Oral Oncology 60 (2016) 55–60

Contents lists available at ScienceDirect

Oral Oncology

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

# Association of pretreatment body mass index and survival in human papillomavirus positive oropharyngeal squamous cell carcinoma

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ARTICLE INFO

*Article history:*
Received 25 May 2016
Received in revised form 30 June 2016
Accepted 4 July 2016
Available online 7 July 2016

*Keywords:*
Body mass index
Survival
Oropharyngeal squamous cell carcinoma
Human papillomavirus

ABSTRACT

*Background:* Pretreatment body mass index (BMI) >25 kg/m$^2$ is a positive prognostic factor in patients with head and neck cancer. Previous studies have not been adequately stratified by human papilloma virus (HPV) status or subsite. Our objective is to determine prognostic significance of pretreatment BMI on overall survival in HPV+ oropharyngeal squamous cell carcinoma (OPSCC).

*Methods:* This is a retrospective review of patients with HPV+ OPSCC treated between 8/1/2006 and 8/31/2014. Patients were stratified by BMI status (>/<25 kg/m$^2$). Univariate and multivariate analyses of survival were performed.

*Results:* 300 patients met our inclusion/exclusion criteria. Patients with a BMI >25 kg/m$^2$ had a longer overall survival (HR = 0.49, P = 0.01) as well as a longer disease-specific survival (HR = 0.43, P = 0.02). Overall survival remained significantly associated with high BMI on multivariate analysis (HR = 0.54, P = 0.04).

*Conclusions:* Pre-treatment normal or underweight BMI status is associated with worse overall survival in HPV+ OPSCC.



## Introduction

The estimated body mass index (BMI) in the United States has increased drastically over the past several decades with estimates from 2008 suggesting that >60% of adult females and 70% of adult males are overweight (BMI > 25 kg/m$^2$) [1]. In the United States, BMI > 25 kg/m$^2$ is considered overweight, BMI > 30 kg/m$^2$ is considered obese [2]. Higher BMI has been associated with worse overall survival and disease-adjusted life years due to comorbidities such as cardiovascular disease and diabetes. There is an increased risk of a number of cancers in patients having a high BMI including esophageal, breast, colon, gallbladder, uterine and pancreatic cancer. Elevated BMI has also been associated with worsened survival in breast, pancreatic and colon cancers [3,4]. However, pretreatment BMI > 25 kg/m$^2$ has been shown to be a positive prognostic factor for disease-specific and overall survival in patients with head and neck cancer [5–10] and specifically those treated with chemoradiation [6,9,10]. Different hypotheses have been proposed for the mechanism of this association with most positing that patients with higher body mass index have a greater reserve to withstand the demands of radiation therapy and its associated short- and long-term side effects [10]. Other hypotheses include concomitant illness causing weight loss or HPV status (and its known better prognosis) trending toward a higher BMI [11].

Despite these studies being adjusted via multivariable analysis, most are not stratified by disease subsite, and only one previous study has been stratified by human papilloma virus (HPV) status, which limits the interpretability of results. One previous study has shown a lack of association in HPV+ patients with survival; however, this study was limited by its inclusion of oral, pharyngeal and laryngeal subsites in the analysis [12]. In review of the literature, a minority of previous studies have evaluated outcomes by disease subsite and, at odds with other analyses of head and neck cancer, the two which have examined disease subsite found obesity to be a negative prognostic factor for disease specific survival

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http://dx.doi.org/10.1016/j.oraloncology.2016.07.003
1368-8375/

in squamous cell carcinoma of the oral cavity and of no effect in the oropharynx [7,13].

Given that more advanced tumors or those involving the larynx or hypopharynx impair swallowing function, and therefore may lead to weight loss and a lower BMI at presentation, it is important to focus on as narrow of a subgroup as possible to delineate causality from association. Further, in an era of increasing HPV incidence (and better prognosis), patients should be stratified into separate groups by HPV status when examining oropharyngeal squamous cell carcinoma [14]. It is easy to imagine a scenario in which HPV + oropharyngeal squamous cell carcinoma (OPSCC) patients have a higher BMI and better prognosis than HPV− OPSCC patients, potentially leading to a Type II error. In a separate analysis not reported here we found a significant difference in BMI between our HPV+ patients and HPV− OPSCC patients (29.6 kg/m$^2$ and 23.9 kg/m$^2$) (data unpublished). Recent studies have also suggested improved long-term dysphagia in HPV+ patients as compared to HPV− patients after intensity-modulated radiation therapy further suggesting that these groups are different and should be stratified as such [15]. Therefore, our primary objective in this study is to determine whether pretreatment body mass index >25 kg/m$^2$ is of prognostic significance for overall survival in patients with HPV positive OPSCC. Our secondary objective in this study is to determine whether disease-specific mortality is associated with pretreatment body mass index >25 kg/m$^2$.

