Oral Oncology 49 (2013) 911–917

Contents lists available at SciVerse ScienceDirect

Oral Oncology

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

Comorbidity, human papillomavirus infection and head and neck cancer survival in an ethnically diverse population

Ashish A. Ankola [a], Richard V. Smith [a,f,1], Robert D. Burk [b,c,d,e], Michael B. Prystowsky [f], Catherine Sarta [a], Nicolas F. Schlecht [e,g,*,1]

[a] Department of Otorhinolaryngology-Head and Neck Surgery, Albert Einstein College of Medicine, Bronx, NY 10461, United States
[b] Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY 10461, United States
[c] Department of Microbiology & Immunology, Albert Einstein College of Medicine, Bronx, NY 10461, United States
[d] Department of Obstetrics, Gynecology & Women's Health, Albert Einstein College of Medicine, Bronx, NY 10461, United States
[e] Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, United States
[f] Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461, United States
[g] Department of Medicine, Albert Einstein College of Medicine, Bronx, NY 10461, United States

ARTICLE INFO

Article history:
Received 11 March 2013
Received in revised form 11 June 2013
Accepted 1 July 2013
Available online 25 July 2013

Keywords:
ACE-27
Comorbidity
Head and neck
Oropharyngeal
Squamous cell carcinoma
Survival
Human papillomavirus

SUMMARY

Objective: To demonstrate the importance of comorbid conditions in head and neck squamous cell carcinoma (HNSCC), we assessed the association between comorbidity and survival in an inner-city population of HNSCC patients.

Patients and methods: Comorbid status at diagnosis was derived using medical records and the Adult Comorbidity Evaluation-27 (ACE-27) index on 288 patients with histologically confirmed HNSCC from Montefiore Medical Center in the Bronx (NY) between 2002 and 2011. The association between comorbidity, tumor human papillomavirus (HPV) status and overall and disease specific survival was assessed by Kaplan–Meier analysis and multivariable Cox regression adjusting for clinico-pathologic factors.

Results: The study population consisted of primary oropharyngeal (36%), laryngeal (33%) and oral cavity cancer patients (31%). Overall, 19% had no comorbidity, 43% mild comorbidity, 29% moderate comorbidity, and 9% severe comorbidity. The most common comorbid conditions were hypertension, diabetes mellitus, respiratory disease, other malignancies, and illicit drug use. Survival analyses revealed that increased comorbidity at diagnosis was significantly related to poorer overall survival ($p = 0.016$), but not to cancer survival ($p = 0.369$) or recurrence ($p = 0.652$). Oropharyngeal cancer patients with HPV DNA positive tumors and lower levels of comorbidity had significantly better overall survival compared to patients with HPV negative tumors (hazard ratio = 0.2, 95%CI: 0.04–0.8), however there was no significant difference in overall (or disease specific) survival by HPV status among patients with higher levels of comorbidity at diagnosis (hazard ratio = 0.7, 95%CI: 0.2–2.8).

Conclusion: In an inner-city predominantly minority population, comorbidity at HNSCC diagnosis is relatively common and associated with poor overall survival, but not cancer survival or recurrence. Interestingly, the relationship between HPV and improved survival appears to be specific to patients with low comorbidity at diagnosis.

Introduction

Cancers of the head and neck constitute an anatomically heterogeneous group arising most often from the oral cavity, oropharynx, hypopharynx, and larynx. Standard practice for patients with head and neck malignancies is to stage them according to the Tumor-Node-Metastasis (TNM) classification system. While appropriate for describing characteristics specific to tumors, more accurate prognostic information has been shown when TNM staging is combined with more patient-specific variables that bear more direct relation to survival [1]. One such variable is comorbidity.

Comorbidity is defined as the presence of a disease or condition that is unrelated to the index disease [2]. Head and neck cancer patients are unique in that they usually have histories of heavy tobacco and alcohol use, both of which contribute significantly to other pathologic conditions throughout the body. While these conditions are separate from the index cancer, they are important overall factors for the patient [3]. Furthermore, in a subset of head

* Corresponding author. Address: Department of Epidemiology & Population Health, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Ave., Bronx, NY 10461, United States. Tel.: +1 (718) 430 2307; fax: +1 (718) 430 3052.
E-mail address: nicolas.schlecht@einstein.yu.edu (N.F. Schlecht).
[1] These authors share senior authorship on this paper.

1368-8375/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.oraloncology.2013.07.001

and neck squamous cell carcinoma (HNSCC), growing epidemiologic evidence supports an etiologic role for human papillomaviruses (HPV), which also constitute a prognostic marker of improved survival and response to therapy.

A number of studies have demonstrated the increased prevalence of comorbidity in head and neck cancer patients [2,4,5], which can impact treatment selection [6,7] and prognosis [8–13]. For example, patients with severe cardiovascular or respiratory comorbidity may be excluded from surgical treatment because of an increased potential for adverse treatment outcomes [14]. The impact of comorbidity has been described for both short and long term survival, and over a variety of different treatment combinations [15–17].

