



Evaluating Quality of Life and Psychosocial Outcomes in HPV-Associated Head and Neck Cancer Survivors

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Abstract

Human Papillomavirus (HPV) -positive Oropharyngeal Squamous Cell Carcinoma (OPSCC) has been increasing in incidence for the past three decades. However, long-term effects of disease and treatment on Quality of Life (QOL) and psychosocial outcomes in the HPV-associated OPSCC population specifically are limited. Understanding the patient-specific factors that lead to changes in post-treatment QOL and psychosocial outcomes of anxiety, depression, and body image disturbance is of utmost importance to support cancer survivorship. This study also sought to define important functional changes and psychosocial outcomes in the HPV-associated OPSCC population to aid in guiding future research into connecting patients with therapeutic resources as part of patient-specific survivorship care plans.

Keywords: Human papillomavirus; Oropharyngeal squamous cell carcinoma; Head and neck cancer; Quality of life

Introduction

Human Papillomavirus (HPV) -positive Oropharyngeal Squamous Cell Carcinoma (OPSCC) has been increasing in incidence for the past three decades [1]. HPV-positive or HPV-associated OPSCC is associated with a younger demographic and studies show 5-year survival rates of 90% [2]. With more favourable outcomes and longer post-treatment survival, these survivors face disease and treatment associated challenges that will require the attention of multidisciplinary care teams.

Patients diagnosed and treated for Head and Neck Cancer (HNC) undergo a range of functional and cosmetic changes that significantly alter physical, functional and emotional well-being. Of all cancer survivors, HNC survivors are among the most likely to suffer from QOL alterations and psychosocial distress [3-9]. There is evidence of significant unmet needs affecting QOL in HNC patients [10], with studies showing up to 68% of post-treatment patients reporting at least one unmet need for which they wanted help [11]. However, long-term effects of disease and treatment on Quality of Life (QOL) and psychosocial outcomes in the HPV-associated OPSCC population specifically are limited. Understanding the patient-specific factors that lead to changes in post-treatment QOL and psychosocial outcomes of anxiety, depression, and body image disturbance is of utmost importance to support cancer survivorship.

To help better address these unmet needs, this cross-sectional, observational pilot study sought to survey patients who have undergone treatment for HPV-associated OPSCC to examine relationships between patient demographic and clinical factors with QOL and psychosocial outcomes, particularly anxiety, depression, and body image disturbance. This study also sought to define important functional changes and psychosocial outcomes in the HPV-associated OPSCC population to aid in guiding future research into connecting patients with therapeutic resources as part of patient-specific survivorship care plans.

Materials and Methods

A preliminary screening using the electronic medical record was performed to identify a total of 95 patients who had completed treatment, including surgery with or without adjuvant therapy, radiation, and chemotherapy with radiation, for documented primary or recurrent HPV-associated OPSCC from a single institution, the Sylvester Comprehensive Cancer Center – Head and Neck

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Received Date: 16 Aug 2022

Accepted Date: 07 Sep 2022

Published Date: 12 Sep 2022

Citation:

Mei C, Hartlein T, Thielhelm T, Lugo-Fagundo M, Nisenbaum E, Landera M, et al. Evaluating Quality of Life and Psychosocial Outcomes in HPV-Associated Head and Neck Cancer Survivors. *Am J Otolaryngol Head Neck Surg.* 2022; 5(8): 1206.

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Cancer Clinic. Patients who met the inclusion criteria were consented for study participation using a University of Miami Institutional Review Board-approved protocol (IRB# 20190128). The inclusion criteria consisted of patients who had been treated for HPV-associated OPSCC cancer, who were 18 years or older, who spoke or read in English or Spanish, and were able to understand and consent to terms of study participation. Patients who had other types of concurrent cancer or those receiving treatment for another cancer were excluded from the study. Demographics, comorbidities, cancer characteristics, and treatment modalities were gathered through retrospective chart review. Patients enrolled completed a Patient Demographic form to provide self-identified information such as country of origin, primary language, race/ethnicity, education level, employment status, marital status, smoking, alcohol and illicit drug use, sexually transmitted infection status, and the number of lifetime sexual partners. In addition, they also completed four surveys validated both in English and Spanish: University of Washington-Quality of Life Head and Neck Questionnaire (UW-QoL HNC), Hospital Anxiety and Depression Scale (HADS), Body Image Scale (BIS), and Performance Status Scale for Head and Neck Cancer Patients (PSS-HN).

