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Title: Factors Influencing Quality of Life in Survivors of Head and Neck Cancer: a preliminary study

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ABSTRACT

Objectives: Time after diagnosis, survivors of head and neck cancer may perceive a decrease in their quality of life due to suffering from different sequelae. This preliminary study aims to describe which factors influence survivors of head and neck cancer quality of life. **Data sources:** A cross-sectional study was performed. Demographic and clinical factors, quality of life (global health status), pain (pressure pain thresholds) physical fitness (overall fitness), functional capacity and fatigue were evaluated. A multiple regression model was undertaken to check which outcomes could impact quality of life. **Results:** Fifty-three survivors of head and neck cancer participated in this study. Upper trapezius presure pain threshold, overall fitness and global fatigue were significant predictors of global health status, and when combined, they explained 42.10% of the variance in the global health status score. **Conclusions:** Quality of life perceived by survivors of head and neck cancer is influenced by pain, physical fitness and fatigue reported. This association of outcomes may act as a symptom cluster for survivors of head and neck cancer. **Implications for Nursing Practice:** The knowledge of this symptom cluster may help developing symptom assessment and management strategies, and therefore improving influence survivors of head and neck cancer quality of life.

Keywords: Head and Neck cancer; Quality of Life; Pain; Physical Fitness; Fatigue.

INTRODUCTION

Overall survival in patients with head and neck cancer (HNC) has been reported to be approximately 66% since 2010[1], and it has increased by up to 5% in recent years[2]. Incidence rates in the United States indicate that 60.6% – 66.2% of patients diagnosed with HNC survive 5 years or more[3]; in the United Kingdom, half of patients diagnosed with HNC survive 10 years or more[4]. These increased survival rates are mainly due to the improvement in diagnosis, staging and treatment strategies made by specialists when facing a cancer diagnosis[2]. Nevertheless, survivorship does not mean illness-free; treatment approaches such as surgery and radiochemotherapy are responsible for the manifestation of different local and systemic sequelae that survivors of HNC (sHNC) have to live with. Furthermore, these sequelae may include both short-term and long-term impacts[5]. Coping with symptoms such as pain, physical impairments and fatigue becomes a part of their daily life and may have a great impact on their quality of life (QoL)[6].

Pain perceived by sHNC is caused mainly by surgery inflammation and radiation-induced fibrosis on the affected tissues[7], and in approximately 40% of patients, this problem remains after the finalization of medical treatment[8]. Moreover, it is known that pain perception may lead to physical inactivity[9]. Considering that most of the patients with HNC already present lower physical fitness levels at diagnosis[10] and increased pain after treatment[8], this could suppose a more noticeable decrease in physical capacity level in sHNC, a fact that has already been evidenced on other cancer diagnoses, such as breast and colon cancer[11,12]. Additionally, fatigue is commonly perceived by cancer survivors after treatment[13]; and expressed as a multidimensional and distressing exhaustion that worsens their QoL by interfering with activities of daily living[14]. Besides, fatigue is related to biological processes such as inflammation and neuroendocrine and central nervous system dysfunction[15,16], all of which may also be associated with other symptoms. Thus, the perception of pain, the decrease in physical fitness and functional capacity and the presence of fatigue may worsen sHNCs' ability to perform activities of daily living or their work. A systematic review showed that these symptoms may be exacerbated by severe medical treatment[17], and they last even years after diagnosis[5]. Together, all these symptoms described above may act as a symptom cluster in sHNC, affecting their QoL in different fields than when only one symptom is perceived. Symptom clusters imply the presence of two or more symptoms that may not share the same etiology[18], and are often divided into different domains (e.g. fatigue-sleep quality and psychological clusters[19]). In other cancer populations (e.g., prostate cancer[20] and breast cancer[21,22]) symptom clusters including both pain and fatigue have been evidenced; however, to date, no symptom cluster in sHNC includes all three symptoms, but focus on other symptoms such as dysphagia or malnutrition[23]. Hence, it is important to look out for these consequences and their implications for QoL among sHNC[24].

