



Original article

Protective myoelectric activity at performing upper limb neurodynamic test 1 in breast cancer survivors. A cross-sectional observational study

Irene de la Rosa-Díaz^a, María Torres-Lacomba^{a,*}, Paz Acosta-Ramírez^b, Itxaso García-de Orive^b, Robert J. Nee^c, Pedro de la Villa-Polo^d, Eva M. Andrés-Esteban^e, Beatriz Sánchez-Sánchez^a

^a Physical Therapist in Women's Health Research Group, Department of Physical Therapy, University of Alcalá, Alcalá de Henares, Madrid, Spain

^b Physical Therapist in Torrejón Hospital, Rehabilitation Department, Torrejón de Ardoz, Madrid, Spain

^c Physical Therapist in School of Physical Therapy, Pacific University, Hillsboro, OR, USA

^d Medical Doctor in the Neurophysiology Research Group, Department of Systems Biology, University of Alcalá, Alcalá de Henares, Madrid, Spain

^e Biostatistician, Department of Preventive Medicine, University of Jaume I, Castellón, Spain

ARTICLE INFO

Keywords:

Mechanosensitivity
Breast neoplasm
Pain
Electromyography
Joint range of motion
Median nerve

ABSTRACT

Myoelectric activity and range of motion during ULNT1 were recorded in 62 breast cancer (BC) survivors who had axillary lymph node dissection (n = 30) or sentinel lymph node biopsy (n = 32) within the previous 18 months, and 63 age-matched healthy women. BC survivors' symptoms were reproduced by ULNT1 and exhibited greater myoelectric activity in the biceps brachii than healthy women (MD (95% CI): 21,26 (10,83-31,70)). No differences between the axillary lymph node dissection and sentinel lymph node biopsy groups (MD (95% CI): 8,47 (-7,84-24,79)) were found. Myoelectric activity in the triceps brachii was greater in the sentinel lymph node biopsy group (MD (95% CI): 2,70 (-2,06-7,60)). BC survivors exhibited less shoulder and elbow range of motion during ULNT1 than healthy women. Increased upper limb nerve mechanosensitivity in BC survivors was associated with a greater protective muscle response during ULNT1.

1. Introduction

Breast cancer incidence has risen worldwide in recent years (Pollan et al., 2010), with greater increases in Spain than in other European countries (Karim-Kos et al., 2008). Nevertheless, early diagnosis has increased breast cancer survival rates worldwide (Pollan et al., 2010). The 5-year survival rate for individuals affected by breast cancer is approximately 70% (La Vecchia et al., 2010). However, conventional treatments (e.g., mastectomy and radiotherapy) often lead to shoulder disturbances such as muscular weakness, restricted range of motion (Fong et al., 2013) and functional impairment. These impairments may persist or even increase several years after treatment and are often severe enough to diminish the quality of life of breast cancer survivors (Andersen et al., 2015).

Approximately 25–60% of breast cancer survivors who receive surgery report a chronic pain condition, termed *persistent pain after breast cancer surgery* (Andersen et al., 2015), that has a significant neuropathic component (Andersen and Kehlet, 2011), and more than 77% have restricted range of motion and impaired sensation in the breast or upper limb, seriously affecting their quality of life (Andersen et al., 2012). Axillary lymph node dissection often involves some nerve

laceration (e.g. long thoracic, thoracodorsal, intercostobrachial nerves) (Ducic et al., 2011). Not only may nerve injury be provoked by direct nerve laceration, but also by positional traction or contusion of neural tissue during surgery (Ducic et al., 2011). That means that sentinel lymph node biopsy, a less aggressive axillary lymph node approach where the neurovascular bundle is moved as needed to provide access, may damage peripheral nervous tissue as well. Aside from surgical effects, post-operative or post-radiation fibrosis in surrounding tissues may be a compressive cause of nerve injury (Ducic et al., 2011; Smoot et al., 2014). It is thought that radiation also may provoke direct nerve damage by neural laceration or microvascular impairment. Consequently, breast cancer survivors who undergo radiation are more likely to develop a brachial plexus neuropathy (Delanian et al., 2012). Lastly, chemotherapy may induce peripheral neuropathy, especially due to secondary neural axoplasmic damage (Brewer et al., 2016).

Nerve damage from surgery, radiation, or chemotherapy may increase nerve mechanosensitivity, and breast cancer survivors exhibit increased sensitivity to upper limb movements that stretch and compress nerves (Smoot et al., 2014; Caro-Morán et al., 2014; Kelley and Jull, 1998). Therefore, increased upper limb nerve mechanosensitivity could be one cause of upper limb functional impairment and pain in

* Corresponding author.

E-mail address: maria.torres@uah.es (M. Torres-Lacomba).

breast cancer, hence the importance of assessing nerve mechanosensitivity in breast cancer survivors. Upper limb nerve mechanosensitivity is assessed by neural provocation tests (Elvey, 1997). A neural provocation test is a sequence of movements designed to assess nerve mechanosensitivity by elongating the length of the nerve bedding and by increasing the pressure in and around the nerve (Elvey, 1997). The neural provocation test for the median nerve, termed upper limb neurodynamic test 1 (ULNT1), is the test most commonly used to assess for upper limb nerve mechanosensitivity in breast cancer survivors (Smoot et al., 2014; Caro-Morán et al., 2014). ULNT1 movements have been shown to apply mechanical forces to the brachial plexus and median nerve (Boudier-Reveret et al., 2017; Greening and Dilley, 2017; Lohman et al., 2015; Nee et al., 2012; Silva et al., 2014; Szikszay et al., 2017).

Evidence of increased upper limb nerve mechanosensitivity in breast cancer survivors has been quantified by greater deficits in elbow extension range of motion at the end of ULNT1 (Smoot et al., 2014; Caro-Morán et al., 2014). Elbow extension range of motion during ULNT1 appears to be related to myoelectric activity in upper extremity muscles associated with a flexor withdrawal response (Jaberzadeh et al., 2005). Earlier onset of this protective myoelectric activity is associated with greater deficits in elbow extension range of motion during ULNT1 in patients with carpal tunnel syndrome who have increased nerve mechanosensitivity (Jaberzadeh and Zoghi, 2013). However, it is unclear whether this same association between earlier protective myoelectric activity and reduced range of motion during ULNT1 exists in breast cancer survivors who have increased upper limb nerve mechanosensitivity.

Our primary aims were to determine whether breast cancer survivors' symptoms likely had a neuropathic component based on symptom descriptors, and whether the presence of any increased upper limb nerve mechanosensitivity was associated with an increased protective muscle response during ULNT1 when compared to healthy women. We had several secondary aims. First, describe the patterns of the protective muscle response in breast cancer survivors and healthy women. Second, describe the deficits in shoulder abduction, external rotation, and elbow extension range of motion during ULNT1. Third, if possible, determine if the protective muscle response as quantified by myoelectric activity and range of motion were influenced by the type of surgical procedure (axillary lymph node dissection vs. sentinel lymph node biopsy) to verify if sentinel lymph node biopsy is associated with less morbidity than axillary lymph node dissection, as has been described (Lauridsen et al., 2008).

2. Methods

This was a matched cross-sectional observational study that was undertaken at Torrejón Hospital in Madrid (Spain), between September 2015 and July 2016. The institutional ethics committee approved the study (Ethical approval number: 21/10/2014). The research was conducted in accordance with the 1964 Helsinki Declaration. Protocols in human research and personal data protection (Organic Law 15/99) were followed. The study was registered at ClinicalTrials.gov (Trial registration: NCT02599467 <https://register.clinicaltrials.gov/>).

2.1. Participants

One hundred and twenty-five women were recruited from the Rehabilitation department of Torrejón Hospital. Two physical therapists (P.A. and I.R.) recruited the sample that included a breast cancer group and a control group. Sixty-two breast cancer survivors (30 with axillary lymph node dissection and 32 with sentinel lymph node biopsy) between 40 and 75 years of age were enrolled by surgery date and axillary approach. The inclusion criteria for the breast cancer survivors were: unilateral breast cancer surgery with axillary neurovascular bundle manipulation (sentinel lymph node biopsy) or dissection

(axillary lymph node dissection) during the last 18 months. A review of medical records and patient report were used to exclude breast cancer survivors who had ipsilateral shoulder pathology or neuropathy (e.g., polyneuropathy, carpal tunnel syndrome, and thoracic outlet syndrome) prior to surgery. Breast cancer survivors were recruited regardless of whether they reported pain in daily life. Those who reported pain at rest or during activities characterized their pain by using a table of neuropathic descriptors that were consistent with the pain questionnaire portion of the LANSS Scale that has been validated in Spanish (Bennett, 2001, 2002). Other descriptors could be used as needed. They also drew the location of their symptoms on a body map.

Sixty-three healthy women were enrolled in the control group. They were matched to breast cancer survivors for age (± 2 years) and hand/upper limb dominance (hand used for writing). Healthy women were excluded when reporting current painful conditions involving their neck or dominant upper-extremity, chronic pain conditions (e.g., Fibromyalgia) or current use of pain relievers. To ensure that sensory responses evoked at the end of ULNT1 in healthy women were most likely related to nerve mechanosensitivity, they needed to change with side-bending of the neck away from the tested limb (i.e., structural differentiation) (Elvey, 1997; Nee et al., 2012). All women provided informed consent prior to participation.

2.2. Sample size

According to *a priori* pilot testing, the sample size estimation was based on finding a 50–60% difference in myoelectrical activity (protective muscle response) during ULNT1 between breast cancer survivors and healthy women. A significance level of 5% ($\alpha = 0.05$), 80% power ($\beta = 0.20$), and a replacement percentage of no more than 10% were assumed. A sample of 64 participants in each group could identify this difference (Warren et al., 2013).

