS \leq 1.8$; risk group 3: $1.8 < RS \leq 2.9$; risk group 4: RS $> 2.9$). Figure 2 shows the Kaplan-Meier curves for OS of the four risk groups resulting from the stratification system. The RS and corresponding risk group could be assessed in 224/239 cases available (i.e., complete data on all parameters that are entered into the RS). OS differed noticeable between Stage I/III, I/IV, and II/IV (each $p < 0.002$) and we saw a tendency in differentiation between Stages I/II, II/III, and III/IV ($p < 0.09$). In comparison, a poorer stratification for UICC 8th edition Stages I versus II and III versus IV ($p = 0.481$, Figure 1) could be seen. The distribution for 5yOS can be seen in Kaplan-Meier curves in Figure 2 (5yOS: risk group I: 92.6%, 95% CI = 82.4%–97.3%; II: 87.6%, 95% CI = 71.8%–95.2%; III: 66%, 95% CI = 24.8%–90.4%; IV: 31.2%, 95% CI = 0.9%–84.7%).

Differences between risk strata groups were statistically noticeable for treatment groups (surgery vs. no surgery), UICC 8th edition stages, smoking, and alcohol abuse ($p < 0.001$, Table 5).

### TABLE 2 Univariable analysis of prognostic factors regarding overall survival in OPSCC ($N = 526$)

| Group                          | $N$   | %    | 5yOS (%) | Lower 95% CI | Upper 95% CI | $p$ value$^a$ |
|-------------------------------|-------|------|----------|--------------|--------------|---------------|
| HPV+                          | 287   | 54.6 | 88.3     | 83.4         | 93.4         | $<0.001$      |
| HPV–                          | 239   | 45.4 | 70.0     | 63.1         | 77.6         |               |
| Age < 65 years                | 352   | 66.9 | 81.0     | 76.1         | 86.2         | 0.050         |
| Age $\geq$ 65 years           | 174   | 33.1 | 75.4     | 67.2         | 84.5         |               |
| Female                        | 132   | 25.1 | 87.3     | 80.6         | 94.5         | 0.068         |
| Male                          | 394   | 74.9 | 76.4     | 71.1         | 82.0         |               |
| Smoking $\leq$ 10 py          | 129   | 25.3 | 87.2     | 80.4         | 94.6         | 0.010         |
| Smoking $>$ 10 py              | 380   | 74.7 | 75.8     | 70.5         | 81.6         |               |
| Alcohol consumption (none/moderate) | 275  | 54.8 | 84.2     | 79.0         | 89.8         | 0.004         |
| Alcohol consumption (intense)  | 227   | 45.2 | 70.9     | 63.4         | 79.2         |               |
| T1/T2                         | 315   | 60.7 | 87.1     | 82.7         | 91.7         | $<0.001$      |
| T3/T4                         | 204   | 39.3 | 62.0     | 53.0         | 72.6         |               |
| N0/N1$^b$                     | 266   | 52.4 | 84.9     | 79.8         | 90.3         | 0.001         |
| N2/N3$^b$                     | 242   | 47.6 | 73.3     | 66.2         | 81.1         |               |
| M0                            | 445   | 94.1 | 81.5     | 77.0         | 86.2         | $<0.001$      |
| M1                            | 28    | 5.9  | 41.2     | 22.8         | 74.2         |               |
| UICC7 I                       | 40    | 7.7  | 92.3     | 84.3         | 100.0        | 0.002         |
| UICC7 II                      | 54    | 10.3 | 76.7     | 61.9         | 95.2         |               |
| UICC7 III                     | 129   | 24.7 | 87.3     | 80.4         | 94.9         |               |
| UICC7 any IV                  | 299   | 57.3 | 73.2     | 67.0         | 80.0         |               |
| UICC8 I$^b$                   | 130   | 24.9 | 93.6     | 89.0         | 98.4         | $<0.001$      |
| UICC8 II                      | 133   | 25.5 | 86.1     | 78.3         | 94.5         |               |
| UICC8 III                     | 93    | 17.8 | 75.2     | 64.4         | 87.9         |               |
| UICC 8 any IV                 | 166   | 31.8 | 57.1     | 47.1         | 69.2         |               |
| No primary surgery            | 168   | 33.9 | 63.8     | 54.8         | 74.4         | $<0.001$      |
| Primary surgery               | 328   | 66.1 | 85.8     | 81.2         | 90.6         |               |

Abbreviations: 5yOS, 5-year overall survival; CI, confidence interval; HPV, human papilloma virus; OPSCC, oropharyngeal squamous cell cancer; py, pack years.

