

Prevalence of Fatigue in Patients with Head and Neck Cancer Submitted to Radio-Chemotherapeutic Treatment: Systematic Review

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Prevalência de Fadiga em Pacientes com Câncer de Cabeça e Pescoço Submetidos ao Tratamento de Radioquimioterapia: Revisão Sistemática

Prevalencia de Fatiga en Pacientes con Cáncer de Cabeza y Cuello Sometidos a Radioquimioterapia: Revisión Sistemática

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ABSTRACT

Introduction: Fatigue is considered a reversible change of biological and psychic functions originated from the organism's unbalance. In patients with cancer, fatigue is usually reported as one of the most frequent symptoms and is defined as chronic mainly in cases when metastases impair the daily life activities significantly. **Objective:** This work aimed to evaluate the prevalence of fatigue in patients with head and neck cancer submitted to radiochemotherapy treatment. **Method:** The standardized methodology was PRISMA and PICO anagram. LILACS, PubMed, Google Scholar and SciELO databases were searched applying the descriptors "fatigue"; "cancer"; "prevalence"; "head and neck cancer". Scientific articles in English published between 2009 and 2019 were included. Five studies have evaluated fatigue isolated occurrence through the questionnaire Brief Fatigue Inventory (BFI) and variables collected by interviews utilized Piper Fatigue Scale. **Results:** Of the 243 patients, 70% showed fatigue. In another 13 studies, fatigue has been assessed along with other symptoms by applying questionnaires already validated in literature. There was a significant increase on fatigue scores as well as in quality of life related symptoms, for instance, pain, stress, and depression for the 1,908 patients interviewed. **Conclusion:** Fatigue's occurrence in the population of head and neck patients was high and commonly related to other symptoms such as pain, sleep disorders, lack of appetite, dyspnea, emotional stress, and depression.

Key words: Prevalence; Fatigue/radiotherapy; Head and Neck Neoplasms/radiotherapy.

RESUMO

Introdução: A fadiga é considerada uma alteração reversível das funções biológicas, físicas e psíquicas, proveniente do desequilíbrio do organismo. Em pacientes com câncer, a fadiga é relatada como um dos sintomas mais frequentes, principalmente nos casos em que apresentam metástases, limitando de forma significativa as atividades diárias, sendo considerada como crônica. **Objetivo:** Avaliar a prevalência de fadiga em pacientes com câncer de cabeça e pescoço sob tratamento radioquimioterápico. **Método:** Foram instituídos a metodologia PRISMA e o anagrama PICO. Realizaram-se buscas nas bases de dados LILACS, PubMed, Google Acadêmico e SciELO com os descritores "fatigue"; "cancer"; "prevalence"; "head and neck cancer". Foram incluídos artigos científicos em inglês publicados entre 2009 a 2019. Cinco estudos avaliaram a ocorrência de fadiga isoladamente por meio do questionário *Brief Fatigue Inventory* (MBFI); e as variáveis coletadas por meio de entrevista utilizaram a *Escala de Fadiga de Piper*. **Resultados:** Do total de 243 pacientes, 70% apresentaram fadiga. Em outros 13 estudos, a fadiga foi avaliada em conjunto com outros sintomas por intermédio de questionários já validados na literatura. Houve aumento significativo nos escores de fadiga bem como nos sintomas relacionados à qualidade de vida a exemplo da dor, estresse e depressão nos 1908 pacientes entrevistados. **Conclusão:** A ocorrência de fadiga na população de pacientes com câncer de cabeça e pescoço foi alta e comumente esteve relacionada a outros sintomas como dor, distúrbios do sono, perda de apetite, dispnéia, estresse emocional e depressão.

Palavras-chave: Prevalência; Fadiga/radioterapia; Neoplasias de Cabeça e Pescoço/radioterapia.

RESUMEN

Introducción: La fatiga se considera una alteración reversible de las funciones biológicas, físicas y psicológicas, como resultado del desequilibrio del cuerpo. En pacientes con cáncer, la fatiga se informa como uno de los síntomas más frecuentes, especialmente en los casos con metástasis, que limita significativamente las actividades diarias y se considera crónica. **Objetivo:** Evaluar la prevalencia de fatiga en pacientes con cáncer de cabeza y cuello sometidos a radioquimioterapia. **Método:** Fueran instituyó la metodología PRISMA y el anagrama PICO. Se realizaron búsquedas en las bases de datos LILACS, PubMed, Google Académico y SciELO con las palabras clave "fatigue"; "cancer"; "prevalence"; "head and neck cancer". Se incluyeron artículos científicos en inglés, publicados entre 2009 y 2019. Cinco estudios evaluaron la aparición de fatiga de forma aislada mediante el cuestionario de *Brief Fatigue Inventory* (MBFI) y las variables recopiladas a través de una entrevista utilizaron la *Escala de fatiga de Piper*. **Resultados:** Del total de 243 pacientes, el 70% tenía fatiga. En 13 estudios, la fatiga se evaluó junto con otros síntomas mediante cuestionarios ya validados en la literatura. Hubo un aumento significativo en las puntuaciones de fatiga, así como en los síntomas relacionados con la calidad de vida, como el dolor, el estrés y la depresión en los 1908 pacientes entrevistados. **Conclusión:** La aparición de fatiga en lo pacientes con cáncer de cabeza y cuello fue alta y se relacionó comúnmente con otros síntomas como dolor, trastornos del sueño, pérdida de apetito, disnea, estrés emocional y depresión.

