Published in final edited form as:

J Surg Oncol. 2009 February 1; 99(2): . doi:10.1002/jso.21190.

Patient and Tumor Factors at Diagnosis in a Multi-Ethnic Primary Head and Neck Squamous Cell Carcinoma Cohort

Seema Sethi, MD¹, Mei Lu, PhD², Alissa Kapke, MS², Michael S Benninger, MD³, and Maria J Worsham, PhD, FACMG^{1,*†‡}

¹Department of Otolaryngology/Head and Neck Surgery, Henry Ford Health Systems, Detroit, Michigan

²Department of Biostatistics and Research Epidemiology, Henry Ford Health Systems, Detroit, Michigan

³Head and Neck Institute, Cleveland Clinic, Cleveland, Ohio

Abstract

Background—A long-term objective is to refine patient diagnosis and prognosis to address heterogeneity in head and neck squamous cell carcinoma (HNSCC) through incorporation of patient and tumor factors. This study examined histopathology and demographic variables at primary diagnosis (early vs. late stage) in a HNSCC patient population with a higher than usual percentage of African American (AA) subjects.

Methods—The primary HNSCC cohort was drawn from a diverse patient population and constructed through re-review of the primary biopsy. Nine specific histopathology and patient factors (race, gender, age) at primary HNSCC diagnosis were evaluated. Logistic regression analyses incorporated univariate and multivariable modeling.

Results—Race, gender, pattern of invasion, tumor necrosis, perineural invasion, site, and tumor grade were included in the first multivariable model. The final multivariable model retained gender, race, grade, site, and perineural invasion as independent risk factors for late stage with goodness-of-fit, the area under the curve (AUC), as 0.691.

Conclusions—This report emphasizes patient and tumor characteristics of race, gender, site, perineural invasion, grade, and pattern of invasion as independent factors of advanced stage HNSCC. Pattern of invasion and necrosis are also important tumor characteristics of late stage disease. These factors may offer clinical perspectives when evaluating patients with indeterminate stage.

Keywords

early stage; late stage; histopathology

© 2008 Wiley-Liss, Inc.

*Correspondence to: Maria J Worsham, PhD, FACMG, Department of Otolaryngology/Head and Neck Surgery; Professor, Department of Pathology Wayne State School of Medicine, Henry Ford Hospital, 1 Ford Place, 1D, Detroit, MI 48202. Fax: 313-874-1079. mworshal@hfhs.org.

†Senior Scientist.

‡Director of Research.

INTRODUCTION

Staging is the process of describing the extent to which cancer has spread from the site of its origin. In head and neck squamous cell carcinoma (HNSCC), the TNM classification system, an anatomic staging system that describes the extent of the primary tumor (T) as well as the involvement of regional lymph nodes (N) and distant metastasis [1], is the prevailing gold standard for staging [1,2]. Currently in its sixth version [2], the TNM is an important tool not only for reporting and comparing outcomes of therapy, but also for improving stratification of patients for inclusion in clinical trials [3].

It is known that tumor behavior is dependent on a complex interrelationship between the tumor and patient [4] and several studies have suggested expansion of the current TNM staging system to include host factors to augment the clinical utility and progress in cancer staging [5]. Accordingly, the system has been periodically revised not only to incorporate information available from advances in diagnosis (e.g., endoscopy and radiologic imaging) but also from improved understanding of the biologic behavior of the numerous tumors that occur in this anatomic area [3].

Studies investigating the association of a broader spectrum of tumor and host factors, particularly in cohorts with an unusually higher proportion of African American (AA) patients would add to our understanding of the extent to which these indicators might contribute to ongoing revisions of the TNM staging system. In the present study, we evaluated the association of a broad spectrum of tumor histopathology characteristics and patient demographic factors at primary diagnosis in a diverse primary care HNSCC patient population with a higher than usual percentage of AA subjects.