Consequently, there is a lack of evidence on the impact of these symptoms and their association as a cluster in sHNC over their QoL. To date, the relationship between these consequences and QoL has not been deeply investigated in sHNC; therefore, the aim of this preliminary study was to evidence how QoL performs in sHNC based on their outcomes regarding pain, physical fitness, functional capacity, and fatigue. We hypothesize that pain, physical fitness, functional capacity, and fatigue influence QoL in sHNC.

MATERIALS AND METHODS

Patients and design

We conducted a cross-sectional study following the STROBE statement checklist recommendations[25] (appendix A). The study population was recruited between

September 2018 and September 2019 at the at the Virgen de las Nieves University Hospital, Granada (Spain). Eligible participants met the following inclusion criteria: aged ≥18 years, diagnosed with HNC squamous cell carcinoma, tumor located in the nasal cavity, paranasal sinus, nasopharynx, oral cavity, oropharynx, hypopharynx, or larynx and having completed the medical treatment in the previous 6-36 months. The exclusion criteria were having a metastasis or active neoplasm or cognitive impairment. Ethical approval for the study was granted by the Biomedical Investigation Ethics Committee, Granada, Spain (CEi-GRANADA Ref: 0045-N-16) and conducted in accordance with the Declaration of Helsinki[26]. All measurements were conducted between March 2019 and March 2020 at the Biomedical research group (BIO277) "CUIDATE" facilities, a cancer rehabilitation research unit of the Mixed Sport and Health Institute, University of Granada (Spain). All participants gave written informed consent before being formally enrolled.

Measures

All measurements were obtained in a single session. To reduce the risk of bias, the same assessor (a physiotherapist with more than 10 years of experience) carried out all the physical measurements.

Demographic and disease/treatment information: Demographic (age and sex) and disease/treatment (time since diagnosis, tumor stage at diagnosis and kind of curative cancer treatment received) data were collected at the appointment with the patient.

Quality of life: The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core-30 (EORTC QLQ-C30) (version 3.0) is a self-report questionnaire assessing QoL in cancer patients[27]. This 30-item questionnaire, scored on a Likert scale, includes one global health status subscale, five other functional subscales, three symptom subscales and six single items. In our study, we only used the global health status subscale that includes two items evaluating overall health and QoL over the week before answering the questionnaire. These two items range in a 6-point scale, from 1 “very poor” to 7 “excellent”. Hence, higher values obtained on this subscale report better health status. The Spanish version of the questionnaire has been transculturally adapted and validated for HNC patients[28] and has shown adequate internal consistency reliability (range 0.76– 0.95).

Pain: The pressure pain threshold (PPT) at the upper trapezius muscle fibers and the masseter muscle were evaluated to objectivize the pain perceived by sHNC, as these PPTs present significantly lower values in sHNC than in the healthy population[29]. For their measurement, an analog algometer (Force Dial FDK 20, Wagner, Greenwich, USA) with a 1-cm^2 rubber point and measuring in kg/cm^2 was used. Participants were lying in a prone position (upper trapezius) and supine position (masseter) during the evaluation and were taught to tell the assessor when the pressure sensation changed to pain. As done previously[29], PPTs were bilaterally explored, and the mean of 3 attempts (performed with a 30-second interval between attempts) on each PPT (i.e. a total of 12 assessments) was calculated. Moreover, for the inclusion of these variables in the following statistical analysis, the mean between both sides was calculated. The assessment of PPTs in general population with an algometer has shown interrater reliability ranging from 0.82-0.97 when performed on the same day[30].

Physical fitness: it was evaluated using the International Fitness Scale (IFIS)[31]. This scale presents five items of which the one of them that evaluates overall fitness was used for this study, whereas four evaluate different components of the physical condition (e.g., cardiorespiratory, muscular, speed/agility and flexibility). All items are scored on a 5-point Likert scale, ranging from 0 “very poor” to 4 “very good”. The questionnaire has been proven to be a reliable instrument with a test-retest reliability coefficient ranging from 0.54-0.65 and is considered a valid instrument for epidemiologic studies in general population[32].

Functional Capacity: Objective physical fitness was evaluated with the 6-minute walking test (6MWT)[33]. For this test, participants were told to walk as fast as possible for 6 minutes on a 30-m hallway, going back and forth (thus doing laps of 60 m). Additionally, the staff counted every lap and gave standardized encouragement[33]. When the 6 minutes were over, participants were asked to stop where they were. Total distance walked was recorded in meters. This test has shown a intraclass coefficient (ICC) of 0.91-0.98 (test-retest reliability) in HNC populations[34].

