Myofascial pain, widespread pressure hypersensitivity, and hyperalgesia in the face, neck, and shoulder regions, in survivors of head and neck cancer

Ortiz-Comino, L., Fernández-Lao, C., Castro-Martín, E., Lozano-Lozano, M., Cantarero-Villanueva, I., Arroyo-Morales, M., & Martín-Martín, L.

Abstract

Purpose Medical treatment for head and neck cancer may induce the presence of inflammation, pain, and dysfunction. The purpose of the current study was to assess the presence of myofascial trigger points (TrPs) and their relationship with widespread pressure hypersensitivity and hyperalgesia in survivors of head and neck cancer (sHNC).

Methods TrPs and pressure-pain thresholds (PPTs) were quantified in different muscles/joints in the head and neck of 30 sHNC (59.45 ± 13.13 years) and 28 age- and sex-matched controls (58.11 ± 12.67 years).

Results The sHNC had more TrPs in all muscles on the affected side (*p* < 0.05) than did the healthy controls, and in the temporalis, masseter, and suboccipitalis muscles on the unaffected side (*p* < 0.05). They also had lower PPTs in all places (*p* < 0.05) except for the temporalis muscle (*p* = 0.114) and C5-C6 joint (*p* = 0.977). The intensity of cervical pain correlated positively with the presence of upper trapezius TrPs.

Conclusions sHNC suffering cervical and/or temporomandibular joint pain have multiple active TrPs and experience widespread pressure hypersensitivity and hyperalgesia, suggestive of peripheral and central sensitization.

Keywords Head and neck cancer . Neck dissection . Trigger points . Hyperalgesia . Pain

# Introduction

Head and neck cancer (HNC) usually begins in the squamous cells that line the moist, mucosal surfaces of the oral cavity, the pharynx, larynx, salivary glands, nasal cavity or paranasal sinuses [[1](#_bookmark3)]. In Europe, the larynx is the most commonly af- fected area, followed by the oropharynx, the oral cavity, and nasopharynx [[2](#_bookmark4)]. HNC accounts for 4% of all cancers world- wide, occurring more frequently in men than in women (4:1)

[[3](#_bookmark5)]. The mean age at first diagnosis is 50 years [[4](#_bookmark6)]. Alcohol and tobacco use are the most important risk factors, explaining the appearance of as many as 75% of all HNCs [[5](#_bookmark7)].

Curative treatment is based on surgery, radiotherapy, and chemotherapy. Surgery strategies may include the resection of the primary tumour and radical, modified, or selective neck dissection. Sentinel node biopsy has also been validated as an alternative procedure with lower side effects [[6](#_bookmark8)]. Depending on its extension, neck dissection can involve the extirpation of

all o r s ome o f t he following structures: t he

sternocleidomastoid muscle, the internal jugular vein, the spi-

nal accessory nerve, and the lymph nodes [[7](#_bookmark9)]. Sacrifice or injury caused to the spinal accessory nerve during surgery can lead to the denervation of the trapezius muscle. Therefore, a greater perception of pain in the shoulder and arm [[8](#_bookmark10), [9](#_bookmark11)], a reduced range of motion (ROM), and loss of strength may appear—a condition referred to as neck dissec- tion syndrome [[10](#_bookmark12), [11](#_bookmark13)]. Radiotherapy is used to treat over 80% of patients with HNC. Unfortunately, nearby tissues can be affected by radiotoxicity, and fibrosis, xerostomia, mu- cositis, mandibular osteoradionecrosis, trismus, and brachial

plexus injury [[12](#_bookmark14)–[14](#_bookmark16)] can appear in the long-term. Moreover, cervical muscles may suffer from painful dystonic spasms due to the radiation-induced fibrosis [[15](#_bookmark17)]. Chemotherapy is com- monly used in locally advanced disease, and it can induce the presence of pain through neuroinflammation [[13](#_bookmark15), [14](#_bookmark16)]. Mucositis can also be worsened because of chemotherapy and its toxicity [[16](#_bookmark18)]. Cervical and shoulder pain may appear after any of the above-mentioned treatments [[1](#_bookmark3)], whereas tem- poromandibular joint (TMJ) pain is mainly due to the radiotherapy-induced fibrosis and the consequent muscle dys- function [[17](#_bookmark19)].

Previous studies have described the presence of neuropath- ic and myofascial pain on this population, but the existence of trigger points (TrPs) has been little studied, and then only in a few head and neck muscles [[18](#_bookmark20)–[20](#_bookmark22)]. The combination of sur- gery and radiochemotherapy can lead to peripheral sensitiza- tion through the activation of nociceptors on A-delta and C fibres [[21](#_bookmark23), [22](#_bookmark24)]. Central sensitization, as evidenced by local and widespread pressure hypersensitivity and hyperalgesia, has been investigated in survivors of breast [[23](#_bookmark25)] and colon [[24](#_bookmark26)] cancers, and when present, it is described to worsen perceived pain [[25](#_bookmark27), [26](#_bookmark28)]. However, to our knowledge, no studies have investigated the peripheral and central sensitization processes that survivors of HNC (sHNC) may experience or its relation- ship with the presence of myofascial TrPs.

