

## Occurrence of Fatigue and Pain in Oncology Patients: Serie of Case Reports

### *Ocorrência de Fadiga e Dor em Pacientes Oncológicos: Série de Casos Clínicos*

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#### Abstract

Fatigue is a reversible change in biological, physical and psychic functions, resulting from the imbalance of the organism. In patients with head and neck cancer (HNC), fatigue has been cited as one of the most frequent symptoms, especially in individuals with metastasis. It can significantly limit daily activities in order to be considered as a chronic condition, in particular, when associated with painful symptoms. The objective of this study was to report the occurrence of fatigue and pain in patients with HNC. This was a series of prospective clinical cases describing the clinical history of four patients with HNC submitted to radio chemotherapeutic treatment, users of a public oncology service. To assess the degree of fatigue, the Brief Fatigue Inventory questionnaire was applied at five different moments during the antineoplastic treatment and pain analysis, an analog pain scale was used. The analysis of the questionnaires showed that fatigue was a frequent complaint and intensified with the advance of antineoplastic therapy. Its occurrence was also related to the difficulty performing daily activities. Painful symptomatology has been reported by patients to varying degrees. The occurrence of fatigue and pain in patients with HNC presents variability due to the individual's own experience, reflected by their socioeconomic and cultural context and their personal perception of the illness process.

**Keywords:** Head and Neck Neoplasms. Quality of Life. Cancer Pain.

#### Resumo

*A fadiga é uma alteração reversível das funções biológicas, físicas e psíquicas, proveniente do desequilíbrio do organismo. Em pacientes com câncer de cabeça e pescoço (CCP), a fadiga tem sido citada como um dos sintomas mais frequentes, principalmente em indivíduos com metástase. Pode limitar de forma significativa as atividades diárias, de modo a ser considerada uma condição crônica, em especial, quando associada à sintomatologia dolorosa. Este trabalho objetiva relatar a ocorrência de fadiga e dor em pacientes com CCP. Tratou-se de uma série de casos clínicos, de caráter prospectivo, que descreve a história clínica de quatro pacientes com CCP submetidos ao tratamento radioquimioterápico, usuários de um serviço de oncologia público. Para avaliação do grau de fadiga, foi aplicado o questionário Brief Fatigue Inventory em cinco momentos distintos, durante o tratamento antineoplásico e para a análise da dor, foi utilizada uma escala analógica de dor. A análise dos questionários demonstrou que a fadiga foi uma queixa frequente e se intensificou com o avanço da terapia antineoplásica. Sua ocorrência também esteve relacionada à dificuldade de execução de atividades cotidianas. A sintomatologia dolorosa foi relatada pelos pacientes em diferentes graus. A ocorrência de fadiga e dor em pacientes com CCP apresenta variabilidade em razão da experiência vivida pelo próprio indivíduo refletida pelo seu contexto socioeconômico e cultural e a sua percepção pessoal acerca do processo de adoecimento.*

**Palavras-chave:** Neoplasias de Cabeça e Pescoço. Qualidade de Vida. Dor do Câncer.

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#### 1 Introduction

Head and neck cancer (HNC) is one of the most incident types in Brazil. This anatomical region comprises the oral cavity, pharynx and larynx. About 40% occurs in the oral cavity, 15% in the pharynx and 25% in the larynx<sup>1</sup>. Evidence shows that the incidence of HNC increases with age<sup>1,2</sup>. Smoking and alcohol are well-established risk factors and although this neoplasm affects males preferably, in recent years there has been a remarkable increase in incidence among women, which should reflect changes in habits<sup>3,4</sup>.

The most used treatment for HNC is surgical, in addition to radio chemotherapy. However, radio and chemotherapy cause physical and emotional side effects that affect the

patient's daily life. Fatigue is one of the most frequent symptoms, as well as pain complaint<sup>4</sup>. It is a reversible change in biological, physical and psychic functions, resulting from the imbalance of the organism.. When related to cancer, it is a complex and multifactorial sensation, with greater presence in cases of metastasis and is reported before, during and after treatment. It is known that it may also be related to the symptom Pain<sup>5,6</sup>. The degree of pain may vary depending on tumor location, presence of metastases and staging of neoplasm<sup>7,8</sup>.

The aim of this study was to report a series of clinical cases of patients with HNC under antineoplastic treatment who reported fatigue and pain complaints, as well as suggest

possible etiological factors related to the occurrence of these symptoms.

## 2 Case Report

It was a series of clinical cases of patients with HNC, through free demand, from December 2019 to March 2020, from the *Irmã Dulce* Social Works (OSID), High Complexity Unit in Oncology (UNACON). The study was submitted and approved to the Ethics Committee in Humans of the same institution, under opinion number CAAE 12743619.5.0000.0047. All patients were informed about the proposal and the objective of the study, as well as the possible risks and benefits, and signed the Free and Informed Consent Form, where they stated that they understood the purpose of the research.

