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ORIGINAL RESEARCH

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Quality of life after radiation and transoral robotic surgery in advanced oropharyngeal cancer

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Abstract

Objectives: Oropharyngeal squamous cell carcinoma (OPSCC) treatment results in impaired swallowing and quality of life (QOL). We analyzed a cross-section of advanced stage OPSCC patients treated with multimodal therapies at our Survivorship Clinic to investigate treatment factors associated with QOL.

Methods: Retrospective analysis of patient-reported outcomes (PROMs) after primary OPSCC treatment using AJCC seventh edition staging.

Results: A total of 73 patients were included (90.1% human papillomavirus positive [HPV+]). There were no QOL differences between robotic surgery with radiation ± chemotherapy patients (n = 29) and those treated by radiation ± chemotherapy (n = 44). Radiation field analysis demonstrated significant correlations between increasing doses to larynx and contralateral parotid and submandibular gland and worse swallowing as measured by the Eating Assessment Tool-10 ($P = .02$; $P = .01$; $P = .01$).

Conclusions: In advanced, mostly HPV+, OPSCC, we did not find clinically significant differences between QOL PROMs between surgical and radiation ± chemotherapy treatment groups. This highlights the need for continued therapy de-escalation along with improved interventions for treatment related toxicities.

Level of evidence: 4.

KEYWORDS
oropharyngeal cancer, quality of life, robotic surgery, survivorship, TORS

1 | INTRODUCTION

Head and neck cancers have long been associated with significant morbidity and mortality both from the cancer itself and the radical treatments required for disease control. The epidemic of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinomas

The abstract was accepted for a podium presentation at the American Head & Neck Society's 10th International Conference on Head and Neck Surgery prior to its postponement due to the COVID19 pandemic.

(OPSCC) has shed new light on a subset of patients with improved survival.[1-3] It has also refocused the attention of the medical community on the side effects of surgery, radiation, and chemotherapy.[4-6]

Several studies have addressed this by looking at the treatment-related morbidity in OPSCC by analyzing quality of life (QOL) outcomes after transoral robotic surgery (TORS), radiation, and chemoradiation.[6-11] Many of these have focused on early-stage OPSCC, in an attempt to identify the optimal balance of treatment aggressiveness and side effects of the treatment itself.[10,12-14] Several studies have examined the differences in QOL between patients treated primarily with TORS and those who underwent nonsurgical treatment yielding mixed results. Some of these studies demonstrated improved outcomes in patients treated primarily with surgery.[12,13] Yet the only published randomized trial, the radiotherapy vs TORS and neck dissection for OPSCC (ORATOR) showed no clinically significant differences in the QOL outcomes between TORS ± adjuvant therapy vs definitive radiation ± chemotherapy.[14]

To better understand and address the morbidity after treatment for head and neck cancer, our center started a multidisciplinary Head and Neck Cancer Survivorship Clinic, focused on addressing patient and care providers' QOL as well as financial toxicities associated with treatment.[15-17] In this retrospective and cross-sectional study using AJCC seventh edition staging criteria, we analyzed predictors of adverse QOL outcomes in OPSCC patients, focusing on the effect of radiation dose-volume parameters on various patient-reported outcomes (PROMs). The purpose of this study was to examine the effects of multimodality therapy in advanced OPSCC on patient QOL.

2 | MATERIALS AND METHODS

After the study was approved by the University of Pittsburgh Institutional Review Board (STUDY18090005), a retrospective chart review was carried out on OPSCC patients seen at a tertiary care center's Head and Neck Survivorship Clinic from 2016 to 2018. All patients gave informed consent for this study. Inclusion criteria consisted of a primary OPSCC cancer that was treated at least 6 months prior to data collection and had all treatment data accessible. All patients were treated with curative intent. Patients also needed to have radiation treatments completed at our institution with radiation target volumes and organs-at-risk (OAR) volumes contoured by one of two radiation oncologists specializing in head and neck cancers. Figure 1 displays a flow chart summarizing the inclusion and exclusion criteria of the cohort. Patient's with early stage tumors (T1N0M0 and T2N0M0 by AJCC seventh edition criteria), tumors treated by surgery alone, incomplete radiation data, and radiation completed at an outside center were excluded.

