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Survival Patterns in Squamous Cell Carcinoma of the Head and Neck: Pain as an Independent Prognostic Factor for Survival

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Abstract: **Survival outcomes in patients with squamous cell carcinoma of the head and neck (HNSCC) vary by extent of disease, behavioral factors, and socioeconomic factors. We assessed the extent to which pretreatment pain influences survival in 2,340 newly diagnosed patients with HNSCC, adjusting for disease stage, symptoms, pain medications, comorbidities, smoking, alcohol consumption, age, sex, and race/ethnicity. Patients rated their pain at presentation to the cancer center (0 = "no pain" and 10 = "pain as bad as you can imagine"). Survival time was calculated from the date of diagnosis to the date of death of any cause or last follow-up. Five-year overall survival was calculated for all the variables assessed in the study. Severe pain (≥7) was most prevalent among those with oral cancer (20.4%; pharynx = 18.8%; larynx = 16.1%) and significantly varied by tumor stage, fatigue severity, smoking status, comorbid lung disease, and race (all *P* < .05) across cancer diagnoses. Overall 5-year survival varied by pain for oral (severe pain = 31% vs nonsevere pain = 52%; *P* < .001) and pharyngeal cancer (severe pain = 33% vs nonsevere pain = 53%; *P* < .001). Multivariable analyses showed that pain persisted as an independent prognostic factor for survival. Pain reported prior to treatment should be considered in understanding survival outcomes in HNSCC patients.**

Perspective: ***Pretreatment pain was an independent predictor of survival in a large sample of HNSCC patients even after accounting for tumor node metastasis stage, fatigue, age, race/ethnicity, smoking, and alcohol intake. Therefore, symptoms at presentation and before cancer treatment are important factors to be considered in understanding survival outcomes in HNSCC patients.***

Key words: *Pain, depression, fatigue, symptoms, survival, head and neck.*

Head and neck cancer is the sixth most common malignancy worldwide. Squamous cell cancer of the head and neck (HNSCC) is the most common head and neck cancer, which includes cancers of the oral cavity (including the gums and tongue), pharynx, and larynx. In the United States, more than 53,640 men and women are expected to be diagnosed with head and neck cancers in 2013.[1] Relative to certain other cancers, patients with HNSCC have a better prognosis. For all stages combined, the 5-year survival rates for oral and pharyngeal cancers and laryngeal cancers are 56% and 62%, respectively.[1] However, an estimated two thirds present with advanced stage of disease and with debilitating symptoms that impact their quality of life.

Pain is often one of the first signs of head and neck cancer. Head and neck cancer pain may be due to the disease itself (tumor) or may be a consequence of therapy. Nociceptive pain may arise as a result of the destructive lesions and direct bone and soft tissue involvement,[22] and neuropathic pain may arise as a result of the invasion of nerves, the inflammatory milieu adjacent to nerves, and the toxicity of treatment.[6,22] Acute pain due to therapy is extremely common secondary to ablative surgery and chemo- and/or radiotherapy.[11,24] Up to 80% of patients with head and neck cancer report pain during treatment, and for some 36%, pain persists beyond treatment.[9] To date, limited data exist on pretreatment pain and its influence on survival outcomes in head and neck cancer patients.

Tumor (T), node (N), and metastasis (M) stage (TNM stage) is the single most important prognostic factor

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and treatment determinant in HNSCC. Patients diagnosed in early stages have better prognosis and health outcomes. Behavioral factors such as alcohol intake and smoking[10,31] have also been shown to influence survival outcomes. Although a number of studies also suggest the importance of pain as an independent predictor of survival in patients with HNSCC and other cancers,[14,19] the limited sample size and a lack of comprehensive assessment of clinical (disease stage, comorbid conditions), behavioral (smoking, alcohol consumption), and epidemiologic (age, sex, race/ethnicity) factors known to influence survival in HNSCC limit the generalizability of study findings.

