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AJCC-8ed nodal staging does not predict outcomes in surgically managed HPV-associated oropharyngeal cancer☆

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ABSTRACT

Objective: To assess the pathological outcomes of surgically-managed human papillomavirus (HPV) positive oropharyngeal squamous cell carcinoma (OPSCC) using the 8th Edition of the American Joint Committee on Cancer Staging Manual (AJCC-8ed).

Materials and methods: A retrospective review was conducted of 156 patients with previously untreated OPSCC who underwent primary TORS between March 2010 and February 2015 to evaluate the impact of the new AJCC-8ed pathologic staging system. Only patients who had complete pathologic staging with neck dissection and at least 2 years of follow-up records or disease recurrence within 2 years were included for analysis.

Results and conclusions: Of the 156 patients, 116 patients had neck dissections and adequate follow-up data. There were 10 total recurrences, including 2 regional recurrences and 1 local recurrence. Lymph node size, number of positive lymph nodes, and presence of any positive nodes were not associated with recurrence for HPV-positive patients. The presence of extranodal extension approached significance. Pathologic N-stage was not predictive of recurrence under the AJCC-7ed or the AJCC-8ed systems. Cancer staging under the AJCC-8ed, but not the AJCC-7ed system was significantly associated with recurrence. In conclusion, pathologic node status as defined in the AJCC-8ed pathologic staging system does not appear to drive prognosis for surgically managed patients. While the new AJCC-8ed staging is an improvement in prognostication, the use of T-stage alone is still a better predictor of recurrence. TORS with adjuvant therapy determined by pathologic findings provides excellent locoregional control for HPV-positive OPSCC.

Introduction

The TNM staging system has long been the cornerstone for anatomical classification of cancer progression. Accurate cancer staging is important for clinical decision-making, patient stratification for research and clinical trials, and patients' perception of their own disease. Periodic updates to the TNM staging system are required as our understanding of cancer tumorigenesis grows, cancer demographics change, and clinical outcomes improve.

Previous studies have demonstrated the shortcomings of the seventh edition of the American Joint Committee on Cancer (AJCC-7ed) staging system for HPV-positive oropharyngeal squamous cell carcinoma (OPSCC), in particular with regards to lymph node metastasis [1–4]. To address these deficiencies, the recently released eighth edition (AJCC-8ed) incorporates a new stage classification to distinguish HPV-related OPSCC from its HPV-negative counterpart [5]. Of note, the pathologic N category for HPV-positive OPSCC now defines pN1 disease as metastasis in 4 or fewer lymph nodes and pN2 disease as metastasis in greater than 4 lymph nodes without any emphasis on lymph node size, laterality, or extranodal extension (ENE). Early evaluation of the new AJCC-8ed with independent datasets appears to show improved discrimination between stages compared to the previous AJCC-7ed [6–8]. The purpose of this study is to assess the pathological outcomes of OPSCC treated with primary transoral robotic surgery (TORS) with attention to nodal status and to evaluate the prognostic impact of the new AJCC-8ed staging system relative to the previous AJCC-7ed system.

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Methods

Following Institutional Review Board (IRB) approval, clinical data were reviewed for all patients undergoing TORS for OPSCC at our institution between March 2010 and February 2015. Patients were included who had no previous history of head and neck cancer and who were treated with curative intent using a primary surgical approach including adjuvant radiation (RT) or chemoradiation therapy (CRT) as appropriate based on pathologic findings. Exclusion criteria included unknown HPV status, insufficient follow-up, and lack of pathologic staging with neck dissection. Sufficient follow-up was defined as 2 years of clinical records beyond treatment completion or a documented recurrence within 2 years.

Pathologic staging

Staging was determined using both the seventh and eighth editions of the American Joint Committee on Cancer (AJCC-7ed, AJCC-8ed) staging systems [1,5]. Only pathological staging is reported. As recommended by the AJCC-8ed, HPV status was determined by the presence of p16 overexpression, defined as > 70% of tumor cells [9–12].