Palabras clave: Prevalencia; Fatiga/radioterapia; Neoplasias de Cabeza y Cuello/radioterapia.

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INTRODUCTION

Head and neck cancer is one of the most predominant neoplasms reported in Brazil¹. It includes the anatomic sites of the oral cavity, such as the lips, floor of the mouth, tongue palate, pharynx, salivary glands, and larynx. Different therapeutic approaches are used as primary treatments for this type of cancer, including surgery, radiotherapy, and chemotherapy. These treatments might be applied as adjuvant therapies aiming to delay metastasis and improve the patient's survival rate². The selection of the best therapeutic option is usually based on tumor location and histological grading³. Thus, the development of these types of neoplasms may contribute to the occurrence of oral and breathing disorders, which cause difficulty in swallowing and verbal communication¹.

The most common complications triggered by head and neck cancer include surgical mutilations and functional impairments such as fatigue, pain, obstructive sleep apnea, dysphagia, dysgeusia, mucositis, and difficulty in chewing. Such symptoms may negatively compromise the patients' physical and psychosocial status⁴.

Cancer-related fatigue is one of the primary symptoms that occurs during and after oncological treatment⁵. It is usually accompanied by depression and/or persistent painful symptomatology and has been defined as a stressful exhaustion stage of higher intensity and duration⁶. These symptoms might have implications for therapeutic decisions as well as for discontinuing or adopting a new treatment plan for the patient⁷. Furthermore, fatigue is a multidimensional phenomenon that negatively affects the physical, cognitive, emotional, and social domains, thereby interfering with activities of daily living⁵. Hence, an increase in the level of fatigue throughout the period of antineoplastic treatment might reduce the patient's survival².

Due to the occurrence and persistence of fatigue in oncologic patients, diagnostic and therapeutic approaches have been established to detect and control these symptoms and other clinical conditions that might trigger its onset⁸.

Through a systematic review, this study aimed to evaluate the prevalence of fatigue in patients with head and neck cancer undergoing radiochemotherapy.

METHOD

This systematic literature review was carried out from December 2019 to April 2020 and aimed to search for articles of the study type in human beings. The main question of this systematic review was "What is the prevalence of fatigue in patients with head and neck cancer

undergoing radiochemotherapy?" The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the PICO anagram, in which information about population (patients with head and neck cancer), therapeutic intervention (radiochemotherapy), and the existence of controls (comparison to healthy individuals or patients with head and neck cancer that had finished radiochemotherapy sessions) and outputs (fatigue occurrence) were used. This review was registered at the PROSPERO database, with registration number CRD42020203964.

The following databases were searched to find related articles: LILACS, PubMed, Google Scholar, SciELO and Virtual Health Library (BVS). The following uniterms were selected (DeCS): "fatigue," "cancer," "prevalence," and "head and neck cancer." The search strategy included the Boolean operator "AND" resulting in the following combinations: "fatigue AND cancer," "fatigue AND prevalence AND head and neck cancer," and "fatigue AND head and neck cancer."

The selected articles were published from 2009 to 2019 in English. Prospective studies like case-control and clinical trials were included in this systematic review. Literature reviews and clinical case reports, as well as those that had no similarity to the proposed theme or had not been published in the stipulated period were excluded.

After looking over the database and applying the search strategies as well as the inclusion and exclusion criteria, double-published articles were identified. Furthermore, the abstracts were screened, and some articles were selected in this phase, which were then read by two independent researchers to determine the eligibility of each article (Figure 1). In case of disagreement between them, a third author would be summoned, which was not necessary.

With regard to the selection of data from the articles, two tables were drawn containing the following information: title, authors, year of publication, type of study, population, results, and outcomes. A descriptive analysis of the studies was conducted. One table included the data related to the articles that assessed fatigue exclusively, while the other included the data description about fatigue and other common symptoms the patients with head and neck cancer reported.