Variables collected from the medical record included demographics, tobacco status, pre- and post-treatment weights, body mass indexes (BMI), time since treatment completion, surgical procedures and margin status, and chemotherapy regimen. Staging information based on AJCC seventh edition staging criteria was collected. For surgical patients, pathologic staging was collected and in primary

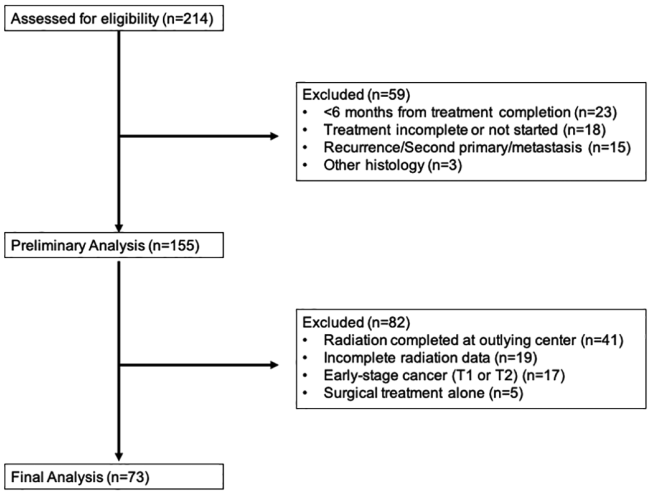

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow chart demonstrating cohort exclusion criteria. All 214 patients had oropharyngeal carcinoma who were seen at our institution's Head and Neck Survivorship Clinic

chemoradiation treated patients, their clinical stage was gathered. Original treatment planning dose-volume histograms were accessed to record doses delivered to OARs, which included the oral cavity, hard palate, pharyngeal constrictor muscles, larynx, esophagus, mandible, and the four major salivary glands. For purposes of dose analysis, parotid and submandibular glands were denoted as ipsilateral if they were on the same side as the primary tumor and contralateral if they were on the opposite side of the primary tumor. Dose delivered to the high-risk cervical lymph node basins in the ipsilateral and contralateral hemi-neck, as judged by the treating radiation oncologist were also recorded. All patients were treated with intensity-modulated radiation therapy (IMRT) on Varian linear accelerators using Eclipse treatment planning software.

At their Survivorship clinic visits, a variety of head and neck cancer validated PROMs were collected including the physical and social subscales from the University of Washington Quality of Life questionnaire (UWQOL),[18] Patient Health Questionnaire-8 (PHQ8),[19] Generalized Anxiety Disorder-7 (GAD7),[20] Eating Assessment Tool-10 (EAT-10),[21] and Neck Disability Index (NDI).[16,22] The UWQOL physical and social subscales are commonly used PROMs that measure patient's chewing, swallowing, speech, taste, saliva, appearance, anxiety, mood, pain, activity, recreation, and shoulder functions.[18] The PHQ8 and GAD7 are very common screening surveys for depression and anxiety, respectively.[19,20] EAT-10 is a well-established survey to diagnose dysphagia severity along with monitoring response to intervention.[21] Lastly, NDI is a measure of neck pain and resulting disability that has been previously shown to be relevant both in surgical and nonsurgical head and neck cancer treatment modalities.[16]

Statistical analysis was performed using SAS (v9.4; SAS Institute, Cary, North Carolina) and RStudio (v1.1.456; RStudio, Inc., Boston, Massachusetts). In the descriptive analysis, we calculated frequency

(percentage) for categorical variables, and mean (SD) for continuous variables for both the whole sample and different treatment groups. In correlation analysis, difference of radiation dose and PROMs between treatment groups was examined using Wilcoxon-rank sum tests and Fisher exact test for continuous and categorical variables, respectively.

