Oral Oncology 65 (2017) 89–93

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Predictors of extracapsular extension in HPV-associated oropharyngeal cancer treated surgically ☆

Mathew Geltzeiler [a,b,*], Daniel Clayburgh [a], John Gleysteen [a], Neil D. Gross [c], Bronwyn Hamilton [d], Peter Andersen [a], Daniel Brickman [a]

[a] Department of Otolaryngology – Head and Neck Surgery, Oregon Health & Science University, Portland, OR 97239, USA
[b] Department of Otolaryngology – Head and Neck Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA
[c] Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[d] Department of Radiology, Oregon Health & Science University, Portland, OR 97239, USA

ARTICLE INFO

Article history:
Received 8 September 2016
Received in revised form 21 December 2016
Accepted 26 December 2016
Available online 3 January 2017

Keywords:
Head and neck cancer
Squamous cell carcinoma
Human papilloma virus
Head and neck radiology
Head and neck imaging
Oropharyngeal cancer
Cervical adenopathy
Extracapsular extension
Head and neck pathology

ABSTRACT

Objectives: Extracapsular extension (ECE) in cervical metastatic lymph nodes remains an indication for adding chemotherapy for patients with oropharyngeal squamous cell carcinoma (OPSCC). The aim of this study is to identify specific imaging characteristics on computed tomography (CT) scan that are predictive of ECE in order to better risk stratify patients preoperatively.

Materials and methods: A single cohort study was performed using a prospectively collected database of patients with HPV-related OPSCC who underwent transoral robotic surgery with cervical lymphadenectomy. CT scans were assessed for the presence of multiple imaging characteristics, including lymph node size, number of nodes positive, cystic appearance, and border irregularity. Univariable and multivariable analyses were performed to analyze each variable's predictability of pathologic ECE.

Results: 100 patients underwent TORS with cervical lymphadenectomy for OPSCC from 2010 to 2015. Ninety-one percent (21/23) of patients with 3 or more radiologically suspicious nodes were found to have pathologic ECE, which was a significantly greater proportion than patients with fewer suspicious nodes ($p < 0.001$). CT scans with 3 or more radiologically suspicious nodes displayed a sensitivity and specificity of 55% and 94%, respectively with a positive predictive value (PPV) of 91% for ECE. Irregular borders and age were also correlated with ECE on multivariable analysis.

Conclusion and relevance: The presence of 3 or more radiologically suspicious lymph nodes on CT scan has a 91% PPV for any histologic evidence of ECE. The absolute number of radiographically suspicious lymph node metastases may be a useful method for risk-stratifying patients for the presence of ECE.

Introduction

The management of oropharyngeal squamous cell carcinoma (OPSCC) has undergone significant transformation over the last 10 years with the advent of transoral robotic surgery (TORS) in the setting of the human papilloma virus (HPV) epidemic [1–4]. The incidence of HPV-related OPSCC is dramatically rising with approximately 45–75% of oropharyngeal malignancy being associated with HPV [2,5–8]. Patients with HPV-related OPSCC also tend to be younger and carry an improved prognosis over traditional HPV negative disease [9]. In this patient population, therapy is focused on simultaneously achieving optimal oncologic outcomes while minimizing long term morbidity. TORS plus selective neck dissection has emerged as an effective treatment option providing

Abbreviations: ECE, extracapsular extension; OPSCC, oropharyngeal squamous cell carcinoma; CT, computed tomography; PPV, positive predictive value; RS, radiographically suspicious; TORS, transoral robotic surgery; HPV, human papilloma virus; CRT, chemoradiation; OHSU, Oregon Health & Science University; IRB, institutional review board; cN+, clinically node positive; OR, odds ration; CI, confidence interval; NPV, negative predictive value; NCCN, National Comprehensive Cancer Network; EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group; ADEPT, Adjuvant Therapy De-intensification Trial for Human Papillomavirus-related, p16+ Oropharynx Cancer.

☆ This work was presented at the International Meeting for the American Head and Neck Society, Seattle, WA July 2016. This work has not been previously published.

* Corresponding author at: Department of Otolaryngology – Head and Neck Surgery, 200 Lothrop St., Suite 500, Pittsburgh, PA 15213, USA.
E-mail address: geltzeilermn@upmc.edu (M. Geltzeiler).

http://dx.doi.org/10.1016/j.oraloncology.2016.12.025
1368-8375/

staging and prognostic information to inform additional therapies as needed [4,9,10].