Fatigue: The Piper Fatigue Scale-Revised[35] is a validated instrument consisting of a self-reported 22-item questionnaire with an 11-point (0–10) scoring that assesses patient fatigue. This tool includes four subscales based on subjective fatigue behavior/severity, affective meaning, sensory and cognitive/mood. To obtain a global fatigue score, all item scores are summed and then divided by the total number of items. This global subscale, which was evaluated for this study, ranges from 0 to 10, where higher scores reflect higher fatigue levels. This questionnaire has shown high reliability (Cronbach's $\alpha = 0.96$)[35] and has been validated for the Spanish population[36].

Statistical analysis

The mean and standard deviation with a 95% confidence interval are shown for continuous variables and frequencies and percentages for categorical variables. Pearson and Spearman correlations were applied as appropriate and categorized according to the Cohen criteria as follows: >0.5, large; 0.5 to 0.3, moderate; <0.3 to 0.1, small; and <0.1, insubstantial[37]. Partial and semipartial correlations were also obtained to control for certain variables, such as age, sex, and tumor stage, and to determine the specific contribution of each outcome itself, respectively. A multiple regression model (method: stepwise) was used to explore which variables could explain the variation in global health status (dependent variable). The requirements to include an independent variable in the multiple regression analysis were as follows: 1) the correlation coefficients between the dependent variable and the independent variables were significant; and 2) the correlation coefficients between the independent variables were ≤0.7. Multicollinearity analysis using both tolerance and variance inflation factor (VIF) to detect linear dependence between predictors was performed. For statistical analyses, the level of significance was established at $p < 0.05$. All analyses were performed with IBM 25 SPSS software (IBM Corp., Armonk, NY, USA).

RESULTS

Of the 70 sHNC invited to participate in the study, 17 (24.30%) refused. A total of 53 sHNC were recruited for this study, of which 37 (69.80%) were men and 16 (30.20%) were women. Their mean±SD age was 60.30±11.32. Table 1 shows clinical data and outcome measure scores. The majority of sHNC had stage IVA disease (34%), and most also received surgery plus radiochemotherapy (52.80%) as medical treatment.

Descriptive analysis

Significant positive correlations were found between global health status and upper trapezius PPT ($r = 0.466$; $p < 0.01$), masseter PPT ($r = 0.373$; $p < 0.01$) and overall fitness ($r = 0.509$; $p < 0.01$). On the other hand, a significant negative correlation was found between global health status and global fatigue ($r = -0.474$; $p < 0.01$) (Table 2).

Partial and semipartial correlations

Partial correlations did indicate minor changes (adjusted by age, sex, tumor stage) with regard to the Pearson coefficients described above: upper trapezius PPT (r = 0.352), masseter PPT (r = 0.278), overall fitness (r = 0.591) and global fatigue (r = -0.423). Semipartial correlations were as follows: upper trapezius PPT 11.02% (r = 0.332), overall fitness 7.61% (r = 0.276) and global fatigue 7.18% (r = -0.268).

Multiple Regression Model

ANOVA revealed that the variance explained by our model was superior to the unexplained variance (F = 13.38 $p < 0.001$). Indeed, there was an effect of three out of six outcomes on global health status. The model explains 45.50% of the variance in global health status; after correcting for the effect of the sample and the independent (explanatory) variables, 42.10% of the variance is explained by the model. Therefore, the multiple regression model revealed that upper trapezius PPT, overall fitness and global fatigue were significant predictors of global health status, and when combined, they explained 42.10% of the variance in the global health status score measured with the EORTC QLQ-C30 (adjusted R2 = 42.10%; F = 6.31; p = 0.015) (Table 3). There was a real effect of these outcomes on global health status ($p < 0.05$). The single maximum correlation regressor was upper trapezius PPT. Only three regressors (upper trapezius PPT, overall fitness and global fatigue) contributed. The rest of the regressors were eliminated. All predictors showed high tolerance (ranging from 0.80-0.93) and low VIF (ranging from 1.06-1.24), which means that there was no collinearity.