In the present work, it was hypothesized that sHNC with cervical and/or TMJ pain have more TrPs and suffer more from pressure hypersensitivity and hyperalgesia than do healthy controls. The aims of this study were therefore (1) to describe bilaterally the differences between sHNC with cervi- cal and/or TMJ pain and healthy age- and sex-matched con- trols in terms of the number of TrPs in the musculature of the head, neck, and shoulder regions; (2) to record the bilateral differences between sHNC with cervical and/or TMJ pain and healthy age- and sex-matched controls in the presence of widespread pressure hypersensitivity and hyperalgesia; (3) to assess the relationship between the intensity of cervical and/or TMJ pain and the presence of TrPs; and (4) to assess the relationship between intensity of cervical and/or TMJ pain and pain-pressure thresholds (PPTs).

# Methods

## Participants

sHNC subjected to treatment for oral cavity, pharyngeal, la- ryngeal, salivary glands or nasal cavity, and paranasal sinuses cancers was recruited to this observational, case-control pilot study from the Oncology Department of the Virgen de las Nieves University Hospital, Granada, Spain. To be eligible for inclusion, patients had to meet the following criteria: (1) to be ≥ 18 years of age, (2) to have ended their treatment in the

previous 6–24 months, (3) to have no metastasis or active cancer, and (4) to have cervical and/or TMJ pain. The exclu- sion criteria were (1) mental or physical illness preventing subjects from participating in the study, (2) previous chronic pain conditions, and (3) previous cervical or TMJ pain.

A control group was formed by healthy age- and sex- matched volunteers who responded to advertisements. They were excluded if they reported a history of cervical and/or TMJ pain, a history of trauma, or if they had any systemic disease. The study protocol was approved by the Biomedical Investigation Ethics Committee, Granada, Spain (CEI- GRANADA. Ref: 0045-N-16), and conducted in accordance with the Declaration of Helsinki. All participants provided written, informed consent to be included.

## Data collected

The following data were collected: age; gender; use of tobacco (non-smoker, ex-smoker, or smoker); alcohol consumption (none, monthly, weekly, daily); and clinical data, i.e., affected and unaffected side (defined as affected-more symptomatic and unaffected-less symptomatic). Affected side in sHNC was compared with dominant side in age- and sex-matched healthy controls and unaffected side to non-dominant side. Affected region, cancer stage at diagnosis, surgery performed, and radiotherapy and/or chemotherapy treatment were record- ed at the beginning of the study.

## Perceived pain

Perceived cervical and TMJ pain was measured (bilaterally) using a validated visual analogue scale (VAS) [[27](#_bookmark29)]. This consisted of a 10-cm horizontal line with the words “no pain” at the left extreme and “pain as bad as it could be” at the right extreme [[28](#_bookmark30)]. Reading from the left, subjects were asked to record the intensity of pain they habitually experienced by making a cross at the appropriate point on the line.

## Myofascial trigger points

TrPs were explored bilaterally over the temporalis, masseter, suboccipitalis, sternocleidomastoid, scalene, upper trapezius, and levator scapulae muscles by a trained, experienced phys- iotherapist. For this study, a Cronbach alpha was performed in order to obtain the intra-examiner reliability of the physiother- apist who underwent the exploration of TrPs, obtaining a Cronbach alpha value of 0.88 (evaluated with 30-min intervals between examinations). TrPs are tender, hyperirritable spots that cause pain in an affected muscle and beyond (referred pain) when that muscle is contracted, stretched, or manually stimulated [[29](#_bookmark31)]. TrPs may be active or latent [[29](#_bookmark31)]. They were considered active when the pain produced by their digital compression was perceived as familiar and being involved

in the pain habitually experienced and latent when the pain reproduced by such compression was not thus recognized [[30](#_bookmark32)].

## Pressure pain thresholds

A PPT is defined as the minimum amount of pressure at which the sensation of pressure changes to pain [[31](#_bookmark33)]. Subjects were instructed to warn the examiner when the sensation of pres- sure changed into pain [[30](#_bookmark32)]. PPTs (kg/cm2) in the temporalis, masseter, upper trapezius and levator scapulae muscles, the C5-C6 zygapophyseal joint, the sternoclavicular joint, and the tibialis anterior muscle (as a distant reference muscle) were explored bilaterally by the same physiotherapist using a Force Dial FDK 20 analogue algometer with a 1-cm2 rubber point (Wagner, Greenwich, USA). Each point (one point for each muscle/joint) was stimulated three times with intervals of 30 s, and the mean PPT was calculated. The reliability of pressure algometry is high when assessments are made on the same day (0.82–0.97) [[32](#_bookmark34)] and indeed other intervals of up to 4 days (0.94–0.97) [[33](#_bookmark35)].

## Sample size determination

Following the criterion of Groef et al. [[34](#_bookmark36)], for 90% statistical power to detect a minimum 20-mm difference in the VAS cervical pain scores between groups, and for an alpha value of 0.05, a total of 56 (28 per group) participants were needed (assuming a 10% dropout rate). Sample calculations were per- formed using EPIDAT v.3.1 software (Xunta de Galicia, Spain).

