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Marital status as a predictor of survival in patients with human papilloma virus-positive oropharyngeal cancer☆,☆☆,★

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ABSTRACT

Purpose: Determine whether marital status is a significant predictor of survival in human papillomavirus-positive oropharyngeal cancer.
Materials and methods: A single center retrospective study included patients diagnosed with human papilloma virus-positive oropharyngeal cancer at Boston Medical Center between January 1, 2010 and December 30, 2015, and initiated treatment with curative intent at Boston Medical Center. Demographic data and tumor-related variables were recorded. Univariate analysis was performed using a two-sample *t*-test, chi-squared test, Fisher's exact test, and Kaplan Meier curves with a log rank test. Multivariate survival analysis was performed using a Cox regression model.
Results: A total of 65 patients were included in the study with 24 patients described as married and 41 patients described as single. There was no significant difference in most demographic variables or tumor related variables between the two study groups, except single patients were significantly more likely to have government insurance ($p = 0.0431$). Furthermore, there was no significant difference in 3-year overall survival between married patients and single patients (married = 91.67% vs single = 87.80%; $p = 0.6532$) or 3-year progression free survival (married = 79.17% vs single = 85.37%; $p = 0.8136$). After adjusting for confounders including age, sex, race, insurance type, smoking status, treatment, and AJCC combined pathologic stage, marital status was not a significant predictor of survival [HR = 0.903; 95% CI (0.126,6.489); $p = 0.9192$].
Conclusions: Although previous literature has demonstrated that married patients with head and neck cancer have a survival benefit compared to single patients with head and neck cancer, we were unable to demonstrate the same survival benefit in a cohort of patients with human papilloma virus-positive oropharyngeal cancer.
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1. Introduction

The overall incidence of oropharyngeal cancer (OPSCC) in the United States has not significantly changed between 1974 and 1999; however, there has been a relative increase in OPSCC incidence compared to other head and neck cancers during the same time period [1]. A likely cause of the relative increase in OPSCC is because of the significant increase in human papilloma virus-positive (HPV+) OPSCC, a sexually transmitted disease, and corresponding decrease in HPV− OPSCC, with up to 70% of newly diagnosed cases of OPSCC attributed to HPV [2,3]. In addition to the increase in incidence of HPV+ OPSCC, it is crucial to note that there are significant differences in risk factors [4–9], prognosis [9–15], and demographic and pathologic features that are predictive of survival in HPV+ OPSCC compared to HPV- OPSCC [12,15–20].

Some of the common risk factors described for HPV+ OPSCC include number of sexual partners and number of partners for oral sex in comparison to the more traditional risk factors described for HPV− OPSCC including smoking and EtOH [2,4,5,7,8,21]. Therefore, a diagnosis of HPV+ OPSCC can be considered both an oncologic and psychosocial diagnosis. Multiple studies have looked at the psychological impact of receiving a diagnoses of HPV+ OPSCC, and more specifically, Milbury et al. described that approximately 20% of patients reported that the HPV+ diagnosis resulted in a negative impact on their relationship, describing reduced trust in the relationship, problems with intimacy,

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reduced sexual contact, and concerns regarding infidelity [22]. Furthermore, D'Souza et al. interviewed patients receiving treatment for HPV + OPSCC and determined that 5% of patients reported tension with their partners after discussing the HPV status of their tumor [23].

Patients that are diagnosed with HPV + OPSCC are significantly more likely to be married than patients diagnosed with HPV − OPSCC [7], and previous literature has described marital status as a predictor of improved overall survival and earlier stage at diagnosis in both head and neck cancer [24–28], and in HPV + cervical cancer [29]. However, there is currently no literature looking at whether marital status is a predictor of survival in patients with HPV + OPSCC. As such, we sought to evaluate whether marital status was a significant predictor of survival for patients diagnosed with HPV + OPSCC at a single institution between 2010 and 2015.

2. Methods

2.1. Study cohort

Institutional IRB approval was obtained at Boston University Medical Center (BUMC) and determined to be exempt (H-35043). Patients were retrospectively identified for inclusion in the study if they presented with a head and neck tumor and received a diagnostic biopsy with positive $P16^{INK4a}$ immunohistochemistry (IHC) staining between January 1, 2010 and December 30, 2015. Patients were excluded: 1) if the primary site of the cancer was not considered oropharynx, because HPV + cancers in other head and neck sites do not demonstrate the same survival benefit as cancers of the oropharynx [11,30,31]; 2) if they presented with a recurrence of an original tumor diagnosed prior to the study period; 3) if they had distant metastases at the time of diagnosis (M1 disease); 4) if they received a diagnostic panendoscopy at BUMC, but did not receive any treatment at BUMC; 5) if they did not receive treatment with curative intent; and 6) if there was missing data regarding treatment modality for the oropharyngeal cancer.

