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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.