## Statistical analysis

Demographic and clinical data were expressed as mean ± SD or, for categorical variables, as absolute percentages. The Kolmogorov-Smirnov test was used to confirm the normal distribution of variables. The Student *t* test was used to detect differences between the sHNC and healthy controls in terms of the cervical VAS scores. Since the sHNC consumed signif- icantly less (*p* < 0.05) alcohol at the time of the present work, ANCOVA rather than ANOVA was performed to detect dif- ferences in TMJ VAS scores between affected/unaffected sides in sHNC, and between the dominant/non-dominant sides in the control group, and when making comparisons between sHNC and controls. The chi2 test was used to analyze differ- ences in TrPs distribution. ANCOVA was also used to analyze the differences when making comparisons between PPTs in the sHNC and the control group and between PPTs at each examined point on the affected/unaffected sides in the sHNC and the dominant/non-dominant sides in the control group. Pearson correlation coefficients (*r*s) were calculated to analyze the association between reported pain (on the VAS) and the

presence of active TrPs, and to determine the association be- tween VAS pain and PPTs. Significance was set at *p* < 0.05. All calculations were made using SPSS statistical software v.24.0.

# Results

## Demographic and clinical data

Thirty sHNC and 28 healthy-matched controls participated on the study. Demographic data as age; gender; smoke habits; and alcohol consumption as well as clinical data including affected side and region, pT-stage, surgery procedure, the use of radiotherapy or radiochemotherapy and the perceived cervical and TMJ pain are detailed in Table [1](#_bookmark0).

## Myofascial TrPs

Figures [1](#_bookmark1) and [2](#_bookmark1) summarize the distribution of TrPs in both groups of subjects. Table [2](#_bookmark2) shows the mean ± SD of active and latent TrPs for the sHNC and for the control group. The sHNC had a larger number of active TrPs on the affected side com- pared with the dominant side in the controls (see Figs. [1](#_bookmark1) and [2](#_bookmark1) for data): temporalis (chi2 = 9.043; *p* = 0.011), masseter (chi2

= 11.888; *p* = 0.003), suboccipital (chi2 = 14.122; *p* = 0.001), sternocleidomastoid (chi2 = 11.445; *p* = 0.003), scalene (chi2

= 7.387; *p* = 0.025), upper trapezius (chi2 = 10.624; *p* = 0.005), and levator scapulae (chi2 = 10.282; *p* = 0.006). The same was also true for the following muscles in unaffected/ non-dominant comparisons between sHNC and the control group: temporalis (chi2 = 7.068; *p* = 0.029), masseter (chi2 = 8.851; *p* = 0.012), and suboccipital (chi2 = 7.490; *p* = 0.024). No significant differences were seen with respect to the sternocleidomastoid (chi2 = 3.468; *p* = 0.177), scalene (chi2

= 5.193; *p* = 0.075), upper trapezius (chi2 = 4.318; *p* = 0.115), and levator scapulae (chi2 = 3.938; *p* = 0.140) muscles.

## PPTs

Table [3](#_bookmark2) summarizes the PPTs (means ± SD and 95% CI) recorded in the examined areas. ANCOVA revealed signifi- cant differences between the sHNC and the control group but did not find statistical differences between affected/unaffected side in sHNC and dominant/non-dominant sides in healthy controls for PPTs in the masseter (group *F* = 14.713; *p* < 0.001; side *F* = 0.011; *p* = 0.915), upper trapezius (group *F*

= 13.474; *p* < 0.005; side *F* = 0.552; *p* = 0.460), and levator scapulae muscles (group *F* = 8.891; *p* = 0.004; side *F* = 0.487; *p* = 0.487), the sternoclavicular joint (group *F* = 6.753; *p* = 0.011; side *F* = 0.121; *p* = 0.729), and the tibialis anterior muscle (group *F* = 13.728; *p* < 0.001; side *F* = 0.006; *p* = 0.940). No significant differences were seen between sHNC