$^a$Log rank test, $p < 0.05$ denoted in bold.

$^b$N stage classified according to the 8th edition UICC (for surgery treatment pathological staging, for nonsurgery treatment clinical staging).
FIGURE 1 Kaplan-Meier curves for overall survival of the 7th and 8th edition UICC/AJCC staging manual regarding HPV+ and HPV− cohort. Pairwise Log rank tests with Bonferroni-Holm correction were performed and significant differences (p < 0.05) are denoted in bold. HPV, human papilloma virus [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Multivariable Cox regression analysis for HPV+ OPSCC

| Group                                      | HR  | Lower 95% CI | Upper 95% CI | β       | SE  | p value |
|--------------------------------------------|-----|--------------|--------------|---------|-----|---------|
| Age (≥65 years vs. <65 years)              | 0.971 | 0.374       | 2.526         | −0.029  | 0.488 | 0.952   |
| Sex (male vs. female)                      | 0.946 | 0.388       | 2.307         | −0.055  | 0.455 | 0.952   |
| Smoking (≤10 py vs. >10 py)                | 2.296 | 0.848       | 6.213         | 0.831   | 0.508 | 0.090   |
| Alcohol consumption (none/moderate vs. intense) | 1.359 | 0.548       | 3.367         | 0.306   | 0.463 | 0.513   |
| UICC 8th edition (II vs. I)                | 1.512 | 0.503       | 4.546         | 0.414   | 0.562 | 0.004   |
| UICC 8th edition (III vs. I)               | 6.241 | 1.554       | 25.065        | 1.831   | 0.709 |         |
| UICC 8th edition (IV vs. I)                | 18.06 | 3.822       | 85.326        | 2.894   | 0.792 |         |
| Therapy (OP vs. none)                      | 0.616 | 0.104       | 3.644         | −0.485  | 0.907 | 0.03    |
| Therapy (RT vs. none)                      | 0.096 | 0.009       | 0.974         | −2.346  | 1.183 |         |
| Therapy (RCT vs. none)                     | 0.101 | 0.023       | 0.444         | −2.297  | 0.757 |         |
| Therapy (OP + RCT vs. none)                | 0.154 | 0.038       | 0.624         | −1.870  | 0.713 |         |
| Therapy (OP + RT vs. none)                 | 0.215 | 0.055       | 0.837         | −1.539  | 0.695 |         |

Note: Results are reported as hazard ratios, corresponding 95% confidence intervals, regression coefficients, SEs, and p values of likelihood ratio tests. The significant p-values are marked in bold.

Abbreviations: β, regression coefficient; CI, confidence interval; HPV, human papilloma virus; HRs, hazard ratios; OP, surgery; OPSCC, oropharyngeal squamous cell cancer; py, pack years; RCT, radiochemotherapy; RT, radiation therapy.
4 | DISCUSSION

This study confirms and validates the improvement of the risk stratification in the 8th edition UICC in this unselected German OPSCC cohort with preferred primary surgery. This demonstrates the prognostic importance of HPV status in OPSCC and the usefulness of the UICC classification systems for prediction of survival.

