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Original research article

Malnutrition and cachexia in patients with head and neck cancer treated with (chemo)radiotherapy

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ARTICLE INFO

Article history:
Received 1 December 2014
Received in revised form
26 December 2014
Accepted 2 March 2015

Keywords:
Weight loss
Malnutrition
Cachexia
Head and neck cancer
Radiotherapy

ABSTRACT

Aim: To highlight the problems associated with nutrition that occur in patients with squamous cell carcinoma of the head and neck (SCCHN).
Background: SCCHN is associated with weight loss before, during and after radiotherapy or concurrent chemoradiotherapy. Because of serious consequences of malnutrition and cachexia on treatment outcome, mortality, morbidity, and quality of life, it is important to identify SCCHN patients with increased risk for the development of malnutrition and cachexia.
Materials and methods: Critical review of the literature.
Results: This review describes pathogenesis, diagnosis and treatment of malnutrition and cancer cachexia. Treatment of malnutrition and cancer cachexia includes nutritional interventions and pharmacological therapy. Advantages and disadvantages of different nutritional interventions and their effect on the nutritional status, quality of life and specific oncological treatment are presented.
Conclusions: Nutritional management is an essential part of care of these patients, including early screening, assessment of nutritional status and appropriate intervention.

1. Background

The majority of tumours (over 90%) in the head and neck area are squamous cell carcinomas,[1] which are the 7th most common malignancy worldwide.[2] Weight loss is common in patients with squamous cell carcinoma of the head and neck (SCCHN) and may occur before and during treatment for SCCHN as well as after the therapy. At the time of diagnosis, 3–52% of SCCHN patients are malnourished. In the pre-therapy phase, this is mainly due to the cancer itself. The common treatments for SCCHN, including surgery, radiotherapy (RT), chemotherapy, or combinations of these three, also lead to changes that further complicate and challenge oral intake. During RT alone or in combination with concurrent chemotherapy (chemoradiotherapy, CRT), malnutrition is already present in 44–88% of patients.[3,4] After treatment completion, however, dysphagia and xerostomia – as the most

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http://dx.doi.org/10.1016/j.rpor.2015.03.001

frequent consequences of therapeutic intervention – can further contribute to poor nutritional status in these patients. Specifically, malnourished patients with SCCHN have multifactorial nutritional problems because of symptoms related to the tumour or specific therapy and iatrogenic causes. Symptoms related to the tumour include mechanical obstruction, dysphagia, odynophagia, anorexia and fatigue secondary to cancer cachexia syndrome.[5] In cachectic patients, weight loss of varying degree occurs in conjunction with significant metabolic abnormalities, skeletal muscle loss and increased lipolysis. Cancer cachexia may be present before any substantial weight loss.[6,7] Tumour-specific therapy has toxic effects, such as nausea, vomiting, xerostomia, mucositis, fatigue and changes in the taste. Pain or leakage linked to the inserted percutaneous endoscopic gastrostomy (PEG) tube, extraction of unhealthy teeth before radiotherapy, opioid-induced gastrointestinal changes, and unawareness of nutritional problems represent iatrogenic causes of weight loss.[8] Many of these problems are still present after completion of treatment and are more pronounced in elderly patients.[9–11] Whatever the reason of malnutrition and cachexia is, it is associated with increased rates of mortality, morbidity, and impaired quality of life (QoL) in patients with SCCHN.[12]

2. Aim

The aim of this review is to highlight the problems associated with nutrition that occur in patients with SCCHN.