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 1 Demographic and  clinical data. Mean ± SD for | sHNC (*n* = 30) | | Healthy-matched controls (*n* = 28) | *p* value |
| continuous data and *n* (%) for  categorical data | Age | 59.4 ± 13.1 | 58.1 ± 12.7 | *p* = 0.618b |
|  | Gender |  |  |  |
|  | Men | 20 (75) | 20 (75) | NA |
|  | Women | 10 (35) | 10 (35) |  |
|  | Smoking habits |  |  |  |
|  | Non-smokers | 10 (33) | 17 (61) | *p* = 0.110a |
|  | Ex-smokers | 17 (57) | 9 (32) |  |
|  | Smokers | 3 (10) | 2 (7) |  |
|  | Alcohol consumption |  |  |  |
|  | No consumption | 14 (47) | 10 (36) | *p* = *0.006*a\* |
|  | Monthly | 6 (20) | 2 (7) |  |
|  | Weekly | 3 (10) | 14 (50) |  |
|  | Daily | 7 (23) | 2 (7) |  |
|  | Affected side |  |  |  |
| Right | | 14 (47) | NA | NA |
| Left | | 14 (47) |  |  |
| Bilateral | | 2 (6) |  |  |
|  | Affected region |  |  |  |
| Oral cavity and oropharynx | | 17 (57) | NA | NA |
| Larynx and hypopharynx | | 8 (27) |  |  |
| Salivary glands | | 3 (10) |  |  |
| Nasopharynx | | 1 (3) |  |  |
| Nasal cavity and paranasal sinuses | | 1 (3) |  |  |
|  | pT-stage |  |  |  |
| I | | 6 (20) | NA | NA |
| II | | 6 (20) |  |  |
| III | | 7 (23) |  |  |
| IV | | 11 (37) |  |  |
|  | Surgery procedure |  |  |  |
| None | | 3 (10) | NA | NA |
| Tumorectomy | | 5 (17) |  |  |
| MRDN | | 16 (53) |  |  |
| RND | | 5 (17) |  |  |
| Laryngectomy + RND | | 1 (3) |  |  |
| Radiotherapy and chemotherapy treatment | | | | |
| None | | 1 (3) | NA | NA |
| Radiotherapy | | 11 (37) |  |  |
| Radiochemotherapy | | 18 (60) |  |  |
| Pain (VAS) | |  |  |  |
| Cervical | | 3.5 ± 3.3 | 1 ± 1.7 | *p* < 0.001b\* |
|  | Temporomandibular joint |  |  |  |
| Affected side Unaffected side | | 2.4 ± 3.4  1.2 ± 2.6 | 0.6 ± 1.57  0.2 ± 1 | *p* = 0.003c\* |

*MRND*, modified radical neck dissection; *NA*, not applicable; *RND*, radical neck dissection; *sHNC*, survivors of head and neck cancer; *VAS*, visual analogue scale

\*Statistically significant difference

a Chi2 test

b *t* test

c ANOVA test

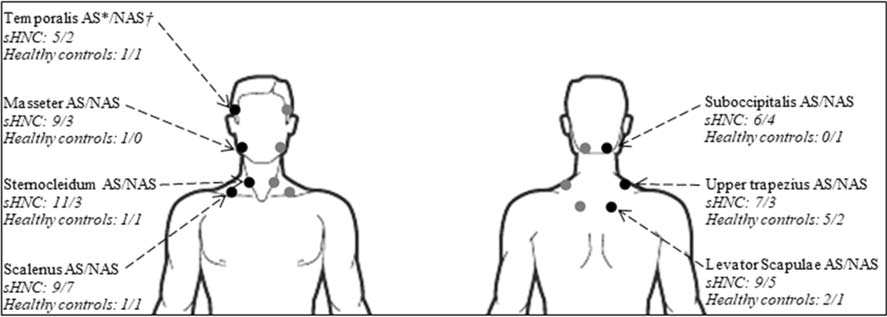


Fig. 1 Active TrPs in sHNC and healthy controls

and the control group neither between affected side and unaf- fected side/dominant side and non-dominant side with respect to the temporalis muscle (groups *F* = 3.644; *p* = 0.060; sides *F*

= 0.000; *p* = 0.998) and C5-C6 zygapophyseal joint (groups *F*

= 3.189; *p* = 0.078; sides *F* = 0.012; *p* = 0.915).

## Perceived pain and relationships with TrPs and PPTs

Cervical pain correlated positively with the number of active upper trapezius TrPs (*r*s = 0.547; *p* = 0.008). No correlation was seen, however, between cervical or TMJ pain and the number of TrPs in the temporalis, masseter, suboccipitalis, sternocleidomastoid, scalene, or levator scapulae muscles (*p*

> 0.05).

An inverse correlation was detected between TMJ pain and the PPT for the masseter (*r*s = − 0.468; *p* = 0.028). No such correlation was detected between TMJ pain and the PPTs of the temporalis, upper trapezius or levator scapu- lae muscles, the C5-C6 zygapophyseal joint, the sternoclavicular joint, or the tibialis anterior muscle (*p* > 0.05). Cervical pain appeared not to be related to any of the explored PPTs (*p* > 0.05).

# Discussion

The present results reveal that, compared with healthy con- trols, sHNC with presence of cervical and/or TMJ pain have more active TrPs in the face, neck, and shoulder muscles, as well as lower muscle and joint PPTs, leading to pressure hy- persensitivity and hyperalgesia. These results suggest periph- eral and central sensitization occur in sHNC with cervical and/ or TMJ pain. Cervical pain was correlated positively with the number of active TrPs over the upper trapezius muscle, where- as a negative correlation was found between TMJ pain and the PPT for the masseter.