An impressive number of 88.3% of HPV+ OPSCC were down staged in our cohort in comparison to 7th edition and 83.6% of HPV+ OPSCC were classified in Stage I and II using the criteria in 8th edition UICC. Nevertheless in our cohort in UICC 8th edition there was no statistical difference between Stages I/II, II/III, and III/IV in HPV+ OPSCC regarding OS. This concurs with current literature where both primary radiation and primary surgery groups resulted in similar survival rates.\textsuperscript{1,9,11,18,19}

On the one hand, the reason for this could be the small number of deaths in HPV+ OPSCC and good response rates to therapy also for advanced tumor and nodal stages in HPV+ cancer, which complicates the discrimination between stages. Furthermore, the classification of UICC 8th edition stages was based on the ICON-S-Study which examined a primary radiotherapy group (98% of cases) and pathological Stage III was based on only 23 patients which could have a bias on classification building.\textsuperscript{7} The lack of discrimination between stages could lead to momentous consequences in de-escalation treatment trials in HPV+ OPSCC.\textsuperscript{20,21}

We therefore defined a new simple RS based on the sum of Cox regression coefficients of different prognostic factors in HPV+ OPSCC to determine the individual risk of every patient.

UICC 8th edition stages, age ($\geq$65 years vs. <65 years), gender, tobacco ($\leq$10 py vs. >10 py), and alcohol (none/moderate vs. intense) abuse were included as important clinical and demographic parameters to build the RS. Based on an optimal stratification of the RS, the proposed staging system showed improvement in differentiation of risk strata in contrast to UICC 8th edition stages (Figure 2).

Following higher UICC stages (III/IV), heavy tobacco use (>10 py) had the biggest impact on the estimated risk in HPV+ OPSCC ($\beta = 0.831$). All patients in risk strata IV

![Proposed system (HPV+)](image)

**Figure 2** Kaplan-Meier curves for overall survival of the proposed risk score system regarding HPV+ OPSCC. Pairwise Log rank tests with Bonferroni-Holm correction were performed and significant differences ($p < 0.05$) are denoted in bold. HPV, human papilloma virus; OPSCC, oropharyngeal squamous cell cancer [Color figure can be viewed at wileyonlinelibrary.com]
were heavy smokers, with the majority in risk strata I being nonsmokers or moderate smokers (82%). In our study, the amount of heavy smokers in HPV+ OPSCC (62.9%) was relatively high being another argument for including this factor in our RS system. Independent of HPV status, absence, or lower tobacco abuse <10 py was associated with improved OS ($p = 0.010; 5yOS: 75.8% vs. 87.2%).

Smoking had a bigger negative impact on survival for cases of HPV/C0 OPSCC compared to HPV+ OPSCC. In general, smoking generates greater genomic instability and reduces intrinsic tumor radiosensitivity. Gillison et al. showed in an analysis of RTOG studies 9003 and 0129 that the risk of death increased in OPSCC independent of HPV status with increasing pack years or former nicotine abuse. Grønhøj et al. confirmed this in a surgical cohort in Denmark and Germany. Other authors state that the individual risk increases 6–7 times when tobacco or alcohol are abused and as much as 15 times in patients who combine both. The majority of patients in the proposed risk strata III and IV consumed alcohol intensively (III: 80%, IV: 77.8%) showing its toxicity. The same was seen in a German single center study with poor prognosis in alcoholics. Nevertheless alcohol has a low risk for poor treatment outcome in this study ($\beta = 0.306$) and should not be overinterpreted as isolated prognostic marker. Still the combination of nicotine and alcohol increases the estimated risk statistically noticeable in this HPV+ OPSCC cohort. The impact of these two important prognostic factors on risk stratification can be seen in the proposed example (Table 4). An UICC 8th edition I stage patient changed to risk strata II because of heavy tobacco and alcohol abuse. Every patient with combination of heavy tobacco and alcohol abuse was classified at least in risk strata II.

It could be discussed that these patients potentially should not be de-escalated in therapy. With these findings, we underline that intensive tobacco and alcohol abuse already have great influence on survival and comorbidities. Some authors also point out that severe comorbidity and bad health are directly connected to these factors. Therefore we did not put special emphasize on performance status like Eastern Cooperative Oncology Group (ECOG) performance status in our RS system.

