

Symptom management during and after treatment with concurrent chemoradiotherapy for oropharyngeal cancer: A review of the literature and areas for future research

Heidi Mason, Mary Beth DeRubeis, Nancy Burke, Melissa Shannon, Danielle Karsies, Gregory Wolf, Avi Eisbruch, Francis Worden

Heidi Mason, Mary Beth DeRubeis, Nancy Burke, Melissa Shannon, Danielle Karsies, Gregory Wolf, Avi Eisbruch, Francis Worden, University of Michigan School of Nursing, Ann Arbor, MI 48109-5482, United States

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Correspondence to: Heidi Mason, RN, MSN, ACNP-BC, University of Michigan School of Nursing, 400 North Ingalls, Ann Arbor, MI 48109-5482, United States. hmason@med.umich.edu
Telephone: +1-734-2166471
Fax: +1-734-9365525

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Abstract

Patients with locally advanced oropharyngeal cancer are at risk for poor outcomes due to the multi-modal

nature of treatment and the potential for treatment-related toxicity. Although treatment with concurrent chemotherapy and radiotherapy has drastically reduced the need for a debilitating and disfiguring surgery, treatment related toxicities are often difficult to control. Acute toxicities include mucositis, skin desquamation, depression, cachexia, fatigue and nausea and vomiting. Failure to control these symptoms can adversely affect the patient's ability to complete their treatment regimen. Although there are many promising new treatments in the area of symptom management for this patient population, a review of the literature reflects the need for more research.

Key words: Head and neck cancer; Chemoradiotherapy; Depression; Fatigue; Cachexia; Nausea; Desquamation; Mucositis; Vomiting

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Core tip: Patients receiving chemoradiotherapy for head and neck cancer have significant side effects which can interfere with treatment and negatively affect quality of life. While narcotics are often required to treat mucositis pain, adjuvant medication and preventative measures are necessary. Further research in this area is imperative. Dietitians should be readily available for consultation as proper nutrition is crucial. Treatment for nausea and vomiting in the delayed setting as well as for patients who are more sensitive to chemotherapy, needs further attention. Exercise can successfully treat and prevent depression and fatigue. Close monitoring by a multidisciplinary team can ensure adequate symptom management.

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INTRODUCTION

Patients with locally advanced oropharyngeal cancer are at risk for poor outcomes due to the multi-modal nature of treatment and the potential for treatment-related toxicity. The primary treatment of patients with locally advanced oropharyngeal cancer no longer includes the debilitating and disfiguring surgery of the past. Currently, the primary treatment is a non-surgical, organ preservation approach that avoids permanent alteration of the patient's ability to speak and swallow. Chemoradiotherapy - concurrent chemotherapy with radiation therapy-for 7 wk has replaced surgery as the standard of care^[1]. Although organ preservation is possible in many of these patients, both the short- and long-term side effects of chemoradiotherapy can also be debilitating. Common acute toxicities include mucositis, skin desquamation, depression and anxiety, cachexia, fatigue, nausea and vomiting^[2]. When these toxicities are not properly managed they can lead to treatment delays, chemotherapy dose deviations, hospitalizations and poor quality of life^[3]. Increased severity of side effects including mucositis, dermatitis and hematological toxicities can have a negative impact on survival rates and quality of life, as well as decrease treatment efficacy secondary to delays in treatment^[4]. Research findings suggest that treatment with chemoradiotherapy has dramatically increased the supportive care needs of the patient with advanced oropharyngeal cancer^[5].

Both emotional and physical functioning may be affected in this patient population^[6]. One third of patients have a high symptom burden prior to beginning treatment secondary to their cancer. These pre-treatment symptoms include pain, fatigue, distress and disturbed sleep, which have a negative impact on the patient's nutritional status^[7]. This necessitates a unique individual symptom profile to be developed for personalized management of each patient^[8].

Although treatment with chemoradiotherapy, rather than surgery, has improved the lives of these patients in many ways, it has also dramatically increased their supportive care needs. Managing these symptoms is key to avoiding treatment delays, chemotherapy dose deviations and hospitalizations^[9]. Although there are many promising new treatments in this area, a review of the literature reflects the need for more research.

A REVIEW OF TREATMENT AND SUPPORTIVE CARE

Mucositis

Mucositis is a major concern during chemoradiotherapy

and can cause pain, poor nutrition and decreased quality of life. In patients receiving aggressive tumor treatment, incidence rates of mucositis as high as 80% have been reported^[10]. Mucositis is known to be more severe and last longer in patients receiving chemoradiation compared to radiation alone. The risk of oral mucositis is higher for smokers, the elderly, those with a high alcohol intake and patients with a lower body mass index^[11]. The standard of care continues to be good oral hygiene, dietary adjustments (such as avoiding spicy foods) and medication^[12].