MATERIALS AND METHODS

Detroit Primary HNSCC Cohort

Henry Ford Health System (HFHS) is one of the largest healthcare organizations in southeastern Michigan. It includes an HMO (Health Alliance Plan-HAP), a medical group (Henry Ford Medical Group, HFMG), and several hospitals. The patients at HFHS are largely from the three-county Metropolitan Detroit area. This study drew from a sizable pool of primary care patients serviced by HAP and a large pool of AA patients (self-reported) who make up about 33% of the total patient population.

Study Design

Ascertainment of cohort subjects (before exclusions) was based on retrieval and review of all reports of primary biopsies with a HNSCC diagnosis within HFHS spanning a period from January 1, 1988 to December 31, 2005. Patients were eligible for this study if they were 21 years or older and had a primary squamous head and neck tumor biopsy performed for diagnostic purposes. H&E slides were reviewed for all eligible subjects using a detailed pathology review form designed to capture the broad spectrum of histological findings evaluated in this study.

HNSCC Pathology Review

Tumor factors evaluated included tumor grade: well (WD)/moderate (MD)/poorly differentiated (PD); lymphocytic response: continuous rim/patchy infiltrate/absent; desmoplastic response: prominent and diffuse/patchy and irregular/focal/absent; pattern of invasion: host/tumor interface with pushing cohesive borders (mode 1)/solid cords (mode 2)/thin irregular cords (mode 3)/single cells (mode 4) [6]; vascular invasion: identified/absent; perineural invasion [7]: identified/absent; mitotic index (<5 mitosis per 10 high power fields

(HPF); >5 mitosis per 10 HPF); necrosis: extensive/minimal/absent, and location of the primary tumor. There were six primary tumor site categories (Table I): (1) oral cavity (OC), (2) oral cavity/tongue (OC-T), (3) larynx, (4) oropharynx (includes tonsil and base of tongue), (5) hypopharynx (includes pyriform sinus), and (6) other (lip-external, nose maxilla, parotid, nasopharynx, sinonasal).

Because undifferentiated implies that the tissue of origin is unknown [8], no tumors with this histopathologic grade were included unless it was implicit in the histopathology review that features of squamous cell differentiation were also present.

Demographic Risk Factors

Demographic risk factors considered for analysis and assessed at the time of primary HNSCC were age (<50 years, 51–64 years and 65 or older), gender (male, female), and race (African American {AA}/Caucasian-American {CA}). Clinical and demographic information was obtained under approved institutional review board protocols from the HFHS Tumor Registry database and the department of Otolaryngology's clinical database.

Primary Tumor Staging

The TNM classification [1,2] was used to classify and stage the primary tumor. Cases were divided into TNM stages early (stage I and II) and late (stage III and IV). The early stage grouping included carcinoma in situ (Tis).

Statistical Methods

To assess significant risk factors of early and late stage HNSCC, univariate logistic regression analysis was performed followed by multivariable modeling. Variables tested in the univariate analysis included demographic factors of age, gender, race, and histopathological factors of tumor grade, pattern of invasion, lymphocytic response, desmoplastic response, vascular invasion, perineural invasion, mitotic index, primary tumor location (site), and necrosis (Table I). There were six primary tumor site categories: (1) OC, (2) OC-T, (3) larynx, (4) oropharynx (includes tonsil and base of tongue), (5) hypopharynx, and (6) other. Individual variables of $P < 0.10$ were tested in the multivariable model. The final multivariable logistic regression model was determined using the backward stepwise selection process and included all factors with $P < .05$. Odds ratios and 95% confidence intervals were calculated for the final multivariable model with area under the curve (AUC) for model predictability.

RESULTS

The final cohort of 428 patients reported in this study represents the initial group of an ongoing NIH study (R01 DE 15990). Eligibility into the study required that patients have an excision biopsy so that tissue is available for the examination of the molecular characteristics of the tumor. In a very few cases, core biopsies (6/428), with adequate tissue were also included. The final cohort of 428 patients reported in this study was drawn from an initial review of 505 patients, of which 77 were ineligible. The latter exclusions occurred primarily because of missing stage, or medical record abstraction for risk factor collection (part of the ongoing NIH study), indicated previous treatment prior to resection of the primary tumor, or the patient's biopsy was not a primary HNSCC due to an earlier primary biopsy either within or outside HFHS. Of the 428 patients, 167 were early and 261 were late stage.