TABLE 1 Oropharyngeal squamous cell carcinoma cancer patients

Treatment groups	Radiation + chemoradiation (n = 44)	Surgery + Adjuvant (n = 29)	*P*-values[a]	Total (n = 73)
Number of males (%)	37 (84)	25 (86)	1	62 (85)
Average age at diagnosis, years (SD)	57.6 (7.2)	56.7 (10.4)	.394	57.3 (8.6)
Smoking status at Survivorship visit				
Never smoker, n (%)	27 (61)	23 (79)	.313	50 (68)
Former smoker, n (%)	13 (30)	5 (17)		18 (25)
Current smoker, n (%)	4 (9)	1 (3)		5 (7)
Primary subsite, n (%)				
Palatine Tonsil	21 (48)	14 (48)	1	35 (48)
Base of tongue	23 (52)	15 (52)		38 (52)
[b]Stage, n (%)				
III	6 (14)	4 (14)	1	10 (14)
IVa	37 (84)	25 (86)		62 (85)
IVb	1 (2)	0 (0)		1 (1)
[b]T stage, n (%)				
T1	17 (39)	16 (55)	.074	33 (45)
T2	15 (34)	10 (34)		25 (34)
T3	4 (9)	3 (10)		7 (10)
T4	8 (18)	0		8 (11)
[b]N stage, n (%)				
N0	0	1 (3)	.442	1 (1)
N1	6 (14)	3 (10)		9 (12)
N2a	6 (14)	5 (17)		11 (15)
N2b	20 (45)	17 (59)		37 (51)
N2c	10 (23)	3 (10)		13 (18)
N3	2 (4)	0		2 (3)
HPV status n (%)				
Positive	37 (84)	29 (100)	.103	66 (90.4)
Negative	3 (7)	0 (0)		3 (4.1)
Unknown	4 (9)	0 (0)		4 (5.5)
Initial treatment, n (%)				
Chemoradiation	44 (60.3)	-	<.001	44 (60.3)
Surgery and adjuvant radiation	-	9 (12.3)		9 (12.3)
Surgery and adjuvant chemoradiation	-	20 (27.4)		20 (27.4)
Time since treatment completion, n (%)				
6–12 months	6 (14)	6 (21)	.275	12 (16)
1–5 years	25 (57)	19 (66)		44 (60)
>5 years	13 (30)	4 (14)		17 (23)
Patients requiring a feeding tube at most recent clinic visit (%)	3 (7)	2 (7)	1	5 (7)
Average pretreatment BMI (SD)	28.7 (5.9)	29.8 (4.3)	.303	29.2 (5.2)
Average posttreatment BMI (SD) at clinic visit	26.5 (4.4)	27.7 (4.4)	.271	26.9 (4.4)

[a]*P*-values: Wilcoxon rank sum tests for continuous variables and Fisher's Exact tests for categorical variables.
[b]AJCC seventh edition.

TABLE 2 Chemotherapy and surgical treatment overview

Treatment groups	Radiation + chemoradiation (n = 44)	Surgery+ Adjuvant (n = 29)	Total (n = 73)
Patients treated with chemotherapy, n (%)	43 (98)	20 (69)	63 (86)
Platinum based, n (%)	37 (84)	18 (62)	55 (75)
Cetuximab, n (%)	5 (11)	2 (7)	7 (10)
Unknown, n (%)	1 (2)	0 (0)	1 (1)
Surgically treated patients, n (%)			
TORS	-	28 (96)	-
Bilateral tonsillectomy	-	1 (4)	-
Neck dissection, n (%)		25 (86)	-
Unilateral	-	22 (76)	-
Bilateral	-	3 (10)	-
Margin status, n (%)			
Negative	-	20 (69)	-
Positive	-	5 (17)	-
Unknown	-	4 (14)	-

Abbreviation: TORS, transoral robotic surgery.

3 | RESULTS

Our clinic saw 214 OPSCC patients from 2016 to 2018. Due to low sample sizes, we excluded patients with stages 1 and 2 tumors (n = 17) along with patients who were treated by surgery alone (n = 5). Ultimately, 73 patients met inclusion criteria (Figure 1). Demographics of this cohort are noted in Table 1 with 14% of patients diagnosed with stage III disease, 85% with stage IV, and 1% with stage IVb according to AJCC 7 criteria. One single patient had an N0 neck and the majority of our patients had N2b disease (51%). HPV testing was positive in 90.4% (n = 66) of patients. Tumor subsites were base of tongue (n = 38, 52%) and palatine tonsil (n = 35, 48%). Most patients (n = 44, 60.3%) were treated with definitive chemoradiation. Twenty-nine patients (39.7%) were treated with surgery and adjuvant radiation ± chemotherapy. These patients were mainly T1 and T2 tumors whereas all T4 tumors (11%) were treated with primary chemoradiation. Five patients were current smokers at their clinic appointment with an average of 17.7 pack-year history. Eighteen patients were former smokers with an average of 14 pack-year history. Fifty patients were never smokers. Median follow-up after completing definitive treatment was 29.7 months (range: 6.1-133 months). At last follow-up, 12 (16%) patients completed their treatment 6 to 12 months prior to their clinic visit, 44 patients (60%) between 1 and 5 years, and 17 (23%) >5 years before their visit. Five patients had feeding tubes at their most recent clinic visit. The average pretreatment BMI was 29.2 and the post-treatment BMI was 26.9.

