The Laryngoscope

Increased Pain Reporting by Head and Neck Cancer Patients at Radiation Oncology Consultation: A Quality-of-Life Analysis

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Objectives: Head and neck cancers (HNC) are associated with significant morbidity. Quality-of-life (QoL) analyses can assist with understanding subjective factors shaping the patient experience. Here, we assess for patient and/or tumor factors associated with increased pain reporting at the time of initial radiation oncology consultation at a single institution in 2015.

Study Design: Prospective cross-sectional questionnaire research.

Methods: All new patient consultations in 2015 were offered the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core-30 (EORTC QLQ-C30) survey. HNC patients were also offered the EORTC QLQ-HN35 module. Retrospective chart review was performed on patients who completed the surveys. Patient demographics, tumor characteristics, and QoL responses were analyzed for potential associations. Statistical analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC), with $P < .05$ considered significant.

Results: Of 771 new patient consultations, 137 consultations were for HNC patients. Of those, 62 patients completed both surveys. HNC patients reported greater pain relative to all other disease sites (odds ratio [OR]: 2.05; $P < .01$). On univariate analysis of the EORTC QLQ-C30 data, increased pain was found to be associated with tumor size > 4 cm (OR: 3.05; $P \leq .05$). The EORTC QLQ-HN35 data revealed lymph node involvement to be independently associated with pain (OR: 3.12; $P \leq .05$). On multivariate analysis, increased pain was associated with lack of pain medication prescription at the time of consultation ($P \leq .05$) and age ≥ 65 years ($P \leq .05$).

Conclusion: Patients with HNC reported significantly more pain at consultation than patients with other primary malignancies. Understanding factors contributing to subjective pain may allow providers to potentially address these symptoms proactively to improve patients' QoL.

Key Words: Head and neck cancer, quality of life, radiation therapy.

Level of Evidence: 2c – Outcomes research.

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INTRODUCTION

Statistical analysis of quality-of-life (QoL) data is challenging due to the relatively large number of variables studied and the subjective factors that shape patients' experiences.[1,2] However, it remains important to develop a holistic view of how cancer affects patient populations by critically analyzing patients' perceptions of their cancer treatment.[3,4]

Head and neck cancers (HNC) primarily arise in the nasal cavity/nasopharynx, oral cavity, pharynx, larynx, and neck. Treatment typically entails a combination of therapies including surgery, chemotherapy, and/or radiation therapy. Multimodality treatment is being used with increasing frequency to treat head and neck tumors, increasing survival rates but simultaneously intensifying morbidities and QoL concerns that may be assessed with standardized tools.[5] In addition to the physical effects of therapy, HNC patients receive complex care that can lead to financial, spiritual, and/or emotional hardships.[6,7] Pain and symptom management are important predictors of QoL because they affect activities of daily living, mood, and patient independence.[8] Advancing understanding of how treatment affects individual patients' lives helps tailor treatment and provide ancillary resources to improve the patient experience, and it potentially decreases ancillary side effects.

Preliminary analysis of patients presenting to our department for radiation therapy consultation noted increased pain reporting for HNC patients compared to the rest of our population ($P = .0007$, data not shown). The purpose of this study is to determine factors within the HNC patient population contributing to patients' increased pain experience, and to compare our findings with the limited literature on patient-reported pain scores and QoL in the general HNC population.

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TABLE I.
Selected Characteristics (n = 62).