Biopsies were mainly excision (86%: 367/428) and a few radical neck dissection surgeries (13%: 55/428); there were only six core biopsies (1%: 6/428). The excisional biopsy group

included resections with the intent of cure. Histopathology factors were recorded for almost all of the patients in the cohort (Table II). Missing data ranged from 0.7% (three cases) to 1.9% (eight cases). Location of the primary tumor based on the six-site categories and stage is presented in Table I.

The mean age of the 428 primary HNSCC study cohort was 63 years (SD = 12.0); range 28–94 years. There were 318 (77%) males and 110 (23%) females; 260 (61%) Caucasian Americans (CA), 160 (37%) AA. In eight cases (2%), race data were missing. Demographic and histopathology variables examined in this study cohort are presented in Table II. Univariate analysis showed gender, race, pattern of invasion, tumor necrosis, perineural invasion, tumor grade, and site as significant risk variables ($P < 0.10$). Perineural invasion was identified in 16 of the 53 evaluable radical neck surgical biopsies (30.2%) as compared to 15 of 357 evaluable excision/core needle biopsies (4.2%). There was a significant correlation between perineural invasion and radical neck dissection as a primary biopsy ($P < 0.001$).

Multivariable modeling retained gender, race, grade, perineural invasion, and site as significant factors ($P < 0.05$) of late stage disease at the time of primary diagnosis (Table III). Although pattern invasion was significant in the univariate model ($P = 0.018$), after adjusting for other significant histopathology parameters it was no longer a significant predictor of stage ($P = 0.173$). The AUC was 0.691, indicating good predictability.

Female patients were less likely to present with late stage HNSCC when compared to male patients (OR = 0.60, 95% CI 0.37, 0.97, $P = 0.035$). AA patients were 1.65 times more likely to have late stage disease when compared to CA patients (OR = 1.65, 95% CI 1.06, 2.57, $P = 0.027$). Poorly differentiated tumors were nearly three times more likely to have late stage disease than well-differentiated tumors (OR = 2.92, 95% CI 1.58, 5.38, $P < 0.001$). Presence of perineural invasion was 2.83 times more likely to predict late stage disease (OR = 2.83, 95% CI 1.15, 6.98, $P = 0.024$).

The most frequent location of the primary tumor was the larynx (Table I). There were 171 laryngeal tumors, 79 (46.2%) early and 92 (53.8%) late stage. This was followed by HNSCC patients in the other category, followed by oral cavity-tongue, oral cavity, hypopharynx, and oropharynx (Table I). When compared to patients with laryngeal site as reference, patients with a primary HNSCC in the hypopharynx were more than three times more likely to present with late stage HNSCC (OR = 3.29, 95% CI 1.13, 9.61, $P = 0.030$). Patients in the site category of oropharynx and other were 3.03 times and 2.19 times, respectively, more likely to present with late stage disease (OR = 3.03, 95% CI 1.38, 6.63, $P = 0.0057$; OR = 2.19, 95% CI 1.13, 4.21, $P = 0.019$, Table III). We ran the same model but with combined OC and OC-Tongue categories and found a marginally significant association between patients with OC or OC-T sites versus laryngeal site (OR = 1.60, 95% CI 0.967, 2.651, $P = 0.067$).

DISCUSSION

Squamous cell carcinoma is the predominant histological type, representing approximately 55.8% of all head and neck cancer cases [9]. Most HNSCC arise from mucosal surfaces of the upper aerodigestive tract (lip, oral cavity, pharynx, and larynx), with the larynx as the most common site [9]. The AJCC–UICC TNM staging system for HNSCC is an international classification tool not only for reporting and comparing outcomes of therapy, but also for improving stratification of patients for inclusion in clinical trials [3]. Although it conveys important clinical information, the attributes contributed by these three indicators, T, N, and M are often imprecise in defining risk groups. Ambiguity in staging leads to

unnecessary side effects of adjuvant chemo- and radiotherapies and increases the cost of treating an individual patient [5]. Several studies have demonstrated the inaccuracies of the TNM staging system in HNSCC, underscoring the need for refinement through consideration of additional patient and tumor factors [5,10,11].