2.3. Electromyography procedure and measurement of myoelectric activity

Surface electromyography recorded the protective myoelectric activity from biceps and triceps brachii muscles during ULNT1 because of their anatomical relationships to the median nerve in the upper arm/axillary region (Johnson et al., 2006). A surface electromyograph (PowerLab 15T, ADInstrument, Oxford, UK) and disposable disc surface hydrogel Ag/AgCl electrodes (Kendall™ 100 Series Foram Electrodes, Covidien, Massachusetts, USA) were used. Electrode application and skin preparation followed recommendations from the European Society of Surface Electromyography (Hermens et al., 2000). Each electrode pair was positioned in a bipolar configuration near the center of the muscle belly and parallel to the direction of muscle fibers. In order to recruit enough motor units, the distance between the center of each electrode was 30 mm (Rissanen et al., 2009; Rade et al., 2014). The common ground electrode was placed over the coracoid process.

Data were collected at a rate of 1000 Hz using a 16-bit A/D converter and processed with a 50-Hz notch filter. Myoelectric signals were amplified ($\times 1000$) and band passed with a 8th Bessel filter at 10–500 Hz (Reaz et al., 2006). Myoelectric signals were analyzed with a root mean square function. Root mean square determined the number of activated motor units of biceps and triceps brachii muscles. Myoelectric signals were processed off-line. Root mean square was automatically calculated by the LabChart 7 software from a 500 msec temporal window during the three measurement points: tightness onset perceived by the participant (tightness onset), evoked-myoelectric activity increase of biceps brachii (evoked-myoelectric activity) determined by one investigator when spikes were twice as large as at tightness onset, and maximal muscle resistance perceived by another investigator who applied ULNT1 or the participant's pain tolerance, whichever occurred first (maximal muscle resistance) within ULNT1 (Fig. 1). Myoelectric data were not normalized by maximal voluntary contraction because myoelectric activity was recorded during a passive movement to determine

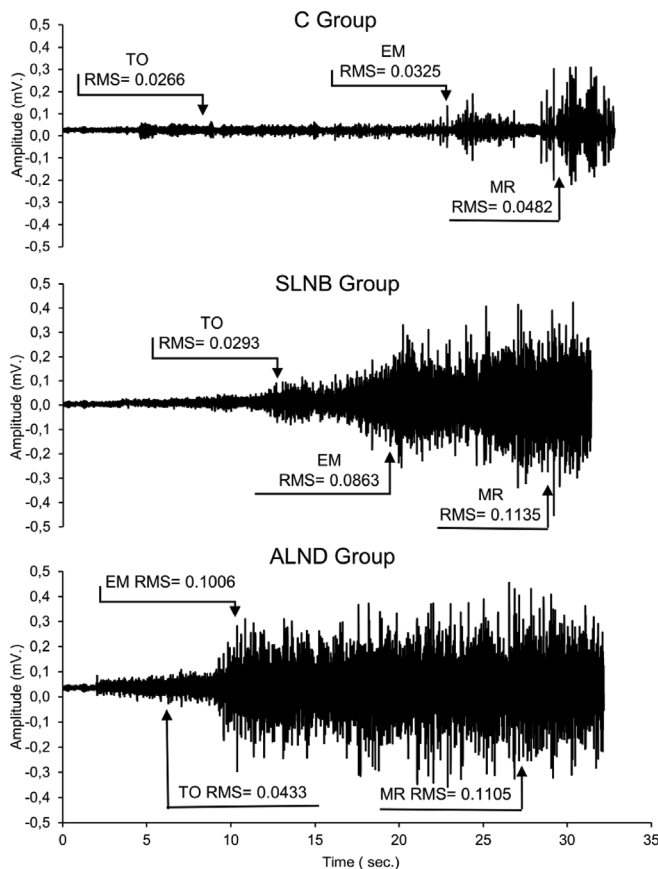


Fig. 1. Event dependent measurement of Electromyographic activity. Biceps Brachii myoelectric trace recordings from women examples of the control (C), sentinel lymph node biopsy and axillary lymph node dissection groups. Sample measurements from myoelectric activity (mV) are pointed out at the time of tightness onset (TO), evoked-myoelectric activity increase (EM) and maximal muscle resistance (MR) within the upper limb neurodynamic test 1.

the protective muscle response during passive nerve strain. This approach has been used previously to measure protective myoelectric activity during ULNT1 (Jaberzadeh et al., 2005) and in upper limb positions that applied mechanical forces to the radial nerve (Rade et al., 2014).

2.4. ULNT1 for assessment of mechanosensitivity and measurement of range of motion

The participant was supine with the neck in contralateral side-bending. By pre-loading the neural tissues with this modified starting position, ULNT1 could likely be performed with less shoulder range of motion while still adequately stressing neural tissues. Less shoulder range of motion places less mechanical stress on non-neural tissues about the shoulder. Changes in myoelectric activity during ULNT1 could therefore more likely be attributed to changes in mechanical stress on neural tissues. The ULNT1 was performed as follows (Elvey, 1997; Beneciuk et al., 2010; Quintner, 1989): *Step 1*) scapular stabilization; *Step 2*) shoulder abduction to the onset of resistance to movement perceived by the examiner (i.e., resistance 1); *Step 3*) shoulder external rotation to resistance 1; *Step 4*) forearm supination; *Step 5*) wrist and finger extension to resistance 1; *Step 6*) elbow extension up to resistance 1. Steps 2 through 6 were repeated to resistance 2 which was defined as the next point where resistance perceived by the examiner increased and again to resistance 3 which was defined as the end of the test as perceived by the examiner or the participant's tolerance, whichever occurred first. This graduated approach to applying ULNT1

allowed for more accurate identification of tightness onset, evoked-myoelectric activity, and maximal muscle resistance which were the points on the electromyographic software where myoelectric signals were analyzed and shoulder abduction range of motion, external rotation range of motion, and elbow extension range of motion deficit were measured (Fig. 2). Marks on the electromyographic software and range of motion measurements were performed by another physiotherapist (P.A), with 10 years of experience. Shoulder and elbow range of motion were measured with a standard goniometer using procedures that are reliable (Blonna et al., 2012; Riddle et al., 1987). ULNT1 was performed three times on each participant so that mean values for myoelectric activity and range of motion could be used for data analysis.

2.5. Data analysis

The investigator who extracted root mean square values and entered data (I.G.), and the person who analyzed the data (E.M.A.E) were blinded to each participant's group assignment. Data were analyzed with the Statistical Package for the Social Sciences software (17.0 version) (SPSS Inc, Chicago IL, USA, 2010). Shapiro-Wilk tests assessed for normal distribution, and student t-tests or non-parametric Mann Whitney U tests determined whether sample characteristics differed between the two groups. Because of non-normally distributed data, Mann Whitney U tests were used to analyze differences in myoelectric activity of biceps and triceps brachii (at tightness onset, evoked-myoelectric activity, and maximal muscle resistance), abduction range of motion, external rotation range of motion, and elbow extension range of motion deficit between breast cancer survivors and healthy women.

For our secondary aim to assess whether sentinel lymph node biopsy was indeed associated with less morbidity than axillary lymph node dissection, differences in myoelectric activity and ULNT1 range of motion between the three groups (sentinel lymph node biopsy, axillary lymph node dissection, control) were assessed with MANOVA. *Post hoc* testing used Bonferroni correction to account for multiple comparisons.

Relationships between myoelectric activity and range of motion were assessed among the three groups. Relationships between myoelectric activity and time elapsed from surgery to physical therapy assessment, range of motion and time elapsed from surgery to physical therapy assessment, myoelectric activity and chemotherapy, and range of motion and chemotherapy were assessed in breast cancer survivors. Pearson *r* was used for parametric data and Spearman *r* for nonparametric data. Results for all analyses were considered statistically significant when $p < 0.05$.

3. Results

Participants' flow throughout the study is shown in Fig. 3. There were no differences in age or body mass index between participants (Table 1). Among breast cancer survivors, the only difference in sample characteristics between the two surgical approaches was that more participants in the axillary lymph node dissection group received chemotherapy (Table 1). All axillary lymph node dissection participants and 81% of sentinel lymph node biopsy participants reported pain with daily activities. All chosen symptom descriptors were consistent with neuropathic pain, with the most frequent descriptor being dysesthesia (Fig. 4). The most frequent location was the armpit plus medial aspect of the arm (Fig. 5). These symptoms were at least partly related to increased upper limb nerve mechanosensitivity because all breast cancer survivors who reported pain at rest or during activities had their symptoms provoked during ULNT1, and these symptoms changed with neck side-bending (Nee et al., 2012).