3. Malnutrition and cancer cachexia: definition and development

In SCCHN studies, malnutrition is usually defined as unintended weight loss of >5–10% during the last 1–6 months and body mass index (BMI) of <18.5–20 kg/m^2.[5,13–15] Malnutrition and poor food intake are associated with lower physical functioning,[16] impaired immunity,[17] more frequent and severe RT-induced late toxicities,[18] more and longer interruptions of CRT course,[15] greater hospital re-admission rate,[19] impaired QoL, and increased mortality.[12,20] Jager-Wittenaar et al.[16] reported significantly worse scores on physical functioning ($p = 0.007$) and fatigue ($p = 0.034$) in malnourished patients after different treatments of oral/oropharyngeal cancer compared to well-nourished patients. Chang et al.[17] retrospectively analysed the data of 194 patients with stages III–IV SCCHN who were treated with CRT. On multivariate analysis, Eastern Cooperative Oncology Group performance status of >1, BMI of <19 kg/m^2, and peripheral blood total lymphocyte count of <700/μL were recognised as independent variables associated with early death that occurred in 14 patients (7.2%), 78.6% of whom died of infection. A retrospective study of 72 patients with stage III or IV SCCHN reported that patients with BMI of 25 or less survive 24.6 months on average compared with 28.3 months for patients with BMI greater than 25.[20] From the afore-mentioned studies, we can conclude that malnutrition should be considered an important risk factor, contributing to a poorer outcome, particularly when other risk factors are present. Because of serious consequences of malnutrition, it is important to recognise SCCHN patients with increased risk for the development of malnutrition and cachexia.

Cachexia is not always present in all malnourished patients, while all cachectic patients suffer from malnutrition.[21,22] Cancer cachexia is a multifactorial metabolic syndrome associated with an underlying malignant disease. Its main characteristics are decreased appetite, weight loss, metabolic alterations, and inflammatory state.[23] Clinical features in patients with cachexia are loss of adipose tissue, skeletal muscle mass and function, resulting in progressive loss of body weight. Furthermore, cachexia is associated with reduced QoL and poor prognosis of the underlying malignant disease. Cachexia is often accompanied by anorexia, which is caused by production of pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α). This leads to predominance of anorexigenic signals, such as pro-opiomelanocortin, and lack of orexigenic signals, such as neuropeptide Y.[10,24,25]

A three-stage classification system of cancer cachexia was proposed by Fearon et al., distinguishing between pre-cachexia, cachexia, and refractory cachexia (Fig. 1). The rate of cancer cachexia progression varies between individuals. Factors such as degree of food intake, absence/presence of systemic inflammation, cancer type, and stage and lack of response to anti-cancer therapy may affect the rate of progression. Pre-cachexia is described as metabolic changes or substantial involuntary weight loss (i.e. ≤5%). Cachexia is diagnosed as weight loss of >5% over past 6 months; or a BMI of less than 20 kg/m^2 and ongoing weight loss of more than 2%; or sarcopenia and ongoing weight loss of more than 2%. Patients with metastatic cancer or very poor response to oncological treatment can develop refractory cachexia. Characteristics of refractory cachexia are poor performance status (WHO score 3 or 4) and short life expectancy (less than 3 months).[21]

The principal initial mechanisms in cancer cachexia that lead to hypercatabolism are systemic inflammatory response with increased production of pro-inflammatory cytokines (interleukins, interferon-γ, TFNα, NFkβ), reactive oxygen species and catabolic mediators produced by tumour and host cells.[10,26] This causes changes in metabolism in terms of altered metabolism of carbohydrates, lipids and proteins. Insulin resistance, glucose intolerance, increased gluconeogenesis from amino acids and lactate are the most important changes in carbohydrate metabolism.[27] Loss of adipose tissue in cachexia is a result of increased lipolysis by tumour or host products.[24,27] The tumour (and host) factor, zinc-alpha-2 glycoprotein, and the lipid-mobilising factor (LMF) also contribute to the loss of adipose tissue with a direct lipolytic effect and increased sensitivity to lipolytic stimuli. Loss of skeletal muscle in cachexia is mainly due to diminished synthesis of muscle protein and increased degradation of proteins.[24] Despite metabolic changes in cancer cachexia, studies show that progressive resistance training (PRT) increases lean body mass. In a series of 41 patients, Lønbro et al. reported that 12 weeks of PRT after RT completion increased lean body mass by more than 4%; self-selected physical activity resulted in a significantly lower increase of lean body mass.[28] Furthermore, studies in healthy subjects showed an additive effect of protein and creatine supplementation on the effect of PRT, which was not confirmed in SCCHN patients.[29]