In the present study, we examined nine specific histopathology characteristics and patient variables of race, gender, and age at primary HNSCC diagnosis in a diverse primary healthcare population. The majority of biopsies were either excision (86%: 367/428) or radical neck dissection surgeries (13%: 55/428), with only six core biopsies (1%). Histopathology factors were recorded for almost all of the patients in the cohort. As indicated in Table II, number of cases in which each of these factors was recorded, missing data ranged from 0.7% (three cases) to 1.9% (eight cases). This high rate of evaluable histopathological factors minimizes the introduction of bias. Gender, race, grade, perineural invasion, and primary tumor location were significant multivariate risk factors for late stage disease.

Perineural spread is the dissemination of a tumor through the planes of the neural sheath or along lymphatics of the epineurium and perineurium toward noncontiguous regions [7]. It has been reported as an independent predictor of local recurrence and regional and nodal metastasis [12], ranging from 6% to 52% [12–15]. Of the 428 patients in this study, perineural invasion was not evaluable in only 3 of 428 patients. Perineural invasion was identified in 16 of the 53 evaluable radical neck surgical biopsies (30.2%) as compared to 15 of 357 evaluable excision/core needle biopsies (4.2%). This may account for the significant correlation between perineural invasion and radical neck dissection as a primary biopsy ($P < .001$), marking it as a surrogate of late stage diagnosis (large tumor size and necrosis).

Tumor grade, although not a staging factor criteria, offers crucial insights into the biological behavior of the tumor. In this study, a tumor grade of poorly differentiated was a predictor of late stage HNSCC (OR = 2.92; 95% CI 1.58, 5.38, $P < 0.001$). These findings are consistent with previous studies demonstrating histologic tumor grade as a powerful predictor of distant metastasis, adding important information to clinical and pathologic neck staging, including consideration for systemic treatment [16]. Histologic grade also emerged as a significant risk factor of local or regional laryngeal cancer recurrence [17]. The 1998 National Cancer Data Base (NCDB) Report on Cancer of the Head and Neck [9] reported that poorly differentiated head and neck cancers were most notably associated with advanced stage. Unfortunately, grade is not often reported in head and neck literature, even in large prospective studies mainly because the impact of tumor grade on management decisions for most cancers of the head and neck is not widely accepted [9]. The histologic grade at the deep invasive front of tongue had high prognostic value for squamous cell carcinoma at this site [4]. The finding of poorly differentiated grade as a significant risk factor for late stage disease in this diverse HNSCC cohort underscores the usefulness of this histological factor as an important variable in staging and prognosis.

HNSCC, often treated as a single entity, is in fact a heterogeneous group of tumors and outcome of both diagnosis and prognosis is strongly influenced by the anatomic site of the primary tumor [18–20]. In this study, to evaluate contribution of site to diagnosis of HNSCC, primary tumors were placed into six anatomic site categories. The influence of location of the primary tumor on late stage diagnosis, with larynx as the reference site, was the highest for SCC in the hypopharynx (OR = 3.29, 95% CI 1.13, 9.61, $P = 0.030$), followed by oropharynx (OR = 3.03, 95% CI 1.38, 6.63, $P < 0.001$), and the site category of other (nasopharynx, maxilla, nose, sinonasal; OR = 2.62, 95% CI 1.46, 4.70, $P = 0.001$).

