Oral Oncology 51 (2015) 514–520

Contents lists available at ScienceDirect

Oral Oncology

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

# High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer

Parul Sinha [a], Dorina Kallogjeri [a,b], Hiram Gay [c], Wade L. Thorstad [c], James S. Lewis Jr. [a,d], Rebecca Chernock [a,d], Brian Nussenbaum [a], Bruce H. Haughey [a,*]

[a] Otolaryngology-Head and Neck Surgery, Washington University School of Medicine, St. Louis, MO, United States
[b] Clinical Outcomes Research, Washington University School of Medicine, St. Louis, MO, United States
[c] Radiation Oncology, Washington University School of Medicine, St. Louis, MO, United States
[d] Pathology, Washington University School of Medicine, St. Louis, MO, United States

ARTICLE INFO

*Article history:*
Received 19 January 2015
Received in revised form 18 February 2015
Accepted 19 February 2015
Available online 12 March 2015

*Keywords:*
Oropharynx cancer
Adjuvant chemotherapy
Adjuvant Radiotherapy
p16 gene
Human papillomavirus
Head and neck cancer
Extracapsular Spread
p16-positive

SUMMARY

*Background:* Due to unique biology and prognosis, precise identification of predictive parameters is critical for p16+ oropharyngeal squamous cell carcinoma (OPSCC). Prior studies showing absence of prognostication from extracapsular spread (ECS) and/or high N-classification in surgically-treated p16+ OPSCC necessitate new, evidence-based prognosticators.

*Methods:* A prospectively assembled cohort of 220, transoral surgery + neck dissection ± adjuvant therapy-treated, p16+ OPSCC patients was analyzed. Disease recurrence and disease-specific survival (DSS) were primary endpoints.

*Results:* Median follow-up was 59 (12–189) months. Distribution of metastatic node numbers was: 0 in 9.5% ($n = 21$), 1 in 33.6% ($n = 74$), 2 in 17% ($n = 38$), 3 in 14.5% ($n = 32$), 4 in 8.2% ($n = 18$), and $\geqslant 5$ in 17% ($n = 37$). ECS was recorded in 80% ($n = 159$), and N2c–N3 in 17% ($n = 38$). Adjuvant radiotherapy and chemoradiotherapy was administered in 44% and 34%. Recurrence developed in 22 patients (10%); 4 local, 5 regional, 2 regional and distant, and 11 distant. The 3- and 5-year DSS estimates were 94.6% and 93%. Multivariable logistic regression identified $\geqslant 5$ nodes and T3–T4 classification as predictors for recurrence. In multivariable Cox analyses, $\geqslant 5$ nodes, T3–T4 classification and margins were prognostic for DSS. ECS, N2c–N3 classification and smoking were not prognostic.

*Conclusions:* Metastatic node number, not ECS or high N-classification is an independent nodal predictor of outcomes in surgically-treated p16+ OPSCC patients. Despite high DSS (~80%), closer surveillance for recurrence is recommended for patients with $\geqslant 5$ metastatic nodes.



## Introduction

Transoral surgery (TOS) for human papillomavirus (HPV)-related, p16+ oropharyngeal squamous cell carcinoma (OPSCC) and neck dissection(s) are performed with intent to cure and minimize disruption of function and quality of life (QOL). Several studies show HPV/p16+ OPSCC as a biologic and clinical entity that is distinct from HPV/p16-negative OPSCC [1–4]. Intensified adjuvant treatments associate with diminution in function and QOL, regardless of the HPV/p16 status [2,5,6]. Furthermore, greater reduction in immediate post-treatment QOL has been observed in HPV-positive OPSCC patients compared to HPV-negative patients [7]. Selection of adjuvant therapy for p16+ OPSCC in future will be tailored specifically to the disease's unique pathologic risk-stratification. To this end, multiple risk-stratifying studies are now underway, which seek maintenance of excellent oncologic outcomes, but reduced treatment-related functional and QOL toxicity in p16+ disease. Extracapsular spread (ECS) and high N-classification are generally acknowledged as negative prognosticators in head and neck carcinoma. However, in surgically-treated p16+ OPSCC, studies have shown no prognostication from ECS or N-classification [8–13], which necessitates identification of risk predictors unique to p16+ OPSCC.

Lymph node number, size of metastatic nodes and lymph node ratio (LNR) have been demonstrated as prognostic in head and

* Corresponding author at: Department of Otolaryngology-Head & Neck Surgery, 660 S. Euclid Avenue, Campus Box 8115, St. Louis, MO 63110, United States. Tel.: +1 314 362 0365; fax: +1 314 362 7522.
*E-mail address:* haugheyb@ent.wustl.edu (B.H. Haughey).

http://dx.doi.org/10.1016/j.oraloncology.2015.02.098
1368-8375/

neck carcinoma. The prognostic significance of these parameters is unknown and needs investigation in p16+ OPSCC, since the latter generally have a good prognosis, despite rates of nodal metastasis approaching 75–90% [14,15]. In the background of recent evidence of non-prognostication from ECS and high N-classification, our objective was to identify the prognostic and treatment implications of other nodal factors that can be significantly associated with recurrence and survival outcomes through an exploratory analysis of a surgically-treated, p16+ OPSCC patient cohort.