In the present study, we used a large sample of patients (N = 2,340) with HNSCC to assess the importance of pain reported at diagnosis, prior to cancer treatment, in predicting survival outcomes. We assessed the relative importance of pain on survival by including the assessment of clinical (disease stage, comorbid conditions), behavioral (smoking, alcohol consumption), and epidemiologic (age, sex, race/ethnicity) factors known to influence survival in HNSCC. Because studies show a high correlation between pain, depression, and fatigue, we also included these symptoms as covariates in our analyses. In the United States, the treatment and management of patients with cancer is based on a multidisciplinary approach, with symptom control as an important aspect in the care of patients with HNSCC. Therefore, understanding the extent to which pretreatment pain reported at presentation impacts survival outcomes has a high clinical significance.

Methods

Study Population

The study population included newly diagnosed patients with HNSCC presenting to the University of Texas M.D. Anderson Cancer Center from January 1, 2000, through December 31, 2009, who received treatment at the Center for HNSCC. This study was approved by the institutional review board at the M.D. Anderson Cancer Center.

Epidemiology and Clinical Data Collection at Presentation to the Cancer Center

Trained M.D. Anderson staff administered questionnaires to patients presenting at the Cancer Center, prior to being seen by clinicians. The questionnaire was developed by an interdisciplinary team of scientists representing the areas of epidemiology, behavioral science, and medical oncology, among others. The overarching goal was to understand the epidemiology of the different types of cancers and the underlying factors associated with, and risk factors for, cancer, cancer progression, and survival outcomes. Many questionnaire items were considered, but the committee was very cognizant of patient burden, and the final set of questions was decided through consensus. Clinical data including stage of disease were abstracted from patients' charts.

Outcome Variable

Survival time was calculated from the date of diagnosis to the date of death of any cause or last follow-up. Patients who were lost to follow-up or were still alive at the end of the follow-up period were considered right-censored in the analyses. Five-year overall survival was calculated for all the variables assessed in the study.

Main Independent Variable

Patients were first asked "Have you experienced pain in the last week?" and asked to "circle the number that best describes the pain you are having" on an 11-point numeric scale (0 = "no pain" and 10 = "pain as bad as you can imagine"), a recommended standard for pain assessment in clinical studies of pain.[5]

Other Cofactors (Potential Confounders)

Clinical factors included the extent of disease using the American Joint Committee on Cancer TNM and comorbid conditions. TNM classification, which includes information on the primary tumor, lymph node involvement, and distant metastasis, was abstracted from medical records by trained and certified tumor registrars. Comorbidities reported by the patients included heart disease, stroke, hypertension, diabetes, and lung disease.

Because studies show a high correlation between pain, depression, and fatigue, we also used "During the past 4 weeks, have you felt downhearted and blue?" and "During the past 4 weeks, did you have a lot of energy?" to assess depressed mood and fatigue, respectively. These items, with a 6-point Likert-type response format, were taken from the 12-Item Short Form Health Survey (SF-12). The SF-12 is a validated measure of quality of life and is extensively used in studies of cancer patients.[34-37]

Behavioral factors included smoking and alcohol intake. Smoking and alcohol intake were assessed at time of presentation and prior to treatment. Smoking was categorized as never smoker, former smoker, and current smoker. Alcohol intake was classified as never, social, moderate, and heavy alcohol use. Heavy alcohol use was defined as 4 or more drinks per day for males and females. Alcohol use was classified as moderate if a patient reported alcohol consumption of greater than 14 drinks per week for males and 7 drinks per week for females[18] but 4 or fewer drinks per day.

Epidemiologic factors included age (at cancer diagnosis), sex, and race/ethnicity. Race/ethnicity was defined as non-Hispanic white, non-Hispanic black, and Hispanic.

Pain Medications

Charts were reviewed for information on pain medications reported by patients at presentation to the Cancer Center. We used the World Health Organization (WHO) 3-step ladder to categorize the medications, as follows: Level 1 includes nonopioid medication such as aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs; Level 2 includes weak opioids such as codeine; and Level 3 includes powerful opioids such as morphine.