University of Washington-Quality of Life Head and Neck Questionnaire (UWQoL HNC)

The UW-QoL HNC is a patient-completed assessment that surveys twelve domains related to QoL, including pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder function, taste, saliva, mood, and anxiety over the period of the last 7 days. Each domain is scored from 0 (worst) to 100 (best), with a total composite score of 1,200 [12-14]. The UW-QoL publishes specific criteria for determining whether each domain is considered a significant problem. This tool has been successfully employed in studies assessing post-treatment QoL in HNC patients [15].

Hospital anxiety and depression scale (HADS)

The HADS is a well-validated 14-item scale completed by the patient with 7 items assessing anxiety and 7 items assessing depression. The assessment is scored from 0 (normal) to 21 (severe) for each subscale of anxiety and depression, with a possible total score of 42 [16,17]. Subscale scores of 8 and above indicate a problem in that particular scale, either anxiety or depression. The HADS has been previously correlated with UW-QoL mood and anxiety domain scores in post-treatment HNC patients [18]. Our group has also validated the HADS for HNC patients in the outpatient clinic setting and correlated findings with body image perception [19].

Body image scale (BIS)

The BIS is a 10-item scale that measures patient feelings towards body image changes related to cancer treatment. Each item is measured on a 4-point scale, with 0 indicating "Not at all" and 3 indicating "Very much" for a total score out of 30 [20,21]. The BIS has been previously used in studies investigating body image distress in HNC patients [22].

Performance status scale for head and neck cancer patients (PSS-HN)

The PSS-HN is a 3-item scale completed by health personnel that surveys the normalcy of diet, public eating practices, and understandability of speech in HNC patients. Moderate and severe impairments are indicated by scores less than 50 in each item. This scale was originally validated in a group of 181 HNC patients as a sensitive and reliable test able to distinguish a wide range of functionality [23].

The PSS-HN has also shown sensitivity in evaluating QOL in post-treatment oral cancer patients [24]. This scale has also been utilized to show better eating and speech function in irradiated HPV-associated HNC patients compared to irradiated non-HPV-associated HNC patients [25].

Statistical analysis

Percentages and 95% Confidence Intervals (CI) were used to explore difference in participant subgroups for categorical outcomes. Median and Interquartile Range (IQR) were used to investigate difference in participant subgroups for continuous outcomes. Associations were examined using Spearman correlations for both numeric and categorical outcomes that had clear ordering; 95% CI were obtained with 1000 bootstrapped replicates.

Eligibility Criteria:

- Patients who have completed treatment for primary, recurrent, or metastatic HPV-related OPSCC with histopathological evidence of p16 positivity.
- Patients at least 18 years or older.
- Patients who speak and read either English or Spanish.
- Patients who were able to understand and willingly agree to informed consent criteria.

Results

Patient population characteristics

Electronic medical records of 100 patients were evaluated between July 2019 and July 2021. 95 patients met inclusion criteria and were consented and included in the study. The mean age at screening was 62 years old (minimum: 48 years old; maximum: 83 years old). 57.9% of patients were non-Hispanic, and 42.1% of patients were Hispanic. 81 (85.3%) participants were male, and 14 (14.7%) were female. Complete patient demographic, cancer staging, and treatment modality data can be found in Table 1. Mean, median, and standard deviation of total population results of each survey tool can be found in Table 2. Several patient factors showed significant relationships with quality of life and psychosocial outcomes as measured by our study, highlighted below.

Staging

Participant disease characteristics were taken to retrospectively stage disease based on the latest AJCC 8th edition, with T stage categorized between T1-T4, N stage categorized between N0-N3, and M stage categorized M0 or M1, and Stage Group between I-IV. 26 (27.4%) participants were T1, 50 (52.6%) participants were T2, 17 (17.9%) participants were T3, and 2 (2.1%) participants were T4. 17 (17.9%) participants were N0, 37 (38.9%) participants were N1, 39 (41.1%) participants were N2, and 2 (2.1%) participants were N3. All 95 participants were M0. AJCC 8th edition staging showed that 43 (45.2%) participants were Stage I, 46 (48.4%) participants were Stage II, 6 (6.3%) participants were Stage III, and 0 (0%) patients were Stage IV.

