Characteristics and outcomes associated with anxiety and depression in a head and neck cancer survivorship cohort☆

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ABSTRACT

Purpose: To assess the prevalence and predictors of mental health disorders (MDHs) among head and neck squamous cell carcinoma (HNSCC) survivors, and the association with health-related quality of life (HRQOL), pain, and survival outcomes.
Materials and methods: This was a retrospective, cross-sectional study of HNSCC survivors surveyed at an outpatient oncology clinic from May 2012 through July 2016.
Results: Among 198 HNSCC survivors, 21% reported a MHD. Female sex (OR 6.60, 95% CI 2.08 to 20.98; $p = 0.001$) and Medicare insurance status (OR 4.95, 95% CI 1.52 to 16.11; $p = 0.008$) were significant predictors of reporting a MHD in the fully adjusted model. Patients reporting a MHD reported significantly worse pain ($p < 0001$) and worse HRQOL on the PROMIS Physical ($p < 0.001$), PROMIS Mental ($p < 0.001$), and FACT-GP ($p < 0.026$) questionnaires. Diagnosis of a MHD was not correlated with 5-year OS (74% vs. 84%; $p = 0.087$).
Conclusion: Initiatives for early identification and intervention of MHDs as part of survivorship initiatives may engender clinically meaningful outcomes in head and neck cancer.

1. Introduction

Cancer survivorship is a broad term that encompasses a patient's journey from cancer diagnosis to the end of life [1]. It includes all of the "medical, psychosocial, interpersonal, financial, and functional consequences" of cancer, even beyond the period of treatment and active surveillance [1]. The lifelong and multifaceted nature of cancer survivorship has garnered much attention in recent years, and it has important implications for patient quality of life [2]. This is especially relevant for patients with head and neck cancer, as both the natural history and treatment of head and neck cancer can drastically alter how patients view themselves, interact with others, and function in society.

The American Head and Neck Society (ANHS) issued a 2021 consensus statement describing the best practices and evidence regarding cancer survivorship [3]. Among these was a recommendation to screen for depression and anxiety at regular intervals and refer to mental health services as appropriate. There is evidence to suggest that the risk of depression and suicide is higher in head and neck cancer survivors than other types of cancer and the general population [4–7]. Despite this, there are limited data describing the influence of mental health disorders (MHDs) on patient-reported outcomes, morbidity, and mortality in head and neck cancer.

We employed a cross-sectional cohort across the spectrum of head and neck cancer survivorship to examine (1) the prevalence and predictors of MHDs; and (2) the association of MHD with health-related quality of life (HRQOL), pain, and survival.

2. Materials and methods

This study was approved by the Institutional Review Board at the

University of North Carolina at Chapel Hill. This study was a secondary data analysis using the University of North Carolina Health Registry/Cancer Survivorship Cohort (HR/CSC). All subjects provided written informed consent to participate in the UNC HR/CSC and use of this resource for future research.

2.1. Study design and sample

This was a cross-sectional study of patients with head and neck squamous cell carcinoma (HNSCC) identified through the UNC HR/CSC. The UNC HR/CSC is a cohort of patients who presented to UNC oncology outpatient clinics at the North Carolina Cancer Hospital between May 2012 through July 2016 [8]. Patients were eligible to participate in the UNC HR/CSC if they were at least 18 years of age and had English or Spanish language proficiency. Patients meeting eligibility criteria were approached by research staff in UNC oncology outpatient clinics, and upon informed consent, were enrolled. The HR/CSC database was queried for patients with a pathologically confirmed diagnosis of HNSCC ($n = 202$). Patients were excluded from this analysis if they were missing data on the primary exposure ($n = 4$). Of eligible HNSCC patients approached in clinic for enrollment, 64% consented to participate.

2.2. Questionnaires and data extraction

Information on demographics, socioeconomic status, and medical history was obtained via a baseline questionnaire. Upon enrollment, patients completed the study questionnaire through an interviewer-administered computer-assisted telephone interview. For the purpose of this study, mental health disorder (MHD) was defined as positive patient response to "have you ever been told by a doctor or other health care professional that you have Depression or Anxiety."