Fakhry et al. showed in a multi-institutional study in 281 patients that females have better OS than males in OPSCC independent of HPV status. We could not find a statistical difference between gender groups in univariable analysis and in our risk strata groups (Table 5). Interestingly, there was a slight risk reduction in male patients ($\beta = -0.055$). However, the low statistical power ($p = 0.904$) should be taken into account here. Furthermore, risk profiles can differ on demographic factors depending on geographic locality. Current US

### TABLE 5 Risk group data of proposed system with HPV+ OPSCC ($N = 239$)

| Risk strata          | I              | II             | III            | IV             | $p$ value$^a$ |
|----------------------|----------------|----------------|----------------|----------------|--------------|
| I                    | No. of patients (%) | No. of patients (%) | No. of patients (%) | No. of patients (%) |            |
| Age < 65 years       | 110 (100)       | 85 (100)       | 20 (100)       | 9 (100)        |              |
| Age ≥ 65 years       | 71 (64.5)       | 61 (71.8)      | 13 (65.0)      | 7 (77.8)       | 0.350        |
| Male                 | 39 (35.5)       | 24 (28.2)      | 7 (35.0)       | 2 (22.2)       |              |
| Female               | 81 (73.6)       | 62 (72.9)      | 15 (75.0)      | 7 (77.8)       | 0.915        |
| Smoking ≤10 py       | 29 (26.4)       | 23 (27.1)      | 5 (25.0)       | 2 (22.2)       | <0.001       |
| Smoking >10 py       | 40 (36.4)       | 74 (87.1)      | 16 (80.0)      | 9 (100)        |              |
| Alcohol consumption (none/moderate) | 95 (86.4) | 42 (49.4) | 4 (20.0) | 2 (22.2) | <0.001 |
| Alcohol (intense)    | 15 (13.6)       | 43 (50.6)      | 16 (80.0)      | 7 (77.8)       |              |
| UICC 8th Stage I$^b$ | 74 (67.3)       | 28 (32.9)      | —              | —              | <0.001       |
| UICC 8th Stage II    | 36 (32.7)       | 48 (56.5)      | —              | —              |              |
| UICC 8th Stage III   | —              | 8 (9.4)        | 17 (85.0)      | 4 (44.4)       |              |
| UICC 8th Stage IV    | —              | 1 (1.2)        | 3 (15.0)       | 5 (55.6)       |              |
| No up-front surgery  | 17 (15.5)       | 19 (22.4)      | 12 (60.0)      | 6 (66.7)       | <0.001       |
| Up-front surgery     | 88 (80.0)       | 58 (68.2)      | 6 (30.0)       | 3 (33.3)       |              |

**Abbreviations**: HPV, human papilloma virus; OPSCC, oropharyngeal squamous cell cancer; py, pack years.

$^a$Kruskal-Wallis test, $p < 0.05$ denoted in bold.

$^b$N stage classified according to the 8th edition UICC (for surgery treatment pathological staging, for nonsurgery treatment clinical staging).
population studies show a trend for increasing rates of HPV+ OPSCC in older patients. In our German cohort, we could not find this causal relationship ($p = 0.396$). In this study, younger patients (<65 years) show more often histological HPV status, which is linked with better survival rates. Nevertheless in the proposed RS system higher age > 65 years even showed a tendency to lower risk ($\beta = -0.029$) but here too, the statistical power was low ($p = 0.952$). Still, age did not show a meaningful difference in OS analysis. This stands in line with two other German studies.\textsuperscript{1,2}

Up to now several risk models were developed using different statistical methods and prognostic factors. The best known are those of Ang et al. and Rietbergen et al.\textsuperscript{13,27} Ang et al. established a risk stratification model in 2010 using recursive partitioning subdividing a highly selected American OPSCC cohort (only T3/T4 carcinomas, ECOG status 1 or 2) with HPV status, smoking status ($\leq$10 py or >10 py), and T/N status in low-, intermediate-, and high-risk patients.\textsuperscript{13} Unfortunately their data were based only on the 7th edition UICC criteria and included only patients who were treated with RCT. Validation showed no better discrimination in this risk stratification model than UICC/AJCC staging manual in several studies.\textsuperscript{11,27}

Nevertheless, Ang classification is used in current de-escalation trials like DE-ESCALATE and RTOG 1016 due to its simplicity.\textsuperscript{20,21} Rietbergen et al. found HPV, T/N status, and ACE27 performance status as most important prognostic factors in their European cohort with mainly RCT patients.\textsuperscript{27}