Adjuvant therapy

Following surgery, all patients were reviewed by a multidisciplinary tumor board to determine adjuvant therapy selection. In general, patients with stage N2a or greater nodal disease under the AJCC-7ed staging system received adjuvant RT. Patients with macroscopic extranodal extension received CRT. Occasionally, RT was also driven by primary site pathologic findings based on the recommendations of the tumor board.

Patient Follow-up

Patients were followed clinically from the time of their treatment to assess for residual disease or recurrence. Clinical assessments were supplemented by examinations under anesthesia, radiological imaging, or biopsy as appropriate. Recurrence was defined as biopsy-proven invasive malignancy or clinical suspicion sufficient to initiate treatment. Partial radiation and partial chemotherapy were defined as initiation of treatment with early termination.

Statistical analysis

Statistical analysis was performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Univariate analysis was performed using Fisher's exact test. Multivariate analysis was performed using the Cox proportional hazard model. Variables considered for inclusion in the multivariate analysis were selected using the selection criteria of $n > 10$ and $p < 0.2$. The survival probability with 95% confidence interval (CI) was estimated using the Kaplan-Meier method. All tests to determine statistical significance were two-sided, and statistical significance was defined as $p < 0.05$.

Results

There were 156 patients with biopsy-proven HPV-positive OPSCC and no history of previous head and neck malignancy or radiation who were treated with primary TORS between March 2010 and February 2015. Of these patients, 36 were excluded due to insufficient follow-up and 4 were excluded who did not undergo neck dissections, leaving a final study population of 116 patients. The median follow-up time from the completion of treatment was 30 months (range 8–82 months). Patient demographics can be found in Table 1.

Table 1
Demographics and disease characteristics (N = 127).

Characteristic	Value (%)
Patients	116
Age	
Median	58
Range	38–87
Sex	
Male	101 (87%)
Female	15 (13%)
Smoking status	
Ever smoker	64 (55%)
Lifetime non-smoker	52 (45%)
Tumor location	
Tonsil	63 (54%)
Base of tongue	52 (45%)
Glossotonsillar sulcus	1 (1%)
Final margins	
Negative	107 (92%)
Positive	9 (8%)
Adjuvant radiation	
Radiation	104 (90%)
No radiation	10 (9%)
Partial radiation	2 (2%)
Adjuvant chemotherapy	
Chemotherapy	65 (56%)
No chemotherapy	48 (41%)
Partial chemotherapy	3 (3%)
Positive lymph nodes	
Any positive nodes	107 (92%)
≤4positive nodes	89 (77%)
> 4positive nodes	18 (16%)
Positive contralateral nodes	5 (4%)
Positive nodes	
Median	2
Range	0–17
Extranodal extension (ENE)	
ENE present	50 (43%)
ENE absent	66 (57%)
Largest positive node (cm)	
Median	4.0
Range	1.0–13.5

ENE = extranodal extension.

Tumor pathology

The most common primary tumor subsites were tonsil in 63 patients (54%) and base of tongue in 52 patients (45%). There were 107 patients with positive nodes (92%). Final margins were negative for 107 (92%) patients and positive for 9 (8%) patients. The median number of positive nodes for all patients was 2 (range 0–17). There were 89 patients with 1–4 positive nodes (77% of all patients, 83% of those with positive nodes) and 18 with more than 4 positive nodes (16% of all patients, 17% of those with positive nodes). There were 5 patients with positive contralateral nodes (4%). There were 50 patients with ENE present (43% of all patients, 47% of those with positive nodes). The median size of the largest positive node was 4.0 cm (range 1.0 cm–13.5 cm). Tumor pathology data can be found in Table 1.

There were 18 patients whose neck pathology reported an entangled mass of lymph nodes or "matted" lymph nodes which could not be definitively quantified. All but one of these lymph node masses demonstrated ENE. There were 6 patients whose only positive neck node was the matted mass. Four patients had 1 other separate node and 3 patients had two other nodes. While the reports mentioned the difficulty in quantifying nodes for these patients, the masses were ultimately considered to be 1 node by the pathologist.