3.1. Myoelectric activity

Mann Whitney U tests for tightness onset, evoked-myoelectric activity, and maximal muscle resistance within ULNT1 showed

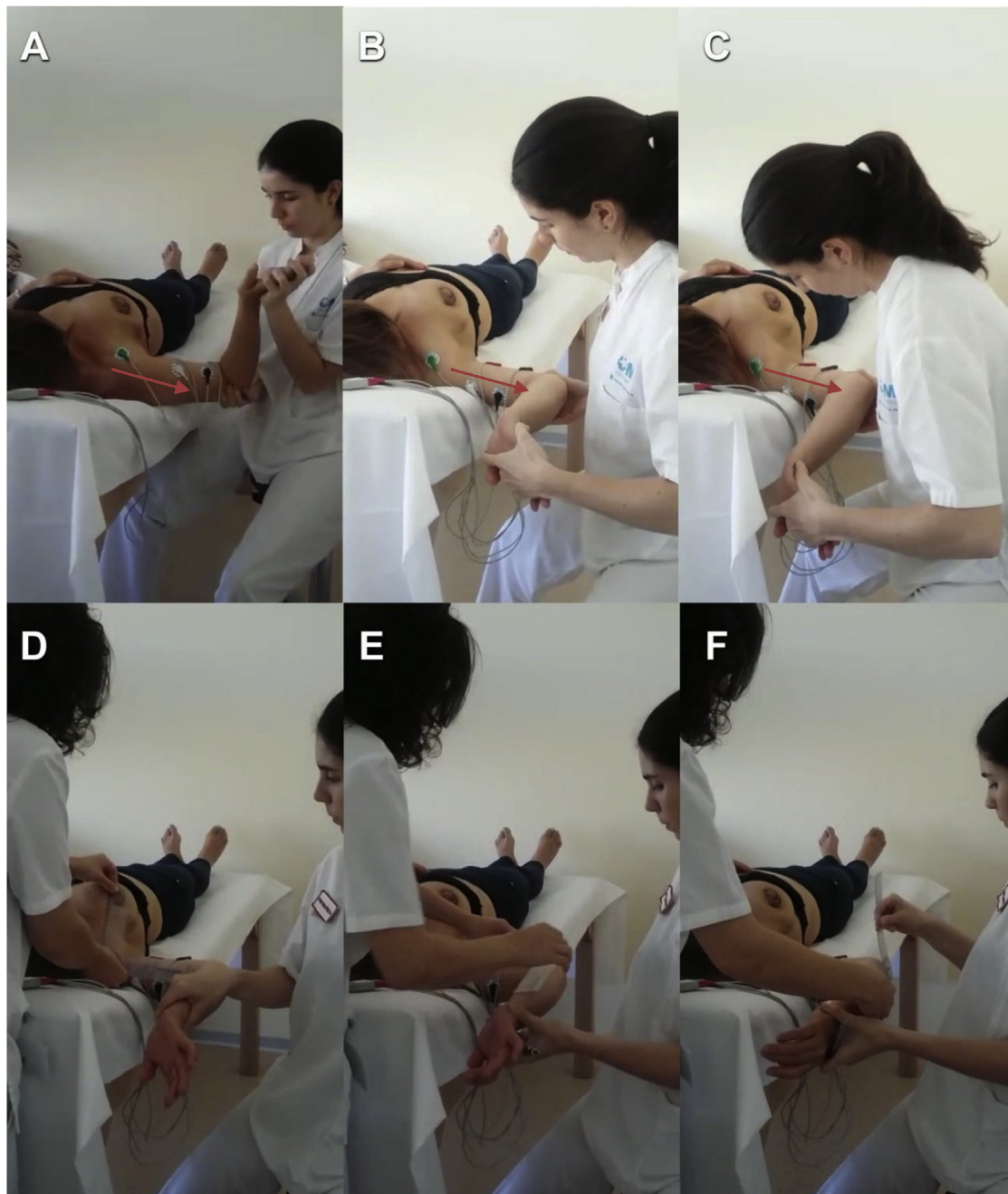


Fig. 2. Electromyographic recording and range of motion measurement during upper limb neurodynamic test 1. Upper limb position at tightness onset (A), evoked-myoelectric activity increase (B), and maximal muscle resistance (C). Measurement of abduction degrees (D), elbow extension deficit degrees (E) and external rotation degrees (F). Humerus traction used together with body weight in supine position to indirectly stabilize the scapula.

significantly greater myoelectric activity of biceps brachii in the breast cancer group compared to the control group ($p < 0.001$ for all analyses) (Table 2, Fig. 6). Although myoelectric activity of triceps brachii, was significantly greater in the breast cancer group at tightness onset ($p = 0.016$), there were no significant differences in triceps activity between the breast cancer and control groups at evoked-myoelectric activity or maximal muscle resistance within ULNT1 (Table 2, Fig. 6).

When we divided the breast cancer group into sentinel lymph node biopsy and axillary lymph node dissection groups, MANOVA analysis for biceps and triceps brachii showed differences between the three groups (Wilks'lambda = 0.754, $p < 0.001$ for biceps brachii and Wilks'lambda = 0.861, $p < 0.001$ for triceps brachii). *Post hoc* comparisons indicated that myoelectric activity in the biceps brachii was significantly greater in the axillary lymph node dissection and sentinel

lymph node biopsy groups when compared to the control group at all measurement points ($p \leq 0.032$). However, there were no differences between the two surgical groups (Fig. 7). In contrast, myoelectric activity in the triceps brachii at tightness onset, evoked-myoelectric activity, and maximal muscle resistance within ULNT1 was significantly greater in the sentinel lymph node dissection group than in the control group ($p \leq 0.041$) and than in the axillary lymph node dissection group ($p \leq 0.034$), with no differences between the axillary lymph node dissection and control groups (Fig. 7).

3.2. Muscle recruitment pattern

Myoelectric activity in the biceps and triceps brachii during ULNT1 in the breast cancer and control groups progressively increased

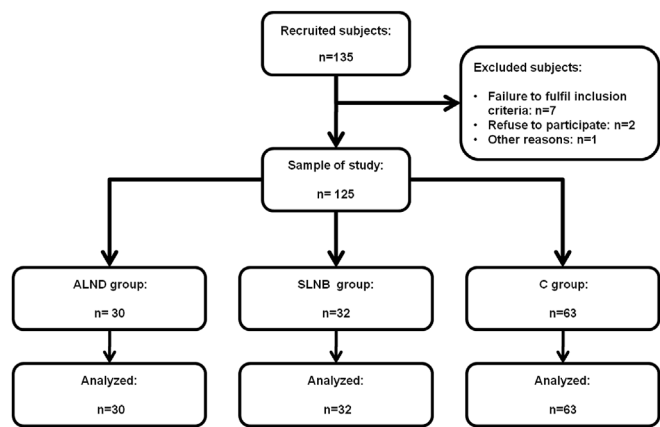


Fig. 3. Participants flow throughout the study progress. ALND group: Axillary lymph node dissection group; SLNB: Sentinel Lymph node biopsy group; C group: Control group.

throughout the test. Friedman tests within each group showed that biceps and triceps activity for all participants increased from tightness onset to evoked-myoelectric activity and again from evoked-myoelectric activity to maximal muscle resistance ($p \leq 0.017$) (Fig. 8: A1 and B1).

In the secondary three-group analysis, biceps brachii activity during ULNT1 progressively increased from tightness onset to maximal muscle resistance within ULNT1 within each group (Friedman tests $p < 0.001$), but the patterns of increase differed between groups. There was a relatively linear increase from tightness onset to maximal muscle resistance within ULNT1 in the control group while the initial increase from tightness onset to evoked-myoelectric activity in the breast cancer groups plateaued as ULNT1 progressed from evoked-myoelectric activity to maximal muscle resistance within ULNT1. Triceps brachii showed smaller increases in activity from tightness onset to maximal muscle resistance within ULNT1 within each group (Friedman tests $p < 0.001$), but again patterns differed between groups. There was a relatively linear increase from tightness onset to maximal muscle resistance within ULNT1 in the control and axillary lymph node dissection groups while the initial increase from tightness onset to evoked-myoelectric activity in the sentinel lymph node biopsy group plateaued as ULNT1 progressed from evoked-myoelectric activity to maximal muscle resistance within ULNT1 (Fig. 8: A2 and B2).

Table 1
Sample characteristics at baseline assessment.

	Breast cancer group n = 62			Control group n = 63	p-values ^a	p-values ^b
	Axillary lymph node dissection group n = 30	Sentinel lymph node biopsy group n = 32	All breast cancer group n = 62			
Age: median (IQR)	53.00 (18.00)	61.50 (19.50)	57.00 (18.00)	57.00 (18.00)	0.886 ³	> 0.05 ¹
BMI: mean (SD)	27.46 (4.65)	26.97 (4.81)	27.21 (4.71)	28.06 (4.59)	0.296 ⁴	> 0.05 ¹
DAA/NDAA	53.3%/46.7%	56%/44%	55,2%/44,8%			> 0.05 ²
Chemotherapy	100%	56%	61,6%			< 0.01 ²
Radiotherapy	80%	66%	64,0%			> 0.05 ²
Hormonal Therapy	57%	69%	68,8%			> 0.05 ²
Breast expander prosthesis	20%	15,60%	17,74%			> 0,05 ²
Lymphedema	0%	0%	0%			> 0,05 ²
TSA: median (IQR)	23.46 (19.83)	22.67 (28.17)	23.0 (25,40)			> 0,05 ³

BMI: Body Mass Index; TSA: Time elapsed (in months) from surgery to physical therapy assessment; SD: Standard deviation; DAA/NDAA: Dominant arm affected/ Non dominant-arm affected; IQR: Interquartile range; ¹: ANOVA Test; ²: Pearson's chi-squared test; ³: Mann Whitney U test; ⁴: Student T test.

^a Comparison Breast cancer group vs Control group.

^b Comparison Axillary lymph node dissection Group-Sentinel lymph node biopsy Group-Control Group.

