Development and Assessment of a Novel Composite Pathologic Risk Stratification for Surgically Resected Human Papillomavirus-Associated Oropharyngeal Cancer

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**IMPORTANCE** Human papillomavirus-associated (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) is a distinct form of head and neck squamous cell carcinoma (HNSCC) with its own American Joint Committee on Cancer staging system. However, pathologic risk stratification for HPV+ OPSCC largely remains based on the experience with HPV-unassociated HNSCC.

**OBJECTIVE** To compare the survival discrimination of traditional pathologic risk stratification for both HPV+ OPSCC and HPV-unassociated HNSCC and derive a novel pathologic risk stratification system for HPV+ OPSCC with improved survival discrimination.

**DESIGN, SETTING, AND PARTICIPANTS** In this retrospective cohort study, we used the National Cancer Database to identify 15,324 patients diagnosed with nonmetastatic HNSCC between January 1, 2010, and December 31, 2013, who were treated with upfront surgery and neck dissection. We compared traditional pathologic risk stratification for HPV+ OPSCC and HPV-unassociated HNSCC and then derived a novel pathologic risk stratification system. Analyses were performed from July 1, 2018, to January 31, 2019.

**EXPOSURES** Definitive primary surgical resection and neck dissection.

**MAIN OUTCOMES AND MEASURES** Survival discrimination of pathologic risk stratification systems measured with concordance indices.

**RESULTS** This retrospective cohort study included 15,324 patients (10,779 men and 4,545 women; mean [SD] age, 59.9 [11.8] years) with surgically treated nonmetastatic HNSCC. Separation of survival curves for HPV-unassociated HNSCC using traditional pathologic risk stratification (5-year overall survival for the low-, intermediate-, and high-risk groups) were 76.2%, 54.5%, and 40.9%, respectively. Separation curves for HPV+ OPSCC were 93.2%, 88.9%, and 83.7%, respectively. Human papillomavirus-unassociated HNSCC had a concordance index of 0.68, whereas HPV+ OPSCC had a concordance index of 0.58. A novel risk stratification system for HPV+ OPSCC that more closely fits actual survival rates for HPV+ OPSCC was derived. The system incorporated the composite number of pathologic adverse features. This composite risk stratification system was associated with an improved concordance index of 0.67 for HPV+ OPSCC. Adjuvant treatment with radiation was not associated with improved survival for patients categorized as low risk according to the new risk stratification system, but this treatment was associated with improved survival for patients in the intermediate- and high-risk groups.

**CONCLUSIONS AND RELEVANCE** Traditional pathologic risk stratification shows poor survival discrimination for HPV+ OPSCC and classifies many patients with an excellent prognosis as high risk. We derived a novel composite pathologic risk stratification system for HPV+ OPSCC that may be associated with improved survival discrimination.
Human papillomavirus–associated (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) is a unique form of head and neck cancer with distinct etiology, pathophysiology, and clinical characteristics. Human papillomavirus–associated OPSCC carries a remarkably improved prognosis compared with HPV-unassociated head and neck squamous cell carcinoma (HNSCC) after treatment with either definitive chemoradiation therapy (CRT) or definitive surgery with adjuvant therapy based on pathologic adverse features. The seventh edition of the American Joint Committee on Cancer (AJCC) staging guidelines had a narrow survival discrimination for HPV+ OPSCC. A separate staging system was created in the eighth edition of the AJCC staging guidelines. However, in patients who undergo definitive surgery, there are a multitude of pathologic adverse features that may provide additional prognostic information and guide adjuvant treatment, but those features are not included in AJCC staging guidelines. The pathologic risk stratification system for HPV+ OPSCC remains largely based on that for HPV-unassociated HNSCC and has not been optimized to reflect the unique nature of HPV+ disease.

Traditional pathologic risk stratification for HNSCC stems from the Radiation Therapy Oncology Group (RTOG) 9501 and European Organization for Research and Treatment of Cancer (EORTC) 22931 trials, whose combined results led to the low-, intermediate-, and high-risk pathologic groups. However, these trials were performed principally in patients with HPV-unassociated HNSCC before the importance of HPV was known. The proportion of patients in the RTOG and EORTC trials with HPV+ OPSCC is estimated to be only 17% and 4%, respectively. This estimate is based on the percentage of patients with OPSCC enrolled in the RTOG and EORTC trials and the proportion of those with HPV+ disease enrolled in other cooperative group trials conducted at the same time. Given the low enrollment of patients with HPV+ OPSCC, the results of these trials should be interpreted cautiously as applied to HPV+ OPSCC. More recent data examining the association of HPV status with survival indicate that many pathologic adverse features carry different prognostic importance in HPV+ OPSCC vs HPV-unassociated HNSCC. Despite evidence that HPV+ disease may have a prognosis and response to treatment different from that of HPV-unassociated disease, the overall pathologic risk stratification system used for HPV+ OPSCC has not been critically evaluated.