RESULTS

ARTICLES THAT ASSESSED FATIGUE EXCLUSIVELY

After screening the title and abstract of the 18 articles found during the database search, only 5 evaluating fatigue as an isolated aspect in patients with head and neck cancer undergoing radiochemotherapy were chosen. A diagram

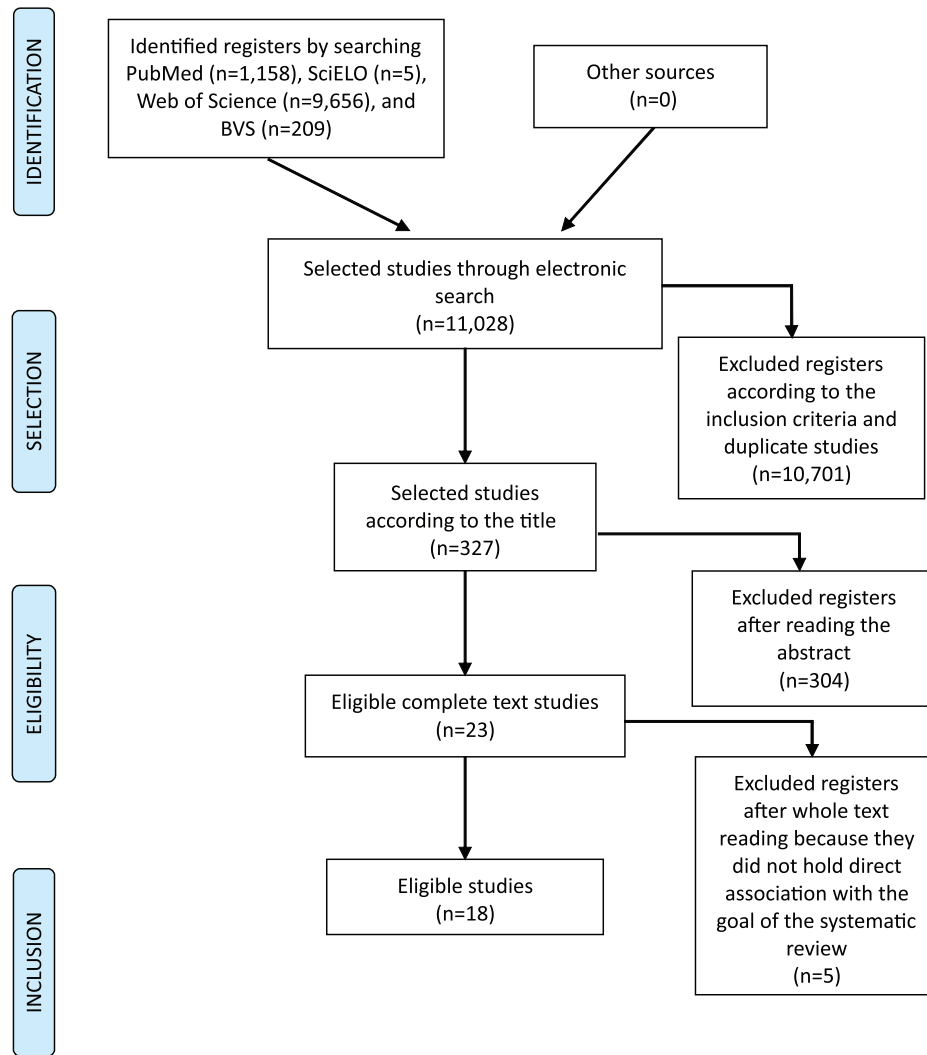


Figure 1. Flowchart to define articles inclusion. Salvador, Bahia, Brazil, December 2019 to April 2020

of the selection process is shown in Figure 1, and the main features of the studies included are presented in Chart 1.

A total of 349 participants were included in these five studies (239 men and 110 women), all of whom underwent radiochemotherapy. Fatigue was evaluated in terms of intensity, and prevalence using the Brief Fatigue Inventory (BFI). The variables were collected through an interview using the Piper Fatigue Scale, which allows the assessment of global, behavioral, affective, and sensorial/psychological domains of each patient.

In these articles, the BFI was efficient in measuring the level of fatigue in patients who were undergoing radiochemotherapy or completed it. In addition, the symptoms of fatigue increased throughout the period of radiochemotherapy, thus failing to achieve the benefits of the therapy. A total of 243 patients reported such symptoms, which accounted for 70% of all participants in the five studies.

ARTICLES THAT ASSESSED FATIGUE ASSOCIATED WITH OTHER SYMPTOMS

This review included 13 articles which evaluated fatigue and other symptoms in patients with head and neck cancer undergoing radiochemotherapy. The main characteristics of the 13 studies are described in Chart 2.

