

A Review of Depression in the Head and Neck Cancer Patient

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Abstract: Head and neck cancer patients experience among the highest rates of major depressive disorder of all oncology patients with an incidence of 15–50%. Correct diagnosis is critical to expeditious management. Oncologists are not always adept at making the diagnosis as medical and treatment side effects can mimic the signs and symptoms of depression. Treatment can be successful and typically involves medical, social, and psychologic interventions. Causes of depression, obtaining an accurate diagnosis, and treatment options are all discussed in this review.

Introduction

A cancer diagnosis typically becomes a watershed event in an individual's lifetime. Facing one's mortality coupled with the fear of the unknown and the potential for pain and suffering suddenly converge to create a feeling of shock and disbelief. The treatment of cancer can also be arduous and debilitating. Psychologic distress is therefore common with many cancer patients suffering psychiatric disorders, typically depression and anxiety.¹⁻²

Head and neck cancer (HNC) patients experience among the highest rates of major depressive disorder (MDD) of all oncology patients. The incidence of depression in HNC patients ranges between 15% and 50%.³⁻¹¹ Depression typically emerges during the course of treatment of HNC with peak symptoms occurring 2–3 months after diagnosis.³⁻¹⁰ Depression may also develop subsequent to the initial diagnosis and therapy.¹²⁻¹⁴ A multitude of factors contribute to the causation of depression in this group. It has been hypothesized that a major reason is the physical location affected by HNC. The most basic aspects of ones' humanity, including the ability to speak, eat, breathe, and appear in public, may all be affected by the cancer or its treatment. Facial disfigurement cannot be concealed, creating significant impairment in social interactions and emotional expression, which can lead to further social withdrawal and avoidance of potentially helpful support systems.

Manifestations of Depression

The magnitude of the resultant disability from depression has important clinical implications. Depression is linked to a lower quality of life, impairments in immune function, prolongation of hospital stays, and reduction in self-care abilities. Fatigue is more disabling in the depressed patient. Completion of the prescribed treatment plan occurs less frequently in depressed patients than nondepressed patients. Each of these issues may independently affect morbidity and/or mortality.

Quality of life has emerged as a critical factor in the measurement of treatment success. Health-related quality of life includes the physical, psychologic, functional, and social well-being of an individual and is particularly relevant to the care of patients with HNC.¹⁵ The structural and functional deficits associated with treatment of HNC have profound physical and psychosocial implications, potentially diminishing health-related quality of life.^{15,16} Clinical depression is one of the few factors consistently found to be an independent predictor of health-related quality of life during treatment of HNC and for years thereafter.^{3,4,17}

Patients who are clinically depressed when the diagnosis of cancer is made are more likely to have a poor health-related quality of life during and after treatment.^{16,18} Though the relationship between depression and health-related quality of life in terms of cause and effect is complex and incompletely understood, diminished quality of life is reflected in increased severity of symptoms and poorer physical, psychologic, and social functioning.¹⁷

Normal functioning of the immune function is necessary for the best possible outcomes in cancer therapy. An extensive body of data links depression with immune dysfunction both in humans and animals.¹⁹ Specifically, depressed patients have been found to have higher levels of pro-inflammatory cytokines, acute phase proteins, chemokines, and suppressed mitogen-induced lymphocyte proliferation along with a reduction in natural killer cell activity (NKCA).²⁰⁻²² Additionally, administration of the cytokine interferon-alpha produces a major depressive disorder in 50% of patients.²³ Increasing attention has been devoted to the relationship between depression and the immune system. Successful pharmacologic and psychotherapeutic treatment of depression has been shown to significantly enhance NKCA.^{20,24-26}

Patient characteristics that predict the most severe alterations of immune function in persons with depression are: older age, male sex, greater life stress, and smoking.^{20,27-30} These risk factors perfectly correspond to the patients most likely to have HNC: older men who smoke and who are under great stress. In fact, smoking

and depression have been found to act synergistically to suppress NKCA.³⁰ Many patients with HNC also misuse alcohol, which is itself a potent modulator of immune function. Additionally, many HNC patients will receive radiation and/or chemotherapy, known suppressors of the immune system. Thus, impairments of immunity associated with depression could interact with the baseline patient characteristics to result in diminished ability to control HNC at the local, regional, and systemic levels.