The data from these studies indicate a need to critically evaluate the traditional pathologic risk stratification system used for HPV+ OPSCC. Optimization of the pathologic risk stratification system for HPV+ OPSCC may improve identification of patients with aggressive disease, and enable tailoring of treatment intensification and deintensification. Our aims were the following: (1) to evaluate the traditional pathologic risk stratification system for HPV+ OPSCC and HPV-unassociated HNSCC and (2) to develop an improved pathologic risk stratification system specific to HPV+ OPSCC.

Key Points

**Question** How does pathologic risk stratification perform in surgically resected human papillomavirus–associated (HPV+) oropharyngeal cancer (OPSCC) and HPV-unassociated head and neck squamous cell carcinoma (HNSCC)?

**Findings** In this retrospective cohort study of 15,324 patients, traditional pathologic risk stratification had poor survival discrimination in patients with HPV+ OPSCC. A novel composite pathologic risk stratification system was developed for HPV+ OPSCC that was associated with improved survival discrimination.

**Meaning** Pathologic adverse features carry different prognostic importance in HPV+ OPSCC than in HPV-unassociated HNSCC. The pathologic risk stratification system used for HPV+ OPSCC after definitive surgery is in need of refinement.

**Methods**

**Data Source and Cohort Selection**

The Wayne State University Institutional Review Board approved a waiver for this study of a deidentified data set based on the Common Rule. Using the National Cancer Database (NCDB), we identified adult patients (older than 18 years) with HNSCC (including oral cavity, oropharyngeal, laryngeal, and hypopharyngeal cancer) who were diagnosed between January 1, 2010, and December 31, 2013. The NCDB is a nationwide oncology registry that gathers information from more than 1,500 Commission on Cancer–accredited hospitals, capturing approximately 70% of all newly diagnosed cancers in the United States. The data used in the study are derived from a deidentified NCDB file. Analyses were performed from July 1, 2018, to January 31, 2019. The Commission on Cancer of the American College of Surgeons has not verified and is not responsible for the analytic or statistical methodology employed, or the conclusions drawn by us. The NCDB shares methods with other national cancer registries to ensure coding and accuracy with state and national cancer registries.

We identified surgically treated patients with invasive, non-metastatic HNSCC (AJCC stages T1-4, N0-3, and M0) using standard coding definitions for HNSCC based on the *International Classification of Diseases for Oncology, 3rd edition* (eTable 1 in the Supplement). We grouped patients into HPV+ OPSCC and HPV-unassociated HNSCC (defined as HPV-unassociated OPSCC and any HNSCC of the oral cavity, larynx, and hypopharynx). We excluded patients with OPSCC who did not undergo HPV testing. Our inclusion and exclusion criteria are outlined in the eFigure in the Supplement. To ensure a uniform cohort of patients with information to permit pathologic risk stratification, we included patients who underwent both definitive primary surgery and an adequate neck dissection. An adequate neck dissection was defined as a lymph node (LN) yield of 15 or higher using the same criteria used in the Eastern Cooperative Oncology Group (ECOG) trial 3311 (NCT01898494). Excluding patients with a LN yield lower than 15 ensured exclusion of patients who underwent LN biopsy alone in whom information on the extent of regional metastatic
disease may be less accurate. To ensure accurate information on treatment, we excluded patients with incomplete information on treatment or follow-up. To eliminate atypical treatment regimens, we excluded patients who underwent upfront surgery with chemotherapy alone.

**Traditional Pathologic Risk Stratification**
We defined the traditional pathologic risk stratification system after review of National Comprehensive Cancer Network guidelines, American Society of Clinical Oncology guidelines, and the ECOG trial 3311 and Post-operative Adjunctive Treatment for HPV-positive Tumors (PATHOS, NCT02215265) clinical trials (Table 1). Because there are minor differences in these sources on the adverse features included in the pathologic risk, we sought to create a consensus definition with the greatest weight given to the National Comprehensive Cancer Network guidelines.