A total of 1,908 participants (1,272 men and 636 women) submitted to radiochemotherapy and surgical treatment were included in these studies. Fatigue and other symptoms associated with quality of life were evaluated using different survey methods such as the BFI, Beck Depression Inventory, Piper Fatigue Scale, Functional Assessment of Head and Neck Cancer Therapy (FACT-H&N), Epworth Sleepiness Scale (ESS), European Organization for Research and Treatment of Cancer QOL Core Questionnaire 30 (EORTC QLQ-C-30) and EORTC QLQ head and neck cancer module (EORTC QLQ-H&N35), Health-Related Quality of Life

Chart 1. Studies that assessed fatigue exclusively (Salvador, Bahia, Brazil, December 2019 to April 2020)

Title/author/year	Study design	Population	Methodology	Results	Outcome
Validation of the Modified Brief Fatigue Inventory in head and neck cancer patients Aynehchi et al., 2012 ⁹	Case-control	Patients with head and neck cancer aged 26 to 86 years; 27 men and 25 women had cancer; 22 men and 35 women were included in the control group (n=109)	The Brief Fatigue Inventory (BFI) survey was used to evaluate the intensity and prevalence of fatigue. BFI was consecutively administrated in 52 patients with head and neck cancer for 3 months after the end of the treatment, and in 57 patients in the control group with the same age but without cancer	The BFI survey had an excellent reliability (r = 0.800, p<0.001). Cancer stage and comorbidity correlated to the linear multiple regression model. No significant relation was found between gender, age, and ethnicity. Of the 52 cancer patients, 8 reported fatigue, totaling 15% of this population	The BFI survey was a reliable and valid tool for measuring the levels of fatigue in patients with head and neck cancer
Fatigue during chemoradiotherapy for nasopharyngeal cancer and its relationship to radiation dose distribution in the brain Powell et al., 2013 ¹⁰	Prospective	Patients with nasopharyngeal neoplasm undergoing chemoradiotherapy. The average age was 53 years; 28 male and 12 female patients (n=40)	Fatigue levels and their evolution during treatment in patients with nasopharyngeal cancer were evaluated using the common terminology criterion for adverse events version 2.0 of the National Cancer Institute, in addition to evaluating the impact of patient-related variables, tumor, and dosimetry on acute fatigue, in particular the radiation dose for central nervous system structures such as brain stem, cerebellum, pituitary gland, pineal gland, hypothalamus, and BG	Approximately 60% of patients reported feelings of fatigue during and after radiotherapy. The average dose delivered to the Basal Ganglia (BG) and hypophysis was significantly associated with fatigue throughout the period of radiation therapy. With regard to the cerebellum, it was associated with fatigue any time after radiotherapy. A total of 60% of cancer patients had fatigue during and after cancer treatment	Interruptions between BG, cerebellum, and cortical center bonding might be implicated by the physiopathology of fatigue due to radiation. The same finding was reported when addressing the interruption of pituitary gland regulated hormonal balance
Fatigue is associated with inflammation in patients with head and neck cancer before and after intensity-modulated radiation therapy Xiao et al., 2015 ¹¹	Prospective	Patients with head and neck cancer before and after radiotherapy. The age ranged from 57 to 76 years; 39 male and 7 female patients (n=46)	The level of patient's fatigue was analyzed using the Multidimensional Fatigue Inventory (MFI) along with the evaluation of inflammatory markers such as IL-6 and C-reactive protein (CRP)	Occurrence of fatigue was significantly associated with IL-6 and CRP independent of time (p<0.05). Furthermore, changes in fatigue level before and after intensity-modulated radiation therapy (IMRT) were positively associated with changes in the levels of IL-6 and CRP (p<0.05). A total of 98% of the patients reported fatigue after radiotherapy and 67% of them reported its severity	Authors suggest that inflammation is possibly associated with fatigue in patients with head and neck neoplasm. This occurs because of the presentation of genetic transcripts related to the expression of proinflammatory cytokines and nuclear factor-kappa B
Associations among human papillomavirus, inflammation, and fatigue in patients with head and neck cancer Xiao et al., 2018 ¹²	Prospective	Patients with squamous cell carcinoma in the head and neck area before and after 1 and 3 months of treatment. A total of 42 men and 8 women had squamous cell carcinoma related to human papillomavirus (HPV) infection. Meanwhile, 28 men and 16 women (n=94) had squamous cell carcinoma not related to HPV infection; the patients' age ranged from 57 to 82 years	The relationship between the presence of HPV, inflammation, and fatigue in patients with squamous cell carcinoma in the head and neck area before treatment and 1 and 3 months after radiotherapy was evaluated. Fatigue level was measured using MFI. Inflammation was indirectly evaluated based on the levels of plasma CRP, interleukin 1 receptor antagonist (IL-1Ra), soluble receptor of tumor necrosis factor 2 (sTNFR2), and IL-6	Patients with HPV infection reported an increase in the levels of fatigue and inflammation from the start until the first month of treatment but did not experience weakening after the third month of therapy. All patients (100%) reported fatigue during cancer treatment	HPV status is a particularly important marker of vulnerability to immunological and behavioral consequences of squamous cell carcinoma as well as its treatment. HPV status helps to determine appropriate strategies to manage the symptoms