These categorizations were reviewed by a pain specialist (K.H.T).

Statistical Analyses

Descriptive statistics were used to summarize the patient characteristics. The Kolmogorov-Smirnov Z test was used to assess the normality distribution for pain, fatigue, and depressed mood. Because normality was not met, we used the National Comprehensive Cancer Network cut-off score of ≥7 for severe pain.

On the basis of our previous studies,[25,26] we also combined responses to the SF-12 questionnaire. For the question "During the past 4 weeks, have you been feeling downhearted and blue?," responses of "most of the time" and "all of the time" were combined to indicate severe levels of depressed mood, and "none of the time," "little of the time," "some of the time," and "good bit of the time" were combined to indicate nonsevere levels of depressed mood. For the fatigue question ("During the past 4 weeks, have you had a lot of energy?"), we combined the responses "none of the time" and "little of the time" to indicate severe levels of fatigue and the responses "most of the time," "all of the time," "some of the time," and "good bit of the time" to indicate nonsevere levels of fatigue.

Pearson's chi-squared tests were used to assess the relationship between pain and clinical, behavioral, and sociodemographic factors. Using the Kaplan-Meier method, we generated 5-year overall survival by selected characteristics and assessed statistical significance using log-rank test. Univariate and multivariable Cox proportional hazards regression analyses were used to estimate the strength of association for variables using hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariable model assessed the effect of pain severity on survival while controlling for pain treatment and clinical (extent of disease, comorbid conditions), epidemiologic (age, sex, race/ethnicity), and behavioral (smoking, alcohol consumption) factors and symptoms (fatigue and depressed mood) found significant in the univariate model ($P < .05$). All statistical analyses were performed using SPSS software (SPSS Inc, Chicago, IL). All of the statistical tests were 2-sided.

Results

Characteristics of the Study Sample

A total of 2,340 patients with HNSCC comprised our sample: 1,196 with cancer of the oral cavity, 696 with cancer of the pharynx, and 448 with cancer of the larynx. A majority of the sample were men (n = 1,788; 76%) and non-Hispanic whites (1,859; 80%). Mean age for the total sample was 59 years (SD = 11.7). The most commonly reported comorbid condition was hypertension (n = 970; 41.5%), followed by heart disease (n = 433; 18.5%) and diabetes (n = 288; 12.3%). One in 4 patients (24.5%) were current smokers and 22% were heavy drinkers. Patients with laryngeal cancer had the highest proportion of heavy drinkers (31%, vs 19.3% for oral and 28.8% pharyngeal; $P < .001$) and smokers (35.6%, vs 20.2% for oral and 26.4% pharyngeal; $P < .001$).

Pain Severity

Severe pain was reported by as many as 19% of the total sample and was most prevalent among those with oral cancer (20.4%), followed by pharyngeal (18.8%) and laryngeal (16.1%).

Table 1 shows that tumor stage, smoking status, lung disease, and race were significant covariates of severe pain ($P < .05$) across all cancer diagnoses (oral, pharyngeal, and laryngeal). Interestingly, alcohol intake was a significant covariate of severe pain for those with oral ($P < .001$) and pharyngeal cancer ($P < .001$) but not for patients with cancer of the larynx. Patients reporting heavy alcohol intake had the highest proportion reporting severe pain. More female patients (24.2%) with oral cancer also reported severe pain relative to males (19%).

Severe fatigue was a significant covariate of severe pain across cancer diagnoses (oral, pharyngeal, and laryngeal), and depressed mood was observed to significantly covary with severe pain among those with oral and pharyngeal cancers but not for those with laryngeal cancer. We also found that pain treatment, categorized using the WHO step ladder, significantly varied by pain severity.

Survival Outcomes

There was a total of 828 deaths (oral = 416, pharyngeal = 251, laryngeal = 161). Median survival (in days) was as follows: oral = 3,143 (95% CI = 2,790, 3,495), pharyngeal = 3,307 (95% CI = 2,628, 3,985), and laryngeal = 3,119 (95% CI = 2,440, 3,797). Fig 1 shows Kaplan-Meier estimates of the effect of pain on survival for the entire sample.