**Statistical Analysis**
Statistical analyses were conducted from July 1, 2018, to January 31, 2019. We calculated observed 5-year overall survival (OS) rates based on the date of diagnosis to the date of death or the last follow-up using the Kaplan-Meier method and then compared the rates using the log-rank test. We constructed univariate and multivariate Cox proportional hazard models to predict the hazard ratio (HR) of mortality as a function of the pathologic adverse features. Multivariate Cox proportional hazard models were adjusted for age, sex, race, comorbidities, insurance status, adjuvant treatment with radiation and/or CRT, and hospital characteristics (academic vs nonacademic). We performed sensitivity analyses to test the robustness of these results. We evaluated the calibration and discrimination of the traditional pathologic risk stratification models for HPV+ OPSCC and HPV-unassociated HNSCC by measuring the concordance index (C statistic). The concordance index ranges between 0.5 and 1.0, wherein a score of 0.5 indicates that the model is no better than random chance, whereas a value of 1.0 indicates perfect discriminatory ability.

After finding a low concordance index in traditional pathologic risk stratification (< 0.6), we sought to develop a novel system to improve pathologic risk stratification. We assigned points to adverse features proportional to the effect size from the univariate and multivariate Cox proportional hazard models and added these scores together to create a composite total score because composite scoring has been shown to improve prognostication. We evaluated various alternatives composite scoring models and selected the best overall composite score based on clinical judgement, optimization of the concordance index, and the Akaike information criterion. All P values were 2-sided. Comparisons were considered statistically significant at P < .05 or associated 95% CIs that did not include 1.00. Statistical analyses were performed with SPSS, version 24 (IBM).

**Results**

**Overall Cohort Characteristics**
We identified 15,324 patients (10,779 men and 4,545 women; mean [SD] age, 59.9 [11.8] years) with nonmetastatic HNSCC treated surgically who met the inclusion criteria. The final study cohort included 2,302 patients (1,963 men and 339 women) with HPV+ OPSCC and 13,022 patients (8,816 men and 4,206 women) with HPV-unassociated HNSCC. Consistent with the demographic and clinical characteristics that previously have been reported for HPV+ OPSCC, a greater proportion of patients were male, young, white, and presented with a smaller tumor.
Table 2. Selected Clinical Characteristics of Study Cohort

| Variable                          | HPV+ OPSCC Cohort (n = 2302) | HPV-Unassociated HNSCC Cohort (n = 13022) |
|-----------------------------------|------------------------------|------------------------------------------|
| **Sex**                           |                              |                                          |
| Male                              | 1963 (85.3)                  | 8816 (67.7)                              |
| Female                            | 339 (14.7)                   | 4206 (32.3)                              |
| **Age, y**                        |                              |                                          |
| <55                               | 911 (39.6)                   | 4071 (31.3)                              |
| 55-64                             | 929 (40.4)                   | 4360 (33.5)                              |
| 65-74                             | 380 (16.5)                   | 2921 (22.4)                              |
| ≥75                               | 82 (3.6)                     | 1670 (12.8)                              |
| **Race**                          |                              |                                          |
| White                             | 2172 (94.4)                  | 11 038 (84.8)                            |
| African American                  | 71 (3.1)                     | 1278 (9.8)                               |
| Other                             | 59 (2.6)                     | 706 (5.4)                                |
| **Tumor location**                |                              |                                          |
| Oral cavity                       | 2302 (100.0)                 | 805 (6.2)                                |
| Oropharynx                        | 2711 (20.8)                  | 363 (2.8)                                |
| Larynx                            | 1364 (10.5)                  | 1530 (11.7)                              |
| Hypopharynx                       | 363 (2.8)                    | 2938 (26.3)                              |
| **Pathologic tumor classification**|                              |                                          |
| T1                                | 1021 (44.4)                  | 3124 (24.0)                              |
| T2                                | 1007 (43.7)                  | 3406 (26.2)                              |
| T3                                | 193 (8.4)                    | 2101 (16.1)                              |
| T4                                | 81 (3.5)                     | 4391 (33.7)                              |
| **Clinical node classification**  |                              |                                          |
| N0                                | 258 (11.2)                   | 6257 (48.0)                              |
| N1                                | 368 (16.0)                   | 2022 (15.5)                              |
| N2a                               | 428 (18.6)                   | 257 (2.0)                                |
| N2b                               | 1087 (47.2)                  | 3003 (23.1)                              |
| N2c                               | 79 (3.4)                     | 1364 (10.5)                              |
| N3                                | 82 (3.6)                     | 119 (0.9)                                |
| **Lymph vascular invasion**       |                              |                                          |
| Absent                            | 1362 (71.3)                  | 8221 (73.7)                              |
| Present                           | 547 (28.7)                   | 2938 (26.3)                              |
| **Level IV-V LN metastasis**      |                              |                                          |
| Absent                            | 1961 (85.2)                  | 11 492 (88.3)                            |
| Present                           | 341 (14.8)                   | 1530 (11.7)                              |
| **Extranodal extension**          |                              |                                          |
| None                              | 1476 (64.1)                  | 10 309 (79.2)                            |
| Microscopic                       | 725 (31.5)                   | 2396 (18.4)                              |
| Macroscopic                       | 101 (4.4)                    | 317 (2.4)                                |
| **Surgical margins**              |                              |                                          |
| Negative                          | 1846 (80.2)                  | 11 393 (87.5)                            |
| Positive                          | 456 (19.8)                   | 1629 (12.5)                              |
| **Primary treatment**             |                              |                                          |
| Surgery alone                     | 489 (21.2)                   | 5531 (42.5)                              |
| Surgery with RT                   | 757 (32.9)                   | 3607 (27.7)                              |
| Surgery with CRT                  | 1056 (45.9)                  | 3884 (29.8)                              |