Population Characteristics	UC (n = 62) N	%	EORTC Reference Data (n = 2,929) N	%
Sex				
Male	43	69.4	2,318	79.1
Female	19	30.7	589	20.1
Not known	0	0.0	22	0.8
Age				
< 40	2	3.2	110	3.8
40–49	8	12.9	480	16.4
50–59	17	27.4	919	31.4
60–69	22	35.5	832	28.4
70–79	9	14.5	489	16.7
80+	4	6.5	97	3.3
Not known	0	0.0	2	0.0
Marital status				
Divorced	12	19.4	Not documented	
Married	31	50.0		
Separated	1	1.6		
Single	13	21.0		
Widowed	5	8.1		
Smoking status (patient-reported)				
Current	9	14.5	Not documented	
Former	36	58.1		
Never	17	27.4		
Alcohol intake (patient-reported)				
Former	5	8.1	Not documented	
High	3	4.8		
Some	22	51.6		
None	32	35.5		
Insurance*				
Government insurance	20	32.8	Not documented	
Private insurance	41	67.2		
Pain medication prescriptions at time of consult				
Narcotics	44	71.0	Not documented	
Non-narcotics	4	6.5		
None	14	22.6		
Tumor characteristics				
Tumor site				
Hypopharynx	4	6.5	74	2.5
Larynx	14	22.6	362	12.4
Nasopharynx	3	4.8	Not documented	
Oral cavity	17	27.4	192	6.6
Oropharynx	17	27.4	80	2.7
Salivary gland	6	9.7	Not documented	
Thyroid	1	1.6	5	0.2
Not known	0	0.0	2,216	75.7
Stage				
I	5	8.3	946	32.3
II	5	8.3		
III	13	21.7	1,722	58.8
IV	6	10.0		
IVA	30	50.0		
IVB	1	1.7		
Recurrent/metastatic	0	0.0	37	1.3
Not known	2	3.2	224	7.6
Node involvement				
Positive	37	59.7	Not documented	
Negative	25	40.3		
Size				
< 4 cm	34	54.8	Not documented	
≥ 4 cm	28	45.2		
p16 status				
Negative	17	27.4	Not documented	
Positive	22	35.5		
Not available	23	37.1		
Node laterality				
Bilateral	11	17.7	Not documented	
Left	14	22.6		
Right	12	19.4		
Node negative	25	40.3		
Previous treatment for relevant tumor				
Yes	35	56.5	Not documented	
No	27	43.6		
Previous treatment type				
None	27	43.6	Not documented	
Radiation	1	1.6		
RT + chemo + surgery	4	6.5		
RT + surgery	4	6.5		
Surgery	26	41.9		

*n = 61

Chemo = chemotherapy; EORTC = European Organization for Research and Treatment of Cancer; RT = radiation therapy; UC = University of Cincinnati.

PATIENTS AND METHODS

Patients

This study was conducted after institutional review board approval (study ID 2016–1281). All new patient consultations to our institution's radiation oncology department in 2015 were offered the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core-30 (EORTC QLQ-C30), a validated patient-reported outcomes survey tool specifically designed for all cancer patients. Exclusion criteria for this study included follow-up visits and seeking radiation therapy for noncancerous conditions or metastatic disease. Of the 771 new patient consultations, 137 (18%) presented with a primary HNC. Sixty-two (45%) of these

patients completed both the EORTC QLQ-C30 and the head and neck module (EORTC QLQ–HN35). Retrospective chart review was performed on the 62 patients with primary HNC who completed both EORTC questionnaires.

EORTC Questionnaires

QoL were assessed using the EORTC QLQ-30 version 3.0.[9] This validated questionnaire includes a QoL scale, five functional scales (physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, nausea), and six single item symptoms commonly experienced by cancer patients (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Patients rate QoL on a 7-point scale and the remaining items on a 4-point scale.

The EORTC QLQ-H&N35 is a validated module designed to address issues faced specifically by HNC patients.[10] This survey tool contains 35 items pertaining to HNC disease and treatment-related side effects. These are composed of seven multi-item scales (pain, swallowing, senses, speech, social eating, social contact, and sexuality) as well as 11 single items common in HNC patients.

Statistical Analysis

The EORTC scoring manual was used to interpret reported scores from the EORTC QLQ-C30 and EORTC QLQ-HN35.[9] Statistical analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC), with $P < .05$ considered significant. Descriptive statistics were performed for demographic information and tumor characteristics of our