Four individuals with HNC who had not started radiotherapy associated with chemotherapy or not were included, with a minimum age of eighteen years. Additionally, patients should agree to respond to the evaluation instrument at all study periods. Patients with tumor recurrence did not

participate in the evaluation.

The clinical cases represented a cut-off of the population evaluated by the Dentistry Service. Patients were followed up by the Dentistry team and participated in a randomized clinical study that covered the use of laser photobiomodulation<sup>9</sup>. Data were collected regarding the type of neoplasm, staging and treatment (dose and sessions). To draw the patients' profile, a questionnaire was completed with information related to age, gender and socio-demographic situation.

In order to follow the development of fatigue and pain symptoms, the *Brief Fatigue Inventory (BFI)*<sup>10</sup> questionnaire and an analog pain scale, with 10 scores (0: Absence and 10: Maximum degree) were applied. These instruments were applied in 5 different moments (1<sup>st</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 18<sup>th</sup> and 24<sup>th</sup> days) counted from the beginning of radiotherapy, by a single previously calibrated interviewer.

The results regarding the patients' socio-demographic profile and characteristics of oncological treatment are compiled in Table 1.

**Table 1** - Sociodemographic and tumor-related data of patients. OSID, Salvador, Bahia, Brazil

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	80	51	71	67
Sex	Female	Male	Female	Male
Housing	Rural zone	Urban zone	Rural zone	Rural zone
Schooling	Illiterate	High School complete	Elementary School incomplete	Elementary School incomplete
Systemic disease	Hypertensive	Hypertensive	Hypertensive	-
Medicines	Nifedipine, Hydrochlorothiazide and Propranolol	No regular use	Losartan and Hydrochlorothiazide	-
Habits	Smoking: 2 years. Withdrawal: 20 years.	No habits.	Smoking: straw cigarette - 40 years Withdrawal: 10 days. Alcohol: cane spirit -40 years. Withdrawal: 35 years.	Smoking: was not able to tell how long. Withdrawal: 1 month. Alcohol: whiskey and cane spirit (not able to tell how long). Withdrawal: 10 days.
Characteristics of the tumor	Leukoplastic lesion in hard palate, soft palate and amigdalial pillar	Right parotid gland	Left lower alveolar ridge	Larynx
Staging	TxNxMx	T2pN0Mx	T4aN0M0	T1N0M0
Treatment	Radio chemotherapy	Surgery Radio chemotherapy	Radio chemotherapy	Radiotherapy

Radiotherapy protocol: total dose 70Gy-fractional in daily doses of 2Gy, totaling 35 sessions.

Chemotherapy protocol: intravenous cisplatin, 21/21 days.

Source: resource data.

Table 2 illustrates patients' answers related to BFI questionnaire questions. In patients 1 and 3, there was an affirmative response for fatigue occurrence in all the

evaluated periods, while patients 2 and 4 did not report fatigue throughout the oncological treatment.

**Table 2** - Data collected from patient responses 1 on the “*Brief Fatigue Inventory*” questionnaire. Irmã Dulce, Assistential Work, Salvador, Bahia, Brazil, January to March 2020