Clinical and oncologic data were abstracted from patient medical records. HRQOL outcomes were measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) [9] questionnaire and the Functional Assessment of Cancer Therapy-General Population (FACT-GP) questionnaire [10], which is further divided into physical, social, emotional, and functional domains. Pain was measured by patient response to the question "In the past 7 days how would you rate your pain on average," with "0" being no pain and "10" being worst imaginable pain.

2.3. Statistical analysis

All variables were examined for missing observations and excluded a priori if >10% of observations were missing; this did not apply to any of the variables. We used descriptive statistics to examine sociodemographic and clinical characteristics of patients with and without a MHD. Bivariate testing methods included two-sided t-tests, Chi-square tests, and Fisher's exact test (for expected observations<5).

We next used univariable and multivariable logistic regression models to estimate significant predictors of reporting a MHD. Multicollinearity was assessed using variance inflation factor (VIF) testing. Number of treatment modalities was omitted from the adjusted models due to collinearity with treatment types. We used simple and multiple linear regression models to examine the relationship of reporting a MHD with HRQOL and pain scores. For the PROMIS scales, we used T scores normalized to population means. The multivariable logistic regression and multiple linear regression models both adjusted for age, sex, race, marital status, education, insurance status, employment status, distance to hospital, history of tobacco use, history of alcohol use, tumor site, overall stage, and treatment type.

We next constructed Kaplan-Meier curves to assess 5-year overall (OS) and cancer specific survival (CSS) in patients with and without a MHD. We used the log-rank test to compare the survival curves and obtain p-values. Updates on patient vital status were provided monthly up until October 1st, 2020 by the North Carolina Department of Health

and Human Services. Vital status and cause of death was known for all subjects at 5 years of follow-up or censoring from initial diagnosis. We performed a sensitivity analysis limited to patients who completed the study questionnaires at least 6 months after their cancer diagnosis (Appendix A). The purpose of the sensitivity analysis was to assess if the associations between MDH and HRQOL persisted in a population farther along in the survivorship trajectory and to minimize the potential effects of unmeasured confounders in the peri-treatment period.

Finally, we performed a power analysis for our primary outcome variables (Appendix B). At an alpha of 0.05 and power of 0.8, our sample was adequately powered to detect differences in the PROMIS Physical and Mental scales, pain scale, FACT GP Emotional scale, and 5-year OS. We used a statistical significance criterion of $p < 0.05$ for all testing. We used Stata 16.0 (StataCorp LP, College Station, TX) for all analyses.

3. Results

3.1. Baseline characteristics correlated with having a mental health disorder

Our final sample consisted of 198 patients with a pathologically confirmed diagnosis of HNSCC. On average, patients completed the study questionnaires 13.6 months (range 6 days to 255 months) after their cancer diagnosis.

The mean follow-up was 5.5 years (SD 2.30) after initial diagnosis, and the median follow-up was 5.2 years (IQR 4.5 to 6.7). The average age was 60 years (SD 10.0). The majority were male (82%) and white (88%), and 70% had advance stage disease (AJCC 7th III/IV) [11].

In this sample, 34 (17%) patients reported a diagnosis of anxiety, 29 (15%) reported a diagnosis of depression, and 42 (21%) reported a diagnosis of either anxiety or depression. Baseline characteristics in patients with and without a MHD were examined (Table 1). Patients reporting a MHD were more likely to be female (36% vs. 13%; $p = 0.001$), not married (43% vs. 27%; 0.045), and have Medicare insurance (48% vs. 27%; $p = 0.013$). There was no significant difference in cancer stage ($p = 0.790$), treatment type ($p = 0.327$), or number of treatment modalities ($p = 0.282$) among patients with and without a MHD.

Sociodemographic and clinical predictors of reporting a MHD were examined using univariate and multiple variable logistic regression models (Table 2). In the fully adjusted model, female sex (OR 6.60, 95% CI 2.08 to 20.98; $p = 0.001$) and Medicare insurance status (OR 4.95, 95% CI 1.52 to 16.11; $p = 0.008$) remained statistically significant correlations.