## Local and referred pain from active TrPs

The examined muscles were selected given their association with the TMJ disorders that can appear in sHNC after radio- therapy [[35](#_bookmark37)]. Active TrPs were deemed to be those appreciat- ed by the subjects as related to the cervical and other pain they habitually experienced. The present results showed the sca- lene (53.3%), sternocleidomastoid (46.6%), levator scapulae (46.6), and masseter (40%) muscles to be the most affected, compared with previous studies that reported the greatest

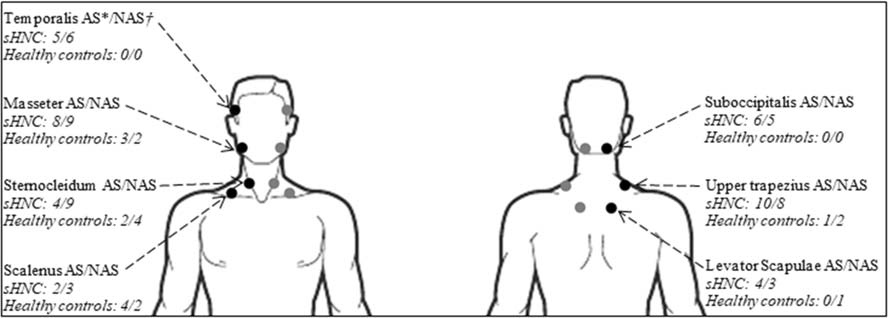


Fig. 2 Latent TrPs in sHNC and healthy controls

Table 2 Myofascial TrPs in sHNC and healthy controls (mean ± SD)

sHNC Control group *p* valuea

surgery may activate TrPs and therefore increase the myofascial pain experiences in cancer survivors. The relationship between

active TrPs and cervical pain suggests that, although the origin

Active 2.8 ± 3.6 0.6 ± 1.2 *p* < 0.001\*

Latent 2.8 ± 2.9 0.7 ± 1.4 *p* = 0.003\*

Total TrPs 5.7 ± 4.2 1.4 ± 2.1 *p* < 0.001\*

*sHNC*, survivors of head and neck cancer; *TrPs*, trigger points

\*Statistically significant difference

a Mann-Whitney *U* test

number of active TrPs in the trapezius muscle [[19](#_bookmark21), [20](#_bookmark22)]. A cross-sectional study reported the presence of TrPs in the head and neck area following treatment for HNC [[20](#_bookmark22)]. They exam- ined the upper trapezius, splenius, and sternocleidomastoid muscles. In a previous observational case-control study [[19](#_bookmark21)], 46% of the patients treated for HNC were reported to have more TrPs in the upper trapezius and levator scapulae muscles on the affected side. These discrepancies may be due to dif- ferences in sample size (153 and 167 subjects respectively in the above studies, and 30 in the present work). A previous observational study [[18](#_bookmark20)] reported the greatest number of ac- tive TrPs to be in the sternocleidomastoid muscle—the muscle with the second highest number of active TrPs in the present study. This similarity might be explained (despite the differ- ence in the protocols followed) in that both studies involved similar sample sizes (25 HNC patients compared with 30 sHNC in the present work).

However, the largest number of active TrPs was found in the affected sternocleidomastoid muscle (in 36.6% of the sHNC). Since neck dissection involves the sternocleidomastoid muscle, it may be the most affected in this respect following such sur- gery. Similar results were found in patients with post- mastectomy pain, in whom the affected pectoralis major muscle had the largest number of active TrPs [[23](#_bookmark25)]. This suggest that

of these active TrPs remains unknown, they may be involved in the pain perceived by sHNC. Other generators of pain, such as nerve injuries caused by treatment, may also be to blame [[13](#_bookmark15), [14](#_bookmark16)]. Moreover, a previous systematic review [[36](#_bookmark38)] stated higher pain experiences in sHNC after radical neck dissection com- pared with modified radical neck dissection or selective neck dissection; the greater the surgery performed, the greater the pain experienced.

## Sensitization mechanisms

The present results suggest peripheral sensitization occurs in sHNC with cervical and/or TMJ pain, mediated by the pres- ence of active TrPs. This agrees with the theory that active muscle TrPs are a source of nociception. TrPs contain high concentrations of algogenic substances [[29](#_bookmark31), [37](#_bookmark39)] that have been shown to sensitize peripheral nociceptors on A-delta and C fibres. These may then become involved in the process of pe- ripheral sensitization [[21](#_bookmark23), [22](#_bookmark24)]. However, both nociceptive and non-nociceptive hypersensitivity at muscle TrPs have been re- ported [[37](#_bookmark39)], suggesting that muscle pain may also be caused by injury to nervous tissue during surgery. The correlation detect- ed between the number of upper trapezius active TrPs and perceived cervical pain, and between the masseter PPT and perceived TMJ pain, strengthens the idea that peripheral sensi- tization occurs in sHNC with cervical and/or TMJ pain.