Surgical and chemotherapy treatment variables are summarized in Table 2. Both groups had similar demographics, smoking history, primary tumor subsite, stage (overall, T, and N), HPV status, and time since treatment completion (Table 1). All surgical patients except one underwent transoral robotic surgical resection (TORS). We compared radiation doses in patients who were treated with surgery with adjuvant therapy (n = 29) vs those treated with primary chemoradiation (n = 44). Two patients in the primary chemotherapy group required neck dissection following treatment. Table 3 demonstrates the average radiation dose to the primary tumor/tumor bed and OARs in the two groups. Those who were treated with surgery and adjuvant therapy had a mean radiation dose of 60.7 Gray (Gy) to the tumor bed with a SD of 3.6, significantly lower than the primary radiation or chemoradiation group (68.9 Gy, SD = 3.2, $P < .0001$). Table 3 also shows the number of patients who received ≤60, 60.1 to 65, 65.1 to 70, and >70 Gy to the primary tumor beds with all primary chemotherapy patients receiving 65 Gy or more and the majority of the surgery with adjuvant patients receiving less than 65 Gy. Surgically treated patients also had significantly lower average radiation doses to several subsites (Table 3; pharyngeal constrictor muscles $P = .00027$; contralateral parotid gland $P = .0003$; ipsilateral submandibular gland $P < .0001$; contralateral submandibular gland $P = .00059$; mandible $P < .0001$; and high-risk cervical lymph node basins $P < .0001$).

When comparing the surgical (surgery followed by radiation ± chemotherapy) and nonsurgical groups (chemoradiation), we did not find substantial differences between their PROMs scores (summarized in Table 4). There were no discernible associations between the prescribed overall radiation doses (with or without surgery) to the primary site and PROMs (Table 4). There was also no difference in PROMs between tumor primary subsites (social UWQOL $P = .97$; physical UWQOL $P = .82$; PHQ8 $P = .96$; GAD7 $P = .09$; NDI $P = .51$; EAT-10 $P = .83$). However, when we analyzed radiation dose-volumes parameters for different OARs, we found several associations. The mean dose delivered to the ipsilateral parotid gland was correlated with worse scores on the social aspects of the UWQOL and significantly more symptoms of anxiety based on GAD7

TABLE 3 Radiation treatment overview

Treatment groups	Radiation + chemoradiation (n = 44)	Surgery + adjuvant (n = 29)	Total (n = 73)	*P*-values
Average radiation dose to primary tumor, Gy (SD)	68.9 (3.2)	60.7 (3.6)	67.5 (4.8)	<.0001
Number of patients receiving primary tumor radiation doses:				
≤60 Gy	0	9	9	
60.1–65 Gy	0	16	16	
65.1–70 Gy	40	0	40	
>70 Gy	4	4	8	
By subsite, Gy (SD)				
Oral cavity	40 (12.6)	38.2 (8.2)	39.3 (11)	.74
Hard palate	22 (11.7)	23.8 (7.2)	22.8 (9.8)	.41
Pharyngeal constrictor muscles	57.3 (9.7)	47.7 (9.3)	53 (10.6)	.00027
Larynx	36.8 (13.5)	32.2 (10.6)	35 (12)	.19
Esophagus	22.4 (7.1)	20.4 (8)	21.6 (7.5)	.16
Parotid-ipsilateral	34.5 (9.8)	33.4 (7.4)	34.1 (8.9(	.91
Parotid-contralateral	27.4 (10.2)	21 (7.2)	24.8 (9.6)	.003
Submandibular gland-ipsilateral	70 (3.9)	62.8 (6.2)	66.4 (6.3)	<.0001
Submandibular gland-contralateral	56.5 (16.8)	42.9 (16)	51.1 (17.7)	.00059
Max dose to mandible	44.1 (7)	35.5 (6)	40.7 (7.8)	<.0001
Neck radiation to high risk cervical lymph node basins				
Ipsilateral neck, n (%)	18 (41)	26 (90)	54 (74)	
Bilateral necks, n (%)	26 (59)	3 (10)	19 (26)	
Average dose in high risk cervical lymph node basins, Gy (SD)	68.9 (3.2)	63.5 (4.5)	66.8 (4.6)	<.0001

Note: *P*-values calculated from Wilcoxon rank sum tests.