Univariate analyses for 5-year overall survival (data not shown) show that among patients with oral cancer, overall 5-year survival was 31% among those with severe pain versus 52% of those without severe pain ($P < .001$). Similarly, among those with pharyngeal cancer, those reporting severe levels of pain, comprising 33% (nonsevere = 53%; $P < .001$), had lower 5-year overall survival.

As expected, extent of disease using TNM as separate variables for tumor size, lymph node involvement, and metastasis were also significant factors, along with behavioral factors (alcohol intake, smoking status), comorbid conditions (heart disease, lung disease, hypertension, stroke), age, and race.

Multivariable Analyses

We conducted multivariable analyses to assess the extent to which symptoms influence survival outcomes for the whole sample by including factors known to influence survival in cancer patients. The variables found significant in the univariate model ($P < .05$) were included in the analyses. We observed (data not shown) that compared to patients with laryngeal cancer, patients with oral cancer and pharyngeal cancer are at an increased risk of mortality (oral HR = 1.39 and pharyngeal HR = 1.52). Pain (HR = 1.30, 95% CI = 1.03, 1.63; $P < .025$) and fatigue (HR = 1.30, 95% CI = 1.06, 1.59; $P < .011$) were significant predictors for overall survival in HNSCC patients. As expected, extent of disease (TNM), smoking

Table 1. Severe Pain by Selected Characteristics*

	Oral (N = 1,196)		Pharynx (N = 696)		Larynx (N = 448)	
Variable	No/Yes	P	No/Yes	P	No/Yes	P
All individuals	952/244		565/131		376/72	
TNM classification						
Tumor		<.001		<.001		.001
0–2	557/87		303/32		189/22	
3–4	343/147		251/90		176/49	
Node		NS		NS		NS
0	356/78		107/28		223/39	
1	120/44		76/13		33/12	
2	176/48		126/25		58/16	
3	37/10		36/16		14/2	
Metastasis		NS		.010		NS
Nonmetastatic	891/233		545/116		360/70	
Metastatic	8/2		8/7		5/0	
Comorbidities						
Heart		.035		.013		NS
No	783/186		480/99		298/61	
Yes	169/58		85/32		78/11	
Lung		.049		<.001		.005
No	871/213		528/109		321/51	
Yes	81/31		37/22		55/21	
Hypertension		NS		NS		NS
No	567/145		351/78		196/33	
Yes	385/99		214/53		180/39	
Stroke		NS		NS		NS
No	918/232		541/120		356/70	
Yes	34/12		24/11		20/2	
Diabetes		.282		.047		NS
No	836/208		507/109		332/60	
Yes	116/36		58/22		44/12	
Behavioral factors						
Alcohol		<.001		<.001		NS
Never	296/79		134/21		92/23	
Social	323/47		188/19		103/14	
Moderate	119/24		81/20		48/6	
Heavy	142/70		131/56		106/24	
Smoking		<.001		<.001		.003
Never	378/71		172/15		44/1	
Yes, but quit	412/90		263/59		208/35	
Yes, current	157/83		126/57		123/36	
Sociodemographic						
Age (years)		NS		NS		NS
<50	183/60		107/28		56/15	
≥50	769/184		458/103		320/57	
Gender		.053		NS		NS
Male	704/165		455/111		301/52	
Female	248/79		110/20		75/20	
Race		<.001		<.001		.020
Non-Hispanic white	778/171		487/95		277/51	
Hispanic	78/34		35/14		44/3	
Non-Hispanic black	33/23		21/18		42/15	
Symptoms						
Depressed mood		<.001		<.001		NS
None–moderate	838/175		498/88		310/56	
Severe	48/49		35/31		31/11	
Fatigue		<.001		<.001		<.001
None–moderate	662/88		410/45		245/17	
Severe	201/120		105/68		92/47	