Increase in the incidence of cancer of the head and neck among minority groups [21] complement the 1998 NCDB Report on Cancer of the Head and Neck [9], which showed a 10.0% proportionate increase in AAs (from 8.0% to 8.8%) and a 21.4% proportionate increase in Hispanic patients (from 2.8% to 3.4%). The disproportionate increase in the number of head and neck mucosal cancers in AAs as compared to whites is supported by other studies. In analyses by race and ethnicity (Cancer Statistics, 2006), AA men and women have 40% and 18% higher death rates from all cancers combined than White men and women, respectively. Racial disparity also extended to disease stage with a greater proportion of advanced-stage cancers (stages III and IV) occurring among lower-income groups, the geographic region of the Southeast, and AAs [9]. The finding of a higher likelihood of AA patients with late stage disease as compared to CA patients is consistent with previous studies [9,22]. Older age, male sex, non-Hispanic AA race/ethnicity, low income, and high grade were all significantly associated with advanced stage squamous cell carcinoma of the base of the tongue [23].

Generally, women have lower rates of head and neck cancer than men worldwide and in the US [24,25], regardless of smoking status [26]. However, smoking was associated with a larger relative increase in head and neck cancer risk in women than in men [26]. An association of gender with differences in stage distribution reported male patients with head and neck cancer had more advanced-stage cancers and fewer stage I cancers, however, this study cohort included thyroid cancer, which is dominated by early-stage disease, and which occurs in women more frequently than in men [9]. In this study, female patients were less likely to present with a late stage diagnosis than male patients with HNSCC (OR = 0.60, 95% CI 0.37, 0.97, $P=0.035$). We will test this observation in the final larger study cohort (currently completing construction) taking into account epidemiological and clinical risk factors including smoking and alcohol, access to care, and comorbidities at the time of primary diagnosis.

A current shortcoming in the more rigorous analysis of race on staging for HNSCC is a dearth of study cohorts with adequate representation of minority patients, in particular multi-ethnic cohorts drawn from primary care patient populations. In this multi-ethnic primary care HNSCC cohort, with 36.4% AA patient representation, we found the AAs were 1.65 times more likely to have advanced stage disease than their CA counterparts. Studies with similar outcomes have cited poor access to health care and lack of medical insurance among AA patients [10,11]. In this report, given the primary care environment from which the study cohort was drawn, access to health care with medical insurance status is pending and will be analyzed for the entire 1,000 HNSCC study cohort (still in the process of being assembled) at a later date.

Mode of invasion, evaluated based on four levels from 1 to 4 [6], has been reported as an independent variable in squamous cell carcinoma of the tongue [6,27]. In this study, although pattern invasion was significant in the univariate model ($P=0.018$), after adjusting for other significant histopathology parameters it was no longer a significant predictor of stage ($P=0.173$). Tumor necrosis as a univariate predictor of late stage outcome ($P=0.02$) in this cohort, concurs with a highly significant association reported for necrosis and higher N-stage disease [28] in HNSCC.

In HNSCC patients, diagnosis relies on the TNM classification, a prevailing gold standard. However, the attributes contributed by these three indicators is often imprecise. The long-term objective is to refine patient diagnosis and prognosis and address heterogeneity in HNSCC through incorporation of clinical and pathological factors to aid in the clinical management of patients at the earliest stages. An improved, comprehensive, multi-

parametric HNSCC staging (diagnosis) algorithm would permit more accurate grouping of tumor subtypes and better distinction of prognostic groups for effective treatment strategies.

This report of a diverse primary care HNSCC patient population with a higher than usual percentage of AA subjects emphasizes patient and tumor characteristics of race, gender, site, perineural invasion, grade, and pattern of invasion as independent factors of advanced stage HNSCC. Pattern of invasion and necrosis are also important tumor characteristics of late stage disease. These factors may offer clinical perspective when evaluating patients with indeterminate stage.

Acknowledgments

R01 NIH DE 15990 (Dr. Worsham)