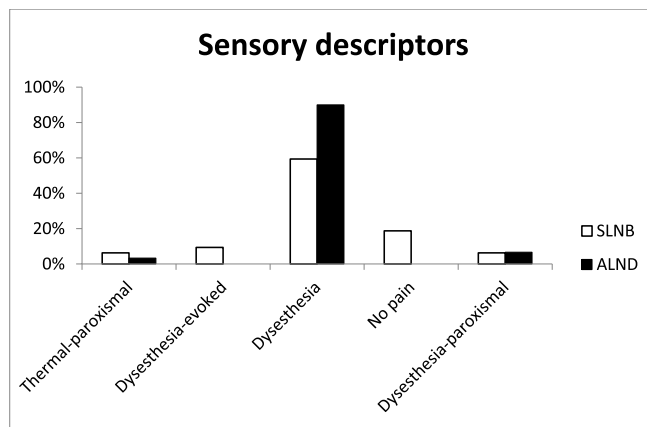


Fig. 4. Percentages (%) of sensory descriptors referred by sentinel lymph node biopsy (SLNB) and by axillary lymph node dissection (ALND) groups.

3.3. Range of motion

Mann Whitney U tests showed significant differences between breast cancer survivors and healthy women for shoulder abduction, external rotation, and deficit in elbow extension range of motion during ULNT1 at tightness onset, evoked-myoelectric activity, and maximal muscle resistance ($p < 0.001$ for all analyses). Breast cancer survivors had significantly less shoulder range of motion and greater deficits in elbow extension at all three measurement points compared to the control group (Table 3, Fig. 9).

When we divided the breast cancer group into sentinel lymph node biopsy and axillary lymph node dissection groups, MANOVA analysis for range of motion during ULNT1 showed differences between the three groups (Wilks'lambda = 0.425, $p < 0.001$ for shoulder abduction, Wilks'lambda = 0.332, $p < 0.001$ for shoulder external rotation and Wilks'lambda = 0.499, $p < 0.001$ for deficit in elbow extension). *Post hoc* analyses showed that the axillary lymph node dissection and sentinel lymph node biopsy groups had less shoulder range of motion and greater deficits in elbow extension range of motion than the control group at all three measurement points (Fig. 10). However, there were no differences in ULNT1 range of motion between the two breast cancer groups (Fig. 10).

3.4. Correlation analyses

The only significant correlations were between myoelectric activity and range of motion in the control and sentinel lymph node biopsy

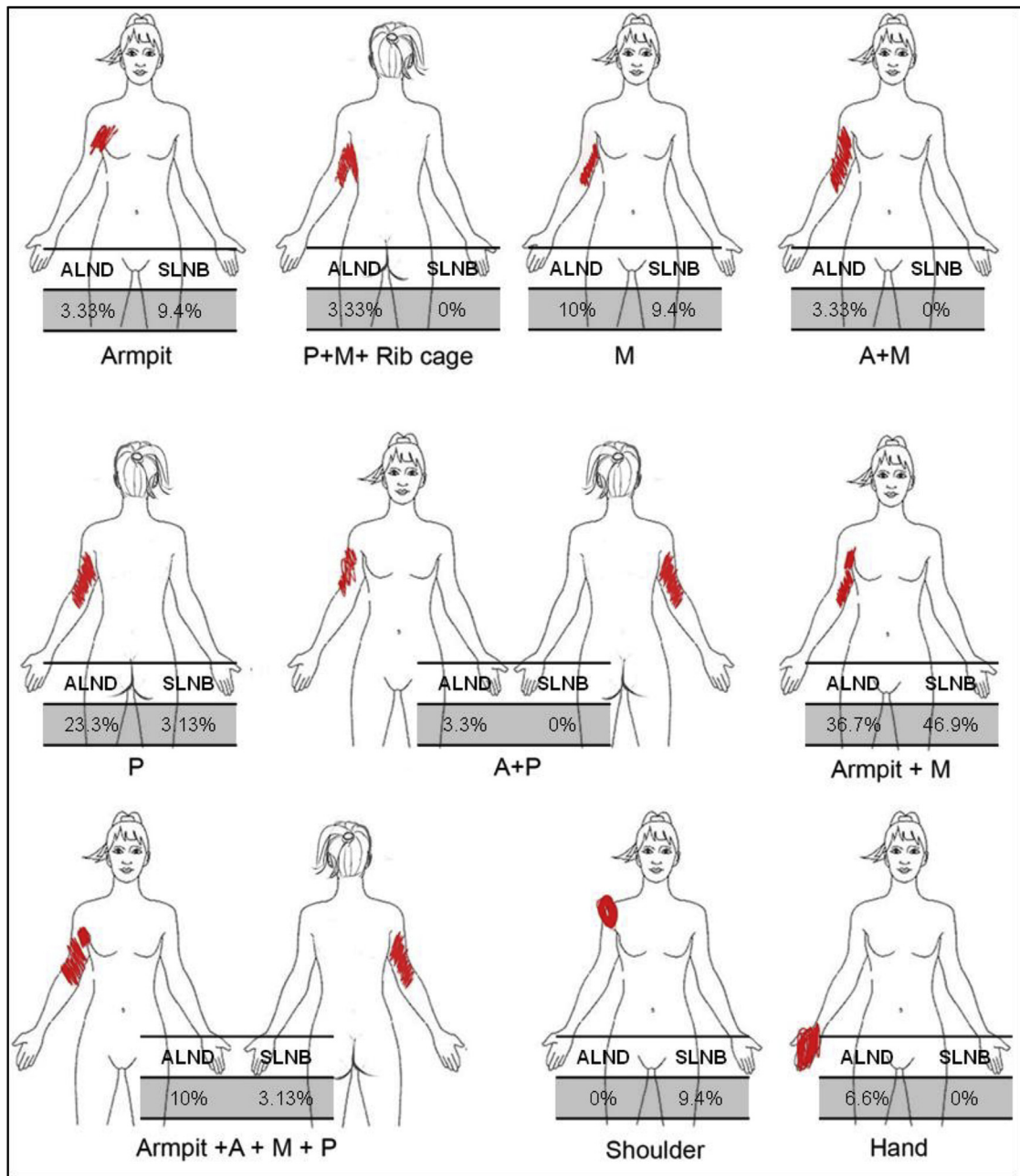


Fig. 5. Percentages (%) of sensory localization on a body map referred by sentinel lymph node biopsy (SLNB) and by axillary lymph node dissection (ALND) groups. P: posterior aspect of the arm; M: medial aspect of the arm; A: anterior aspect of the arm.

groups and between time elapsed from surgery to physical therapy assessment and range of motion in the axillary lymph node dissection group. Where present, significant correlations showed that greater myoelectric activity in biceps and triceps brachii were associated with less shoulder or elbow range of motion during ULNT1 (Table 4). In the axillary lymph node dissection group, greater time elapsed from surgery to physical therapy assessment, was associated with less shoulder abduction range of motion during ULNT1 (Table 4).

4. Discussion

Our findings are consistent with *persistent pain after breast cancer surgery* likely having a significant neuropathic component (Andersen and Kehlet, 2011) and being associated with increased upper limb nerve mechanosensitivity (Smoot et al., 2014; Caro-Morán et al., 2014; Kelley and Jull, 1998). Breast cancer survivors' symptoms were readily

characterized by neuropathic descriptors (Bennett, 2001). These symptoms were also at least partly related to increased upper limb nerve mechanosensitivity because they were provoked during ULNT1 and changed with structural differentiation (neck side-bending away from the tested arm) (Nee et al., 2012).

The biceps brachii protective muscle response during ULNT1 was significantly increased in breast cancer survivors compared to healthy women, and our secondary analysis showed that this increased protective muscle response was present regardless of the type of axillary surgery. Because the biceps brachii helps protect the median nerve from tensile forces related to elbow extension (Jaberzadeh et al., 2005; Jaberzadeh and Zoghi, 2013), this greater myoelectric activity is consistent with a greater muscle response to protect mechanically sensitive neural tissues during application of ULNT1. A greater protective muscle response during ULNT1 has also been documented in patients with carpal tunnel syndrome who had increased neural tissue

Table 2

Breast cancer and control group medians (in μ Vs) and interquartile ranges for myoelectrical activity of Biceps Brachii muscle and Triceps Brachii muscle at tightness onset, evoked-myoelectric activity increase and maximal muscle resistance within ULNT1.

	Breast cancer group (n = 62) Median (IQR)	Control group (n = 63) Median (IQR)	p value
Biceps activity at tightness onset	61.45 (39.10, 84.10)	28.60 (22.9, 73.0)	< 0.001
Biceps activity at evoked-myoelectric activity	85.55 (54.0, 100.0)	39.60 (30.90, 77.10)	< 0.001
Biceps activity at maximal muscle resistance within ULNT1	88.85 (64.5, 101.0)	64.40 (44.30, 86.00)	< 0.001
Triceps activity at tightness onset	64.50 (57.9, 73.0)	61.80 (54.6, 67.6)	0.016
Triceps activity at evoked-myoelectric activity	68.90 (60.1, 77.0)	65.10 (58.7, 71.5)	0.065
Triceps activity at maximal muscle resistance within ULNT1	72.00 (64.0, 79.9)	68.60 (62.3, 77.8)	0.355

mechanosensitivity (Jaberzadeh and Zoghi, 2013). Biceps brachii activity may be triggered by a nociceptive flexor mediated reflex as ULNT1 increases mechanical tension in peripheral nerves (Jaberzadeh and Zoghi, 2013; Rade et al., 2014).

Only the sentinel lymph node biopsy group exhibited increased protective activity in the triceps brachii during ULNT1, a response that has also been documented in patients with carpal tunnel syndrome who had increased neural tissue mechanosensitivity (Jaberzadeh and Zoghi, 2013). Although the exact neurophysiological mechanism is unclear, triceps brachii activity may be related to an inverse myotatic reflex triggered by biceps brachii activity (Jaberzadeh and Zoghi, 2013). A biceps/triceps brachii co-contraction might also be elicited by failure of reciprocal inhibition (Jaberzadeh and Zoghi, 2013). Increases in protective muscle activity in the sentinel lymph node biopsy group that were similar to (biceps brachii) or greater than (triceps brachii) the axillary lymph node dissection group could support the hypothesis that manipulation of neural tissue during surgery is enough to lead to increased upper limb nerve mechanosensitivity (Smoot et al., 2014).