to be continued

Chart 1. continuation

Title/author/year	Study design	Population	Methodology	Results	Outcome
Fatigue in patients with head and neck cancer undergoing radiation therapy: a prospective study Avelar et al., 2019 ⁶	Prospective	Patients with head and neck cancer undergoing radiotherapy were evaluated at the beginning (Time 1), middle (Time 2), and end of treatment (Time 3) Patients' age ranged from 18 to 80 years; 53 male and 7 female patients (n=60)	The frequency of fatigue symptoms and the domains of patients with head and neck neoplasm were identified. Important variables were collected through an interview using the Piper Fatigue Scale, which evaluates the global, behavioral, affective, sensorial, and psychological domains	The dominance of male patients aged between 41 and 60 years was assessed. The predominance of low education and regular alcohol and cigarette use was also evaluated. When compared with values in Time 1, the fatigue scores were usually increased in Times 2 and 3 (p<0.05). All patients (100%) reported fatigue during cancer treatment	Fatigue levels increased throughout the radiotherapy treatment period, and all domains were affected

Chart 2. Studies that assessed fatigue with other related symptoms (Salvador, Bahia, Brazil, December 2019 to April 2020)

Title/author/year	Study design	Population	Methodology	Results	Outcome
Predictors of functional decline in locally advanced head and neck cancer patients from south Brazil Silver et al., 2010 ¹³	Prospective	Patients with spinocellular carcinoma of the head and neck in the south region of Brazil; the age ranged from 60 to 70 years; 53 male and 7 female patients (n=60)	The anthropometry and biological/ physiologic predictors of functional impairment in patients diagnosed with spinocellular carcinoma were investigated. The data of patients registered in the regional oncologic center of Curitiba within the 6-month period were obtained	The total fatigue score increased 64% as well as the levels of stress and serum cortisol. The level of difficulty for performing the instrumental activities of daily life doubled, while that for performing the basic actives of daily life quadrupled (p<0.001). Problems with chewing or swallowing, weight loss, fatigue, and stress were also reported A total of 64% of patients reported increased fatigue	The study showed evidences to support the necessity of interventions to manage stress and fatigue
Depression, fatigue, and health-related quality of life in head and neck cancer patients: a prospective pilot study Sawada et al., 2012 ¹⁴	Prospective	Patients with head and neck cancer undergoing radiotherapy. Patients' age ranged between 30 to 90 years; 35 male and 6 female patients (n=41)	The Piper Fatigue Scale, Beck's Depression Inventory (BDI), and Functional Evaluation of Therapy of Head and Neck (FACT-H&N) were used to evaluate the patients three times throughout the treatment period (at the beginning of treatment, 15 days after treatment, and at the end of treatment). Prevalence of depression and fatigue was related to patients' quality of life	BDI and Piper increased throughout the radiotherapy treatment period. The BDI scores did not indicate presence of depression. The average of FACT-H&N decreased at the middle and end of therapy	There was an increase in fatigue symptoms during the progress of radiotherapy, which indicated a worsening of patients' quality of life
Time course and predictors for cancer-related fatigue in a series of oropharyngeal cancer patients treated with chemoradiation therapy Spratt et al., 2012 ⁴	Prospective	Patients with oropharyngeal neoplasm undergoing radiotherapy; average age ranged between 58 years; 68 male and 19 female patients (n=87)	The association between fatigue and cancer in patients with oropharyngeal carcinoma undergoing radiotherapy (2008-2010) receiving a radiation dose of 70 Gy was evaluated	The median follow-up of living patients was 14 months. The level of fatigue peaked 1-2 weeks after radiotherapy and remained higher than baseline for up to 2 years after radiotherapy in 50% of the patients. The average fatigue score at the conclusion of the treatment and 1 year after radiotherapy was significantly higher than the baseline value (p<0.05). All patients (100%) experienced the fatigue symptom	Radiotherapy was highly correlated with worsening of fatigue and pain