Table 1. Continued

	Oral (N = 1,196)		Pharynx (N = 696)		Larynx (N = 448)	
Variable	No/Yes	P	No/Yes	P	No/Yes	P
WHO ladder		<.001		<.001		<.001
None	696/139		430/76		283/40	
Level 1	110/19		47/11		38/8	
Level 2	105/53		64/27		40/9	
Level 3	41/33		24/17		15/15	

*Missing data for some variables.

and alcohol intake, lung disease, and age and race were also significant predictors of survival. When we accounted for pain treatment, using WHO step ladder categories, Table 2 shows that pain and fatigue, disease-related variables (TNM), and sociodemographic (age and race/ethnicity) and behavioral factors (smoking and alcohol intake) persisted as important factors for survival.

Discussion

Our study is one of the first to examine pretreatment pain severity as a predictor of survival in a large sample of HNSCC patients. The results indicate that pretreatment pain is an independent predictor of 5-year overall survival in patients with HNSCC. Previous studies have found that pain severity at post treatment[30] and 2 years after treatment[32] were significant predictors of survival in patients with head and neck cancer; however, these studies had limited sample size and lacked a comprehensive assessment of the influence of clinical (disease stage, comorbid conditions), behavioral (smoking, alcohol consumption), and epidemiologic (age, sex, race/ethnicity) factors known to influence survival in HNSCC, thus limiting the generalizability of study findings.

Studies have hypothesized the potential link between symptoms and survival as reflecting inflammatory processes that also underlie cancer progression; for example, increased preoperative concentration of C-reactive protein was found to be associated with poorer survival in patients with oral cancer.[7] Pain molecules including endothelin, prostaglandin, bradykinin, and nerve growth factor—molecules that have been shown to evoke pain in animal models—also influence growth and neovascularization of tumors.[17] Another study[15] demonstrated a direct role for protease-activated receptor 2 (PAR2) in acute cancer pain. PAR2 is known to uniquely trigger tumor cell migration. The authors suggested that PAR2 upregulation may favor the development and maintenance of chronic cancer pain and that targeting the PAR2–serine protease interaction is a promising approach to the treatment of acute cancer pain and prevention of chronic cancer pain. Additional research is needed to explore the biological mechanisms that might explain the association between pain and survival in HNSCC.

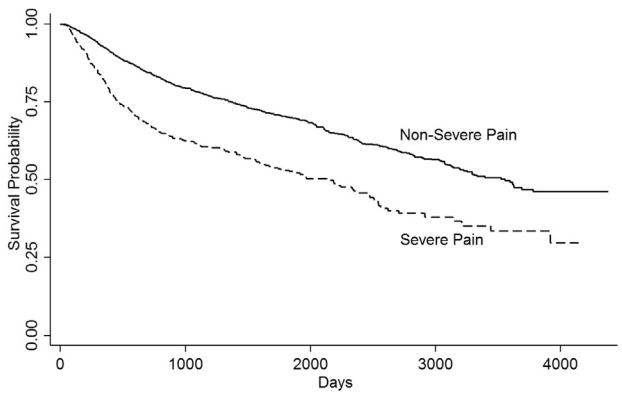

Figure 1. Kaplan-Meier estimates of the effect of pain on survival probability.

Severe pain was reported prior to cancer treatment by 19% of the total sample and was most prevalent (20.4%) among patients with oral cancer. These results are somewhat higher than those found in a previous study of patients with HNSCC. Scharpf and colleagues[30] found a prevalence rate for severe pretreatment pain of 10.9% in a sample of 339 patients with head and neck cancer. However, a study of Sato and colleagues[29] showed that 37% of patients with untreated primary oral cancer reported spontaneous pain. The differing prevalence rates may be due to characteristics of these samples, including sample size and the distribution of oral, pharyngeal, and laryngeal cancers. In addition, pain in cancer patients may arise from several factors, including tumor growth, treatment, or other causes unrelated to cancer. In our sample, pain was assessed prior to treatment, thus excluding treatment-related pain, but we cannot exclude pain unrelated to cancer (eg, back pain).