Extracapsular extension (ECE) from cervical lymph node metastases remains a primary indication for adding chemotherapy to radiation in the adjuvant setting [11,12]. Given the favorable prognosis for the majority of patients with HPV-associated OPSCC treated with TORS, the addition of adjuvant chemoradiation (CRT) likely represents overtreatment. Patients undergoing triple modality therapy would be expected to have worse long-term functional outcomes than either single or dual-modality therapy [13,14]. However, there is currently no reliable method of preoperatively detecting the presence of ECE [15]. Previous studies have shown that current imaging technology cannot reliably define the presence of microscopic ECE, thus pathologic examination of the lymph nodes remains paramount in determining the need for adjuvant therapies [16,17]. The aim of our study was to review a cohort of patients with HPV-associated OPSSC treated with TORS, in order to identify imaging characteristics that may help identify ECE on preoperative computed tomography (CT) imaging.

Methods

Oregon Health & Science University (OHSU) Institutional Review Board (IRB) approval was obtained. OHSU maintains a prospectively collected database of all patients treated with TORS. All consecutive TORS patients from March 2010 through January 2015 who were treated for primary HPV + OPSCC were included. HPV positivity was determined by p16 positivity on immunohistochemical staining. Salvage cases were excluded. Patients were also excluded if a pre-operative CT scan of the neck with contrast was greater than 6 weeks prior to the operative date or the scan was unavailable for review.

Patient demographic and tumor clinical characteristics were collected. Contrast-enhanced CT scans were reviewed on all patients undergoing TORS. For this study, patients with radiographic evidence of nodal involvement (cN+) underwent a secondary imaging review by a blinded, board certified neuroradiologist. The scans were then independently evaluated for specific features that may potentially be associated with ECE. These features included size of the largest node, total number of radiographically suspicious (RS) nodes, cystic vs. solid nodes, border irregularity, adjacent tissue stranding, level 4 adenopathy, and presence of matted nodes. A node was only considered RS if it had one or more of the follow criteria: greater than 2 cm in a single dimension, heterogeneous appearance, cystic change, and/or irregular borders (Fig. 1). For cystic nodes, a 3-point categorical scale of cystic, partially cystic, or solid was used. For borders, a 3-point categorical scale of regular, partially irregular or severely irregular was used. Other features were categorized as either present or absent. Age was analyzed as a continuous variable. Reviewers were blinded to the pathologic ECE status of the patients. Clinical and radiographic were analyzed as potential predictive factors for the presence of ECE. Univariable and stepwise multivariable regression analyses were performed to analyze each aforementioned variable and its predictability of pathologic ECE. A total of 14 items were screened for preliminary entry into the model at 0.250 level of significance. Final models were selected using a manual, step-wise procedure with forward inclusion ($p = 0.100$) and backward elimination ($p = 0.050$) process. Age was analyzed as a continuous variable. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CI) are reported. All statistical analyses were performed using a commercially available statistical software program (SPSS v.22.0; IBM Corp., Armonk, NY).

Results

One hundred total patients met criteria for inclusion in the study. Patient demographics and tumor clinical characteristics can be seen in Table 1 along with the relative proportion of ECE within each group. Seventy patients were clinically N+ and underwent secondary blinded review of preoperative CT imaging. Thirty-nine patients were found to have microscopic ECE on final pathology. A neuroradiologist successfully predicted ECE in 25 patients (64%) yielding a sensitivity and specificity 64% and 68%, respectively, with a positive predictive value (PPV) and negative predictive value (NPV) of 71% and 61%, respectively.

Univariate correlations of the individual demographic and clinical characteristics as related to pathologic ECE were evaluated. Table 2 shows CT imaging characteristics with their relative rate of ECE. Table 3 shows the rate of ECE as compared with the preoperative clinical nodal classification. Clinically N0 patients had an ECE rate of 3.3% and were less likely to have ECE than the other groups ($p < 0.001$). Additionally, N2b patients carried an ECE rate of 69.2%, which was significantly more likely to display ECE than the other groups ($p < 0.001$).

Node sizes, cystic or matted appearance, presence of stranding, or level 4 nodes were not significantly associated with ECE. After stepwise multivariable analysis, depicted in Table 4, we determined that advanced age, number of RS nodes, and border irregularity were correlated with ECE.

Fig. 1. CT Scan with RS nodes. Computed-tomography scan of neck with contrast reveals 3 radiographically suspicious (RS) nodes on the left (arrows).