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Chart 2. continuation

Title/author/year	Study design	Population	Methodology	Results	Outcome
Experiences of pain: a longitudinal, qualitative study of patients with head and neck cancer recently treated with radiotherapy Schaller et al., 2015 ¹⁵	Prospective	Patients with head and neck neoplasm undergoing radiotherapy; the average age was 64 years; 19 male and 7 female patients (n=26)	Qualitative semi-structured interviews were conducted 1 and 6 months after completing the treatment. The influence of radiotherapy on symptoms related to pain, general fatigue, and psychological suffering was assessed	Patients reported pain in the head and neck area, severe fatigue, mood changes, anxiety, and low level of relationship. Physical pain, psychological suffering, and social distancing due to treatment were frequently reported on both interviews. Patients did not clearly state the relationship between pain and psychological changes. Approximately 70% of cancer patients showed fatigue	Pain had an influence on social life of patients with head and neck cancer
Psychological distress and health-related quality of life among head and neck cancer patients during the first year after treatment Ninu et al., 2015 ¹⁶	Prospective	Patients with head and neck neoplasm; the average age was 67 years; 60 male and 26 female patients (n=86)	The quality of life and psychological changes after administering different treatments in patients with head and neck cancer assessed in the first year after completing the treatment were examined. The patients were evaluated using the European Organization for Research and Treatment of Cancer QOL Core Questionnaire 30 (EORTC QLQ-C30) and EORTC QLQ-H&N35 surveys	Concerning fatigue, the kind of treatment did not impact the occurrence of ($p > 0.05$). All patients experienced fatigue regardless of the type of therapy (surgery, chemotherapy, and/or radiotherapy). A total of 41.1% of cancer patients claimed fatigue	Applied questionnaires were efficient in following up the signs and symptoms of the target population. One of those symptoms was fatigue
A descriptive, longitudinal study of quality of life and perceived health needs in patients with head and neck cancer Sandstrom et al., 2016 ¹⁷	Prospective	Patients with head and neck cancer from the beginning of treatment up to 12 months after treatment; the age range was not mentioned; 40 male and 20 female patients (n=60)	Health-related quality of life (HRQOL) and health-related needs of patients who received radiation as treatment for head and neck cancer were described	The study showed that fatigue and anxiety had the highest average scores ($p < 0.001$). An HPV positive status was associated with high levels of anxiety; the lowest socioeconomic level affected the occurrence of fatigue negatively; the most common concerns were related to salivary flow, taste capacity, swallowing, and pain. Approximately 56% of patients with cancer had fatigue	The HRQOL instrument used was efficient for detecting fatigue, anxiety, and other aspects affecting the patients' quality of life of in this study
Prevalence of obstructive sleep apnoea syndrome following oropharyngeal cancer treatment: a prospective cohort study Loth et al., 2017 ¹⁸	Prospective	Healthy individuals (control group), and patients with advanced oropharyngeal cancer, stage III or IV, undergoing radiochemotherapy; the average age was 61 years; 37 male and 14 female patients (n=51)	Patients answered three types of questionnaires (Epworth Sleepiness Scale [ESS], EORTC QLQ-C30, and EORTC (QLQ-H&N35) to assess the prevalence of obstructive sleep apnea syndrome (OSAS) in patients with advanced oropharyngeal cancer stage III or IV as well as to assess its impact on quality of life, which included fatigue as one of the symptoms examined	OSAS was found in 25.49% of patients undergoing oncological treatment. There was no significant difference in occurrence of apnea among all types of treatments (surgery, chemo and/or radiotherapy) ($p > 0.05$). With regard to global quality of life and individual's fatigue occurrence, apnea had a significant impact ($p < 0.05$). A total of 72% of cancer patients expressed fatigue	In patients with advanced-stage oropharyngeal cancer, any therapeutic strategy might carry a risk of developing sleep obstructive apnea, thus impairing patients' quality of life negatively. Additionally, all patients reported symptoms of fatigue

