Head Neck Cancer Treatment-Related Toxicities

Subjects: Oncology

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Patients with head and neck cancer (HNC) are at high risk of malnutrition, with up to 90% of patients developing this condition. Common treatments used for HNC can often lead to adverse side effects, including oral health conditions, gastrointestinal upsets, and several metabolic changes. Consequently, treatments can cause inadequate nutritional intake, resulting in a reduction in energy consumption, and alterations in energy utilization, contributing to the development of malnutrition. There are interventions available (nutritional, medicinal, and physical therapies) that have demonstrated potential effectiveness in reducing the severity of symptomatic toxicities, reducing the risk of malnutrition, and improving survival outcomes of patients with HNC. Based on the findings of this review, there is an urgent need for the implementation or continuation of multi-disciplinary strategies, as well, as updated and improved guidelines to assist in the prevention and treatment of malnutrition caused by treatment-related toxicities in patients with HNC.

Keywords: head and neck cancer ; treatment ; toxicities ; malnutrition

1. Introduction

Cancers of the head and neck region represent a significant global health burden, with approximately 1.5 million new cases diagnosed every year, resulting in over one million deaths [1]. The term head and neck cancer (HNC) encompasses a range of neoplasms that originate in this anatomical region, including tumors of the oral cavity, upper aerodigestive tract (including the pharynx, larynx and esophageal opening), the sinuses, salivary glands, bone and soft tissue of the head and neck [2]. The incidence of HNC is increasing in developed countries, with risk factors including the use of tobacco products, consumption of alcohol, genetics, age, and viral infections such as human papillomavirus (HPV) [2][3].

The combination of treatments, their associated toxicities, and tumor location place patients with HNC at high risk of malnutrition, with up to 90% of patients developing it during active treatment [4]. Malnutrition is defined as “an acute, subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity have led to a change in body composition and diminished function” [5]. The diagnostic criteria of malnutrition includes involuntary weight loss, low body mass index (BMI), reduced muscle mass, reduced food intake, and disease burden and inflammation [6]. This population experiences malnutrition due to their tumor and/or treatments directly impacting on the ability to masticate, swallow, and tolerate food [7].

Health-related consequences of malnutrition in oncology patients can have detrimental effects on their cancer treatment outcomes, including impaired treatment response (i.e., due to reduced absorption and utilization of the medication) that can result in extended periods undergoing treatment [8]. Malnutrition can also reduce recovery following RT and CT, and contribute to an overall reduction in physical strength and quality of life (QoL) [8], with increased levels of mortality rates observed (10–20%) that are specifically related to the symptoms of malnutrition rather than the diagnosis itself [4][9].

2. Current Treatments for Head and Neck Cancer

The treatments used for HNC can often contribute to the development of malnutrition in patients, with the exact prescription of treatments dependent on a variety of factors (i.e., location, stage, and severity of the tumor). Treatments can include surgery, RT and CT used in isolation, or as concurrent chemo-radiotherapy (CRT) [10], with less common treatments including immunotherapy, hormonal therapy and targeted therapy [11]. These treatments also have potential disadvantages and associated toxicities, which can contribute to the development of malnutrition in patients with HNC. It should also be highlighted that patients are at risk of the development of malnutrition-related symptoms prior to the commencement of their oncology treatment, such as a reduction in weight and caloric intake, due to factors including tumor size, with treatments having the potential to exacerbate these effects [12].

2.1 Surgery

Surgical procedures for patients with HNC are initially utilized for primary tumors, and can be performed for preventative, curative, palliative, and reconstructive purposes, with outcomes largely dependent on the stage of the tumor at the time of surgery [13]. These can also be invasive and may result in changes to the functional properties of affected areas, such as impacts on the cranial nerves [14], and changes to the soft tissue and associated structures [15]. Notably, reductions in sensory function may occur, such as reduced or altered taste and smell experience, or reductions to mechanical function, such as mechanical mastication and overall facial and neck movement [14][15].

2.2 Radiotherapy

One of the primary modes of treatment used (approximately 75% utilization) in the HNC population is RT [10] and is often used in adjunct with other treatment forms [16]. Administration of RT is site-specific and localized, causing direct damage to all cells (including healthy cells) in this area. Consequently, damage to the structures involved with the consumption of food and for the early stages of digestion (i.e., salivary glands) are also inadvertently affected. This reduces the capability of adequate early digestion processes, as well as changes in taste perception of different foods. In combination with other side effects such as gastrointestinal upsets and loss of appetite, the effects of RT can also result in the inhibition of patients with HNC's ability and desire to consume food. Fortunately, the application of intensity-modulated radiotherapy (IMRT) has been demonstrated to reduce RT-related toxicities [17], with this treatment being increasingly optimized [18].

2.3 Chemotherapy

Commonly utilized in combination with RT is CT, in particular cisplatin [19]. This treatment is often utilized as adjunctive therapy to ensure that all neoplastic cells are removed following surgery [20], or combined with RT in the case of metastasized cancer as an efficient method of treatment distribution to all tumor cells [20]. Use of CT can also lead to gastrointestinal upsets and loss of appetite, further resulting in the loss of desire to consume food and can potentially lead to reduced efficiency in nutrient absorption [20]. Additionally, the use of CT can exacerbate the toxicities caused by RT, such as oral mucositis (OM), when used in combination [21].

