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Staging HPV-related oropharyngeal cancer: Validation of AJCC-8 in a surgical cohort☆

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ABSTRACT

Importance: The American Joint Committee on Cancer, 8th edition (AJCC-8) contains a new staging system for human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC). Our study aim was to evaluate the effectiveness of the AJCC-8 relative to the AJCC 7th edition (AJCC-7).

Materials and methods: A retrospective chart review was performed on a multi-institutional, prospectively collected dataset from two tertiary referral centers. All patients had HPV+ OPSCC treated primarily with surgery. The prognostic value of AJCC-7 and AJCC-8 were compared for 5-year overall survival (OS) and disease-specific survival (DFS).

Results: AJCC-8 pathological staging effectively risk stratified patients, creating a Cox model with a better fit (lower Akaike's Information Criterion, $p < 0.0001$) when compared to AJCC-7 pathological stages for both OS and DFS. The AJCC-8 pathologic staging did not produce a better fit than the AJCC-8 clinical staging ($p = 0.15$) for OS, however, AJCC-8 pathologic was more effective than AJCC-8 clinical for DFS ($p < 0.0001$). 76% of patients did not change their stage between clinical and pathologic AJCC-8 staging; 14% were upstaged by 1, < 1% were upstaged by 2, 7% were downstaged by 1, and 3% downstaged by 2.

Conclusions and relevance: The new AJCC-8 staging system represents a significant improvement over AJCC-7 for risk stratification into groups that predict overall survival and disease-specific survival of surgically treated HPV + OPSCC patients. The AJCC- 8 pathologic staging system was not significantly better than the AJCC-8 clinical staging system for overall survival, however, the pathologic staging system was better than the clinical for disease free survival.

Introduction

Over the last two decades, human papillomavirus related (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) has been recognized as a fundamentally different disease than tobacco and alcohol related (HPV−) OPSSC [1–3]. While both diseases are squamous cell carcinomas that arise in the oropharynx, HPV+ disease tends to affect a younger cohort of patients with a different set of risk factors [1–3], and has been shown to have different molecular biology than HPV negative disease [4]. Importantly, patients with HPV+ disease have a substantially improved prognosis [1–3,5]. Because of the improved survival in the HPV+ cohort, a new staging system separate from the HPV-

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OPSCC staging system was required to accurately risk stratify these patients [5,6].

The American Joint Committee on Cancer (AJCC) recently released a new staging system in the 8th edition of their Cancer Staging Manual (AJCC-8) based primarily on work from the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) and Haughey et. al. [7–9] Compared to the AJCC-7, patients with HPV+ OPSCC are now substantially down-staged, primarily reflecting their excellent prognosis despite regional nodal disease [9,10]. Additionally, AJCC-8 has different definitions for clinical and pathologic nodal stage and variations in the definitions of clinical and pathologic overall stage for HPV+ OPSCC. These differences reflect the fact that the ICON-S and Haughey study populations were treated differently, the former being primarily chemoradiated and the later having undergone surgery plus adjuvant therapy as indicated [7,8].

Given that the AJCC-8 was recently released, it still requires validation. The goals of our study are to apply the AJCC-8 to a multi-institutional cohort of surgically treated patients with HPV-related OPSCC and validate the staging prognostic stratification. We also examine the clinical and pathologic staging of these patients to determine how pathologic data effects patients' staging.

Methods

University of Pittsburgh Medical Center (UPMC) and Oregon Health & Science University (OHSU) Institutional Review Board (IRB) approval was obtained. A retrospective review of a prospectively collected multi-institutional dataset was performed. Included patients had HPV+ OPSCC as determined by p16 immunohistochemistry and were treated primarily with surgery. All surgical approaches were included including traditional transoral surgery, transoral laser microsurgery and transoral robotic surgery (TORS).

The tumor (T), lymph node (N) and distant metastatic (M) classifications vary from AJCC-7 to the AJCC-8. Additionally, AJCC-8 has different clinical and pathologic staging definitions. Each patient was staged both clinically and pathologically according to both the AJCC-7 and AJCC-8 criteria. Clinical T-stage was determined by pre-operative physical examination and imaging while pathologic T-stage was recorded on the surgical pathology report. Clinical N-stage was determined by preoperative computed tomography (CT) imaging while pathologic N-stage was determined by the surgical pathology report. Comparisons between the staging systems could then be performed.