Depression may indirectly influence cancer treatment outcomes because the pessimism and hopelessness of the depressed individual may cause them to make treatment decisions, which nondepressed persons would not make. Although not studied in HNC, this has been demonstrated in breast cancer subjects in a study examining their degree of acceptance of adjuvant cytotoxic drugs.³¹ Women in the study who were depressed accepted the adjuvant therapy only 51% of the time compared with 92% in the nondepressed subjects.

Depressed subjects also take more treatment breaks and require a longer time to complete prescribed therapy. This may be critically important in HNC patients because success of radiation therapy depends in part on completing the course of therapy as near as possible to the prescribed time. Therefore, given all of these adverse factors, survival is likely to be worse in patients suffering from depression when compared to those who are not.³²

In a small group of subjects taking part in a randomized placebo-controlled depression prevention trial, the combined outcome of poorer survival and disease recurrence was more likely to occur in patients that had been depressed at some point in the study.³³ Groups were similar in demographic factors and stage of disease. This association is indirect because the cause and effect relationship between depression and poorer survival and disease recurrence could not be established in this trial. However, the potential for depression to play a conceivably important role in overall mortality is provocative. Suicide is likely an underreported problem in HNC patients. Several studies that assessed the role of suicide among cancer patients demonstrated an increased risk in both men and women.^{34,35} The risk is highest in the first 3 months for men and the first year for women. When looking at specific cancer diagnoses and suicide risk, Hem and colleagues found men with respiratory cancers and women with buccal and pharyngeal cancers had the highest risk of suicide, and again noted the highest risk in the first 3 months after diagnosis.³⁵ Misonoa and coauthors recently reported suicide rates among U.S. cancer patients. Oral cavity and pharynx patients (standardized mortality ratio [SMR]=3.66;

95% confidence interval [CI], 3.16–4.22) and larynx (SMR=2.83; 95% CI, 2.31–3.44) were in the top 4 highest rates of suicide.³⁶ A study evaluating suicides among cancer patients over an 8-year period found that tongue and larynx cancer, which represented only 2% of all cancer patients, accounted for almost 20% of total suicides.³⁷ Mann and associates, in a general review of suicide and its prevention, noted that 90% of suicides involve a psychiatric disorder, usually depression.³⁸ They found that an astonishing 80% of people are untreated at the time of suicide. It is important to emphasize that this discussion is not dealing with the question of suicide at the end of life but rather the premature termination of life due to active depression, a potentially preventable tragedy.

Causes of Depression in Head and Neck Cancer Patients

De Leeuw and coworkers have reported risk factors for development of depression in HNC patients.¹⁴ They found that the most predictive risks were depressive symptoms, a lack of emotional support, a lack of a social network, avoidant style of coping, advanced tumor stage, gender (women, especially when facial surgery was involved), and a lack of openness to discuss cancer in the family. Llewellyn and colleagues demonstrated 5 psychosocial factors that impacted survival in patients with HNC.³⁹ These factors included social support, satisfaction with consultation and information, behavioral factors (alcohol and tobacco usage), personality, and the presence of depressive symptoms. All 5 of these factors are relevant to this discussion so each will be briefly discussed.

Social Support

Social support tends to be one of the most difficult problems for physicians and patients. A critical first step is to recognize its importance and attempt to mitigate the problem with assistance from social workers, clergy, friends, and loved ones. It is important for the patient to recognize their personal support network and use it to the fullest extent possible. More often than not, friends and loved ones want to help but do not know what is needed. Open communication and overcoming a reluctance to ask for help is vital.

The physician should encourage utilization of social networks when possible. In the physician's office, easy access to social workers and information on local and regional programs offering support, such as support groups, should be readily available. Granting the patient access to nurses in the office further supports the patient in a tangible and reassuring manner.⁴⁰

Consultation and Information

Information to adequately inform and instruct the patient helps to reduce uncertainty. The fear of the unknown has been repeatedly emphasized as contributing to the onset of anxiety and potentially to depression as well. Information can be obtained from written material about treatment options, the disease course, staging and important issues related to healing.⁴¹ Reading this type of material may offer some sense of order in an otherwise chaotic time.