The pain of mucositis is often described as a burning sensation. Narcotics can help ease the pain, but does not completely eliminate the discomfort, especially during eating. This will often lead to difficulty maintaining adequate caloric intake, leading to subsequent weight loss. Prophylactic placement of a feeding tube is controversial, secondary to the increased risk of esophageal stenosis during radiation if the patient does not continue to swallow or perform swallowing exercises during therapy. Guidelines from The National Comprehensive Cancer Network (NCCN) only support prophylactic placement in patients with significant weight loss, dysphagia, aspiration, dehydration or comorbidities that impact the ability to eat or drink^[12]. The placement of feeding tubes is not without risk. Complications include bleeding, bowel perforation, infection, potential seeding of tumors and swallowing resistance, all leading to a greater risk of fibrosis and long-term dependence. One randomized study conducted in a curative setting, however, demonstrated that patients who had a feeding tube placed prior to the start of treatment reported higher qualities of life (QoL) following treatment^[13]. Another randomized clinical trial in a palliative setting using the prophylactic placement of feeding tubes demonstrated higher post-treatment quality of life in this patient population^[14].

Even with high-dose narcotics, patients receiving concurrent chemoradiotherapy for head and neck cancer are still not able to achieve adequate pain control from oral mucositis^[15]. Hence, the development of pharmacological treatments for oral mucositis is urgent^[15]. Since narcotics are not as effective in controlling burning pain, further research in this area is crucial.

Some treatments, however, have been shown to be effective. The European Society for Medical Oncology guidelines recommend the prophylactic use of Benzylamine, which has been shown to lower the severity of pain associated with mucositis^[16]. Additionally, lactobacillus lozenges were also found to reduce the incidence of oral mucositis^[17]. Low-level laser therapy (LLLT), which has been used for over a decade in Europe and South America to prophylactically treat mucositis in head and neck cancer patients during radiation therapy, has demonstrated positive results. LLLT, administered three times per week after radiation therapy, is thought to work on the mitochondria to displace the nitric oxide that is generated from radiation therapy. It is now being studied in the United States. The procedure is not presently

reimbursed, therefore, further research is still necessary in this area^[18].

Neuropathic pain due to oral mucositis is common^[10]. Use of gabapentin or pregabalin has been found to be useful in controlling pain and limiting the use of other narcotics^[10]. A study of 155 patients discovered that using a doxepin rinse (25 mg in 5 mL of water) improved mucositis pain when compared to a placebo (*p* 0.001). Doxepin, a tricyclic antidepressant, most likely functions locally on nerves in the oral cavity^[19]. Based on current literature, it is clear that more research in the area of neuropathic pain and mucositis is warranted.

Currently, there is not a FDA approved cytoprotective agent that reliably reduces or prevents radiation induced mucositis. There are clinical trials investigating the use of innate immune defense regulators (IDR). Mucositis has been linked to the dysregulation of innate defense mechanisms. This can lead to a cascade of inflammatory action, causing further damage to the mucosal lining^[20]. This is still under investigation, but looks to be promising.

The standard of care for oral mucositis continues to be excellent oral hygiene. NCCN guidelines for oral hygiene recommend that patients brush their teeth with a soft toothbrush twice per day, floss once per day and rinse with a bland rinse. A simple bland rinse is saline, sodium bicarbonate and water^[3]. Moreover, patient education is an important component. In one study, patients who received an oral care protocol suffered less pain from oral mucositis and reported improved QoL compared to patients in the control group^[21].

In general, development of pharmacological treatments for oral mucositis is urgent, in addition to further research for LLLT and IDRs.

Skin desquamation

Skin desquamation is also a major source of discomfort for this patient population. Radiation causes direct tissue injury and inflammation. This leads to an increased expression of epithelial growth factor receptors in keratinocytes, which assist in repopulation^[22]. Grade 1 skin desquamation is mild erythema or dry desquamation. Grade 2 desquamation involves erythema and moist desquamation in the skin folds. Grade 3 desquamation demonstrates erythema and more wide-spread moist desquamation^[23].