The protective nature of the increased myoelectric activity in biceps and triceps brachii is further supported by reductions in ULNT1 range of motion and negative correlations between myoelectric activity and ULNT1 range of motion. In particular, greater deficits in elbow extension at the end of ULNT1 in breast cancer survivors is consistent with previous studies that showed increased upper limb nerve mechanosensitivity in this population (Smoot et al., 2014; Caro-Morán et al.,

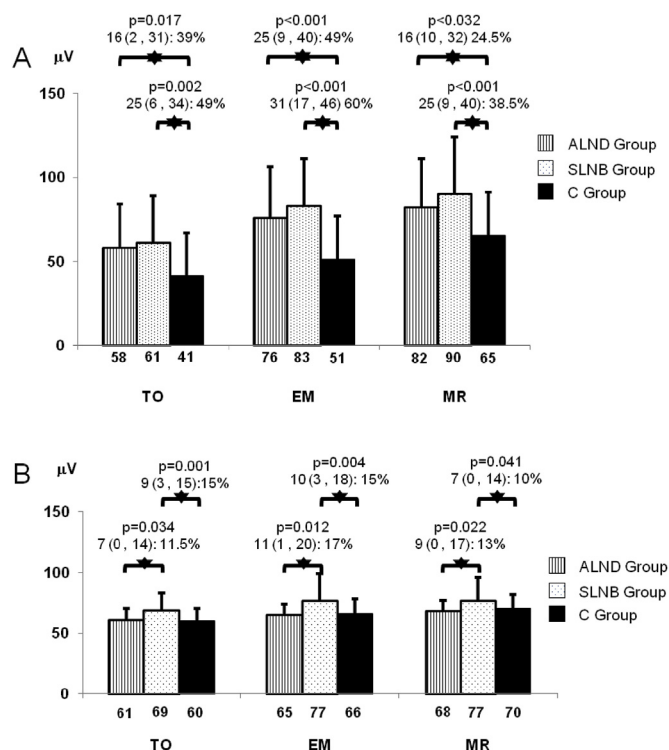


Fig. 7. Group means, differences between group means and 95% confidence intervals for myoelectrical activity of Biceps Brachii muscle (A) and Triceps Brachii muscle (B) at tightness onset (TO), evoked-myoelectric activity increase (EM) and maximal muscle resistance (MR) within ULNT1. Significant differences have also been expressed as percentage differences (%). ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy, C: Control. *Post-hoc significant difference.

2014) and in other symptomatic populations (Jaberzadeh and Zoghi, 2013; Sterling et al., 2004). Negative correlations indicate that increased myoelectric activity in biceps and triceps brachii were associated with less shoulder range of motion during ULNT1 in the sentinel lymph node biopsy participants. Although this protective muscle activity could be elicited by strain on other soft tissues (Coppieters et al., 2002), we think it is plausible that it is related to strain on sensitive neural tissues (Elvey, 1997; Hall and Elvey, 1999), especially at tightness onset. We pre-positioned the neck in contralateral side-bending before moving the upper limb when performing ULNT1 in order to pre-load the brachial plexus. By pre-loading the brachial plexus, shoulder

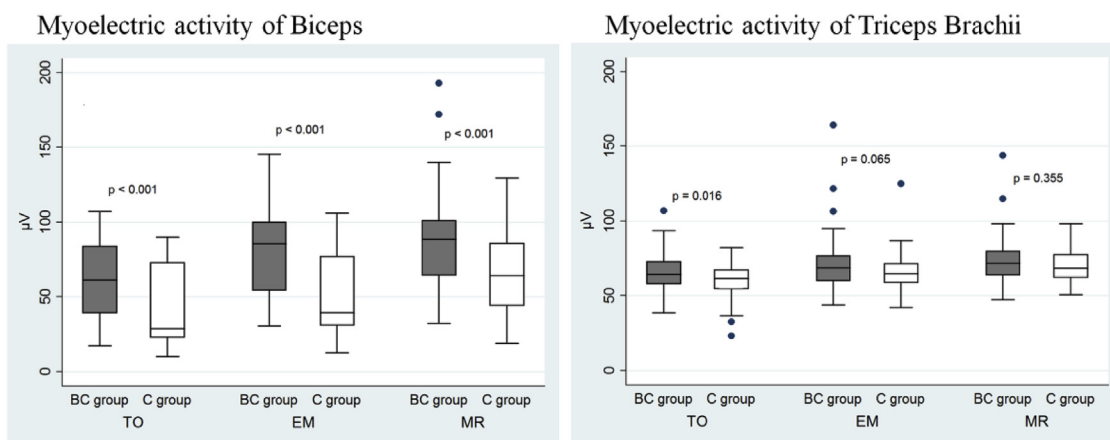


Fig. 6. Breast cancer and control group medians (in μ Vs) and interquartile ranges for myoelectrical activity of Biceps Brachii muscle and Triceps Brachii muscle at tightness onset, evoked-myoelectric activity increase and maximal muscle resistance within ULNT1. P values from Mann Whitney U test.

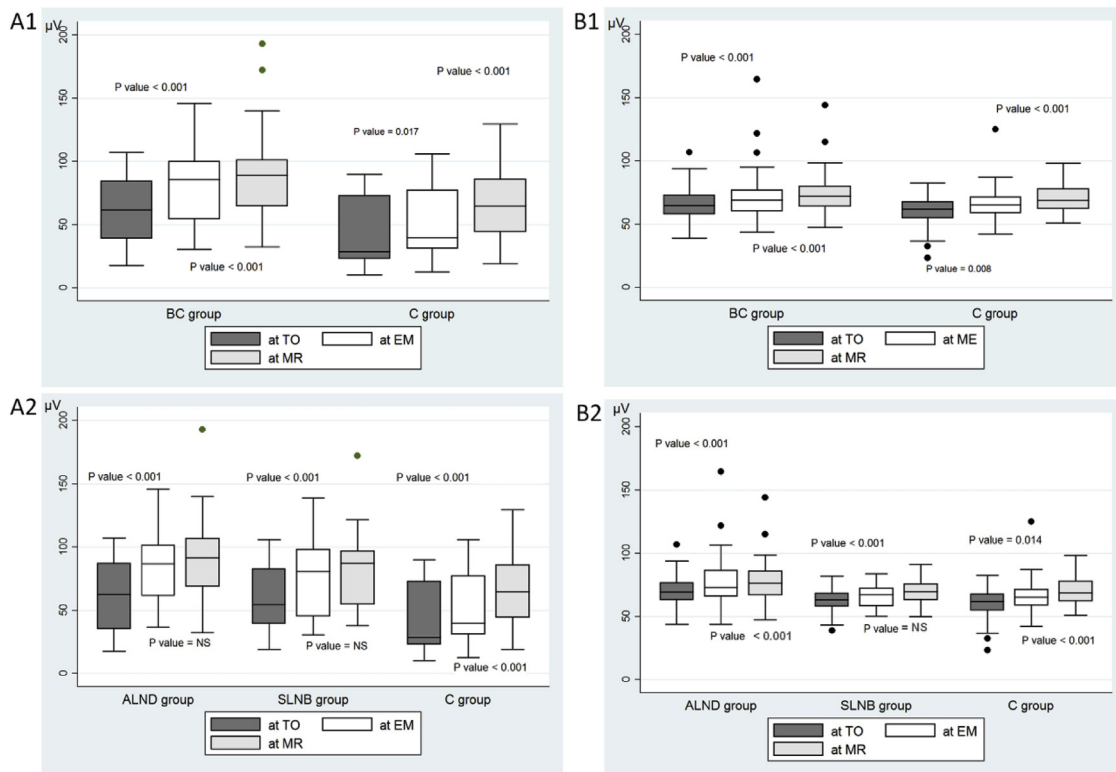


Fig. 8. Muscle recruitment pattern within the upper limb neurodynamic test 1 (ULNT1) of biceps brachii (A1) and triceps brachii (B1) in two-group analysis and three-group analysis (A2 and B2 respectively). Wilcoxon Test p values from the increase of myoelectric activity from tightness onset (TO) up to evoked-myoelectric activity (EM) and from evoked-myoelectric activity (EM) up to maximal muscle resistance (MR) within each group. ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy, C: Control, NS: No significant.

movements to tightness onset may more likely be related to stimulation of sensitive neural tissues because abduction less than 90° and external rotation less than 70° may be less likely to stress other soft tissues around the shoulder. However, this hypothesis needs to be tested in future studies that explore whether myoelectric activity during ULNT1 is affected by structural differentiation maneuvers.

The significant correlation between time elapsed from surgery to physical therapy assessment and abduction range of motion in the breast cancer group suggests that abduction range of motion decreases over time. This may be due to the cumulative effects of surgical

scarring, radiation-induced fibrosis, and pain-inhibited movement that alter shoulder mechanics during daily activities (Crosbie et al., 2010).

There was a relatively linear increase in biceps brachii activity in healthy women as mechanical forces applied to neural tissues increased during progression of ULNT1 from tightness onset to maximal muscle resistance. In contrast, the pattern of recruitment in breast cancer survivors was greatest during the early stages of ULNT1 (tightness onset to evoked-myoelectric activity) and plateaued thereafter. Lack of a proportional increase in biceps brachii activity as mechanical forces applied to sensitive neural tissues continued to increase could be

Table 3

Breast cancer and control group medians (degrees) and interquartile ranges for range of motion of shoulder abduction, external rotation and elbow extension at tightness onset, evoked-myoelectric activity increase and maximal muscle resistance within ULNT1.