Larger primary tumor (higher T stage) was associated with worse PSS understandability of speech and total score (PSS Understandability of Speech Spearman correlation: -0.23, 95% CI [-0.42, -0.03], PSS Total Score Spearman correlation: -0.24, 95% CI: [-0.43, -0.04]). Higher T category was also associated with worse swallowing scores at time of survey, and better month-before QOL scores on UW-QOL

Table 1: Participant demographic factors, disease characteristics, and treatment modality of study population.

Variable	N	%
Time Post Treatment		
0-3 months	11	11.6
3-6 months	10	10.5
6 months - 1 year	10	10.5
1-5 years	53	55.8
5-10 years	9	9.5
>10 years	2	2.1
Treatment Modality		
Surgery	10	10.5
Rads	5	5.3
Chemorads	44	46.3
Surgery, rads	18	18.9
Surgery, chemorads	18	18.9
Highest Level of Education		
Some high school	3	3.2
High School Degree	19	20
Some college	25	26.3
College Degree	22	23.2
Graduate Degree	26	27.4
Smoking Status		
Current	1	1.1
Former	38	20
Never	54	56.8
NA	2	2.1
Alcohol Status		
Current	61	64.2
Former	26	21.1
Never	14	14.7
Race and Ethnicity		
White, non-Hispanic	40	42.1
White, Hispanic	39	41.1
Black, non-Hispanic	4	4.2
Black, Hispanic	0	0
Caribbean	7	7.4
APIA	1	1.1
Other, Hispanic	1	1.1
Other	3	3.2
Marital Status		
Single	6	6.3
Married	63	66.3
Divorced	23	24.2
Widowed	3	3.2
Sex		
Male	81	85.3
Female	14	14.7
T category		

1	26	27.4
2	50	52.6
3	17	17.9
4	2	2.1
N category		
0	17	17.9
1	37	38.9
2	39	41.1
3	2	2.1
M category		
0	95	100
1	0	0
8th edition Stage Group		
1	43	45%
2	46	48.4
3	6	6.3
4	0	0

N: Number of Participants

(UW-QOL Swallowing Domain Spearman correlation: -0.28, 95% CI [-0.47, -0.06], 0.24), Month Before QOL Spearman correlation: 0.24, 95% CI [0.01, 0.43]), indicating that larger tumors were related to more difficulty swallowing post-treatment. N category did not have any significant relationships with outcomes tested, and M category did not have adequate grouping to calculate outcome relationships. AJCC 8th edition staging also showed no significant relationships with outcomes tested.

Treatment modality

Participants’ treatment modality was categorized as definitive surgery, definitive radiation, chemoradiation, surgery and radiation, surgery and chemoradiation. Ten (10.5%) respondents received surgery only, 5 (5.3%) received radiation only, 44 (46.3%) received chemoradiation, 18 (18.9%) received surgery and radiation, and 18 (18.9%) received surgery followed by chemoradiation.

Treatment with surgery only was associated with better saliva domain scores on the UW-QOL HNC than surgery and radiation, radiation only, and chemoradiation (Saliva Domain Median and IQR: Surgery only 100 [78,100], surgery and radiation 70 [70,70], radiation only 70 [70,70], chemoradiation 70 [30,70]).

Time post-treatment

Participants’ time post-treatment was categorized as “0 to 3 months,” “greater than 3 to 6 months,” “greater than 6 months to 1 year,” “greater than 1 to 5 years,” “greater than 5 to 10 years,” and “greater than 10 years” after successful completion of treatment. 11 (11.6%) respondents were 0 to 3 months post-treatment, 10 (10.5%) were 3 to 6 months post-treatment, 10 (10.5%) were 6 months to 1 year post-treatment, 53 (55.8%) were 1 to 5 years post-treatment, 9 (9.5%) 5 to 10 years post-treatment, and 2 (2.1%) were greater than 10 years post-treatment.

Greater time post-treatment was correlated with improved taste or higher scores within the taste domain of the UW-QOL HNC assessment (Spearman correlation 0.24, 95% CI [0.03, 0.45]). Greater time post treatment was negatively correlated within the Depression subscale of the HADS (HADS Depression Spearman Correlation:

Table 2: Quality of life and psychosocial outcome analysis of participants who were diagnosed and treated for HPV-associated HNC using the UW-QoL, HADS, BIS, and PSS instruments.