Abbreviations: CRT, chemoradiation therapy; ENE, extranodal extension; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; LN, lymph node; OPSCC, oropharyngeal squamous cell carcinoma; RT, radiation therapy.

* Based on the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th ed.24

and more advanced node stage (Table 2). Patients with HPV+ OPSCC were also more likely to receive adjuvant treatment.

**Evaluation of Traditional Pathologic Risk Stratification**

Using traditional pathologic risk stratification, the proportion of patients with HPV-unassociated HNSCC classified as low, intermediate, and high risk was 31.9%, 40.4%, and 27.2%, respectively. Patients with HPV+ OPSCC were more likely to have high-risk pathologic adverse features (46.1% [n = 1061 of 2302 patients]) rather than low-risk (24.5% [n = 564 of 2302 patients]) or intermediate-risk pathologic adverse features (29.4% [n = 677 of 2302 patients]). To examine the prognostic importance of individual pathologic adverse features in HPV+ OPSCC and HPV-unassociated HNSCC, we examined 5-year OS and conducted univariate and adjusted multivariate Cox proportional hazard analyses (Table 3). In HPV-associated HNSCC, all pathologic adverse features except for the size of metastatic LN were significantly associated with mortality on multivariate analysis. In HPV+ OPSCC, however, only T stage, lymphovascular invasion (LVI), number of LN metastases, and extranodal extension (ENE) were significantly associated with mortality on multivariate analysis. Correspondingly, the size of metastatic LNs, stage IV and V metastatic LNs, bilateral LN metastases, and surgical margins were not associated with mortality on multivariate analysis.

In HPV-unassociated HNSCC, 5-year OS decreased from 76.2% with low-risk pathologic adverse features to 54.5% with intermediate-risk adverse features and 40.9% with high-risk adverse features based on the traditional pathologic risk stratification (Figure 1). In contrast, in HPV-unassociated OPSCC, 5-year OS only decreased from 93.2% with low-risk pathologic adverse features to 88.9% with intermediate-risk adverse features and 83.7% with high-risk adverse features based on the traditional pathologic risk stratification.

Survival discrimination was evaluated using concordance indices. In HPV-unassociated HNSCC, the concordance index of the traditional pathologic risk stratification was 0.68, whereas the concordance index for HPV+ OPSCC was 0.58. We evaluated alternative pathologic risk stratification systems, including a various combination of adverse features that could improve the concordance index and more closely fit actual survival rates for HPV+ OPSCC. We present the final composite system that was associated with optimally improved risk stratification.

**Development of Novel Composite Pathologic Risk Stratification System**

We empirically derived a novel risk stratification system for HPV+ OPSCC by assigning points to adverse features based on effect size in the univariate and multivariate Cox models. We added these points together to create a composite total score, with 0 to 3 points representing low risk, 4 to 5 points representing intermediate risk, and 6 or more points representing high risk. A comparison of the traditional and composite pathologic risk stratification systems is shown in Table 1. The new composite pathologic risk stratification was associated with an improved concordance index of 0.67 when grouping into 3 categories or 0.73 for individual risk points.
Table 3. Comparison of Overall Survival for Pathologic Adverse Features