The skin should be dry and clean prior to the patient's radiation treatment. Patients should be counseled to avoid sunlight and skin irritants. Aquaphor, aloe vera, biafine or non-perfumed moisturizers are recommended for dry desquamation. Patients should avoid clothes that rub. Moreover, they should use mild soaps and detergents. Drying gels, zinc oxide past, silver sulfadiazine or a chlorhexidine-based solution without alcohol are suggest for moist desquamation. It is important to watch for infections^[24].

Depression and fatigue

Current literature supports that depression is a significant problem for patients receiving treatment for head

and neck cancer^[25-29]. Depression is experienced by 22%-57% of these patients^[30]. The incidence of suicide is four times higher in head and neck cancer patients than in the general population^[31]. This also contributes to greater difficulty with smoking cessation among smokers, which can indirectly compromise treatment outcomes. Although depression appears to be highest at diagnosis and during active treatment, it may continue for up to 6 mo following treatment, leading to frustration and further isolation since patients are unable to return to their normal activities of daily living^[32-35]. One study found a direct correlation between overall symptom severity and the patient's radiation dosage and depression level^[36]. The severity of symptoms and depression increased as radiation treatments progressed, peaking around 2 mo from the start of therapy.

Anti-depressants and anti-anxiety medications are often necessary during treatment. Since there are higher rates of mental health issues and elevated risks of suicide in this population, anti-depressants have a positive effect on patients. After assessing a patient's perception of the benefit of including a psychologist in their care, one trial found that integrated psychological care improves care for head and neck cancer patients^[37]. Assessment for the presence of psychosocial distress has led to early intervention for patients and their loved ones. Use of The NCCN's Emotional Distress Thermometer assessment tool demonstrated patient distress - worry, fatigue, pain, nervousness and depression^[38]. The use of the thermometer prompted the providers to refer their patients with high distress levels to an onsite social worker.

Fatigue is a common treatment-related side effect of chemoradiotherapy and can be more pronounced when patients experience pain. Fatigue tends to peak within the first 1-2 wk following the completion of radiation, and these symptoms can remain an issue for up to 2 years post radiation therapy^[39]. It often leads to a sedentary lifestyle during the course of treatment, despite substantial evidence demonstrates that QoL can be enhanced with the use of moderate physical activity^[40,41].

Although little research has been done specifically with head and neck cancer patients, the literature supports the use of exercise to improve quality of life in the domain of emotional well-being, self-esteem, social functioning, pain and anxiety in cancer patients during and after treatment^[42-50]. Physical activity was shown to be beneficial with depression and fatigue in men receiving androgen deprivation therapy for prostate cancer^[51]. Another study also found exercise intervention to be beneficial on psychological distress from cancer patients receiving chemotherapy with low to moderate levels of baseline psychomorbidity^[51]. Yet another study demonstrates the positive effects of moderate activity in improving depression and fatigue in cancer patients^[52]. A prospective randomized clinical trial compared resistance exercise, walking and a home program with a trainer *via* phone to usual care. Signs of improvement (*P* < 0.05) were seen in mental health, night time sleeping and

strength^[53]. Capozzi *et al*^[54] concluded that progressive strength training programs are feasible for head and neck cancer survivors during and following treatment. Such programs are associated with improved acute and chronic fitness outcomes and symptom management.

More research is needed in the area of exercise and depression, as well as the use of exercise as a tool to prevent fatigue and depression in head and neck cancer patients^[55].

Cachexia and sarcopenia

Head and neck cancer patients experience one of the highest rates of malnutrition, with 25%-50% being classified as nutritionally compromised prior to initiation of treatment^[56]. A study comparing elderly patients (over 65) with those under 65 found that the elderly patients under intensive nutritional support were able to tolerate aggressive therapy as well as the group under 65^[57].

The literature supports that early and intensive nutrition intervention can minimize weight loss and physical functioning while improving overall QoL^[58,59]. Another study found that nutritional counseling had an equal or greater benefit than oral supplementation, thereby highlighting the importance of dietitians on the multidisciplinary team^[60].

Ensuring adequate nutritional support through regular nutrition therapy in combination with oral supplements has been shown to decrease the incidence of mucositis, dysphagia and skin desquamation^[61].

Sarcopenia (the isolated loss of lean body mass) has been shown to negatively affect locoregional control, overall survival and disease specific survival^[62].

