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Anxiety symptoms as a predictor of head and neck cancer survival and potential for mediation by cancer treatment response.

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Introduction

Approximately 630,000 people are expected to develop head and neck cancer (HNC) this year, ranking it the sixth most common cancer worldwide(Parkin, Bray, Ferlay, & Pisani, 2005). White males are the most at-risk group for developing HNC--almost 3 times more likely than white females—and tobacco and alcohol use greatly increase that risk(U.S. Cancer Statistics Working Group, 2018). The impacts of HNC on patients include significant decreases in health-related quality of life (HRQOL) paired with invasive surgeries that often result in severe facial disfigurement. Tumors of the head and neck are rarely diagnosed in their early stages and are often aggressive in nature, which emphasizes their high mortality. Additionally, many do not respond well to treatment, causing complications while costing patients valuable time. Therefore, the typical patient newly diagnosed with HNC can expect his/her tumor(s) to already be at an advanced stage, a decline in his/her ability to eat and/or communicate, expensive and invasive multimodal treatment, and facial disfigurement after surgery, if performed. Each of these likely circumstances contribute to patient feelings of anxiety about what brand of suffering awaits him/her, which may influence the patient's attendance to treatment and even the treatment's outcome.

The Diagnostic and Statistical Manual (DSM-5) defines generalized anxiety to be excessive worry that is difficult to control and causes significant impairment in social, occupational, or other important areas of functioning(American Psychiatric Association, 2013). Research has shown evidence of anxiety in HNC patients at all stages of the disease, but its association with clinical outcomes remains underrepresented in the literature(Howren, Christensen, Karnell, & Funk, 2013). For example, one study used a modified distress thermometer to assess "mask anxiety" before and during radiotherapy (RT) but did not investigate the effect of that anxiety on treatment outcomes. "Mask anxiety" does well to illustrate the experience of many HNC patients. RT is the most common treatment for HNC and demands the patient lie motionless under an immobilizing mask for up to 15 minutes while radiation is applied to the target site. RT sessions are thus understandably a source of anxiety for HNC patients, but it is only one of many worries for this patient population. A diagnosis of HNC often includes anxiety for the receiving patient, which, depending on coping style, can decrease treatment adherence(de Oliveira et al., 2017). Anxiety has also been shown to relate to difficulty with remembering and recalling medical information, contributing to the likelihood of making underinformed treatment decisions(Kessels, 2003).

From a traditional physician's perspective, treating a patient's cancer may seem to be the most effective way to alleviate accompanying anxiety. However, this approach neglects to consider an anxious cancer patient's role in treatment, specifically how his/her anxiety may affect adherence to treatment and treatment decisions (e.g. whether to begin chemotherapy). One longitudinal study of 50 Non-Small-Cell Lung Cancer patients found that those who reported

heightened baseline anxiety were significantly more likely to experience treatment delay and/or reduction(Greer, Pirl, Park, Lynch, & Temel, 2008). Rather, coping style, (the patterns of behavior one is likely to respond with when confronted with stress) may provide a more accurate predictor of behavior regarding treatment. An avoidant coping style is characterized by a diversion of attention from a stress-causing stimulus. In the case of a cancer patient, an avoidant coping style could mean that he/she does not return to a healthcare facility for follow-up scans or even for expensive treatments such as RT. As for making appropriate treatment decisions, the presence of anxiety brings with it the potential to misinterpret the severity of one's own condition. As more medical information is presented to a patient, more is forgotten, and the amount forgotten is positively correlated with anxiety level(Ley, 1979). This could include details about the disease's progression or treatment recommendations. For example, in this situation an anxious individual may conclude that he/she is not ill enough to justify beginning a chemotherapy regimen, thus potentially making a decision against his/her best interest due in part to anxiety's influence on his/her memory for medical information. However, anxiety's effects are not limited to treatment adherence and decisions. There are also biological mechanisms that can be uniquely detrimental to cancer patients.