TABLE 4 Patient reported outcome measures (PROMs) between treatment groups

Treatment groups	"Normal"[a]	Radiation + chemoradiation (n = 44)	Surgery + adjuvant (n = 29)	Total (n = 73)	*P*-values
University of Washington Quality of Life-Physical, Average score (SD)[18]	80-100	72.1 (15.5)	70 (12.8)	71.2 (14.6)	.34
University of Washington Quality of Life-Social, Average score (SD)[18]	69-89	77.3 (17.4)	74.1 (17.5)	76 (17.6)	.39
Patient Health Questionnaire-8, Average score (SD)[19]	<10	6.3 (5.7)	7.2 (5.6)	6.7 (5.6)	.71
General Anxiety Disorder-7, Average score (SD)[20]	<10	2.9 (5.1)	2.3 (4)	2.6 (4.7)	.77
Eating Assessment Tool-10, Average score (SD)[21]	<3	10 (8.5)	12.8 (9.3)	11.1 (8.8)	.18
Neck Disability Index, Average score (SD)[16]	<5	6.2 (5.3)	8.3 (8.3)	7 (6.7)	.52

Note: *P*-values calculated with Wilcoxon rank sum tests.
[a]"Normal" data are based on prior publications that are cited in the table. These patients would be considered asymptomatic on their respective PROM.

(Spearman correlation coefficient = −.27; $P = .02$; Wilcoxon rank-sum $P = .012$). As expected, EAT-10 scores were significantly higher in patients with gastrostomy tubes (10.6 in those without vs 27.5 in patients with gastrostomy tubes; Wilcoxon rank sum $P = .005$). More interestingly, EAT-10 scores had several significant relationships with radiation doses. Higher mean radiation dose to the larynx, contralateral submandibular gland, and contralateral parotid doses were all significantly associated with worse EAT-10 scores (Spearman correlation coefficient = .28, $P = .02$; Spearman correlation coefficient = .31, $P = .01$; Spearman correlation coefficient = .31, $P = .01$; respectively). No other treatment variables were significantly associated with adverse PROMs (ie, PHQ8, Physical UWQOL, and NDI).

4 | DISCUSSION

This exploratory study aimed to identify treatment details in the context of the definitive management of OPSCC that affected subjective patient outcomes. More specifically, we amassed a study of patient treatment features that included not only surgical variables, but also information regarding organ-specific radiation doses rather than the overall prescribed radiation dose to the primary site. Furthermore, all patients were treated with modern radiation techniques (ie, IMRT), which allows for a conformal dose distribution and sparing normal organs of high radiation doses, and outside of one patient all surgically treated patients were treated with TORS. To assess the impact of these variables, we surveyed our survivorship patients on a variety of PROMs that included anxiety, depression, neck disability, overall QOL, and dysphagia. Within our survivorship clinic, each patient's PROM is reviewed prior to the patient interview allowing our clinicians to ensure complete collection of the various surveys and assess specific issues they raise. We noted dysphagia to be the most impacted when related to the specifics of treatment.

In assessing the influence of treatment modality on PROMs, we compared two treatment groups: surgery with adjuvant therapy vs primary chemoradiation. The two treatment arms shared statistically similar demographic and staging profiles (Table 1). Not surprisingly, the TORS treated group favored smaller primary tumors but this did not reach statistical significance ($P = .074$). This surgically treated group also had significantly less radiation overall and to organ specific subsites. Despite these differences in radiation doses, even when 10% of the TORS treated group had adjuvant radiation to bilateral necks compared to 59% of the nonsurgical group, we found no significant differences in PROMs between these two treatment groups.