	Breast cancer group (n = 62) Median (IQI)	Control group (n = 63) Median (IQI)	p value
Shoulder abduction range of motion at tightness onset	86.75 (82.00,93.00)	109.00 (97.00, 120.50)	< 0.001
Shoulder abduction range of motion at evoked-myoelectric activity	101.00 (94.50, 110.00)	138.00 (127.50, 147.00)	< 0.001
Shoulder abduction range of motion at maximal muscle resistance within ULNT1	104.75 (97.00, 116.50)	153.00 (138.00, 171.00)	< 0.001
Shoulder external rotation range of motion at tightness onset	61.25 (49,50, 69.50)	95.00 (89.00, 106.00)	< 0.001
Shoulder external rotation range of motion at evoked-myoelectric activity	75.25 (67,00, 86.00)	108.50 (103.50, 117.50)	< 0.001
Shoulder external rotation range of motion at maximal muscle resistance within ULNT1	84.75 (77,00, 90.50)	114.00 (107.00, 120.50)	< 0.001
Deficit in elbow extension range of motion at tightness onset	92,50 (85.40, 101,2)	62.00 (46.00, 75.50)	< 0.001
Deficit in elbow extension range of motion at evoked-myoelectric activity	83.75 (80.00, 88.63)	44.50 (30.50, 60.00)	< 0.001
Deficit in elbow extension range of motion at maximal muscle resistance within ULNT1	76.00 (66.25, 83.12)	34.00 (17.00, 47.50)	< 0.001

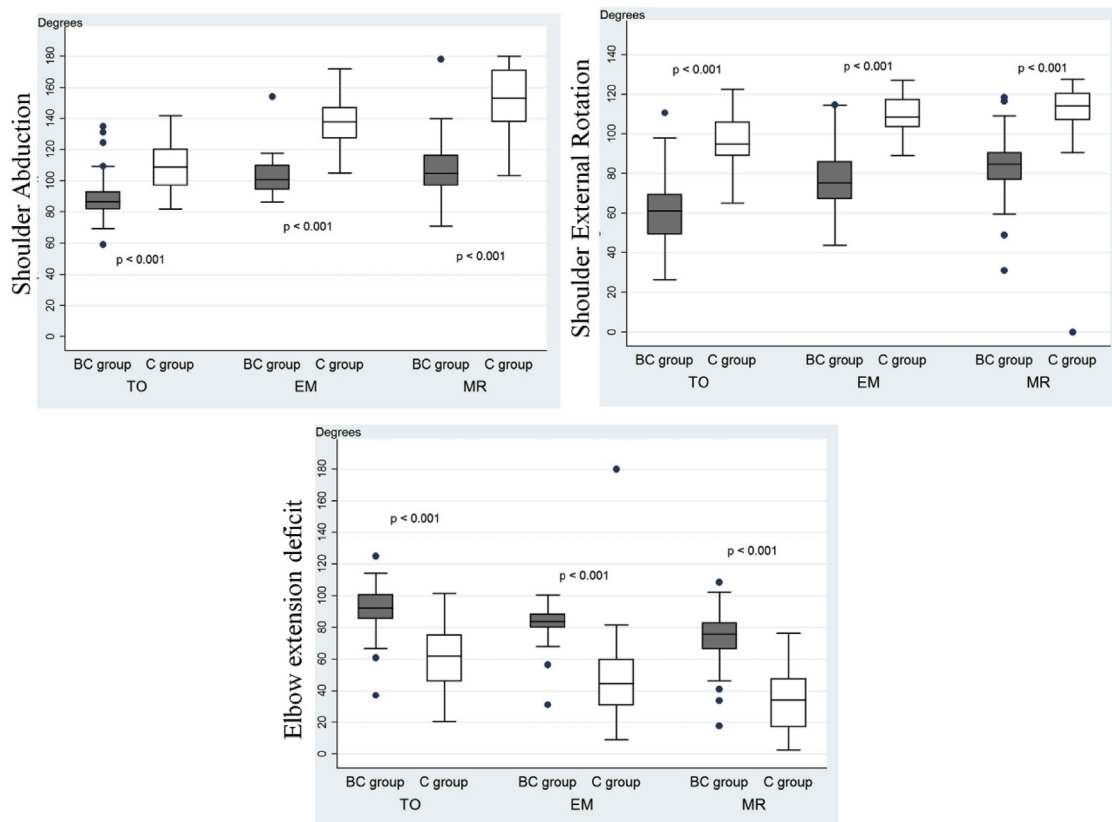


Fig. 9. Group medians, interquartile ranges, p values from Mann Whitney test for median differences between BC (breast cancer) group and C (control) group of range of motion degrees of abduction, external rotation and elbow extension deficit at tightness onset (TO), evoked-myoelectric activity increase (EM) and maximal muscle resistance (MR) within the upper limb tension test 1.

consistent with a central sensitization process that could happen after breast cancer treatment (Nijs et al., 2016; Fernandez-Lao et al., 2011). It is also possible that small diameter nerve fiber damage related to radiation or chemotherapy could reduce this proportional protective response. Boyd et al. (2010) showed that individuals with more severe diabetic peripheral neuropathy have a diminished protective response to progressive increases in neural tissue loading during straight leg raise neurodynamic testing. Lastly, the lack of a proportional increase in protective biceps brachii activity might also be related to psychosocial factors such as pain cognitions, pain catastrophizing, and expectations of pain during testing that have been shown to influence neurodynamic test responses (Beneciuk et al., 2010; Lloyd et al., 2016; McCracken et al., 1993; Moseley, 2004). We did not assess breast cancer survivors for signs of central sensitization, small diameter nerve fiber damage, or psychosocial factors. Therefore, future mechanistic studies are required to understand the nature of this lack of a proportional increase in protective biceps brachii activity during ULNT1 in breast cancer survivors.

Although it occurred to a lesser extent, there was also a relatively linear increase in triceps brachii activity in healthy women as ULNT1 progressed from tightness onset to maximal muscle resistance within ULNT1. The fact that only the sentinel lymph node biopsy group, rather than both the sentinel lymph node biopsy and axillary lymph node dissection groups, showed a different pattern of triceps brachii recruitment during ULNT1 was an unexpected finding. Further research needs to determine whether this finding can be replicated and what mechanisms (peripheral, central, and/or psychosocial) may be involved.

4.1. Limitations and strengths of the study

This is the first study to analyze the amplitude of protective myoelectric activity during ULNT1 in breast cancer survivors. Root mean square analysis allowed for accurate detection of minimal changes in amplitude of myoelectric activity (Karlsson and Gerdlé, 2001). The increased myoelectric activity in the recorded muscles was expected, because they can protect the nerve from excessive strain when upper limb nerve mechanosensitivity is increased. However, additional muscles that can protect the median nerve from strain (e.g., upper trapezius (Jaberzadeh and Zoghi, 2013)) could be recorded in future studies to better understand the protective muscle pattern during ULNT1 in breast cancer survivors.

The contralateral upper limb was not used for comparison because of concerns of central sensitization that reportedly occurs after breast cancer treatment (Nijs et al., 2016). Neurodynamic testing in breast cancer survivors has shown increased neural mechanosensitivity in the uninvolved arm (Smoot et al., 2014; Kelley and Jull, 1998). We therefore felt that a comparison to age-matched healthy women would provide a better indication of the magnitude of upper limb nerve mechanosensitivity and protective muscle activity during ULNT1 in breast cancer survivors (Smoot et al., 2014).

The secondary analyses that compared all three groups (sentinel lymph node biopsy, axillary lymph node dissection, and control) need to be interpreted cautiously. The sample size calculation was based on a two-group analysis (breast cancer survivors and control), which meant that the secondary three-group analysis was likely underpowered. Future studies with larger samples of each type of surgical procedure need to determine if our observed results can be replicated.

Lastly, it would have been ideal to perform measurements of isolated shoulder range of motion prior to ULNT1 testing. Although