When an individual experiences significant symptoms of anxiety, he/she is subjected to consistently high levels of nervousness and worry that together create the psychological experience of distress. There are numerous physiological consequences of chronic stress such as immune system suppression(Segerstrom & Miller, 2004) and damaged hippocampal receptors causing impaired memory(Wingenfeld & Wolf, 2014). Chronic stress has also been linked to the upregulation of the nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB) pathway, which mediates the synthesis of proinflammatory molecules throughout the body(Gupta et al., 2011). This is significant because when dysregulated, this pathway is heavily implicated in the expression of symptoms of cancer: depression, fatigue, disordered sleep, anxiety, cognitive impairment, cachexia, anorexia, delirium, and neuropathic pain. One study found a clear relationship between anxiety and NF-κB activity in breast cancer patients(Antoni et al., 2012). The experiment involved treating patients with a cognitive-behavioral stress management intervention and measuring the activity of NF-κB at baseline, 6, and 12-month follow-ups. It was concluded that the intervention had a significant effect on the NF-κB pathway, decreasing its activity and therefore decreasing its threat to patient health. This study serves to highlight two ideas important to this paper: how maladaptive thinking - such as that present in anxiety - can influence a patient's physical health via the NF-κB pathway, and how treating that maladaptive thinking has the potential to ameliorate health problems exacerbated by NF-κB activation

Upregulation of NF-κB may be stimulated by distress, diet, chemotherapy, infection, obesity, and addiction with the presence of more than one stimulus creating a cumulative effect on the pathway(Gupta et al., 2011). That is, an individual who is distressed, obese, and/or possesses an infection will have a more active NF-κB pathway than an individual who is only obese (depending on the severity of each condition). Therefore, an individual facing multiple upregulating stimuli has a greater chance of exhibiting the debilitating symptoms of cancer. In a patient already diagnosed with cancer, these upregulating stimuli serve to exacerbate their

condition. Note that chemotherapy itself has been shown to dysregulate NF-κB signaling, meaning that even treatment has the potential to work against the patient to some degree. A typical cancer patient faces more than one of the above stimuli simultaneously and experiences more than one symptom of the disease(Cleeland, 2007). In this situation, a predisposition to anxiety may further magnify the effects of cancer on the body. Therefore, the presence of anxiety in the cancer patient population is one of physiological concern because it influences the severity of cancer symptoms.

Beyond contributing to symptoms, NF-κB has been linked to cancer progression with some calling it the root cause of head and neck squamous cell carcinoma(Monisha et al., 2017). Research has indicated the activation of NF-κB is a precursor to malignancy and metastasis in HNC, resulting in poorer overall survival[13]. Further, NF-κB is a transcription factor for anti-apoptotic genes, meaning its persistent activation endorses the survival of cancer cells and allows them to proliferate in the body(Vander Broek, Snow, Chen, & Van Waes, 2014). As a key regulator of cell life and death(Colombo, Zambrano, & Agresti, 2018), these findings are concurrent with the influence of NF-κB signaling on symptomology and represent NF-κB as not only a factor that influences cancer symptoms, but also one that contributes to the disease itself. Strong evidence suggests that the NF-κB pathway links the experiences of stress and other stimuli to the behavior of cancer, and that it represents an obstacle in the treatment of HNC. While assessment of NF-κB is beyond the scope of the current study, we present these data to support the notion that symptoms of anxiety may be biologically linked to the progression of cancer.

As a cancer patient continues along the treatment trajectory, improvement in his/her condition is measured by means of tumor response to treatment, which is evaluated via change in tumor size. A tumor's size is determined by its largest dimension(Shanbhogue, Karnad, & Prasad, 2010), and its response to treatment is categorized by the change in that dimension before and after treatment. From there, response to treatment is assessed to be in one of four categories: complete response (CR) if a tumor appears to be completely eliminated, partial response (PR) if the tumor's largest dimension decreases by more than 50%, stable disease (SD) if the tumor's largest dimension reduces by less than 50% or increases by less than 25%, or disease progression (DP) if the tumor's largest dimension increases by more than 25%. Imaging technologies such as computerized tomography (CT) and positron emission tomography (PET) are used to determine response to treatment and are typically employed 3-6 months post-treatment to avoid misinterpretations related to delayed effects of radiation on the body (e.g., inflammation)(Hermans, 2004). Although there have been great advances in RT over the years(Gregoire, Langendijk, & Nuyts, 2015), most HNC patients are diagnosed at an advanced stage (III or IV) and often face poor prognoses(Cognetti, Weber, & Lai, 2008). Even those who respond well to treatment remain at risk, as up to 60% of patients diagnosed with HNC develop recurrent disease, sometimes years after completing treatment. Even soon after completing treatment, recurrences or treatment failures may occur.