REFERENCES

1. Sobin LH. TNM: Evolution and relation to other prognostic factors. *Semin Surg Oncol*. 2003; 21:3–7. [PubMed: 12923909]
2. Greene, FL.; Page, DL.; Fleming, ID., et al., editors. *AJCC Cancer Staging Manual*. New York, NY: Springer; 2002.
3. Patel SG, Shah JP. TNM staging of cancers of the head and neck: Striving for uniformity among diversity. *CA Cancer J Clin*. 2005; 55:242–258. quiz 61–2, 64. [PubMed: 16020425]
4. Kurokawa H, Zang M, Matsumoto S, et al. The high prognostic value of the histologic grade at the deep invasive front of tongue squamous cell carcinoma. *J Oral Pathol Med*. 2005; 34:329–333. [PubMed: 15946179]
5. Piccirillo JF. Importance of comorbidity in head and neck cancer. *Laryngoscope*. 2000; 110:593–602. [PubMed: 10764003]
6. Spiro RH, Guillaumondegui O Jr, Paulino AF, et al. Pattern of invasion and margin assessment in patients with oral tongue cancer. *Head Neck*. 1999; 21:408–413. [PubMed: 10402520]
7. Caldemeyer KS, Mathews VP, Righi PD, et al. Imaging features and clinical significance of perineural spread or extension of head and neck tumors. *Radiographics*. 1998; 18:97–110. quiz 47. [PubMed: 9460111]
8. Lacy PD, Piccirillo JF. Development of a new staging system for patients with recurrent laryngeal squamous cell carcinoma. *Cancer*. 1998; 83:910–917. [PubMed: 9731894]
9. Hoffman HT, Karnell LH, Funk GF, et al. The National Cancer Data Base report on cancer of the head and neck. *Arch Otolaryngol Head Neck Surg*. 1998; 124:951–962. [PubMed: 9738803]
10. Nichols AC, Bhattacharyya N. Racial differences in stage and survival in head and neck squamous cell carcinoma. *Laryngoscope*. 2007; 117:770–775. [PubMed: 17473666]
11. Gourin CG, Podolsky RH. Racial disparities in patients with head and neck squamous cell carcinoma. *Laryngoscope*. 2006; 116:1093–1106. [PubMed: 16826042]
12. Fagan JJ, Collins B, Barnes L, et al. Perineural invasion in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg*. 1998; 124:637–640. [PubMed: 9639472]
13. Brasilino de Carvalho M. Quantitative analysis of the extent of extracapsular invasion and its prognostic significance: A prospective study of 170 cases of carcinoma of the larynx and hypopharynx. *Head Neck*. 1998; 20:16–21. [PubMed: 9464947]
14. Johnson JT, Myers EN, Bedetti CD, et al. Cervical lymph node metastases. Incidence and implications of extracapsular carcinoma. *Arch Otolaryngol*. 1985; 111:534–537. [PubMed: 4026664]
15. Moor JW, Jose J, Johnston C, et al. Upper aerodigestive tract squamous cell carcinoma: Distribution of extracapsular spread and soft tissue deposits in the neck. *Acta Otolaryngol*. 2004; 124:97–101. [PubMed: 14977085]
16. Fortin A, Couture C, Doucet R, et al. Does histologic grade have a role in the management of head and neck cancers? *J Clin Oncol*. 2001; 19:4107–4116. [PubMed: 11689578]