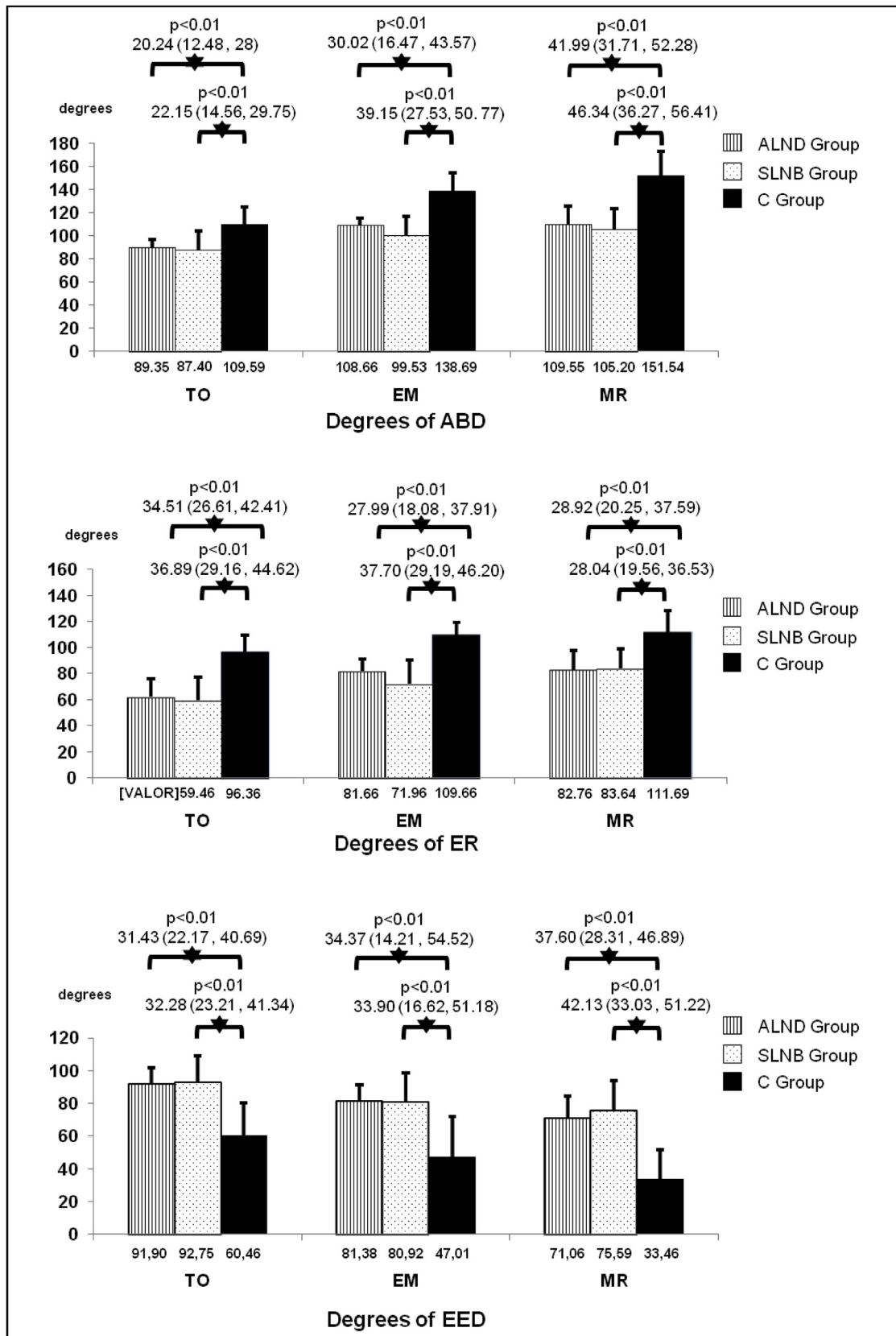


Fig. 10. Group means, differences between group means and 95% confidence intervals for range of motion degrees of abduction (ABD), external rotation (RE) and elbow extension deficit (EED) at tightness onset (TO), evoked-myoelectric activity increase (EM) and maximal muscle resistance (MR) within the upper limb tension test 1. ALND: Axillary lymph node dissection, SLND: Sentinel lymph node biopsy, C: Control. *Post-hoc significant difference.

Table 4
Correlation analyses. Pearson *r* values reported unless noted otherwise.

	Biceps activity at tightness onset	Biceps activity at evoked-myoelectric activity increase	Biceps activity at maximal muscle resistance within ULNT1	Triceps activity at tightness onset	Triceps activity at evoked-myoelectric activity increase	Triceps activity at maximal muscle resistance within ULNT1	TSA at tightness onset	TSA at maximal muscle resistance within ULNT1
Shoulder abduction range of motion	Control:-0.40^b (p = 0.001)	Control:-0.33^b (p = 0.01)	Control:-0.45^b (p = 0.000)	Control:-0.20 (p = 0.10)	Control:-0.13 (p = 0.32)	Control:-0.09 (p = 0.48)	ALND:-0.47 ^a (p = 0.008)	ALND:-0.47 ^a (p = 0.008)
	SLNB:-0.02 (p = 0.91)	SLNB:-0.13 (p = 0.71)	SLNB:-0.14 (p = 0.42)	SLNB:-0.03 (p = 0.83)	SLNB:-0.33 (p = 0.35)	SLNB:-0.50 (p = 0.004)		
	ALND:-0.05 (p = 0.78)	ALND:0.23 (p = 0.45)	ALND:-0.28 (p = 0.13)	ALND:0.35 (p = 0.85)	ALND:0.24 (p = 0.45)	ALND:-0.12 (p = 0.53)		
	Control:-0.40^b (p = 0.001)	Control:-0.24 (p = 0.07)	Control:-0.28^b (p = 0.02)	Control:-0.19 (p = 0.12)	Control:-0.13 (p = 0.32)	Control:-0.00 (p = 0.98)		
Shoulder external rotation range of motion	SLNB:-0.47^b (p = 0.006)	SLNB:-0.04 (p = 0.90)	SLNB:-0.05 (p = 0.78)	SLNB:-0.37^b (p = 0.03)	SLNB:-0.20 (p = 0.57)	SLNB:-0.46 (p = 0.008)		
	ALND:-0.27 (p = 0.14)	ALND:0.27 (p = 0.38)	ALND:-0.19 (p = 0.30)	ALND:-0.003 (p = 0.98)	ALND:0.33 (p = 0.28)	ALND:-0.19 (p = 0.30)		
	Control:-0.13 (p = 0.28)	Control:-0.25 (p = 0.06)	Control:0.39^b (p = 0.002)	Control:-0.09 (p = 0.46)	Control:0.15 (p = 0.27)	Control:-0.07 (p = 0.59)		
	SLNB:-0.16 (p = 0.92)	SLNB:-0.30 (p = 0.39)	SLNB:0.03 (p = 0.88)	SLNB:-0.26 (p = 0.14)	SLNB:0.12 (p = 0.72)	SLNB:0.15 (p = 0.40)		
Deficit in elbow extension range of motion	ALND:-0.32 (p = 0.08)	ALND:0.22 (p = 0.47)	ALND:-0.20 (p = 0.28)	ALND:-0.15 (p = 0.40)	ALND:0.12 (p = 0.70)	ALND:-0.19 (p = 0.30)		

The data highlighted in bold indicate statistically significant differences.

ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy; TSA: Time elapsed (in months) from surgery to physical therapy assessment; ULNT1: upper limb neurodynamic test 1.

^a Spearman *r*.

^b Positive correlation means that greater myoelectric activity associated with greater deficit in elbow extension range of motion at the end of ULNT1.

shoulder pathology was an exclusion criterion, knowledge of isolated shoulder range of motion would provide more confidence that shoulder range of motion restrictions during ULNT1 were indeed related to increased upper limb nerve mechanosensitivity, rather than local shoulder dysfunction.

5. Conclusion

Symptoms reported by breast cancer survivors in our study likely had a neuropathic component because they were readily characterized by neuropathic pain descriptors. The likely neuropathic component to these symptoms is consistent with *persistent pain after breast cancer surgery*. Reproduction of symptoms and the ability to change symptoms with structural differentiation during ULNT1 also suggest that these symptoms were at least partly related to increased upper limb nerve mechanosensitivity. This increase in upper limb nerve mechanosensitivity during neurodynamic testing was present regardless of the type of axillary approach or adjuvant treatments (e.g., radiation, chemotherapy). Increased upper limb nerve mechanosensitivity was associated with a greater protective muscle response, particularly in biceps brachii, and reduced shoulder and elbow range of motion during ULNT1 when compared to healthy women. The pattern of the protective muscle response was consistent with central sensitization that reportedly occurs after breast cancer treatment. Our findings add to the understanding of the nature of increased upper limb nerve mechanosensitivity in breast cancer survivors after surgery. They also suggest that sentinel lymph node biopsy is sufficient to lead to increased upper limb nerve mechanosensitivity in this population. Clinicians should therefore assess for increased upper limb nerve mechanosensitivity in breast cancer survivors after surgery, regardless of the axillary surgery approach.

Funding

No funding.

Disclosure of potential conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

We thank Torrejón Hospital for easing us to conduct this study, especially to Dr. Sergio Trinidad, who helped to inform breast cancer survivors and encouraged them to participate. We also thank all participants for collaborating and permitting clinicians to keep learning.