Treatment failure is a useful predictor of overall survival in cancer research. For example, a study involving patients with non-small-cell lung cancer was able to develop formulas to

determine the effect of treatment response on one-year survival(Shanafelt, Loprinzi, Marks, Novotny, & Sloan, 2004). An individual whose response to treatment is categorized as SD will generally have shorter-term survival compared to an individual with an identical condition (type, stage, and site) categorized as CR or PR, and the category CR does well to represent patients' disease trajectory as optimistic. While the relationship between optimal treatment response and overall survival is frequently used in early evaluations assessing the efficacy of new cancer treatments, treatment failure commonly portends poorer overall survival.

Anxiety's role in overall survival is less clear mainly because it is understudied(Roth & Massie, 2007). Nevertheless, biological evidence suggests it plays a role in the development/escalation of cancer symptoms, therefore having a negative effect on survival. Further, proinflammatory cytokines produced by the NF-κB pathway--which is upregulated by factors including stress and anxiety--are implied to cause mood disruption that can worsen the quality of life of a patient undergoing cancer treatment(Capuron, Ravaud, & Dantzer, 2000; Jehn et al., 2006; Musselman et al., 2001). In this manner, anxiety has the potential to complicate the treatment of HNC and increase mortality.

In contrast to the effects of depression on cancer symptomology and trajectory, the effects of anxiety on the cancer patient population beginning treatment remain understudied(Howren et al., 2013). This includes the effect of anxiety on treatment response and overall survival, which should be investigated due to the posited relationship between anxiety and NF-κB activation, especially since literature on the relationship between anxiety and treatment response is scant. It is also plausible that treatment response may explain some of the influence of anxiety level and on overall survival, meaning treatment response likely plays a mediating role on anxiety and survival. This study aims to address the variables of anxiety, treatment response, and overall survival via a longitudinal design that measures anxiety symptoms at the start of treatment, tumor response after completion of treatment 5 months later, and two-year overall survival. We hypothesize that higher pretreatment anxiety levels in HNC patients will predict poorer overall two-year survival. We also hypothesize that higher pretreatment anxiety levels will predict a higher likelihood of subsequent HNC treatment failure. Finally, we expect that the relationship between higher pretreatment anxiety and poorer two-year overall survival will be mediated by treatment failure.

Methods

Participants and Procedures

All new patients who presented to the multidisciplinary head and neck cancer clinic at the James Graham Brown Cancer Center between October, 2013 and March 2017 were reviewed. This study received approval from our institutional review board with a waiver of informed consent and an approval number of 13.0053. Participants completed anxiety assessments prior to or during presentation at the multidisciplinary treatment planning visit. Patients had typically received notice of their biopsy-proven diagnosis of HNC 1-4 weeks before presentation.

Treatment recommendations generally included surgical extirpation of disease, radiation, chemotherapy or some combination of the three. Our clinic sees approximately 200 HNC patients per year, including patients with recurrent or metastatic disease, and patients with disease at sites other than of the head and neck (e.g., thyroid, skin melanoma). Approximately 400-500 new primary HNC patients were referred to our clinic during the 4.5-year study period. Patients who returned completed data on anxiety symptoms (approximate N=450) are the focus of the current analysis.