3.2. Health-related quality of life and pain outcomes

In the unadjusted model, patients reporting a MHD had significantly worse HRQOL on both general (PROMIS) and cancer-specific (FACT-GP) quality of life scales (Table 3). Specifically, patients reporting a MHD had worse physical [mean difference (MD) = −5.3, 95% CI −8.2 to −2.3; $p < 0.001$] and mental (MD = −7.0, 95% CI −9.9 to −4.1; $p < 0.001$) HRQOL on the PROMIS scales. On the FACT-GP scale, patients reporting a MHD had significantly worse physical (MD = −2.4, 95% CI −4.1 to −0.7; $p = 0.005$) and emotional (MD = −3.5, 95% CI −5.0 to −2.0; $p < 0.001$) HRQOL scores. Patients with a MHD also reported significantly worse pain in the past 7 days (MD = 1.7, 95% CI 0.8 to 2.6; $p < 0.001$). These associations persisted in the adjusted model (Table 3).

3.3. Relationship between mental health disorders and survival

Five-year OS was approximately 10% lower among patients reporting a MHD, but this difference did not reach statistical significance (74% vs. 84%; $p = 0.087$). There was no difference in 5-year CSS in patients with and without a MHD (82% vs. 86%; $p = 0.565$). Kaplan Meier curves for 5-year OS and 5-year CSS were constructed to display these relationships (Figs. 1 and 2).

Table 1
Baseline characteristics in patients with and without depression or anxiety.

	Patients with depression or anxiety (n = 42)	Patients without depression or anxiety (n = 156)	p-value
Age (mean, SD)	61.6 (9.0)	59.3 (10.3)	0.191
Sex			**0.001**
Male	27 (64.3)	136 (87.2)	
Female	15 (35.7)	20 (12.8)	
Race			0.961
White	37 (88.1)	137 (87.8)	
Non-white	5 (11.9)	19 (12.2)	
Marital status			**0.045**
Married	24 (57.1)	112 (73.2)	
Not married	18 (42.9)	41 (26.8)	
Education			0.713
High school or less	28 (66.7)	92 (60.5)	
College graduate	9 (21.4)	35 (23.0)	
Post-graduate/ professional degree	5 (11.9)	25 (16.5)	
Insurance Status			**0.013**
Private	17 (40.5)	96 (61.5)	
None	0 (0.0)	8 (5.1)	
Medicare	20 (47.6)	42 (26.9)	
Medicaid	5 (11.9)	10 (6.4)	
Currently work for pay	17 (40.5)	77 (50.3)	0.258
Distance to hospital (mean in miles)	67.9 (75.2)	70.7 (58.7)	0.812
History of any tobacco use	26 (65.0)	95 (61.7)	0.700
History of any alcohol use	20 (47.6)	79 (50.6)	0.728
Tumor site			0.400
Oral cavity	19 (45.2)	51 (32.7)	
Oropharynx	18 (42.9)	78 (50.0)	
Hypopharynx	0 (0.0)	6 (3.9)	
Larynx	4 (9.5)	13 (8.3)	
Other	1 (2.4)	8 (5.1)	
Overall Stage (AJCC 7th edition)			0.790
Early (I/II)	11 (28.2)	45 (30.4)	
Advanced (III/IV)	28 (71.8)	103 (28.2)	
Treatment			0.327
Surgery alone	12 (28.6)	43 (27.7)	
Surgery + aRT	5 (11.9)	20 (12.9)	
Surgery + aCRT	13 (31.0)	34 (21.9)	
RT or Chemotherapy alone	5 (11.9)	11 (7.1)	
Chemoradiation therapy	7 (16.7)	47 (30.3)	
Number of Treatment Modalities			0.282
1	17 (40.5)	53 (34.0)	
2	12 (28.6)	67 (43.0)	
3	13 (31.0)	34 (21.8)	

3.4. Sensitivity analysis

In a sensitivity analysis limited to patients completing the questionnaires at least 6 months after cancer diagnosis (n = 80), the prevalence of a MHD was 21%, and female sex was associated with reporting a MHD (p = 0.016) (Appendix A).