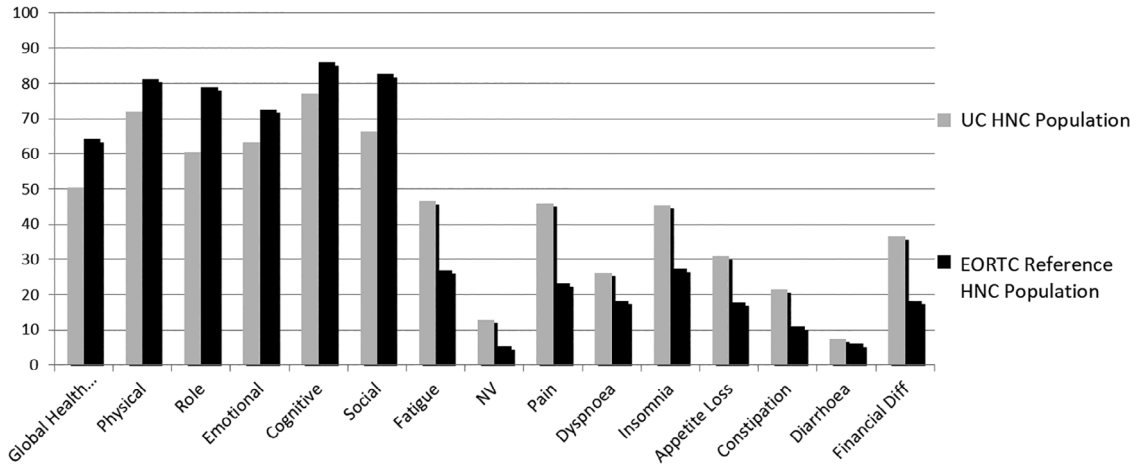

Fig. 1. Average scores reported on the EORTC QLQ-30 for HNC patients. EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core-30; HNC = head and neck cancers.

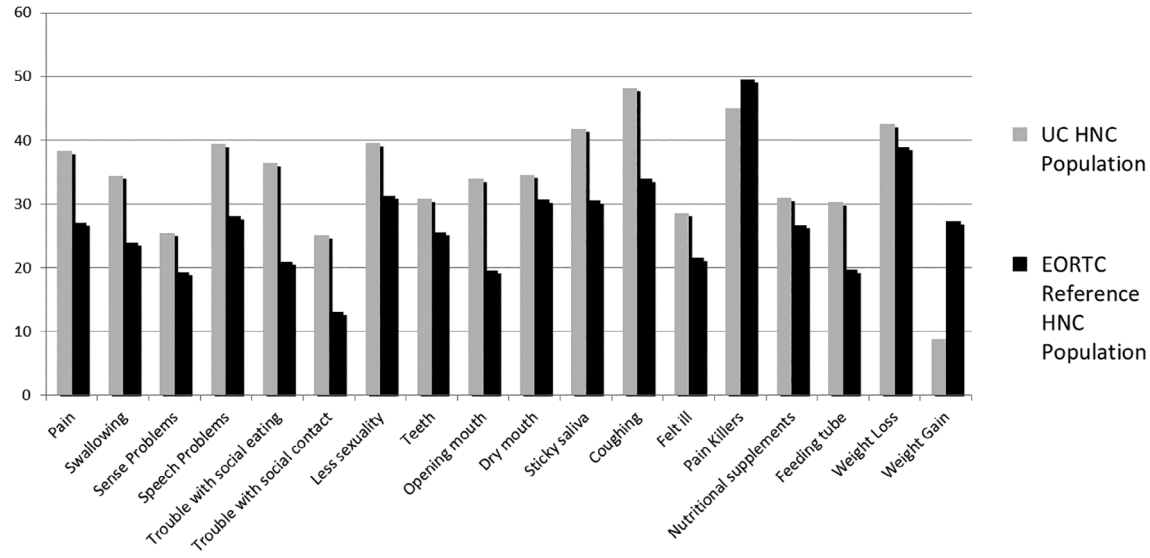

Fig. 2. Average scores reported on the EORTC QLQ-HN35 for HNC patients. EORTC QLQ-HN35 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire head and neck module-35; HNC = head and neck cancers.

study population. Using the EORTC data, we compared the means of the reported scales to our patient-reported data. Univariate analysis was conducted using our retrospectively collected patient information to determine associations between variables of interest. Multivariate analysis (MVA) was performed using basic multiple logistic regression analysis. No stepwise or backward elimination models were used because all variables were removed with these approaches. This analysis did not exclusively include statistically significant variables found in our univariate analyses, but also variables that we held strong suspicion could have been confounders but did not reach statistical significance given our small sample size. These variables included lack of pain medication prescription, age > 65 years, previous treatment status, and disease stage.

RESULTS

The demographics of the 62 HNC patients are summarized in Table I. The population is predominantly male (69.35%), with the majority of patients under 65 years old (62.90%). A significant number of patients had a history of cigarette smoking (72.58%) and a prescription for narcotic pain medication (70.97%) at the time of consultation. Of the patients who required a pain medicine prescription, 92% notably had a prescription for narcotic medication.

Primary tumors characteristics of the 62 HNC patients are also summarized in Table I. The oropharynx and oral cavity were the most common primary tumor sites (each 27.42%), followed by the larynx (22.58%). At the time of initial consultation, 83.34% of patients presented with advanced stage (American Joint Committee on Cancer III or IV) cancer, and 56.45% of patients had received previous treatment for the tumor in question. Twenty-two of the patients had undergone surgery within 30 days prior to consultation, six patients within 1 to 3 months, and the remainder range from 6 months to several years prior to consultation. For comparison, Table I also outlines the analogous characteristics of the HNC population used to determine the EORTC QLQ-C30 reference values.