DISCUSSION

The aim of this preliminary study was to analyze QoL among sHNC based on other outcomes, such as pain, physical fitness, functional capacity, and fatigue, once cancer treatment is finished to fill the knowledge gap about the management of sHNC and their sequelae when different outcomes impact their QoL. The present work supports the idea of a symptom cluster concerning pain, physical fitness, and fatigue in sHNC after finishing medical treatment.

The studied population of sHNC was diagnosed 26 months on average before participating, and presented a lower perception of global health status (i.e., QoL) according to reference values established in European sHNC[38]. Globally, most sHNC surpass more than 24 months of survivorship[5], yet their QoL decreases, as shown in a previous study[39]. This decline may be influenced by different symptoms, as described in this study. First, pain perception evaluated by PPTs in the areas described in this study are also in accordance with those presented in a previous study[29]; pain in neck and shoulder regions with a neuropathic (more in neck) and myofascial (more in shoulder) origin have already been widely described in this population[40], in addition to the presence of muscular trigger points located in several locations in sHNC[29], as well as hyperpathia and allodynia sensations. They also exhibited a reduced functional capacity, with a 35% reduction compared to a healthy population[41] and 33% to a general cancer population[42]; added to a low overall fitness perception, in accordance with another group of cancer patients[12] and in connection to the findings stating that most sHNC do not feel capable of performing high intensity physical activities[43]. Last, our population also showed a mild level of perceived fatigue with respect to established severity thresholds[44] and was consistent with the levels found in studies with sHNC[45].

Regarding pain, it may appear as a surgical consequence, as upper trapezius muscle fibers may be sensitized and then be the origin of pain; moreover if during neck dissection, the accessory nerve is resected[46]. Previous research has related QoL to perceived pain and has also found a clear negative influence of pain on QoL[47]. Similarly, the levels of physical fitness and physical activity have been found to influence cancer patients' QoL in the literature[10]. An influencing factor in the activity levels and physical fitness is chemotherapy treatment; it has been related to systemic organ injury, damaging normal tissue and consequently affecting cardiopulmonary function and exercise capacity in the cancer population[48]. It also causes muscle weakness[49], deterioration of cardiac function[48] and cardiotoxicity[50]; as a consequence, it may have an impact in the same way in sHNC, negatively affecting their QoL[51]. These symptoms may also lead to the presence of fatigue, interfering indeed with their activities of daily living[14], and which is physiologically related to inflammation and neuroendocrine and central nervous system impairments[15,16].

As previously found in the literature[52], our results showed positive correlations between global health status, PPTs in cervical and temporo-mandibular areas and overall fitness and a negative correlation between global health status and global fatigue perception. All these correlations were adjusted by age, sex and tumor stage; this allowed us to verify the minor influence of demographic and clinical factors on bivariate correlations. Thereby, there was a positive correlation between the upper trapezius and masseter PPTs, which could suggest that both PPTs share the same origin[47], although they are two different muscles and thus measure pain in two different regions. In addition, the regression analysis showed that the PPT on upper trapezius muscle fibers, overall fitness and global fatigue were significant predictors of impaired QoL; it should be pointed out that upper trapezius PPT explains 11.02% of the regression model by itself, as it is shown semipartial correlations describes above.

Our analysis revealed that the outcomes studied in the model were independently associated with global health status, as no predictors showed collinearity. Moreover, a correlation between overall fitness and fatigue was found, whereas pain was not related to these predictors of QoL. Although symptoms in a cluster are usually interrelated, two systematic reviews have evidenced that this relation may change over time after diagnosis[18,53]. Presumably, with a smaller range of time since diagnosis as an inclusion criterion or a bigger sample size, our analysis could have also shown an interrelation between pain, overall fitness, and fatigue.