## Methods

This retrospective review was approved by the University of Pittsburgh Institutional Review Board. Patients were identified through a review of our head and neck SPORE database with inclusion criteria consisting of patients with HPV+ OPSCC treated either surgically or non-surgically at the University of Pittsburgh Medical Center between 8/1/2006 and 8/31/2014. Tumors were considered to be HPV-positive if immunostaining of their tumor was positive for either HPV or p16. All patients had HPV testing by either p16 immunohistochemistry (IHC) or HPV in situ hybridization. IHC for p16 (G175–405; BD Pharmingen, San Diego, California) as a surrogate marker for HPB was performed as per the manufacturer's protocol. Cases were considered positive if >80% of tumor cells showed diffuse strong cytoplasmic and nuclear positivity staining. HPV detection was performed by in situ hybridization using probes targeting a wide spectrum of HPV strains (Y1404; Dako, Carpinteria, California). Cases with punctate nuclear signal were considered positive. The majority of patients had either of the HPV testing modalities as part of the initial diagnostic evaluation. All methods of treatment for HPV+ OPSCC (surgical, chemoradiation, radiation) were included. Patients were excluded for unknown BMI status prior to the initiation of treatment, unknown HPV status, and for less than one year of follow-up. Medical records were queried for pertinent clinical characteristics and outcomes. BMI data was obtained from the medical record, as recorded within one month of the initiation of treatment. Demographic and clinical characteristics including gender, age, race, T-stage, N-stage, alcohol use at diagnosis, smoking history, radiation dose, and primary treatment (either surgery or radiation/chemoradiation) were summarized and tested for association with body mass index (BMI), using Chi-square tests or Fisher's exact test for categorical variables, a *t*-test for age, and the Wilcoxon-Mann-Whitney test for the ordinal stage variables. Patients were stratified by BMI status (>/<25 kg/m$^2$).

Survival curves were generated using the Kaplan-Meier survival method. Hazard ratios for overall survival and disease specific survival were calculated for BMI status in multivariate Cox proportional hazards models. Other factors adjusted for in the models included gender, age, race, T-stage (specifically T4), N-stage (specifically N2c/N3), alcohol history, and tobacco use history. Factors were selected for inclusion in the multivariate models if they were considered clinically significant or demonstrated univariate associations with both survival and BMI status. Results were based on 2-tailed tests and were considered significant when $P < 0.05$. Analyses were performed in SAS 9.4 (SAS Institute, Cary NC) and in R version 3.1.1.

## Results

Based on our initial search criteria of OPSCC with at least 1 year of follow-up 579 patients were initially identified. 139 patients were excluded for unknown HPV status and 78 were excluded for HPV negative status. 62 patients were excluded for unknown BMI status at the time of diagnosis leaving 300 patients that met our inclusion criteria (Table 1). The mean age at time of diagnosis was 57 years with the predominance of these patients being male (253/300, 84.3%). 250/296 (84.5%) of the patients were T1/T2 at presentation but most (155/297, 52.2%) had advanced N-stage at presentation (N2b or greater). The most common oropharyngeal subsite was the tonsil. Most patients (198/297, 66.7%) were current or former tobacco users. In this cohort, most were treated primarily with a combination of radiation +/− chemotherapy (182/300, 60.7%) with the remainder undergoing primary surgical therapy. Of the surgical therapy group, 77/118 patients (65.3%) had some form of adjuvant radiation therapy >5000 cGy.

Of the 300 patients that met our inclusion criteria, 4 (1.3%) were underweight (BMI $\leqslant$ 18.5 kg/m$^2$), 48 (16.0%) were normal weight (18.5 kg/m$^2$ < BMI < 25 kg/m$^2$), 122 (40.7%) were overweight (25 kg/m$^2$ < BMI < 30 kg/m$^2$) and 126 (42.0%) were obese (BMI > 30 kg/m$^2$). The mean BMI at diagnosis was 29.6 kg/m$^2$. When comparing patients stratified by BMI >/<25 kg/m$^2$, patients who were <25 kg/m$^2$ were treated with higher doses of radiation (6890 cGy vs. 6672 cGy, P = 0.048), were more likely to be current tobacco users (44% vs. 26%, P = 0.04) and were more likely to be treated primarily with chemo/radiation (73% vs. 58%, P = 0.04). There was no difference in proportion of T4 tumors (7.7% vs. 7.0%, P = 0.853) or N2c/N3 nodal disease (15.7% vs. 13.4%, P = 0.669) between the two groups. Otherwise, there were no differences in baseline characteristics between these two groups (Table 1). There was no difference in local, regional or distant recurrence rates between the two groups although there was a trend toward more distant metastasis among patients with BMI < 25 kg/m$^2$ (13.5% vs. 6.1%, P = 0.08). In a univariate analysis, overall survival was significantly longer in the BMI > 25 kg/m$^2$ cohort with a hazard ratio (HR) = 0.49 (95% confidence interval (95% CI) 0.28–0.87), P = 0.01 (Fig. 1). Disease-specific survival was also significantly longer in the BMI > 25 kg/m$^2$ cohort with a HR 0.43 (95% CI 0.21–0.89), P = 0.02 (Fig. 2). The association between BMI status and overall survival remained statistically significant in multivariate analysis (HR 0.54 (95% CI 0.30–0.98), P = 0.04) (Table 2) however disease-specific survival did not reach statistical significance (see Table 3). Radiation dose, among subjects who received radiation therapy, was not associated with survival and therefore was not included in the final Cox proportional hazards model (P = 0.18). Primary treatment (either surgery or chemo/radiation) was also not found to be associated with survival and was not included in the final Cox model (P = 0.53).

## Discussion

This study demonstrates that patient body mass index >25 kg/m$^2$ is an independent positive prognostic indicator for overall survival in HPV-positive oropharyngeal squamous cell carcinoma.