References

- Andersen, K.G., Kehlet, H., 2011. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. *J. Pain* 12 (7), 725–746.
- Andersen, K.G., Jensen, M.B., Kehlet, H., Gartner, R., Eckhoff, L., Kroman, N., 2012. Persistent pain, sensory disturbances and functional impairment after adjuvant chemotherapy for breast cancer: cyclophosphamide, epirubicin and fluorouracil compared with docetaxel + epirubicin and cyclophosphamide. *Acta Oncol.* 51 (8), 1036–1044.
- Andersen, K.G., Duriaud, H.M., Jensen, H.E., Kroman, N., Kehlet, H., 2015. Predictive factors for the development of persistent pain after breast cancer surgery. *Pain* 156 (12), 2413–2422.
- Beneciuk, J.M., Bishop, M.D., George, S.Z., 2010. Pain catastrophizing predicts pain intensity during a neurodynamic test for the median nerve in healthy participants. *Man. Ther.* 15 (4), 370–375.
- Bennett, M., 2001. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 92 (1–2), 147–157.
- Bennett, M., 2002. La Escala de Dolor de LANSS: la evaluación de síntomas neuropáticos de Leeds. *Rev. Soc. Esp. Dolor* 9, 74–87.
- Blonna, D., Zarkadas, P.C., Fitzsimmons, J.S., O'Driscoll, S.W., 2012. Accuracy and inter-observer reliability of visual estimation compared to clinical goniometry of the elbow. *Knee Surg. Sports Traumatol. Arthrosc.* 20 (7), 1378–1385.
- Boudier-Reveret, M., Gilbert, K.K., Allegue, D.R., Moussadyk, M., Brismee, J.M., Sizer Jr., P.S., Feipel, V., Dugaillly, P.M., Sobczak, S., 2017. Effect of neurodynamic mobilization on fluid dispersion in median nerve at the level of the carpal tunnel: a cadaveric study. *Musculoskelet Sci Pract* 31, 45–51.
- Boyd, B.S., Wanek, L., Gray, A.T., Topp, K.S., 2010. Mechanosensitivity during lower extremity neurodynamic testing is diminished in individuals with Type 2 Diabetes Mellitus and peripheral neuropathy: a cross sectional study. *BMC Neurol.* 10, 75.
- Brewer, J.R., Morrison, G., Dolan, M.E., Fleming, G.F., 2016. Chemotherapy-induced peripheral neuropathy: current status and progress. *Gynecol. Oncol.* 140 (1), 176–183.
- Caro-Morán, E., Díaz-Rodríguez, L., Cantarero-Villanueva, I., Galiano-Castillo, N., Arroyo-Morales, M., Fernández-Lao, C., 2014. Nerve pressure pain hypersensitivity and upper limb mechanosensitivity in breast cancer survivors: a case-control study. *Pain Med.* 15 (10), 1715–1723.
- Coppieters, M., Stappaerts, K., Janssens, K., Jull, G., 2002. Reliability of detecting 'onset of pain' and 'submaximal pain' during neural provocation testing of the upper quadrant. *Physiother. Res. Int.* 7 (3), 146–156.
- Crosbie, J., Kilbreath, S.L., Dylke, E., Refshauge, K.M., Nicholson, L.L., Beith, J.M., Spillane, A.J., White, K., 2010. Effects of mastectomy on shoulder and spinal kinematics during bilateral upper-limb movement. *Phys. Ther.* 90 (5), 679–692.
- Delanian, S., Lefaix, J.L., Pradat, P.F., 2012. Radiation-induced neuropathy in cancer survivors. *Radiother. Oncol.* 105 (3), 273–282.
- Ducic, I., Seiboth, L.A., Iorio, M.L., 2011. Chronic postoperative breast pain: danger zones for nerve injuries. *Plast. Reconstr. Surg.* 127 (1), 41–46.
- Elvey, R.L., 1997. Physical evaluation of the peripheral nervous system in disorders of pain and dysfunction. *J. Hand Ther.* 10 (2), 122–129.
- Fernandez-Lao, C., Cantarero-Villanueva, I., Fernandez-de-las-Penas, C., Del-Moral-Avila, R., Menjon-Beltran, S., Arroyo-Morales, M., 2011. Widespread mechanical pain hypersensitivity as a sign of central sensitization after breast cancer surgery: comparison between mastectomy and lumpectomy. *Pain Med.* 12 (1), 72–78.
- Fong, S.S., Ng, S.S., Luk, W.S., Chung, J.W., Chung, L.M., Tsang, W.W., Chow, L.P., 2013. Shoulder mobility, muscular strength, and quality of life in breast cancer survivors with and without Tai chi Qigong training. *Evid Based Complement Alternat Med* 2013, 787169.
- Greening, J., Dilley, A., 2017. Posture-induced changes in peripheral nerve stiffness measured by ultrasound shear-wave elastography. *Muscle Nerve* 55 (2), 213–222.
- Hall, T.M., Elvey, R.L., 1999. Nerve trunk pain: physical diagnosis and treatment. *Man. Ther.* 4 (2), 63–73.
- Hermens, H.J., Freriks, B., Disselhorst-Klug, C., Rau, G., 2000. Development of recommendations for SEMG sensors and sensor placement procedures. *J. Electromyogr. Kinesiol.* 10 (5), 361–374.
- Jaberzadeh, S., Zoghi, M., 2013. Mechanosensitivity of the median nerve in patients with chronic carpal tunnel syndrome. *J. Bodyw. Mov. Ther.* 17 (2), 157–164.
- Jaberzadeh, S., Scutter, S., Nazeran, H., 2005. Mechanosensitivity of the median nerve and mechanically produced motor responses during Upper Limb Neurodynamic Test 1. *Physiotherapy* 91 (2), 94–100.
- Johnson, E.O., Vekris, M.D., Zoubos, A.B., Soucacos, P.N., 2006. Neuroanatomy of the brachial plexus: the missing link in the continuity between the central and peripheral nervous systems. *Microsurgery* 26 (4), 218–229.
- Karim-Kos, H.E., de Vries, E., Soerjomataram, I., Lemmens, V., Siesling, S., Coebergh, J.W., 2008. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 44 (10), 1345–1389.
- Karlsson, S., Gerde, B., 2001. Mean frequency and signal amplitude of the surface EMG of the quadriceps muscles increase with increasing torque—a study using the continuous wavelet transform. *J. Electromyogr. Kinesiol.* 11 (2), 131–140.
- Kelley, S., Jull, G., 1998. Breast surgery and neural tissue mechanosensitivity. *Aust. J. Physiother.* 44 (1), 31–37.
- La Vecchia, C., Bosetti, C., Lucchini, F., Bertuccio, P., Negri, E., Boyle, P., Levi, F., 2010. Cancer mortality in Europe, 2000–2004, and an overview of trends since 1975. *Ann. Oncol.* 21 (6), 1323–1360.
- Lauridsen, M.C., Overgaard, M., Overgaard, J., Hessov, I.B., Christiansen, P., 2008. Shoulder disability and late symptoms following surgery for early breast cancer. *Acta Oncol.* 47 (4), 569–575.
- Lloyd, D.M., Helbig, T., Findlay, G., Roberts, N., Nurmikko, T., 2016. Brain areas involved in anticipation of clinically relevant pain in low back pain populations with high levels of pain behavior. *J. Pain* 17 (5), 577–587.
- Lohman, C.M., Gilbert, K.K., Sobczak, S., Brismee, J.M., James, C.R., Day, M., Smith, M.P., Taylor, L., Dugaillly, P.M., Pendergrass, T., et al., 2015. 2015 young investigator award winner: cervical nerve root displacement and strain during upper limb neural tension testing: Part 1: a minimally invasive assessment in unembalmed cadavers. *Spine* 40 (11), 793–800.
- McCracken, L.M., Gross, R.T., Sorg, P.J., Edmands, T.A., 1993. Prediction of pain in patients with chronic low back pain: effects of inaccurate prediction and pain-related anxiety. *Behav. Res. Ther.* 31 (7), 647–652.
- Moseley, G.L., 2004. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *Eur. J. Pain* 8 (1), 39–45.
- Nee, R.J., Jull, G.A., Vicenzino, B., Coppieters, M.W., 2012. The validity of upper-limb neurodynamic tests for detecting peripheral neuropathic pain. *J. Orthop. Sports Phys. Ther.* 42 (5), 413–424.
- Nijs, J., Leysen, L., Adriaenssens, N., Aguilar Ferrandiz, M.E., Devoogdt, N., Tassenoy, A., Ickmans, K., Goubert, D., van Wilgen, C.P., Wijma, A.J., et al., 2016. Pain following cancer treatment: guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain. *Acta Oncol.* 55 (6), 659–663.
- Pollan, M., Michelena, M.J., Ardanaz, E., Izquierdo, A., Sanchez-Perez, M.J., Torrella, A., 2010. Breast cancer incidence in Spain before, during and after the implementation of screening programmes. *Ann. Oncol.* 21 (Suppl. 3), ii97–102.

- Quintner, J.L., 1989. A study of upper limb pain and paraesthesiae following neck injury in motor vehicle accidents: assessment of the brachial plexus tension test of Elvey. *Br. J. Rheumatol.* 28 (6), 528–533.
- Rade, M., Shacklock, M., Rissanen, S.M., Peharec, S., Bacic, P., Candian, C., Kankaanpaa, M., Airaksinen, O., 2014. Effect of glenohumeral forward flexion on upper limb myoelectric activity during simulated mills manipulation; relations to peripheral nerve biomechanics. *BMC Musculoskel. Disord.* 15, 288.
- Reaz, M.B., Hussain, M.S., Mohd-Yasin, F., 2006. Techniques of EMG signal analysis: detection, processing, classification and applications (Correction). *Biol. Proced. Online* 8, 163.
- Riddle, D.L., Rothstein, J.M., Lamb, R.L., 1987. Goniometric reliability in a clinical setting. *Shoulder measurements. Phys. Ther.* 67 (5), 668–673.
- Rissanen, S.M., Kankaanpaa, M., Tarvainen, M.P., Meigal, A.Y., Nuutinen, J., Tarkka, I.M., Airaksinen, O., Karjalainen, P.A., 2009. Analysis of dynamic voluntary muscle contractions in Parkinson's disease. *IEEE Trans. Biomed. Eng.* 56 (9), 2280–2288.
- Silva, A., Manso, A., Andrade, R., Domingues, V., Brandao, M.P., Silva, A.G., 2014. Quantitative in vivo longitudinal nerve excursion and strain in response to joint movement: a systematic literature review. *Clin Biomech (Bristol, Avon)* 29 (8), 839–847.
- Smoot, B., Boyd, B.S., Byl, N., Dodd, M., 2014. Mechanosensitivity in the upper extremity following breast cancer treatment. *J. Hand Ther.* 27 (1), 4–11.
- Sterling, M., Jull, G., Vicenzino, B., Kenardy, J., 2004. Characterization of acute whiplash-associated disorders. *Spine* 29 (2), 182–188.
- Szikszy, T., Hall, T., von Piekartz, H., 2017. In vivo effects of limb movement on nerve stretch, strain, and tension: a systematic review. *J. Back Musculoskelet. Rehabil.* 30 (6), 1171–1186.
- Warren, W.S., Newman, T.B., Hulley, S.B., 2013. Estimating sample size and power: applications and examples. In: *Designed Clinical Research*, 4 edn. Lippincott Williams & Wilkins, Philadelphia.