The statistically significant associations between MHD and worse HRQOL and pain persisted in the unadjusted analysis (PROMIS Physical, p = 0.007; PROMIS Mental, p = 0.001; FACT GP Physical, p < 0.001; FACT GP Emotional, p = 0.011; pain, p < 0.001). However, in the fully adjusted model, only PROMIS Mental (p = 0.020) and FACT GP Emotional (p = 0.022) remained significant (Appendix A).

There remained no significant association between MHD and 5-year OS (82% vs. 86%; p = 0.744) or 5-year CSS (82 vs. 87%; p = 0.618) in the sensitivity analysis (Appendix A).

Table 2
Examining predictors of anxiety or depression among head and neck cancer survivors using univariate and multivariable logistic regression models.

Variable	Unadjusted		Adjusted[a]	
	OR and 95% CI	p-value	OR and 95% CI	p-value
Age > 60 years (vs. </=60 years)	0.71 (0.36 to 1.42)	0.334	1.62 (0.52 to 5.02)	0.404
Female sex	3.78 (1.72 to 8.30)	**0.001**	6.60 (2.08 to 20.98)	**0.001**
Non-white race (vs. white)	0.97 (0.34 to 2.78)	0.961	0.85 (0.19 to 3.83)	0.832
Not married (vs. married)	2.05 (1.01 to 4.16)	**0.049**	1.78 (0.67 to 4.77)	0.249
Education (vs. high school or less)				
College graduate	0.84 (0.36 to 1.97)	0.696	0.87 (0.28 to 2.66)	0.803
Post-graduate/ professional degree	0.66 (0.23 to 1.88)	0.433	0.72 (0.16 to 3.16)	0.664
Insurance (vs. private)				
Medicare	2.69 (1.28 to 5.64)	**0.009**	4.95 (1.52 to 16.11)	**0.008**
Medicaid	2.82 (0.89 to 9.29)	0.088	1.55 (0.21 to 11.64)	0.668
Currently work for pay	0.67 (0.34 to 1.34)	0.259	0.96 (0.34 to 2.70)	0.942
Distance to hospital above median (>52 miles)	0.79 (0.38 to 1.64)	0.527	0.81 (0.32 to 2.07)	0.665
History of any tobacco use	1.15 (0.56 to 2.38)	0.700	0.97 (0.35 to 2.70)	0.960
History of any alcohol use	0.89 (0.48 to 1.75)	0.728	1.72 (0.65 to 4.55)	0.278
Tumor site (relative to oral cavity)				
Oropharynx	0.62 (0.30 to 1.29)	0.202	0.80 (0.23 to 2.76)	0.726
Larynx	0.83 (0.24 to 2.85)	0.762	0.40 (0.05 to 3.41)	0.399
Other	0.34 (0.04 to 2.86)	0.318	0.26 (0.02 to 2.96)	0.280
Advanced Stage (vs. Early)	1.11 (0.51 to 2.43)	0.790	1.64 (0.50 to 5.31)	0.412
Treatment (vs. Surgery alone)				
Surgery + aRT	0.90 (0.28 to 2.89)	0.854	1.37 (0.30 to 6.36)	0.687
Surgery + aCRT	1.37 (0.55 to 3.38)	0.495	1.69 (0.43 to 6.62)	0.448
RT or Chemotherapy alone	1.63 (0.47 to 5.60)	0.439	2.02 (0.33 to 12.20)	0.443
Chemoradiation therapy	0.53 (0.19 to 1.48)	0.227	0.50 (0.09 to 2.76)	0.424
Number of Treatment Modalities (relative to 1)			Omitted due to multicollinearity	
2		0.165		

Table 2 (*continued*)

Variable	Unadjusted		Adjusted[a]	
	OR and 95% CI	p-value	OR and 95% CI	p-value
3	0.56 (0.25 to 1.27) 1.19 (0.51 to 2.76)	0.682		

[a] Adjusted for age, sex, race, marital status, education, insurance status, employment status, distance to hospital, history of tobacco use, history of alcohol use, tumor site, overall stage, and treatment type.