3. Treatment-Related Toxicities

The location of the initial tumor can have an impact on patients with HNC's ability to consume food. Furthermore, up to 90% of patients experience symptoms that impact on their oral intake, either due to the tumor location, or their prescribed treatments [22]. The treatments administered for patients with HNC are applied near many vital structural and functional organs responsible for the consumption of food. Patients with HNC experience multiple, interconnected side effects that impact their oral intake, further contributing to malnutrition.

3.1 Oral Health Problems

3.1.1 Oral Mucositis

Current oncology treatments are based on destroying the rapidly dividing cancer cells; however, this is also a characteristic of the oral cavity epithelium cells which are consequently disrupted or destroyed. Therefore, these treatments often result in the development of OM, negatively affecting the oral cavity and upper digestive tract [23]. The OM begins with an increased inflammatory response signaling the initiation of apoptosis, leading to inflammation, and resulting in erythema and edema of affected areas. As the condition develops, ulceration can also occur due to an increased risk of secondary infections at the site [21]. Approximately 60% of patients are at risk of progressing to the ulcerative stage [23], however patients with HNC receiving RT have a definitive risk of developing symptoms [24].

There is currently no established 'gold-standard' treatment for OM [25], however the most common and simplistic intervention utilized is the maintenance of oral hygiene [24]. The optimal interventions for OM are orientated towards reducing the pain sensation, eradicating any pathogenic microbiota, and commencing the wound healing process, and some examples are outlined in Table 1.

Table 1. The available interventions to improve treatment toxicities in patients with head and neck cancer (HNC) to prevent the development of malnutrition.

Side Effect	Intervention	Description	Objective of Intervention

		Nutritional counseling [26]	
		Oral nutritional supplements (ONS) [26]	Weight maintenance and increased protein and energy intake.
Altered dietary intake	Nutritional therapies	Enteral nutrition; Percutaneous or nasogastric tube feeding [27]	Administered in the presence of an obstruction or severe toxicity, or when inadequate dietary intake is consumed (60% of their estimated energy expenditure). Improves nutritional intake, however, is associated with hospital admissions.
		Parenteral nutrition [4]	Only required when HNC patient is unable to meet nutritional needs orally or enterally.
	Oral hygiene	Tooth brushing, flossing, and alcohol-free mouthwashes [24]	Ensures basic dental hygiene is met to reduce the severity of mucositis symptoms.
Oral Mucositis	Sterile solutions	Saline and sodium bicarbonate [28]	Maintenance of oral hygiene to compliment additional interventions to reduce mucositis symptoms.
	Traditional therapies	Honey [29]	Reduction in severity and duration of severe symptoms, weight maintenance and weight gain.
Xerostomia	Systemic and topical sialagogues	Medications that promote the secretion of saliva [30]	Improvements in salivary flow, decrease in requirement of oral comfort agents such as artificial saliva.
	Cytoprotective agents	Aim to protect healthy tissue from oncology treatments [31]	Reduction of clinical xerostomia cases.
Dysphagia	Physical rehabilitation	Swallowing therapies; motor exercises and swallowing maneuvers [32]	Improvement in swallow function oral intake.
		Tongue strengthening exercises [33]	Reduced symptoms; only evidence for HNC survivors.
Reduced Exercise	Resistance training	Increase in skeletal muscle and lean body mass [34][35][36][37]	Improvement in fatigue and acute QoL symptom management.

3.1.2 Xerostomia

Xerostomia is a term used to describe dryness of the mouth, with approximately 80% of patients with HNC developing the symptoms [38]. Patients can develop xerostomia due to a surgical incision of their salivary glands, leading to an alteration in salivary function. However, the most common cause of this toxicity is the use of RT [38] due to the direct impact and damage to the salivary glands made by the active treatment [39], leading to a reduction in salivary production as well as

cracking of the lips, tongue, and bleeding gums [40]. Xerostomia can also impact the patient's social functioning due to changes in speech and causing psychological distress [39]. The functional changes causing reduced salivary levels can also contribute to a reduction in dietary intake [41].

While there is no consistent evidence available to support the use of any single treatment for xerostomia, various strategies are suggested for the management of its symptoms (Table 1). However, patients have reported that the most beneficial relief solution for their xerostomia is frequent hydration [42].

3.1.3 Dysphagia

The treatments for HNC can also have negative impacts on swallowing processes, due to the proximity of the treatments to the required physiological structures (i.e., tongue and cranial nerves) resulting in dysphagia [43]. Dysphagia can also lead to the functional tissue becoming fibrotic, which physically inhibits the swallowing process In addition, surgical interventions can lead to dysphagia, with its severity being dependent on multiple risk factors, including the primary tumor size and location, degree of surgical excision, and the requirement of surgical reconstruction [43]. The presence of dysphagia is directly linked to altered usual dietary intake [44]. Consequently, weight loss is identified as an independent predictor commonly associated with the presence of malnutrition in this population [41].

