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Nomogram for preoperative prediction of nodal extracapsular extension or positive surgical margins in oropharyngeal squamous cell carcinoma

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ABSTRACT

Introduction: Extracapsular extension (ECE) in regional lymph nodes and positive surgical margins (PSM) are considered high-risk adverse pathologic features in patients with oropharyngeal squamous cell carcinoma (OPSCC) that each constitute an indication for postoperative adjuvant chemoradiation. We identify pre-operative clinical factors that can predict post-operative ECE and/or PSM and create a nomogram to help clinical decision making.

Methods: Adult patients with non-metastatic OPSCC with initial surgical treatment and confirmed HPV status diagnosed between 2010 and 2014 were selected from the National Cancer Database. Clinical staging was modified to American Joint Committee on Cancer 8th edition parameters. Logistic regression was used for multivariate analysis to identify predictors of pathologic ECE and/or PSM.

Results: 5065 patients were included. 47.5% of the 3336 HPV-positive (HPV+) patients had ECE/PSM. 40.4% of the 1729 HPV-negative (HPV−) patients with had ECE/PSM. A model was built that included age, clinical ECE, tumor grade, and clinical T and N staging for HPV+ patients. Increasing N-classification was highly predictive of pathologic ECE and/or PSM (N1 OR = 3.6, N2 OR = 7.0, N3 OR = 11.2, $p < 0.01$). Clinical ECE (OR = 4.1, $p < 0.01$), tumor grade (ORs 2.2–4.4 with $p < 0.05$), and increasing clinical T-classification (ORs 1.2–1.8, $p < 0.05$) were also associated with ECE and/or PSM. A similar model was built for HPV− with similar predictive capability. Two internally validated nomograms were designed that demonstrated good discrimination (HPV+ AUC = 0.66, 95% CI: 0.64–0.68, and HPV− AUC = 0.70, 95% CI: 0.67–0.72) and good calibration (goodness-of-fit statistic of HPV+ 6.32, p = 0.61 and HPV− 11.66, p = 0.17).

Conclusions: These are the first nomograms designed to help predict ECE or PSM for both HPV+ and HPV− OPSCC. The nomograms can facilitate shared decision-making between clinicians and patients as they consider upfront treatment selection for OPSCC.

Introduction

The management of oropharyngeal squamous cell carcinoma (OPSCC) has undergone a significant transformation over the last two decades, reflecting the increasing incidence of human papillomavirus (HPV) that some experts have called an epidemic [1]. Patients with HPV-associated OPSCC are primarily younger, healthier individuals with little or no tobacco exposure [2]. They tend to have increased response to treatment compared to patients with OPSCC associated with tobacco and alcohol use and thus have much better oncologic outcomes [2,3]. With these improved outcomes in patients with HPV-associated OPSCC, the American Joint Committee on Cancer (AJCC) 7th edition staging algorithm lost its ability to differentiate outcomes between stages, thus reducing its predictive capacity, and a new staging system was designed with HPV status distinguishing the OPSCC subtypes [4].

Historically, before the advent of sophisticated radiation techniques and transoral robotic surgery, OPSCC was managed surgically with invasive procedures that often-required reconstruction with a vascularized flap. Despite this aggressive locoregional therapy, many patients still needed post-operative radiation. Definitive radiation and subsequently chemoradiation (CRT) were shown to be just as effective as

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surgical resection with decreased morbidity and mortality [5,6]. Despite its efficacy, CRT itself has been found to be associated with long-term toxicity and functional impairment, including feeding tube dependence and pharyngeal or laryngeal dysfunction [7–11]. The short and long-term side effects of radiation and chemotherapy, coupled with the younger average age of HPV-driven OPSCC patients, has led to an increase in surgical management, particularly minimally invasive transoral surgery [12–14]. Today, many clinicians have a keen interest in de-escalation therapy, especially for the mostly young and healthy population of HPV-positive (HPV+) OPSCC patients [14,15].

Despite an interest in de-escalation therapy, extracapsular extension (ECE) or positive surgical margins (PSM) remain a poor prognostic sign in head and neck squamous cell carcinoma. Since the seminal trials from the late 1990s that demonstrated adjuvant CRT over adjuvant radiation therapy alone improved locoregional control and overall survival for patients with PSM and/or ECE, these two risk factors have constituted indications for adjuvant CRT [5,6,16]. While this continues to be the unopposed status quo for HPV-negative (HPV−) patients, recent studies from several institutions have suggested that for surgically treated HPV+ patients with OPSCC, ECE does not predict poor clinical behavior [17,18]. Other studies have indicated that ECE and/or PSM still portend high risk for metastatic disease [19]. Studies have also not been conclusive when it comes to PSM. While surgical margin status is dependent on numerous factors including the skill of the surgeon and type of surgery, studies have noted greater local recurrence rates and worse survival among patients with head and neck squamous cell carcinoma (HNSCC) with positive margins [20,21]. However, other authors have not found margin status to be prognostic within OPSCC [22,23].