We did find statistically significant differences when normal organ dose-volume parameters were correlated with PROMs. The most notable findings in this study are related to swallowing function. We found a significant correlation between increasing radiation doses to the larynx, and the major salivary glands on the opposite side of the primary tumor site, and adverse scores on the EAT-10 questionnaire. Independent of their treatment type, we also found that patients with higher radiation doses to the parotid gland on the same side as the primary tumor had increasing anxiety based on GAD7 and correlated with worse social function based on the UWQOL. We expected that the contralateral major salivary glands, more often spared due to increased distance from the primary tumor, to have a larger impact on QOL because preservation of at least one major salivary gland can decrease the rate of post-radiation xerostomia.[23,24] However, salivary function is only one aspect of social and physical UWQOL. In our sample, we suspect that increased radiation to the ipsilateral parotid gland is indicative of a larger primary tumor, a tumor that is closer to midline, and/or a tumor that is closer to the parotid gland. All of these factors would likely lead to difficulty sparing the ipsilateral parotid gland and an increase in radiation to the taste buds, muscles of mastication, and external skin, thereby affecting taste, chewing, and trismus.

QOL and survivorship specifically have come to the forefront of head and neck cancer treatment in recent years. This is likely multifactorial from increased knowledge and appreciation of the short and long-term impacts of curative treatment along with improved outcomes of HPV + OPSCC. Due to these improved outcomes, there has been a significant push for de-intensification of therapy within this subset of head and neck cancer patients with several studies comparing decreasing chemoradiation doses[25-27] and surgical vs radiation treatments in early stage OPSCCs.[10,12,14] Another recent study assessing treatment toxicity was the randomized phase II ORATOR trial, which demonstrated a statistically significant, but not a clinically significant difference in the swallowing outcomes of patients treated with radiation primarily vs TORS with neck dissection.[14] Another publication, *Sethia* et al, directly compared QOL outcomes between TORS alone vs TORS with adjuvant radiation or chemoradiation in mostly early-stage OPSCC cancers and noted significantly worse swallowing and eating at the early time points in patients treated with adjuvant radiation and chemoradiation compared to those treated with TORS alone.[10] However, similar to ORATOR they did not find meaningful differences in QOL between the groups at 1 year follow-up. Despite differences in study design, PROMs, and patient populations, our study similarly did not show clinically significant differences in patient reported QOL between surgical and chemoradiation treatment arms.

Another relevant study to this topic looked at chemoradiated patients with decreased IMRT dose to the swallowing organs. *Eisbruch* et al's prospective study of OPSCC assessed long-term IMRT dose-volume relationships to swallowing outcomes (both subjective and objective) in advanced OPSCC patients treated with primary chemoradiation.[26] They found that worse swallowing outcomes were related to increasing mean radiation doses to the esophagus, pharyngeal constrictors, and the supraglottic larynx.

Ultimately, our own study did not find a significant correlation within these radiation doses. This study incorporated a multimodality approach to better understand patient QOL following multimodality therapies. To do so, we looked beyond the total prescribed dose of radiation and collected IMRT field data along with the surgical treatment variables in an attempt to gain a more comprehensive assessment of how these variables interact.

Unfortunately using this approach, we lost a significant amount of statistical power offering the potential that a larger study may improve our understanding. We had to exclude a substantial portion of patients who were not treated at our primary institution and therefore, lacked necessary treatment information such as operative notes and radiation dose planning. It is also important to note that participation in a survivorship clinic, such as ours, may create a selection bias with participating patients being the most symptomatic. In our study, the effect of this bias is likely a reflection of the patient population that was accrued, namely an advanced stage cancer sample that underwent multimodality therapy, thereby excluding patients who underwent surgery alone for small tumors. Another weakness is the retrospective and cross-sectional design of our study. Although this expanded our sample available to study, it is also not possible to

compare patient's functional outcomes longitudinally or compare their post and pre-treatment PROMs.

OPSCC treatment continues to evolve with several studies and trials looking at further deintensification of therapy. Coinciding research on the functional outcomes of these new treatment regimens will play an instrumental role in guiding clinicians to improve their patients' QOL as well as survival.

5 | CONCLUSIONS

In this study, we sought to better understand the complicated effects of multimodality treatments on patient's QOL. Despite finding statistically significant associations between treatment and QOL, ultimately our data did not show clinically significant differences when comparing different types of treatment in advanced stage, mostly HPV + OPSCC patients. This highlights the need for improved interventions for the toxicities related to the treatment of these tumors.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose and no funding sources.

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