Deschuymer et al. further refined Rietbergen’s system on basis of the 8th edition UICC.\textsuperscript{11}

They demonstrated that their new risk stratification system was equally to the 8th edition UICC but showed no significant improvement. In their study, only radiated HPV+ OPSCC was examined. Studies with primarily surgical treatment are rare. Wagner et al. built a risk model on a comparable German cohort with primarily treated surgery.\textsuperscript{4} They assessed HPV and ECOG performance status as the most important factors and stated that up-front surgery is more effective in small and intermediate OPSCC. They state that the classification of Ang et al. has certain negative effects in primary surgery cohort and risk modeling has to be adapted concerning treatment strategies.\textsuperscript{4}

All these risk model studies have the common aim to find the ideal subgroup in HPV-associated cancer for de-escalating therapy. Our RS system is a simple prognosis model, which shows the patients individual risk for treatment outcome by emphasizing demographic and lifestyle parameters beside UICC 8th edition in HPV+ OPSCC. Thereby we contribute to individualized therapy and patient selection for future de-escalation studies.

Still, a lot of patients with HPV+ OPSCC received up-front surgery with adjuvant RCT (37.1%) in our study. This stands in contrast to ongoing de-escalation trials and underlines the current treatment strategy in Germany where de-escalation is only allowed in treatment trials.

Limitation of our study is its retrospective examination, which has a certain bias in risk factor collection especially regarding nicotine and alcohol consumption. Furthermore, our cohort is limited to a single center so external validity is low. The proposed RS system has to be proofed in future multicenter studies. Our RS system shows an ideal system (“optimal stratification”) in this cohort and has to be validated in other cohorts and meta-analysis.

In summary, the individual risk profile of the patients with HPV+ OPSCC will guide treatment strategies in future. According to our proposed RS system, patients with HPV+ OPSCC classified in risk strata I (UICC 8th Stage I-II, no heavy tobacco and alcohol abuse, independent of age and gender) have an excellent 5yOS of 92.6% (CI = 82.4%–97.3%) and could profit of de-escalated therapy.

5 | CONCLUSION

We confirm that the 8th edition UICC/AJCC TNM staging system shows improved risk stratification in this unselected OPSCC cohort with primarily treated surgery. Still, there are weaknesses in the stratification of UICC stages in HPV+ OPSCC, which is still leading to cautious treatment de-escalation in Germany.

With our simple RS system, we underline the necessity to include age, gender, tobacco, and alcohol consumption behavior into UICC staging manual to further improve risk stratification in HPV+ OPSCC.

ACKNOWLEDGMENT

We thank the patients for taking part in this study and the statistical assistance given by the Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.
REFERENCES

1. Würdemann N, Wagner S, Sharma SJ, et al. Prognostic impact of AJCC/UICC 8th edition new staging rules in oropharyngeal squamous cell carcinoma. Front Oncol. 2017;7:129.

2. Beltz A, Gösswein D, Zimmer S, et al. Staging of oropharyngeal squamous cell carcinoma of the head and neck: prognostic features and power of the 8th edition of the UICC staging manual. Eur J Surg Oncol. 2019;45(6):1046-1053.

3. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. J Clin Oncol. 2015;33(29):3235-3242.

4. Wagner S, Wittekindt C, Sharma SJ, et al. Human papillomavirus association is the most important predictor for surgically treated patients with oropharyngeal cancer. Br J Cancer. 2017;116(12):1604-1611.

5. Fakhry C, Westra WH, Wang SJ, et al. The prognostic role of sex, race, and human papillomavirus in oropharyngeal and nonoropharyngeal head and neck squamous cell cancer. Cancer. 2017;123(9):1566-1575.

6. Thompson LDR, Burchette R, Iganej S, Bhattasali O. Oropharyngeal squamous cell carcinoma in 390 patients: analysis of clinical and histological criteria which significantly impact outcome. Head Neck Pathol. 2019;14(3):666-688.

7. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol. 2016;17(4):440-451.