Compared with the controls, widespread pressure hyper- sensitivity on both sides of the body was detected in the pres- ent sHNC with cervical and/or TMJ pain, reflected as lower PPTs for the masseter, upper trapezius and levator scapulae muscles, sternoclavicular joint, and tibialis anterior muscle. However, no significant differences were seen between the

Table 3 Pressure-pain thresholds (kg/cm2) in sHNC and healthy controls

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | sHNC |  |  | Healthy-matched controls |  | *p* valuea |  |
| Affected side | Unaffected side |  | Dominant Non-dominant |  | Between groups | Between sides |
| Temporalis | 2.4 ± 1.4 (0.2; 6.6) | 2.2 ± 1.4 (0.3; 7.6) |  | 2.5 ± 0.9 (1.6; 5.0) 2.4 ± 0.9 (1.2; 4.7) |  | *p* = 0.060 | *p* = 0.998 |
| Masseter | 1.4 ± 0.8 (0.0; 3.8) | 1.6 ± 0.7 (0.0; 3.4) |  | 2.2 ± 0.8 (0.7; 4.3) 2.1 ± 0.7 (1.0; 3.8) |  | *p < 0.001\** | *p* = 0.915 |
| Upper trapezius | 3.0 ± 2.14 (0.0; 7.9) | 3.6 ± 2.4 (0.5; 9.6) |  | 4.3 ± 2.3 (1.4; 9.0) 4.5 ± 2.2 (1.3; 8.8) |  | *p < 0.005\** | *p* = 0.460 |
| Levator scapulae | 3.7 ± 2.3 (0.0; 9.1) | 4.4 ± 2.5 (0.6; 9.6) |  | 5.5 ± 2.7 (1.5; 11.7) 5.3 ± 2.3 (1.6; 9.4) |  | *p = 0.004\** | *p* = 0.487 |
| C5-C6 zygapophyseal joint | 2.7 ± 1.5 (0.0; 6.7) | 2.7 ± 1.5 (0.4; 5.8) |  | 3.2 ± 1.5 (0.8; 6.8) 3.2 ± 1.5 (0.8; 6.9) |  | *p* = 0.078 | *p* = 0.915 |
| Sternoclavicular joint | 2.8 ± 1.9 (0.2; 10) | 3.0 ± 2.1 (0.4; 1) |  | 3.5 ± 1.6 (1.1; 7.3) 3.7 ± 1.8 (1.2; 7.3) |  | *p = 0.011\** | *p* = 0.729 |
| Tibialis anterior | 5.4 ± 3.0 (1.1; 12.9) | 5.2 ± 2.8 (1; 14.0) |  | 7.2 ± 2.9 (2.4; 13.3) 7.0 ± 2.6 (2.4; 12.4) |  | *p < 0.001\** | *p* = 0.940 |

Values are expressed as means ± SD (95% confidence interval)

*sHNC* survivors of head and neck cancer

\*Statistically significant difference

a ANCOVA test

groups in terms of the PPTs of the temporalis and cervical muscles. In earlier work comparing PPTs in survivors of breast cancer and healthy controls [[38](#_bookmark40)], no significant differ- ences were seen in terms of C5-C6 zygapophyseal joint pain. Similarly, other authors report a lack of any clear difference in temporalis muscle PPTs between healthy subjects and patients with tension-type headache [[39](#_bookmark41)]. It may be that different pop- ulations simply share age-related cervical complaints.

The present results show a large difference between the sHNC and the control group in terms of the PPT of the tibialis anterior muscle (~ 70% lower in sHNC). The PPT of this mus- cle has previously been used as a distant point in order to pro- vide stronger evidence of central sensitization. Similar differ- ences were obtained in an earlier study comparing patients with breast cancer and healthy controls (40% lower PTT in the pa- tients) [[23](#_bookmark25)]. This difference between sHNC and breast cancer patients suggests central sensitization is stronger in sHNC. By sustaining peripheral noxious inputs into the central nervous system, the damage caused by surgical procedures and medical treatments may play an important role in the sensitization mech- anisms acting in patients with cancer [[40](#_bookmark42), [41](#_bookmark43)].

To our knowledge, this is the first study examining sensiti- zation processes in sHNC with cervical and/or TMJ pain. The present work suffers from the limitation that its design pre- cludes the establishment of cause-effect relationships, and thus the contribution of treatment to sensitization processes. It would be interesting to examine patients before treatment and assess the change in mechanical pain sensitivity over time. In addition, the present sHNC had different stages of disease at the time of diagnosis, had disease in different locations, and underwent different treatments. Future research may study the pain pro- cesses in different groups of sHNC. Due to the neck dissection, there may be loss of sensitivity, but we did not evaluate this outcome, so future works should be developed to examine this issue. Thus, while the present work is of interest as a pilot study, future work should involve larger samples of sHNC that can be stratified in terms of the above-mentioned variables.

## Clinical implications

Curative treatment may induce the presence of sensitization processes over sHNC; therefore, a precise choice before the medical intervention has to be made in order to reduce its side effects. The muscle pain in the upper trapezius, levator scap- ulae, and TMJ muscles detected in sHNC could be treated. Physical therapy programs focused on the TrPs in the temporalis, masseter, suboccipital, sternocleidomastoid, sca- lene, upper trapezius, and levator scapulae muscles may re- duce pain. Multimodal treatments (physical therapy, exercise, lifestyle change, etc.) help reducing the sensitization that oc- curs in sHNC, perhaps with lasting results. Thereby, the knowledge about pain patterns could be interesting for other different health professionals, as physicians, nurses,

occupational therapists, or dietists, who may better understand the condition of this population and could adapt their treat- ments and advices to them. However, more studies are needed to confirm this information.