Behavioral Factors

Tobacco and alcohol cessation is clearly important. The link between tobacco addiction, alcohol addiction, and depression is beginning to emerge. Recent studies have shown a correlation between susceptibility to depression and nicotine addiction. In fact, it has been suggested that some tobacco users are actually attempting to treat their depression with nicotine, and therefore, quitting makes them feel worse by unmasking depression. The treatment for nicotine addiction involves a multifaceted approach, utilizing one or more of the following interventions: the atypical antidepressant bupropion, the nicotine receptor blocker varenicline, nicotine replacement therapy, and counseling. Of the pharmacologic options, bupropion may be a particularly good choice when depression is present. Nonetheless, caution must be used in prescribing bupropion in patients with seizure disorders, particularly those associated with alcohol. Also, it may exacerbate sleeplessness in some individuals. Access to tobacco cessation programs should be available through the Head and Neck Oncologists' clinic.⁴²⁻⁴³

HNC patients with a history of tobacco and alcohol use often feel responsible for and thus deserving of their condition which creates additional anxiety.⁴¹ Furthermore, if they are not successful in discontinuing the use of tobacco and/or alcohol, they may experience additional guilt and their family may feel that they are not trying. This can lead to further alienation and loss of social support. Among individuals with a history of tobacco and alcohol abuse prior to developing HNC, personality characteristics of dependence, poor ability to change habits, and poor adaptive coping skills predispose them to psychological morbidity.⁴⁴

An emerging risk factor for HNC is human papilloma virus (HPV), particularly HPV-16. HPV infection in the oral cavity and pharynx has been linked to the lifetime number of oral sex partners and number of open-mouth kissing partners.⁴⁵ Furthermore, a distinct risk factor profile is emerging linking the number of oral sex partners and/or number and frequency of marijuana joints to oral and oropharyngeal cancer.⁴⁶

These high-risk behaviors may also be associated with depression.

Pre-existing Personality Traits and the Role of Inescapable Stress

It has been seen that a personality with high levels of neuroticism predicts worse quality of life, whereas extraversion seems associated with improved quality of life.

An animal model for depression may provide some insight into the development of depression during cancer therapy. Learned helplessness is a model for depression in laboratory animals brought on by exposure to severe, inescapable stress. Learned helplessness has been extensively studied in the rat, but also can be demonstrated in a range of other species, including humans. In the rat, learned helplessness can be prevented by treatment with antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs), if these agents are administered in repeated doses prior to inescapable stress exposure. Antidepressants given prior to stress maintain levels of cortical serotonin and prevent stress-induced depletion of serotonin in proportion to prevention of stress-induced depressive behavior.¹⁷

Family History and Prior Personal History of Depression

Either a family or personal history of depression increases the risk for development of major depressive disorder (MDD). However, many depressed HNC patients have no personal or family history of depression. It is important to understand that anyone can develop depression. It is not a sign of weakness, but a medical illness that requires attention.

Medical Causes of Depression

Along with the psychosocial factors related to depression, there are medical causes as well. Hypothyroidism is common in HNC patients particularly after surgery and radiation to the head and neck. Symptoms of fatigue, weight gain, and hyper-somnolence should be investigated with a thyroid-stimulating hormone test. Hyperthyroidism may also present with similar confusing somatic complaints, although treatment of HNC rarely results in this disorder. Electrolyte imbalances such as a low sodium or calcium can be ruled out by routine studies. Anemia is common following radiation and chemotherapy and may contribute to feelings of fatigue and somnolence. Uncontrolled pain, particularly chronic pain, may result in symptoms and development of depression. These disorders need to be diagnosed and treated as part of the overall management. Drugs such as steroids or interferon can also cause depression; however,

they may be a necessary part of therapy and unavoidable, though sometimes the dose may be reduced or the course of therapy limited.