17. Ritoie SC, Verbeek AL, Krabbe PF, et al. Screening for local and regional cancer recurrence in patients curatively treated for laryngeal cancer: Definition of a high-risk group and estimation of the lead time. *Head Neck*. 2007; 29:431–438. [PubMed: 17120311]
18. Ildstad ST, Tollerud DJ, Bigelow ME, et al. A multivariate analysis of determinants of survival for patients with squamous cell carcinoma of the head and neck. *Ann Surg*. 1989; 209:237–241. [PubMed: 2916867]
19. Medow MA, Weed HG, Schuller DE. Simple predictors of survival in head and neck squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg*. 2002; 128:1282–1286. [PubMed: 12431171]
20. Leemans CR, Tiwari R, Nauta JJ, et al. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. *Cancer*. 1994; 73:187–190. [PubMed: 8275423]
21. Kosary, CL.; Ries, LAG.; Miller, BA., et al. SEER Cancer Statistics Review, 1973–1992 : Tables and Graphs. Bethesda, Md: National Cancer Institute; 1995. NIH publication 96-2789 1995.
22. Shavers VL, Harlan LC, Winn D, et al. Racial/ethnic patterns of care for cancers of the oral cavity, pharynx, larynx, sinuses, and salivary glands. *Cancer Metastasis Rev*. 2003; 22:25–38. [PubMed: 12716034]
23. Zhen W, Karnell LH, Hoffman HT, et al. The National Cancer Data Base report on squamous cell carcinoma of the base of tongue. *Head Neck*. 2004; 26:660–674. [PubMed: 15287033]
24. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005; 55:74–108. [PubMed: 15761078]
25. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin*. 2006; 56:106–130. [PubMed: 16514137]
26. Freedman ND, Abnet CC, Leitzmann MF, et al. Prospective investigation of the cigarette smoking-head and neck cancer association by sex. *Cancer*. 2007; 110:1593–1601. [PubMed: 17724671]
27. Lim SC, Zhang S, Ishii G, et al. Predictive markers for late cervical metastasis in stage I and II invasive squamous cell carcinoma of the oral tongue. *Clin Cancer Res*. 2004; 10:166–172. [PubMed: 14734465]
28. Kuhnt T, Mueller AC, Pelz T, et al. Impact of tumor control and presence of visible necrosis in head and neck cancer patients treated with radiotherapy or radiochemotherapy. *J Cancer Res Clin Oncol*. 2005; 131:758–764. [PubMed: 16088405]

TABLE I

Primary Site Location Categories of the HNSCC Study Cohort

Site	Early stage (N = 167)	Late stage (N = 261)	Total (N = 428)
Oral cavity	27 (6.3%)	35 (8.2%)	62 (14.5%)
Oral cavity-tongue	23 (5.4%)	38 (8.9%)	61 (14.3%)
Larynx	79 (18.5%)	92 (21.5%)	171 (40%)
Oropharynx	10 (2.3%)	35 (8.12%)	45 (10.4%)
Hypopharynx	6 (1.4%)	17 (4%)	23 (5.4)
Other	22 (5.1%)	44 (10.3%)	66 (15.4%)

TABLE II

Univariate Logistic Regression Results for Late Versus Early Stage

Parameter: number of cases	Comparison	P-value
Gender: 428	Female vs. male	0.068
Race: 420	Black vs. white	0.005 *
Age: 428	10 unit increase	0.219
Desmoplastic response: 428	Patchy and irregular vs. prominent and diffuse	0.192
	Focal vs. prominent and diffuse	
	Absent vs. prominent and diffuse	
Pattern invasion: 420	Solid cords vs. pushing cohesive	0.018 *
	Thin irregular cords vs. pushing cohesive	
	Single Cell vs. pushing cohesive	
Lymphocyte response: 420	Patchy infiltrate vs. continuous rim	0.154
	Absent vs. continuous rim	
Tumor necrosis: 428	Minimal vs. none	0.020 *
	Extensive vs. none	
Vascular invasion: 425	Identified vs. not identified	0.115
Perineural invasion: 425	Identified vs. not identified	0.057
Overall grade: 428	Moderately differentiated vs. well differentiated	<.001 *
	Poorly differentiated vs. Well differentiate	
Mitoses per 10HPF: 428	Frequent < 5/10 HPF vs. frequent > 5/10 HPF	0.179
Site: 428		0.039 *

* $P < 0.05$.

TABLE III

Final Multivariable Survival Model

Variable	OR	95% CI	P-value
Race: AA vs. Caucasian	1.65	1.06, 2.57	0.027
Overall grade: poorly differentiated vs. well differentiated	2.92	1.58, 5.38	0.0006
Perineural invasion: identified vs. not identified	2.83	1.15, 6.98	0.024
Site: OC vs. larynx	1.46	0.78, 2.73	0.237
Site: OC-T vs. Larynx	1.76	0.93, 3.31	0.081
Site: OP vs. larynx	3.03	1.38, 6.63	0.0057
Site: HP vs. larynx	3.29	1.13, 9.61	0.030
Site: other vs. larynx	2.19	1.13, 4.21	0.019
Gender: female vs. male	0.60	0.37, 0.97	0.035

Area under the curve (AUC) = 0.691.