Systemic symptoms tend to appear in clusters and seem to have a more important impact on long-term QoL. When the inflammatory response resulting from the disease and the treatment is very exuberant or persistent, functional or anatomical central nervous system changes may develop, resulting in anxiety, depression, pain, cognitive impairments and others[54,55]. In this work, a symptom cluster concerning pain, a decrease in physical fitness and the presence of fatigue in sHNC after finishing medical treatment is described. The effects of this cluster on QoL remain after controlling for age, sex and tumor stage. Previous works have described similar clusters of symptoms in oncology populations, including pain and fatigue[20–22], and have also shown how the existence of multiple symptoms at a time negatively affects QoL in sHNC[56,57]. One of the most recent studies has described two symptom clusters related to pain and fatigue and associated with QoL in HNC with endotracheal tubes[57]. Nevertheless, some differences have to be stated between patients with endotracheal tubes and our study population, as the former group of patients does not suffer only the disease and the side effects of the treatment but also the invasion of the tube.

It has already been recommended to take into account clinical factors affecting a symptom cluster to anticipate them and improve patients' factor experience[19]. Therefore, to find a better understanding of the clustering of systemic symptoms, the relationship between them and their underlying pathophysiology in sHNC, several works have been published[54,55,58]. Some studies have approached the functioning of the symptom clusters: regarding pain, it may make the patient wake up at night, and this lack of rest could lead to the presence of fatigue during the day[19]. This same mechanism could also explain a decreased perception of physical fitness and therefore will influence inactivity.

On the other hand, time since diagnosis, functional capacity (expressed in distance paced during the 6MWT) and masseter PPT were not predictors of impaired QoL. As mentioned previously, time after diagnosis, sHNC continue to perceive symptoms such as pain, impairments on physical fitness or fatigue among other psychosocial impairments on both short and long-term after the termination of medical treatment[5] that is why it was included on our model; however, our sample size and/or the heterogeneity between participants and their characteristics related to this outcome implied that it did not appear as a predictor of impaired QoL. 6MWT was chosen because of being a good functional capacity indicator; it was thought that functional capacity could predict QoL, as this outcome may be influenced by others commonly presented in sHNC, such as the decrease on nutritional and/or psychological status[59,60]. Although the perception of physical fitness was a predictor of QoL, these results could be due to the discrepancy between objective parameters (i.e. meters in 6MWT) and subjective perceptions: that is why both outcomes are not necessarily correlated, as previously described on a similar context[61]. Regarding masseter PPT, it was chosen by its location, as the presence of lower masseter PPTs may affect the swallowing process[62], whereas not all sHNC on our study received medical treatment on the facial region and thus masseter PPT is not affected on all participants, as compared with upper trapezius PPT.

This study has some limitations. First, the heterogeneity of the tumor locations in sHNC covers areas related to the nasal cavity, paranasal sinuses, nasopharynx, oral cavity, oropharynx, hypopharynx, or larynx, all of which have different health issues. It would be desirable to increase the sample size to conduct a subgroup analysis to determine the stability of the cluster in different tumor locations. This same limitation may appear with the time since diagnosis, as the challenges sHNC perceive vary on time; however, due to the difficulty on recruitment, we had to extend this inclusion criteria. Therefore, we did not include outcomes such as swallowing difficulty, anxiety, depression or sleep quality, which have also been shown to decrease QoL in this population[44] and could have enhanced our analysis by explaining more variation in the global health status in sHNC, but this was not possible as our sample size did not allow to include more outcomes on the regression model.

Despite the described limitations, our study has some implications for clinical practice helping with symptom management. Due to the existence of different types of sHNC and standardized several treatments, it is necessary to find specific strategies that can control symptoms in a more effective way. In this sense, as previously stated, identifying and treating the first presenting or the most influential symptom and better control and prevention of the rest can be achieved[23]. Likewise, managing symptoms by group[63] as well as prescribing treatment strategies that cover multiple symptoms may be helpful[19]. Therapists should then be able to apply several techniques to encompass all symptoms. In addition, knowledge of the clusters of symptoms that frequently appear in this population makes it possible to inform sHNC of their cooccurrence. This allows not only anticipate the symptoms but also to better manage them and not associate the symptom cluster with a poor assimilation of their treatments or a disease worsening[19]. In the same line, this preliminary study may help researchers to deep into these outcomes and explore the symptom clusters with bigger sample sizes, that allows to include other outcomes (e.g. anxiety, depression, sleep quality) to see their association as well as if they are predictors of QoL.