It is not surprising that we observed severe pain as more common among cancer patients with advanced disease. Pain in advanced cancer may result from the primary activation of visceral or somatic nociceptors by a metastatic tumor (nociceptive pain), the impingement of the tumor on adjacent tissues,[22] the obstruction of blood vessels, or the inflammation caused by tumor-induced mediators, such as cytokines.[28] The finding that severe pain was more prevalent among non-Hispanic black and Hispanic patients is consistent with other studies demonstrating a higher prevalence of severe pain among racial and ethnic minority patients with cancer.[2] The racial and ethnic differences in pain persisted even when we stratified by stage of disease or TNM stage. Additional research is needed to identify the causes of the higher pain prevalence among minority patients with head and neck cancer.

Table 2. Predictors of Survival in Patients With HNSCC (Multivariable Analyses)

Variable	Odds Ratio	95% CI Lower	95% CI Upper	P Value
Cancer				.004
Larynx	1.0	Ref		
Oral	1.111	.896	1.379	.337
Pharynx	.719	.567	.912	.007
Symptoms				
Pain severity (0–10)	1.038	1.005	1.073	.023
WHO ladder				
None	1.0	Ref		.286
Level 1	1.033	.759	1.406	.835
Level 2	.818	.614	1.089	.169
Level 3	1.215	.860	1.716	.269
Fatigue severity				
Nonsevere	1.0	Ref		
Severe	1.302	1.06	1.59	.011
TNM classification				
Tumor				
0–2	1.0	Ref		
3–4	1.646	1.355	1.999	<.001
Node				<.001
0	1.0	Ref		
1	1.117	.868	1.437	.391
2	1.141	.905	1.437	.264
3	2.229	1.628	3.052	.000
Metastasis				
Nonmetastatic	1.0	Ref		
Metastatic	4.220	2.525	7.052	.000
Comorbidities				
Lung diseases				
No	1.0	Ref		
Yes	1.527	1.194	1.954	.001
Behavioral factors				
Alcohol intake				.077
Nondrinker	1.0	Ref		
Social	.989	.765	1.279	.933
Moderate	1.175	.869	1.588	.294
Heavy	1.314	1.019	1.695	.035
Smoking				<.001
Never	1.0	Ref		
Yes, but quit	1.557	1.188	2.040	.001
Yes, current	1.882	1.406	2.518	.000
Sociodemographic				
Race				.025
Non-Hispanic white	1.0	Ref		
Hispanic	.950	.690	1.308	.753
Non-Hispanic black	1.514	1.110	2.064	.009
Age (years)				
<50	1.0	Ref		
≥50	2.256	1.686	3.018	.001

It should be noted that the significant covariates of severe pain differed somewhat across cancer diagnoses. Metastatic disease was a significant covariate among patients with cancer of the pharynx but not among patients with oral or laryngeal cancer. Alcohol intake was a covariate of severe pain for patients with oral and pharyngeal cancers. Associations between pain and alcohol consumption have been shown in population-based studies.[4,20] However, there have been limited investigations of these associations in cancer patients. Among patients with oral cancer, we observed that more women than men with oral cancer report severe pain. This is consistent with previous studies of orofacial pain. Women have a greater risk of pain and report more severe pain, more frequent pain, and longer pain durations than men.[8] These gender differences are partially attributed to the action of sex hormones, which may influence central and peripheral mechanisms of nociceptive pain transmission, pain sensitivity, and pain perception.[38]

We also observed that compared to patients with laryngeal cancer, patients with oral or pharyngeal cancer are at an increased risk of mortality (oral HR = 1.39 and pharyngeal HR = 1.52). Although these results can be partially explained by the fact that there are more effective surgical treatment options for salvage of recurrent laryngeal cancer compared to oral and pharyngeal cancers, it should be noted that when we accounted for pain medications, the increased risk for mortality among patients with oral cancer was no longer statistically significant.