Survey Measure	Mean	Median	SD
UW-QoL			
Pain	86.702128	100	20.266755
Appearance	81.914894	75	18.01277
Activity	79.521277	75	20.721605
Recreation	84.840426	100	19.410769
Swallowing	75	70	25.425064
Chewing	83.333333	100	26.862351
Speech	86.595745	100	23.216849
Shoulder	86.276596	100	25.103329
Taste	64.623656	70	28.522852
Saliva	62.234043	70	28.320252
Mood	81.382979	75	22.571044
Anxiety	78.191489	70	25.720737
Month Before	61.968085	50	29.009851
HR QoL	70.851064	60	19.133746
Overall Average QoL	73.297872	80	20.275591
Total	79.198582	81.25	13.856563
HADS			
Depression	3.2421053	2	3.1545839
Anxiety	5.2526316	4	4.2199335
Total	9.0105263	7	8.1833962
BIS			
Total	4.2	2	5.1086077
PSS			
Normalcy of Diet	79.052632	90	25.089484
Public Eating	88.157895	100	23.27242
Understandability of Speech	90.789474	100	19.290628
Total	257.05263	280	59.20671

UW-QoL: University of Washington – Quality of Life Head and Neck Questionnaire; HADS: Hospital Anxiety and Depression Scale; PSS: Performance Status Scale; BIS: Body Image Scale

-0.22, 95% CI [-0.39, -0.01]).

Education level

Participants’ highest completed levels of education were categorized as “Less than high school,” “High school degree,” “Some college,” “College Degree,” or “Graduate Degree.” The distribution was as follows: Three participants (3.2%) reported an education level less than a high school degree, 26 (27.4%) reported completion of a graduate degree, 22 (23.2%) reported completion of a college degree, 25 (26.3%) reported completion of some college, and 19 (20.0%) reported completion of a high school degree. Higher levels of education correlated with higher scores within the Activity and Recreation domains of the UW-QoL HNC assessment (Activity Spearman Correlation: 0.27, 95% CI [0.06, 0.45]; Recreation Spearman Correlation: 0.24, 95% CI [0.04, 0.42]), suggesting that completion of college and graduate school may provide protective factors for activity- and recreation-related QoL in HNC. Higher levels of education also correlated with lower total HADS scores and lower scores within the Depression subscale of the HADS (HADS

Total Spearman Correlation: -0.27, 95% CI [-0.45, -0.06]; HADS Depression Spearman Correlation: -0.34, 95% CI [-0.51, -0.14]). Notably, education level did not correlate with numerical anxiety scores on the HADS (HADS Anxiety Spearman Correlation: -0.19, 95% CI [-0.38, 0.03]).

Marital status

Participants’ current marital statuses at time of survey were reported as “Single/Never Married,” “Married/Partnered,” “Separated/Divorced,” “Widowed,” or “Other.” A majority of participants were married or partnered (63 participants, 66.3%), 23 (24.2%) participants were separated or divorced, 6 patients (6.3%) were single or never married and 3 patients (3.2%) were widowed. Participants who were widowed reported significantly lower activity and recreation levels within the UW-QoL Activity and Recreation domains when compared to single, married, or divorced participants (Activity Domain Median and IQR: Widow 50 [25,75], Single 100 [100,100], Married 75 [75,100], Divorced 75 [75,100]; Recreation Domain Median and IQR: Widow 50 [38,75], Single 100 [81,100], Married 100 [75,100], Divorced 100 [75,100]). Widowed participants also reported lower overall QoL scores (Overall QoL Median and IQR: Widow 40 [30,60], Single 80 [65,95]). Analysis of BIS scores and marital status revealed differences between single or never married and widowed participants: Widowed participants reported higher BIS scores than single participants, indicating more extensive perceived body image changes related to HNC and its treatment (BIS Median and IQR: Widow 12 [6,13]; Single 2 [0.25,3]). In addition to QoL and body image, analysis by marital status also revealed differences in HADS Anxiety and Depression subscale scores between single and widowed participants (HADS Anxiety Median and IQR: Widow 10 [6,11], Single 2 [2,2.8]; HADS Depression Median and IQR: Widow 8 [4,8,0.5], Single 2 [1.3,3.5]). Widowed participants also displayed lower overall PSS scores and lower scores on the Public Eating and Understandability of Speech domains of the PSS when compared to both married and single participants (PSS Overall Median and IQR: Single 280 [270,300], Married 290 [240,300], Widow 210 [110,240]; PSS Eating Median and IQR: Single 100 [100,100], Married 100 [88,100], Widow 75 [38,88]; PSS Speech Median and IQR: Single 100 [81,100], Married 100 [88,100], Widow 75 [38,75]).