<b>Patient 1</b>	<b>1<sup>st</sup> Session</b>	<b>6<sup>th</sup> Session</b>	<b>12<sup>th</sup> Session</b>	<b>18<sup>th</sup> Session</b>	<b>24<sup>th</sup> Session</b>
Did you feel constantly tired or fatigued in the last week? (Yes or no)	Yes	Yes	Yes	Yes	Yes
1. Evaluate yours now	4	8	4	6	9
2. Evaluate your fatigue in the last 24h	7	8	7	7	5
3. Evaluate the worst moment of your fatigue in the last 24h	8	5	10	9	9
4A. Your fatigue interfered in your general activities in the last 24h	3	5	8	6	7
4B. Your fatigue interfered in your mood in the last 24h	2	4	9	5	8
4C. Your fatigue interfered in your walking skill in the last 24h	2	2	3	4	3
4D. Your fatigue interfered in your general works in the last 24h	0	0	0	3	5
4E. Your fatigue interfered in your relationship with people in the last 24h	0	0	0	7	10
4F. Your fatigue interfered in your quality of life in the last 24h	2	8	10	7	10
<b>Patient 2</b>	<b>1<sup>st</sup> Session</b>	<b>6<sup>th</sup> Session</b>	<b>12<sup>th</sup> Session</b>	<b>18<sup>th</sup> Session</b>	<b>24<sup>th</sup> Session</b>
Did you feel constantly tired or fatigued in the last week? (Yes or no)	No	No	No	No	No
1. Evaluate yours NOW	0	1	1	0	2
2. Evaluate your fatigue in the last 24h	0	2	3	0	2
3. Evaluate the worst moment of your fatigue in the last 24h	2	2	3	0	2
4A. Your fatigue interfered in your general activities in the last 24h	0	0	0	0	0
4B. Your fatigue interfered in your mood in the last 24h	0	0	0	2	2
4C. Your fatigue interfered in your walking skill in the last 24h	0	3	2	0	0
4D. Your fatigue interfered in your general works in the last 24h	0	0	0	0	0
4E. Your fatigue interfered in your relationship with people in the last 24h	1	0	0	0	0
<b>Patient 3</b>	<b>1<sup>st</sup> Session</b>	<b>6<sup>th</sup> Session</b>	<b>12<sup>th</sup> Session</b>	<b>18<sup>a</sup> Sessão</b>	<b>24<sup>th</sup> Session</b>
Did you feel constantly tired or fatigued in the last week? (Yes or no)	Yes	Yes	Yes	Yes	Yes
1. Evaluate yours now	1	5	0	10	0
2. Evaluate your fatigue in the last 24h	10	5	5	10	10
3. Evaluate the worst moment of your fatigue in the last 24h	10	10	5	10	10
4A. Your fatigue interfered in your general activities in the last 24h	10	10	5	10	10
4B. Your fatigue interfered in your mood in the last 24h	10	10	0	10	10
4C. Your fatigue interfered in your walking skill in the last 24h	10	10	4	5	5
4D. Your fatigue interfered in your general works in the last 24h	10	10	0	10	8
4E. Your fatigue interfered in your relationship with people in the last 24h	10	10	0	5	6
4F. Your fatigue interfered in your quality of life in the last 24h	10	10	0	10	8
<b>Patient 4</b>	<b>1<sup>st</sup> Session</b>	<b>6<sup>th</sup> Session</b>	<b>12<sup>th</sup> Session</b>	<b>18<sup>a</sup> Session</b>	<b>24<sup>th</sup> Session</b>
Did you feel constantly tired or fatigued in the last week? (Yes or no)	No	No	No	No	No
1. Evaluate yours now	2	0	2	0	2
2. Evaluate your fatigue in the last 24h	3	0	2	2	2
3. Evaluate the worst moment of your fatigue in the last 24h	3	0	3	3	2
4A. Your fatigue interfered in your general activities in the last 24h	0	0	0	0	0
4B. Your fatigue interfered in your mood in the last 24h	0	0	0	0	0
4C. Your fatigue interfered in your walking skill in the last 24h	0	0	0	0	0
4D. Your fatigue interfered in your general works in the last 24h	0	0	0	0	0
4E. Your fatigue interfered in your relationship with people in the last 24h	0	0	0	0	0
4F. Your fatigue interfered in your quality of life in the last 24h	0	0	0	0	0

Source: resource data.

Table 3 shows the answers regarding the analog pain scale. In patient 1, there was an improvement in pain between the 6<sup>th</sup> and 12<sup>th</sup> session, but it returned to higher scores during radiotherapy sessions. Patient 3 presented high scores in all analyzed sessions and patients 2 and 4 presented low scores.

**Table 3** - Data collected from patients' responses on the analog pain scale. Irmã Dulce, Assistential Work, Salvador, Bahia, Brazil, January to March 2020

Radiotherapy session	1 <sup>st</sup> Session	6 <sup>th</sup> Session	12 <sup>th</sup> Session	18 <sup>th</sup> Session	24 <sup>th</sup> Session
Pain Scale Patient 1	10	6	6	8	8
Pain Scale Patient 2	2	2	3	4	3
Pain Scale Patient 3	10	10	10	10	10
Pain Scale Patient 4	0	2	0	0	0

Source: resource data.

## 2.1 Discussion

Smoking, alcoholism, age, hereditary factors, immunosuppression and association with pre-existing viral infections represent risk factors for the HNC<sup>1,11</sup> development. About 70-80% of the cases are diagnosed in the advanced phase<sup>12</sup> due to neglect of symptoms and delay to referral, which results in worse quality of life, higher rates of morbidity and mortality and greater complexity of treatment. In this series of cases, two patients were smokers and drinkers, while two others were only smokers or drinkers, respectively. The presence of these risk factors ratifies similar results cited in the literature<sup>13,14</sup>.