4. Discussion

The prevalence of MHDs was 21% within a cohort of head and neck cancer patients across the survivorship spectrum. Female sex and Medicare insurance were significantly associated with reporting a MHD. Furthermore, reporting a MHD was associated with worse HRQOL and pain. Overall, the results of this study highlight the importance of identifying and treating MHDs in head and neck cancer survivors.

The observed prevalence of MHDs is similar to that reported in other population- and institutional-based HNSCC studies, with most estimates ranging from 20 to 30% [4,12–14]. Our finding that female sex was associated with MHDs is also supported by larger population-based studies, with one study reporting an approximately 1.5 times increased risk of MHDs in females with head and neck cancer [12]. Another study reported an increased risk of body image disturbance among females with head and neck cancer [15], which has also been linked to depression [16]. Despite these findings, recent literature suggests that the apparent increased risk of MDH in females is biased by current diagnostic tools which fail to capture symptoms of depression that are more specific to men, as well as gender-role socialization which may lead to reduced reporting of and help-seeking for MDH among men [17–21]. An understanding of this context is especially important for HNSCC where the majority of patients are male. Providers should be aware of the broad manifestations of MDH such as irritability, impulsivity, somatic symptoms, aggression, and substance use.

We report a novel association between Medicare insurance status and MHDs in head and neck cancer. It is possible that Medicare insurance status in this study is a proxy for older age and/or social isolation, which are known risk factors for depression [22,23]. Alternatively, there may be a component of selection bias as Medicare provides coverage for mental health services whereas other types of insurance may not. Providers caring for head and neck cancer survivors should be aware of the increased risk of MHDs in these populations, although it is important to recognize that Medicare insurance is likely a surrogate for underlying sociodemographic factors.

Other studies have shown that MHDs and pain are associated with functional impairment [24], poor quality of life [25,26], and prolonged opioid use in head and neck cancer [27]. Although no statistically significant association was found between MHDs and survival in our study,
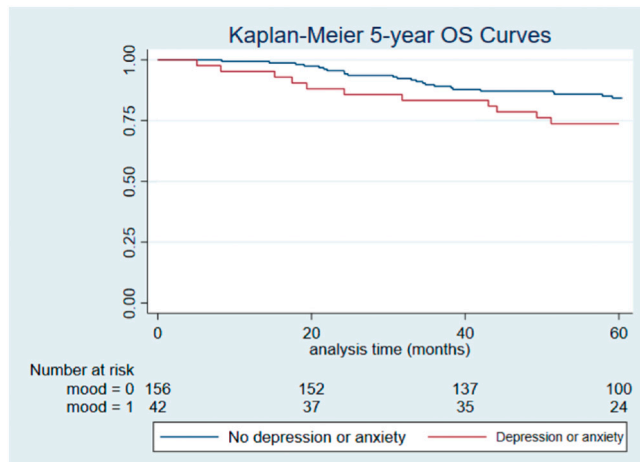

Fig. 1. Kaplan Meier Curves for 5-year OS.
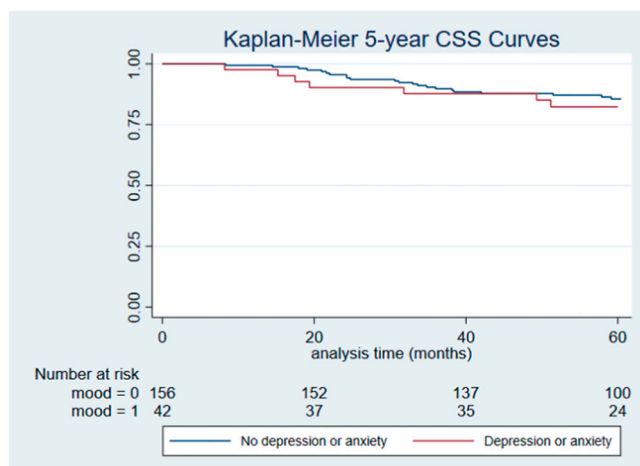
Fig. 2. Kaplan Meier Curves for 5-year CSS.

Table 3
Relationship between Anxiety or Depression with HRQOL and Pain Outcomes.