8. Cramer JD, Hicks KE, Rademaker AW, Patel UA, Samant S. Validation of the eighth edition American Joint Committee on Cancer staging system for human papillomavirus-associated oropharyngeal cancer. Head Neck. 2018;40(3):457-466.

9. Sano D, Yabuki K, Ariy H, et al. The applicability of new TNM classification for human papillomavirus-related oropharyngeal cancer in the 8th edition of the AJCC/UICC TNM staging system in Japan: a single-centre study. Auris Nasus Larynx. 2018;45(3):558-565.

10. Machczyński P, Majchrzak E, Niewinski P, Marchlewksa J, Golusinski W. A review of the 8th edition of the AJCC staging system for oropharyngeal cancer according to HPV status. Eur Arch Otorhinolaryngol. 2020;277(9):2407-2412.

11. Deschuymer S, Dok R, Laenen A, Hauben E, Nuys T. Patient selection in human papillomavirus related oropharyngeal cancer: the added value of prognostic models in the new TNM 8th edition era. Front Oncol. 2018;8:273.

12. Tribius S, Würdemann N, Laban S, Hoffmann TK, Sharma SJ, Klussmann JP. Update zu HPV-assoziierten Kopf-Hals-Karzinomen – highlights der ASCO-Jahrestagung 2019. HNO. 2019;67(12):912-917.

13. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24-35.

14. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol. 2012;30(17):2102-2111.

15. Hartz SM, Oehlert M, Horton AC, et al. Daily drinking is associated with increased mortality. Alcohol Clin Exp Res. 2018;42(11):2246-2255.

16. Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. Chichester, UK: Wiley; 2017.

17. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer. TNM Classification of Malignant Tumours. Chichester, UK: Wiley-Blackwell; 2010.

18. van Gysen K, Stevens M, Guo L, et al. Validation of the 8th edition UICC/AJCC TNM staging system for HPV associated oropharyngeal cancer patients managed with contemporary chemo-radiotherapy. BMC Cancer. 2019;19(1):674.

19. De Felice F, Bird T, Michaelidou A, et al. Radical (chemo) radiotherapy in oropharyngeal squamous cell carcinoma: comparison of TNM 7th and 8th staging systems. Radiother Oncol. 2020;145:146-153.

20. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. Lancet. 2019;393(10166):51-60.

21. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multi-centre, non-inferiority trial. Lancet. 2019;393(10166):40-50.

22. Grönhøj C, Jensen JS, Wagner S, et al. Impact on survival of tobacco smoking for cases with oropharyngeal squamous cell carcinoma and known human papillomavirus and p16-status: a multicentre retrospective study. Oncotarget. 2019;10(45):4656-4663.

23. Berkis U, Lifsics A, Rate E, et al. Smoking and alcohol abuse – predictive factors in oropharyngeal squamous cell carcinoma: a retrospective study. SJS Web Conf. 2019;68:02013.

24. Fazel A, Quabius ES, Fabian A, et al. The influence of smoking and co-morbidity on dose achievement in primary or adjuvant radio(chemo)therapy in head and neck squamous cell carcinoma (HNSCC). Front Oncol. 2020;10:398.

25. Baumeister P, Rauch J, Jacobi C, et al. Impact of comorbidity and anemia in patients with oropharyngeal cancer primarily treated with surgery in the human papillomavirus era. Head Neck. 2017;39(1):7-16.

26. Rettig EM, Fakhry C, Khararjian A, Westra WH. Age profile of patients with oropharyngeal squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg. 2018;144(6):538-539.

27. Rietbergen MM, Brakenhoff RH, Bloemena E, et al. Human papillomavirus detection and comorbidity: critical issues in selection of patients with oropharyngeal cancer for treatment De-escalation trials. Ann Oncol. 2013;24(11):2740-2745.

How to cite this article: Oberste M, Riders A, Abbaspour B, Kerschke L, Beule AG, Rudack C. Improvement of patient stratification in human papilloma virus-associated oropharyngeal squamous cell carcinoma by defining a multivariable risk score. Head & Neck. 2021;43(11):3314-3323. https://doi.org/10.1002/hed.26822