Correlation analysis of survey measures

Each domain from the UW-QoL questionnaire was compared with the HADS, BIS, and PSS questionnaires. Complete correlation data between each of the survey tools can be found in Table 3. Pain, activity, recreation, speech, mood, anxiety, health-related QoL, and overall QoL have a statistically significant negative correlation with HADS anxiety. Alternatively said, better scores in these QoL domains (less pain, better activity, etc.) were correlated with less anxiety symptoms measured by HADS. Additionally, better scores in pain, appearance, activity, recreation, swallowing, chewing, speech, taste, mood, anxiety, health-related QoL, and overall QoL were correlated with less depressive symptoms measured by HADS. HADS total scores were also significantly lower with better scores in UW-QoL domains of pain, appearance, activity, recreation, chewing, speech, mood, anxiety, and overall QoL. Better scores in QoL domains of pain, appearance, activity, recreation, swallowing, chewing, speech, mood, anxiety, health-related QoL, and overall QoL, correlated with better BIS outcomes. Better scores in all QoL domains except anxiety were found to be related to better scores with PSS-HN normalcy of diet. Additionally, patients with better scores in appearance, activity, recreation, swallowing, chewing, speech, health-related QoL, and

Table 3: Correlation Analysis of UW-QoL, HADS, BIS, and PSS instruments.

Survey Measure	Spearman correlation	95% Confidence Interval
UW-QoL Pain		
HADS anx	-0.24	(-0.43, -0.02)
HADS dep	-0.36	(-0.53, -0.16)
HADS total	-0.36	(-0.54, -0.17)
BIS	-0.28	(-0.49, -0.08)
UW-QoL Appearance		
PSS norm	0.22	(0.03, 0.41)
PSS pub	0.22	(0.01, 0.45)
PSS understand	0.28	(0.06, 0.49)
PSS total	0.3	(0.09, 0.48)
HADS dep	-0.38	(-0.56, -0.19)
HADS total	-0.27	(-0.44, -0.05)
BIS	-0.51	(-0.65, -0.33)
UW-QoL Activity		
PSS norm	0.27	(0.06, 0.43)
PSS pub	0.41	(0.21, 0.58)
PSS understand	0.32	(0.1, 0.5)
PSS total	0.4	(0.19, 0.56)
HADS anx	-0.32	(-0.49, -0.11)
HADS dep	-0.53	(-0.67, -0.37)
HADS total	-0.48	(-0.62, -0.3)
BIS	-0.36	(-0.53, -0.17)
UW-QoL Recreation		
PSS norm	0.35	(0.13, 0.51)
PSS pub	0.37	(0.17, 0.55)
PSS understand	0.33	(0.09, 0.51)
PSS total	0.41	(0.22, 0.57)
HADS anx	-0.34	(-0.52, -0.13)
HADS dep	-0.52	(-0.67, -0.32)
HADS total	-0.51	(-0.66, -0.32)
BIS	-0.43	(-0.59, -0.22)
UW-QoL Swallowing		
PSS norm	0.63	(0.48, 0.75)
PSS pub	0.48	(0.31, 0.62)
PSS understand	0.4	(0.19, 0.57)
PSS total	0.61	(0.45, 0.73)
HADS dep	-0.28	(-0.44, -0.08)
BIS	-0.31	(-0.49, -0.1)
UW-QoL Chewing		
PSS norm	0.46	(0.26, 0.62)
PSS pub	0.4	(0.18, 0.6)
PSS understand	0.43	(0.21, 0.65)
PSS total	0.51	(0.3, 0.66)
HADS dep	-0.35	(-0.52, -0.14)
HADS total	-0.24	(-0.42, -0.04)
BIS	-0.33	(-0.52, -0.12)