2.2. HPV testing

We chose to use $P16^{INK4a}$ IHC staining as a surrogate marker for HPV because although testing for HPV DNA is considered the gold standard, using IHC staining for $p16^{INK4a}$ is an established biomarker for HPV-mediated carcinogenesis, and it is inexpensive, nearly universally available, and relatively straightforward to interpret [32], making the results of this study more generalizable. The reported sensitivity and specificity of $P16^{INK4a}$ IHC staining for HPV + OPSCC is 94% and 83%, respectively [33]. $P16^{INK4a}$ IHC staining was performed on paraffin embedded surgical specimens.

2.3. Study outcomes and variables

The primary endpoint of the study was 3-year overall survival (OS) with an endpoint of death, while the secondary endpoint was 3-year progression free survival (PFS) with an endpoint of death, or recurrence during the follow-up period. The main predictor variable in the study was marital status, which was defined as married or single (never married, divorced, or widowed). Other variables included in the study were age at date of diagnosis; sex; race defined as white or other; health insurance defined as private insurance or government insurance (Medicare, Medicaid, other government insurances); smoking status defined as "light/never smoker," which included anyone that had less than a 10 pack year smoking history, and "smoker," which included anyone with a 10 pack year smoking history or greater; primary site defined as tonsil or base of tongue (BOT); tumor size according to greatest pathologic dimension; combined pathologic stage according to the AJCC cancer staging manual 7th edition, with stage 1 and 2 described as "early stage" and stage 3 and 4 described as "late stage," combined clinical stage based on the AJCC cancer staging manual 7th edition was used wherever pathologic stage was missing; treatment modality described surgery +/− adjuvant therapy or non-surgical therapy (non-surgical therapy is defined as radiation therapy, chemotherapy, or chemoradiation); positive or negative surgical margin status, and the presence of absence of extracapsular extension, perineural invasion, and lymphovascular invasion.

2.4. Statistical analysis

Univariate analysis to determine whether there was an association between variables was performed using a two-sample *t*-test for continuous variables and a chi squared test ($n > 5$) or Fisher's exact test ($n \leq 5$) for categorical variables. Univariate survival analysis comparing married and single patients was performed using Kaplan-Meier curves with the log-rank test. Multivariate survival analysis was performed using Cox-Regression Models and included variables that were clinically relevant to patient prognosis. The proportional hazards assumption was tested by including time varying effects in the model. Pathologic features such as extracapsular extension, perineural invasion, margin status, and lymphovascular invasion were not adjusted for in the multivariate model because these features are not considered high risk features in HPV + OPSCC [12,18,20], and >40% of patients were missing this data. Significance was determined at an alpha level less than or equal to 0.05. Statistical analysis was performed using SAS version 9.3 (Cary, NC).

3. Results

A total of 65 patients were included in this study, with 24 patients described as married and 41 patients described as single [single ($n = 22$), divorced ($n = 18$), and widow ($n = 1$)]. The average age at diagnosis for married patients was 62.59 ± 10.04 years compared to 60.57 ± 7.84 for single patients with no significant difference in age between groups ($p = 0.3689$) (Table 1). The majority of the patients included in this study were male (80.00%) and white race (69.23%), with no significant difference by gender or race between married and single patients ($p = 1.000$, $p = 0.4407$, respectively). Married patients were more likely to have private insurance compared to single patients (62.50% vs 36.57%); with a significant difference between the two groups ($p = 0.0431$).

69.23% of patients presented with tonsillar cancer, while the remainder of patients presented with cancer of the base of tongue, with no significant difference in cancer subsite between married and single patients ($p = 0.7318$) (Table 1). Focusing on extent of disease, the average tumor size, based on greatest dimension was 3.13 ± 1.11 cm for married patients compared to 3.15 ± 1.10 cm for single patients ($p = 0.9381$), with 95.39% of tumors described as unilateral and 4.61% of cancers described as bilateral. Additionally, there was no significant difference in tumor grade ($p = 0.5744$), or AJCC combined staging ($p = 0.1889$) at presentation between married and single patients. 89.23% of patients included in the study presented with late stage disease (combined stage 3 and stage 4).

A majority of patients received surgery +/− adjuvant therapy compared to those patients receiving non-surgical therapy (55.38% vs 44.62%); however, there was no significant difference in treatment between married and single patients ($p = 0.8799$). Additionally, there was no significant difference regarding whether patients received a neck dissection ($p = 0.8184$), margin status ($p = 1.000$), presence of extracapsular extension ($p = 0.0656$), presence of perineural invasion ($p = 0.0592$), or lymphovascular invasion ($p = 0.6479$).

The median follow up time of patients in the study was 23.16 months with a median follow up of 22.80 months for married patients and 24.08 months for single patients. There were 7 deaths within the total study population during the study period. Univariate survival analysis revealed that there was no significant difference in 3-year overall survival (married = 91.67% vs single = 87.80%; $p = 0.6532$) or progression

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