| Variable | HPV+ OPC (n = 2302) | HPV-Unassociated HNSCC (n = 2302) |
|----------|---------------------|----------------------------------|
|          | 5-y OS %            | Difference in OS vs Reference    | Univariate | HR (95% CI) | Multivariate | Univariate | HR (95% CI) | Multivariate |
| T stage  |                     |                                  |            |            |             |            |            |             |
| T1       | 92.0 [Reference]    | 1 [Reference]                   | 1 [Reference] | 74.9 [Reference] | 1 [Reference] | 1 [Reference] |             |             |
| T2       | 87.3 −4.7           | 1.55 (1.11 to 2.15)             | 1.29 (0.94 to 1.79) | 62.1 −12.8 | 1.76 (1.62 to 1.91) | 1.52 (1.37 to 1.67) |             |             |
| T3       | 76.9 −15.1          | 3.16 (2.06 to 4.83)             | 2.01 (1.31 to 3.07) | 46.6 −28.3 | 2.74 (2.51 to 2.99) | 2.32 (2.09 to 2.58) |             |             |
| T4       | 61.6 −30.4          | 6.77 (4.23 to 10.85)            | 4.13 (2.56 to 6.65) | 45.1 −29.8 | 2.93 (2.72 to 3.16) | 2.42 (2.20 to 2.67) |             |             |
| Lymphovascular invasion |           |                                  |            |            |             |            |            |             |
| Absent   | 90.7 [Reference]    | 2.49 (1.88 to 3.12)             | 1.54 (1.15 to 2.06) | 40.4 −22.4 | 2.06 (1.95 to 2.18) | 1.17 (1.10 to 1.26) |             |             |
| Present  | 77.4 −13.3          |                                  |              |             |             |            |            |             |
| No. of metastatic LNs<sup>a</sup> |           |                                  |            |            |             |            |            |             |
| 0        | 88.8 −4.6           | 1.83 (1.10 to 3.06)             | 1.31 (0.53 to 3.27) | 71.3 15.7 | 0.57 (0.52 to 0.62) | 0.47 (0.40 to 0.54) |             |             |
| 1        | 93.4 [Reference]    | 1 [Reference]                   | 1 [Reference] | 55.6 [Reference] | 1 [Reference] |             |             |             |
| 2-4      | 87.7 −5.7           | 1.93 (1.32 to 2.83)             | 1.84 (1.24 to 2.73) | 45.2 −10.4 | 1.45 (1.34 to 1.56) | 1.36 (1.24 to 1.50) |             |             |
| 5+       | 74.5 −18.90         | 4.04 (2.72 to 5.99)             | 2.89 (1.82 to 4.59) | 26.4 −29.20 | 2.70 (2.49 to 2.93) | 2.14 (1.90 to 2.41) |             |             |
| Size of metastatic LN, cm |           |                                  |            |            |             |            |            |             |
| 0        | 88.8 [Reference]    | 1 [Reference]                   | 1 [Reference] | 71.0 [Reference] | 1 [Reference] |             |             |             |
| 0-1      | 90.0 1.2            | 1.04 (0.46 to 2.35)             | 1.11 (0.38 to 3.27) | 51.1 −19.9 | 2.09 (1.91 to 2.29) | 0.84 (0.71 to 1.00) |             |             |
| 1-3      | 87.1 −1.7           | 0.97 (0.58 to 1.61)             | 0.62 (0.25 to 1.56) | 43.5 −27.5 | 2.55 (1.39 to 2.72) | 0.83 (0.70 to 0.97) |             |             |
| 3-6      | 87.8 −1.0           | 0.89 (0.55 to 1.44)             | 0.59 (0.24 to 1.48) | 45.3 −25.7 | 2.80 (2.57 to 3.04) | 0.80 (0.67 to 0.96) |             |             |
| >6       | 85.7 −3.1           | 1.23 (0.63 to 2.38)             | 0.71 (0.26 to 1.94) | 38.5 −32.5 | 3.37 (2.84 to 3.99) | 1.06 (0.83 to 1.34) |             |             |
| Level IV-V LN metastases |           |                                  |            |            |             |            |            |             |
| Absent   | 88.2 [Reference]    | 1 [Reference]                   | 1 [Reference] | 60.3 [Reference] | 1 [Reference] |             |             |             |
| Present  | 83.4 −4.8           | 1.52 (1.08 to 2.13)             | 0.89 (0.62 to 1.28) | 33.5 −26.8 | 2.48 (2.32 to 2.65) | 1.19 (1.10 to 1.30) |             |             |
| Bilateral/contralateral metastatic LN |           |                                  |            |            |             |            |            |             |
| Absent   | 88.3 [Reference]    | 1 [Reference]                   | 1 [Reference] | 60.4 [Reference] | 1 [Reference] |             |             |             |
| Present  | 68.7 −19.6          | 2.34 (1.41 to 1.91)             | 1.35 (0.82 to 2.23) | 28.6 −31.8 | 2.61 (2.44 to 2.79) | 1.12 (1.03 to 1.23) |             |             |
| High-Risk Adverse Features |           |                                  |            |            |             |            |            |             |
| Extramedullary extension |           |                                  |            |            |             |            |            |             |
| None     | 90.7 [Reference]    | 1 [Reference]                   | 1 [Reference] | 63.7 [Reference] | 1 [Reference] |             |             |             |
| Microscopic |                   |                                  |            |            |             |            |            |             |
| Macroscopic |                |                                  |            |            |             |            |            |             |
| Surgical margins |           |                                  |            |            |             |            |            |             |
| Negative | 89.0 [Reference]    | 1 [Reference]                   | 1 [Reference] | 59.2 [Reference] | 1 [Reference] |             |             |             |
| Microscopically positive margin |         |                                  |            |            |             |            |            |             |
| Grossly positive margin |       |                                  |            |            |             |            |            |             |
| Other Potential Pathologic Adverse Features |           |                                  |            |            |             |            |            |             |
| Oropharyngeal subsite |           |                                  |            |            |             |            |            |             |
| Tonsil   | 87.7 [Reference]    | 1 [Reference]                   | 1 [Reference] | NA NA NA NA |             |             |             |             |
| BOT      | 87.9 0.2            | 0.96 (0.70 to 1.33)             | 1.07 (0.79 to 1.46) | NA NA NA NA |             |             |             |             |
| Soft palate/lateral/posterior/NOS | 80.8 −6.9 | 2.29 (1.38 to 3.78)             | 1.44 (0.84 to 2.48) | NA NA NA NA |             |             |             |             |
| Differentiation |            |                                  |            |            |             |            |            |             |
| Well/moderately differentiated | 86.0 −2.2 | 1.20 (0.91 to 1.60)             | 1.21 (0.91 to 1.60) | 59.9 7.7 | 0.76 (0.72 to 0.80) | 0.98 (0.92 to 1.05) |             |             |
| Poorly differentiated/other | 88.2 [Reference] | 1 [Reference]                   | 1 [Reference] | 52.2 [Reference] | 1 [Reference] |             |             |             |