Currently, expert guidelines continue to consider ECE and/or PSM as indications for adjuvant CRT, irrespective of HPV status [24,25]. Patients undergoing this triple modality therapy would be expected to have worse long-term functional outcomes than either unimodality or bimodality therapy [7]. In the European Organization for Research and Treatment of Cancer Trial 22931, the increased 13% 5-year survival benefit with CRT came at the cost of significant increased grade 3 mucosal toxicity from 21% to 41%. Preoperative risk stratification of patients according to the risk of pathologic ECE or PSM may, therefore, offer tremendous benefit in guiding treatment selection and avoiding the toxicity of triple modality therapy. However, to our knowledge, there is currently no reliable method of preoperatively predicting the presence of ECE or likelihood of PSM for either HPV+ or HPV− patients [26,27]. Using the National Cancer Database (NCDB), we sought first to identify preoperative clinical characteristics that predict pathologic ECE and/or PSM in HPV− and HPV+ patients with OPSSC and then to build a prediction model and nomogram to guide clinical decision-making in the era of AJCC 8th edition staging between the providers, and provider and patient.

Methods

Data source and patient selection

The NCDB, a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society, is a hospital-based registry capturing approximately 70% of incident cancer cases in the United States and drawing data from > 1500 Commission on Cancer accredited cancer programs. The NCDB contains detailed information regarding demographic, clinical, and treatment-related factors. The current analysis was performed with the approval of our local Institutional Review Board.

We queried the NCDB for all cases of oropharyngeal SCC diagnosed from 2010 through 2014 among patients aged ≥18 years as HPV status was sparsely recorded prior to this date. The cohort was limited to squamous cell carcinoma histologic codes (International Classification of Diseases for Oncology [third edition] histology codes 8051–8052, 8070–8075, 8083–8084, and 8094), patients with known HPV status, and patients with initial primary surgical intervention including a neck dissection. We excluded patients with distant metastases (M1), incomplete clinical T and N staging, and incomplete post-operative lymph node assessment. Patients with high-risk HPV status were classified as HPV+ and those with low-risk or negative HPV were classified as HPV−. Patients included in our study had a known pathological ECE status and surgical margin status. See Fig. 1 for a flow diagram.

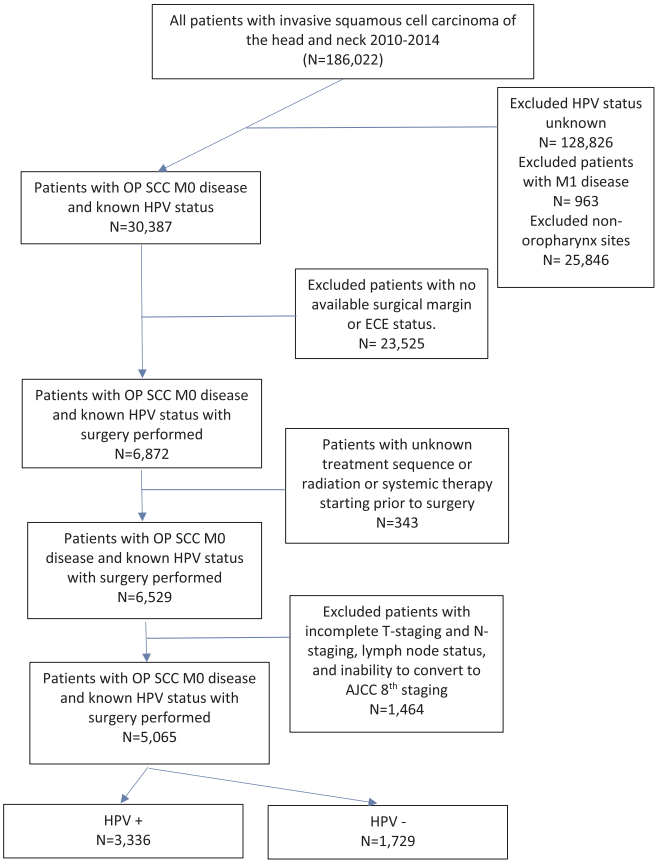

Fig. 1. Flowchart illustrating patient selection for the final analysis and exclusion criteria.

Patient demographics, outcome, and treatment variables

Age was categorized as 18–69 years or ≥70 years as this is a commonly used cutoff to denote "older" patients in HNSCC [28,29]. Race was categorized as White, Black, or other. Insurance status was classified as private, Medicaid, Medicare, government, and uninsured. Residence zip code was coded according to US Department of Agriculture Economic Research Service as within, near, or distant from a metropolitan area. The median household income in each patient's zip code was assessed as quartiles with respect to the US population in 2012. The institution type was classified as an academic program versus nonacademic. Morbidity was classified according to the Charlson-Deyo comorbidity score, dichotomized as 0 or ≥1 morbidity [30]. Patients were assigned T-classification and N-classification corresponding to the AJCC 8th edition by using HPV status, staging information according to AJCC 7th edition, and clinical evidence of extracapsular extension (defined as radiologic evidence of fixed or matted nodes) [4]. Given the strong association between p16-positive disease and HPV-associated OPSSC, unknown primary tumors were categorized as T0/TX. Clinical T-staging was stratified to group T3 and T4 tumors together. Tumor grade was defined by NCDB as "well differentiated," "moderately differentiated," "poorly differentiated," undifferentiated," and