Regarding the age of the patients, three were elderly. It is known that advancing the age group represents an additional risk factor because it leads to physiological decline of immunity, in addition to longer exposure to other risk factors. Age was evaluated by Razak et al.<sup>15</sup>, who identified this variable as an important factor in the survival of oral cancer. Ribeiro et al.<sup>16</sup>, stated that the survival rates are lower in older patients and may be related to the higher prevalence of debilitating diseases associated with aging or late diagnosis of HNC.

Of the four patients analyzed, the two female patients presented advanced staging and died after the end of treatment. The diagnosis of HNC in advanced phases may impact the worsening of quality of life and shorten the patients' life expectancy<sup>17</sup>. For Felippu et al.<sup>18</sup>, it is not only the intellectual and social state of the patient that impacts the difficulty of oncological treatment, but also the numerous deficiencies of the public health service, including referral, scheduling of examinations and treatment.

Cancer-related pain and fatigue are the most frequent manifestations reported by patients and are directly related to staging, as well as the therapeutic modality outlined, which directly contributes to the reduction of quality of life. Wilkie

et al.<sup>19</sup>, observed that fatigue usually has greater impact on quality of life than pain. The result obtained in this study indicated that patients reported association of low quality of life with recreation, entertainment, activity and fatigue. Although these symptoms act together, in head and neck neoplasms, there is a significantly greater perception of pain, and may have a direct or indirect association with the tumor, as demonstrated by Lima et al.<sup>20</sup>.

According to Bower et al.<sup>21</sup>, there is a relationship between the increase of pro-inflammatory cytokines and the worsening of fatigue in patients with breast and prostate cancer during antineoplastic treatment. In this sense, Doehner et al.<sup>22</sup> reported that patients with breast neoplasms expressed reduced cortisol levels in the morning, suggesting possible changes in the hypothalamic-pituitary-adrenal axis (HPA) and greater occurrence of fatigue in this population. Regarding HNC, the study by Langendijk et al.<sup>23</sup>, identified that the effects of radiation increase fatigue and negatively affect the biopsychosocial profile. Similar results were reported by Avelar et al.<sup>24</sup>.

Even though it is a common symptom, the etiology of fatigue during radio chemotherapeutic treatment is poorly understood. It may be due to the loss of recruitment of high-threshold motor units, reduced central impulse of the increase of the inhibitory input of the interneuron to the motor cortex and (or) weakness of the motor cortex failure in recruiting muscles. Peripheral fatigue represents the total sum of central and peripheral mechanisms, involving changes in skeletal muscle homeostasis and reduction of contractile force, such as impaired calcium release and reuptake in the sarcoplasmic reticulum and bioenergetic failure due to damaged oxidative phosphorylation<sup>25</sup>. Some studies indicate that oncological fatigue is most often central in origin<sup>21,26,27</sup>. In the present study, it was observed that the degree of fatigue was higher in patients who underwent combined radio chemotherapeutic treatment. This seems to suggest that the cumulative effects of these two therapeutic modalities can amplify the feeling of fatigue.

Pain, in turn, has been described as the most prevalent symptom in women. The influence of sex hormones, differences in psychosocial, cognitive, emotional and labor experiences<sup>28,29</sup> can justify this prevalence. According to the analysis of the analog scale used in this study, painful experience was more evident in women. Considering age, since both patients were elderly, sex hormone rates could be at relatively low levels. However, there is the possibility of social and occupational role and biopsychosocial factors also directly influence this sensory response.

Gonadal hormones influence the release and levels of neurotransmitters involved in pain perception, such as acetylcholine. Estrogenic levels and their cyclic variations can influence the release of acetylcholine in the central nervous system, directly modifying the stratification processes of pain perception. In addition, persistent painful stimulation

can activate the hypothalamus and hippocampus neurons, both involved in attention, learning and memory functions, modifying the waking state and emotional state<sup>30,31</sup>.

Finally, it should be noted that the investigation of these symptoms presents some challenges. First of all, it is important to point out that there is a subjectivity related to the symptoms in question, which permeates the social, cultural, perception of the disease and personal history. The use of standardized questionnaires, such as *BFI* and analog pain scales, can be of great value to try to measure the impact of these symptoms on the daily life of cancer patients, especially the HNC.

The fact that this study addresses a number of clinical cases represents a limitation and it is recommended to conduct prospective studies with a larger sample of individuals in order to acquire more forceful evidence regarding the impact of fatigue and pain on the quality of life of patients with HNC.

### 3 Conclusion

The present series of cases showed that the occurrence of fatigue and pain in patients with HNC presents variability due to the individual's own experience, reflected by their socioeconomic and cultural context and their personal perception of the illness process. The authors encourage the realization of new studies on this subject with a view to obtaining more robust results, which contemplate the prospection of a larger number of patients throughout the antineoplastic treatment.

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