UW-QoL Speech		
PSS norm	0.3	(0.06, 0.5)
PSS pub	0.49	(0.27, 0.68)
PSS understand	0.72	(0.55, 0.84)
PSS total	0.53	(0.35, 0.68)
HADS anx	-0.24	(-0.43, -0.03)
HADS dep	-0.38	(-0.55, -0.19)
HADS total	-0.33	(-0.48, -0.14)
BIS	-0.34	(-0.52, -0.12)
UW-QoL Taste		
PSS norm	0.41	(0.2, 0.6)
PSS total	0.33	(0.1, 0.54)
HADS dep	-0.3	(-0.47, -0.09)
UW-QoL Saliva		
PSS norm	0.46	(0.26, 0.63)
PSS total	0.39	(0.15, 0.55)
UW-QoL Mood		
PSS norm	0.23	(0.01, 0.41)
PSS understand	0.29	(0.08, 0.48)
HADS anx	-0.57	(-0.68, -0.4)
HADS dep	-0.54	(-0.67, -0.34)
HADS tot	-0.6	(-0.73, -0.45)
BIS	-0.49	(-0.64, -0.3)
UW-QoL Anxiety		
PSS understand	0.23	(0.01, 0.43)
HADS anx	-0.52	(-0.65, -0.31)
HADS dep	-0.36	(-0.53, -0.19)
HADS tot	-0.47	(-0.63, -0.3)
BIS	-0.45	(-0.64, -0.26)
UW-QoL HR-QoL		
PSS norm	0.22	(0.03, 0.24)
PSS public	0.22	(0.03, 0.37)
PSS understand	0.29	(0.12, 0.45)
PSS total	0.29	(0.07, 0.45)
HADS anx	-0.35	(-0.5, -0.16)
HADS dep	-0.51	(-0.64, -0.31)
BIS	-0.44	(-0.57, -0.24)
UW-QoL Overall QoL		
PSS norm	0.23	(0.02, 0.42)
PSS public	0.26	(0.06, 0.45)
PSS understand	0.3	(0.09, 0.47)
PSS total	0.32	(0.09, 0.49)
HADS anx	-0.38	(-0.57, -0.17)
HADS dep	-0.57	(-0.7, -0.41)
HADS tot	-0.55	(-0.69, -0.39)
BIS	-0.38	(-0.55, -0.2)
PSS normalcy of diet		
HADS dep	-0.26	(-0.42, -0.06)

BIS	-0.23	(-0.42, -0.01)
PSS Public Eating		
HADS anx	-0.21	(-0.41, -0.02)
HADS dep	-0.33	(-0.51, -0.14)
HADS tot	-0.28	(-0.45, -0.09)
BIS	-0.25	(-0.43, -0.03)
PSS understandability of speech		
HADS dep	-0.31	(-0.48, -0.11)
HADS tot	-0.25	(-0.44, -0.08)
BIS	-0.42	(-0.58, -0.2)
PSS total		
HADS dep	-0.35	(-0.51, -0.15)
BIS	-0.33	(-0.52, -0.14)
HADS anxiety		
BIS	0.37	(0.16, 0.53)
HADS depression		
BIS	0.43	(0.25, 0.59)
HADS total		
BIS	0.44	(0.24, 0.59)

UW-QOL: University of Washington – Quality of Life Head and Neck Questionnaire; HADS: Hospital Anxiety and Depression Scale; PSS: Performance Status Scale; BIS: Body Image Scale

overall QOL on UW-QOL demonstrated better PSS-HN public eating scores. Increased understandability of speech measured by PSS-HN also had better scores in appearance, activity, recreation, swallowing, chewing, speech, mood, anxiety, health-related QOL, and overall QOL measured by UW-QOL.

The scores of the different items in the PSS-HN questionnaire, the normalcy of diet, public eating practices, and understandability of speech, were also compared with anxiety and depression scores in the HADS questionnaire, as well as BIS scores. PSS-HN normalcy of diet and understandability of speech have a statistically significant negative correlation with HADS depression- such that patients endorsing more normal diets had less depressive symptoms per HADS. Public eating practices measured by PSS-HN also showed correlation with fewer depressive symptoms as measured by HADS and BIS.

Finally, HADS anxiety and depression scores were compared to BIS scores, with statistically significant positive correlations, showing that better mood was related to better body image perception.