(continued)
Table 3. Comparison of Overall Survival for Pathologic Adverse Features (continued)

| Variable | HPV+ OPC (n = 2302) | | HPV-Unassociated HNSCC (n = 2302) | |
| --- | --- | --- | --- | --- |
| | 5-y OS | Difference in OS vs Reference | HR (95% CI) | 5-y OS | Difference in OS vs Reference | HR (95% CI) |
| Traditional Pathologic Risk Stratification | | | | | |
| Low | 93.2 [Reference] | 1 [Reference] | 1 [Reference] | 76.2 [Reference] | 1 [Reference] | 1 [Reference] |
| Intermediate | 88.9 [5.3] | 1.53 (0.96 to 2.45) | 1.70 (1.05 to 2.76) | 54.5 [5.3] | -21.7 | 2.08 (1.94 to 2.24) |
| High | 83.7 [9.5] | 2.46 to 1.63 (1.37) | 2.70 (1.73 to 4.23) | 40.9 [9.5] | -35.3 | 3.87 (3.61 to 4.15) |
| Composite Pathologic Risk Stratification | | | | | |
| Low (0-3 points) | 91.8 [Reference] | 1 [Reference] | 1 [Reference] | NA | NA | NA |
| Intermediate (4-5 points) | 83.1 [8.7] | 2.10 (1.5 to 2.94) | 2.31 (1.62 to 3.29) | NA | NA | NA |
| High (≥6 points) | 53.2 [36.8] | 6.96 (4.99 to 9.71) | 7.33 (5.08 to 10.58) | NA | NA | NA |

Abbreviations: BOT, base of tongue; ENE, extranodal; HR, hazard ratio; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; LN, lymph node; NOS, not otherwise specified; OPSCC, oropharyngeal squamous cell carcinoma; OS, overall survival. 

b The reference category for number of metastatic LN was set to 1 LN because there were few patients with HPV+ OPSCC with 0 LN and the reference category was unstable.