Survey	Patients with anxiety or depression mean (SD)	Patients without anxiety or depression mean (SD)	Mean difference (95% CI), Unadjusted	p-value	Mean difference (95% CI), Adjusted[a]	p-value
FACT GP Total	76.9 (20.1)	83.2 (15.0)	−6.3 (−11.9 to −0.8)	**0.026**	−8.0 (−14.1 to −1.9)	**0.011**
FACT GP Physical	20.9 (6.5)	23.3 (4.4)	−2.4 (−4.1 to −0.7)	**0.005**	−3.0 (−4.9 to −1.1)	**0.003**
FACT GP Social	21.8 (4.6)	20.9 (5.8)	0.8 (−1.1 to 2.8)	0.382	1.3 (−0.8 to 3.3)	0.224
FACT GP Emotional	16.8 (6.5)	20.3 (3.6)	−3.5 (−5.0 to −2.0)	**<0.001**	−3.6 (−5.4 to −1.7)	**<0.001**
FACT GP Functional	17.4 (7.1)	18.7 (7.2)	−1.3 (−3.8 to 1.2)	0.303	−2.7 (−5.5 to 0.1)	0.056
PROMIS Physical	44.3 (8.4)	49.5 (8.8)	−5.3 (−8.2 to −2.3)	**<0.001**	−4.9 (−8.3 to −1.5)	**0.005**
PROMIS Mental	47.1 (8.9)	54.1 (8.2)	−7.0 (−9.9 to −4.1)	**<0.001**	−6.6 (−9.8 to −3.3)	**<0.001**
Pain in past 7 days	4.4 (2.8)	2.7 (2.7)	1.7 (0.8 to 2.6)	**<0.001**	1.5 (0.4 to 2.6)	**0.007**

[a] Adjusted for age, sex, race, marital status, education, insurance status, employment status, distance to hospital, history of tobacco use, history of alcohol use, tumor site, overall stage, and treatment type.

a recent meta-analysis of seven studies [28–34] found that head and neck cancer patients with pre-treatment depression or depressive symptoms had significantly worse overall survival in the pooled analysis (HR 1.33, 95% CI 1.16 to 1.52; $p < 0.001$) [35]. Another study reported a nearly two-fold increased risk of suicide among head and neck cancer survivors compared to patients with other types of cancer [6].

Taken together, these findings underscore the importance of early identification and treatment of MHDs in head and neck cancer survivors. Despite the prevalence and associated morbidity of MHDs in this population, only a fraction of patients with MHDs report using antidepressants or seeking psychotherapy [29]. Solutions to this problem may include implementation of screening paradigms for depression or anxiety, establishing appropriate referral pathways to behavioral health services, and incorporation of psychosocial services into a multidisciplinary survivorship clinic. In one survey of head and neck cancer survivors, 66.7% stated that they would be "more likely to follow up with psychiatric services integrated within the HNC team than if referred to an outside behavioral health clinic." [36] Integrated psychiatric services would help decrease the stigma of mental health treatment and reduce the number of patient visits needed.

Given that this study relied on voluntary participation from patients at a single outpatient oncology clinic, there is potential for selection bias. Patients who were approached in clinic but declined to participate were disproportionately older ($p = 0.007$) and had more advanced cancer stage ($p = 0.002$) than the patients who provided consent. This study was also limited by the initial survey design which relied on patient-reported diagnosis of MHDs rather than validated diagnostic tools or established/confirmed diagnoses. Additionally, it is important to recognize that there are many MHDs other than anxiety and depression that were not measured or reported. Our findings likely underestimate the true burden of MHDs in the head and neck survivor population, especially among men. Finally, our study lacked sufficient statistical power for some of the quantitative outcomes as well as the sensitivity analysis (Appendix B). However, we include these findings for context and to help guide future research.

5. Conclusions

MHDs disproportionately affect head and neck cancer survivors and are associated with worse pain and HRQOL outcomes. Among head and neck cancer survivors, females and patients with Medicare are more likely to report MHD. Early identification and management of MHDs in head and neck cancer survivors has the potential to reduce pain and improve quality of life.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjoto.2022.103442.

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