Patient responses to the EORTC QLQ-C30 are divided into a global QoL scale, five functional scales, three symptom scales, and six single items.[9] The average scores of responses in these 15 categories are represented in Figure 1 for both the University of Cincinnati HNC patient population and the reference EORTC HNC population. A higher score for the functional scales indicates a higher level of functioning. The average rating of the global function scale was 50.31 for the University of Cincinnati population, lower than the reference population and with significant heterogeneity (standard deviation = 24.71, SE = 3.36). Average scores on all five functional scales were also below the mean reference values for HNC patients (P = .50): physical function 71.9 (University of Cincinnati) versus 81.2 (EORTC), role 60.4 versus 78.9, emotional function 63.3 versus 72.5, cognitive function 77.0 versus 85.9, and social function 66.4 versus 82.6.[11] The differences in average score of symptom scales between the two populations are not significant (P = .593), nor are the differences in single item scales (P = .531). However, among the symptom scales/items, our patient population reported the highest scores in fatigue (average 46.69), pain (average 45.99), and insomnia (average 45.32). HNC mean reference values for these categories were 26.9, 23.2, and 27.3, respectively. Higher scores for the symptom scales indicate higher levels of symptomatology.

TABLE II.
Cochran–Mantel–Haenszel Univariate Analysis of Association With Higher Pain Reporting.

Characteristic	Odds Ratio	95% CI	*P* Value
EORTC QLQ-30			
Tumor size ≥ 4 cm	3.06	1.01–9.24	**.046**
No pain med prescription	2.93	0.86–9.95	.080
Male gender	2.97	0.85–9.95	.080
p16 positive	2.33	0.80–10.42	.085
Age > 65 years	0.46	0.15–1.41	.171
Previous treatment received	1.78	0.62–5.16	.289
Government insurance	1.76	0.59–5.29	.314
Current cigarette smoker	0.44	0.08–2.30	.322
Lymph node involvement	0.81	0.29–2.31	.699
Advanced stage (III, IV)	1.22	0.32–4.63	.766
EORTC QLQ-HN35			
Tumor size ≥ 4 cm	0.51	0.18–1.41	.197
No pain med prescription	0.51	0.15–1.75	.285
Male gender	2.74	0.88–8.55	.081
p16 positive	1.47	0.52–4.17	.475
Age > 65 years	0.73	0.26–2.06	.556
Previous treatment received	1.02	0.37–2.78	.974
Government insurance	0.56	0.53–4.58	.419
Current cigarette smoker	0.255	0.048–1.34	.092
Lymph node involvement	3.12	1.07–9.05	**.035**
Advanced stage (III, IV)	2.17	0.578–8.13	.249

CI = confidence interval; EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core-30; HN35 = head and neck module-35; med = medication.

TABLE III.
Cochran–Mantel–Haenszel Univariate Analysis of Association With Higher Pain Reporting on the EORTC QLQ-C30.

Tumor Subsite	Odds Ratio	95% CI	*P* Value
Oral cavity	2.49	0.79–7.81	.115
Oropharynx	0.63	0.19–2.08	.445
Thyroid	0.55	0.02–13.96	.443
Larynx	0.61	0.17–2.23	.457
Hypopharynx	1.76	0.23–13.43	.584
Salivary gland	0.83	0.14–4.95	.842
Nasopharynx	0.84	0.07–9.82	.891

CI = confidence interval; EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core-30.

TABLE IV.
Comparison of Studies Evaluating EORTC QLQ-30 and EORTC QLQ-HN35 Associations With Higher Pain Reporting.

Characteristic	Lopez et al. (n = 109) *P* Value	Oliveira et al. (n = 127) *P* Value	Hammerlid et al. (n = 232) *P* Value	Our Study (n = 62) *P* Value
EORTC QLQ-30				
Age	**.009**		*	.171
Sex	.281		*	.085
TNM stage	.546	**.001**	*	.766
Tumor location	.27			.115
Treatment received	.276			.289
EORTC QLQ-HN35				
Tumor location	.605			*
Age	.212		*	.556
Sex	.653		*	.081
TNM stage	.803	**< .001**	**< .05**	.249
Treatment received	**.045**			.974
Node status				**.035**

*Indicates no significance.
EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core-30; HN35 = head and neck module-35; TNM = tumor–node–metastasis.