Evaluation of Novel Composite Pathologic Risk Stratification System

Using the composite pathologic risk stratification for 2302 patients with HPV+ OPSCC, 545 (23.7%) patients had 0 points, 315 (13.7%) had 1 point, 468 (20.3%) had 2 points, 405 (17.6%) had 3 points, 258 (11.2%) had 4 points, 160 (7.0%) had 5 points, 82 (3.6%) had 6 points, 41 (1.8%) had 7 points, 21 (0.9%) had 8 points, 6 (0.3%) had 9 points, 1 (0.0%) had 10 points. Composite pathologic-risk stratification predicted survival in a stepwise fashion. When we grouped the composite risk stratification into 3 risk categories based on the number of points, 1733 (75.3%) patients were in the low-risk category with 0 to 3 points, 418 (18.2%) were in the intermediate-risk category with 4 to 5 points, and n = 151 (6.6%) were in the high-risk category with ≥6 points. We observed improved separation in the survival curves for these groups (5-year survival for low-, intermediate-, and high-risk groups was 91.8%, 83.1%, and 53.2%, respectively).

Composite Risk Stratification and Adjuvant Treatment

We next examined the association between adjuvant treatment and survival in these new composite pathologic risk groups. The addition of adjuvant RT/CRT did not improve survival for patients categorized as low risk in the composite system (HR, 0.76; 95% CI, 0.47-1.24 for adjuvant RT and HR, 0.76; 95% CI, 0.46-1.25 for adjuvant CRT with surgery alone as reference) (Figure 2). Compared with surgery alone, adjuvant treatment with RT or CRT was associated with improved survival for patients in the intermediate-risk group (HR, 0.37; 95% CI, 0.16-0.87 for adjuvant RT and HR, 0.32; CI 0.15-0.67 for adjuvant CRT) and for patients in the high-risk group (HR, 0.67; 95% CI, 0.02-0.29 for adjuvant RT and HR, 0.16; 95% CI, 0.06-0.41 for adjuvant CRT). CRT, excluding patients treated with upfront surgery.25 We evaluated the traditional pathologic risk stratification systems in surgically treated patients with HPV+ and HPV-unassociated HNSCC. First, we found that traditional pathologic risk stratification is only weakly prognostic for OS in HPV+ OPSCC, demonstrating a need for refinement. Second, we validated previous studies11-15 reporting that specific pathologic adverse features carry different prognostic importance in HPV+ OPSCC and HPV-unassociated HNSCC. Specifically, the size, laterality, and level of metastatic LNs were not prognostic in HPV+ disease. The prognostic importance of surgical margins was diminished in HPV+ OPSCC compared with HPV-unassociated HNSCC. Third, we derived a novel composite pathologic risk stratification system for HPV+ OPSCC that demonstrated improved prognostic ability. This increased the proportion of patients with low-risk disease from 24.5% (n = 564 of 2302 patients) to 75.3% (n = 1733 of 2302 patients), and decreased the proportion with high-risk disease from 45.1% (n = 1038 of 2302 patients) to 6.6% (n = 151 of 2302 patients).

Previous efforts to evaluate the staging system for HPV+ OPSCC have focused on patients treated with definitive CRT.23 In the landmark ICON-S study, only 2% of patients were treated surgically, which prohibited evaluation of pathologic adverse features.23 However the additional histopathologic staging information from the primary tumor and nodal specimens that definitive surgery provides can further enhance prognostication.33 At many centers, this full histopathologic staging information is used to risk-stratify patients and determine the need, if any, for adjuvant therapy.18 There is a need to critically evaluate the method of pathologic risk stratification for HPV+ OPSCC.

Pathologic Adverse Features in HPV+ OPSCC

Previous studies show that several histopathologic adverse features show diminished prognostic importance in HPV+ OPSCC, including surgical margins,13 ENE,11-13,26 perineural invasion (PNI),13,15 and LVI.13,15 Conversely, advanced T stage (T3-4) has been previously associated with a magnified...
importance in HPV+ OPSCC compared with its importance in HPV-unassociated disease. Furthermore, although the number of metastatic LNs has been shown to be important for prognosis, the size and laterality of LNs has been found to be less important in HPV+ OPSCC. Finally, although level IV and V metastatic LNs are considered an intermediate-risk adverse feature for HPV+ OPSCC, this pathologic adverse feature has not been specifically assessed in this disease. There is a need to consolidate these findings into a pathologic staging system for HPV+ OPSCC that optimizes prognostication. In the present large cohort of surgically treated patients, we verified many of these findings for specific adverse features. On multivariate analysis, the prognostic importance of the number of metastatic LNs, degree of ENE, T4 stage, and LVI was enhanced in HPV+ OPSCC. In contrast, surgical margins as well as the size, level, and laterality of metastatic LNs were not prognostically important. Overall, we determined that traditional pathologic risk stratification for HPV+ OPSCC is weakly prognostic, with a concordance index of less than 0.6.