The management of the symptoms of dysphagia are focused on physical rehabilitation, in particular swallowing therapies rather than the use of medical interventions (Table 1), however modifying the texture of foods allows for the consumption of an adequate diet [45].

3.1.4 Dysgeusia

The administration of treatment can affect taste receptors, with taste reportedly one of the main characteristics to be susceptible to alteration [46]. For patients with HNC receiving RT, there is no correlation observed between the dose of administered RT and taste sensation, with these changes also experienced prior to treatment due to loss of taste buds caused by surgery, or the tumor location [47]. Several changes in taste perception are reported, including the absence or incorrect perception of flavor; most commonly the perception of metallic, salty, and bitter tastes. The loss of taste associated with dysgeusia is also paired with a reduction in appetite and the enjoyment of food consumption [46]. Patients have also reported altering their usual food consumption to increase food palatability, including reducing consumption of foods with adverse flavors [44]. This can lead to an overall reduction in food intake, leading to a higher risk of malnutrition [48].

3.2 Gastrointestinal Upsets

Exposure to oncological treatments can result in a variety of gastrointestinal complications. These toxicities are more likely to be experienced by patients who are receiving CT, either in isolation or as CRT, in comparison to isolated RT [49], which adversely affects the tissue in the head and neck region, rather than the lower digestive tract. The symptoms of nausea and vomiting are reported simultaneously, potentially becoming so severe that patients may request the temporary discontinuation of their active treatments [50]. Further symptoms of gastrointestinal upset include diarrhea (3.5%) and constipation (10%), which are more likely to be caused by CT than RT [51]. However, the experience of constipation is more likely to occur due to the administration of anti-nausea medication than CT itself [52]. The altered lifestyle experienced during HNC treatment may also contribute to the development of constipation, through increasing a sedentary lifestyle, dehydration, and an altered dietary intake with a reduction in dietary fiber due to the changes occurring to patient’s oral health [53].

3.3 Pain and Fatigue

During HNC treatment, patients experience pain as one of the most commonly reported symptoms (up to 90%) experienced from the time of diagnosis [41] due to a variety of different factors [54]. These include the effects of the primary tumor or its subsequent metastases, pain from surgery, or the consequence of the toxicities induced by treatments [55]. Furthermore, this can result in a variety of negative health consequences, including problems related to nutritional intake, such as the ability to consume food and drink [43], with an increase in pain being inversely related with the low amount of energy consumed per day [41].

Fatigue is a commonly experienced side effect of oncology treatments, with evidence suggesting that it is prevalent in nearly all patients with HNC [53]. Fatigue has been demonstrated to have an impact on the patients’ social functioning, including their motivation for social interactions and personal care, including the desire to source and prepare nutritional meals, and their ability to earn an income [56]. Despite the certainty of this population experiencing fatigue, it has been demonstrated that exercise, can reduce the experience of fatigue in this population [34][35] (Table 1).

3.4 Metabolic Alterations

The effects of the tumor and the treatments received by patients with HNC can cause specific altered metabolic responses, including an altered resting energy expenditure [57]. These oncology treatments cause systemic inflammation, and play a role in the disruption of the metabolism of macronutrients, consequently causing changes in energy expenditure requirements [58]. The alterations in metabolism, in combination with reduced food intake causing a negative energy and protein balance, can lead to the development of cancer cachexia [59], experienced by approximately 45% of HNC patients [60]. This is characterized by an ongoing loss of skeletal muscle, with or without the loss of fat mass, leading to progressive functional impairment that cannot be improved by conventional nutritional support [59][61]. Further, the presence of sarcopenia, or muscle wasting, is associated with the development of malnutrition, as well as the progression of treatment-related toxicities [62].

Patients with HNC who have an increased resting energy expenditure may not be able to achieve adequate nutritional intake due to the other treatment side effects, such as oral health or gastrointestinal upsets, however there are nutritional interventions available to this population (Table 1). The prevention or management of malnutrition through the minimization of treatment-related toxicities should also be addressed from the initiation of active treatment, to prevent the requirement of these advanced dietary methods.

While nutrition interventions can assist patients in receiving adequate nutrition they require, these interventions alone do not have an impact on the maintenance and development of lean body mass. The decrease in lean muscle mass that can occur during treatment can contribute to weight loss, and can be attributed to decreased physical function and QoL, and is associated with a treatment dose-limiting response, leading to extended periods of recovery [63][64]. The treatment-related toxicities experienced in this population are considered barriers to completing physical activity (PA) [65]. However, participation in PA programs, particularly resistance training, has been demonstrated to improve lean muscle mass (Table 1), including in late-stage and cachectic patients [36][37].

4. Consequences of Malnutrition

All of the oncology treatment side effects have the potential to contribute to the development of malnutrition in the HNC population [66]. It should be highlighted that the discussed treatment toxicities are not experienced in isolation, and they occur simultaneously with others. In addition, malnutrition in patients with HNC has the potential to lead to a cyclic exacerbation of the discussed treatment toxicities that play a role in its initial development [67]. Further, these toxicities, and the resulting malnutrition can cause further consequences, such as reduced QoL, that have the potential to negatively affect cancer prognosis.

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