to be continued

Chart 2. continuation

Title/author/year	Study design	Population	Methodology	Results	Outcome
Pretreatment neurocognitive function and self-reported symptoms in patients with newly diagnosed head and neck cancer compared with noncancer cohort Bernstein et al., 2018 ¹⁹	Case-control	Patients newly diagnosed with head and neck cancer compared with those without cancer; the average age was 54 years; 35 male and 5 female patients (n=40)	Patients newly diagnosed with head and neck cancer were compared with healthy individuals in terms of the risk for developing impaired neurocognitive function (NCF) due to illness, treatment, and lifestyle	The comparison revealed that the treatment group developed worse symptoms of cognitive dysfunction, fatigue, and anxiety ($p < 0.05$). However, both treated patients and control groups had NCF ($p > 0.05$) and 50% of patients reported fatigue	Patients with head and neck cancer undergoing treatment developed cognitive disorders
Stress and quality of life in cancer patients: medical and psychological intervention Barre et al., 2018 ⁸	Prospective	Patients with head and neck, breast, and lung cancer; the age ranged from 27 to 65 years; 19 male and 11 female patients (n=30)	The impact of cancer-related hospitalization and a combination of medical attention and psychological interventions (psychoeducation, guided imagery, relaxation technique, and cognitive therapy) on stress and quality of life of patients with head, neck, breast, and lung cancer were analyzed through paired tests, Cohen's d, and descriptive statistics	The study showed significant improvements in physical and emotional conditioning, reduction of fatigue, pain, insomnia, lack of appetite, diarrhea, and constipation ($p < 0.01$). Approximately 16.58% of patients with cancer reported fatigue during cancer treatment	The combination of medical attention and psychological interventions impacted the quality of life of patients positively
Socioeconomic status and quality of life in patients with locally advanced head and neck cancer Tribius et al., 2018 ²⁰	Prospective	Patients with locally advanced head and neck cancer; the average age was 60 years; 111 male and 50 female patients (n=161)	The patients were examined at the end of therapy and at 12 and 24 months of follow-up using EORTC QLQ-C30 and QLQ-H&N35 questionnaires to assess the differences in the quality of life in patients who have different socioeconomic levels after receiving modulated intensity radiotherapy	After administering intensity-modulated radiation therapy (IMRT) in patients with advanced head and neck cancer, those with high socioeconomic levels reported worse quality of life compared with patients who had middle or low socioeconomic status. A total of 97% of cancer patients reported fatigue	The magnitude of health improvement in patients with low socioeconomic status is significantly lower than in those with high socioeconomic status
Assessment of fatigability, depression, and self-esteem among head-and-neck carcinoma patients in a tertiary care hospital in South India Joseph et al., 2019 ²¹	Prospective	Patients with head and neck cancer before, during and after treatment; the age ranged between 45 and 65 years; 52 male and 18 female patients (n=70)	Fatigue, depression, and self-esteem were assessed in patients who were newly diagnosed with head and neck cancer paired by age and gender. Patients were assessed using the standardized questionnaire, the Piper Fatigue Scale, before starting concurrent chemoradiotherapy (CCRT). Patients from the study group were interviewed again in the fourth week and after completion of CCRT, in the seventh week	Values of fatigue and depression were significantly higher compared with the values of self-esteem. Analysis showed that basal fatigue was significant ($p < 0.001$) as well as depression after the end of the whole radiochemotherapy cycle. The basal levels of depression influenced the variables analyzed. All patients (100%) reported the fatigue symptom	Fatigue and depression might be periodically evaluated to determine whether corrective measures should be initiated in patients before the start of radiochemotherapy
Big data analysis of associations between patient reported outcomes, observer reported toxicities, and overall quality of life in head and neck cancer patients treated with radiation therapy Wilkie et al., 2019 ²²	Prospective	Patients with head and neck cancer undergoing radiotherapy; the average age was 63 years; 448 male and 164 female patients (n=612)	The associations between different variables related to patient and observer and the toxicities strongly linked to quality of life were evaluated. Three survey methods were used: Patient reported outcomes (PROs), observer reported toxicities (ORTs), and overall quality of life (QOL) in 1,273 follow-up visits	Results reported by patients were strongly linked to low QOL. The factors mentioned were recreation, entertainment, activity, and fatigue; however, no statistical significance was noted ($p = 0.51-0.60$)	PRO analysis identified activity, lifestyle, and fatigue for consideration to be included in clinical surveys because of high toxicity

to be continued

Chart 2. continuation

Title/author/year	Study design	Population	Methodology	Results	Outcome
Sensitivity to change of the EORTC quality of life module measuring cancer-related fatigue (EORTC QLQ-Fa12): results from the international psychometric validation Weis et al., 2019 ²³	Randomized clinical trial	Patients with head and neck cancer undergoing curative and palliative treatments; the average age was 60 years; 258 male and 275 female patients (n=533)	European Organization for Research and Treatment of Cancer Quality of Life Group (EORTC QLQ) has developed a multidimensional tool to measure cancer-related fatigue, called the EORTC QLQ-FA12. It was used to assess patients with cancer undergoing palliative and curative treatment at T1 period. They were followed up throughout the treatment period (T2) and four weeks after treatment completion (T3)	In this study, all fatigue scores were significantly higher in the group who received palliative treatment compared with those in the curative group (p<0.001). Physical fatigue was described by 27.34% of patients, emotional fatigue by 29.01% and cognitive fatigue by 21.38%. A total of 83.38% of the patients claimed fatigue	The use of EORTC QLQ-FA12 allowed the identification of clinically significant changes in fatigue throughout the curative and palliative treatment periods

(HRQOL), Concurrent Chemoradiotherapy (CCRT), Patient Reported Outcomes (PROs), Observer Reported Toxicities (ORTs), General Life Quality, and EORTC QLQ fatigue module (EORTC QLQ-FA12).

These studies have reported a significant increase in fatigue score as well as quality of life-related symptoms, such as pain, stress, and depression ($p < 0.05$). All authors have concluded that such symptoms interfered with the performance of patients' daily life activities as well as with the success of the treatment.