Discussion

Demographic and health behavior features of an HPV-associated OPSCC patient population

Uncovering the pathogenesis and epidemiology of HPV-associated OPSCC has been one of the greatest achievements of head and neck cancer research in recent decades. We now know that HPV-positive or HPV-associated OPSCC is a unique and distinct disease process from HPV-negative OPSCC or non-HPV-associated OPSCC, with its own pathogenesis, presentation, prognosis, and treatment response. The typical patients diagnosed with either HPV-associated or non-HPV-associated OPSCC differ in fundamental ways. Demographically, HPV-associated patients are more likely to be white, younger, married, educated, and employed [26-28], and non-HPV-associated OPSCC patients are more likely to be non-white

and belong to lower Socioeconomic Status (SES) [29]. Clinically, HPV-associated OPSCC patients have fewer comorbidities, better treatment response, and higher overall survival rates than HPV-negative patients [30,31]. Thus, it has become critical to identify potential post-treatment issues these patients may face, to fully support patients as they transition to survivors.

Effect of patient demographic and social support on QOL and psychosocial outcomes

Studies have shown that lower education levels are correlated with an increased risk of HNC, with one study demonstrating that participants who attained less than a high school education had approximately four times the risk of HNSCC compared to those who completed higher education [32,33]. Although multiple studies have demonstrated that HPV-associated HNC patients have higher educational attainment when compared to their HPV-negative counterparts, SES disparities within the group of patients with HPV associated oropharyngeal cancer also reflect lower SES showing higher cancer mortality rates [34,35]. Yet, literature on how education level affects psychosocial and functional outcomes in HPV-associated HNC patients remains relatively scarce. Our data also suggests that more educated patients may experience improved QoL with respect to activity and recreation. Additionally, our data suggests that higher levels of education overall correlates to better psychosocial outcomes in HPV-associated HNC patients. Specifically, completion of a college and/or graduate degree may be protective against depression-related symptoms in HPV-associated OPSCC patients and should be a topic of further investigation. It is important to note that educational attainment may be a proxy measure for economic status and access to resources to manage post-treatment morbidity, and these factors should be further deconstructed in larger studies.

Another important consideration in the post-treatment period is patient social support and caregiver availability, who is often a spouse or a life partner. Marital status is commonly recognized as a psychosocial factor that impacts cancer prognosis [36]. Analysis of over 51,000 patients from the Surveillance, Epidemiology, and End Results (SEER) database revealed that married patients with HNC were more likely to receive definitive treatment and had better survival rates than their non-married counterparts. This may be related to greater perceived or actual social and spousal support mechanisms [37]. Our results indicate that marital status plays an important role in QOL and psychosocial measures in HPV-associated OPSCC patients. Specifically, being widowed had a negative impact on QOL and showed a relationship with increased endorsement of psychosocial distress in the post-treatment period. Thus, marital status may play an important protective role against psychosocial issues in HPV-associated HNC patients. However, generalizability of this result is limited due to small sample size of two widowed participants. Nevertheless, it may be of key importance to note education and social support levels in the HPV-associated OPSCC patient population early in the diagnosis and treatment process to connect patients with adequate support in the form of functional rehabilitation, support groups, and psychologic and psychiatric support.

Effect of clinical features on QOL and psychosocial outcomes

In 2017, the American Joint Committee on Cancer (AJCC) released 8th edition guidelines, which established a separate staging system for HPV-related HNC [38,39]. Treatments based on these

staging guidelines are annually outlined by the NCCN Cancer Care Guidelines. Treatment modalities include surgery, radiation, and chemotherapy, and the decision for single or multiple-modality is based on extent of disease. Traditionally, post-treatment surveillance is centered around cancer recurrence, with a recommended NCCN clinical surveillance schedule of every 1 to 3 months for the first year, every 2 to 6 months for the second year, every 4 to 8 months for years 3 to 5, and annually thereafter [40].

Interestingly, studies show that recurrence is discovered most often in the presence of patient symptoms, including pain and dysphagia. In an important study, Frakes et al. [41] showed that most HPV-associated OPSCC recurrences are distant metastases, and the majority of locoregional recurrences will be found in the first 6 months in symptomatic patients. These results led to this study team to recommend intensive early follow-up for all HPV-associated OPSCC survivors, de-escalation of the NCCN follow-up schedule for the asymptomatic survivor population that do not experience early adverse events. De-escalation could mean lessening side effects from treatment protocols and promoting survivorship. However, while HPV-positivity has been shown to provide prognostic information, clinical evidence to alter therapy, personalized decisions for de-escalation protocols in cancer treatment are made by patients and their multidisciplinary teams for inclusion in clinical trials [42-45].