The EORTC QLQ-HN35 emphasizes head and neck cancer-specific assessment, involving seven multi-item scales (pain, swallowing, senses, speech, social eating, social contact, and sexuality) as well as eleven single items. Figure 2 illustrates the average score of responses to questions in these 18 categories for both the University of Cincinnati HNC population and the EORTC reference HNC population. We found higher average pain reporting among our population in comparison to the published reference mean for this module (38.2 vs. 27.1, respectively).[11] However, our population reported lower average use of pain medication than the reference mean (45.1 vs. 49.5). The only other symptom for which our population reported a lower average score was weight gain (8.8 lbs. vs. 27.3). Average score differences between the two populations among the seven multi-item scales were not significant ($P = .50$), nor were differences in the 11 single items ($P = .61$).

Compared with all respondents to the EORTC QLQ-C30 among our new patient consults (n = 338), HNC patients reported significantly higher levels of pain at the time of consultation (OR = 2.1, $P = .0007$). As mentioned above, our HNC population also reported a higher average pain score than the EORTC reference population mean, despite lower pain medication use. We used the published mean pain score from the reference population (27.1) as a cutoff for patients reporting high versus low pain in our analysis. Univariate analysis was performed to assess for association between the characteristics outlined in Table II, with higher pain reporting in our population. We found tumor size ≥ 4 cm to be significant ($P = .046$) upon analysis of the EORTC QLQ-C30 survey data. Univariate analysis for association between stage of disease and pain experience was performed both by individual stage and by grouping higher stage disease (stage III and IV), none of which produced a significant association with higher pain reporting in our population.

MVA was performed on the EORTC QLQ-C30 data using the following variables: lack of pain medication prescription, age > 65 years, previous treatment status, and disease stage. Analysis by backward stepwise elimination revealed lack of pain medication prescription ($P = .034$) and age > 65 years ($P = .048$) to be significantly associated with higher pain reporting.

We also performed univariate analysis using the same initial set of characteristics to assess for an association with pain reporting in the EORTC QLQ-HN35 module, the results of which are shown in Table II. For the head and neck module, lymph node involvement was significantly associated with higher pain reporting at the time of consultation. MVA of this module revealed no significant findings.

We also performed univariate analysis for association with higher pain reporting stratified by specific tumor site. We found that the primary tumor site is not significantly correlated with the severity of pain reported. These results are outlined in Table III.

DISCUSSION

In this study, we attempt to better characterize risk factors for higher pain levels reported at the time of consultation for radiation treatment in the HNC population. Tumor size ≥ 4 cm and lymph node involvement at the time of consultation are significantly correlated with higher pain reporting in our patient population. Twenty-two patients had undergone surgery within 30 days prior to consultation, and three of these 22 patients did not have a pain medication prescription at the time of consultation. Although recent surgery is likely associated with higher levels of pain reporting, in this subset previous

treatment was not found to be significantly associated with pain score. Tumor subsite was also not significantly associated with increased pain.

While assessing for pain associations in our patient population, we noted worse QoL outcomes in almost all categories compared with the reference EORTC population, although these differences were not significant. A number of possible factors could explain why our patient population reported higher scores in symptomatology and lower functional scale scores than the reference population. The EORTC QLQ-C30 reference manual is based on pretreatment baseline QoL data last published in 2008, whereas more than half of our population received prior treatment (chemotherapy, surgery, radiation, or some combination of these treatments) for the tumor in question.[11] As mentioned above, several of our patients had undergone recent surgery and likely were still suffering increased morbidity from these procedures. Additionally, the reference population data was largely collected from clinical trials and epidemiological studies, which is a selective population that may have a higher performance status than the average patient population in an urban practice. The composition of the patient populations is also not directly comparable. Most (83.3%) of our study population had advanced stage disease (stage III and IV) at the time of presentation versus 59% in the reference HNC population.

As challenging as the interpretation of QoL can be, it is an important component of the patient experience. Unfortunately, the literature discussing pain reporting with relation to QoL outcomes for HNC cancer patients is sparse. Table IV summarizes the results of the three studies that have previously assessed correlations between pain and population or tumor characteristics identified in our extensive literature review. López-Jornet et al. looked at Spanish HNC patients at least 6 months posttreatment and found significant association between pain and patient age in the EORTC QLQ-C30, with patients < 65 years old reporting better QoL scores.[12] One limitation in comparing our data with this study is that nearly half our population is treatment-naïve. Moreover, in the current study we analyzed pain score prior to treatment completion. We did not find age to be significantly correlated with pain outcomes on univariate analysis, but this finding could indicate that younger populations are more tolerant of treatment and thus report better QoL outcomes.