# Conclusions

The present work reveals the existence of multiple, active TrPs in the head, neck, and shoulder musculature of sHNC with presence of cervical and or TMJ pain, and widespread pres- sure pain hypersensitivity and hyperalgesia. These findings suggest both peripheral and central sensitization mechanisms are active in sHNC.

Acknowledgments The authors thank all individuals who participated in this study. We are also grateful to Mr. Adrian Burton for assistance with the English language.

Funding information The study was partially funded by the Fondos Estructurales de la Unión Europea (FEDER). This study took place be- cause of the additional funding from the University of Granada, Excellence Actions: Units of Excellence; Unit of Excellence on Exercise and Health (UCEES). This work was part of a PhD thesis con- ducted in the Clinical Medicine and Public Health Doctoral Studies of the University of Granada, Spain.

## Compliance with ethical standards

The study protocol was approved by the Biomedical Investigation Ethics Committee, Granada, Spain (CEI-GRANADA. Ref: 0045-N-16), and conducted in accordance with the Declaration of Helsinki. All partici- pants provided written, informed consent to be included.

Conflict of interest The authors declare that they have no competing interests.

# References

1. Mendenhall WM, Mancuso AA, Amdur RJ, Stringer SP, Villaret DB, Cassisi NJ (2001) Squamous cell carcinoma metastatic to the neck from and unknown head and neck primary site. Am J Otolaryngol 22(4):281–287
2. Gatta G, Botta L, Sánchez MJ, Anderson LA, Pierannunzio D, Licitra L (2015) Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. Eur J Cancer 51(15):2130–2143
3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mor- tality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386
4. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68(1):7–30
5. Giraldi L, Leoncini E, Pastorino R, Wünsch-Filho V, de Carvalho M, Lopez R, Cadoni G, Arzani D, Petrelli L, Matsuo K, Bosetti C, La Veccchia C, Garavello W, Poleser J, Serraino D, Simonato L, Canova C, Richiardi L, Boffetta P, Hashibe M (2017) Alcohol and cigarette consumption predict mortality in patients with head and neck cancer: a pooled analysis within the international head and