DISCUSSION

Head and neck cancer is a heterogenic group of neoplasms that affects some regions responsible for basal functions as breathing, chewing, and verbal communications²⁴. The primary etiological causes of developing this type of cancer are alcohol and tobacco use, both associated with genetic susceptibility, human papillomavirus infection, and other co-factors⁶. Therapeutic modalities as radiotherapy and chemotherapy cause unexpected symptoms, which affect patients' quality of life and their capacity to perform the activities of daily living as the level of pain increases along with the severity of fatigue symptoms²⁵.

Fatigue has been described as a feeling of unusual tiredness or lack of energy, which varies in level and frequency, and may last for a long time due to emotional stress, pain, sleep disorders, treatment-associated drugs, and other related symptoms²⁶. As the nature of fatigue is multifactorial, it directly impacts the survival and quality of life of patients with cancer, especially those with head and neck cancer²⁷. Generally, severe metabolic stages of cancer, along with negative feelings and symptoms associated with treatment, as poor nutrition, lead to general weakness in these patients¹⁸. From this point of view, ambient social and physical circumstances are

affected once these individuals are unable to maintain their daily life activities, which makes them even more dependent on others¹⁴. The prevalence of fatigue in the studies that assessed fatigue exclusively was approximately 79.1% and in the studies that assessed fatigue with other related symptoms was approximately 49%.

Although the dental surgeon's primary concern is the treatment of head and neck cancer, the approach is to treat the patient as a global unit or as an integrated system. Additionally, the multidisciplinary health team²⁸ must consider patient's psychological, social, ethnic, and religious needs. This systematic review aimed to evaluate the prevalence of fatigue in patients with head and neck cancer to expand the understanding of the frequency of these symptoms and how health professionals can assess fatigue to provide an integrated treatment.

In this study, the fatigue investigated is a common and debilitating cancer comorbidity, which results from a combination of biological and psychological factors²⁶. Moreover, immune responses to tumors can trigger an increase in serum levels of proinflammatory cytokines, as IL-1 beta, IL-6, and TNF-alpha²⁷. Such cytokines, which originate from tumoral responses or even from a tumor in the immune system, act to promote a balance between the cell and humoral immunity and are fundamental for the central and surrounding nervous systems. Likewise, cytokines present in several cerebral regions might trigger changes in neural activity overtime because of the transmission of the surrounding cytokine signals to the central nervous system, inducing symptoms such as pain, fatigue, depression, and other behavioral change^{11,27}.

There are many methods and tools that have been used to follow up on patients with fatigue symptoms during the period of oncological treatment, including short questionnaires and graduation scales. Most are self-reported, which can be used to assess fatigue from the physical, psychological, and cognitive dimensions²⁹.

The questionnaires used in previous studies to measure the symptoms of fatigue were accepted by patients, reported as easy to use, quick and reliable. Therefore, it is crucial in clinical practice to utilize questionnaires to determine the prevalence of fatigue and other possible symptoms²⁶.

Managing cancer-related fatigue requires a broader comprehension about patients and their symptoms and an individualized treatment²⁶. Therefore, some studies have proposed alternative therapies, such as relaxation techniques including deep breathing and meditation, physical activity, acupuncture, behavioral cognitive therapy, sleep therapy, use of natural and pharmacological drugs for treating fatigue, and improving the patient's quality of life^{30,31}.

In this study, it was determined the importance of health professionals involved in caring for patients with cancer to identify fatigue and its physiopathological mechanisms. When these factors are detected, therapeutic strategies can be initiated to prevent remission and improve patients' well-being before and after treatment.

According to Bower³², fatigue is a subjective experience and patient self-reported is the gold-standard method for its assessment. Many measures have been used to evaluate fatigue's degree which varies from single-item assessments to multi-dimensional scales and questionnaires. However, self-reported methods are considered a true limitation of the studies analyzing fatigue because it is necessary to rely on the patients to fill them correctly without any professional supervision.

It was also observed a great variation of methods to assess fatigue in the present study. It was difficult to compare their different results, although BFI, MFI and other scales are widely used in the literature and many authors have validated them.

CONCLUSION

In conclusion, the studies analyzed in this review demonstrated that fatigue was one of the most prevalent symptoms in patients with head and neck cancer and it was usually related to other symptoms such as pain, sleep disorders, lack of appetite, dyspnea, emotional stress, and depression.

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CONTRIBUTIONS

All authors have reviewed and approved the final version of the manuscript, and each author believes the manuscript is a trustworthy reflection of their work. Ana Carolina Lopes de Souza participated of the wording of the text, resources, and formal analysis. Juliana Borges de Lima Dantas, Gabriela Botelho Martins, Ana Carla Barletta Sanches and Manoela Carrera collaborated in the methodology, resources, article review, English proofreading and critical review. Alena Ribeiro Alves Peixoto Medrado oversaw all the stages of the work.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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