In another study, Oliveira et al. analyzed patients with untreated head and neck squamous cell carcinoma. They looked only at whether pain reporting is affected by tumor–node–metastasis (TNM) stage and found significant associations in the EORTC QLQ-HN35 module but not in the EORTC QLQ-C30.[8] In the third study, Hammerlid et al. assessed QoL in Swedish patients for 3 years following initial HNC diagnosis.[13] They did not find any significant association between pain and age, sex, or TNM stage. One limitation of our study, and the comparison of those described above, is that our dataset comes from a single point in time, when the patients initially presented for radiation oncology consultation. Although we do not assess our patients over time in this study, we use a consistent data point in our department. This is also a clinically meaningful time point in that this pain is explicitly not due to acute toxicity attributable to radiation treatment, with nearly half (44%) of patients having received no prior treatment at all. In the referenced studies above, each study assesses patients at a different phase of the treatment process. As demonstrated with just these four studies, the limited data available regarding pain reporting in HNC patients is heterogeneous. This is a difficult area of study due to the subjective nature of response; the variety of treatment paradigms employed; and the wide variety of clinical, social, and financial factors to account for.

There was no association with prior treatment and pain in our study, although 56% of our patients did have some type of prior treatment before consultation with radiation oncology. However, there remains concern about subjective pain and worse patient-reported QoL outcomes with the rising incidence of multimodality therapy. There is emerging data to support this for other treatment sites, including prostate and colon cancers,[14,15] but there is limited data on the effects of long-term toxicity in the HNC population with multimodality treatment. One 2015 study by Taberna et al. found significantly increased late toxicity following radical treatment of locally advanced cancers in HNC patients, suggesting a correlation of worse QoL measures with increasingly aggressive treatment.[16] And whereas López-Jornet et al. suggest an association with prior treatment at least 6 months from treatment completion, our study is limited in that it evaluates pain at a single time point prior to radiation treatment. Despite these limitations, clearly symptom management is a concern for patients throughout their cancer care. Further thought should be given to the development of multidisciplinary nurse navigation or the inclusion of longitudinal symptom management clinics, with specific attention to pain assessment and management.

In our study population, univariate analyses for associations between higher pain reporting and specific characteristics revealed significant association with tumor size ≥ 4 cm on the EORTC QLQ-C30 and lymph node involvement in the head and neck module. MVA revealed significant associations of older age and lack of pain prescription, with higher pain reporting in the EORTC QLQ-C30 data but no significant associations in the head and neck module. This lack of agreement between the univariate and multivariate models could be explained by small sample size, missing data, larger-than-expected variation within groups, or potentially an unmeasured interaction. Additionally, we looked at whether patients had prescriptions for pain medications but not medication usage at the time of consult. There could be inconsistencies between what the patient has available and what is actually used, which could affect our results. Inconsistent findings of significant associations between patient or tumor characteristics with higher pain reporting are to be expected, with differences in patient populations and

time of data collection regarding QoL. These are known limitations of studying patient-reported outcomes; nonetheless, these results remain valuable in targeting symptom management and care for the HNC population throughout cancer treatment.

CONCLUSION

It has been determined by the EORTC QoL Group that the EORTC QLQ-HN35 module is missing important QoL issues faced by HNC patients following targeted or multimodal therapy.[5] An updated module has been created to better address the side effects of current treatment modalities.[17] This new tool may be able to better inform us of the factors affecting HNC patients' pain to guide treatment teams' targeted care and improve QoL outcomes. It will also be important to standardize the completion of these survey tools for more rigorous data, for instance, making sure the patient completes the survey and not the caregiver.

The goal of the EORTC QoL surveys is not to evaluate pain per se but rather functional impairment as a result of pain. Ideally, the metrics presented here would be paired with unidimensional pain scores (typically acquired by clinic nurses). The advantage of unidimensional pain scores is that they are simple, able to confirm the presence of pain, and can be used to evaluate pain over time. Multidimensional pain tools including the Brief Pain Inventory and the McGill Pain Questionnaire have the added advantage of assessing not only location and severity of pain but also impairment; therefore, they may be more useful in the oncologic setting.[18,19] There remains a paucity of data evaluating factors leading to the increased pain experienced by head and neck cancer patients. The subjective experience of patients has proven exceedingly difficult to evaluate. However, by identifying and recognizing factors associated with increased pain in this population, treatment teams can better predict which HNC patients will suffer worse QoL as a result of their disease or treatment course and then target appropriate interventions.

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