CONCLUSION

QoL among sHNC is influenced by the pain perceived in the cervical and shoulder regions, the perception of their physical fitness and the fatigue reported in the long term after completion of medical treatment. This association of outcomes may act as a symptom cluster so that an adequate treatment strategy is needed to maintain or increase sHNC QoL.

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Declarations of interest

None

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Table 1. sHNC demographic and clinical data

Clinical characteristics	**Frequency (%)**
Gender	
Male	16 (30.20)
Female	37 (69.80)
Stage of tumor	
I	6 (11.30)
II	10 (18.90)
IIIA	11 (20.80)
IVA	18 (34)
IVB	2 (3.80)
Systemic treatment	
RT	1 (1.90)
RCT	7 (13.20)
Surgery & RT	15 (28.30)
Surgery & RCT	28 (52.80)
Outcomes	**Mean (SD); CI 95%**
Age (years)	60.30 (11.32); CI 95% 57.18 to 63.42
Time since diagnosis (months)	26.34 (16.86); CI 95% 21.69 to 30.99
Global health status (EORTC QLQ-C30)	61.05 (23.78); CI 95% 54.43 to 67.67
Upper trapezius PPT (Algometry, Kg/cm2)	3.12 (1.75); CI 95% 2.63 to 3.60
Masseter PPT (Algometry, Kg/cm2)	1.45 (0.62); CI 95% 1.28 to 1.62
Overall fitness (IFIS)	2.94 (1.04); CI 95% 2.66 to 3.23
Distance (Six minutes walking test, m)	399.75 (156.41); CI 95% 351.62 to 447.89
Global fatigue (Piper Fatigue Scale-Revised)	2.65 (2.50) CI 95% 1.96 to 3.34

CI: Confidence interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Core-30; IFIS: International Fitness Scale; PPT: Pressure Pain Threshold; RCT:

Radiochemotherapy; RT: Radiotherapy; SD: Standard deviation. Lost data: tumor stage (n=6); medical treatment (n=2); global health status (n=1); Distance (n=10)

Table 2. Pearson and Spearman's correlation matrix for the study variables

Outcomes	Global health status (EORTC QLQ-C30)	Time diagnosis (months)	Upper trapezius PPT (Kg/cm2)	Masseter PPT (Kg/cm2)	Overall fitness (IFIS)	Distance (6MWT)	Global fatigue (PFS-R)
Global health status (EORTC QLQ-C30)	1	-0.023[b]	0.466[a]	0.373[a]	0.509[a]	0.068	-0.474[a]
Time diagnosis (months)	-0.023[b]	1	-0.051[b]	-0.105[b]	-0.256[b]	0.196[b]	-0.229[b]
Upper trapezius PPT (Kg/cm2)	0.466[a]	-0.051[b]	1	0.584[a]	0.239	-0.126	-0.161
Masseter PPT (Kg/cm2)	0.373[a]	-0.105[b]	0.584[a]	1	0.162	0.011	-0.115
Overall fitness (IFIS)	0.509[a]	-0.256[b]	0.239	0.162	1	-0.066	-0.410[a]
Distance (6MWT)	0.068	0.196[b]	-0.126	0.011	-0.066	1	-0.234
Global fatigue (PFS-R)	-0.474[a]	-0.229[b]	-0.161	-0.115	-0.410[a]	-0.234	1

[a]p<0.01 [b]Spearman. All other values are Pearson Correlation Coefficient. 6MWT: 6 Minutes Walking Test; C30: European Organization for Research and Treatment of Cancer Quality of Life Core-30; IFIS: International Fitness Scale; PFS-R: Piper Fatigue Scale-Revised; PPT: Pressure Pain Threshold.

Table 3. Summary of multiple lineal regression (stepwise) to determine possible predictors of global health status (r^2 = 45.5%). Level of significance $p < 0.05$.

Independent variables	***B***	***t***	***p***	***Semipartial correlations***
Upper trapezius PPT	0.343	3.115	0.003	0.332
Overall fitness (IFIS)	0.307	2.587	0.013	0.276
Global fatigue (PFS-R)	-0.293	-2.512	0.015	-0.268

IFIS: International Fitness Scale; PFS-R: Piper Fatigue Scale-Revised; PPT: Pressure Pain Threshold