neck cancer epidemiology (INHANCE) consortium. Ann Oncol 28(11):2843–2851

1. Broglie MA, Haile SR, Stoeckli SJ (2011) Long-term experience in sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. Ann Surg Oncol 18(10):2732–2738
2. Robbins KT, Shaha AR, Medina JE, Califano JA, Wolf GT, Ferlito A, Som PM, Day TA (2008) Consensus statement on the classifi- cation and terminology of neck dissection. Arch Otolaryngol Head Neck Surg 134(5):536–538
3. Chaplin JM, Morton RP (1999) A prospective, longitudinal study of pain in head and neck cancer patients. Head Neck 21(6):531–537
4. Van der Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J (2007) Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol 18(9):1437–1449
5. Van Hinte G, Wetzels JGH, Merkx MAW, de Haan AFJ, Koole R, Speksnijder CM (2019) Factors influencing neck and shoulder function after oral oncology treatment: a five year prospective co- hort study in 113 patients. Support Care Cancer 27(7):2553–2560
6. Baggi F, Santoro L, Grosso E, Zanetti C, Bonacossa E, Sandrin F, Massaro MA, Tradati N, Simoncini MC (2014) Motor and func- tional recovery after neck dissection: comparison of two early phys- ical rehabilitation programmes. Acta Otorhinolaryngol Ital 34(4): 230–240
7. Strojan P, Hutcheson KA, Eisbruch A, Beitler JJ, Langendijk JA, Lee AWM, Corry J, Mendenhall WM, Smee R, Rinaldo A, Ferlito A (2017) Treatment of late sequelae after radiotherapy for head and neck cancer. Cancer Treat Rev 59:79–92
8. Park SB, Krishnan AV, Lin CS, Goldstein D, Friedlander M, Kiernan MC (2008) Mechanisms underlying chemotherapy- induced neurotoxocity and the potential for neuroprotective strate- gies. Curr Med Chem 15(29):3081–3094
9. Cai Z, Li Y, Hu Z, Fu R, Rong X, Wu R, Cheng J, Huang X, Luo J, Tang Y (2016) Radiation-induced brachial plexopathy in patients with nasopharyngeal carcinoma: a retrospective study. Oncotarget 7(14):18887–18895
10. Stubblefield MD (2011) Radiation fibrosis syndrome: neuromuscu- lar and musculoskeletal complications in cancer survivors. PM R 3(11):1041–1054
11. Bilbault JE, Morelle M, Perrier L, Pommier P, BOisselier P et al (2016) Toxicity and efficacy of cetuximab associated with several modalities of IMRT for locally advanced head and neck cancer. Cancer Radiother 20:357–361
12. Wu VWC, Lam TN (2016) Radiation-induced temporo-mandibular joint disorder in post-radiotherapy nasopharyngeal carcinoma pa- tients: assessment and treatment. J Med Radiat Sci 63(2):124–132
13. Sist T, Miner M, Lema M (1999) Characteristics of postradical neck pain syndrome: a report of 25 cases. J Pain Symptom Manage 18(2):95–102
14. Van Wilgen CP, Dijkstra PU, van der Laan BF, Plukker JT, Roodenburg JL (2004) Morbidity of the neck after head and neck cancer therapy. Head Neck 26(9):785–791
15. Cardoso LR, Rizzo CC, Oliveira CZ, dos Santos CR, Carvalho AL (2015) Myofascial pain syndrome after head and neck cancer treat- ment: prevalence, risk factors, and influence on quality of life. Head Neck 37(12):1733–1737
16. Lam DK, Schmidt BL (2011) Orofacial pain onset predicts transi- tion to head and neck cancer. Pain 152(5):1206–1209
17. Ghei A, Khot S (2010) Pain management in patients with head and neck carcinoma. Int J Otorhinolaryngol Clin 2(1):69–75
18. Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-las-Peñas C, Del-Moral-Ávila A-NL, Arroyo-Morales M (2010) Myofascial trigger points in neck and shoulder muscles and widespread pres- sure pain hypersensitivity in patients with postmastectomy pain. Evidence of peripheral and central sensitization. Clin J Pain 26(9): 798–806
19. Sánchez-Jiménez A, Cantarero-Villanueva I, Molina-Barea R, Fernández-Lao C, Galiano-Castillo N, Arroyo-Morales M (2014) Widespread pressure pain hypersensitivity and ultrasound imaging evaluation of abdominal area after colon cancer treatment. Pain Med 15(2):233–240
20. De Groef A, Meeus M, De Vrieze T, Vos L, Van Kampen M, Geraerts I, Devoogdt N (2018) Unraveling self-reported signs of central sensitization in breast cancer survivors with upper limb pain: prevalence rate and contributing factors. Pain Physician 21(3): E247–E256
21. Pereira CM, Sehnem D, da Fonseca EO, Barboza HFG, de Carvalho ACP, DaSilva AFM, Moura-Neto V, DosSantos MF (2017). miRNAs: important targets for oral cancer pain research. Biomed Res Int 2017:4043516.
22. Jensen MP, Karoly P (2011) Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R (eds) Handbook of pain assessment. Guildford Press, New York, pp 19–44
23. Jensen MP, Karoly P, Braver S (1986) The measurement of clinical pain intensity: a comparison of six methods. Pain 27(1):117–126
24. Simons DG, Travell J, Simons LS (1999) Travell and Simons’ Myofascial pain and dysfunction: the trigger point manual, volume 1, 2nd edn. Williams and Wilkins, Baltimore, pp 13–34
25. Scott J, Huskisson EC (1976) Graphic representation of pain. Pain 2(2):175–184
26. Vanderweeën L, Oostendorp RA, Vaes P, Duquet W (1996) Pressure algometry in manual therapy. Man Ther 1(5):258–265
27. Chesterton LS, Sim J, Wright CC, Foster NE (2007) Inter-rater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. Clin J Pain 23(9):760–766
28. Jones DH, Kilgour RD, Comtois AS (2007) Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. J Pain 8(8):650–656
29. De Groef A, Van Kampen M, Vervloesem N, Dieltjens E, Christiaens MR, Neven P, Vos L, De Vrieze T, Geraerts I, Devoogdt N (2018) Effect of myofascial techniques for treatment of persistent arm pain after breast cancer treatment: randomized controlled trial. Clin Rehabil 32(4):451–461
30. Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP (2003) Oral sequelae of head and neck radiotherapy. Crit Rev Oral Biol Med 14(3):199–212
31. Gane EM, Michaleff ZA, Cottrell MA, McPhail SM, Hatton AL, Panizza BJ, O’Leary SP (2017) Prevalence, incidence, and risk factors for shoulder and neck dysfunction after neck dissection: a systematic review. Eur J Surg Oncol 43(7):1199–1218
32. Li LT, Ge HY, Yue SW, Arendt-Nielsen L (2009) Nociceptive and non-nociceptive hypersensitivity at latent myofascial trigger points. Clin J Pain 25(2):132–137
33. Caro-Morán E, Fernández-Lao C, Díaz-Rodríguez L, Cantarero- Villanueva I, Madeleine P, Arroyo-Morales M (2016) Pressure pain sensitivity maps of the neck-shoulder region in breast cancer survi- vors. Pain Med 17(10):1942–1952
34. Andersen S, Weinreich-Petersen M, Sand-Svendsen A, Gazerani P (2015) Pressure pain thresholds assessed over temporalis, masseter, and frontalis muscles in healthy individuals, patients with tension- type headache, and those with migraine- a systematic review. Pain 156(8):1409–1423
35. Mendell LM, Wall PD (1965) Responses of single dorsal cord cells to peripheral cutaneous unmyelinated fibres. Nature 206:97–99
36. Gottrup H, Andersen J, Arendt-Nielsen L, Jensen TS (2000) Psychophysical examination in patients with post-mastectomy pain. Pain 87(3):275–284