We observed that patients who smoke had a higher prevalence of severe pain than nonsmokers.[21,33] It has been hypothesized that smoking has a bidirectional relationship with pain. Smoking leads to physiologic changes, that is, downregulation in the hypothalamic pituitary axis that may increase pain sensitivity and pain perception. Alternatively, smoking is a way of coping for patients with pain. Additional studies are needed to further explore this relationship in patients with cancer.

Severe fatigue and depression were significantly associated with severe pain in our patient sample. These findings are consistent with other studies[27] demonstrating that the 3 symptoms are often associated in samples of patients with cancer. For many patients with cancer, receiving a diagnosis of a potentially fatal disease and the prospect of aggressive disease management generate significant emotional turmoil. Most individuals with cancer report some feelings of distress, depression, or anxiety during the course of their disease and its treatment.[23] Scharpf and colleagues[30] found that posttreatment depression was significantly associated with severe pain in their sample of patients with head and neck cancer. Fatigue has been correlated with severe pain and depression in other samples of patients with cancer. It has been suggested that these symptoms share common biological pathways and may be related to inflammatory changes associated with cancer and cancer treatment.[16,28]

In addition to pain, fatigue was a significant predictor of survival across cancer diagnoses. Fatigue is one of the most common and distressing symptoms associated with cancer.[3] To our knowledge, our study is one of the first to evaluate pretreatment fatigue as a predictor of survival in head and neck cancer patients. A previous study of breast cancer patients found that fatigue was a significant predictor of recurrence-free survival, after controlling for clinical variables.[13] Indeed, both pain and fatigue may be important markers for survival due to

their association with inflammatory changes. Among cancer patients, chronic inflammation acts as a tumor promoter, resulting in aggressive tumor growth and spread.

Aside from pain and fatigue, significant predictors of overall survival across cancer diagnoses (oral, pharyngeal, laryngeal) in multivariable analyses included extent of disease (TNM). TNM stage is the single most important risk factor for recurrence and the most important survival and treatment determinant for HNSCC. It also is not surprising that the comorbidity of chronic lung disease influences overall survival. Patients who have comorbid conditions in addition to HNSCC are at risk for early mortality from multiple causes.

Our results also support the importance of assessing alcohol intake and smoking status, behaviors that were significant predictors of survival in our total sample. Patients who report smoking and/or significant alcohol intake can be referred for smoking-cessation programs and/or further assessment and treatment of possible alcohol abuse. Thompson and colleagues[32] found that patients with pain or poor overall quality of life 2 years after diagnosis were more likely to die from all causes, whereas those still smoking were more likely to die from their cancer. They concluded that in addition to older age and advanced stage, pain, poor quality of life, and tobacco use 2 years after diagnosis characterize patients who might need longer and more intense follow-up care.[32]

There are limitations to our study. We did not include type of cancer treatment as a covariate because treatment is driven by extent of disease and thus is inextricably associated with tumor stage (hence high multicollinearity). Information on human papillomavirus status was missing. Studies have found that patients with human papillomavirus–positive tumors tend to have better survival rates than patients with human papillomavirus–negative tumors.[12] Another limitation is our measure of depression, which relied on patient self-report. A structured psychiatric interview would provide a more reliable assessment of clinical depression. Anxiety, a known covariate of pain, was also not assessed.

We also acknowledge that other limitations include the lack of information on the location, type (eg, back pain), and etiology of pain. Further, pain was only assessed at presentation, and follow-up pain assessments were not conducted. The study was also limited to head and neck cancer patients at one tertiary care cancer center. Thus, additional prospective studies are needed to validate our findings.

In sum, our study provides empirical evidence that pain at presentation is a prognostic marker for survival, even after accounting for disease, sociodemographic factors, and other clinical factors associated with survival outcomes. Among the important implications of our findings is that patients who present with severe pain at diagnosis need to be closely monitored, with prompt treatment and management of symptoms incorporated in treatment planning. Additional prospective studies are needed to validate our findings.

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