Measures

Clinical Variables

Patient demographics of age, sex, and alcohol and smoking history were collected from intake forms. Only patients with HNC as a primary disease were analyzed, excluding those with recurrent or metastatic disease. Staging followed the guidelines of the American Joint Commission on Cancer and was determined at the time of presentation using all available clinical, pathologic, and radiographic data. Tumor location was classified into 1 of 4 categories: oral, oropharyngeal, hypopharyngeal, or laryngeal. Medical records were reviewed after all participants had completed treatment, and they provided data on tumor response to treatment and overall two-year survival. Patients were coded as poorly responsive if their records showed clinical evidence of disease persistence or tumor progression. Response to treatment was assessed to be in one of four categories: complete response (CR) if a tumor appeared to be completely eliminated, partial response (PR) if the tumor's largest dimension decreased by more than 50%, stable disease (SD) if the tumor's largest dimension reduced by less than 50% or increased by less than 25%, or disease progression (DP) if the tumor's largest dimension increased by more than 25%. Overall two-year survival was calculated from the date patients entered the study, which was also the date that patients met with physicians to plan their treatment regimen.

Anxiety

Anxiety symptoms were measured at the time of entry using the Generalized Anxiety Disorders – 7 item scale (GAD–7), which has demonstrated adequate reliability as well as construct, criterion, and procedural validity(Spitzer, Kroenke, Williams, & Löwe, 2006). It instructs respondents to indicate on a scale of 0-3 how frequently they have been bothered by 7 different anxiety-related problems (e.g. "worrying too much about different things") over the past 2 weeks, with 0 representing "not at all" and 3 representing "nearly every day." Scores range from 0-21 and encompass 3 categories of symptom severity. Scores from 5-9 indicate mild severity, scores from 10-14 indicate moderate severity, and scores above 14 indicate the presence of severe anxiety symptoms. A score of 10 is generally accepted as a clinical cutoff for significant symptomology that may require treatment. The GAD-7 has been tested as a screening tool for Generalized Anxiety Disorder in cancer patients and has been concluded to possess adequate diagnostic accuracy among this population(Esser et al., 2018). Further, it has previously been used to study HNC patients, where it was found to have adequate sensitivity and specificity

in determining the presence and severity of distress in its respondents(Polidoro Lima & Osório, 2014).

Statistical Analysis Plan.

Descriptive and summary statistics

Descriptive and summary statistics will be used to characterize clinical and demographic features of the patient sample. Before analyses, independent variables will be centered at the mean, and we will confirm all statistical assumptions are met when running tests of hypotheses.

Hypothesis Tests

The relationship between pretreatment anxiety and two-year overall survival will be examined with a Cox proportional hazards model. The relationship between pretreatment anxiety and treatment failure will be tested with a logistic regression model. Tests of mediation on the relationship between pretreatment anxiety and overall survival will then be performed in accordance with the MacArthur approach, in which centered predictors and their interaction term are included(Kraemer, Kiernan, Essex, & Kupfer, 2008). To show that B mediates A on C, it must be shown that A, B, and C happen in that order, that A and B are correlated, and that B explains all (complete) or part (partial) of the association between A and C. In a linear model, that means that the main effect of B, the interaction between A and B, or both are statistically significant. Cox models will be constructed to include pretreatment anxiety symptoms, treatment failure, and the interaction between the two.

In order to check for possible proxy relationships that may impact our tests of hypotheses, Spearman rank correlations will assess clinical and demographic indicators, including cancer stage, site of disease, age at diagnosis, sex, and tobacco history in pack-years. Those that correlate with both anxiety and survival will be considered possible proxies according to the MacArthur definition(Kraemer et al., 2008). When this occurs, Cox models will be constructed to include pretreatment anxiety symptoms, the possible proxy, and the interaction between the two. All statistical tests will be 2-sided with α set at .05 (SPSS 25; IBM, Armonk, New York).

Power Analysis

A power analysis was completed based on a comparable study reporting depressive symptoms as a significant predictor of head and neck cancer survival among 134 patients experiencing 18 deaths(Zimmaro et al., 2018). The results suggested that our sample of ~450 patients would attain 100% power to detect significant effects in hypothesized relationships.

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