Statistical methods

Exploratory data analysis quantified the demographic and medical characteristics and verified the assumptions of the corresponding statistical tests. Unadjusted Cox proportional hazard ratios were computed to determine the overall effect of the demographics on survival. Primary outcomes were overall survival (OS) and disease-free survival (DFS) at five years. OS was defined as the time from diagnosis to the date of last follow up or death from any cause. DFS was defined as the time from diagnosis to the date of last follow up or first detectable disease recurrence in any location. Censoring occurred when a patient was lost to follow up. The Kaplan-Meier survival curves were compared across stages within a given AJCC guideline with log-rank tests. Given the paucity of patients with Stage IV disease by AJCC-8 criteria, Stage IVa and IVb were grouped together. Multivariate Cox proportional hazard regression models were used to evaluate associations between clinical variables and survival outcomes. Akaike's Information Criteria (AIC) was used to compare models representing AJCC guidelines. AIC is a value that quantifies the fit of the model to the data and penalizes models with more covariates. When comparing models, the one with the lower the AIC represents a better fit to the data. While giving no information about the absolute quality of a model, the AIC can help comparatively rank one model vs another. Confidence intervals for the AIC values were obtained using 1000 bootstrap samples. This involves resampling the data with replacement creating a new dataset of the same size while retaining the staging results and outcomes together for each participant. The models are then run with this dataset and the AIC values recorded. This is repeated 1000 times to create estimates of the alternative distributions for the appropriate comparisons. The confidence intervals are computed as the 2.5 and 97.5 percentiles of the estimated alternative distributions. The p-value for the AIC values was obtained using permutation tests. This involves taking the staging results and shuffling them so that they are no longer related to the outcomes. The models were then run with the dataset and the AIC values recorded. Again, this is was repeated 1000 times to create estimates of the null distribution for the appropriate comparisons. The p-values were computed as the number null distribution simulations that were more extreme than the statistic obtained when using the full un-modified dataset. The c-statistic for each model was computed with a macro from Mayo Clinic [11]. All test were 2-tailed and our alpha-value was 0.05. Data was analyzed using SAS version 9.4.

Results

Patients (n = 309) who were included in the study had dates of surgery from March 1983 to December 2015. Median follow up was 33 months (range 12–340). The mean age at diagnosis was 57 years (range of 30–80). Thirty-four percent of the primary tumors were located in the base of tongue (BOT) while 64% were found in the tonsil and 2% in other oropharyngeal sites. The remainder of the patient characteristic data can be seen in Table 1 with associated Cox univariate associations with OS. Of note, smoking status was associated with OS (Never smoker HR = 1, Former smoker HR = 2.3 p = 0.07, Current smoker HR = 2.9 p = 0.004; overall p = 0.015). Additionally, primary site was associated with OS (BOT HR = 1, Tonsil HR = 0.92 p = 0.8, NOS HR = 3.9 p = 0.03, Soft Palate HR = 7.3 p = 0.06; overall p = 0.03). Lastly, the decade of presentation was not associated with OS (p = 0.22).

The patients' clinical and pathologic staging as categorized by AJCC-7 and AJCC-8 can be seen in Table 2. Table 3 shows the 5-year overall survival for the different staging systems. The 5-year Kaplan-Meier overall survival curves can be seen in Fig. 1, and disease-free survival is shown in Fig. 2. After five years, the AJCC-7 pathologic stages did not have different survival probabilities (78.2–88.8%, p = 0.87), nor did the AJCC-7 clinical stages (73.8–88.9%, p = 0.09). However, the differences in five-year survival using the AJCC-8 pathologic stages did significantly differ (0.0–99.2%, p < 0.0001), as did the five-year survival using the AJCC-8 clinical stages (51.3–89.7%, p = 0.0001). After 1000 bootstrap samples, the AIC value for the Cox model using AJCC-7 pathologic stages was 18.8 (95% CI: 2.5, 40.2) points higher than the Cox model using the AJCC-8 pathologic stages (p < 0.0001), indicating that using the AJCC-8 pathologic stages produced a significantly better model fit for overall survival. Additionally, the AIC value for the Cox model using AJCC-8 pathologic stages does not have a statistically different model fit than the Cox model using the AJCC-8 clinical stages (difference = 4.3, 95% CI: −12.7, 22.7, p = 0.152) for overall survival.

Table 3 shows the 5-year disease-free survival for the different staging systems. The 5-year Kaplan-Meier disease-free survival is shown in Fig. 2. After five years, the AJCC-7 pathologic stages did not have different survival probabilities (74.6–92.3% p = 0.47), nor did the AJCC-7 clinical stages (74.7–89.2% p = 0.17). However, the differences in five-year survival using the AJCC-8 pathologic stages did significantly differ (66.6–91.3%, p < 0.0001), as did the five-year survival using the AJCC-8 clinical stages (56.7% to 86.7%, p = 0.014). After 1,000 bootstrap samples, the AIC value for the Cox model using AJCC-7 pathological categories was not significantly higher than Cox model using AJCC-7 clinical (2.2, p = 0.38) supporting that the pathological and clinical stages do not differ. In addition, the AIC value