Given its demonstrated importance in patients with head and neck cancer, the American College of Surgeons, the American Cancer Society, and the International Head and Neck Scientific Group have advocated for the routine inclusion of comorbidity information in cancer registries [18]. However, no studies have assessed the independent effect of comorbidity and HPV on survival in HNSCC. We sought to assess the degree of comorbidity at diagnosis in an inner-city population of HNSCC patients that is largely ethnic minority with high levels of drug use, HIV/AIDS, Hepatitis C, and other diseases.

Methods

Study design

Our study population included HNSCC patients admitted to Montefiore Medical Center (MMC) in the Bronx (NY) between 2002 and 2011. The study was approved by the Institutional Review Boards at MMC and Albert Einstein College of Medicine. Standard histological confirmation of tumors was performed for all cases, with TNM staging based on the American Joint Committee on Cancer classification. Details on smoking history and alcohol consumption were collected by medical interview at enrollment. Additional clinico-pathologic factors collected included: age, gender, race, ethnicity, tumor anatomic site, primary treatment modality and detection of HPV16 DNA in the tumor (targeting the oncogenic type found in almost all HPV positive HNSCC) using previously described PCR protocols [19].

Comorbidity measures

Methods for assessing comorbidity vary, including patient interviews and patient chart reviews [20]. A number of different indices exist that differ in the level of detail collected on the severity of comorbid conditions [11,21–24]. We employed the Adult Comorbidity Evaluation-27 (ACE-27), which includes 27 different comorbid elements and disease severity, as this has been shown to perform best in head and neck cancer patients [12,25].

A single trained individual (AAA) abstracted comorbidity information collected at diagnosis through retrospective review of patient medical records. Materials used included admission notes, routine laboratory assessments, and radiation oncology records. A score of 0, 1, 2, or 3 was assigned for each of 27 conditions assessed representing none, mild, moderate, or severe comorbidity, respectively. An overall comorbid score was then assigned according to the highest scoring single condition. In the event where there were two moderate level comorbidities, an overall score of severe was assigned [11,24].

Statistical methods

Contingency tables with Chi-square or Fisher's exact tests were used to describe the study population and the cross-sectional associations between comorbid conditions and disease characteristics at diagnosis. Patients were followed from time of diagnosis as part of an ongoing cohort study [26]. Overall and disease specific survival were defined as time from diagnosis (in months) to death from all causes or head and neck cancer, respectively. Disease recurrence was defined as the time from treatment start to first incidence of local or regional recurrence or distant metastasis. Remaining subjects were censored at the time they were last known to be alive. Kaplan–Meier analyses and Cox proportional hazards regression were used to assess the relationship between comorbidity and overall survival, cancer survival or recurrence. The multivariate Cox regression analyses included an exhaustive search for significant covariate predictors, identified by univariate analyses. The potential for confounding was examined using a change-in-point estimate criterion in adjusted survival models incorporating covariates with the variable for comorbidity, and were subsequently controlled for in the final multivariable regression models [27]. Covariates examined included all clinico-pathologic factors assessed at diagnosis, including: age, gender, race, ethnicity, smoking history, alcohol consumption, tumor anatomic site, TNM stage, and primary treatment modality, as well as HPV detection in the tumor (available on 151 patients). Proportional hazards assumptions were tested by Schoenfeld residuals. Evidence of statistical interaction (effect modification) by HPV status and tumor site was also assessed by testing for significant cross-product terms between these covariates and comorbid status in the final multivariate regression models. Inference was based on the Wald chi-square test statistic for two-way interaction. Statistical analyses were conducted with the STATA 12 software package (College Station, TX), and significance was based on a two-sided p-value of less than 0.05 or 95% confidence interval that does not include 1.0.

Results

Population description

A total of 338 patients were identified for the current study. Of this group, 50 patients were excluded due to insufficient prior medical records, leaving a total of 288 patients. The mean age at diagnosis was 61.7 years (±11.6 standard deviation), ranging from 22–89. The study population was comprised of mostly men (72.2%), and consisted of 28.8% African–American and 27.4% Hispanic subjects. Of the various primary sites, 86 patients (30.6%) had SCC of the oral cavity, 92 patients (32.7%) of the larynx, and 103 patients (35.8%) of the oropharynx. Two-hundred and six patients (71.5%) had late stage disease (TNM stages III–IV). The remaining demographic, diagnostic and clinico-pathologic characteristics of the study population are shown in Table 1.

Comorbidity in the population

Of the 288 patients in the study sample, 55 (19.1%) had no comorbidity at the time of diagnosis; 125 (43.4%) had mild overall comorbidity, 81 (28.1%) had moderate comorbidity, and 27 (9.4%) had severe comorbidity. Table 2 details the distribution of comorbid scores in the population and the prevalence of some of the more common comorbid conditions.

Patients with laryngeal SCC were significantly more likely to have severe comorbidity when compared to either oral cavity or oropharyngeal SCC patients ($p = 0.002$; Table 3). Smokers, including past and current, were significantly more likely to have mild (51.5% and 38.9%), moderate (29.2% and 28.3%) or severe comorbidity (6.2% and 15.9%) compared to non-smokers (31.8%, 25%, and 2.3%, respectively, $p = 0.001$). With respect to age, patients