Treatment for HNC is incredibly challenging, and patients have been shown to experience significant psychosocial distress and limitations of their QOL from treatment side effects. Treatment with surgical resection can lead to significant functional defects in speaking and swallowing, depending on extent and location of resection. Further, surgery can cause obvious and distressing cosmetic defects in a highly central and visible location. The advent of Transoral Robotic Surgery (TORS) has shown improved QOL in patients with small pharyngeal tumors and is quickly becoming standard of care for select complex situations- which may present advantages in impact of cosmetic and functional effects of surgical treatment, and decrease the side effects of non-surgical treatment modalities [46]. Treatment with targeted radiation in the sensitive head and neck area can lead to significant side effects of mucositis and xerostomia, as well as functional challenges in the realm of eating, drinking, talking, and socializing [47-49]. Chemotherapy used for HNC can worsen radiation effects of mucositis and dermatitis, and cause systemic side effects of fatigue, loss of appetite, neuropathy, and hearing loss [50].

Clinical characteristics of an HPV OPSCC post-treatment patient included in our study were staging of cancer, treatment modality, and elapsed time post-treatment. When looking at treatment modality, our findings show that treatment with surgery only was associated with better saliva domain scores than other modalities alone and combination treatment: Surgery and radiation, radiation only, and chemoradiation, radiation only, and chemoradiation. When considering time post-treatment, our study showed that taste showed a positive recovery with increased time post-treatment. Further, symptoms of depression may recover with increased time post-treatment. These side effects of treatment are critical to consider when evaluating the QOL and psychosocial state of HPV OPSCC survivors. To this, it is vital to set expectations for symptoms and functional capacity in patients prior to receiving treatment, and care should be taken to monitor these patients in the post-treatment period for signs of psychosocial distress. Education level could impact patient expectations after treatment and by the same token impact their mental health and quality of life measures.

Correlation of performance status and social re-integration with psychosocial outcomes

Long-lasting dysfunction can arise from both the disease and the treatment in HNC. Functional outcomes are known to affect health-related QOL, with OPSCC studies focusing largely on the experiences of taste and dysphagia post-treatment. The patient functional experience is most often surveyed by Patient-Reported Outcome Measures (PROMs). In swallowing and eating dysfunction, PROMs include the Performance Status Scale – Head and Neck (PSS-HN), which has three subgroups that can be directly supported by speech language pathologists and is focused on components necessary for the re-integration into the social experiences of speaking and eating with others.

Impacted social experience of eating and speaking can lead to severe psychosocial distress, which is defined as an unpleasant emotional experience of a psychosocial (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope with cancer, its physical symptoms, and its treatment. Psychosocial distress screening is now recommended by NCCN, Institute of Medicine, and Psychosocial Oncology Society for high-quality cancer care plans. Psychosocial distress is broad but includes anxiety, depression, and body image distress. Thus, surveys aimed at these elements of distress can be used.

Our study found that better scores of all domains of the PSS-HN correlated with lower HADS depression scores in the surveyed HPV-associated OPSCC population. Interestingly, only worse scores in the public eating domain correlated with lower BIS scores, which may indicate that public eating is a component of body image in these patients. Research has begun in implementation of tailored psychosocial distress screening protocols and should be investigated by larger-scale studies specific to HPV-associated OPSCC [51-55].

Limitations of Study

This study was intended as a pilot study to identify important patient characteristics and QOL measures for further investigation. As such, we were unable to examine the role of confounding variables in the metrics we examined, something that must be elucidated in future larger studies. Interaction of the variables was studied in a cross-sectional fashion and it would be important to analyze those over time for individual patients or patients at risk for poor outcome. Educational attainment may also likely be a proxy for other variables such as socioeconomic status and access to supportive care, and further studies should include financial assessment. Additional investigation in QOL and psychosocial outcomes in the HPV-associated HNC survivor population will shed light on patient-specific intervention across the cancer timeline and should be prioritized by otolaryngologists and multidisciplinary care teams.

Conclusion

Preparing for survivorship of HPV-associated HNC patients is of utmost importance as these patients undergo diagnosis, treatment, and beyond. In this study, T stage, treatment modality, time post-treatment, education level and marital status were found to significantly affect quality of life and psychosocial outcomes. Further, we examined the impact of function, body image, and psychosocial distress on quality of life and social experiences of these survivors. Survivorship can be supported by thorough QOL screening pre- and post-treatment, and linking patients to symptom-based, functional support. Psychosocial distress screening and support is also of key

importance in this patient population and should be a focus of future research in head and neck oncology.

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