Diagnosis of Depression

Oncologists are not particularly adept at recognizing psychologic distress in their patients. In a 2001 study by Sollner and coauthors, only 11 of 30 subjects with severe distress were successfully identified.⁴⁷ The role of depression and depressive symptoms requires careful examination and attention by the doctor and patient, as making the diagnosis can be difficult. Potential for depression can be considered a complicated interplay between genetic predisposition and environmental influences. Concurrent life events such as the diagnosis of cancer and its treatment or a major lifestyle change such as loss of employment, magnified by a lack of interpersonal support, results in a significantly elevated risk of depression. Finally, the symbolic meaning of loss, such as the actual physical loss of voice, can be profound and this is why the first step in treating depression is to identify the problem.

Depression can present with somatic and nonsomatic symptoms. Physical symptoms include sleep disturbances such as not being able to get to sleep, waking up early and not getting back to sleep, or sleeping an excessive amount. Fatigue is common with depression as is weight change. These physical symptoms are part of the depression syndrome, but are also frequently experienced by those being treated for HNC and so are often ignored. Although these symptoms are common to both depressed and nondepressed individuals with HNC, they are still a vital indicator for both diagnosis and treatment. Conversely, feelings of guilt, helplessness, hopelessness, and suicidal thoughts are not typically the result of standard cancer treatment. These are sometimes the best clues that depression is present and can aid in the diagnosis of depression during and immediately after treatment.

Identifying patients at higher risk is an important component to diagnosis. Kugaya and associates identified patients at highest risk as those with advanced stage disease, unmarried, and having a helpless/hopeless coping strategy.¹³ De Leeuw and coauthors reported 8 pretreatment variables used to predict depression up to 3 years after treatment.¹⁴ Using factors such as, tumor stage, sex, depressive symptoms, openness to discuss cancer in the family, available appraisal support, emotional support, tumor-related symptoms, and size of the informal social network, they calculated a risk score to predict depression.

There are many ways to approach screening and diagnosis of depression. The simplest screen, and one that

has shown surprisingly good discriminating ability is the question: “Do you often feel sad or depressed?”⁴⁸ Studies using this screening question in older patients or in those with medical illness have generally shown comparable sensitivity and specificity to more detailed depression questionnaires. In settings where time is limited, this single item may be the ideal way to ensure that this crucial dimension of patient well-being is addressed.

Beyond the single screening question, there is an array of rating scales available that can be administered by a clinician or by the patient. These scales again may be very brief or quite detailed. The 2 most commonly used scales in the research setting are the Hamilton Depression Rating scale (HAMD) and the Montgomery-Asberg Depression Rating Scale (MADRS). Both are complex enough to require a trained administrator.

One popular depression rating scale designed to be used in medically ill patients is the Hospital Anxiety and Depression (HAD) scale.⁴⁹ This scale is filled out by the patient and has the advantage of covering 7 questions related to depression and 7 items related to mood. Unfortunately, this scale is not capable of generating a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of MDD.

Two very useful and well designed, new rating scales are the Quick Inventory of Depressive Symptoms—one for use by a clinician and one for self-rating (the QIDS-C and QIDS-SR respectively). These brief depression measures were developed to improve on available clinician and patient ratings by providing equivalent weightings for each depressive symptom, providing clear anchors for each item, including all of the DSM-IV-TR criteria required to diagnose MDD. In nonpsychotic outpatients with major depression and without overt cognitive impairment, the QIDS-SR16 produces results as good, or in some cases better, than those with the clinician-administered Hamilton Rating Scales, the HAMD-1750 and HAMD-24.⁵¹ Both QIDS versions are accurate measures of symptom severity and are sensitive to change.⁵² Indeed, the QIDS-SR16 was used as one of the principal outcome measures in the National Institute of Mental Health (NIMH)-sponsored STAR*D trial, the largest depression study done to date.⁵³

Treatment Options

Treatment options for clinical depression include psychotherapy, pharmacologic therapy, and electroconvulsive therapy, or combinations thereof. Electroconvulsive therapy is generally reserved for difficult to treat depression that has failed other treatment attempts.