**Selection of Composite Risk Stratification**

We chose to use composite risk stratification because the combined importance of multiple adverse pathologic features in HPV+ OPSCC may improve prognostic ability of the stratification system. The 8th edition of the AJCC staging guidelines acknowledges the importance using a composite of pathologic features to identify patients with HPV+ OPSCC who have a poor
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Improving Pathologic Risk Stratification for HPV+ OPSCC

A, Human papillomavirus–associated (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) with 0 to 3 composite risk points. B, Human papillomavirus–associated OPSCC with 4 to 5 composite risk points. C, Human papillomavirus–associated OPSCC with ≥6 composite risk points. Survival curves were adjusted for age, sex, race, comorbidities, insurance status, adjuvant treatment with radiation and/or CRT, and hospital characteristics using a Cox proportional hazard model.

In terms of pathology, no single tumor or regional node classification is sufficient to diagnose a patient as having stage III cancer. The only way cancer can be pathologically considered stage III is if a combination of both T3 or T4 primary disease and N2 are present. Albergotti et al. found that in HPV+ OPSCC, both PNI and LVI provide modest prognostic information alone; however, when both are present, the prognostic importance of these adverse features is multiplied. Inspired by the prognostic importance associated with multiple adverse pathologic features in HPV+ OPSCC, we evaluated a new composite pathologic risk stratification system based on the risk of mortality that each individual pathologic adverse feature imparts. This composite pathologic risk stratification system considerably improves identification of the small number of patients who have the highest risk for poor outcomes.

Although this new composite pathologic risk stratification system is more complex than current assessment methods, it can be used by quickly reviewing standard pathologic information that is universally available and does not require sophisticated testing. Additionally, adverse features identified in our effort to develop a composite pathologic risk stratification system are in line with the AJCC 8th edition pathologic staging system. For example, patients with stage II cancer with both T4 and N2 disease (5+ metastatic LN) would receive at least 6 points, imparting high-risk status.

Treatment

We explored differences in survival based on this composite pathologic risk stratification system and treatment. We found no statistically significant differences in survival for low-risk patients when adding adjuvant radiation or chemo-radiation, indicating potential clinical applicability. It should be emphasized that in our composite risk stratification system, 75% of patients (n = 1733 of 2302) with HPV+ OPSCC were classified as low risk, whereas only 24.5% of patients (n = 564 of 2302) were classified as low risk using the traditional pathologic risk stratification system. However, our findings require verification and refinement in additional data sets before considering altering treatment in standard practice.

Follow-up studies should evaluate for potential refinement by incorporating information on PNI, close margins, and smoking status, which were not available in the present data set. Furthermore, the ECOG 3311 (NCT01898494) and PATHOS (NCT02215265) cooperative group trials may provide some modification to the risk stratification of patients with ENE in the primary analysis. In addition, these trials will provide an opportunity for secondary analyses, including the potential to validate and refine our proposed composite pathologic risk stratification using prospectively collected data from these cohorts. Furthermore, composite risk stratification may be further improved by incorporating novel biomarkers of recurrence.
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Limitations
In addition to the previously mentioned limitations, there are several additional considerations to highlight. First, like all studies using national oncologic registries, the NCDB has the potential for errors in coding. Second, the NCDB does not contain information on recurrence, an important secondary outcome to assess in any risk stratification system. Investigating if this composite pathologic risk stratification predicts recurrence is an important further step in additional data sets. Third, because we derived the composite pathologic risk stratification system from an NCDB data set, there is a potential for overfitting of the data. This limitation emphasizes the importance of validation using additional data sets. Because we anticipate a need for further refinement, we did not attempt validation in a subset of this data set. Despite these limitations, we feel that it is a powerful place to begin to define a pathologic risk stratification system that is specifically optimized for HPV+ OPSCC.

Conclusions
This retrospective cohort study provides evidence that the traditional pathologic risk stratification for HNSCC is weakly prognostic when applied to HPV+ OPSCC. This finding validates previous studies that show that many traditional adverse features have limited prognostic importance in HPV+ OPSCC. Based on the prognostic importance of each pathologic adverse feature in HPV+ OPSCC, we developed a new composite pathologic risk stratification system that was associated with improved prognostication for HPV+ OPSCC. This system could downstage a substantial percentage of patients to low- or intermediate-risk groups, potentially making them candidates for less adjuvant therapy. Although these potential treatment implications require further investigation, they provide an exciting avenue to be investigated in the next generation of surgical deintensification trials.
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