Nausea and vomiting

Nausea and vomiting can affect a patient's ability to tolerate and complete treatment. The risk of post-treatment nausea and vomiting is higher in patients under 40, those with a prior history of chemotherapy induced nausea and vomiting (CINV), high pre-treatment expectations and those with weight loss of greater than 5% from their baseline. Alternatively, patients with a history of alcohol abuse have a lower incidence of CINV^[63]. Our own clinical practice has demonstrated that a history of motion sickness and nausea during pregnancy can also be predictors of difficulty in controlling chemotherapy induced nausea. Pre-treatment assessment for the presence of such risk factors is as vital as prophylactic treatment of nausea and can help increase the likelihood of treating nausea while preventing anticipatory nausea^[64].

Since more intensive treatment regimens integrate concurrent chemotherapy along with radiation, nausea and vomiting associated with these treatments have become a greater concern in recent years. Following standard prevention guidelines based on emetogenicity can help reduce CINV, but complete prevention remains challenging because of individual patient factors^[65]. NCCN guidelines recommend that chemotherapeutic

agents deemed as moderate to highly emetogenic, such as platinum based agents, should be administered with prophylactic antiemetics from different drug classes. These should include a 5-HT₃ receptor antagonist (that inhibits serotonin), a substance P and Neurokinin 1 receptor antagonist and dexamethasone^[66]. Adding olanzapine to moderate or highly emetogenic chemotherapeutic regimen can increase the complete control rate of nausea and vomiting^[67]. A newer agent, sustained-release Granisetron (a 5-HT₃ receptor antagonism), has been shown to prevent acute and delayed nausea and vomiting over multiple cycles of chemotherapy regimen that are moderately to highly emetogenic. The transdermal administration of this drug makes it ideal for patients having difficulty swallowing secondary to pain, tumor or nausea.

Furthermore, non-pharmacological approaches to treatment of nausea are important. Ettinger *et al*^[68] suggests preventing dyspepsia, eating small frequent meals at room temperature, keeping well hydrated and maintaining electrolyte balance. The use of ginger as an effective antiemetic is also a promising treatment during the acute phase of nausea and vomiting. It appears to work through 5-HT₃ receptor antagonism^[69]. It has not, however, proven beneficial in the delayed phases of nausea and vomiting^[70,71].

Additionally, there are some alternative therapies, such as oral marijuana, that have shown to be effective both alone and in combination with other traditional antiemetics^[72,73]. More research in the prevention of nausea and vomiting is needed, especially in the treatment of delayed nausea and vomiting. Delayed nausea and vomiting is a multifactorial problem and may not be triggered by serotonin alone, hence, cannabis may be an effective alternative. However, toxicities, such as delirium, disturbance in coordination, memory and perception loss, tachycardia and hyperemesis, make cannabis as the first line of therapy less appealing^[74,75].

COMPREHENSIVE SYMPTOM MANAGEMENT

Patients receiving concurrent chemoradiotherapy for head and neck cancer have significant side effects which threaten to limit their ability to complete their treatment course without interruptions or dose reductions. Mason *et al*^[9] found that head and neck cancer patients receiving concurrent chemoradiotherapy benefit from close monitoring for toxicities by nurse practitioners. In a retrospective trial, patients seen weekly in a nurse practitioner symptom management clinic had less hospitalizations, dose reductions and treatment deviations. This illustrates the importance of having providers, trained in symptom management, follow these patients closely during and immediately after treatment. Mucositis and adequate pain control remain areas of major concern. Insufficient treatment of these symptoms leads to malnutrition, dehydration and increased fatigue. While narcotics are

often necessary, the use of adjunctive medications needs to be further explored. Although several promising treatments to avoid mucositis are being analyzed, further research is warranted.

Vigilant monitoring with a multidisciplinary team is essential. Registered dietitians, social workers, physicians and nurse practitioners are crucial members of the head and neck cancer team and should be readily available for consultation during clinic. Treatment for nausea and vomiting, in the delayed setting and with patients deemed to be more sensitive to the emetic effects of chemotherapy, needs further attention. The literature supports the importance of following established guidelines in treating nausea and vomiting, yet individualized assessment and recommendations are vital since personal characteristics play an important role in a patient's ability to tolerate chemotherapy. Exercise, depression and fatigue are all inter-related, and there is ample research available regarding the importance of exercise. More specific research relating to patient's with head and neck cancer receiving concurrent chemoradiotherapy is needed, especially since the rate of suicide is substantially higher in this population.

Finally, patients receiving concurrent chemoradiotherapy for head and neck cancer require close monitoring by a multi-disciplinary health care team to ensure adequate symptom management. Such a multi-disciplinary in the optimal setting provides the expertise to promote the best possible care of these complex patients.

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