Medication and/or psychotherapy are both effective in the majority of medically ill patients suffering from

mild to moderate depression.⁵⁴ Counseling and psychotherapy are important and helpful avenues for therapy. An interesting randomized trial of usual care versus usual care plus a nurse-delivered complex intervention in subjects with cancer and MDD suggested an improvement with the addition of nurse intervention.⁵⁵ Counselors and psychologists play a vital role in assisting patients with emotional needs and certain patients with mild to moderate depression. This is particularly true of patients with depression following cancer therapy. Many people find support groups to be of great benefit. There is little question that having a strong social network will help in recovery. However, some patients with HNC may have significant impairment in communication, making psychotherapy more difficult and possibly limiting its effectiveness particularly in the first 3 months following diagnosis of cancer. Antidepressant medications may be particularly advantageous for these patients.

Psychiatrists and psycho-oncologists are trained to treat the complicated cases of depression in the oncology patient. They have the ability to utilize both talk therapy and pharmacologic therapy and are in an excellent position to determine the correct balance. Referral should generally be made when suicide is threatened, initial counseling or medication trials are unsuccessful, or if the clinician feels unable to assist the patient.

Antidepressants are considered to be safe for the treatment of depression in cancer patients.⁵⁵ The 2 main classes of medication utilized are SSRIs and other new antidepressants such as bupropion, venlafaxine, and mirtazapine. Advantages of the SSRIs are that the side effects typically occur at the beginning of treatment and are usually mild and transient. They may include sexual dysfunction, insomnia, dry mouth, nausea, anxiety, or mild weight loss. There has been a question of an increased risk of suicide associated with SSRIs. It is not clear whether this is a risk in cancer patients, but it is important to be aware of this risk. SSRIs are also generally safe in overdose. Treatment courses tend to run approximately 4–9 months. The dose is typically slowly reduced to avoid an abrupt stoppage of the medication. One SSRI does not appear to have significantly better results than another. As noted above, bupropion might be an attractive alternative medication in the depressed patient who smokes because it has been shown to be associated with smoking cessation. The clinician should select the therapy based on side effect profiles, individual tolerance, cost, and experience of the clinician.

With the commonality of the risk factors for depression existing in abundance during the initial diagnosis and treatment of cancer, the question of prevention has been intriguing. Prevention of illness is typically favored when the illness exists in significant enough numbers and

creates a burden when diagnosis is late. Depression fits this description in that it is prevalent in HNC patients, occurs at a predictable time period, and there are agents that could be effective. Agents utilized in prevention strategies must be safe, effective, and have a reasonable cost to benefit ratio. Stockler and coauthors reported the results of a randomized trial using sertraline in a group of subjects with advanced cancer who had moderate intensity depressed mood, fatigue, or anxiety, but no major depression.⁵⁷ In that population of less severely ill depressed patients, the authors did not find any benefit with respect to prevention of depression, fatigue, or general well-being.

Fisch and associates examined the role of fluoxetine in a randomized fashion; again in patients with advanced cancers of various types.⁵⁸ In this trial, a benefit was seen with the addition of the active drug. This was particularly true in those with the worst cases of depression on the brief inventory.

The role of depression prevention prior to initiation of HNC therapy is currently being investigated. Since HNC is a disease with a generally higher incidence of emergent depression and a higher rate of suicide, prevention may be of unique significance. In a randomized placebo-controlled pilot trial of citalopram, we found a nonstatistically significant benefit in terms of quality of life and reduction in depression during therapy for those in the group given a prophylactic antidepressant.¹¹ Taken together, these results suggest that the role of prevention using antidepressants is ambiguous but in its earliest stages of investigation. Additional research must be done to see what role, if any, these drugs might play in prevention.

The overall most important goal of this review is to stress the need for oncologists to discuss emotional health with their patients and to recognize depressive symptoms, and in turn make accurate diagnoses. Depression is a disease that can cause tremendous hardship in an individual with HNC. Effective treatments do exist, but they can only be used to treat a patient who has been diagnosed.

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