## Material and methods

A prospectively assembled Human Research Protection Office-approved registry of consecutive TOS-treated head and neck carcinoma patients from 1996 through 2012 at Washington University School of Medicine was searched for OPSCC. The inclusion criteria were:

1. Primary, biopsy-proven OPSCC (Any T, any N, M0).
2. Curative treatment with TOS + neck dissection ± adjuvant therapy.
3. Tumor p16 positivity by immunohistochemistry (IHC).
4. Availability of complete neck dissection pathology report.
5. Minimum follow-up of 12 months, or to death.

Demographic variables, comorbidities, smoking status (never vs. ever) and lifetime tobacco exposure (⩽10 vs. >10 pack-years), tumor stage, and treatment were documented in the data registry at the time of patient enrolment, and follow-up was updated in real time. All variables were verified and updated for the current study. Pathologic American Joint Committee on Cancer (AJCC) T- and N-classification were recorded. In approximately two-thirds of this study cohort, results on a broad spectrum of traditional prognostic factors, but not the multiple nodal factors in the current study, were reported earlier [8].

### *Treatment*

Patients underwent neck dissections in the same surgical session as the TOS [transoral laser microsurgery (TLM) or transoral robotic surgery (TORS)]. The clinically negative contralateral neck was electively treated in the same or staged surgical session (within 1–2 weeks) in patients with T3–T4 primaries, and/or when tumors approached or extended across the midline. The decision for adjuvant therapy accounted for the presence of ECS, multiple metastatic nodes, patient preference, and relevant laboratory and performance status parameters. The study period experienced a distinct change in adjuvant therapy policy after 2004 to adjuvant chemoradiotherapy from radiotherapy in the presence of ECS.

### *Pathology*

Prior to 2010, archival tissue specimens were procured for p16 IHC testing with methods and cutoffs as previously described [8]. From January 2010 forward, routine p16 testing on OPSCC ensued using the same methodology. In addition to T- and N-classification, resection margins, metastatic and total dissected node number, metastasis size, ECS, perineural invasion (PNI), and lymphovascular invasion (LVI) were recorded from the original pathology reports. In patients with pN+ necks, LNR was calculated as the ratio of metastatic to total dissected node number.

### *Study endpoints*

The primary endpoints were, (1) the disease recurrence, defined as frequency of first detected recurrence(s) of OPSCC {local, regional or distant}, and (2) disease-specific survival (DSS), defined as the time from surgery to death from OPSCC. Disease-free survival (DFS) defined as the time from surgery to recurrence or death from any cause, whichever occurred first, was the secondary endpoint. Inclusion of non-cancer deaths as events in DFS allows for patients who died from causes other than cancer but may have later developed delayed recurrence, a behavior specifically observed in p16+ OPSCC [1].

### *Statistical analysis*

Descriptive analysis was performed to report the patient, tumor and treatment characteristics. Univariable and multivariable logistic regression were performed to determine the Odds Ratios (OR) and 95% confidence intervals (CIs) for disease recurrence. Kaplan–Meier analysis was performed for DSS and DFS; estimates were compared by log-rank statistic. All statistical analyses were two-sided, and evaluated at an alpha-level of 0.05. The impact of prognostic variables on DSS and DFS was investigated through Cox proportional hazard (PH) regression analyses. Hazard ratio (HR) was calculated with 95% CIs. The PH assumption was assessed using estimated −log(−log) survival plots and goodness-of-fit tests based on the Schoenfel residuals. Acknowledging small number of patients experiencing disease recurrence and/or deaths even in an extended cohort, we limited the number of factors included in the model in order to reduce the risk of model over-fitting. The *c* index was used to determine the discriminative power of the models in logistic and Cox PH regression analyses [16]. The *c* index varies between 0.5 and 1; 0.5 indicates an uninformative model and 1, a perfect model. In addition, bootstrapping with 100 samples drawn with replacement was used for internal validation of the models to correct for over-optimism of *c*-index. A corrected *p* value was computed to determine the best cut-off points for metastatic node number [17]. Data was analyzed using SAS 9.2 (SAS Institute Inc., Cary, NC) and STATA/SE 12.1 (College Station, TX:StataCorp LP).

## Results

### *Patient characteristics*

A total of 298 OPSCC patients were identified in the TOS registry, 276 previously untreated. Exclusions, illustrated in Fig. 1, left a final cohort of 220 patients who met inclusion criteria. There were 191 males and 29 females with a median (minimum–maximum) cohort age of 56.7 (27.5–84) years. For pertinent demographic, tumor, and treatment characteristics, see Table 1.

### *Treatment*

Resection was achieved using TLM in 214 and TORS in six. Amongst the 17 patients with positive margins reported on final pathology, 4 refused re-resection, while re-resections were performed in 13. Of these 13, tumor was pathologically detected in 3, and was resected to negative margins. The contralateral neck was dissected in 51 patients (23%), of which 26 were staged. A total of 172 patients (78%) received adjuvant therapy; 97 (44%) receiving radiotherapy alone and 75 (34%) receiving concurrent chemoradiotherapy.

### *Primary tumor and nodal characteristics*

Tumor classification was T1 in 96 (43%), T2 in 70 (32%), T3 in 30 (14%) and T4 in 24 (11%) patients. Of the 220 patients, 21 (10%) had